MODEL PROFILE
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CANCER COUNCIL NSW

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

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READER'S GUIDE

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

PURPOSE

The model platform known as 'Policy1-Cervix' was developed to address several questions related to cervical cancer. The platform has recently been used to evaluate the timeline for the elimination of cervical cancer for Australia and for 181 countries.[1] It has also been used to perform 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[2,3], and for screening policy evaluations for New-Zealand[4] and England[5]. It has previously been extensively validated and used to evaluate changes to the cervical cancer screening interval in Australia and the United Kingdom,[6,7] the role of alternative technologies for screening in Australia, New Zealand and England,[8-11] the role of HPV triage testing for women with low-grade cytology in Australia and New Zealand,[9,12] the role of HPV testing for the follow-up management of women treated for cervical abnormalities[13] and the cost-effectiveness of alternative screening strategies and combined screening and vaccination approaches in China.[14,15] The model has also been used to evaluate the impact of the nonavalent HPV vaccine in four developed countries[16] and to assess the cost-effectiveness of the nonavalent HPV vaccine in Australia.[17] 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.[18] Model predictions of age-specific cervical cancer incidence and mortality, the rate of histologically confirmed high-grade lesions per 1,000 women screened and overall screening participation rates have been previously validated against national data from Australia, England and New Zealand[2,19,20] after taking into account local age-specific screening behaviour obtained via analysis of screening registry data.

MODEL OVERVIEW

SUMMARY

This section provides an overview of the Policy1 Cervix model. The model consists of four core components: 1) dynamic HPV transmission, 2) Cervical carcinogenesis, 3) Screening and treatment and 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: 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 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 four possible HPV type groups: HPV16, HPV18, HPV31/33/45/52/58 (hi-5) and other Hr-HPV types.

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 cause) in the population.

Vaccination. The dynamic model simulates vaccination uptake by single year of age, sex, and 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).

Screening and treatment: The sensitivity and specificity of cytology are setting-specific and fitted to data on the distribution of cytology test results (e.g., 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 10-year period is simulated, according to last screening test result, the follow-up recommendation and 10-year age group. Following treatment for CIN, post-treatment natural history and surveillance for recurrent disease are based on meta-analysis of the literature on outcomes after pre-cancer treatment (100). 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 are updated regularly. When data is not available from the literature, expert opinion is sought.

ASSUMPTION LISTING

1. Dynamic HPV Transmission:

We assume men and women fall within 4 possible sexual behaviour groups, and if infected with HPV, each sexual act has a chance to transmit the virus. Viral clearance and progression are also modeled. In policy1-Cervix, vaccine efficacy is incorporated by modifying uptake (e.g. 95% efficacy with 80% uptake is input as 76% uptake.)

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.[18]

2. 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, have CIN1, CIN2, CIN3 or cancer. Women can have multiple infections and multiple lesions associated with different infections. We consider four HPV type-groups, including HPV 16, 18, high-5 (31/33/45/52/58) and other high-risk HPV types, and progression and regression rates are modelled as a function of HPV type and age. HPV types/groups 16, 18, HI5 and OHR are independent and simultaneous (i.e. a woman 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 2 states away (for instance, women with CIN1 can transition to uninfected, HPV infected, CIN2 or

CIN3), with the exception of cervical cancer which can only be accessed from the CIN3 state.

3. Screening and treatment:

We assume that screening test results are based on a woman's health state and underlying HPV type. Women who undergo pre cancer treatment have a small chance of treatment failure; for developed settings, we assume the treatment failure is caught within 6 months and the lesion accurately removed. We assume that after pre cancer treatment, women are at higher risk of cervical precancer and cancer for the remainder of their lives.

4. 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 time since diagnosis and is assumed to be higher 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 by age in a well-screened setting.

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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. Calibration targets are used in the calibration process but are not directly required to operate the model, e.g. HPV prevalence. Calibrated parameters are obtained through the calibration process and provide the best fit to the calibration targets, e.g. health state transition rates.

PARAMETER LISTING OVERVIEW

Dynamic HPV Transmission:

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 was found to be similar in USA.

- 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:

- 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 prevalence)
- HPV type distribution in cancer (Calibration target – Saiyara published data)

Screening and treatment:

- Test Positive Matrices (TPMs) are from published test performance data for USA for HPV and cytology testing.
- Treatment failure rates

Cancer treatment and survival:

- 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 the 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, 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: 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 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 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 feedback 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 feeds into the cervical carcinogenesis component.

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 components cease to operate and the cancer treatment and survival component commences.

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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. Calibrated input parameters are varied based on this fitting algorithm. Validation outputs are compared to study data but aren't considered in the calibration algorithm. Input parameters aren't changed to match these targets, they 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 also have use 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/Hi5/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: high grade/low grade histologies
- 5-year risk by cytology test result

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Predictive Outcomes:

- Health state dwell times of cancer-causing HPV infections
- Health outcomes: life years.
- 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 been used for a number of evaluations of cervical cancer interventions, such as cost-effectiveness of HPV vaccination and evaluation of cervical cancer screening technology, interval and management. Policy1-Cervix has also been used in comparative modelling exercises within the CISNET group to better understand the natural history of the disease.

RESULTS LIST

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