Combined Model Profile
Version: 1.0.00
Released: 2025-09-30

Cervical Cancer Combined Model Profile

Individual Model Profiles

DRIVE CERVICAL (Data-driven Recommendations for Interventions against Viral infection)
Massachusetts General Hospital
Version: 1.0.00
Released: 2025-09-30

Harvard Cervical: Model Profile
Harvard T.H. Chan School of Public Health
Version: 1.0.00
Released: 2025-09-30

POLICY1-CERVIX: Model Profile
University of Sydney
Version: 1.0.00
Released: 2025-09-30

The hybrid microsimulation model STDSIM-MISCAN-Cervix: Model Profile
Erasmus University Medical Center
Version: 1.0.00
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UMN Cervical: Model Profile
University of Minnesota
Version: 1.0.00
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Combined Model Profile Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

MGH
Version: 1.0.00
Released: 2025-09-30

DRIVE CERVICAL (Data-driven Recommendations for Interventions against Viral infection)

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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

MGH
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.

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

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

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

Output Overview
Definitions and methodologies for the basic model outputs.

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

MGH
Model Purpose

Model Purpose

Summary

The purpose of this mathematical model is to study the impact of HPV vaccination, cervical cancer screening and treatment, accounting for HIV infection dynamics including HIV disease progression by CD4 count and antiretroviral therapy (ART) on cervical cancer outcomes. We created a model that simulates heterosexual transmission of oncogenic HPV (high-risk HPV;hrHPV) and heterosexual HIV transmission. The model is parameterized to KwaZulu-Natal, South Africa (KZN), a region with high HIV prevalence.

Purpose

The model reproduces population-level HIV and HPV disease dynamics and stratifies the population by age, gender, and sexual risk. We model HIV progression by CD4+ T-cell (CD4) count and HIV RNA concentration (viral load). The impact of ART scale-up targeted to HIV-positive persons is also modelled starting in 2004.

HPV progression is modelled by progression through a precancer pathway that leads to cervical cancer. The interaction between HPV and HIV in coinfected subpopulations is modelled by accounting for the increased risk of HPV transmission to an HIV-positive person and the accelerated disease progression of cervical lesions in HIV-positive women.

Using demographic data from the population under study, the model is calibrated to recapitulate observed patterns of HIV and HPV disease. The population-level impact of HPV vaccination is then assessed by comparing health outcomes in vaccine vs. non-vaccine scenarios.

MGH
Model Overview

Model Overview

Summary

There are three key components to the model: 1) Dynamic HPV and HIV transmission, 2) HIV progression and ART scale up, and 3) HPV-related pre-cancer/cancer progression.

Purpose

Our dynamic transmission compartmental model examines the impact of HPV vaccination on HIV-positive and HIV-negative women in a high HIV-prevalence setting. Model parameters on transition rates for HIV and HPV disease states were derived by synthesizing relevant findings in the literature. Parameter calibration was performed to enhance the model's ability to reflect observed disease patterns.

Background

HPV and HIV infections can interact to increase cervical cancer (CC) risk. The 9-valent HPV (9vHPV) vaccine has high demonstrated effectiveness against HPV types causing 90% of CC [1]. Additionally, one dose of the 9vHPV vaccine has the potential to achieve greater coverage at lower costs than a two-dose schedule. However, the potential impact of single-dose 9vHPV vaccine accounting for HPV-HIV interactions has not been estimated. This model adapts a previously published dynamic compartmental HIV transmission model.

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MGH
Assumption Overview

Assumption Overview

Summary

This section describes the basic assumptions made by MGH's HIV-HPV coinfection model.

Background

Compartmental models divide the population under study into various compartments that are characterized by demographic and health-related features. In the present model, this is achieved by stratifying groups according to HIV disease state, HIV Viral Load, Vaccine type HPV disease state, non-vaccine disease state, cervical cancer or hysterectomy status, vaccination and screening history, gender, age, and risk based on sexual activity.

Maximum likelihood-based calibration is used to calibrate model parameters to various data sources and to infer the value of parameters that cannot be obtained through direct observation.

Assumption Listing

In compartmental models, it is assumed that the members within each compartment are homogeneous in nature. As such, the model is not designed to answer questions pertaining to individual-level interventions or health outcomes. However, in the absence of granular individual-level data, the assumption of homogeneity provides for an economical model that can be used to determine the impact of population-level interventions and health outcomes.

Susceptible females can acquire high-risk (HR) HPV infection from a male sexual partner and progress to precancerous lesions categorized as cervical intraepithelial neoplasia, grades 1, 2, or 3 (CIN 1, 2, or 3). HPV infection and CIN1, CIN2, and CIN3 lesions can regress to normal over time and females with CIN3 can develop cervical cancer (categorized in 3 stages: local, regional, and distant). Given the strong connection between HPV infection and cervical cancer incidence, we assume that the pathogenesis of all cervical cancers begins with HPV infection. We assume females who clear their HPV infection can develop low-level natural immunity while males who clear HPV infection do not develop natural immunity. The model estimates the force of HPV infection as a function of sexual mixing (by age and sexual activity), proportion of HPV infected individuals of the opposite sex, and HPV transmission probability, which depends on HIV status and CD4 count if HIV-positive. Once females are infected, the probability of HPV disease progression is governed by age, HIV-status, and CD4 count if infected with HIV.

HIV-positive females have a higher risk of HPV acquisition and CIN1-2 progression and a lower probability of disease regression and infection clearance. HPV disease progression is inversely related to CD4 count; women at the lowest category CD4 counts are least likely to clear and more likely to experience disease progression.

Parameter Overview

Summary

This section contains the parameters used to inform the natural history model.

Background

The MGH natural history model is based on data published in the literature. HIV transition rates by CD4 count and viral load level are informed by previous clinical studies. Transition rates for HPV infection and CIN were also informed by existing literature. The transition from CIN3 to cervical cancer was inferred through calibration as this quantity could not be obtained through direct observation.

Parameter Listing Overview

The parameters used to inform the model follow below:

Population Demographics

- Population Size – based on the United Nations Population estimates, and KZN population estimates.
- South Africa's age-specific mortality before 1950, values are based on United Nations 2019 Population prospects. After the start of the generalized HIV epidemic, values are based on IHME Global Burden of Disease Study[1,2].
- Fertility rates are based on the United Nations Population Division total fertility estimates, and KZN population estimates. Future simulations model fertility rates from 2020 to 2035 to match the projected United Nations Population estimates for population size, age distribution and fertility[1,3,4,5].
- Fertility rate by age and HIV status. Females on ART are assumed to have equal fertility to HIV-negative females[6,7].

Sexual History and Sexual Mixing

- Sexual risk distribution by age and sex. Values are based on Africa Centre cohort partnership data from KwaZulu Natal, South Africa[8]. Risk distribution derived from male partner data is used for both men and women.
- Annual number of sexual partnerships by age, gender, and sexual risk group. Values are based on Africa Centre cohort partnership data from KwaZulu Natal, South Africa[8].
- The number of coital acts per partnership by sex, age, and sexual risk group. Values are calibrated to fit age-specific HIV and HPV prevalence data.
- Sexual mixing by age and sexual risk group. The mixing parameter varies from random to assortative, calibrated to fit age-specific HIV incidence and prevalence data[9].

HIV

- HIV prevalence and incidence by gender and age over time in KZN. Values are based on Africa Centre cohort partnership data from KwaZulu Natal, South Africa[8,10].
- HIV-associated mortality. Values are estimates are from observational studies of untreated HIV-positive persons. Persons age 0 to 4 and older than 50 are assumed to have greater mortality as observed[11-14].
- Risk multipliers for HIV transmission by viral load[15-19].
- The duration of time in each CD4 and viral load stage by sex and age[17,20,21,22].
- Proportion of births from HIV-positive females that results in mother-to-child transmission. The rate decreases linearly from 2004 to 2005 and from 2005 to 2008[9,23,24].
- Proportion of persons living with HIV on ART and virally suppressed coverage over time[25].

HPV and Cervical Cancer

- HPV prevalence in women and men in South Africa. Mbulawa et al[26-28].
- HPV prevalence in women without CIN2/3[29].
- CIN2/3 prevalence by HIV status[27,28].

- Cervical cancer mortality by disease stage, CD4 count and HIV status[30,31].
- Cervical cancer incidence based on 2018 GLOBOCAN estimates. Values are adjusted to in KZN rather than South Africa nationally by age to take into account higher HIV prevalence in KZN[32].

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Component Overview

Summary

This section describes the components of our natural history model.

Overview

There are three key components to the model: 1) Dynamic HPV and HIV transmission, 2) HIV progression and ART scale up, and 3) HPV-related pre-cancer/cancer progression.

Component Listing

Dynamic HPV and HIV transmission

Our model simulates the transmission of HPV and HIV across the population, which is divided into various compartments based on health states (ex. HPV-Infected, HIV-positive, CD4 count etc.) and demographic factors (age, gender, sexual risk level). The rate of infection that a susceptible compartment is subject to depends on a) the mixing patterns corresponding to the gender, age, and sexual risk level used to describe the compartment, b) the prevalence of infection in other compartments that interact with the susceptible compartment.

HIV progression and ART scale up

HIV progression is simulated by modelling the rate of progression through HIV disease states as described by CD4 count and viral load level. ART scale-up is modelled by representing the rate of ART uptake as a function of time and CD4 count to reflect the reported clinical criteria for ART uptake. In the model, ART uptake reduces the probability of HIV transmission and attenuates a HIV-positive person's rate of progression through the HPV and cervical pre-cancer pathway.

HPV-related pre-cancer/cancer progression

HPV progression is simulated by modelling the rate of progression through HPV disease states. The HPV disease pathway consists of three cervical pre-cancer lesion stages: CIN1, CIN2, and CIN3. The transitions between these stages are modelled as a reversible process to reflect the possibility of spontaneous pre-cancer lesion clearance. Meanwhile, the transition from CIN3 to cervical cancer (CC) is modelled as an irreversible process. The CC associated mortality rate increases with the severity of the cancer, which is described by local, regional, and distant cervical cancer stages in the model.

Further details about the model can be found below:

HIV Natural History

The natural history of HIV infection is modeled in stages defined by CD4 count and viral load as shown in Figure S1. When a person becomes HIV-infected, s/he enters the acute stage characterized by a short duration and high probability of HIV transmission. The person then progresses through stages of CD4 count and viral load at rates ω^d and l^d, respectively, where d represents the current HIV disease state defined by CD4 count and v represents the current viral load. Transition rates are based on literature describing the average duration in each stage by gender and age[1-4]. The average life expectancy from infection to death for untreated persons is 10.7 years.

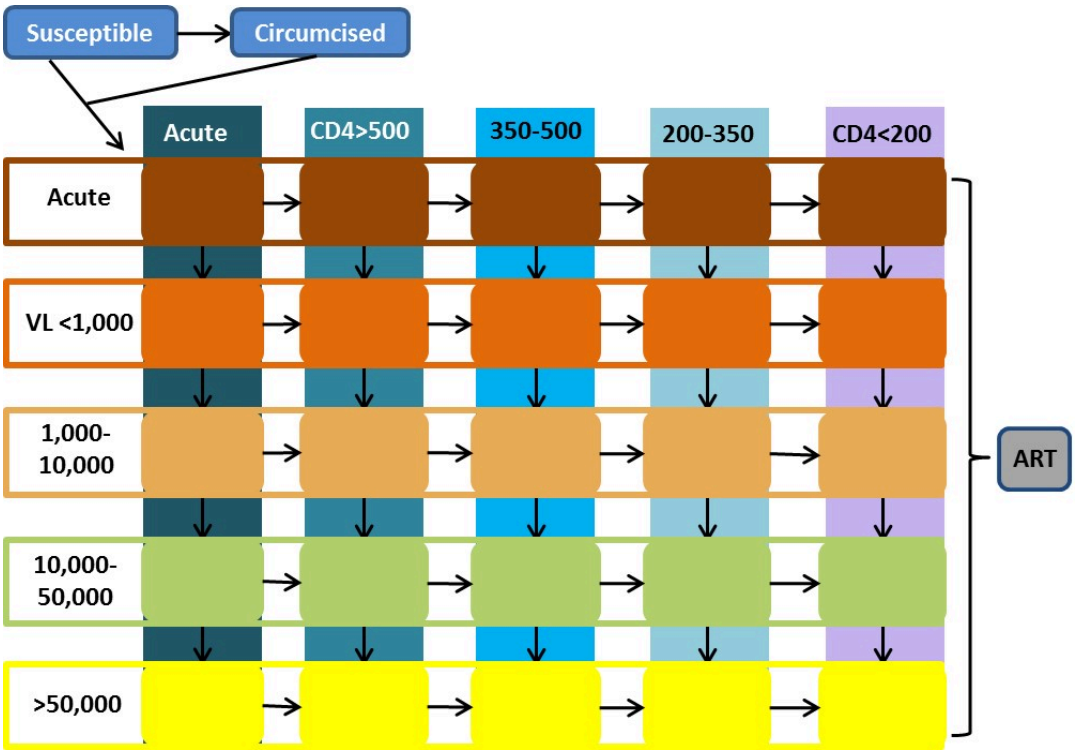

Figure S1. Model transition diagram. A diagram of the natural history of HIV infection. All movement is in one direction except for enrollment in and dropout from interventions from ART.

Ordinary Differential Equations

Throughout each simulation, we track a population demographics in five-year age-groups and the number of individuals with infection, with progressed disease or with preventative or therapeutic treatment capturing vertical transmission and aging. The system of ODE's describes the states $X_{g,a,r}^{d,v,h,s,x,p}(t)$ with the following indices:

- d refers to HIV disease state defined by CD4 cell count, circumcision status, and ART status
  $d = 1$ for HIV-negative, uncircumcised; $d = 2$ for HIV-negative, circumcised; $d = 3$ for HIV-positive, acute infection; $d = 4$ for HIV-positive, CD4 > 500 cells/μL; $d = 5$ for HIV-positive, CD4 350–500 cells/μL; $d = 6$ for HIV-positive, CD4 200-350 cells/μL; $d = 7$ for HIV-positive, CD4 200 £ cells/μL; $d = 8$ for HIV-positive, on ART.

- v refers to disease state defined by HIV viral load
  $v = 1$ if $(2 < d < 8)$, Acute infection, if $(d = 1, 2)$, HIV-negative: $VL = 0$; $v = 2$ for Asymptomatic: $VL = 3.0 - 4.5log10$; $v = 3$ for Pre-AIDS symptomatic: $VL = 4.0 - 5.5log10$; $v = 4$ for AIDS: $= 5.5 - 7.0log10$; $v = 5$ for Late-stage; $v = 6$ for on ART and virally suppressed: $VL = 0.0$

- h refers to vaccine-type HPV precancer or disease state
  $h = 1$ for Susceptible; $h = 2$ for Infected; $h = 3$ for CIN1; $h = 4$ for CIN2; $h = 5$ for CIN3; $h = 6$ for Cervical Cancer or hysterectomy; $h = 7$ for Immune

- s refers to non-vaccine-type HPV precancer or disease state
  $s = 1$ for Susceptible; $s = 2$ for Infected; $s = 3$ for CIN1; $s = 4$ for CIN2; $s = 5$ for CIN3; $s = 6$ for Cervical Cancer or hysterectomy; $s = 7$ for Immune

- x refers to cervical cancer or hysterectomy status
  $x = 1$ if $(h = 6$ or $s = 6)$, Cervical cancer, local, undiagnosed; else, no cancer or hysterectomy; $x = 2$ for Cervical cancer, regional, undiagnosed; $x = 3$ for Cervical cancer, distant, undiagnosed; $x = 4$ for Cervical cancer, local, diagnosed & untreated; $x = 5$ for Cervical cancer, regional, diagnosed & untreated; $x = 6$ for Cervical cancer, distant, diagnosed & untreated; $x = 7$ for Cervical cancer, local,

treated; $x = 8$ for Cervical cancer, regional, treated; $x = 9$ for Cervical cancer, distant, treated; $x = 10$ for Hysterectomy

- p refers to vaccination and screening history
  $p = 1$ for Non-vaccinated, non-screened; $p = 2$ for Vaccinated; $p = 3$ for Screened; $p = 4$ for Vaccinated and screened
- g refers to gender
  $g = 1$ for Men; $g = 2$ for Women
- a refers to age
  $a = 1$ for ages 0-4; $a = 2$ for ages 5-9; $a = 3$ for ages 10-14 ...; $a = 16$ for ages 75-79
- r refers to sexual risk group defined by number of sexual partnerships per year
  $r = 1$ for low risk; $r = 2$ for moderate risk; $r = 3$ for high risk

We calculate changes in HIV stages defined by CD4 count, viral load, and treatment status. The HIV-negative population can acquire HIV after sexual debut with a force of infection that is reduced by circumcision among men and condom use by either gender. We only track circumcision among HIV-negative men. Individuals with HIV infection experience HIV-associated mortality, CD4 and viral load stage progression, and ART initiation and discontinuation. CD4 and viral load stage are not tracked among persons on treatment. The ODEs for the eight HIV disease states are:

$$\frac{dX^{1,1,h,s,x,p}_{g,a,r}(t)}{dt} = -\left(\psi_{\text{HIV}g} \cdot \lambda_{\text{HIV}g,a,r}(t) + P_{g,a}(t)\right) X^{1,1,h,s,x,p}_{g,a,r}(t)$$

HIV-negative, circumcised

$$\frac{dX^{2,1,h,s,x,p}_{g,a,r}(t)}{dt} = P_{g,a}(t) \cdot X^{1,1,h,s,x,p}_{g,a,r}(t) - \left(\psi_{\text{HIV}g} \cdot \rho_{\text{HIV}g} \cdot \lambda_{\text{HIV}g,a,r}(t)\right) X^{2,1,h,s,x,p}_{g,a,r}(t)$$

HIV-positive, acute infection

$$\begin{aligned}\frac{dX^{3,1,h,s,x,p}_{g,a,r}(t)}{dt} = \; & \psi_{\text{HIV}g} \cdot \lambda_{\text{HIV}g,a,r}(t) \cdot X^{1,1,h,s,x,p}_{g,a,r}(t) + \psi_{\text{HIV}g} \cdot \rho_{\text{HIV}g} \cdot \lambda_{\text{HIV}g,a,r}(t) \\ & \cdot X^{2,1,h,s,x,p}_{g,a,r}(t) + \sigma^{3,1}_{g,a,r}(t) \cdot X^{8,6,h,s,x,p}_{g,a,r}(t) \\ & - \left(\mu^{3}_{\text{HIV}g,a} + \omega^{3} + A^{3}_{g,a}(t)\right) X^{3,1,h,s,x,p}_{g,a,r}(t)\end{aligned}$$

HIV-positive, CD4 > 500 cells/μL

$$\begin{aligned}\frac{dX^{4,v,h,s,x,p}_{g,a,r}(t)}{dt} = & \; \omega^{3} \cdot X^{3,v,h,s,x,p}_{g,a,r}(t) \\ & + l^{v-1} \cdot X^{4,v-1,h,s,x,p}_{g,a,r}(t) \\ & + \sigma^{4,v}_{g,a,r}(t) \cdot X^{8,6,h,s,x,p}_{g,a,r}(t) \\ & - \left(\mu^{4}_{\text{HIV}g,a} + \omega^{4} + l^{v} + A^{4}_{g,a}(t)\right) X^{4,v,h,s,x,p}_{g,a,r}(t)\end{aligned}$$

HIV-positive, CD4 350-500 cells/μL

$$\begin{aligned}\frac{dX^{5,v,h,s,x,p}_{g,a,r}(t)}{dt} = & \; \omega^{4} \cdot X^{4,v,h,s,x,p}_{g,a,r}(t) \\ & + l^{v-1} \cdot X^{5,v-1,h,s,x,p}_{g,a,r}(t) \\ & + \sigma^{5,v}_{g,a,r}(t) \cdot X^{8,6,h,s,x,p}_{g,a,r}(t) \\ & - \left(\mu^{5}_{\text{HIV},g,a} + \omega^{5} + l^{v} + A^{5}_{g,a}(t)\right) X^{5,v,h,s,x,p}_{g,a,r}(t)\end{aligned}$$

HIV-positive, CD4 200-350 cells/μL

$$\begin{aligned}\frac{dX^{6,v,h,s,x,p}_{g,a,r}(t)}{dt} &= \omega^5 \cdot X^{5,v,h,s,x,p}_{g,a,r}(t) \\ &+ l^{v-1} \cdot X^{6,v-1,h,s,x,p}_{g,a,r}(t) \\ &+ \sigma^{6,v}_{g,a,r}(t) \cdot X^{8,6,h,s,x,p}_{g,a,r}(t) \\ &- \left(\mu^6_{\text{HIV},g,a} + \omega^6 + l^v + A^6_{g,a}(t)\right) X^{6,v,h,s,x,p}_{g,a,r}(t)\end{aligned}$$

HIV-positive, CD4 ≤ 200 cells/μL

$$\begin{aligned}\frac{dX^{7,v,h,s,x,p}_{g,a,r}(t)}{dt} &= \omega^6 \cdot X^{6,v,h,s,x,p}_{g,a,r}(t) \\ &+ l^{v-1} \cdot X^{7,v-1,h,s,x,p}_{g,a,r}(t) \\ &+ \sigma^{7,v}_{g,a,r}(t) \cdot X^{8,6,h,s,x,p}_{g,a,r}(t) \\ &- \left(\mu^7_{\text{HIV},g,a} + \omega^7 + l^v + A^7_{g,a}(t)\right) X^{7,v,h,s,x,p}_{g,a,r}(t)\end{aligned}$$

HIV-positive, on ART

$$\frac{dX^{8,6,h,s,x,p}_{g,a,r}(t)}{dt} = \sum_{d=3}^{7}\sum_{v=1}^{5}\left(A^d_{g,a}(t) \cdot X^{d,v,h,s,x,p}_{g,a,r}(t) - \sigma^{d,v}_{g,a,r}(t) \cdot X^{8,6,h,s,x,p}_{g,a,r}(t)\right)$$

The equation variables are:

Variable	Description
$\mu\_HIV^d_{g,a}$	Annual HIV-associated mortality rate by gender g, age a, and HIV disease stage d for $3 \le d \le 8$.
$\lambda\_HIV_{g,a,r}(t)$	Force of HIV infection for HIV-negative persons by gender g, age a, and risk r.
ρ_HIV_g	Reduction in HIV acquisition due to circumcision by gender. Only men receive circumcision ($\rho\_HIV_2 = 1$).
ψ_HIV_g	Reduction in HIV acquisition due to population-level condom use by gender.
ω^d	The rate of progressing from HIV stage d to $d+1$, for $3 \le d \le 7$.
l^d	The rate of progressing from viral load stage v to $v+1$, for $1 \le v \le 5$.
$P_{g,a}(t)$	The proportion of HIV-negative persons of gender g and age a that are circumcised. Only men receive circumcision ($P_{2,a}(t) = 0$).
$A^d_{g,a}(t)$	The proportion of persons living with HIV of disease stage d, gender g, and age a that initiate ART.
$\sigma^{d,v}_{g,a,r}(t)$	The proportion of persons who discontinue ART based on the recent distribution of persons initiating ART by gender g, age a, risk r, disease d, and viral v.

HPV Natural History

We calculate changes in HPV status and precancer or disease stage for women without hysterectomy ($1 \le x \le 9$). We track vaccine-type and non-vaccine type HPV independently, but only count cancer incidence for the first infection to progress to local cervical cancer. CIN1,2,3 can regress, and HPV infection can clear naturally. Women who clear HPV temporarily develop partial natural immunity against reinfection with the same HPV type group while men who clear HPV do not develop natural immunity. Persons susceptible to type-specific HPV infection or with temporary natural immunity can acquire HPV after sexual debut. Individuals with HIV experience higher rates of HPV acquisition and disease progression, and lower rates of HPV clearance, immunity waning, and disease regression. Cervical cancer mortality varies by cancer stage, whether it is treated, and HIV status, and affects individuals regardless of type-specific etiology. We assume that the nonavalent HPV vaccine provides lifelong protection against vaccine-type HPV and no protection against non-vaccine-type HPV. We assume the vaccine is ineffective for persons with current vaccine-type HPV infection, and the equations therefore only reflect vaccination of persons susceptible or immune to vaccine-type HPV. Vaccination does not depend on non-vaccine-type HPV infection status. Although not shown in the equations below, persons are screened according to their age a and lose their screened status upon aging out of the screened age group.

The ODEs for vaccine-type HPV and precancer equations are:

Men, susceptible

$$\frac{dX_{1,a,r}^{d,v,1,s,1,1}(t)}{dt} = l_1 \cdot \zeta_v^{d,2,1} \cdot k_{v,1,a}^{2,1} \cdot X_{1,a,r}^{d,v,2,s,1,1}(t) - \left(\xi_d \cdot \psi_{\text{HPV},1} \cdot \lambda_{v\text{HPV},1,a,r}(t) + V_{1,a}^d\right) X_{1,a,r}^{d,v,1,s,1,1}(t)$$

Men, HPV-infected

$$\frac{dX_{1,a,r}^{d,v,2,s,1,1}(t)}{dt} = \xi_d \cdot \psi_{\text{HPV},1} \cdot \lambda_{v\text{HPV},1,a,r}(t) \cdot X_{1,a,r}^{d,v,1,s,1,1}(t) - l_1 \cdot ж_v^{d,2,1} \cdot k_{v,1,a}^{2,1} \cdot X_{1,a,r}^{d,v,2,s,1,1}(t)$$

Men, susceptible, vaccinated

$$\frac{dX_{1,a,r}^{d,v,1,s,1,2}(t)}{dt} = V_{1,a}^d \cdot X_{1,a,r}^{d,v,1,s,1,1}(t) + l_1 \cdot \zeta_v^{d,2,1} \cdot k_{v,1,a}^{2,1} \cdot X_{1,a,r}^{d,v,2,s,1,2}(t) - \phi_a \cdot ж_d \cdot \psi_{HPV1} \cdot \lambda_{v\text{HPV},1,a,r}(t) \cdot X_{1,a,r}^{d,v,1,s,1,2}(t)$$

Men, HPV-infected, vaccinated

$$\frac{dX_{1,a,r}^{d,v,2,s,1,2}(t)}{dt} = \phi_a \cdot ж_d \cdot \psi_{\text{HPV},1} \cdot \lambda_{v\text{HPV1},a,r}(t) \cdot X_{1,a,r}^{d,v,1,s,1,2}(t) - l_1 \cdot \zeta_v^{d,2,1} \cdot k_{v,1,a}^{2,1} \cdot X_{1,a,r}^{d,v,2,s,1,2}(t)$$

Women, susceptible

Untreated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,1,s,[1,2,3,4,5,6],[1,3]}(t)}{dt} = \zeta_v^{d,7,1} \cdot r_2 \cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[1,3]}(t) - \left(ж_d \cdot \psi_{\text{HPV}2} \cdot \lambda_{v\text{HPV}2,a,r}(t) + V_{2,a}^d + \mu_{\text{utHPV}2}^{d,1,s,[1,2,3,4,5,6]}\right) X_{2,a,r}^{d,v,1,s,[1,2,3,4,5,6],[1,3]}(t)$$

Treated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,1,s,[7,8,9],[1,3]}(t)}{dt} = \zeta_v^{d,7,1} \cdot r_2 \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[1,3]}(t) - \left(\xi_d \cdot ж_{\text{HPV}2} \cdot \lambda_{v\text{HPV},2,a,r}(t) + V_{2,a}^d + \mu_{\text{tHPV},2}^{d,1,s,[7,8,9]}\right) X_{2,a,r}^{d,v,1,s,[7,8,9],[1,3]}(t)$$

Women, immune

Untreated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[1,3]}(t)}{dt} = V_{2,a}^d \cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[1,3]}(t) + \zeta_v^{d,2,7} \cdot k_{v,2,a}^{2,7} \cdot X_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[1,3]}(t) - \left(\zeta_v^{d,7,1} \cdot k_{v,2,a}^{7,1} + \xi_{2,a} \cdot ж_d \cdot \psi_{\text{HPV},2} \cdot \lambda_{v\text{HPV},2,a,r}(t) + V_{2,a}^d + \mu_{\text{utHPV},2}^{d,7,s,[1,2,3,4,5,6]}\right) X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[1,3]}(t)$$

Treated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,7,s,[7,8,9],[1,3]}(t)}{dt} = V_{2,a}^d \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[1,3]}(t) + \zeta_v^{d,2,7} \cdot k_{v,2,a}^{2,7} \cdot X_{2,a,r}^{d,v,2,s,[7,8,9],[1,3]}(t) - \left(\zeta_v^{d,7,1} \cdot k_{v,2,a}^{7,1} + \xi_{2,a} \cdot ж_d \cdot \psi_{\text{HPV}2} \cdot \lambda_{v\text{HPV},2,a,r}(t) + V_{2,a}^d + \mu_{\text{tHPV},2}^{d,7,s,[7,8,9]}\right) \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[1,3]}(t)$$

Women, HPV-infected

Untreated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[1,3]}(t)}{dt} = \zeta_v^{d,3,2} \cdot k_{v,2,a}^{3,2} \cdot X_{2,a,r}^{d,v,3,s,[1,2,3,4,5,6],[1,3]}(t) + ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) \cdot X_{2,a,r}^{d,v,1,s,[1,2,3,4,5,6],[1,3]}(t) + \xi_{2,a} \cdot ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) \cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[1,3]}(t) - \left(\zeta_v^{d,2,7} \cdot k_{v,2,a}^{2,7} + \zeta_v^{d,2,3} \cdot k_{v,2,a}^{2,3} + \mu_{\text{utHPV2}}^{d,2,s,[1,2,3,4,5,6]}\right) \cdot X_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[1,3]}(t)$$

Treated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,2,s,[7,8,9],[1,3]}(t)}{dt} = \zeta_v^{d,3,2} \cdot k_{v,2,a}^{3,2} \cdot X_{2,a,r}^{d,v,3,s,[7,8,9],[1,3]}(t) + ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) \cdot X_{2,a,r}^{d,v,1,s,[7,8,9],[1,3]}(t) + \xi_{2,a} \cdot ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[1,3]}(t) - \left(\zeta_v^{d,2,7} \cdot k_{v,2,a}^{2,7} + \zeta_v^{d,2,3} \cdot k_{v,2,a}^{2,3} + \mu_{t\text{HPV2}}^{d,2,s,[7,8,9]}\right) \cdot X_{2,a,r}^{d,v,2,s,[7,8,9],[1,3]}(t)$$

Women, susceptible, vaccinated

Untreated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,1,s,[1,2,3,4,5,6],[2,4]}(t)}{dt} = \zeta_v^{d,7,1} \cdot r_2 \cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[2,4]}(t) + V_{2,a}^d \cdot X_{2,a,r}^{d,v,1,s,[1,2,3,4,5,6],[1,3]}(t) - \left(\phi_a \cdot ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) + \mu_{\text{utHPV2}}^{d,1,s,[1,2,3,4,5,6]}\right) \cdot X_{2,a,r}^{d,v,1,s,[1,2,3,4,5,6],[2,4]}(t)$$

Treated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,1,s,[7,8,9],[2,4]}(t)}{dt} = \zeta_v^{d,7,1} \cdot r_2 \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[2,4]}(t) + V_{2,a}^d \cdot X_{2,a,r}^{d,v,1,s,[7,8,9],[1,3]}(t) - \left(\phi_a \cdot ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) + \mu_{t\text{HPV2}}^{d,1,s,[7,8,9]}\right) \cdot X_{2,a,r}^{d,v,1,s,[7,8,9],[2,4]}(t)$$

Women, immune, vaccinated

Untreated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[2,4]}(t)}{dt} = \zeta_v^{d,2,7} \cdot k_{v,2,a}^{2,7} \cdot X_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[2,4]}(t) + V_{2,a}^d \cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[1,3]}(t) - \left(\zeta_v^{d,7,1} \cdot k_{v,2,a}^{7,1} + \phi_a \cdot \xi_{2,a} \cdot ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) + \mu_{\text{utHPV2}}^{d,7,s,[1,2,3,4,5,6]}\right) \cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[2,4]}(t)$$

Treated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,7,s,[7,8,9],[2,4]}(t)}{dt} = \zeta_v^{d,2,7} \cdot k_{v,2,a}^{2,7} \cdot X_{2,a,r}^{d,v,2,s,[7,8,9],[2,4]}(t) + V_{2,a}^d \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[1,3]}(t) - \left(\zeta_v^{d,7,1} \cdot k_{v,2,a}^{7,1} + \phi_a \cdot \xi_{2,a} \cdot ж_d \cdot \psi_{\text{HPV2}} \cdot \lambda_{v\text{HPV},2,a,r}(t) + \mu_{t\text{HPV2}}^{d,7,s,[7,8,9]}\right) \cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[2,4]}(t)$$

Women, HPV-infected, vaccinated

Untreated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[2,4]}(t)}{dt} = &\ \zeta_v^{d,3,2}\cdot k_{v,2,a}^{3,2}\cdot X_{2,a,r}^{d,v,3,s,[1,2,3,4,5,6],[2,4]}(t)\\ &+\phi_a\cdot \text{ж}_d\cdot \psi_{\text{HPV2}}\cdot \lambda_{v\text{HPV},2,a,r}(t)\cdot X_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[2,4]}(t)\\ &+\phi_a\cdot \xi_{2,a}\cdot \text{ж}_d\cdot \psi_{\text{HPV2}}\cdot \lambda_{v\text{HPV},2,a,r}(t)\cdot X_{2,a,r}^{d,v,7,s,[1,2,3,4,5,6],[2,4]}(t)\\ &-\left(\zeta_v^{d,2,7}\cdot k_{v,2,a}^{2,7}+\zeta_v^{d,2,3}\cdot k_{v,2,a}^{2,3}+\mu_{\text{utHPV2}}^{d,2,s,[1,2,3,4,5,6]}\right)\cdot X_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],[2,4]}(t)\end{aligned}$$

Treated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,2,s,[7,8,9],[2,4]}(t)}{dt} = &\ \zeta_v^{d,3,2}\cdot k_{v,2,a}^{3,2}\cdot X_{2,a,r}^{d,v,3,s,[7,8,9],[2,4]}(t)\\ &+\phi_a\cdot \text{ж}_d\cdot \psi_{\text{HPV2}}\cdot \lambda_{v\text{HPV},2,a,r}(t)\cdot X_{2,a,r}^{d,v,2,s,[7,8,9],[2,4]}(t)\\ &+\phi_a\cdot \xi_{2,a}\cdot \text{ж}_d\cdot \psi_{\text{HPV2}}\cdot \lambda_{v\text{HPV},2,a,r}(t)\cdot X_{2,a,r}^{d,v,7,s,[7,8,9],[2,4]}(t)\\ &-\left(\zeta_v^{d,2,7}\cdot k_{v,2,a}^{2,7}+\zeta_v^{d,2,3}\cdot k_{v,2,a}^{2,3}+\mu_{t\text{HPV2}}^{d,2,s,[7,8,9]}\right)\cdot X_{2,a,r}^{d,v,2,s,[7,8,9],[2,4]}(t)\end{aligned}$$

Women, CIN1

Untreated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,3,s,[1,2,3,4,5,6],p}(t)}{dt} = &\ \zeta_v^{d,4,3}\cdot k_{v,2,a}^{4,3}\cdot X_{2,a,r}^{d,v,4,s,[1,2,3,4,5,6],p}(t)\\ &+\zeta_v^{d,2,3}\cdot k_{v,2,a}^{2,3}\cdot X_{2,a,r}^{d,v,2,s,[1,2,3,4,5,6],p}(t)\\ &-\left(\zeta_v^{d,3,4}\cdot k_{v,2,a}^{3,4}+\zeta_v^{d,3,2}\cdot k_{v,2,a}^{3,2}+\mu_{\text{utHPV2}}^{d,3,s,[1,2,3,4,5,6]}\right)\cdot X_{2,a,r}^{d,v,3,s,[1,2,3,4,5,6],p}(t)\end{aligned}$$

Treated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,3,s,[7,8,9],p}(t)}{dt} = &\ \zeta_v^{d,4,3}\cdot k_{v,2,a}^{4,3}\cdot X_{2,a,r}^{d,v,4,s,[7,8,9],p}(t)\\ &+\zeta_v^{d,2,3}\cdot k_{v,2,a}^{2,3}\cdot X_{2,a,r}^{d,v,2,s,[7,8,9],p}(t)\\ &-\left(\zeta_v^{d,3,4}\cdot k_{v,2,a}^{3,4}+\zeta_v^{d,3,2}\cdot k_{v,2,a}^{3,2}+\mu_{t\text{HPV2}}^{d,3,s,[7,8,9]}\right)\cdot X_{2,a,r}^{d,v,3,s,[7,8,9],p}(t)\end{aligned}$$

Women, CIN2

Untreated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,4,s,[1,2,3,4,5,6],p}(t)}{dt} = &\ \zeta_v^{d,5,4}\cdot k_{v,2,a}^{5,4}\cdot X_{2,a,r}^{d,v,5,s,[1,2,3,4,5,6],p}(t)\\ &+\zeta_v^{d,3,4}\cdot k_{v,2,a}^{3,4}\cdot X_{2,a,r}^{d,v,3,s,[1,2,3,4,5,6],p}(t)\\ &-\left(\zeta_v^{d,4,5}\cdot k_{v,2,a}^{4,5}+\zeta_v^{d,4,3}\cdot k_{v,2,a}^{4,3}+\mu_{\text{utHPV2}}^{d,4,s,[1,2,3,4,5,6]}\right)\cdot X_{2,a,r}^{d,v,4,s,[1,2,3,4,5,6],p}(t)\end{aligned}$$

Treated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,4,s,[7,8,9],p}(t)}{dt} = &\ \zeta_v^{d,5,4}\cdot k_{v,2,a}^{5,4}\cdot X_{2,a,r}^{d,v,5,s,[7,8,9],p}(t)\\ &+\zeta_v^{d,3,4}\cdot k_{v,2,a}^{3,4}\cdot X_{2,a,r}^{d,v,3,s,[7,8,9],p}(t)\\ &-\left(\zeta_v^{d,4,5}\cdot k_{v,2,a}^{4,5}+\zeta_v^{d,4,3}\cdot k_{v,2,a}^{4,3}+\mu_{t\text{HPV2}}^{d,4,s,[7,8,9]}\right)\cdot X_{2,a,r}^{d,v,4,s,[7,8,9],p}(t)\end{aligned}$$

Women, CIN3

Untreated cervical cancer health states

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,5,s,[1,2,3,4,5,6],p}(t)}{dt} = &\ \zeta_v^{d,4,5}\cdot k_{v,2,a}^{4,5}\cdot X_{2,a,r}^{d,v,4,s,[1,2,3,4,5,6],p}(t)\\ &-\left(\zeta_v^{d,5,6}\cdot k_{v,2,a}^{5,6}+\zeta_v^{d,5,4}\cdot k_{v,2,a}^{5,4}+\mu_{\text{utHPV2}}^{d,5,s,[1,2,3,4,5,6]}\right)\cdot X_{2,a,r}^{d,v,5,s,[1,2,3,4,5,6],p}(t)\end{aligned}$$

Treated cervical cancer health states

$$\frac{dX_{2,a,r}^{d,v,5,s,[7,8,9],p}(t)}{dt} = \zeta_v^{d,4,5} \cdot k_{v,2,a}^{4,5} \cdot X_{2,a,r}^{d,v,4,s,[7,8,9],p}(t) - \left(\zeta_v^{d,5,6} \cdot k_{v,2,a}^{5,6} + \zeta_v^{d,5,4} \cdot k_{v,2,a}^{5,4} + \mu_{t\text{HPV2}}^{d,5,s,[7,8,9]}\right) \cdot X_{2,a,r}^{d,v,5,s,[7,8,9],p}(t)$$

Non-vaccine-type HPV and precancer equations

The non-vaccine-type HPV and precancer equations follow the same pattern as the vaccine-type HPV equations with a few updates. All values of s equal the values of h in the vaccine-type equations, and h equals any value. The appropriate force of infection, transition rates, and transition rate multipliers for individuals living with HIV should be used. Vaccination does not depend on non-vaccine-type HPV infection status.

Cervical cancer equations

Female cervical cancer, local

(where $h = 6$)

$$\frac{dX_{2,a,r}^{d,v,6,s,x,p}(t)}{dt} = \zeta_v^{d,5,6} \cdot k_{v,2,a}^{5,6} \cdot X_{2,a,r}^{d,v,5,s,x,p}(t)$$

(where $s = 6$)

$$\frac{dX_{2,a,r}^{d,v,h,6,x,p}(t)}{dt} = \zeta_v^{d,5,6} \cdot k_{v,2,a}^{5,6} \cdot X_{2,a,r}^{d,v,h,6,x,p}(t)$$

(where $h = 6$ or $s = 6$, and $x = 1$ or $x = 4$)

$$\frac{dX_{2,a,r}^{d,v,h,s,[1,4],p}(t)}{dt} = -\left(\phi_2^{h,s,[1,4],[2,5]} + \mu_{\text{utHPV2}}^{d,h,s,[1,4]}\right) \cdot X_{2,a,r}^{d,v,h,s,[1,4],p}(t)$$

(where $h = 6$ or $s = 6$, and $x = 7$)

$$\frac{dX_{2,a,r}^{d,v,h,s,7,p}(t)}{dt} = -\mu_{t\text{HPV2}}^{d,h,s,7} \cdot X_{2,a,r}^{d,v,h,s,7,p}(t)$$

Female cervical cancer, regional

(where $h = 6$ or $s = 6$, and $x = 2$ or $x = 5$)

$$\frac{dX_{2,a,r}^{d,v,h,s,[2,5],p}(t)}{dt} = \phi_2^{h,s,[1,4],[2,5]} \cdot X_{2,a,r}^{d,v,h,s,[1,4],p}(t) - \left(\phi_2^{h,s,[2,5],[3,6]} + \mu_{\text{utHPV2}}^{d,h,s,[2,5]}\right) \cdot X_{2,a,r}^{d,v,h,s,[2,5],p}(t)$$

(where $h = 6$ or $s = 6$, and $x = 8$)

$$\frac{dX_{2,a,r}^{d,v,h,s,8,p}(t)}{dt} = -\mu_{t\text{HPV2}}^{d,h,s,8} \cdot X_{2,a,r}^{d,v,h,s,8,p}(t)$$

Female cervical cancer, distant

(where h=6 or s=6, and x=3 or x=6)

$$\frac{dX_{2,a,r}^{d,v,h,s,[3,6],p}(t)}{dt} = \phi_2^{h,s,[2,5],[3,6]} \cdot X_{2,a,r}^{d,v,h,s,[2,5],p}(t) - \mu_{\text{utHPV2}}^{d,h,s,[3,6]} \cdot X_{2,a,r}^{d,v,h,s,[3,6],p}(t)$$

(where h=6 or s=6, and x=9)

$$\frac{dX_{2,a,r}^{d,v,h,s,9,p}(t)}{dt} = -\mu_{t\text{HPV2}}^{d,h,s,9} \cdot X_{2,a,r}^{d,v,h,s,9,p}(t)$$

Rate of Symptomatic Detection of Cervical Cancer

Female cervical cancer, local, untreated

$$\frac{dX_{2,a,r}^{d,v,h,s,4,p}(t)}{dt} = (1-\rho_{tx,2}) \cdot k_{sy}^{1} \cdot X_{2,a,r}^{d,v,h,s,1,p}(t)$$

Female cervical cancer, local, treated by other modalities

$$\frac{dX_{2,a,r}^{d,v,h,s,7,p}(t)}{dt} = \left[\rho_{tx,2} \cdot \left(1-\rho_{hy,2}^{1}\right)\right] \cdot k_{sy}^{1} \cdot X_{2,a,r}^{d,v,h,s,1,p}(t)$$

Female cervical cancer, regional, untreated

$$\frac{dX_{2,a,r}^{d,v,h,s,5,p}(t)}{dt} = (1-\rho_{tx,2}) \cdot k_{sy}^{2} \cdot X_{2,a,r}^{d,v,h,s,2,p}(t)$$

Female cervical cancer, regional, treated by other modalities

$$\frac{dX_{2,a,r}^{d,v,h,s,8,p}(t)}{dt} = \left[\rho_{tx,2} \cdot \left(1-\rho_{hy,2}^{2}\right)\right] \cdot k_{sy}^{2} \cdot X_{2,a,r}^{d,v,h,s,2,p}(t)$$

Female cervical cancer, distant, untreated

$$\frac{dX_{2,a,r}^{d,v,h,s,6,p}(t)}{dt} = (1-\rho_{tx,2}) \cdot k_{sy}^{3} \cdot X_{2,a,r}^{d,v,h,s,3,p}(t)$$

Female cervical cancer, distant, treated by other modalities

$$\frac{dX_{2,a,r}^{d,v,h,s,9,p}(t)}{dt} = \left[\rho_{tx,2} \cdot \left(1-\rho_{hy,2}^{3}\right)\right] \cdot k_{sy}^{3} \cdot X_{2,a,r}^{d,v,h,s,3,p}(t)$$

Female cervical cancer, treated by hysterectomy

$$\begin{aligned}\frac{dX_{2,a,r}^{d,v,h,s,10,p}(t)}{dt} = & \left[\rho_{tx,2} \cdot \rho_{hy,2}^{1}\right] \cdot k_{sy}^{1} \cdot X_{2,a,r}^{d,v,h,s,1,p}(t) \\ & + \left[\rho_{tx,2} \cdot \rho_{hy,2}^{2}\right] \cdot k_{sy}^{2} \cdot X_{2,a,r}^{d,v,h,s,2,p}(t) \\ & + \left[\rho_{tx,2} \cdot \rho_{hy,2}^{3}\right] \cdot k_{sy}^{3} \cdot X_{2,a,r}^{d,v,h,s,3,p}(t)\end{aligned}$$

The equation variables are:

Variable	Description
$\mu_{t}HPVg^{d,h,s,x}$	Annual untreated cervical cancer-associated mortality rate by gender g, HIV disease stage d, vaccine-type HPV stage h, non-vaccine-type HPV stage s, and cervical cancer stage x for $1 \le x \le 6$. Only women have cervical cancer-associated mortality ($\mu_{H}PV1^{d,h,s,x} = 0$) and only when $h = 6$ or $s = 6$.
$\mu_{t}HPVg^{d,h,s,x}$	Annual treated cervical cancer-associated mortality rate by gender g, HIV disease stage d, vaccine-type HPV stage h, non-vaccine-type HPV stage s, and cervical cancer stage x for $7 \le x \le 9$. Only females have treated cervical cancer-associated mortality ($\mu_{t}HPV1^{d,h,s,x} = 0$) and only when $h = 6$ or $s = 6$.
$\lambda_{v}HPV_{g,a,r}(t)$	Force of vaccine-type HPV infection for susceptible persons of gender g, age a, and risk r.
$\lambda_{nvHPV_{g,a,r}}(t)$	Force of non-vaccine-type HPV infection for susceptible persons of gender g, age a, and risk r.
$\varkappa_{d}$	HPV acquisition risk multiplier for HIV-positive individuals with CD4 count $4 \le d \le 7$.
$\xi g, a$	HPV acquisition reduction multiplier by gender and age for individuals with type-specific natural immunity. Only women temporarily develop partial natural immunity ($\xi 1, a = 0$). Older women develop stronger natural immunity than young girls.
$\psi_{\text{HPV}g}$	HPV acquisition reduction multiplier due to population-level condom use by gender.
ϕa	Vaccine-type HPV acquisition reduction multiplier by age.
$k_{vg,a}^{h,h'}$	Transition rate of progressing or regressing from vaccine-type HPV precancer or disease stage h to stage h'. Only women develop precancerous lesions and cervical cancer ($k_{v1,a}^{h,h'} = 0$ except for HPV clearance when $h = 2$ and $h' = 1$).
$k_{nvg,a}^{s,s'}$	Transition rate of progressing or regressing from non-vaccine-type HPV precancer or disease stage s to stage s'. Only women develop precancerous lesions and cervical cancer ($k_{v}1, a^{s,s'} = 0$ except for HPV clearance when $s = 2$ and $s' = 1$).

Variable	Description
$\varphi_g^{h,s,x,x'}$	Progression rate of cervical cancer from stage x to stage x'. Only women develop cervical cancer ($\varphi_1^{h,s,x,x'} = 0$) and ($\varphi_2^{h,s,x'} > 0$ only when h or $s = 6$). Only untreated cervical cancers progress from stage x to stage x'.
r_g	Rate of waning natural immunity. Only women temporarily develop partial natural immunity ($r_1 = 0$).
$\zeta_v^{d,h,h'}$	Transition rate multiplier for individuals with HIV progressing or regressing from vaccine-type precancer or disease stage h to stage h' with CD4 count d. Transition rate multipliers for individuals with HIV are the same for vaccine-type and non-vaccine-type HPV.
$\zeta_{nv}^{d,s,s'}$	Transition rate multiplier for individuals with HIV progressing or regressing from non-vaccine-type precancer or disease stage s to stage s' with gender g and CD4 count d. Transition rate multipliers for individuals with HIV are the same for vaccine-type and non-vaccine-type HPV ($\zeta_v^{d,h,h'} = \zeta_n v^{d,s,s'}$ when $h = s$ and $h' = s'$).
l_g	Additional multiplier for clearance of vaccine or non-vaccine-type HPV infection. Only applied to men ($l_2 = 1$).
$V_{g,a}^d$	The proportion of persons with HIV disease status d, gender g, and age a vaccinated.
$k_{sy_g^x}$	Annual probability of being diagnosed with cervical cancer due to symptoms by cervical cancer stage x $(1 \leq x \leq 3)$.
$\rho_t x g$	The proportion of women who are diagnosed with cervical cancer and continue to treatment.
$\rho_h y g^x$	The proportion of women who are diagnosed and treated with cervical cancer who are treated with hysterectomy, by cancer stage x $(1 \leq x \leq 3)$.

Demography

At each iteration, the force of infection and the number of births are calculated and then used to evaluate the ODEs along with mortality and disease progression. The numbers of incident infections, HIV-related deaths, and individuals entering CD4≤200 cells/μL are also calculated to determine QALYs.

Births

The number of infant births of HIV disease stage d and gender g, $b_{g,a,r}^{d,1,h,s,x,p}(t)$ determines how many newborns enter the population. We assume that all newborns are born as low risk, no vertical transmission of HPV, and that if HIV is vertically transmitted, that infected newborns are born into the acute stage of HIV and that women age 15–49 give birth. Fertility rates are stratified by age and stage of disease. Births from uninfected mothers and women on ART, $b_s(t)$, and from HIV-positive mothers, $b_i(t)$, are:

$$b_s(t) = \sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{3}\sum_{p=1}^{4}\sum_{a=4}^{10}\sum_{r=1}^{3}\left[\gamma_a^1(t)\cdot X_{g,a,r}^{1,1,h,s,x,p}(t) + \gamma_a^8(t)\cdot X_{g,a,r}^{8,6,h,s,x,p}(t)\right]$$

$$b_i(t) = \sum_{d=3}^{7}\sum_{v=1}^{5}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{3}\sum_{p=1}^{4}\sum_{a=4}^{10}\sum_{r=1}^{3}\left[\gamma_a^d(t)\cdot X_{g,a,r}^{d,v,h,s,x,p}(t)\right]$$

HIV-negative, uncircumcised births

For $h = s = x = p = a = r = 1$,

$$b_{g,a,r}^{1,1,h,s,x,p}(t) = 0.5\cdot(b_s(t) + (1-\eta(t))\cdot b_i(t))$$

else,

$$b_{g,a,r}^{1,1,h,s,x,p}(t) = 0$$

HIV-positive births

For $h = s = x = p = a = r = 1$,

$$b_{g,a,r}^{3,1,h,s,x,p}(t) = 0.5\cdot\eta(t)\cdot b_i(t)$$

else,

$$b_{g,a,r}^{3,1,h,s,x,p}(t) = 0$$

The equation variables are:

Variable	Description
$\gamma_a^d(t)$	The annual fertility rate for women by age a and HIV disease stage d. Women aged 15-49 bear children.
$\eta(t)$	The proportion of births from women living with HIV that result in vertical transmission. Each birth is multiplied by 0.5 given an assumed gender ratio at birth of 1:1. The proportion of births from HIV-positive mothers that result in infection, $\eta(t)$, decreases linearly from 34% in 2004 to 29.2% in 2005, then to 7.1% in 2008[5-7].

Mortality

People leave the population due to death or aging past age 79. Annual background mortality rate by gender g and age a is represented by $\mu_{bkrdg,a}(t)$.

$$\frac{dX_{g,a,r}^{d,v,h,s,x,p}(t)}{dt} = -\mu_{bkrd,g,a}(t) \cdot X_{g,a,r}^{d,v,h,s,x,p}(t)$$

Force of Infection

The force of infection represents the cumulative risk of acquiring HIV or HPV from all possible partners, and depends on the adjusted contact rate, the per-partnership probability of transmission, and the proportion of sexually active persons who are HIV- or HPV-infected.

For HIV:

$$\lambda_{\text{HIV},g,a,r}(t) = \sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c_{g,a,a',r,r'}^{*}(t) \cdot \left[\frac{-\sum_{v'=1}^{6}\sum_{x'=1}^{4}\ln\left(1-\beta_{\text{HIV},g,a,r}^{v',x'}\right)\cdot\sum_{d'=3}^{8}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}\right]\right)$$

Similarly, the force of infection $\lambda_{vHPV\,g,a,r}(t)$ determines vaccine-type HPV transmission:

$$\lambda_{v\text{HPV},g,a,r}(t) = \sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c_{g,a,a',r,r'}^{*}(t) \cdot \left[\frac{-\sum_{v'=1}^{6}\sum_{x'=1}^{4}\ln\left(1-\beta_{\text{HPV},g,a,r}^{v',x'}\right)\cdot\sum_{d'=1}^{8}\sum_{h'=2}^{6}\sum_{s'=1}^{7}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}\right]\right)$$

and $\lambda_{nvHPV\,g,a,r}(t)$ defines non-vaccine-type HPV transmission:

$$\lambda_{\text{nvHPV},g,a,r}(t) = \sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c_{g,a,a',r,r'}^{*}(t) \cdot \left[\frac{-\sum_{v'=1}^{6}\sum_{x'=1}^{4}\ln\left(1-\beta_{\text{HPV},g,a,r}^{v',x'}\right)\cdot\sum_{d'=1}^{8}\sum_{h'=1}^{7}\sum_{s'=2}^{6}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4}X_{g',a',r'}^{d',v',h',s',x',p'}(t)}\right]\right)$$

The equation variables are:

Variable	Description
$c_{g,a,a',r,r'}^{*}(t)$	Adjusted yearly contact rate for persons of gender g, age a, and risk group r, with persons of the opposite gender, age a', and risk group r'.
$\beta_{HIV\,g,a,r}^{v',x'}$	Annual per-partnership probability of HIV transmission from a person with HIV with viral load v' and cervical cancer stage x' to an HIV-susceptible partner with gender g, age a, and risk group r.
$\beta_{HPV\,g,a,r}^{v',x'}$	Annual per-partnership probability of HPV transmission from an HPV-infected person with viral load v' and cervical cancer stage x' to an HPV-susceptible partner with gender g, age a, and risk group r.

Mixing Matrix

Using methods similar to other models, the mixing matrix, $\rho_{g,a,a',r,r'}(t)$ describes patterns of sexual contact by calculating the proportion of one's sexual partners that come from a specific age and sexual-risk group[5].

$$\rho_{g,a,a',r,r'}(t) = \left(\epsilon_a \cdot \frac{\sum_{r'=1}^{3}\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)}{\sum_{a'=1}^{16}\sum_{r'=1}^{3}\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)} + (1-\epsilon_a)\cdot\delta_{g,a,a'}\right)$$
$$\cdot\left(\epsilon_r \cdot \frac{c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{r'=1}^{3}\left(c_{g',a',r'} \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{g',a',r'}^{d',v',h',s',x',p'}(t)\right)} + (1-\epsilon_r)\cdot\delta_{g,r,r'}\right)$$

The equation variables are

Variable	Description
$c_{g,a,r}$	Number of partners a person has per year of gender g, age a, and sexual-risk group r (i.e., the partner exchange rate or contact rate).
ϵ_a	Mixing parameter by age a. We assume a mixing pattern that is partially random and partially off-diagonal ($0 < \epsilon_a < 1$), where $\epsilon_a = 0$ indicates completely off-diagonal mixing, and $\epsilon_a = 1$ indicates completely random mixing.
ϵ_r	Mixing parameter by sexual-risk group r. We assume a mixing pattern that is partially random and partially on-diagonal ($0 < \epsilon_r < 1$), where $\epsilon_r = 0$ indicates completely on-diagonal mixing, and $\epsilon_r = 1$ indicates completely random mixing.
$\delta_{g,a,a'}$	Mixing pattern by age. In completely non-random mixing by age, women are most likely to form partnerships with men of the next oldest age group. We represent this pattern using an off-diagonal matrix. For men ($g = 1$) of age a mixing with women of age a': - $= 0.3$ if $(a = a')$ - $= 0.7$ if $(a = a' + 1)$ - $= 0.0$ if $(a = a' = 1)$ - $= 0.0$ if $(a = 2)$ and $(a' = 1)$ - $= 0.0$ if $(a = 2)$ and $(a' = 2)$ - $= 0.0$ if $(a = 3)$ and $(a' = 2)$ For women ($g = 2$) of age a mixing with men of age a': - $= 0.3$ if $(a = a')$ - $= 0.7$ if $(a = a' - 1)$ - $= 0.0$ if $(a = a' = 1)$ - $= 0.0$ if $(a = 1)$ and $(a' = 2)$ - $= 0.0$ if $(a = a' = 2)$ - $= 0.0$ if $(a = 2)$ and $(a' = 3)$
$\delta_{r,r'}$	Mixing pattern by risk. Completely non-random mixing by risk confines sexual encounters to individuals within the same risk group. We represent this pattern using an identity matrix: - $= 1.0$ if $(r = r')$ - $= 0.0$ if $(r \neq r')$

We assume that mixing is partially random and partially designated by a mixing pattern $\delta_{g,a,a'}$ or $\delta_{r,r'}$. The overall mixing matrix is therefore a weighted average of random mixing proportional to the number of available partnerships of each group and mixing among groups with similar characteristics. The off-diagonal pattern results in females of age a being more likely to form partnerships with males of age $a = a' - 1$, which is consistent with reports of such age discrepancies in KZN[6,7]. Although an off-diagonal mixing pattern results in the first and last ages groups (ages 10-14 and 75-79) having fewer than 100% of their partnerships, these age groups have relatively few partnerships and contribute marginally to overall infection transmission.

Per-Partnership Probability of Transmission

The per-partnership probability of transmission, $\beta_{\text{HIV}}{}_{g,a,r}^{v',x'}$, depends on the sexual risk group of the HIV-negative partner and the disease state of the HIV-positive partner. $\chi_{\text{HIV}}{}_{g}^{v',x'}$ is the per-act probability of HIV transmission to a person of gender based on the viral load of the partner living with HIV. We assume the probability of female-to-male HIV transmission is equal to the probability of male-to-female transmission across all viral load stages ($\chi_{\text{HIV}}{}_{1}^{v'} = \chi_{\text{HIV}}{}_{2}^{v'}$). We reduce HIV per-act transmission as a proxy for decreased sexual activity during late-stage HIV ($v' = 5$), regional or distant cervical cancer ($x' = 2$ or $x' = 3$), or hysterectomy ($x' = 4$). $A_{g,a,r}$ is the number of acts a person has per partnership of gender g, age a, and sexual-risk group r. We assume zero acts for individuals below the age of sexual debut (age 10). The probabilities of transmission per partnership are:

Per-partnership probability of HIV transmission to a male partner

$$\beta_{\text{HIV},1,a,r}^{v',x'} = 1 - \left(1 - \chi_{\text{HIV},1}^{v',x'}\right)^{A_{1,a,r}}$$

Per-partnership probability of HIV transmission to a female partner

$$\beta_{\text{HIV},2,a,r}^{v',x'} = 1 - \left(1 - \chi_{\text{HIV},2}^{v',x'}\right)^{A_{2,a,r}}$$

The per partnership probability of transmission, $\beta_{\text{HPV}}{}_{g,a,r}^{v',x'}$ is calculated in a similar manner for HPV. $\chi_{\text{HPV}}{}_{g}^{v',x'}$ is the per-act probability of HPV transmission to a person of gender by an an HPV-positive partner:

We calculate the per-partnership probability of HPV transmission to a male partner:

$$\beta_{\text{HPV}}{}_{1,a,r}^{v',x'} = 1 - \left(1 - \chi_{\text{HPV}}{}_{1}^{v',x'}\right)^{A_{1,a,r}}$$

Similarly, the per-partnership probability of HPV transmission to a female partner:

$$\beta_{\text{HPV}}{}_{2,a,r}^{v',x'} = 1 - \left(1 - \chi_{\text{HPV}}{}_{2}^{v',x'}\right)^{A_{2,a,r}}$$

Rate of Partner Change

Data on sexual behavior and specifically, sexual contact rates, $c_{g,a,r}$ are often subject to biases leading to contact rate data that, when assuming solely heterosexual contact, are inconsistent between males and females[8]. We account for this variability by using an adjusted contact rate, $c^*_{g,a,a',r,r'}(t)$ which equilibrates the reported number of sexual partners by males and females[5]. The adjusted contact rate can be male- or female-driven, as determined by the parameter θ, where $\theta = 1$ for male-driven, $\theta = 0$ for female-driven, and $\theta = 0.5$ when compromised equally. We assume $\theta = 0.5$ given the lack of data to assume otherwise. The adjusted contact rate for females is:

$$c^*_{2,a,a',r,r'}(t) = \; c_{2,a,r} \cdot \rho_{2,a,a',r,r'}(t) \cdot B_{a,a',r,r'}(t)^{\theta} \cdot \left(\frac{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{1,a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d=1}^{8}\sum_{v=1}^{6}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{4}\sum_{p=1}^{4} X_{2,a,r}^{d,v,h,s,x,p}(t)} \right)^{-(1-\theta)}$$

For males, the adjusted contact rate is:

$$c^*_{1,a,a',r,r'}(t) = \; c_{1,a,r} \cdot \rho_{1,a,a',r,r'}(t) \cdot B_{a,a',r,r'}(t)^{-(1-\theta)} \cdot \left(\frac{\sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{1,a',r'}^{d',v',h',s',x',p'}(t)}{\sum_{d=1}^{8}\sum_{v=1}^{6}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{4}\sum_{p=1}^{4} X_{2,a,r}^{d,v,h,s,x,p}(t)} \right)^{\theta}$$

The discrepancy between the two populations, $B_{a,r}^{a',r'}(t)$, is defined as:

$$B_{a,a',r,r'}(t) = \; \frac{c_{1,a,r} \cdot \rho_{1,a,a',r,r'}(t) \cdot \sum_{d'=1}^{8}\sum_{v'=1}^{6}\sum_{h'=1}^{7}\sum_{s'=1}^{7}\sum_{x'=1}^{4}\sum_{p'=1}^{4} X_{1,a',r'}^{d',v',h',s',x',p'}(t)}{c_{2,a,r} \cdot \rho_{2,a,a',r,r'}(t) \cdot \sum_{d=1}^{8}\sum_{v=1}^{6}\sum_{h=1}^{7}\sum_{s=1}^{7}\sum_{x=1}^{4}\sum_{p=1}^{4} X_{2,a,r}^{d,v,h,s,x,p}(t)}$$

Model Calibration

The model was calibrated through a phased approach to fit HIV, HPV, cervical cancer and population dynamics from 1996 to 2019. We used hand calibration to explore the sensitivity of model outcomes to individual parameters (Phase 0), informing our decision to divide the Bayesian calibration into three phases. In Phase 1, a Bayesian algorithm was used to fit sexual behavior and HIV natural history parameters to observed demographic and HIV prevalence data. Randomly resampling from the 50 best-fitting parameter sets of Phase 1, we then used the same Bayesian algorithm to fit HPV natural history parameters to observed data on HPV prevalence, CIN prevalence, cervical cancer incidence, and type distribution for Phase 2. Phase 3 was added to the calibration to fit parameters of probabilities of cervical cancer symptomatic detection by stage. Phase 3 involved randomly resampling from the 50 best-fitting parameter sets of Phase 2 and the corresponding parameter sets of Phase 1 and fitting to observed data on cervical cancer stage distribution before widespread cervical screening in South Africa. All our outputs followed independent normal distributions. For prevalence data, we assumed a normal approximation of the binomial distribution, and for incidence data, we assumed a normal approximation of a Poisson distribution. We assumed a normal distribution for the total population size of KwaZulu-Natal and that the 2019 estimate had the same variance as the 2011 estimate.

Population Aging

To age the population, one-fifth of each compartment enters the next age group while maintaining the same gender,disease state and sexual risk $\phi_{g,a,r}$. When individuals age to the next five-year group, they are redistributed into the closest unfilled risk group to match observed data on the age distribution of low, moderate and high-risk individuals. All compartments, except for the youngest and oldest age-groups, experience influx from the prior age and efflux into the next age. The 0 to 4 age-group only receives influx through births while the 75 to 79 age-group exits the population rather than entering the next age. Therefore, each state has a second ODE that occurs at each time step:

$$\frac{dX_{g,1,r}^{d,v,h,s,x,p}(t)}{dt} = -\frac{1}{5}\sum_{r=1}^{3}\left(X_{g,1,r}^{d,v,h,s,x,p}(t)\cdot\phi_{g,a,r}\right)$$

(for $a = 1$)

$$\begin{aligned}\frac{dX_{g,a,r}^{d,v,h,s,x,p}(t)}{dt} = & -\frac{1}{5}\sum_{r=1}^{3}\left(X_{g,a,r}^{d,v,h,s,x,p}(t)\cdot\phi_{g,a,r}\right) \\ & +\frac{1}{5}\sum_{r=1}^{3}\left(X_{g,a-1,r}^{d,v,h,s,x,p}(t)\cdot\phi_{g,a-1,r}\right)\end{aligned}$$

(for $a \neq 1$)

Interventions

ART Treatment:

We define ART coverage as the percentage of all persons living with HIV and age-eligible for ART who are on treatment and virally suppressed. Coverage of ART treatment for HIV-positive persons increased from 0% in 2004 to 44% for men and 60% for women in 2017[9]. The proportion of persons living with HIV who are virally suppressed remains at the estimated levels for 2017 for the simulation. Individuals on treatment with viral suppression are assumed to have zero probability of transmitting HIV and have reduced HIV-associated mortality. The probability of ART initiation is uniform by age or risk group. However, we do not model the discontinuation process of ART and the resulting loss of viral suppression, such that the cumulative probability of being on ART increases with age. Therefore, we apply age-specific minimum and maximum limits for viral suppression, ensuring that it is distributed appropriately across all age groups while also matching population-level levels of viral suppression by gender in the observed data. HIV-associated mortality among treated persons living with HIV decreases over time, reflecting higher baseline health among individuals initiating treatment. From 2004 to 2011, HIV-associated excess mortality among virally suppressed persons living with HIV was 0.5x the background rate. This multiplier decreases to 0.4x, 0.25x, and 0.15x the background mortality rate in 2011, 2015, and 2016, respectively.

Circumcision:

We model medical circumcision beginning in 1960 for age groups 15-19 and 20-24. Data suggest that circumcised males have a 60% ($\psi_0 = 0.6$) lower risk of acquiring HIV but are not at a reduced risk of transmitting HIV[10-12]. Therefore, the model does not track the circumcision status of HIV-positive persons. Before the initiation of the South Africa National VMMC program in 2010, circumcision was primarily targeted to young adult men as a rite of passage[13]. Starting circumcision in 1960 among youth resulted in circumcision prevalence among men aged 50 and older in 2012 corresponding to observed estimates[14]. We assume coverage increases linearly from 1960 to 2000 and between 2000 and 2008 to match coverage level estimates[13,15]. Following the initiation of the national VMMC program in 2010, we model scale-up of circumcision for all men aged 15 or older at levels extrapolated backward from 2012 to 2017[9,14,16]. In our future scenarios, the proportion of men circumcised remains at 2017 levels for the duration of the simulations.

HPV vaccination:

HPV vaccination begins in 2014 for 57% of nine-year-old girls . Our model was designed to evaluate the impact of the 9vHPV vaccine. However, the current vaccination program in South Africa uses the bivalent vaccine, which targets only two of the seven oncogenic types in the 9vHPV vaccine. To account for this, in the years 2014-2023 (when we assume bivalent vaccination is conducted), we adjust the 57% coverage by a factor

of (0.7/0.9), based on evidence that HPV types 16 and 18 contribute to approximately 70% of cervical cancer cases relative to the 90% attributable to one or more of the types included in the 9vHPV[17]. We assume that vaccination provides complete protection against the seven oncogenic types included in the 9vHPV vaccine and 0% protection against other hrHPV types. We assume lifelong protection from vaccination. Vaccine efficacy and uptake are assumed not to vary by HIV status. We model vaccine efficacy using a beta probability distribution that aligns with the results from a licensure trial of the bivalent vaccine, with an efficacy of 100% (95% CI 74.4, 100)[18,19]. The parameters of the beta distribution are $\alpha = 2.0$ and $\beta = 0.04$.

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Output Overview

Summary

This section describes outputs from the model.

Overview

The model tracks the prevalence and incidence of HPV, HIV, Cervical Cancer and their associated outcomes in each compartment for the entire simulated period. This allows for comparisons of population-level health outcomes in the absence and presence of various prevention and intervention strategies. Ultimately, this facilitates the study of the efficacy and cost-effectiveness of said strategies.

Output Listing

The results that are currently being produced are:

- Overall HIV prevalence
- Proportion of HIV-positive population on ART
- Population-level distribution of CD4 count and viral load among HIV-positive individuals
- HIV prevalence by age and gender
- HPV prevalence
- HPV health states
- CIN 2/3 prevalence by HIV status
- Cervical cancer health states
- Cervical cancer incidence
- New cervical cancer cases
- Cervical cancer mortality
- Deaths
- Screening and Treatment
- Vaccinations

MGH
Results Overview

Results Overview

Summary

A guide to the results obtained from the model.

Overview

The following is a list of publications which showcase results from DRIVE.

Results List

[1] Liu G, Mugo NR, Bayer C, Rao DW, Onono M, Mgodi NM, Chirenje ZM, Njoroge BW, Tan N, Bukusi EA, Barnabas RV. Impact of catch-up human papillomavirus vaccination on cervical cancer incidence in Kenya: A mathematical modeling evaluation of HPV vaccination strategies in the context of moderate HIV prevalence. EClinicalMedicine. 2022 Feb 19;45:101306. doi: 10.1016/j.eclinm.2022.101306. PMID: 35243272; PMCID: PMC8860915. [original work].

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Harvard Cervical: Model Profile

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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

Harvard School of Public Health
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.

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.
  .
- 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.

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.

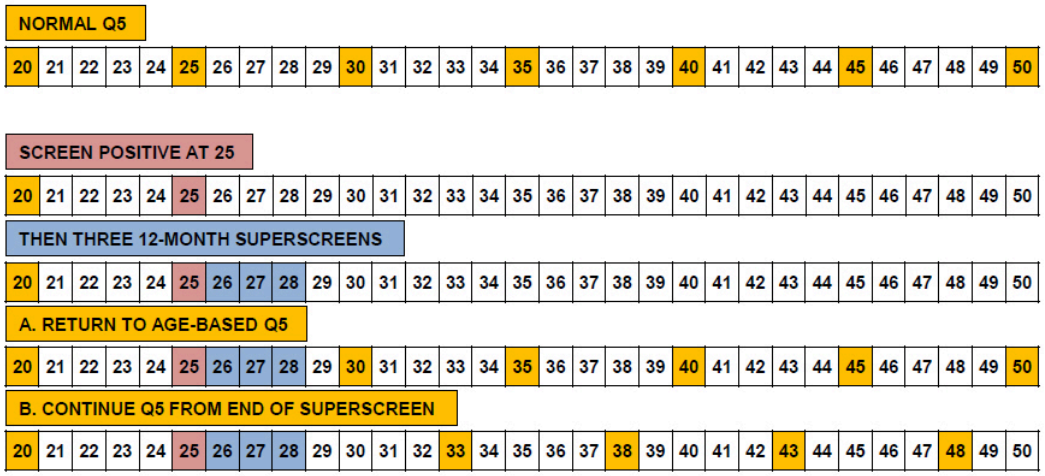
Vaccination parameters include:

- 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

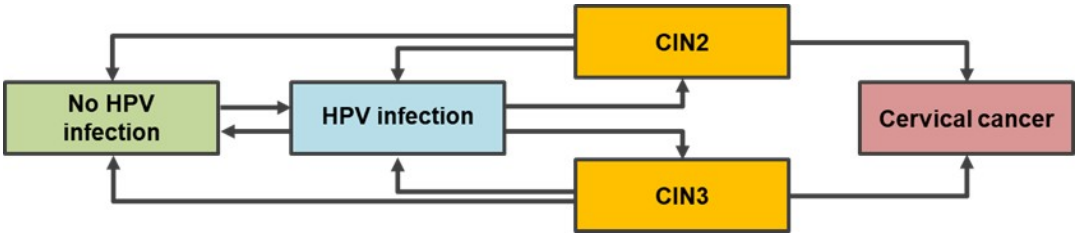
The natural history component includes: risk factors for cervical cancer (e.g., age of sexual debut), acquisition of type-specific HPV infections, probability of HPV persistence, risk of progression to (and regression from) precancerous lesions cervical intraepithelial neoplasia grades 2 and 3 (CIN2; 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.

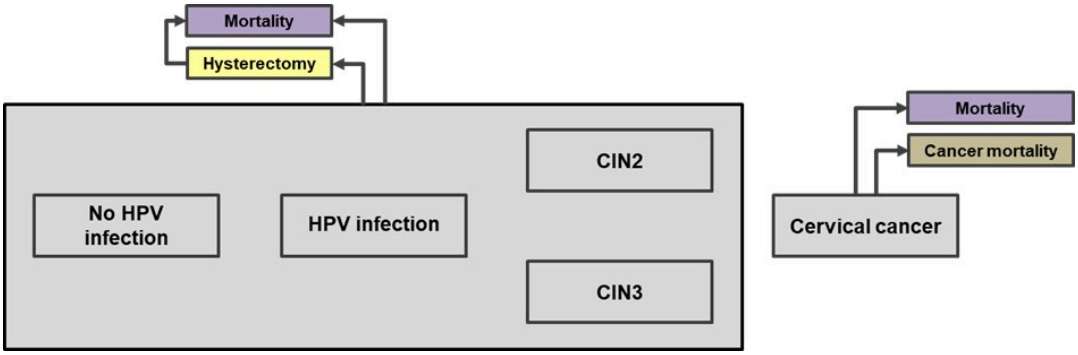
The probabilities governing these monthly transitions depend on age; HPV type; duration of HPV infection; type-specific natural immunity; as well as a woman's history of prior infection, previously treated CIN, and patterns of screening. Each month, simulated women can become infected with HPV and those 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.

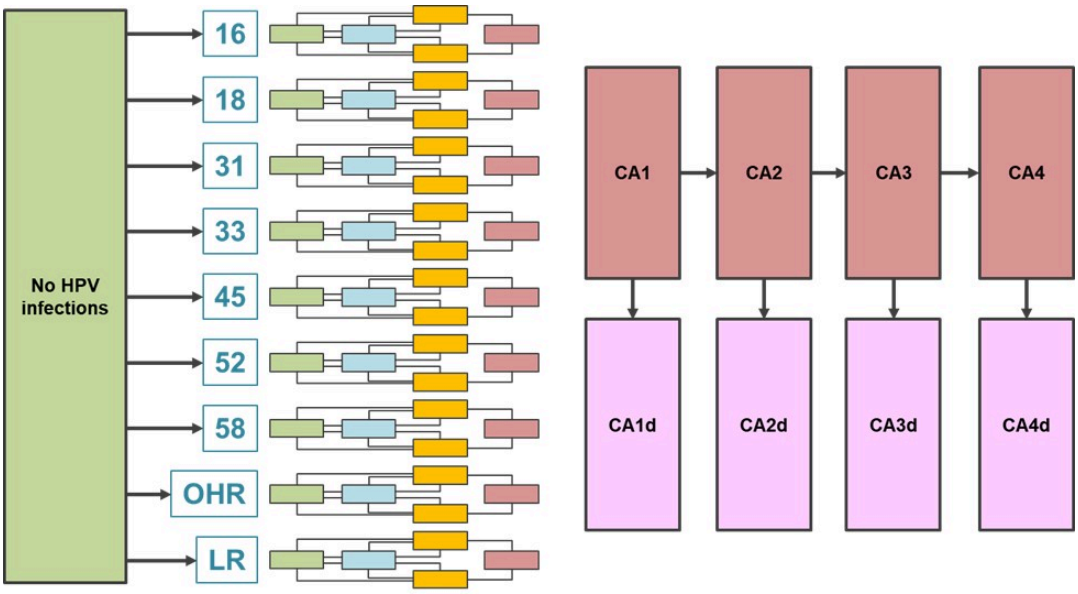
Below is a general schematic of transition states in the model.



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



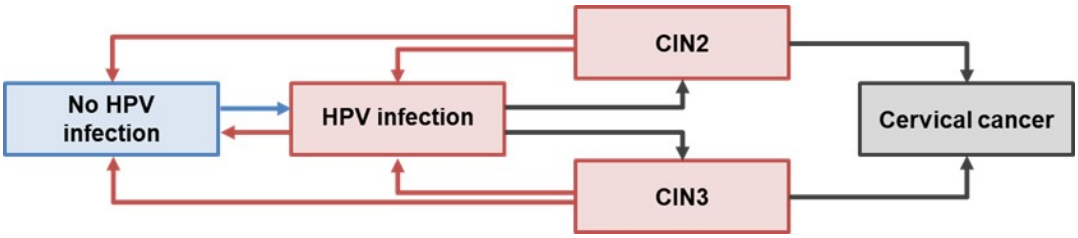
The schematic can again be modified to show the different HPV types HARVARD-CC simulates -- high-risk type 16; high-risk type 18; high-risk type 31; high-risk type 33; high-risk type 45; high-risk type 52; high-risk type 58; other high-risk types (OHR); and low-risk types (LR). Each HPV type can be acquired 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.

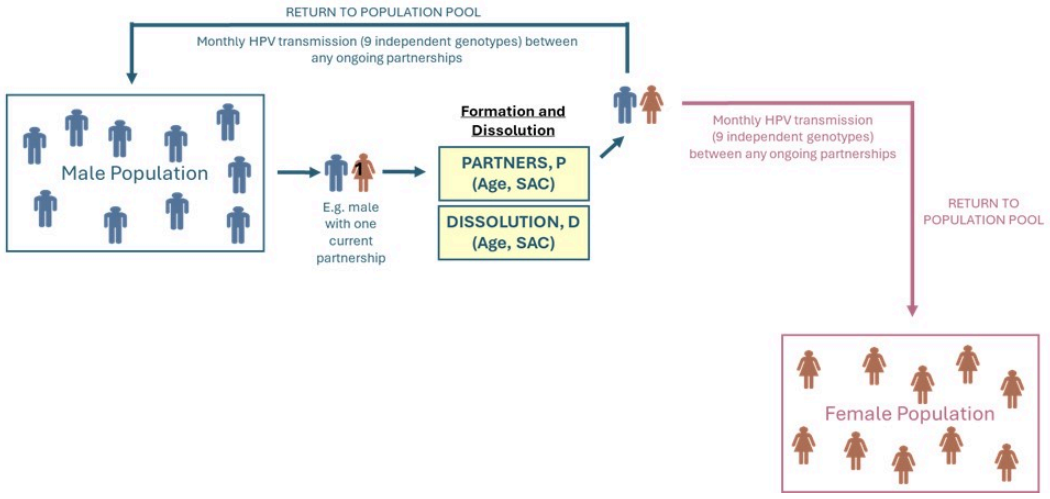
If the expected number of partners for his age is greater than the number of partners, the acquisition of partner(s) will be attempted. The model restricts the population to a pool of available women (i.e. women who have not reached their expected number of partners) who match the desired age and SAC 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).

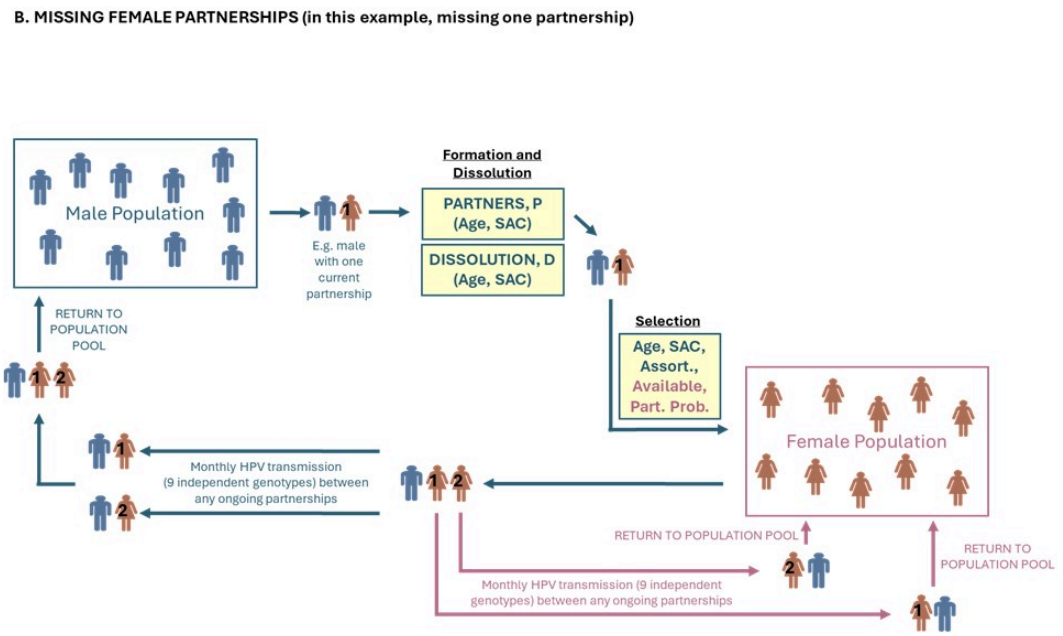
The following figures depict an example of the sexual mixing component in HARVARD-HPV. The first figure (A) shows an example of a male who is not missing any expected partnerships; the second figure (B) shows an example of a male who is seeking one additional partner.

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



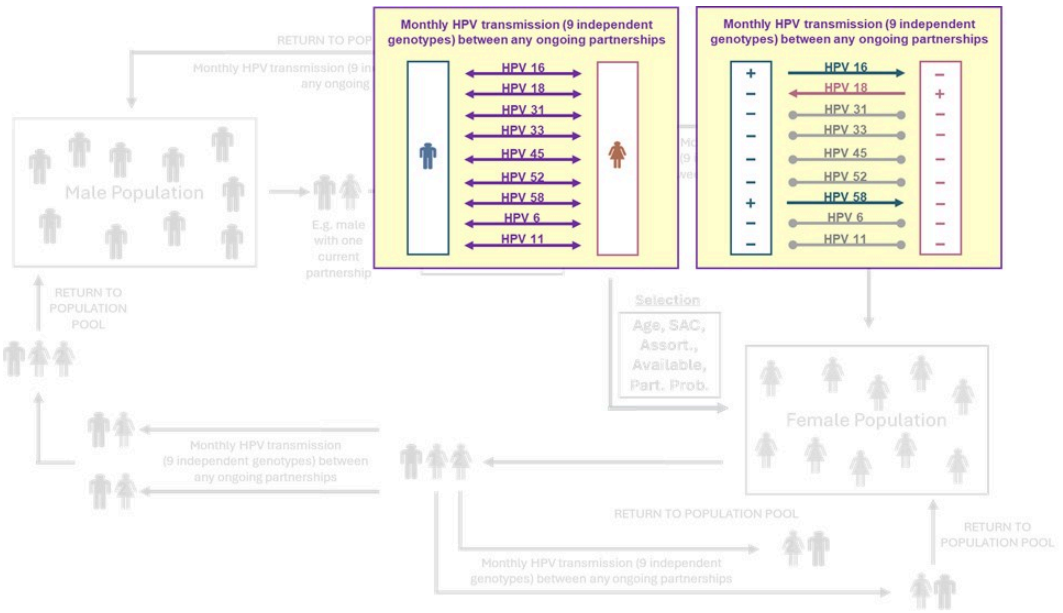


HARVARD-HPV: HPV Transmission

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.

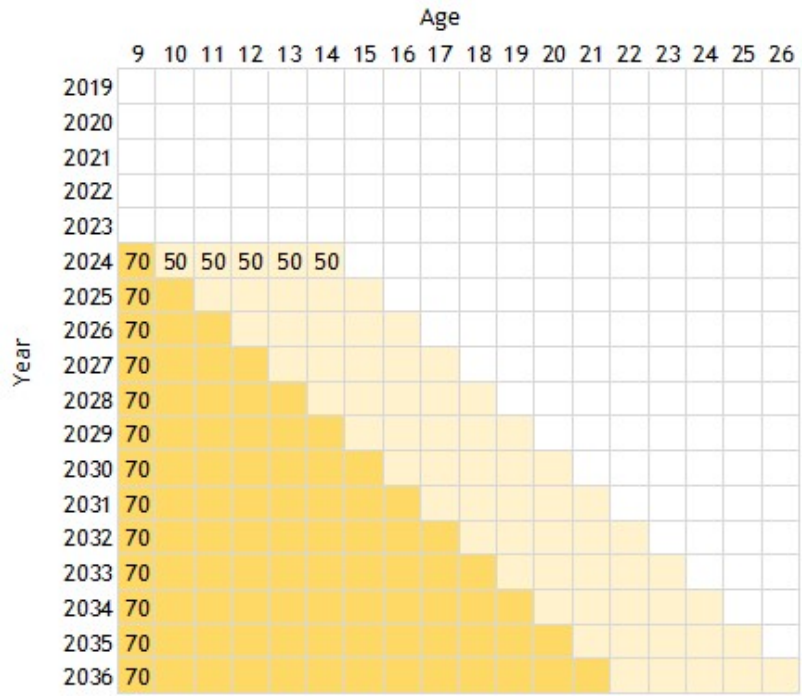


HARVARD-HPV: Vaccination

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

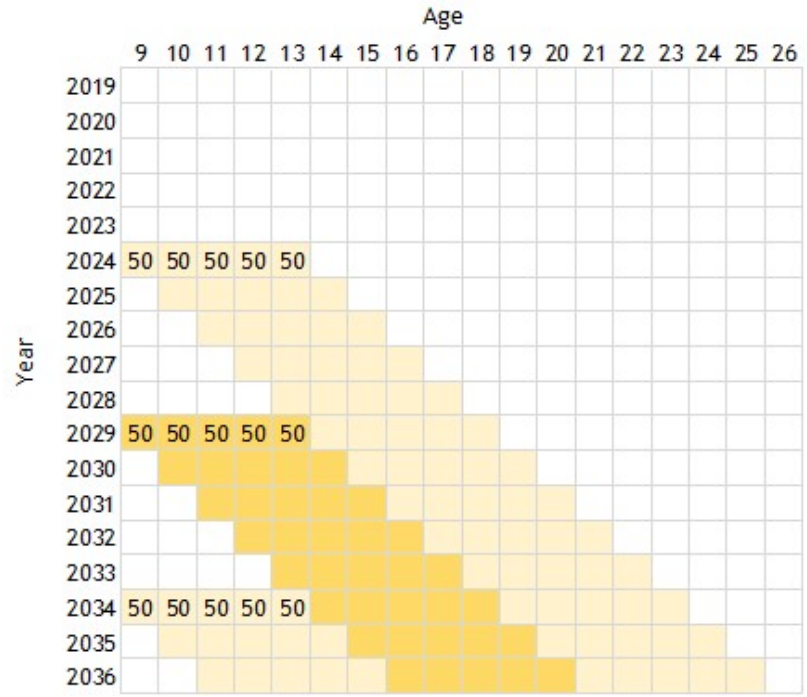
Most standard vaccination programs fall under the routine category. Under routine vaccination, the model can set coverage levels (among the unvaccinated) for every cohort at every age and every time. The most common scenario is to set coverage for incoming cohorts at a certain age, as well as set a catch-up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

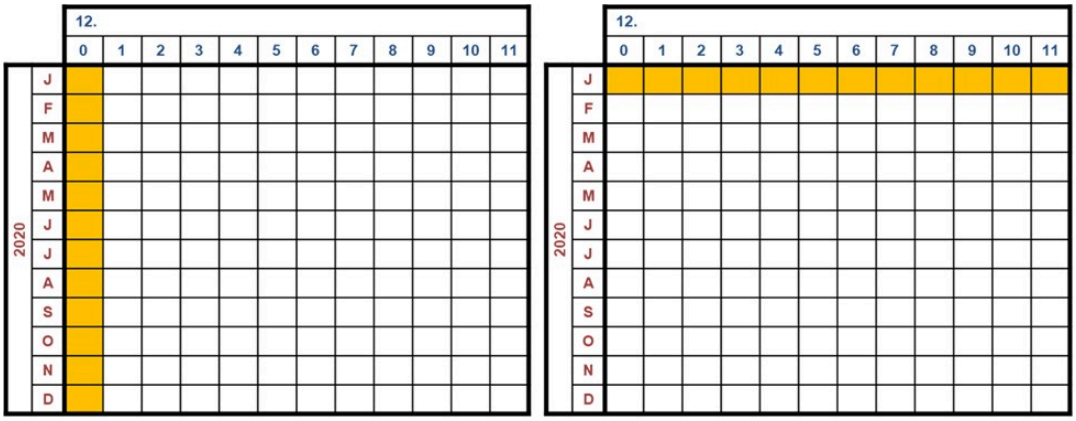


Aside from vaccine coverage over time, other characteristics of vaccination in HARVARD-HPV include:

- 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.

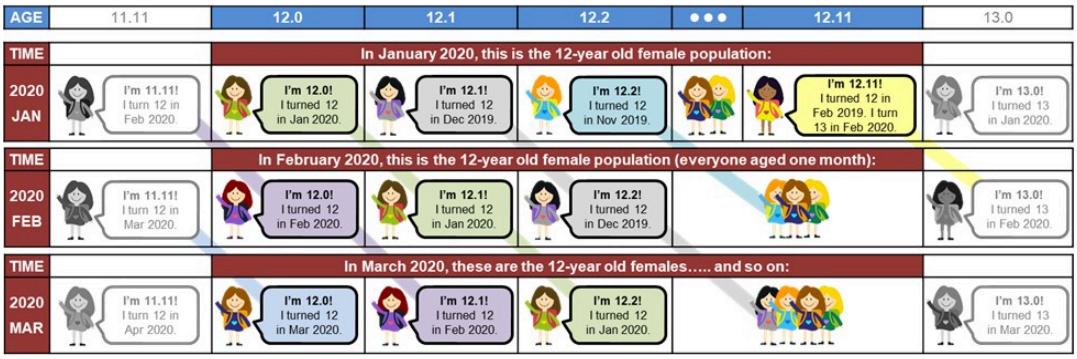
HARVARD-CC simulates one cohort; therefore, model output for HARVARD-CC is only for that single cohort. Outputs representing aggregate counts are out of the initial cohort size; for example, total number of detected cervical cancer cases out of one million. Outputs that are a function of time are also 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).

		12.												13.											
		0	1	2	3	4	5	6	7	8	9	10	11	0	1	2	3	4	5	6	7	8	9	10	11
2020	J																								
	F																								
	M																								
	A																								
	M																								
	J																								
	J																								
	A																								
	S																								
	O																								
	N																								
	D																								

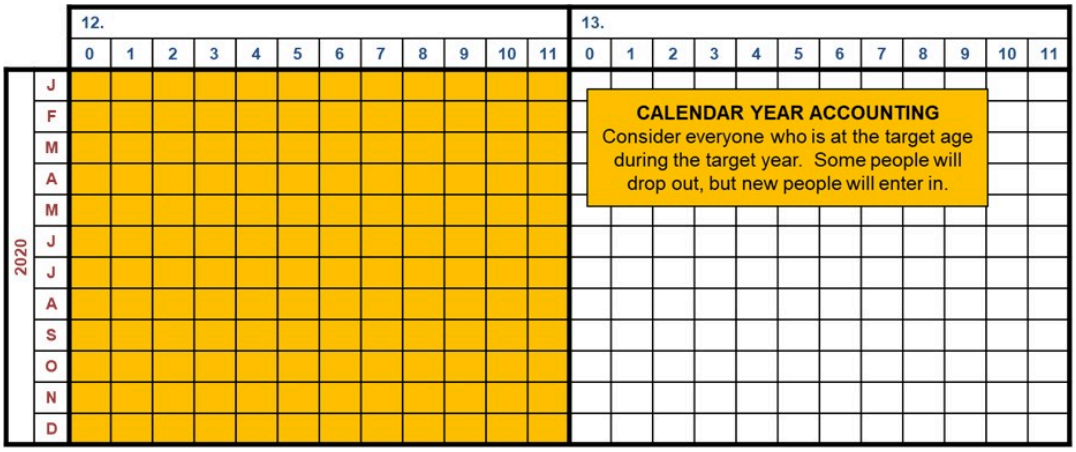
We can ask the question: who do we consider to be "12-year olds" in 2020? The following visualization may help clarify.



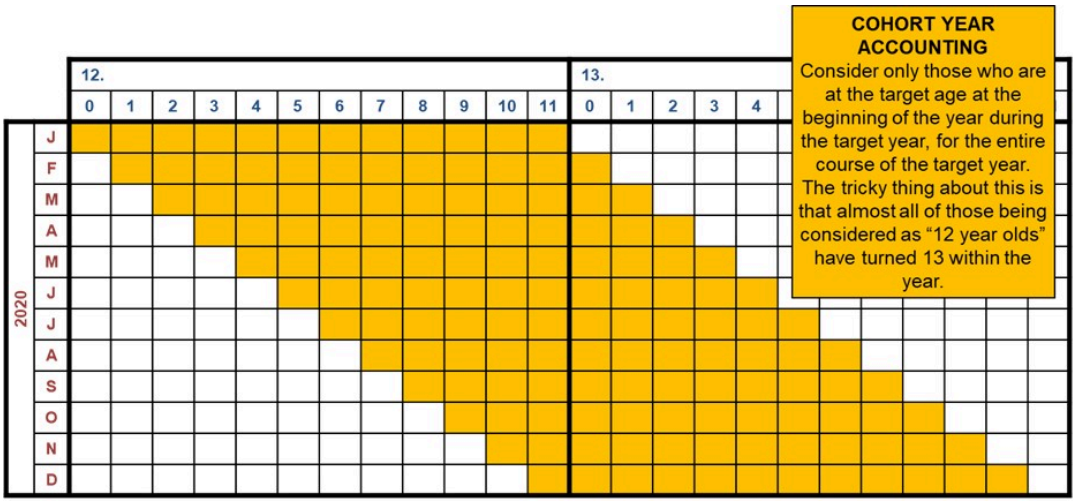
In January 2020, there are 12 cohorts of "12-year olds" – ranging from those who just turned 12 that month (i.e. 12.0, 12 years, 0 months), to those who are in their last month of being 12 (i.e. 12.11, 12 years, 11 months). In February 2020, everyone ages one month, and a group of 11.11-year olds in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

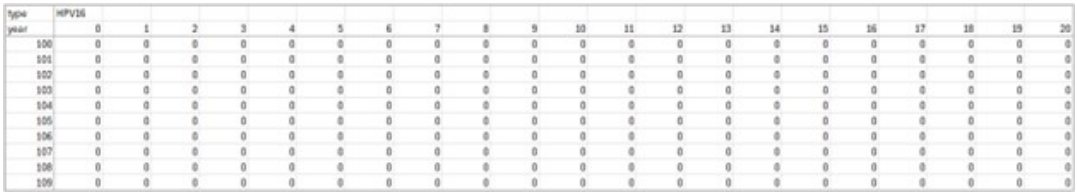
have progressed to CIN2, CIN3, and CA. Screening trials can easily produce this kind of data for the model to match to.

- 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

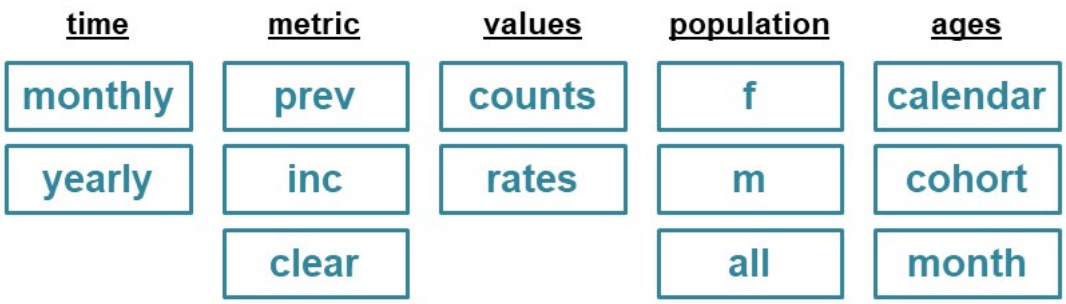
For disease outputs, HARVARD-HPV produces a generic three-dimensional output template, with age, time, and HPV type as the axes. To represent the output in a two-dimensional spreadsheet, age and HPV type are flattened and combined onto one axis, with time on the other axis.

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

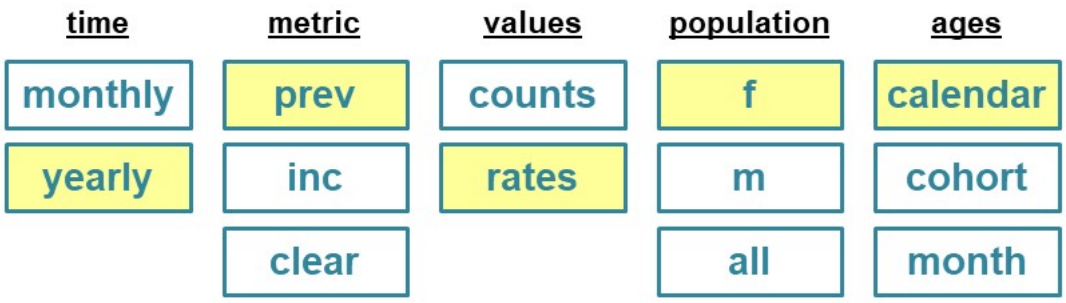
The main HARVARD-HPV outputs can be summarized by the following graphic:



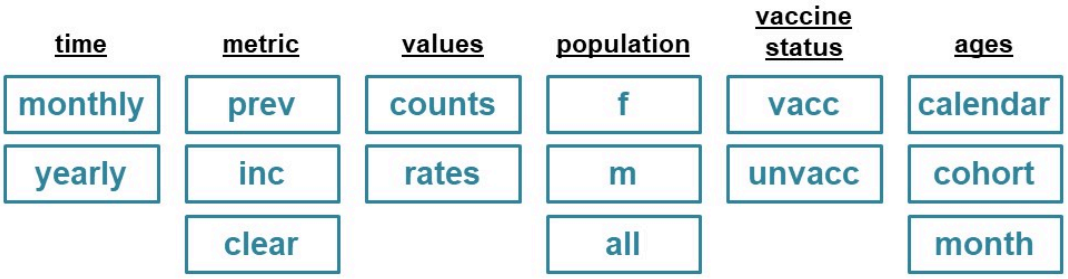
There are five components to an output file, and the model can output each possible combination.

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

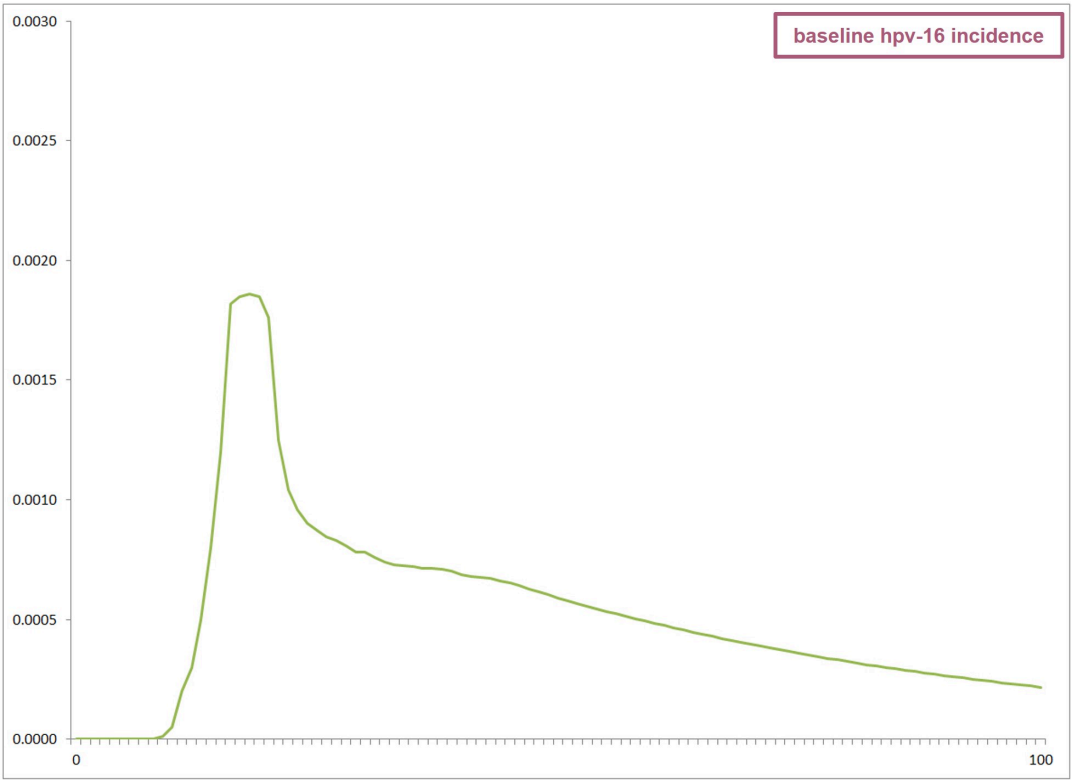
Model calibration for both HARVARD-CC and HARVARD-HPV involves adjusting values of unobservable variables, and then running the models with these values to fit setting-specific epidemiological targets.

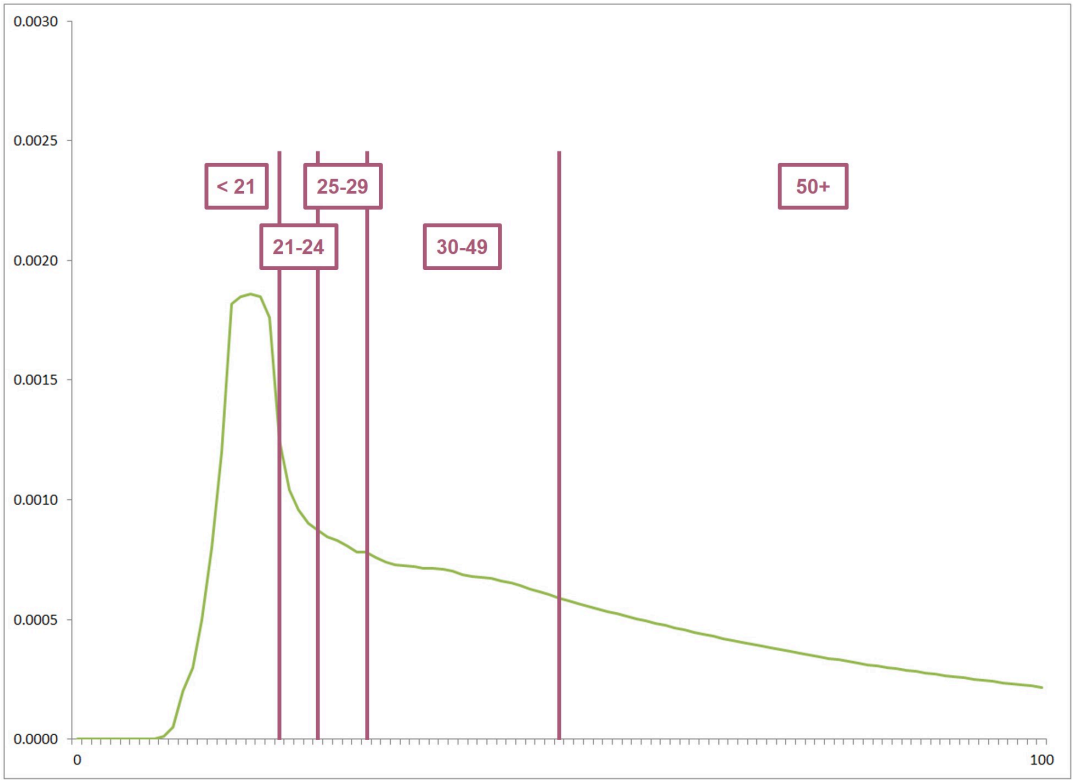
HARVARD-CC

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.

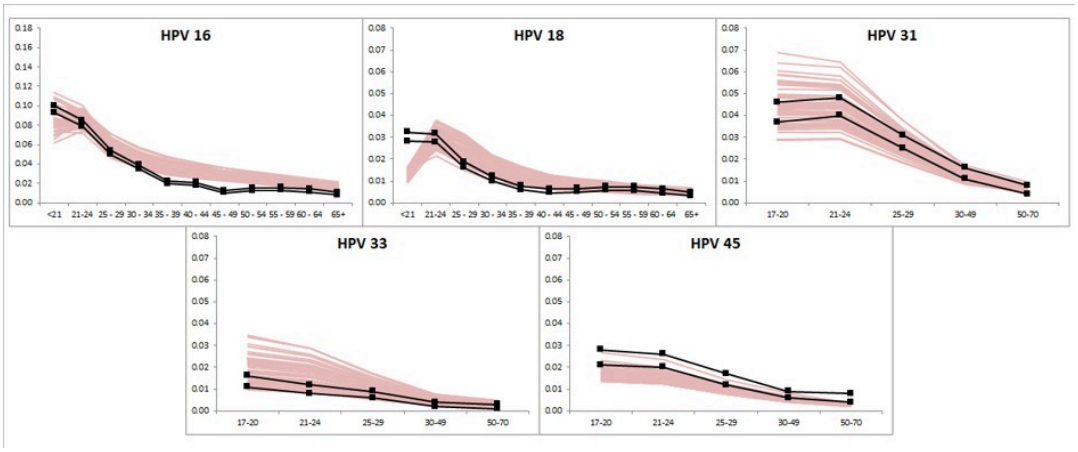
HARVARD-CC

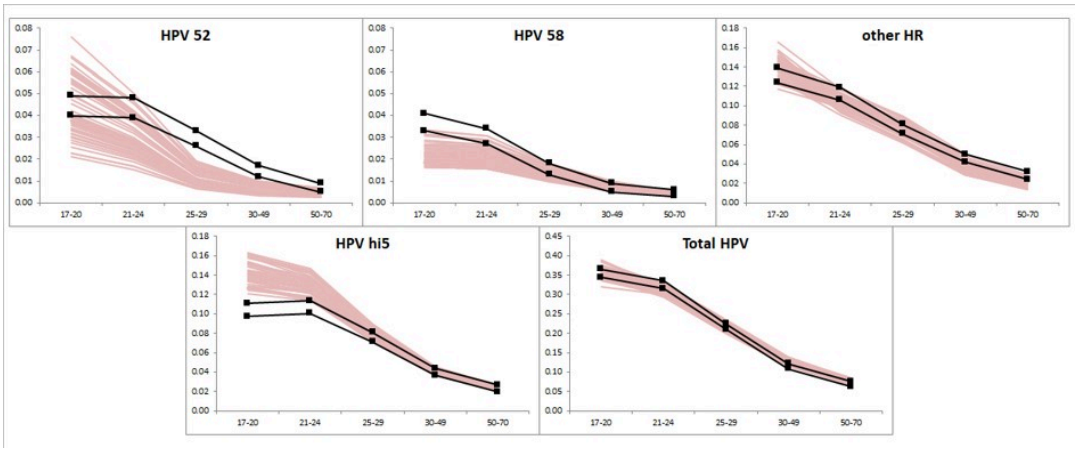
For a U.S.-based setting, calibration targets for HARVARD-CC include:

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

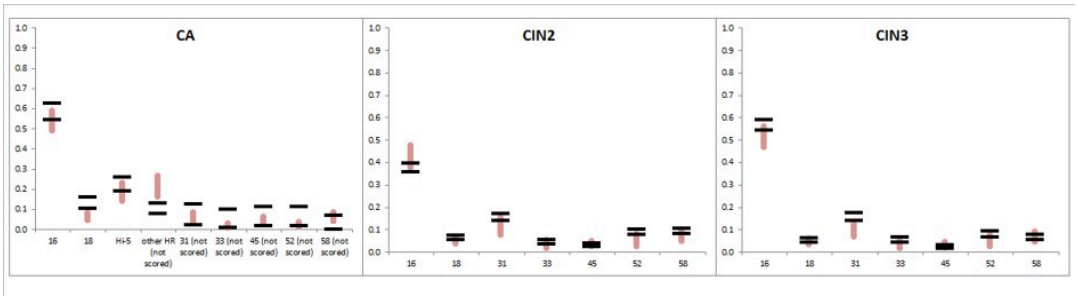
Below are graphs of the top 50 parameter sets (pink) to these targets (black).

HPV prevalence:

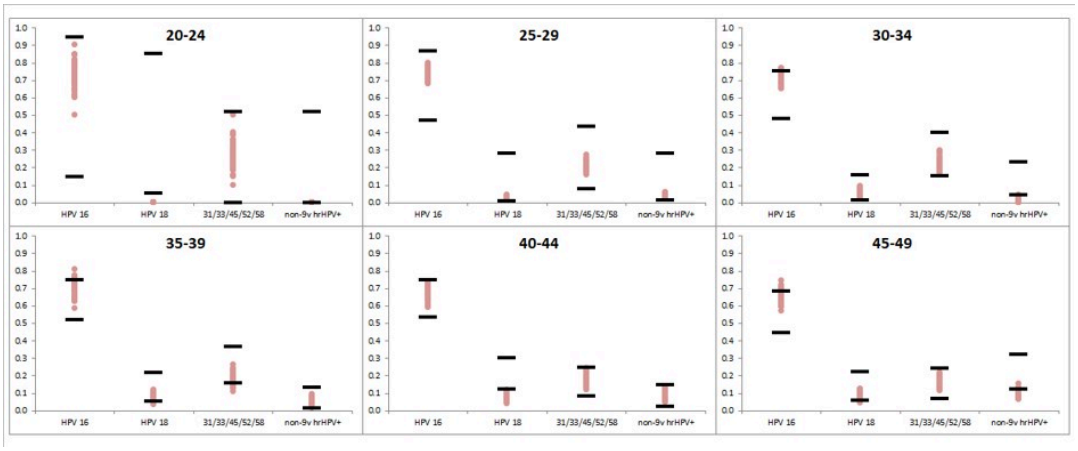


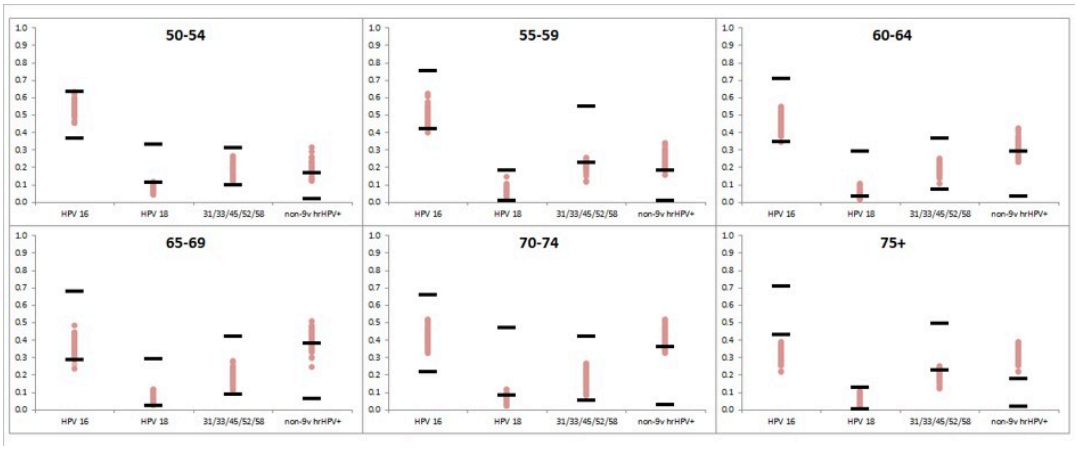


HPV type distribution (overall):



HPV type distribution (by age):

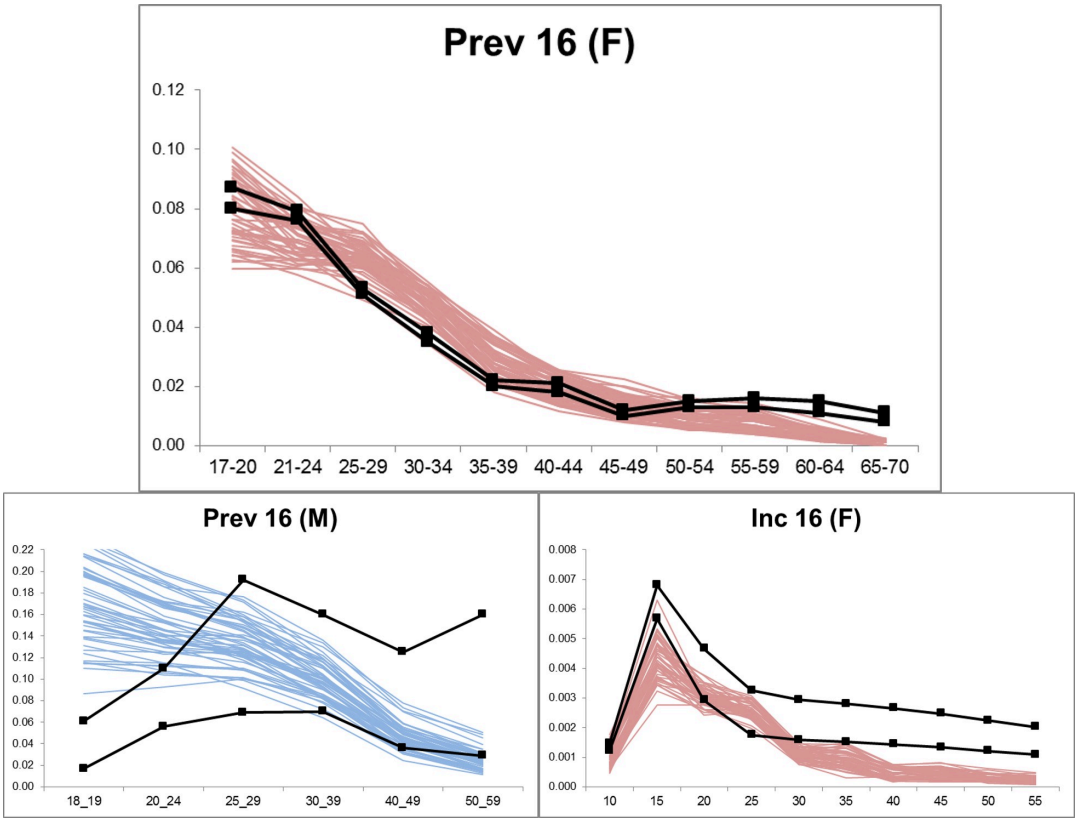




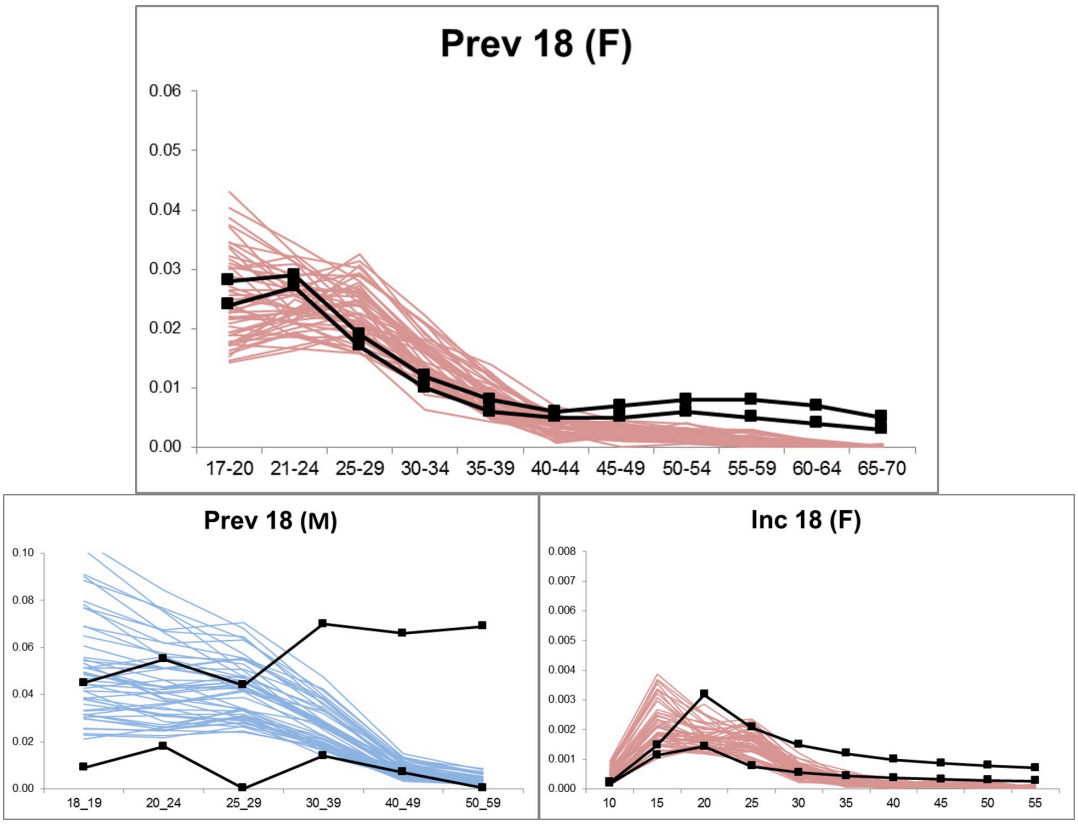
HARVARD-HPV

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.)

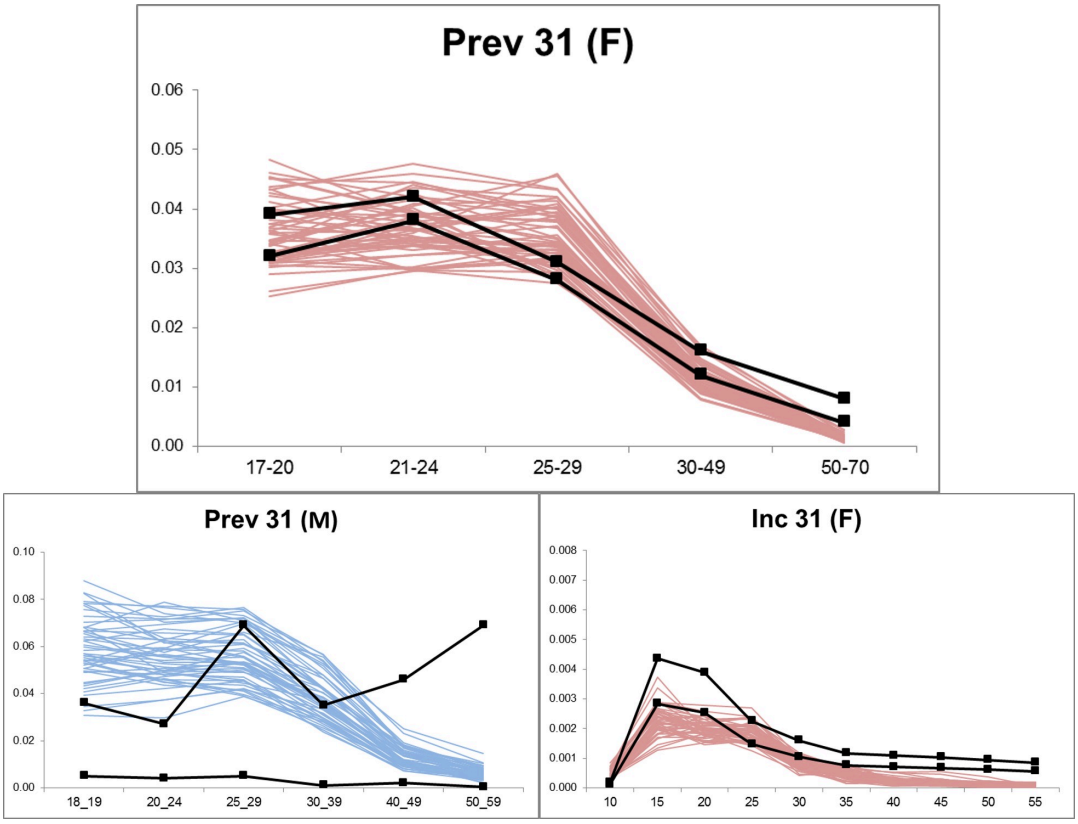
HPV-16:



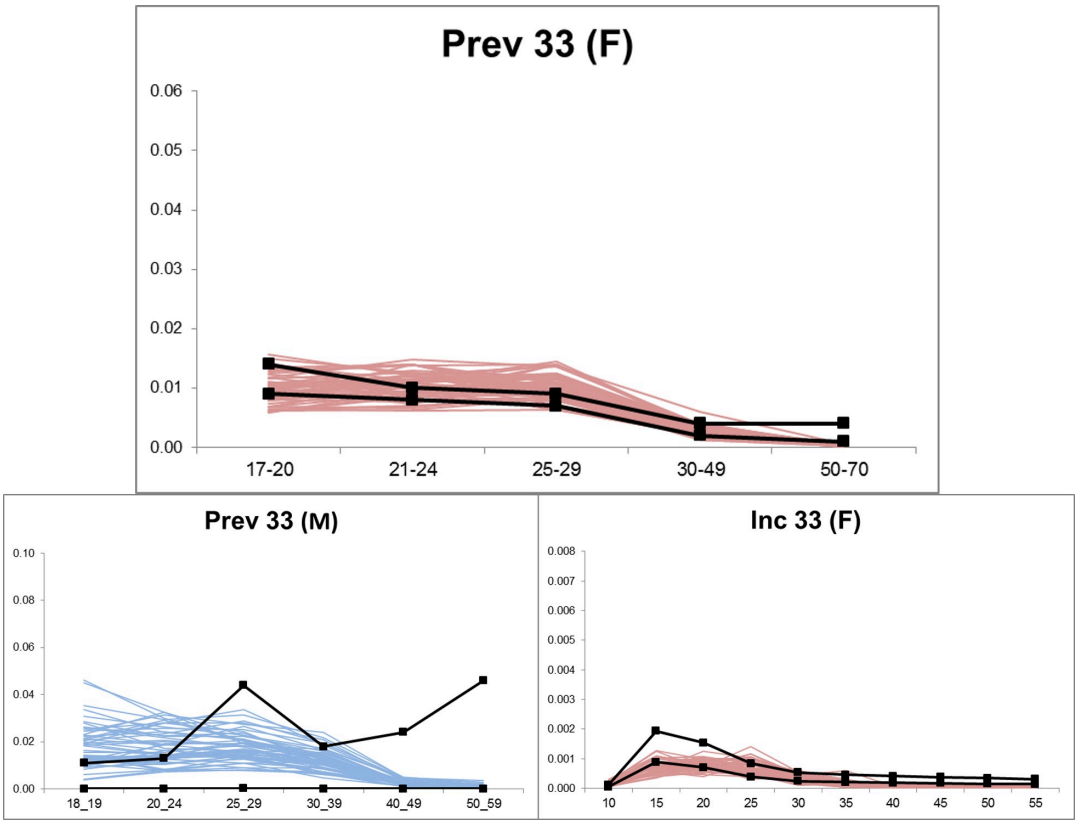
HPV-18:



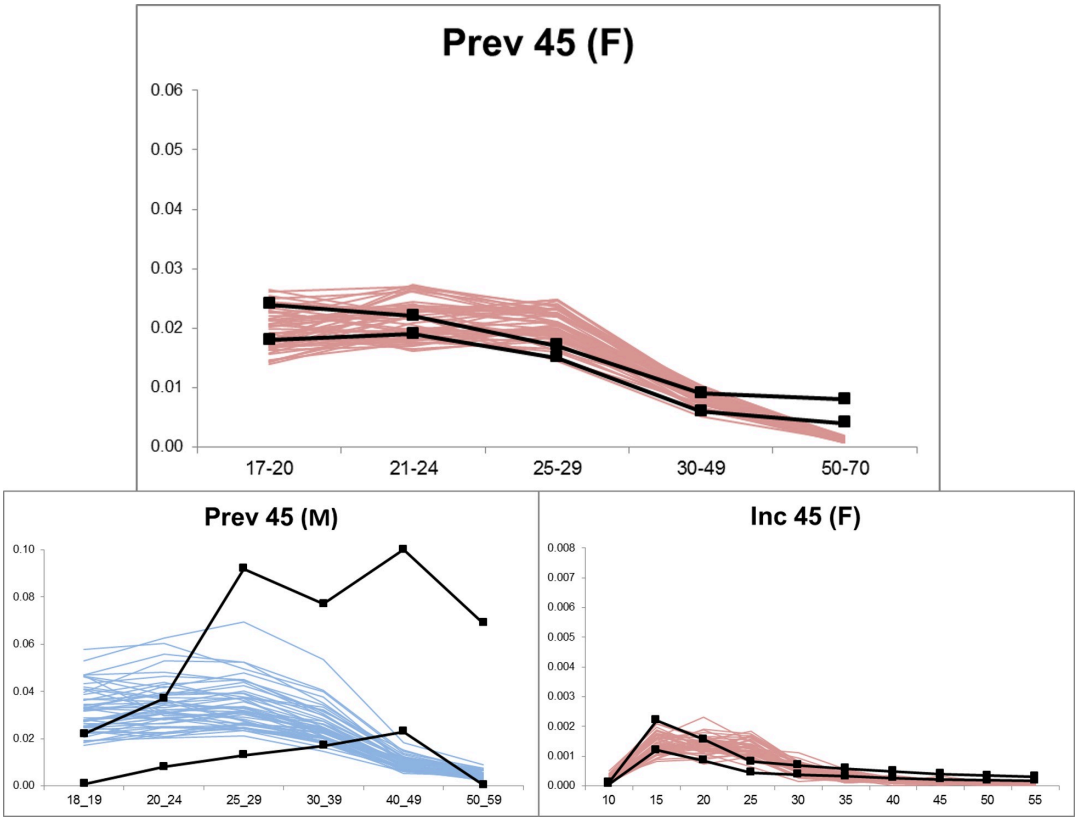
HPV-31:



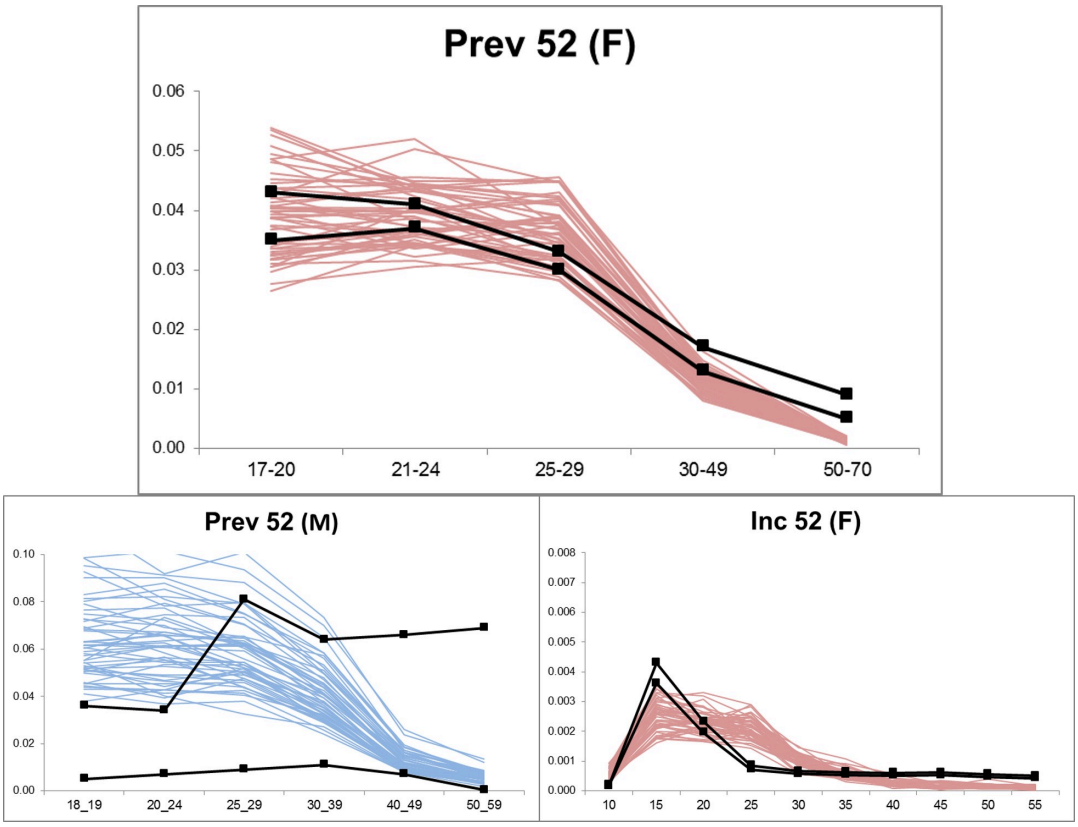
HPV-33:



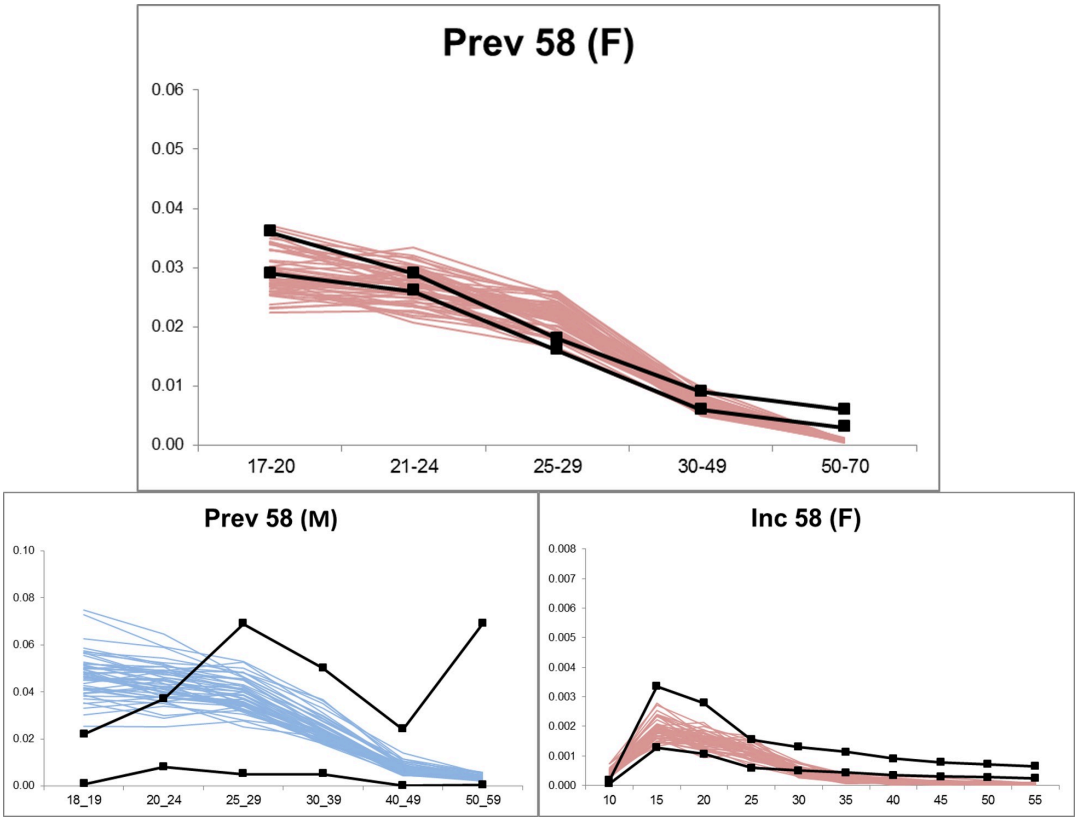
HPV-45:



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.

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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.

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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.

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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.

University of Sydney
Version: 1.0.00
Released: 2025-09-30

POLICY1-CERVIX: Model Profile

University of Sydney

Contact

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Funding

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Suggested Citation

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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

University of Sydney
Readers Guide

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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.

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

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

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

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Model Purpose

Purpose

The model platform known as '*Policy1-Cervix*' was developed to address several questions related to cervical cancer. *Policy1-Cervix* has been used for a number of evaluations of cervical cancer interventions, such as cost-effectiveness of HPV vaccination, and evaluation of cervical screening technology, intervals, and management. The *Policy1-Cervix* model was one of three models used by the WHO Cervical Cancer Elimination Modeling Consortium (CCEMC) to evaluate the impact of cervical cancer elimination targets in 78 LMIC and was reviewed and endorsed by the WHO Advisory Committee on Immunization and Vaccines-related Implementation Research (IVIR-AC) for the use in CCEMC modelling of elimination for WHO.[1,2] *Policy1-Cervix* was also used to predict the timeline to elimination of cervical cancer for 181 countries,[3] for USA,[4] and Australia.[5] It has been used for a range of government-commissioned studies on behalf of national cervical screening programs in Australia, New Zealand, the United Kingdom and Ireland. Some specific examples of this include: the effectiveness modelling and economic evaluation of cervical screening for both unvaccinated cohorts and cohorts offered vaccination, as part of the Renewal of the cervical screening program in Australia,[6] as well as similar screening policy evaluations for New-Zealand[7] and England.[8] It has also been used to provide estimates of resource utilization and disease impacts during the transition from cytology to HPV screening in Australia and New Zealand,[9-11]to inform clinical management guidelines in Australia[12] and evaluate the impact of adopting self-collected HPV testing in Australia.[13] It has previously been extensively validated and used to evaluate changes to the screening interval in Australia and the United Kingdom,[8,14]the role of alternative technologies for screening in Australia, New Zealand and England,[8,15,16,17]the role of HPV testing for the follow-up management of women treated for cervical abnormalities,[18] the cost-effectiveness of alternative screening strategies and combined screening and vaccination approaches in China,[19,20]the impact of HPV vaccine hesitancy in Japan[21] and the cost-effectiveness of primary HPV testing and the potential for elimination in Malaysia.[22] The model has also been used to evaluate the impact of HPV vaccination[23] and the incremental impact of vaccinating males in Australia,[24,25]the impact of the nonavalent HPV vaccine on optimal cervical screening in four developed countries[25] and to assess the cost-effectiveness of the nonavalent HPV vaccine in Australia.[26] Predictions from the dynamic HPV transmission and vaccination model have also been validated against observed declines in HPV prevalence in women aged 18-24 years after the introduction of the quadrivalent vaccine.[27] The *Policy1-Cervix* model was used to predict outcomes for different screening strategies across all 78 LMICs to support the 2021 update of WHO cervical cancer screening guidelines for the general population,[28] as well as for women living with HIV.[29] *Policy1-Cervix* has been used for several analyses in the USA. Some examples include assessing the cost-effectiveness of HPV vaccination for adults aged 30-45 years,[30] estimating cancer risk in females eligible to exit screening,[31] and examining disparities in cervical cancer elimination timing.[32] *Policy1-Cervix* was used to estimate the impact of COVID-19 related disruptions to screening and diagnosis on cervical cancer incidence,[33,34]as well as disruptions to HPV vaccination.[35]

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Model Overview

Summary

This section provides an overview of the *Policy1-Cervix* model. The model consists of four core components:

1. Dynamic HPV transmission and vaccination
2. Cervical carcinogenesis
3. Screening and treatment
4. Cancer treatment and survival

A summary of each component is provided below, and these components will continue to be referred to throughout this document.

Background

Dynamic HPV transmission and vaccination

Heterosexual behavior is modeled by stratifying the population by sex, age, and level of sexual activity (i.e., four sexual activity groups) using data from national behavioral surveys of sexual behavior. The model has been extended to include semi-assortative and age-and sex-specific mixing parameters; a revised sexual mixing matrix; the capacity to vary the annual per-partner transmission probability according to HPV type, sex, and sexual activity group; and the ability to capture the effects of more rapid change in behavior (by single year of age) during adolescence and early adulthood. There is capacity to simulate alternative assumptions for the duration of naturally-conferred type-specific immunity against HPV infection and its waning. A multi-type structure is used, and women can become infected with eight possible HPV type groups: HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58 and other Hr-HPV types grouped.

The dynamic model simulates vaccination uptake by single year of age, sex, and chronological time. Vaccination of older females (and males) in catch-up programs, if applicable, is modeled by single year of age, taking into account the potential for prior HPV type-specific exposure and its impact on type-specific vaccination efficacy at different ages. Male vaccination uptake is also modeled to account for incremental herd immunity effects in females. The model allows varying vaccine properties (e.g., efficacy, waning).

Cervical carcinogenesis

This component takes cohort- and type-specific HPV incidence from the dynamic model as input and involves a complex multi-cohort microsimulation implementation of the natural history of cervical pre-cancer. Progression and regression between states representing HPV infection, CIN1, 2 and 3 (due to particular HPV types or groups) are modeled, as is progression from CIN3 to invasive cervical cancer. The model accounts for age-specific hysterectomy rates (for any reason) in the population.

Screening and treatment

The sensitivity and specificity of cytology are setting-specific and fitted to local data (e.g., on the distribution of cytology test results, cytology-histology correlations) in a particular setting. Fitted test characteristics are constrained to be consistent with findings from international meta-analyses which report the absolute and relative sensitivity and specificity of cytology and HPV testing. Detailed analysis of registry data on the age at which young women first initiate screening is performed, and for all ages rates of return to screening or follow-up management over a multi-year period is simulated, according to last screening test result, the follow-up recommendation and age. Post-treatment natural history and recurrent disease following treatment for CIN are based on a review of the literature on outcomes after pre-cancer treatment. A separate model has been developed for estimating adverse reproductive outcomes in the population given alternative screening strategies and associated CIN excisional treatment rates by age.

Cancer treatment and survival

Cancer staging and progression is modeled, accounting for symptomatic detection and the possibility of downstaging at diagnosis due to screening. Predictions for age-specific cervical cancer incidence and mortality have been calibrated to observed rates in unscreened populations. The model is then additionally validated against country-specific registry data for incidence and mortality, when run with an overlay of screening according to country-specific guidelines. The stage and interval-specific cancer survival parameters are based on analysis of data from cancer registries and validated against observed data.

Assumption Overview

Summary

This section outlines the key assumptions made in the *Policy1-Cervix* model and will provide justification for assumptions as appropriate.

Background

The model assumptions are informed from the literature, and updated regularly. When data is not available from the literature, expert opinion is sought.

Assumption Listing

Dynamic HPV Transmission

We assume men and women fall within 4 possible sexual behaviour groups, and if one partner is infected with HPV, each heterosexual partnership has a chance to transmit the virus. Viral clearance and progression are also modeled.

Vaccine duration is an input parameter and can be lifelong or waning. Predictions from the dynamic HPV transmission and vaccination model have also been validated against observed declines in HPV prevalence in women aged 18-24 years after the introduction of the quadrivalent vaccine.

Cervical carcinogenesis

We consider lesions and cervical cancers are caused by HPV and do not model precancer lesions that arise in the absence of the virus (as these lesions do not progress to cancer). Woman can be uninfected, infected with HPV (with two states for productive infection, labelled HPV and CIN1), or CIN2, CIN3 or invasive cancer. Women can have multiple infections and multiple lesions associated with different infections. We consider eight HPV type-groups, including HPV 16, 18, 31, 33, 45, 52, 58 and other high-risk HPV types (as a pooled group), and progression and regression rates are modelled as a function of HPV type/ group and age. The HPV types/groups modelled are assumed to be independent and simultaneous (i.e. a female can have one infection per type/group but an infection of one type/group does not impact the incidence or transition rates of another type/group). We also assume that health states can transition from any CIN/infected state to a state that is within a distance of two states away with the exception of cervical cancer which can only be accessed from the CIN3 state.

Screening and treatment

We assume that screening test results are based on a woman's true underlying health state, including any underlying HPV type. Women who undergo precancer treatment have a small chance of treatment failure; for developed settings, we simulate near-term follow-up with successful re-treatment. We assume that the subgroup of women who have a CIN2/3 lesion identified are at somewhat higher risk of cervical precancer and cancer (even after treatment) for the remainder of their lives.

Cancer treatment and survival

Women who progress to cancer will initially progress to localized cancer and, until cancer is detected, stage progression may occur and is a function of age. Cancer survival is a function of stage at diagnosis and time since diagnosis and is assumed to be better for women who had cancer detected through screening rather than symptomatic presentation. We have also previously validated our model against observations of the proportion of cancers that are localized, regional and distant at the time of diagnosis, by age, in a well-screened setting.

University of Sydney
Parameter Overview

THE UNIVERSITY OF SYDNEY

Parameter Overview

Summary

This document describes the parameters used to inform the *Policy1-Cervix* model.

Background

The model assumptions are informed from the literature and are updated regularly. When data is not available from the literature, expert opinion is sought, and differing parameter values are explored to identify the impact of the unknown parameter values on key outcomes. When an evaluation is performed, extensive sensitivity analysis is performed to capture uncertainties in parameter values.

In this section, the parameters for *Policy1-Cervix* are outlined for each of the four core components. The parameters in the *Policy1-Cervix* model also fall under three general classifications: 1) Input Parameters, 2) Calibrated Parameters, and 3) Calibration Targets. Input parameters use available data from literature or external analysis that can be incorporated into the model, e.g. life tables. Calibrated parameters are obtained through the calibration process and provide the best fit to the calibration targets, e.g. health state transition rates. Calibration targets are used in the calibration process but are not directly required to operate the model, e.g. HPV prevalence.

Parameter Listing Overview

Dynamic HPV transmission and vaccination component

- We assume a median age of sexual debut of 16-17 for females and males, and a median lifetime number of sexual partners of 4 in females and 7 in males, with these numbers informed from sexual behavior data from Australia (ASHR). Age of sexual debut and lifetime number of sexual partners were reviewed for the USA and found to be similar to Australia.
- Vaccine efficacy rates are based on published trial data and coverage by age and year is based on local reported coverage rates specific to a setting.

Cervical carcinogenesis component

- Life tables, by age (Input parameter – Berkeley Life Table)
- Hysterectomy rates, by age (Input parameter – NHDS/Doll/SASD)
- HPV incidence rates, by age (Output of HPV Transmission component)
- Disease state transition rates, by age (Calibrated parameters)
- Cancer stage progression rates, by age (Calibrated parameters)
- Symptomatic cancer detection rates, by age and stage (Calibrated parameters)
- HPV prevalence, by age and type (Calibration target – New Mexico HPV Pap Registry)
- HPV type distribution in CIN1, 2 and 3 (Calibration target – New Mexico HPV Pap Registry)
- HPV type distribution in cancer (Calibration target – Saiyara published data)

Screening and treatment component

- Test Positive Matrices (TPMs) are from published test performance data for USA for HPV and cytology testing.
- Screening initiation, routine attendance, and follow-up attendance rates (Input parameter – NMHPVPR/KPNC)
- Treatment failure rates (Input parameter – English NHS)

Cancer treatment and survival component

- The model is calibrated to cancer incidence in an unscreened population, by age (Calibration target – cancer incidence across 22 unscreened settings from IARC)
- Cancer survival by stage and time since diagnosis (based on SEER data on survival)

Component Overview

Summary

This document describes how the separate components of *Policy1-Cervix* link together to create a cohesive model.

Overview

The *Policy1 Cervix* model has four core components: dynamic HPV transmission and vaccination, cervical carcinogenesis, screening and treatment, and cancer treatment and survival. All four components work in conjunction to produce evaluations of cervical cancer prevention strategies.

Component Listing

Dynamic HPV transmission and vaccination

This component can be operated independently of the other core components. Its primary purpose is to provide the HPV incidence parameters used by the cervical carcinogenesis component. The dynamic HPV transmission component incorporates vaccination parameters, such as efficacy and duration, and outputs the resulting relative reduction of HPV incidence by age and HPV type. These relative reduction outputs are applied to the setting-calibrated HPV incidence parameters and fed into the cervical carcinogenesis model.

Cervical carcinogenesis

The predicted rate of new infections output from the dynamic HPV transmission and vaccination component feed into the cervical carcinogenesis component. This component operates in conjunction with the screening and treatment component, which is essentially an overlay onto the cervical carcinogenesis component. These two components operate simultaneously and directly feed back into each other. Screening outcomes depend on progression along the cervical carcinogenesis pathway, and treatment will alter the course of the cervical carcinogenesis pathway.

Screening and treatment

This component captures detailed screening pathways management and overlays the cervical carcinogenesis component, as described above.

Cancer treatment and survival

This component is directly linked to the cervical carcinogenesis component. Upon transition from preclinical cancer to clinical cancer, the cervical carcinogenesis component ceases to operate and the cancer treatment and survival component commences.

Output Overview

Summary

This document describes the outputs produced by *Policy1-Cervix*.

Overview

Policy1-Cervix produces outputs that can be generally categorised into one of three groups: calibration outputs, validation outputs, and predictive outcomes. Calibration outputs are used by a calibration algorithm to achieve a 'best fit' with target data, by varying calibrated input parameters based on this fitting algorithm. Validation outputs are compared to observed data but aren't considered in the calibration algorithm. Input parameters aren't changed to match these targets; these validation targets are instead used as a flag to highlight issues with the model. Predictive outcomes are the outputs that are used for evaluation of cervix cancer interventions. These outcomes are also used in comparing different models and seeing the effects of different assumptions on how the underlying model operates.

Output Listing

Calibration Outputs

- HPV prevalence by HPV type (16/18/31/33/35/52/58/OHR): age based, recorded in yearly intervals, includes CIN lesions as well as HPV
- Cancer incidence: recorded upon detection of underlying cancer either through symptoms or screen detection
- HPV type distribution in cancer: age based, recorded in yearly intervals, the proportion of total cancer incidence made up by each type of HPV infection
- HPV type distribution in CIN: age based, recorded in yearly intervals, the proportion of total cancer incidence made up by each type of HPV infection

Validation Outputs

- Cancer mortality
- Hysterectomy incidence and prevalence
- Screening tests: cytology tests, HPV tests, colposcopies
- Screening outcomes: histologically-confirmed high grade/low grade abnormalities
- 5-year risk of CIN3+ by cytology test result

Predictive Outcomes

- Health state dwell times of cancer-causing HPV infections
- Health outcomes: life years, cancer cases, cancer deaths
- Resource outcomes: screening tests, colposcopies, pre-cancer treatments
- Health economic outcomes: costs, quality adjusted life years (QALYs), cost-effectiveness of cervical cancer interventions.

Results Overview

Summary

This document describes the results produced by *Policy1-Cervix*.

Overview

Policy1-Cervix has produced results used for several evaluations of cervical cancer interventions, such as the impact of HPV vaccination, evaluation of cervical screening technology, intervals, and management, and modelling around cervical cancer elimination timing and planning.

Results List

Cervical cancer elimination modelling

- Impact of elimination targets in 78 LMIC. [1,2]
- Timeline to elimination for 181 countries, Australia and the USA. [3-5]
- Disparities in elimination timing in the USA. [6]
- Potential for elimination in Malaysia. [7]

Evaluations of cervical screening

- Effectiveness of HPV screening in Australia, New Zealand, England and China, [8-12]including in follow-up management after treatment for cervical abnormalities in Australia. [13]
- Resource utilization and health impacts during transition from cytology to HPV screening in Australia and New Zealand. [14-16]
- Informing clinical management guidelines in Australia. [17]
- Impact of changes to the screening interval in Australia and the United Kingdom. [10,18]
- Impact of adoption of self-collected HPV testing in Australia. [19]
- The role of alternative technologies for screening in Australia, New Zealand and England. [10,20,21,22]
- Estimating cancer risk when exiting screening in the USA. [23]
- Impact of disruptions to screening due to COVID-19 in Australia and the USA. [24,25]
- Cost-effectiveness of screening strategies in 78 LMICs. [26,27]

Evaluations of HPV vaccination

- Impact of HPV vaccination in Australia. [28]
- Incremental impact of male HPV vaccination in Australia. [29,30]
- Impact of vaccine hesitancy in Japan. [31]
- Cost-effectiveness of vaccination in Australia [32], and for adults aged 30-45 years in the USA. [33]
- Optimal screening in the context of HPV vaccination in Australia, New Zealand, England and the USA. [30]
- Impact of disruptions to HPV vaccination due to COVID-19 in Australia. [34]

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The hybrid microsimulation model STDSIM-MISCAN-Cervix: Model Profile

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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

Erasmus MC
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.

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

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

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

Output Overview
Definitions and methodologies for the basic model outputs.

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

Model Purpose

Summary

This document describes the primary purpose of the model.

Purpose

Despite successful cervical cancer screening in the United States (US), over 12,000 women develop and 4,000 women die from cervical cancer each year (1). New technologies, including screening tests and vaccines against human papillomavirus (HPV), a sexually-transmitted virus known to cause cervical cancer, are dramatically changing the landscape of cervical cancer control in the US and worldwide. The STDSIM/MISCAN-CERVIX modeling approach combines a microsimulation model (STDSIM) to simulate the transmission of HPV and vaccination with the microsimulation model (MISCAN) to simulate the natural history of cervical carcinogenesis and screening. The STDSIM microsimulation model was originally developed for decision support in STD control. MISCAN-CERVIX was originally developed to model the natural history of cervical disease and to evaluate screening of disease. The model produces output on the effects of HPV vaccination and screening procedures, morbidity and mortality, which can be used to explain and predict trends in cervical cancer incidence and mortality, and to quantify the effects of primary and secondary prevention.

Three main aims of the STDSIM/MISCAN-CERVIX model are defined as follows:

1. to evaluate the harms, benefits and costs of cervical cancer prevention strategies, including HPV vaccination and screening.
2. to identify the most efficient and cost-effective cervical cancer control strategies, taking into consideration new and forthcoming technologies for the overall population and high-risk subgroups
3. to integrate findings of MISCAN-CERVIX and STDSIM (a stochastic microsimulation model for the transmission of HPV) in order to identify the most cost-effective cervical cancer control strategies in women.

Model Overview

Age-specific HPV incidence is estimated by STDSIM, which is a stochastic microsimulation model which has been extensively used to model the heterosexual transmission and control of sexually transmitted infections (STIs) (8-11). By using the age-specific HPV incidence over time estimated by STDSIM as input for MISCAN-Cervix, both the direct and indirect effects of vaccination can be incorporated in the evaluation of screening and the impact of vaccination on cervical disease.

STDSIM

Summary

STDSIM simulates the life course of individuals in a dynamic population, in which they interact through a dynamic network of sexual relationships. Each individual has its own characteristics that are either constant (e.g., date of birth, sex) or subject to change (e.g., number of sexual partners, infection status). All events are determined by probability distributions and can lead to new events (e.g., birth leads to a future event of becoming sexually active) or a cancellation of future events (e.g., death cancels all scheduled events concerning sexual activity or STI transmission for this person and to or from his/her partner).

Purpose

Using STDSIM, we can estimate the impact of HPV vaccination strategies on HPV incidence and prevalence over time. The model captures both the direct and indirect (i.e. herd immunity) effects of vaccination.

Model Description

The model consists of four modules: demography, sexual behavior, transmission and natural history, and interventions. The demography module implements the processes of birth, death, and migration. Processes for initiation and dissolution of sexual relationships, for mixing according to age preference, for sexual contacts within relationships and for sexual contacts between clients and sex workers are defined in the sexual behavior module. In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and other simulated STIs. Finally, the interventions module specifies the timing and effectiveness of (multiple) control measures in curbing transmission or enhancing survival.

Demography

Demographic processes that result in a dynamic population of individuals in STDSIM comprise of: 1) birth; 2) mortality; and 3) migration (figure 1). Births are assigned randomly to sexually active women between the ages 15 and 49, and the probability of having a child depends on the age of the women. At birth, the age at (non-HIV) death of each individual is drawn from pre-defined, sex-specific survival curves. Finally, individuals are removed from the population through age and sex specific emigration probabilities. Clones of existing people in the population can migrate into the population at age- and sex specific rates.

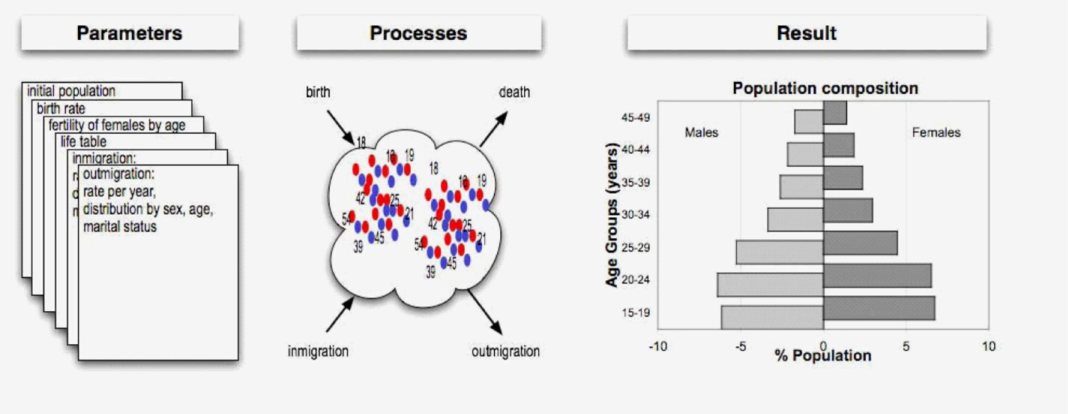

Figure 1. Demographic mechanisms in STDSIM

Sexual behavior

The model contains three types of sexual relationships: steady relationships, casual relationships, and once-offcontacts . The formation of partnerships occurs according to a supply- and demand-based mechanism. People become available for a sexual relationship at an age of sexual debut, which is randomly drawn at birth from a uniform distribution. Each time the partnership status of a person changes (e.g. a partnership is formed or ended), a new duration until the person becomes available for a new relationship (time until availability) is drawn from a predefined exponential distribution with μ being the mean time until availability defined as: $\mu = \tau_{\sim s,r\sim} / (r_{\sim s,a\sim} \times p)$, with:

- $\tau_{\sim s,r\sim}$ = time interval by person's sex (s) and relationship status (r)
- $r_{\sim s,a\sim}$= specific partner change factor by sex (s) and age (a)
- p = personal partner change level

The personal partner change factor (p) reflects the heterogeneity in the tendency to form partnerships between individuals, and is given by a gamma distribution with an average value (pm) of 1.0, and a situation specific shape parameter.

The duration of the availability period of an individual is given by an exponential distribution, with mean time to find (κ) defined as: $\delta / (r_{\sim s,a\sim} \times p)$, where the δ is an average duration of the availability period [2]. $R_{\sim s,a\sim}$ and p are explained above. When a person is available for a new relationship, he/she can be selected by an individual of the opposite sex who has ended his/her availability period. If a person is not selected at the end of the availability period, he/she will select a partner from the pool of available persons of the opposite sex.

The type of relationship (steady or casual) that is formed when a partner is selected depends on the age of the male partner, and is defined as a probability of a steady relationship. The probability of a new relationship being a casual relationship is given by 1 – probability of a steady relationship. A relationship starts with a sexual contact. After each contact, the time until a new sexual contact within the relationship is drawn from an exponential distribution with a mean frequency of sexual contact depending on relationship type and the age of the male partner. Finally, the duration of a new relationship is drawn from an exponential distribution, where the average relationship duration is depends on the relationship type.

Partner selection at the end of the time to find is guided through an age preference matrix, which defines the probability of selecting a partner from a certain age class. When there is no partner available in the preferred age class, immediate re-sampling is done of a new preferred age-class using the remaining age groups with a probability larger than 0.0. If no partner can be found in any of the age-classes, a new time to find is drawn from the above described equation. Probabilities in the age-preference matrix are chosen to have men prefer slightly younger women. The above described mechanisms of partnership formation result in a dynamic sexual network in the population (figure 2)

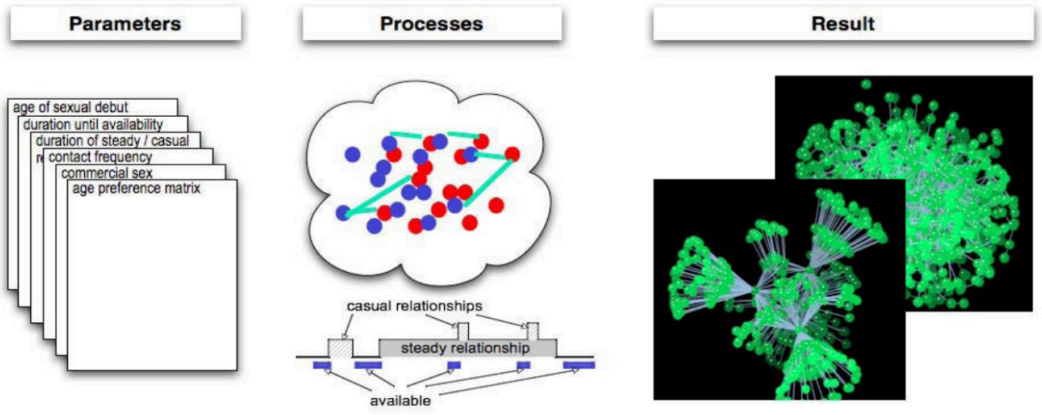

Figure 2 Mechanisms of sexual behavior in STDSIM create a dynamic sexual network

In the model, individuals can also have once-off sexual contacts. The mechanism was originally developed to simulate commercial sex, and works as follows: male clients can visit female sex workers (FSW). A male's frequency of FSW visit is determined by defining frequency classes (e.g. 0, 1, and 12 times per year [9]). For each class, the proportion of men with and without a steady relationship falling in that category can be specified. A personal sex-worker-visiting propensity (ranging from 0 to 1, assigned to each male at birth) determines which individual males are assigned to which frequency classes. At sexual debut and at each FSW visit, the next FSW visit is scheduled according to an exponential distribution with the mean duration until next visit based on the FSW visit frequency of the individual.

The number of FSWs in the model results from the male demand. New FSWs are recruited from sexually active females with a defined age range. The number of available FSWs and their predefined number of clients per week is checked each year and matched with the number of visitors. If the number of FSWs is too low, new FSWs are recruited. If the number is too high, a random selection terminates their career. FSWs are always part of the general population, which means that they are also part of the general sexual network and can form partnerships. Once the career of the FSW is terminated, her participation in the network through relationship formation continues until she either migrates out or dies.

We adapted this mechanism so that it captures once-off contacts in high-income settings, by recalibrating the male tendencies and female frequencies so that it reproduced data on once-off contacts (i.e. one-night stands) in The Netherlands.

Transmission and natural history

The transmission and natural history module specifies the duration, per-act transmission probabilities, and immune responses after infection clearance of the different diseases and/or disease stages for (figure 2.3). We simulate four distinct HPV types: HPV16, HPV18, a combined type representing the other five high-risk nonavalent types (HPVh5: HPV31, 33, 45, 52, and 58), and a combined type representing the other high risk types (HPVoHR). Individuals can become infected when having an unprotected sexual contact with an infected partner. Transmission probabilities are described using a single parameter (per act transmission probability). Upon infection, the duration of the infection is drawn from a weibull distribution. Upon infection clearance, each individual develops immunity, which wanes after a duration drawn from a weibull distribution.

Interventions

HPV vaccination results in the protection against the acquisition of vaccine sensitive HPV types. The efficacy can be specified and follows a take approach (e.g. at 95% efficacy, 95% will have full protection and 5% will have no protection). In addition, efficacy can be specified for specific HPV types, so that e.g. lower-level cross-protection to other high-risk types in response to bivalent or nonavalent vaccines can be implemented. Vaccines can be targeted at both girls and boys, at different ages and coverage levels over time. Waning of vaccine efficacy can also be specified, operationalized as a duration until vaccine induced protection ends. Vaccination while being infected with HPV does not affect the clearance of the infection, but does result in vaccine-level protection for subsequent infection after clearance.

MISCAN-CERVIX

Summary

The MISCAN-Cervix model, first developed in 1985, is a micro-simulation model in which individuals are simulated successively and independently of each other (2-3). In MISCAN, a comparison is made between the situation with and without screening. The model consists of three main parts:

1. demography
2. natural history
3. screening

Based on assumptions on trends in demography, natural history, treatment, screening dissemination and impact of screening MISCAN-Cervix projects cancer incidence and mortality by stage, age and calendar year.

Purpose

The MISCAN simulation program was developed at the Department of Public Health, Erasmus University Rotterdam, The Netherlands, and has been used to evaluate breast, cervix, colon, prostate, lungs and esophageal cancer screening programs (2-6). Using the MISCAN-CERVIX model, we can simulate how HPV infections / lesions develop in individuals, how they might lead to cervical cancer, up to the moment when an individual eventually dies: from cervical cancer or from another cause of death. The results derived from the model can be used to evaluate the long-term effectiveness and cost-effectiveness of various early detection and prevention strategies for cervical cancer.

Background

MISCAN-CERVIX reproduces the US female population and by using demographic and epidemiologic data obtained from SEER database. The model simulates the disease process and the impact of screening strategies. It will provide opportunities to disseminate findings and improve transparency, understanding, and confidence in model-based analyses of cervical cancer control strategies.

Model Description

Figure 1 shows the structure of MISCAN-CERVIX. In the static MISCAN model, acquired HPV infection (four categories HPV16, HPV18, 5 HPV types included in the 9-valent vaccine types such as 31/33/45/52/58 and all other high-risk types excluding three last categories mentioned) can progress to pre-invasive cervical intraepithelial neoplasia (CIN). The progression of cervical disease is subdivided into seven sequential stages: three pre-invasive stages (CIN grade 1, 2 and 3), and four invasive stages: microinvasive (FIGO IA), local (FIGO IB), regional (FIGO II/III) and distant (FIGO IV). Cancer may be detected clinically (stages IB, II/III and IV) or through screening (all stages). In the model, most HPV infections will clear without ever resulting in neoplasia, and lesions in pre-invasive stages can regress spontaneously (7). CIN grades 1 and 2 can also develop in the absence of a high-risk HPV infection; these lesions will never progress to cancer. CIN grade 3 and cancer can only develop if a high-risk HPV infection is present.

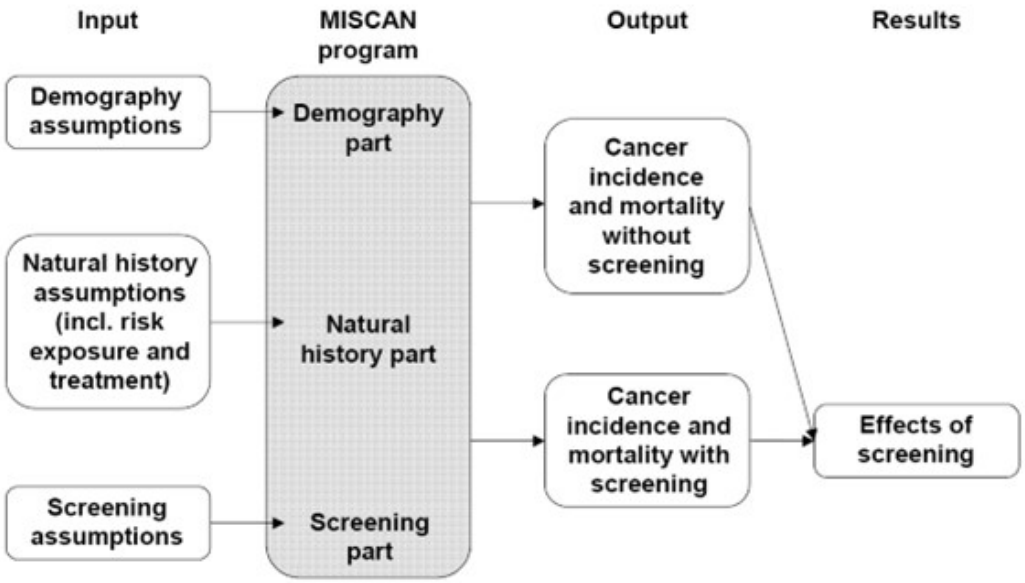

Figure 3: Basic structure of MISCAN-CERVIX

Figure 3 shows that the model consists of the following three parts: 1. demography, 2. natural history, 3. screening

Demography

MISCAN-Cervix model generates a simulated population, which corresponds with the 1963 US birth cohort. General characteristics of the simulated population (i.e. those not related to the disease) are based on demographic and hysterectomy data; mortality from other causes was estimated using the observed age-specific mortality in the United States.

For each woman, a time of death from other causes (i.e. causes other than cervical cancer) is generated; this time of death is independent of the cervical cancer disease. In the model, a woman's lifetime cannot exceed 100 years. The time of death from other causes is generated using a life table for women from SEER US cohort 2000. The assumed hysterectomy rates vary by age. These rates are based on hysterectomy incidence data such as single year of age data available from to 1998-2009 (NHDS) and age grouped data available (NHDS & NIS).
Rates were scaled to adjust for outpatient procedures for 2000-2009 using literature (Doll and SASD).

Natural history

During her lifetime, each woman has an age-specific risk of acquiring high-risk HPV infections (i.e. an infection caused by an HPV type that can cause cancer and that can be detected by the HPV test) and CIN lesions without a (detectable) high-risk HPV infection. Most HPV infections clear or regress naturally, some HPV infections can progress to CIN 1, CIN 2, CIN 3, cervical cancer, and death from cervical cancer. Transitions from HPV infection to CIN and cancer are sequential.

The age-specific onsets of HPV infections that progress to cervical cancer were calibrated to the age-specific incidence of cervical cancer, which was obtained from the SEER database 2008-2012.The age-specific incidence of pre-invasive lesions that do not progress to cervical cancer was calibrated so that the simulated detection rates of CIN lesions fit the observed detection rates in the US (NMHPVRR, Kinney 2014, 2007-2011 data).

The incidence of high-risk HPV infections that do not progress to CIN was calibrated so that the simulated prevalence of all high-risk HPV infections fits the observed high-risk HPV prevalence (NMHPVPR, Wheeler 2013).

In MISCAN-Cervix different disease pathways are distinguished. Each instance of these disease pathways represents an HPV infection or a 'lesion' (i.e. CIN of a certain grade or a stage of cervical cancer). Each disease pathway starts as either an HPV infection (HPV16, HPV18, 9-valent vaccine HPV types and other high-risk HPV) or as an HPV negative CIN 1 lesion.

Screening

In the third part of the program, screening for cervical cancer is simulated. The life histories of women will be adjusted for the effects of screening. The screening part is simultaneously run with the natural history part of the model, making detection of CINs and cancers in different states possible. The aggregated changes in life history constitute the effectiveness of the screening.

When a screening test is applied, each infection or lesion prevalent at the time of screening has a probability of producing a positive test (i.e. the sensitivity). If a test result is positive, all prevalent CIN lesions are diagnosed and can be successfully removed/treated. The difference between the situation with and without screening is the screen effect.

In the model, detection of cervical cancer by screening prevents death from cervical cancer in some but not all cases. However, if death from cervical cancer is not prevented, the time of death from cervical cancer is not changed by screening.

Effectiveness as a complementary / additional part of the model

For each simulated woman who is alive, MISCAN-Cervix can determine the state [Normal, HPV infected, CIN (CIN 1, CIN 2, CIN 3), cervical cancer by stage (microinvasive, local, regional, distant+)]. A woman can have multiple HPV infections or CIN lesions at the same time. Her state is determined by the most severe disease stage present, using the order HPV infection, CIN 1, CIN 2, CIN 3, microinvasive cervical cancer, local cervical, regional cervical cancer and distant cervical cancer; if no HPV infection, CIN lesion, or cancer is present, the woman's state is Normal.

The model produces the number of life years spent in each state as well as the number of certain events (e.g. screenings and cervical cancer diagnoses) in a lifetime. For each of these events, the amount of quality-adjusted time lost can be presented. To calculate the total disutility of a screening scenario, a sum can be taken over all the numbers of events multiplied by their associated quality-adjusted time lost.

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Assumption Overview

STDSIM

Summary

Summarizes the assumptions used in the present version of the STDSIM model.

Background

The following outlines the assumptions made in the STDSIM model:

Assumption Listing

1. Demography assumptions
    - The model simulates a dynamic population. Children are born to sexually active women between age 15 and 49, at user specified age-specific fertility rates. At birth, the age of death us drawn from user defined life tables.
    - In the version used for simulating HPV transmission in the US, we ignore in- and out-migration.
2. Sexual behavior assumptions
    - At birth, individuals in the model are assigned an age of sexual debut, after which they become available for sexual relationships
    - The model only simulates heterosexual relationships
    - We assume three different types of relationships: casual (i.e. short duration partnerships), steady (i.e. long-term relationships resembling marriage), and once-off contacts.
    - Individuals in the model can have multiple overlapping relationships of different types.
    - The tendency to form new relationships is governed by the partner change rate parameter, assigned at birth and randomly drawn from a gamma distribution. This is a lifelong characteristic that does not change with age.
    - Age specific multipliers of the partner change rate parameter ensure that partner change rates follow age patterns observed in data
    - Once-off contacts are governed by a separate process, in which a proportion of the male and female population is assigned the propensity to engage in once-off contacts, at user specified frequencies. The proportions of men and women engaging in once-off contacts can differ based on relationship status (e.g. lower for those who are in a steady relationship)
3. Natural history assumptions
    - The model simulates 4 distinct HPV types: HPV16 and HPV18 as standalone types, and HPVh5 (31, 33, 45, 52, 58) and HPVoHR (35, 39, 56, 51, 59) as composite types.
    - Transmission of each type can occur during sexual contact between an infected and an uninfected individual in the model, and each type is modelled independently, so that co-infections with multiple types can occur.
    - Upon infection, the model draws a duration of infection from a user defined, type specific probability distribution
    - After infection clearance, a duration of immunity is drawn from a probability distribution.

4. Vaccination assumptions
    - Vaccinations can be given at user defined ages, either as a routine vaccination (given at birthday) or catch-up campaign (cross sectional distribution in defined age bracket)
    - Vaccination efficacy is modeled as a take approach, e.g. 95% are fully protected, and 5% are not
    - Cross-protection of the 4v and 2v vaccines is incorporated

MISCAN-cervix

Summary

Summarizes the assumptions used in the present version of the MISCAN-CERVIX model.

Background

The following outlines the assumptions made in the MISCAN-CERVIX model:

Assumption Listing

1. Demography assumptions
    - Multiple cohorts are simulated to describe the US population. The simulated individuals are born in different years and will die from cervical cancer or from other causes at different moments in time.
    - In the model, it is assumed that death from cervical cancer is independent from death from other causes. Whichever comes first determines the actual moment of death.
2. Natural history assumptions:

    Human papillomavirus

    - Each individual has an age-specific risk of acquiring hrHPV infections.
    - An individual can acquire multiple hrHPV infections during their lifetime, and these hrHPV infections may be present at the same time. The progression of these lesions are modelled independently, there is no interaction.
    - If vaccination is introduced, there will be an age-specific relative reduction of the age-specific risk of acquiring hrHPV infections, depending on the vaccination type and vaccination coverage.
    - Most hrHPV infections will clear naturally before progressing to CIN.
    - As described in the natural history section of the model overview, the model distinguishes four categories of hrHPV genotypes. The duration of hrHPV-infections and subsequent CIN lesions are assumed equal for all genotypes and independent of age. However, the progression probabilities from all pre-invasive health states are different between all genotypes and are dependent on age as well.
    - If an individual has a hysterectomy because of cervical cancer or for other reasons than cervical cancer, all cervical hrHPV infections are considered removed as well. No new hrHPV cervical infections can be acquired.

    Cervical Intraepithelial Neoplasia (CIN)

    - Most CIN1 lesions will develop from an hrHPV infection
    - Each individual has an age-specific risk of developing a CIN1 lesion in the absence of hrHPV.

- Progression probabilities for CIN lesions depend on lesion grade, age and hrHPV genotype. Most CIN1 lesions will clear before progression to CIN2. Those that progress to CIN2 will mostly clear before progression to CIN3. hrHPV-negative CIN3 will never progress to cancer.22
- If an individual has a hysterectomy because of cervical cancer or for other reasons than cervical cancer, all CIN lesions are considered removed as well. No new CIN lesions can be developed.

Cervical cancer development

- Cervical cancer can develop only following a hrHPV-positive CIN3 lesion.
- After the detection of cervical cancer, the individual has a hysterectomy. Therefore, we do not assume any possibility of having recurrent cervical cancer.
- Preclinical microinvasive cancer does not cause symptoms yet and will therefore never be clinically detected. Local preclinical cancers or higher stages can be detected clinically in the absence of screening or can progress to a higher cancer stage (Figure 4).
- Durations of the different cancer stages do not depend on age or genotype
- Once a lesion has become cancer, progression probabilities to higher cancer stages depend on age, but are equal across genotypes.
- Clinically detected cervical cancer can either be cured or cause cervical cancer death. The probability of dying from cervical cancer is dependent on the cancer stage and the age of the individual.
- If the individual is cured, they will stay in the cancer state until death from other causes. If the individual is not cured, they will die of cervical cancer within a maximum of 10 years after diagnosis.

Hysterectomy

- Individuals who do not have cervical cancer have an age-specific probability of getting a hysterectomy for reasons other than cervical cancer.
- A hysterectomy is assumed to remove all prevalent hrHPV cervical infections and CIN lesions.
- Individuals who have had a hysterectomy will no longer acquire new hrHPV infections or develop new CIN lesions and will no longer be invited for screening tests

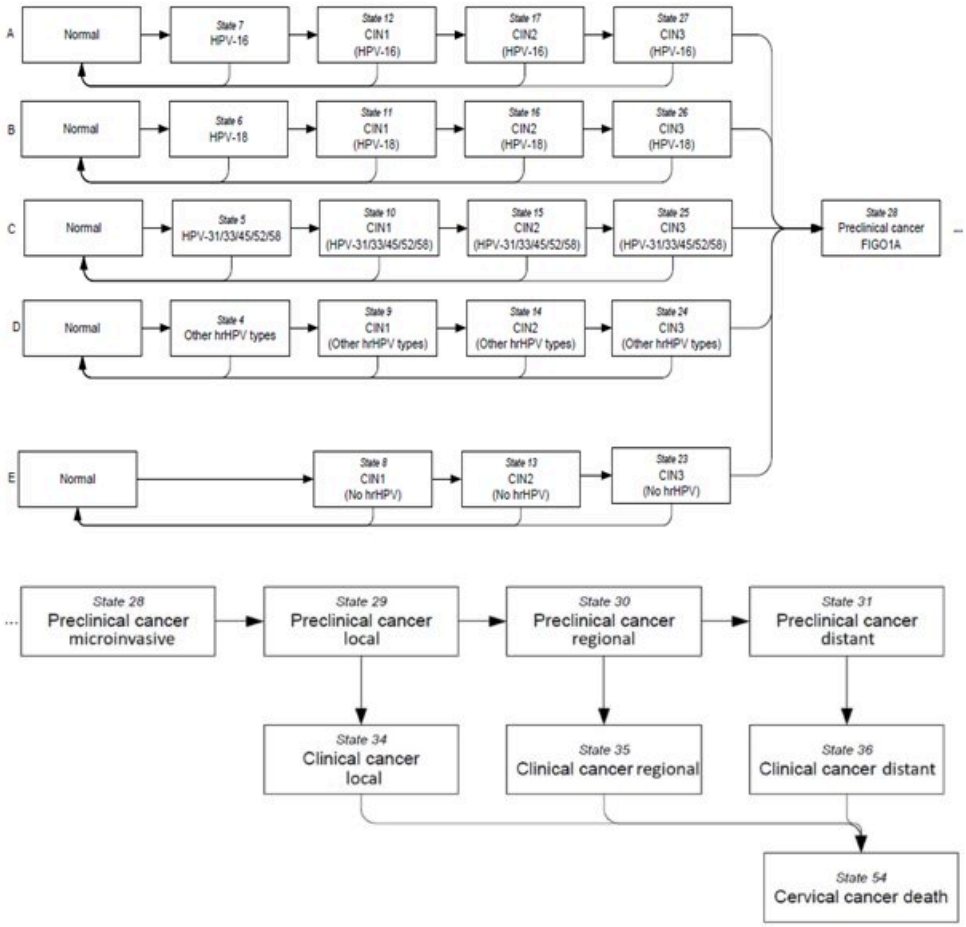

Figure 4. Schematic representation of the MISCAN-cervix model, with disease pathways A through F

Notes: All lesions start as either an HPV infection without CIN or as a CIN 1 lesion without HPV infection. Cleared/regressed denotes the absence of CIN and HPV infection; CIN 0 denotes the absence of CIN and cervical cancer. All cervical cancer states are HPV positive. The arrows between the states show which types of transitions can occur. In every state before death, a transition to "Other-cause death" can occur, and in every state before cancer, a transition to "Hysterectomy" can occur (connecting arrows not shown); in these cases, the transition applies to all HPV infections and CIN lesions of that person simultaneously.

3. Screening Assumptions

Performance of the screening test

- The probability of having a positive test result depends on the lesion grade and the hrHPV status of the individual for both cytology and the hrHPV-test.
- No differences in test characteristics are assumed for different hrHPV genotypes, both for cytology and the hrHPV-test.
- Systematic positive and systematic negative test results over time are possible for cytology for certain individuals, infections or lesions.

Screening behaviour

- Individuals are divided into different screening frequency intervals (i.e. every 1/2/3/5 years or never).
- If an individual attends the primary test and is referred to triage testing or colposcopy, he or she might not adhere to this referral.

Colposcopy

- When an individual is referred to colposcopy, all prevalent CIN lesions will be diagnosed and the individual will be referred to treatment if any CIN lesion is found.
- Colposcopy is 100% accurate and will show the highest prevalent lesion.
- Individuals with a prevalent hrHPV infection but without a prevalent CIN will not be referred to treatment. The hrHPV infection may still progress to CIN after the colposcopy.
- Early detection of cervical cancer by screening in the model may prevent death from cervical cancer. However, if the death from cervical cancer is not prevented, the duration until death from cervical cancer will not be different from clinically detected cancers.

Treatment

- When an individual is referred to treatment, all prevalent CIN lesions will removed/treated
- Treatment may not be fully effective.

Parameter Overview

STDSIM

Summary

Provides a complete overview of the parameters used to quantify the STDSIM model.

Background

The STDSIM model uses four types of parameters: demography parameters, sexual behavior parameters, natural history parameters, and vaccination parameters. Below, we only list the parameters that were varied to simulate HPV transmission in the US.

Parameter Listing Overview

1. Demography parameters
    - Fertility rates by age of female (in 5-year age brackets between 15 and 49 years)
    - Mortality due to all causes
    - Size of the starting population
2. Sexual behavior parameters
    - Age sexual debut
    - Multiplier of individual partner change rate index
    - Proportion of male population engaging in once-off contacts by contact frequency
    - Proportion of female population engaged in once-off contacts, by number of contacts per week
3. Natural History
    - Per-act transmission probability for each HPV type
    - Shape and mean of Weibull distribution for duration of each HPV type
    - Shape and mean of Weibull distribution for immunity for each HPV type
4. Vaccination parameters
    - Age(s) of routine vaccination
    - Age(s) of catch-up vaccination
    - Efficacy per HPV type and vaccine type
    - Coverage by gender (e.g. female only versus gender neutral), age, and calendar year

MISCAN-cervix

Summary

Provides a complete overview of the parameters used to quantify the MISCAN-CERVIX model.

Background

The MISCAN-CERVIX model uses four types of parameters: demography parameters, natural history parameters, screening parameters and output parameters.

Parameter Listing Overview

1. demography parameters

- Number of women to be simulated
- Proportion of the simulated population in each birth cohort
- For each birth cohort the calendar year(s) of birth
- For each birth cohort the proportion of women that are vaccinated
- For each birth cohort the age-specific probabilities to die of other causes than cervical cancer
- For each birth cohort the age-specific probabilities to have a hysterectomy

2. natural history parameters

- HPV16 onsets
- HPV18 onsets
- HPV hi-5 types onsets
- other high-risk HPV types onsets
- HPV- CIN1 onsets
- Transition probabilities of HPV infections to either clear or progress to CIN1 (by HPV-type and age)
- Progression/regression probabilities of CIN 1-3 lesions (by HPV-type and age)
- Transition probabilities of preclinical cancers to become clinical or a progress to a higher stage.
- Mean and shape of Weibull distribution for the duration of HPV infections that will clear before progressing to CIN1 (by HPV type)
- Mean and shape of Weibull distribution for the duration of HPV infection that will progress to CIN 1 (by HPV type)
- Mean and shape of Weibull distribution for the duration of CIN lesions that will progress (by CIN grade and HPV type)
- Mean and shape of Weibull distribution for the duration of CIN lesions that will regress (by CIN grade and HPV type)
- Mean and shape of Weibull distribution for the duration of cancer (by stage)
- Survival probabilities and durations after clinical diagnosis of cancer.

3. screening test parameters

- parameters for the dissemination of screening
- sensitivity, specificity of different screening test
- parameters for survival after screen detected diagnosis
- surveillance and treatment assumptions after a positive test result

4. output parameters

- Ages for which events should be reported in the outputs
- Calendar years for which events should be reported in the outputs
- Ages for which durations should be reported in the outputs
- Calendar years for which durations should be reported in the outputs
- How modelled events should be aggregated

Categories

The above parameters can be divided into three categories:

- parameters that are directly estimated from available data
- parameters for which no data (or only limited data) are available
- parameters that will be varied to fit reference data

Table 1 shows which parameters belong to each of these categories.

Table 1: Classification of the parameters in the model

Parameters that can be calculated directly from available data	Parameters that are derived from literature	Parameters that will be varied to fit reference data (calibrated)
Birth table parameters Life table parameters Hysterectomy (organ removal) parameters Survival data	Duration distribution in preclinical states up to and including CIN2 Test sensitivity of HPV test	Onsets for HPV16, HPV18, HPV hi-5 and other high-risk HPV types Probability for an HPV infection to either progress to CIN or clear Probability for a CIN to either progress to the next CIN grade (or cancer for CIN3), or clear Probabilities for cancers to either progress to the next cancer stage or be clinically detected before that Test characteristics of cytology

The parameters are based on literature, expert opinion and SEER data.

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Component Overview

STDSIM

Summary

An overview of the major components in the STDSIM model.

Overview

There are five major components in STDSIM:

1. Population component which represents the simulated population
2. Sexual behavior component which describes the sexual behavior and mixing
3. Natural history component which describes the characteristics of HPV
4. Intervention component which describes HPV vaccination
5. Output component which describes the outputs used

Component Listing

1. Population component
    - The birth of new children
    - Mortality of the population
2. Sexual behavior component
    - Ages at sexual debut
    - Individual tendencies to form relationships
    - Age specific multipliers of tendencies to capture trends over age
    - Probabilities of steady versus casual relationships by age
    - Frequency of sexual contact by age and relationship type
    - Age preference of female and male population
    - Proportions and frequencies engaged in once-off contacts
    - Durations of relationships
3. Natural history component
    - Infection probabilities
    - Durations of HPV types
    - Immune response upon clearance of HPV types
4. Intervention component
    - Targeting of vaccination by age, year, and type
    - Efficacy of protection
5. Output component
    - Define which outputs are desired (prevalence, incidence, demography, and/or sexual behavior outputs, cross-sectional population level outputs or individual level outputs)

MISCAN-cervix

Summary

An overview of the major components in the MISCAN-CERVIX model.

Overview

These are the primary components in the MISCAN-CERVIX model:

1. Population component which represents the simulated population
2. Natural history component which describes the development of disease in the population
3. Screening component which describes the screening protocol(s), screening behavior and test characteristics
4. Output component which defines how the modelled events should be logged
5. Post calculations component to analyze the model results for the specific analysis

Component Listing

1. The population component consists of the following:
    - The size of the simulated population
    - The proportion of the simulated population in each birth cohort
    - The distribution of births over the birth years in each birth cohort
    - The vaccination coverage for each of those birth years
    - The life tables of each birth cohort (probability to die of other causes than cervical cancer)
    - The hysterectomy tables (lifetime probability of a hysterectomy and distribution over the ages)
2. The natural history component consists of the following:
    - The age-specific hazard rates to get an HPV infection (by HPV type, adjusted for vaccination effects from component 2)
    - The transition probabilities for each disease state (Figure 2) to either progress to the next stage, or to clear/regress/be clinically detected.
    - The durations of each transition (Weibull distribution with mean and shape)
    - The survival probabilities and durations of cancer by stage and age
3. The screening component consists of the following:
    - The test characteristics (sensitivity and specificity by disease state, which can be correlated with previous screening test results).
    - The screening protocol, including the primary test, triage/repeat tests, colposcopy (including treatment for high grade lesions) and surveillance after colposcopy
    - Screening behavior, including screening interval, adherence to each follow-up test(s), colposcopy and treatment
    - Effects of screen detection of cancer on survival
4. Output component consists of the following:
    - Definition of which events and/or durations should be logged and whether they should be logged on an aggregated level or individual level
5. The post calculations component consists of the following
    - Depending in the analysis this component performs calculations on the model outputs. This could for example be age-standardization of results or performing a cost-effectiveness analysis.

Output Overview

STDSIM

Summary

Describes the outputs generated by the STDSIM model

Overview

The STDSIM model provides output on demography, epidemiology, sexual behavior, and intervention uptake over time

Output Listing

1. Demography
    - Number of people in the population by age (5 year age brackets) and sex
2. Epidemiology
    - Number of people in each disease stage by age (5 year age brackets) and sex (prevalence) for each year
    - Disease state transitions at the individual level (incidence)
    - Stratified incidence and prevalence by vaccination status
3. Sexual behavior
    - Proportion of the population with 0,1,2 to 4 and 5 or more recent (last 12 months) partners by age and sex
    - Proportion of the population with 0, 1, 2 to 4, 5 to 9, or 10+ lifetime partners by age and sex
    - Number of people engaged in once-off contacts by age and sex
    - Number of once-off contacts over the past year by age and sex
4. Intervention uptake
    - Numbers of vaccines distributed by age, sex, and calendar year

MISCAN-cervix

Summary

Describes the outputs generated by the MISCAN-CERVIX model.

Overview

The MISCAN-CERVIX model simulates among others the Base Case outputs. In case the screening part is activated MISCAN-CERVIX also provides output on screening effects. It is also possible to consider quality of life. This also generates extra output.

Output Listing

The output component produces the final output of the model:

1. Base Case
    - Incidence counts by calendar year (1972-2071), stage and age in every year
    - Mortality counts by calendar year (1972-2071) and age in every year

- Population on January 1 of each calendar year (1972-2071) by age in five year age groups
- HPV infection prevalence by calendar year (1972-2071) and age in every year
- CIN 1, CIN 2 and CIN 3 prevalence by calendar year (1972-2071) and age in every year
- Cervical cancer prevalence counts by calendar year (1972-2071), stage, location and age in five year age groups

2. Screening

- Number of invitations for screen-tests, of screen-tests, diagnostic tests, surveillance and opportunistic screen tests for each year
- Number of positive and negative HPV test results (primary screening and surveillance) per HPV type (divided in HPV16, HPV18, HPV hi-5, HPV other high-risk types) and per year
- Number of positive and negative test results (primary screening and surveillance) per CIN state, HPV type and per year
- Number of positive and negative test results (primary screening and surveillance) per preclinical state and per year (preclinical FIGO 1A, 1B, 2 and 3)
  -Number of positive and negative test results (primary screening and surveillance) per clinical state and per year (clinical FIGO 1A, 1B, 2 and 3)
- Total number of life years, life years lost due to cancer, number of specific deaths and non-specific deaths
- Number of tests per calendar year both in screening and surveillance
- Number of life years gained due to screening by year of screening
- Interval cancers

3. Quality of life

- Total number of life years after screen-detected HPV infection for each type
- Total number of life years after screen-detected CIN for each type
- Total number of life years after screen-detected or clinical invasive cancer for each state
- Total number of life years lost
- Total number of life in screen and clinically detected cancer by stage

Results Overview

Summary

A guide to the results obtained from the model.

Overview

The following is a list of publications which showcase results from STDSIM and MISCAN-CERVIX.

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UMN Cervical: Model Profile

University of Minnesota

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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

University of Minnesota
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.

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

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

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

Output Overview
Definitions and methodologies for the basic model outputs.

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

Model Purpose

Summary

This document summarizes the overall goal of the University of Minnesota Cervical Cancer model (UMN-HPV CA).

Purpose

The UMN-HPV Cancer (CA) Model was developed to model the natural history of human papillomavirus (HPV) infection and resulting health outcomes related to cervical cancer. UMN-HPV CA simulates different interventions to quantify the effectiveness of HPV vaccination and cervical cancer screening. Model findings are intended to inform public health policies and explain population-level trends in cervical cancer incidence and mortality.

UMN-HPV CA Model consists of two models: a dynamic transmission model and a cohort model. The dynamic transmission model is able to replicate sexual acquisition of type-specific HPV and HPV-induced cervical carcinogenesis. The HPV transmission is simplified in the cohort model and is modeled as an incidence rate. Both models simulate the natural history of HPV infection, cervical pre-cancer and cancer, as well as primary and secondary prevention through vaccination and screening. The UMN-HPV CA Model can be run in two ways 1.) simulation of a single birth cohort 2.) simulation of multiple cohorts reflecting the United States population.

Model Overview

Summary

This document provides an overview of the UMN-HPV CA Model's structure and components.

Purpose

The UMN-HPV CA Model was developed to examine HPV transmission and cervical cancer natural history dynamics and the cost-effectiveness of vaccination and screening strategies. Results from the model are intended to be disseminated broadly to decision-makers and stakeholders to provide evidence and recommendations for cancer prevention and control guidelines. Refer to Model Purpose for detail.

Background

The American Cancer Society estimates that more than 13,000 new cervical cancer cases and 4,000 cervical cancer deaths will occur in 2024. Increasing human papillomavirus (HPV) vaccination coverage and cervical cancer screening uptake are two major interventions targeting populations of different ages who are at risk of cervical cancer. It is important for decision-makers and stakeholders to know the effectiveness of implementing cervical cancer preventive interventions.

The UMN HPV CA model was developed based on the well-understood cervical cancer natural history.

The UMN HPV CA Model contains:

1. A natural history component that tracks progression and regression between HPV infection, precancer states, and cancer states stratified by different HPV types.
2. A vaccination component that allows for a reduction in the likelihood of HPV infections and captures herd immunity benefits;
3. A screening and treatment component that allows for the detection and removal of precancerous lesions and diagnosis of preclinical cervical cancers; and
4. A detection and survivor component for all women diagnosed with cervical cancer.

The UMN HPV CA Model specifically incorporates:

1. Population-level sexual behavior trends by age and sex.
2. Population-level trends in vaccination rates and vaccine efficacy.
3. Population-level trends in competing risks for cervical cancer, namely hysterectomy and background mortality;
4. Population-level trends in cervical cancer screening participation rates and test performance of various screening options to detect precancerous and cancerous lesions.

The primary model outcomes are HPV prevalence, cervical cancer incidence, and cervical cancer deaths. These outcomes are compared to country and state-level cancer registry data, incidence data from the Surveillance, Epidemiology, and End Results (SEER), and mortality data from the US Vital Statistics. Additional outcomes include number of life years and quality-adjusted life years (QALY's) gained under various screening and vaccination strategies as compared to natural history.

Model Description

The natural history of HPV infection and cervical is a state-transition micro-simulation model that simulates women who are at average risk (defined as not immune-compromised and not HPV vaccinated). The transitions are age dependent. The cycle length is 1 year. The cohort starts at age 9 and all girls are assumed to

be normal (i.e., not HPV infected). Every year, women are at risk of becoming infected with HPV stratified by type (described later). Women who are infected can clear their infection, stay infected or progress to CIN (either CIN 1 or directly to CIN 2/3). Women with CIN 1 can progress to CIN 2 or CIN 3 and/or regress (to normal or HPV). Women with CIN 2 can remain in the same state, progress to CIN 3, or regress (to CIN 1, HPV or normal). Women with CIN 3 can remain in the same state, progress to cancer (Stage I), or regress (to either CIN or normal). Cancer is modeled as 4 stages (Stage I, Stage II, Stage III and Stage IV). The state-transition diagram of the natural history of HPV infection and cervical cancer stratified by age and HPV type is shown in Figure 1.

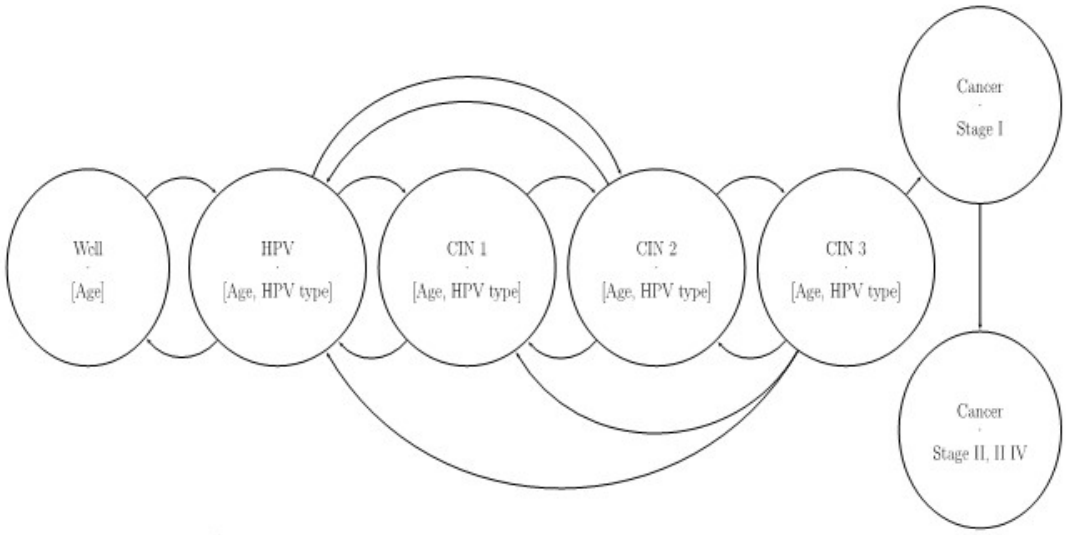

Figure 1. State-transition diagram of the natural history of HPV infection and cervical.

Assumption Overview

Summary

This section outlines the UMN-HPV CA model assumptions.

Background

The UMN-HPV CA model relies on assumptions regarding aspects of the disease's natural history prior to diagnosis, screening effectiveness and outcomes, vaccination efficacy, and the costs and harms resulting from different prevention strategies.

Assumption Listing

Population demographics

Both the cohort and dynamic models assume birth and mortality rates consistent with U.S. census data available in the Human Mortality Database (formerly Berkeley Lifetables). These rates are annual based on 2015 cohort life tables.

Sexual behavior

We used National Survey for Family Growth (NSFG) data from 2010-2011 to assign sex- and age-specific distributions of the maximum number of heterosexual partners possible in a given year. Sexual mixing is assumed to be dependent on an individual's age and maximum number of partners. We assume that concurrent partnerships are possible.
Sexual partnerships were assigned a duration according to sex- and age-specific NSFG data. Individuals that age into a new age group may be reassigned a maximum number of partners and partnership duration. Type-specific sexual transmission of HPV is possible between either gender. We assume all individuals without any immunity in the model are susceptible to HPV infection upon sexual debut, which is age specific.

Natural history of HPV infection

Natural immunity following HPV infection is assumed to provide a varying degree of protection for a lifetime. Natural immunity only occurs in females and is type-specific. We categorized HPV type into four groups based on genotypes: 1.) HPV16 2.) HPV18 3.) High-5 (other pentavalent vaccine types - 31, 33, 45, 52, 58) and 4.) other high-risk (all other HPV types not covered by the nonavalent vaccine - 35, 39, 51, 56, 59, 66, 68). We assumed that co-infection with multiple HPV types is possible. HPV infection can occur at any state in the model among individuals who are sexually active. Transmission is modeled as an annual probability per partnership.

Natural history of pre-cancer

HPV infection may progress to precancer, represented in the model as cervical intraepithelial neoplasia stages 1, 2, and 3, with direct progression allowed to any of the three CIN states. Limited empirical evidence exists to inform rates of progression and regression between precancer stages. Therefore, estimates of natural history regression and progression have been calibrated according to HPV prevalence and cancer incidence targets, and transitions depend on age and HPV type. Each year there is a greater probability that the disease will progress to the next proximal stage or regress to the previous stage, but progression and regression may also skip stages. Annual probabilities of total hysterectomies are based on hysterectomy rates in the US in 2009 for ages (15–99) from the National Hospital Discharge Survey (NHDS). Hysterectomy and background mortality are modeled as competing risks.

Natural history of cancer and associated mortality

UMN-HPV CA models adenocarcinoma (ADC) and squamous cell carcinoma (SCC) as combined cervical cancer. Cancer stages are modeled as Stage 1, 2, 3, and 4, according to the International Federation of Gynecology and Obstetrics (FIGO) staging. Women may progress from CIN3 to Stage 1 cancer. Symptomatic

cancers can result in cancer-related mortality. The probability of expressing symptoms is dependent upon the cancer stage. We assume that cancer survivors are no longer at risk of cancer recurrence.

Screening behavior and performance

Screening algorithms are implemented in accordance with the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) Updated Consensus Guidelines for Managing Abnormal Cervical Cancer Screening Tests and Cancer Precursors. This algorithm recommends a series of primary, triage, and surveillance tests according to prior test results and outcomes. These strategies include cytology, HPV genotyping test, and co-testing, with each test(s) absolute and relative performance modeled in the algorithm. Colposcopy and biopsy can have variable sensitivity and specificity although the base case usually assumes 100% test accuracy. All lesions detected through screening are assumed to be treated although this assumption can be varied.

Vaccination

We assume perfect vaccine efficacy and lifetime vaccine acquired-immunity against vaccine-preventable HPV types in the base case analysis. In secondary analyses, we assume that vaccine failure is possible. Full protection is assumed for a variable duration of time (if no primary failure), after which immunity waves. Both women and men aged 11 to 26 years may be vaccinated in the model in accordance with vaccination guidelines. The vaccination series is modeled based on current guidelines but can be administered at varying intervals.

Costs and harms

Each step in screening, (pre)cancer and cancer diagnosis and treatment can have an associated disutility and cost. These are based on the literature and are detailed in elsewhere.

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Parameter Overview

Summary

This section describes the key parameters of the UMN-HPV CA Model.

Background

This model is informed by data sources common to the CISNET modeling group.

Transition probabilities

We model the transition probabilities from four different health states of the natural history model of HPV infection and cervical cancer: HPV, CIN1, CIN2, CIN3. The transition probability is a function of age and HPV type.

Parameter Listing Overview

Parameter Listing	Relevant assumptions	Data Source
Population parameters		
Population size	Variable	-
Population distribution	We assume a female population for cohort model; the sex ratio at birth is used to estimate the female-to-male ratio of newborns in the population (0.51)	Human Mortality Database, formerly Berkeley Lifetables (1995).
Background mortality	Annual probability of death (age, yearly, by gender)	Human Mortality Database, formerly Berkeley Lifetables (1995).
Disease transmission parameters		
Birth rate	Annual birth rate (age, yearly, by gender)	Human Mortality Database, formerly Berkeley Lifetables (1995).
Age distribution of population	Assumed distribution of population at model initiation by age and gender given by lifetables	Human Mortality Database, formerly Berkeley Lifetables (1995).
Sexual activity	(5-year age groups, based on NSFG gender-specific distributions of number of partners in the last 12 months). Partnerships may be concurrent.	CDC. National Survey of Family Growth. 2010-2011.
Partner age	Distribution of partner age	CDC. National Survey of Family Growth. 2010-2011.
Partnership duration	Maximum number of years a partnership can last	CDC. National Survey of Family Growth. 2010-2011.
Initial infection (cohort model)	(by HPV type)	Calibrated
HPV transmission	Gender-specific annual probability of contracting HPV per infected partner	Calibrated
HPV type	Distribution of HPV type (16, 18, HI-5, other high-risk) condition on infection	Han JJ, Beltran TH, Song JW, Klaric J, Choi YS. Prevalence of genital human papillomavirus infection and human papillomavirus vaccination rates among US adult men: National Health and Nutrition Examination Survey (NHANES) 2013-2014. JAMA Oncol. 2017;3(6):810-816. doi:10.1001/jamaoncol.2016.6192.
HPV clearance	Annual probability of clearing HPV infected	Calibrated
Natural History parameters		

Parameter Listing	Relevant assumptions	Data Source
Competing risk of hysterectomy	New denominator at younger ages corrected for screening coverage	NHDS (2009) and US Census data (2009), (BRFSS)
Infection progression / regression for normal – CIN3 states	By HPV type and age	Calibrated
Transition probabilities for cancer states	Assumed to be constant for all types	Calibrated
Cancer symptom detection	Assumed to be constant for all types	Informed by Myers, E., McCrory, D., Nanda, K., Bastian, L., & Matchar, D. (n.d.). Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. American Journal of Epidemiology., 151(12), 1158-1171.
Cancer survival	Currently modeled as constant across ages (5-year probability at time of detection given years of survival)	SEER 9, year of diagnosis = 1975+
Targets		
HPV Prevalence	Used linear interpolation to generate yearly targets. (age, and type-specific)	Wheeler CM, Ph D, Hunt WC, et al. A Population-based Study of HPV Genotype Prevalence in the United States: Baseline Measures Prior to Mass HPV Vaccination. 2014;132(1):1-19. doi:10.1002/ijc.27608.A. Additional age ranges per personal correspondence
Cancer Incidence	These values were generated by fitting a line just above the incidence curves from IARC CI5C, 1959-1963, CTR, 1950-1954, and CTR, 1955-1959, and by applying type-specific % from Mona Saraiya, personal communications (see HPV Type Distribution in Cancer)	IARC CI5C, 1959-1963, CTR, 1950-1954, and CTR, 1955-1959. Mona Saraiya, personal communications. Data received 10/03/2016 via email
HPV Type Distribution in Cancer	Total cervical cancer (ADC +SCC), conditioned on HPV+ status	Mona Saraiya, personal communications. Data received 10/03/2016 via email
CIN Prevalence	CIN curves generated by review of recent literature and clinical trials	**1.** Goldie SJ, Grima D, Kohli M, Wright TC, Weinstein M, Franco E. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. Int J Cancer. 2003;106(6):896-904. doi:10.1002/ijc.11334. **2.** Hariri S, Johnson ML, Bennett NM, et al. Population-based trends in high-grade cervical lesions in the early human papillomavirus vaccine era in the United States. Cancer. 2015;121(16):2775-2781. doi:10.1002/cncr.29266. **3.** Joura EA, Ault KA, Bosch FX, et al. Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease. Cancer Epidemiol Biomarkers Prev. 2014;23(10):1997-2008. doi:10.1158/1055-9965.EPI-14-0410. **4.** Kitchener HC, Canfell K, Gilham C, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: Extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess (Rockv). 2014;18(23):1-195. doi:10.3310/hta18230. **5.** Peto J, Gilham C, Deacon J, et al. Cervical HPV infection and neoplasia in a large population-based prospective study: the Manchester cohort. Br J Cancer. 2004;91(5):942-953. doi:10.1038/sj.bjc.6602049. **6.** Ramanakumar A V, Naud P, Roteli-Martins CM, et al. Incidence and duration of type-

Parameter Listing	Relevant assumptions	Data Source
		specific human papillomavirus infection in high-risk HPV-naïve women: results from the control arm of a phase II HPV-16/18 vaccine trial. BMJ Open. 2016;6(8):e011371. doi:10.1136/bmjopen-2016-011371. **7.** Sawaya GF, McConnell JK, Kulasingam SL, Lawson HW, Kerlikowske K, Melnikow J, Lee NC, Gildengorin G, Myers ER, Washing EA. Risk of Cervical Cancer Associated with Extending the Interval between Cervical-Cancer Screenings George. N Engl J Med. 2003;349(16):1501-1509. doi:10.1056/NEJMoa1310480. **8.** Vesco KK, Whitlock EEP, Eder M, et al. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S Preventive Services Task Force. Evid Synth. 2011;(86):1-263. doi:AHRQ Publication No. 13-05194-EF-1 **9.** Vesco KK, Whitlock EP, Eder M, Burda BU, Senger CA, Lutz K. Review Annals of Internal Medicine Risk Factors and Other Epidemiologic Considerations for Cervical OF. Ann Intern Med. 2011;(14):698-705 **10.** Wright TC, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: Design, methods, and baseline results. Am J Obstet Gynecol. 2012;206(1):46.e1-46.e11. doi:10.1016/j.ajog.2011.07.024.
HPV Type Distribution in CIN	-	Joste NE, Ronnett BM, Hunt WC, Pearse A, Langsfeld E, Leete T, Jaramillo M, Stoler MH, Castle PE, and Wheeler CM. New Mexico HPV Pap Registry Steering Committee. Cancer Epidemiol Biomarkers Prev January 1 2015 (24) (1) 230-240;DOI: 10.1158/1055-9965.EPI-14-0775, NMHPVPR
Vaccination parameters		
Vaccine efficacy	Vaccine failure possible. Full protection assumed at 100% efficacy and lifetime duration for vaccine-preventable HPV types in base case analysis.	-
Natural immunity	Full protection assumed for lifetime. Natural immunity is assumed to occur in females only.	-
Vaccination parameters		
Cytology test performance	Pooled absolute sensitivity and specificity	Koliopoulos, George et al. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: A systematic review and meta-analysis of non-randomized studies. Gynecologic Oncology. January 2007 (104) (1) 232-246
HPV and Cotest test performance	Relative sensitivity and specificity	Arbyn M, Ronco G, Anttila A, Meijer C, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R and Peto J. Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer. Vaccine, November 20 2012 (30) F88-F99. ATHENA Summary of cobas HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=25 years) at Baseline
Screening practice	% of women who screen at different intervals (Q1-Q5)	Cuzick J, Myers O, Hunt W C, Saslow D, Castle, PE, Kinney W, Waxman A, Robertson M, Wheeler CM. and on behalf of the New Mexico HPV Pap Registry Steering Committee (2015), Human papillomavirus testing 2007–2012: Co-testing and triage utilization and impact on subsequent clinical management. Int. J. Cancer, 136: 2854–2863. doi:10.1002/ijc.29337; NMHPVPR - sent by Curtis Hunt on 1/17/2013

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Component Overview

Summary

This document outlines the components that make up the UMN-HPV CA Model.

Overview

The model is made up of the following components: (1) an HPV transmission component that simulates the heterosexual HPV transmission, (2) a cervical carcinogenesis component that simulates the progression of HPV infection to cervical cancer, (3) a vaccination component that simulates the protective effect of the HPV vaccine, (4) a screening, diagnosis and treatment component that simulates early detection and treatment of precancerous lesion and cancer, and (5) a cancer treatment and survival component that simulate survival of clinically detected cancers.

Component Listing

HPV transmission

Transmission of HPV infections in males and females is modeled in the dynamic individual-based model, with individual partnerships characterized by sex, age, and duration. Females and males form heterosexual partnerships as they age, and transmission of type-specific HPV can occur as a function prevalence of HPV in the population and female-to-male or male-to-female transmission probabilities of HPV per susceptible-infected partnership. Following clearance of HPV, female individuals may develop natural immunity, reducing future risk of that same type of infection. Women with high-risk infection can develop precancerous lesions (i.e., cervical intraepithelial neoplasia (CIN1, CIN2 or CIN 3), which may regress naturally, and those with CIN 3 may develop invasive cancer. Death can occur from age- and sex-specific background mortality or excess mortality in women with invasive cervical cancer.

Cervical carcinogenesis

Both the dynamic and cohort models include health states that reflect cervical carcinogenesis associated with HPV-16, 18 and other high-risk HPV types. In these models, women transition between health states, which reflect the individual's underlying true health and include HPV infection status, grade of CIN (CIN 1, CIN 2 and CIN 3), and stage of invasive cancer (I through IV). In the cohort model, women enter the model before sexual debut and transition between health states according to probabilities that depend on age, HPV type, type-specific natural immunity, CIN status, and treatment history. Death can occur each year from non-cervical cancer causes from all health states, or from cervical cancer after its onset. Hysterectomy is modeled as a competing risk.

Vaccination

The dynamic model is used to project the effects of HPV vaccination in reducing HPV-16, HPV-18 and other vaccine-preventable high-risk type infections over time, capturing both direct and indirect benefits. The dynamic model can also account for the impact of these effects on CIN and cancer. The immunity conferred by vaccination has full protection of a lifetime. The model can account for vaccine inefficacy.

Screening, diagnosis and treatment of CIN

Both models can accommodate detailed features of screening strategies, including algorithms that are based on a single test or multiple tests (either in parallel or serial). The models reflect screening, follow-up, and treatment recommendations based on American Cancer Society (ACS), US Preventive Services Task Force (USPSTF) and American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, but assumptions can be modified flexibly. The models both incorporate a detailed post-treatment surveillance component. (3)

Cancer treatment and survival

The models include cancer states by stage (I through IV) and conditional probabilities of survival based on stage of detection. The models also include a separate state for survivors and cancer-related deaths based on data from the Surveillance, Epidemiology, and End Results (SEER) Program.

Output Overview

Summary

This is a general overview of the outputs generated by the UMN-HPV CA model.

Overview

Base Case Outputs

Base Case outputs assume that no screening is performed, and the model is calibrated to yearly HPV prevalence, cancer incidence, and CIN1, CIN2, and CIN3 targets. The following outputs are generated and aggregated in five-year age groups for comparison to other CISNET models:

1. HPV prevalence by age and HPV genotype
2. HPV type distribution in cancer by age
3. Prevalent preclinical (undetected) cancer by age, cancer stage and HPV genotype
4. Prevalent clinical (detected) cancer by age and cancer stage
5. Clinical cancer stage distribution (proportion) by age
6. Clinical cancer incidence per 100,000 by stage and age or overall clinical cancer incidence
7. HPV-type distribution in CIN1, 2, and 3
8. CIN 1, 2, and 3 prevalence
9. Cancer mortality per 100,000

Cervical Cancer Screening Outputs

Screening outputs after overlaying screening on natural history are generated. Screening outputs were generated from various screening strategies with different primary screening tests and triage methods. The following outputs were generated and aggregated in five-year age groups for comparison to other CISNET models:

1. Average Screening tests per woman by age groups
2. Average Pre-cancer treatments per woman by age groups
3. Average colposcopies per woman by age groups
4. Average false-positive test results per women by age groups
5. Life years gained through screening

Output Listing

Cohort Model Base Case Outputs	
Note: these outputs also produced when initial screening carried out	
Total population alive: Hysterectomized women included and excluded	Counts by age, year, and hysterectomy status
HPV Prevalence:	Counts by age, year, and HPV type (four groups: HPV16, HPV18, High 5 HPV types, all other high-risk HPV)
Prevalent (undetected) Cancer Cases	Counts by age, year, and cancer stage
Prevalent Clinical Cancer Cases	Counts by age, year and cancer stage
Incident Clinical Cancer Cases by type	Counts by age, year and HPV type
Incident Clinical Cancer Cases by stage	Counts by age, year and cancer stage
Total Cancer Rate per 100,000 women	Counts by age and year
Clinically Detected Cancer Deaths	Counts by age and year
Cancer Death per 100,000 women	Counts by age and year
Prevalent Counts of CIN 1	Counts by age, year, and HPV type
Prevalent Counts of CIN 2	Counts by age, year, and HPV type
Prevalent Counts of CIN 3	Counts by age, year, and HPV type

Screening Outputs	
Average Screening tests per woman by age groups	Counts by age, year and screening strategy
Average Pre-cancer treatments per woman by age groups	Counts by age, year and screening strategy
Average colposcopies per woman by age groups	Counts by age, year and screening strategy
Life years gained through screening	Total life years per strategy (no screening, Q1-Q5)
Quality adjusted life years	Total quality-adjusted life years per strategy
Outcomes for cervical cancer screening strategies over the lifetime of screening (screening end age 65)	
Number of Cytology tests performed	Total number of cytology tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Number of HPV tests performed	Total number of HPV genetic tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Number of Total tests performed	Total number of tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Total number of Colposcopies performed	-
Total number of CIN2, CIN3 lesions detected through screening	-
Total number of CIN3 lesions and cervical cancers detected through screening	Excludes symptomatic cancers diagnosed clinically
False positive colposcopies	Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection
Total number of cervical cancer cases per 100,000	-
Total number of deaths due to cervical cancer per 100,000	-

Results Overview

Summary

This document outlines the results that the UMN-HPV CA Model generates.

Results List

Expanding upon US Preventive Services Task Force Decision Analysis Screening Outputs

CISNET teams carried out the full screening algorithm to expand upon Harvard's analysis of the U.S. Preventive Services Task Force Decision Analysis of primary HPV testing by 1) adding costs, 2) including screening adherence, 3) reflecting obstetric harms from pre-cancer excisional treatment. UMN-HPV CA provides comparative results for this analysis carried out by the Harvard CISNET group. This analysis was composed of 19 screening strategies including cytology, HPV primary testing, cotesting, and combinations of these tests in accordance with the algorithm. Outcomes were calculated from age 21 to 100 years. A series of sensitivity analyses will be carried out by varying the triage methods, screening interval, and adherence to recommendations. The following results were compared per 1,000 women:

1. Number of cytology tests
2. Number of HPV tests
3. Total number of tests, irrespective of primary, triage, or surveillance context
4. Number of colposcopies
5. Number of CIN2 and CIN3 lesions detected
6. Number of CIN3 lesions or higher detected (not including those detected by clinical symptoms)
7. Number of false positives, defined as the total colposcopies that did not result in CIN2, CIN3 or cancer detection
8. Number of cervical cancer cases
9. Number of deaths due to cervical cancer
10. Number of life-years

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