Erasmus MC
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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.

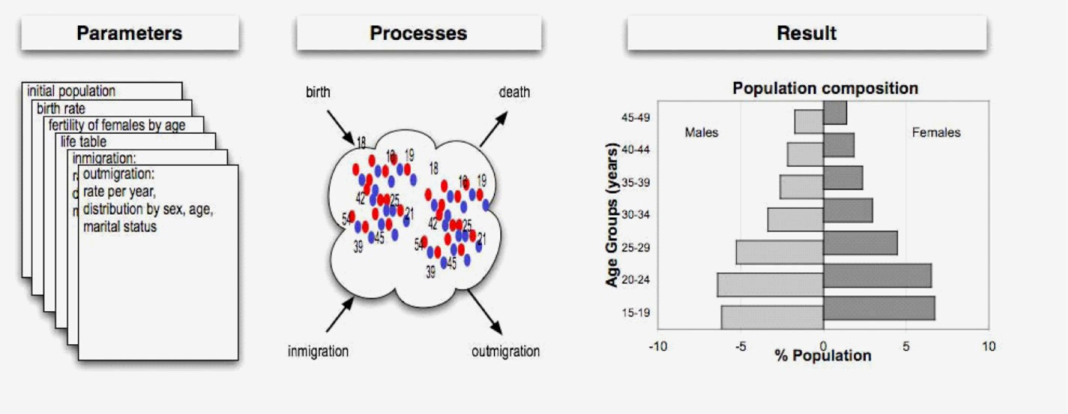

Figure 1. Demographic mechanisms in STDSIM

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)

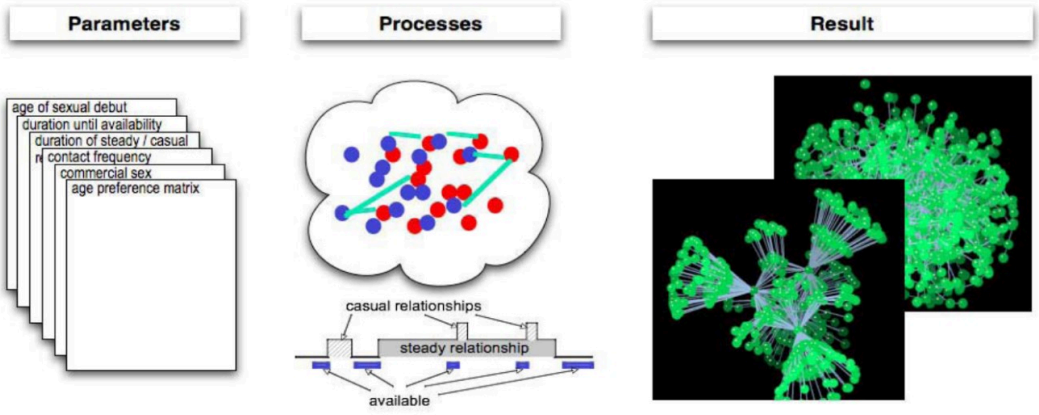

Figure 2 Mechanisms of sexual behavior in STDSIM create a dynamic sexual network

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.

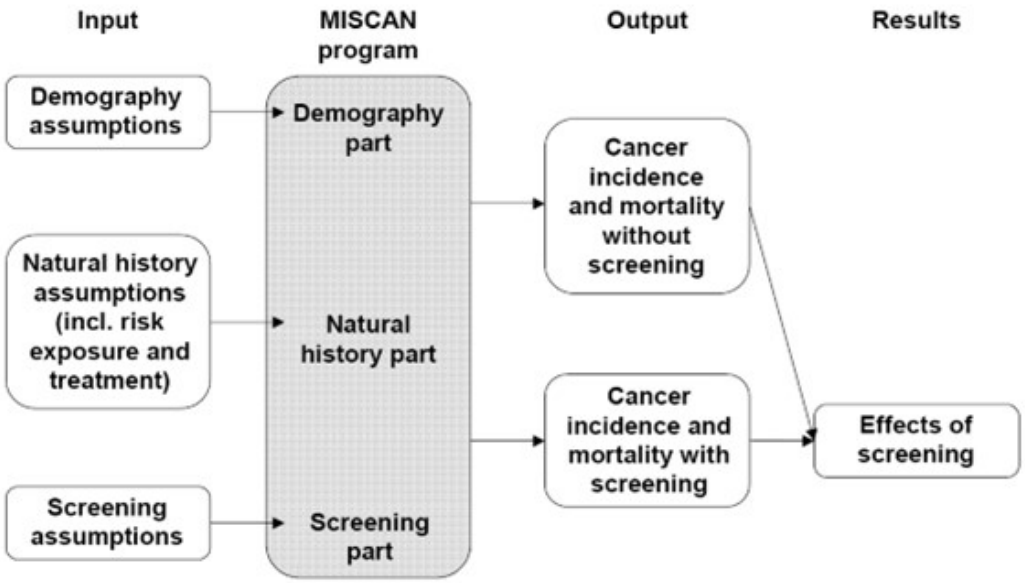

Figure 3: Basic structure of MISCAN-CERVIX

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

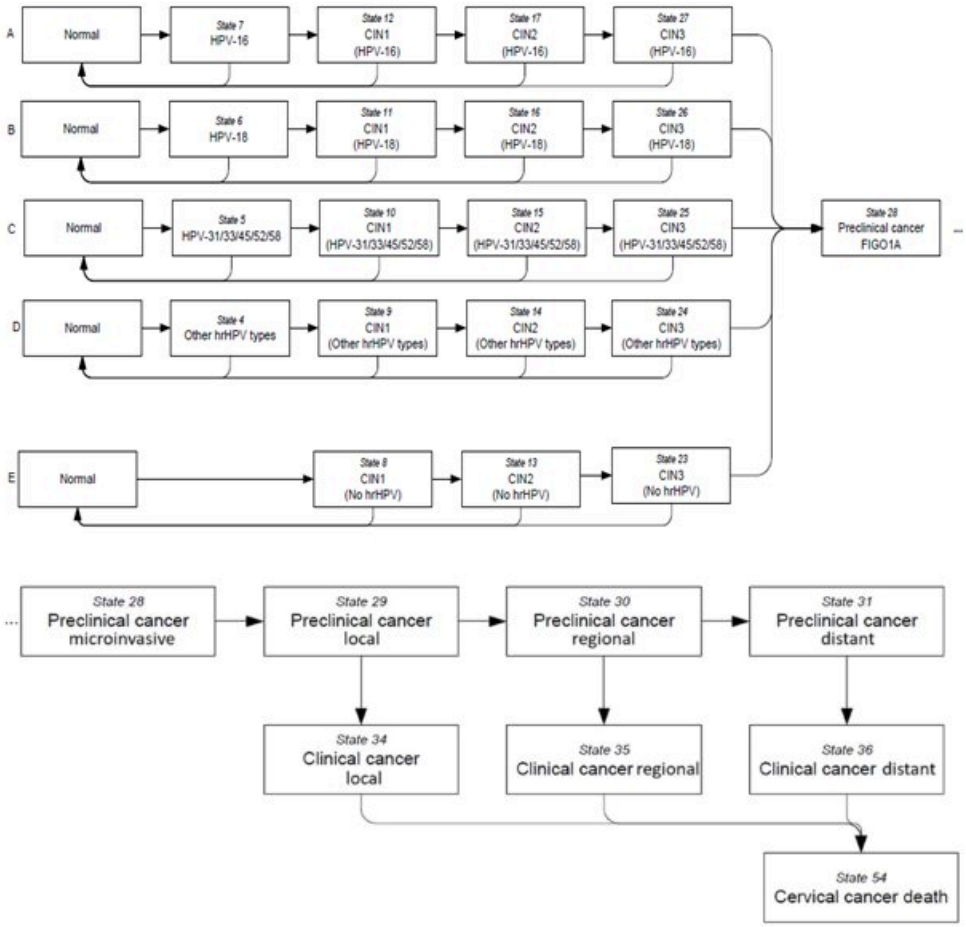

Figure 4. Schematic representation of the MISCAN-cervix model, with disease pathways A through F

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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