Cancer Council NSW

Cancer Research Division

Policy1-Cervix Documentation

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Version 1.0

Contents

Part 1: Overview of Policy1-Cervix

Policy1-Cervix is a dynamic model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis and treatment. The platform has recently been used to evaluate the timeline to the elimination of cervical cancer in Australia[1] and globally[2]. 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[3,4], for New-Zealand[5] and England[6]. It has previously been extensively validated and used to evaluate changes to the cervical cancer screening interval in Australia and the United

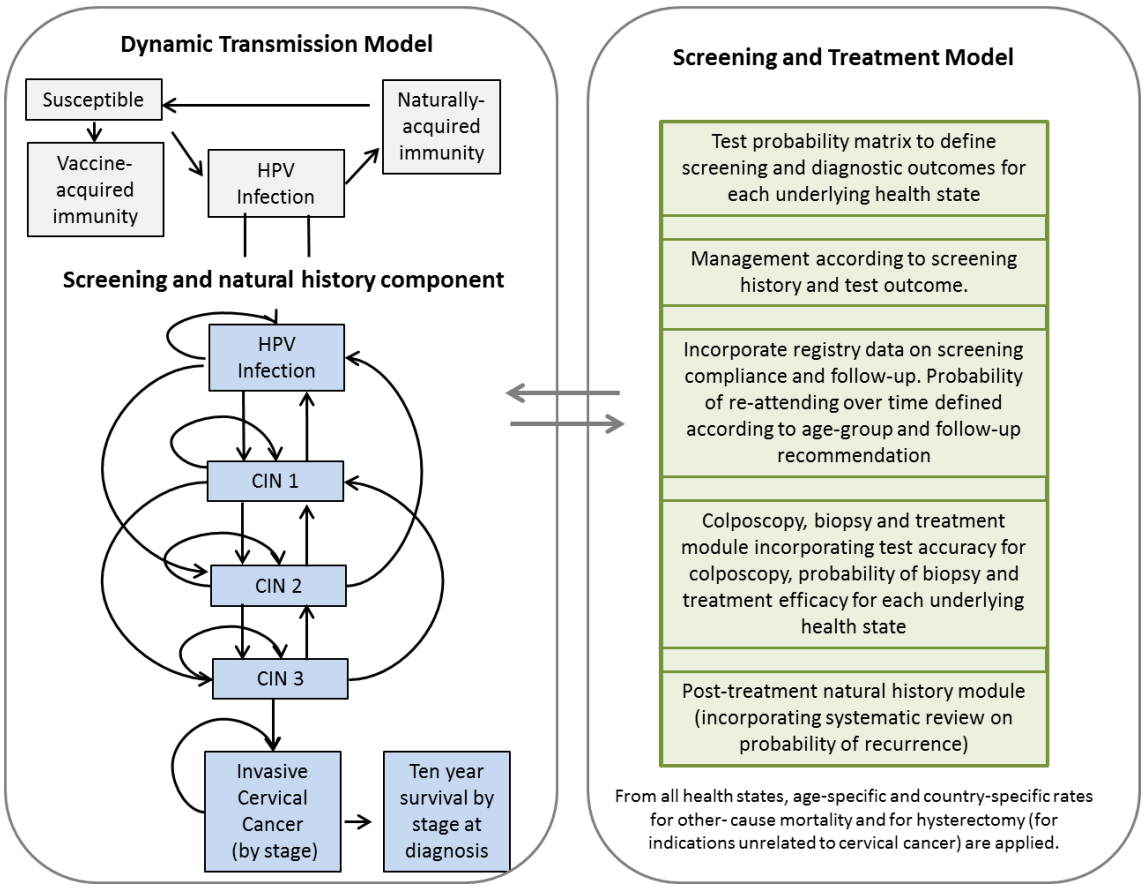
Kingdom,[7,8] the role of alternative technologies for screening in Australia, New Zealand and England,[9-12] the role of HPV triage testing for women with low-grade cytology in Australia and New Zealand,[10,13] the role of HPV testing for the follow-up management of women treated for cervical abnormalities[14] and the cost-effectiveness of alternative screening strategies and combined screening and vaccination approaches in China[15,16]. The model has also been used to evaluate the impacts of the nonavalent HPV vaccine in four developed countries[17] and to assess the cost-effectiveness of the nonavalent HPV vaccine in Australia.[18] Predictions from the dynamic HPV transmission and vaccination model have also recently been validated against observed declines in HPV prevalence in women aged 18-24 after the introduction of the quadrivalent vaccine.[19] Model predictions of age-specific cervical cancer incidence and mortality, the rate of histologically confirmed high-grade lesions per 1,000 women screened and screening adherence rates have been previously validated against national data from Australia, England and New Zealand[3,20,21] after taking into account local screening behaviour obtained via analysis of screening registry data. The model is shown schematically in Figure 1.

The model simulates HPV infection which can persist and/or progress to cervical intraepithelial neoplasia grades I, II and III (CIN1, CIN2, CIN3); CIN 3 can then progress to invasive cervical cancer. Progression and regression rates between states are modelled separately for types HPV 16, HPV 18, other high-risk nonavalent-included types (31/33/45/52/58), and other non-nonavalent-included high risk types. The model platform captures the increased risk of CIN2+ recurrence in even successfully treated women (compared to the baseline risk of CIN2+ in the population), as previously described.[22]

To capture the impact of HPV vaccination, we used a general dynamic transmission model, which assumes 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 behaviour data from Australia. Both males and females can move from an initial state of being susceptible to HPV infection, to being infected with HPV, recovering from an infection and being immune, and then

returning to a state of being susceptible. In addition, women can potentially progress from infection with HPV to CIN and invasive cancer, or regress from precancerous states to a state where type-specific immunity to HPV has been conferred. Susceptible individuals can also become immune via vaccination against HPV. Additionally, individuals in any of the previously described states can die from other causes, and females can also undergo a benign hysterectomy. The dynamic transmission model stratified the population by sex, 5-year age group, and 4 sexual behaviour classes, each with varying levels of activity, defined by the annual number of new sexual partners. To characterise the behaviour in young people (under 25 years) while controlling for changing sexual practices over time, we generally restricted the analysis of behaviour to those born after 1974. Two types of data are available on the age at first intercourse – retrospective reporting of the age of first intercourse, and cross-sectional reporting of whether sexual activity has been initiated. We also reviewed the literature to assess the extent to which sexual partnership formation tends towards assortative (like-with-like) mixing in terms of age and sexual activity levels.[23] More details on the parameter assumptions for the dynamic model can be found in previous publications.[24] The model is shown schematically in Figure 1:

Figure 1 Model description for Policy1-Cervix



Vaccination

The effects of vaccination are modelled using the most recent data available on coverage rates relevant to each setting. For instance, for the Australian vaccination program, coverage rates are available each year by age and gender. The model can capture different efficacy rates of the vaccines and can capture cross-protective efficacy of varying duration. The model has the capacity to simulate vaccination against HPV types 16, 18 or other high-risk types. The vaccine is assumed to provide protection to females and males who are naïve to a given HPV type. Therefore, the vaccine will provide no protection in women who have been pre-exposed to a given HPV type.

Herd immunity effects on the modelled cohort from vaccination delivered to both other females, including older birth cohorts and younger birth cohorts, and adolescent males were fully taken into account by the dynamic transmission model. Thus the effects of any catch-up programs and male

vaccination programs can be captured. The overall effectiveness of the vaccine administered to the female catch-up cohorts was expected to be lower because some of these women will have had prior exposure to HPV, however for HPV-naïve women in the catch-up cohorts, the vaccine is assumed to be effective, and these effects were taken into account in the dynamic transmission model. The outcomes for catch-up cohorts are therefore expected to be intermediate to those predicted and presented here for HPV-naïve vaccinated cohorts and unvaccinated cohorts.

In the model we used a hierarchical approach to lesion type-assignment when fitting the model to observed data (fitting HPV 16 positive first; then HPV 18 positive, then other oncogenic types). Because of the potential for multiple infections, this method may have resulted in misclassification of the causal type of the lesion, as in some cases HPV 16 or HPV 18 may have been incidentally present, and not causally associated with the lesion. This therefore may have resulted in an overestimate of the disease which may be preventable by vaccination and an underestimate in the model of the incidence and prevalence of other- oncogenic type infections and related lesions. When the vaccine strains are removed or reduced as a result of vaccination against types 16/18, this previous misclassification may lead to an apparent increase in disease due to other high-risk HPV types (also known as 'unmasking'). To address the potential underestimate of other oncogenic HPV types, the prevalence of these other oncogenic types was assumed to increase by 8% in the absence of HPV 16 and 18, to represent potential unmasking effects.[25]

Cancer diagnosis, treatment and survival

Detailed annual stage-specific survival parameters for 10 years following a cancer diagnosis are input into the model. We assume that survival in screen-detected cancers is higher than in symptomatically detected cancers, based on published rates.[26-28] Specifically, we assume individuals diagnosed with screen-detected localised have a 15% higher relative survival rate compared to symptomatically-

detected localised cancers, and individuals with regional/distant have a 17% higher relative survival rate.

Part 2: Model parametrization

Invasive cancer parameters

Invasive cervical cancer is modelled based on country-specific information of staging (e.g FIGO versus localised, regional and distant) and survival by stage. We assume that survival for screen-detected cancers is slightly higher than that for symptomatically detected cancers, based on international evidence of this effect thought to be due to within-stage shift and increased chance of healthcare seeking behaviour in women who chose to screen compared to women who did not.[29-31]

As an example, for the Australia platform, invasive cervical cancer was modelled by extent of disease (localised, regional and distant), and at each stage there were separate heath states for undiagnosed or diagnosed. The progression of undiagnosed invasive cervical cancer was obtained via a calibration approach previously implemented in the New Zealand version of the model (because in that setting more data on cancer staging by age were available) which calibrated the invasive cancer natural history to the age-specific proportion of cancer diagnosed at each extent of disease to the data observed in New Zealand over the period 1994-2003. For Australia, the stage-specific and interval specific cancer survival parameters used in the model were based on analysis of data obtained from NSW Central Cancer Registry [30]. The modelled cancer incidence and mortality was calibrated to observed registry data in Australia, and has also been validated against observations of the proportion of cancers that are localized, regional and distant by age in a well-screened setting.[1]

Hysterectomy rate

Depending on the setting, women may have a total hysterectomy for reasons other than cervical cancer. In some settings (such as Australia, New Zealand and USA), rates of hysterectomy are quite high – up to 40% lifetime risk of hysterectomy in women in the USA. The impact of screening and vaccination programs is affected by the model assumptions for hysterectomy, and so it is important

to capture this. In Australia, data on the annual age-specific probability of having a hysterectomy were derived from the 2001 and 2005 National Health Surveys.[32,33] For other settings, when possible, local data on hysterectomy procedures by age and birth cohort are used to inform the model.

Mortality rate

Life tables are obtained from national statistics sources to inform the model. For Australia, The age-specific deaths from causes other than cervical cancer were calculated using all-cause mortality after subtracting the cervical cancer mortality rate.[34,35] When these are unavailable for other countries, data from the WHO database are used to inform life tables.

Key screening parameters

Detailed screening algorithms are coded into the model, including colposcopies, follow-up tests, precancer treatment procedures and cancer diagnoses. This allows the model to produce detailed outputs across three categories:

- Health outcomes: Rates and case numbers for cancer incidence, cancer mortality, and histologically confirmed high-grades;
- Health-economic outcomes: cost-effectiveness, QALY's and life-years saved, annual budget impact; and
- Resource-utilisation outcomes: Rates and case numbers for colposcopies, biopsies, precancer treatments (LEEP/CKC/cryotherapy), HPV tests, triage tests and other relevant procedures.

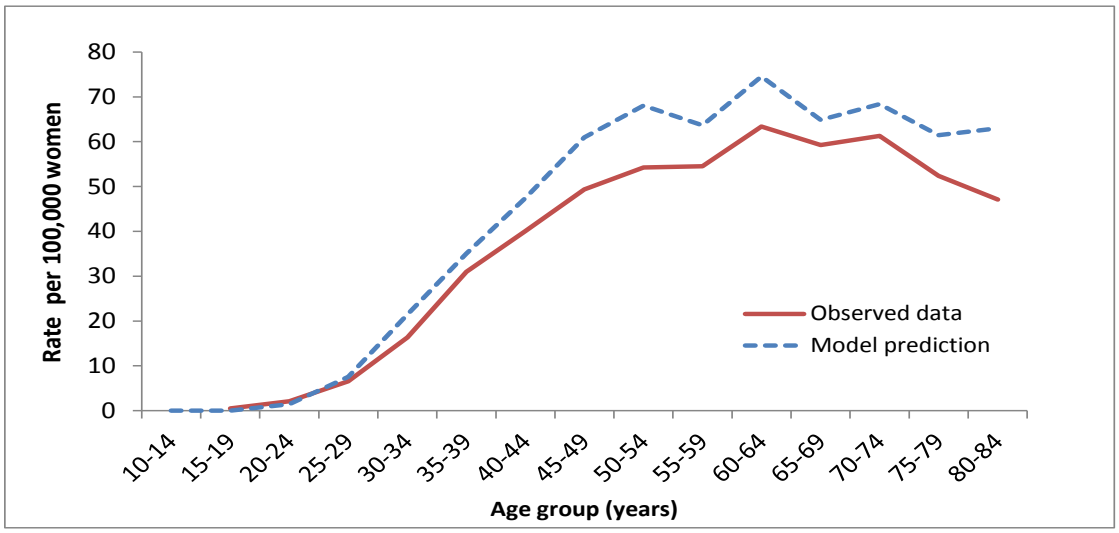
Detailed input for screening attendance rates by age and by recommendation (i.e attendance for routine screening versus attendance for colposcopy or follow-up) are obtained from local sources when available.

Part 3: Calibration – example from Australia

The average age-specific incidence of cervical cancer in 25 developing countries without significant levels of cervical screening was estimated from data IARC data.[36] The modelled cancer incidence is

broadly consistent with the observed data. Over the age of 50 years, the model predicts a plateau in age-specific cancer incidence; the decrease observed in the data from developing countries is likely to reflect cohort effects in women over 65 years of age (owing to a lesser risk of exposure to HPV infection as younger women). The predicted cumulative lifetime risk of cervical cancer was 3.19% in an unscreened screening among women without hysterectomy.

Figure 2 Predicted cervical cancer incidence in an unscreened setting, compared to data from 25 developing countries



Source: Cancer incidence in five continents Vol. VIII [36]

Following calibration of the natural history model, the complete model of screening, diagnosis and management in Australia was implemented. The full model was of considerable complexity and incorporated data on age-specific screening initiation and compliance with screening and management recommendations in Australian women (which was informed by an analysis of data obtained from Victoria Cervical Cytology Registry (VCCR) data) and the estimates of test characteristics of conventional cytology and colposcopy.

The output of the full screening model was compared with:

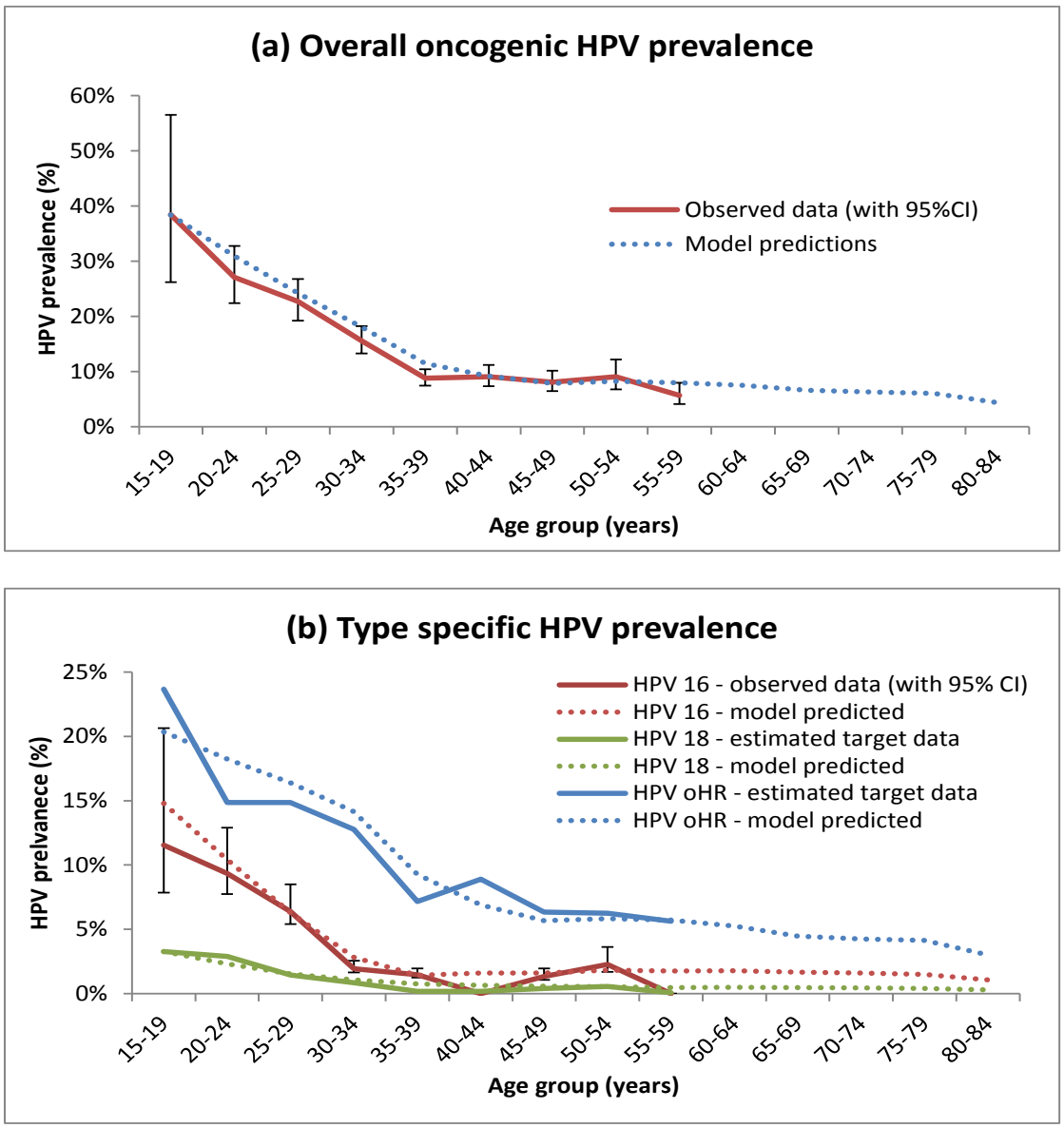
- HPV prevalence rates by age in Australia
- The age-specific and age-standardised incidence of cervical cancer in Australia over the period 2002–2004 and 2005-2007 [37]
- The age-specific and age-standardised mortality due to cervical cancer in Australia over the period 2005–2007 [37]
- The number of cancer cases and deaths observed in Australia in 2010 [37]
- The age-specific and age-standardised rate of histologically confirmed high-grade and low-grade CIN [38]
- The number of low-grade and high-grade cytology abnormalities detected in 2011 [38]
- The age-specific proportion of HPV type infection detected among women with histologically confirmed high-grade observed in Australia [39] and New Zealand [40]

HPV prevalence in Australia

The natural history model specified separate natural history model for oncogenic HPV type 16, type 18 (not 16) and other oncogenic types (not 18 and 16). The age-specific prevalence of all oncogenic HPV and HPV 16 were calibrated to the data observed in a population of 805 non-Indigenous, cytologically-normal women attending for routine screening who were recruited to the Women, Human Papillomavirus Prevalence, Indigenous, Non-Indigenous, Urban, Rural Study (WHINURS) (pers. comm., Prof. Suzanne Garland). The target prevalence of HPV 18 and other oncogenic types for calibration were estimated from the prevalence of all oncogenic HPV observed in WHINURS study and assuming the age-specific proportion of HPV 18 (not 16) and other oncogenic HPV type (not 18 or 16) as observed among cytologically-normal women who tested positive by Hybrid-Capture 2 HPV test in a UK trial [31].

As shown in Figure 3, the predicted overall and type-specific prevalence of oncogenic HPV compares well with the observed data.

Figure 3: (a) Predicted age-specific overall oncogenic HPV prevalence; (b) predicted prevalence of HPV 16, HPV 18 (not 16) and other oncogenic HPV types (not 18 and 16) among sexually active women, compare to the observed data in Australia (WHINURS)



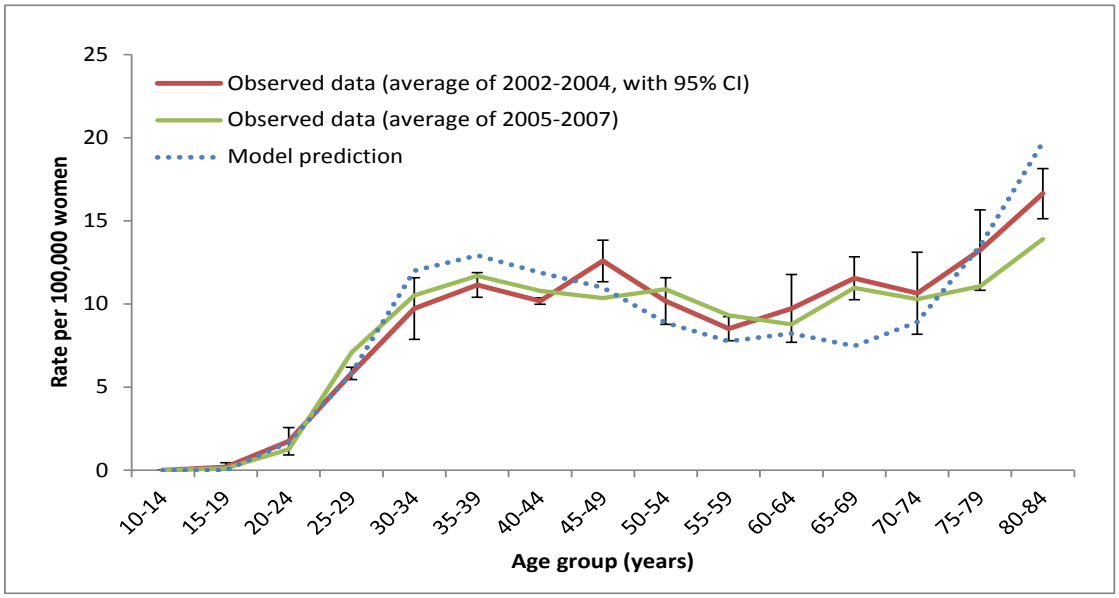
Note: HPV prevalence illustrated in the above graphs indicate HPV prevalence before the effect of HPV vaccination takes place. Target prevalence for HPV 18 (not 16) and oncogenic HPV (not 16 or 18) were estimated using the type proportion observed in a UK trials (ARTISITIC).

CI– confidence interval; oHR – other oncogenic HPV types (not 16 or 18)

Cancer incidence and mortality - Australia

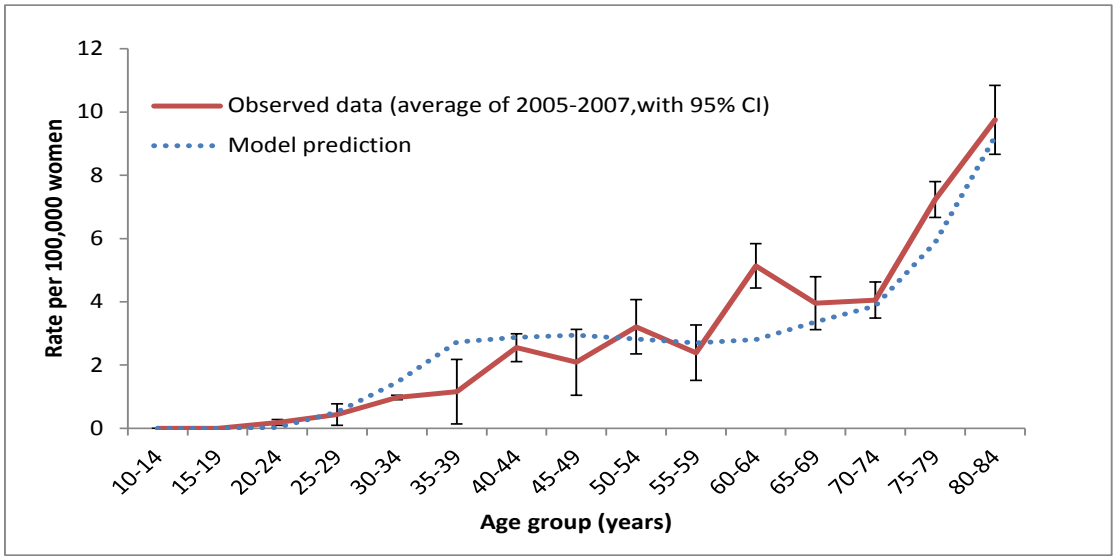
The modelled cervical cancer incidence and cervical cancer mortality compared to the data observed in Australia in the period between 2002 and 2004 and between 2005 and 2007 [37] are shown in Figure 4 and Figure 5. Incidence rates show close agreement with modelled values.

Figure 4: Predicted age-specific rate of cervical cancer incidence, compared to the average observed rates in 2002-2004 and 2005-2007 in Australia



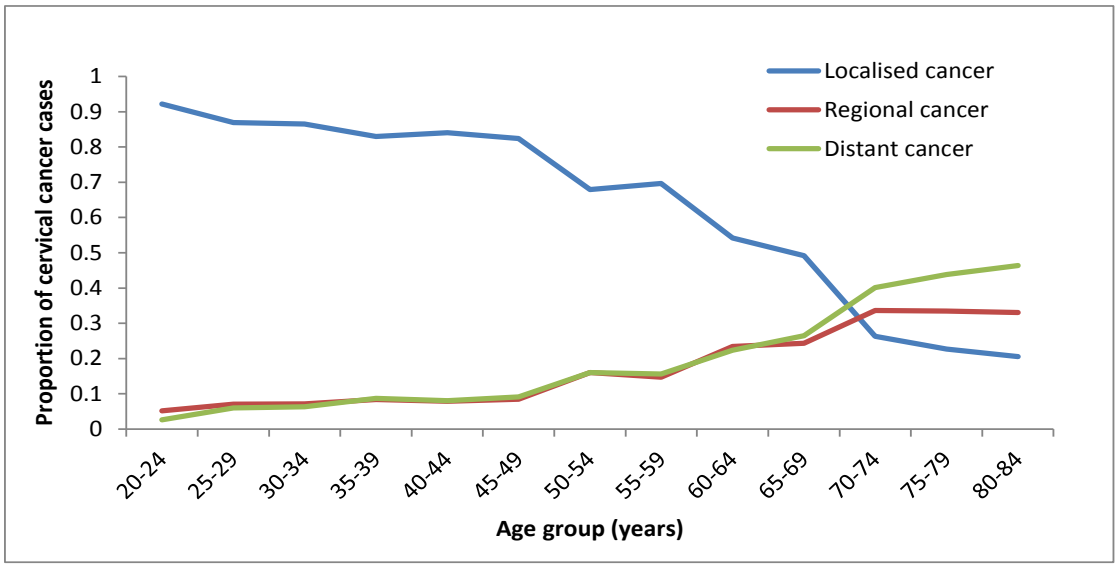
Note: We have chosen to compare with the age-specific rates from 2002-2004 because the latest data on age-specific mortality rates is from 2005-2007, and we assume that incidence rates from the years 2002-2004 would be the main drivers of observed mortality in 2005-2007.

Figure 5 Predicted age-specific cervical cancer mortality, compared with the average observed rate from 2005 to 2007 in Australia



The model predicted stage distribution among diagnosed cervical cancer cases by age is shown in Figure 6. No published data was available at the time of writing for the model predictions to compare with.

Figure 6: Predicted cervical cancer stage distribution by age

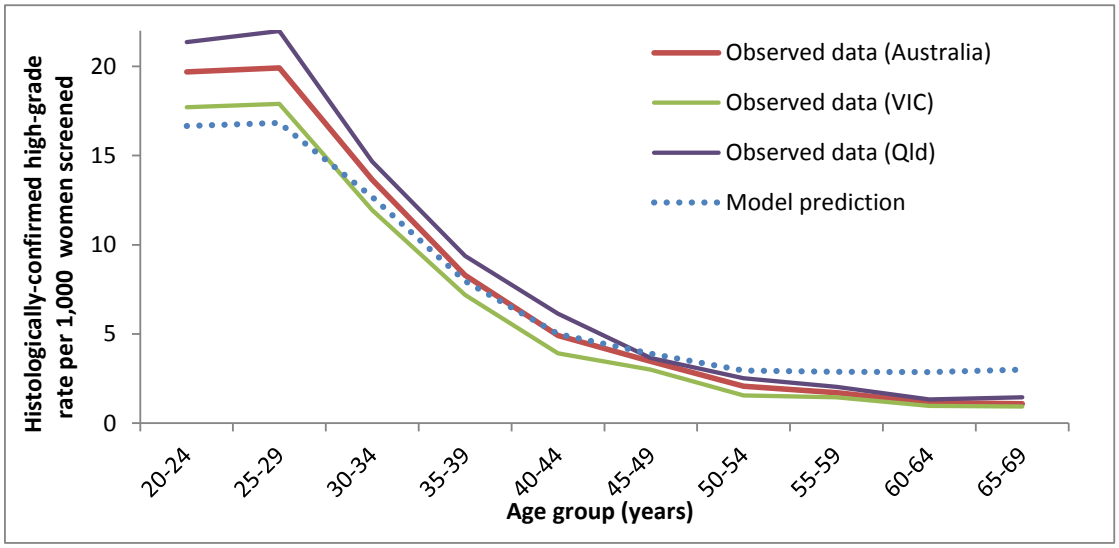


Screening-related outcomes - Australia

Figure 7 shows the model predicted rates of women with histology-confirmed high-grade abnormalities per 1,000 women screened by age. The high-grade abnormalities detection rate varied across states and territories in Australia. The age-standardised rate in women aged 20-69 years was found to be highest in NT (11.6 per 1,000 women screened) lowest in ACT (6.2 per 1,000 women screened) [38]. The data observed Victoria and Queensland are also shown in the figure to demonstrate the variation in the detection rate by age. Compared to data observed in Australia, although the predicted histology-confirmed high-grade cases are broadly consistent with observed data [38], they are comparatively lower in women younger than 30 years and a slightly higher in women aged 55 years or older. This discrepancy in the age group younger than 30 years is likely due to the model's simulating current NHMRC guideline management [41] and assuming all women aged younger than 30 year-old under routine screening management who have a low-grade cytology result are referred to a 12 month follow-up. We have found in the previous work [42,43] that rates of both low-grade and high-grade histology-confirmed abnormalities would increase if a proportion of these women were referred to immediate colposcopy instead of follow-up at 12 months (since some women with high-grade CIN may be misclassified by cytology and have a low-grade cytology result).

The rates of women with histology-confirmed low-grade per 1,000 women screened in Australia was not available in the recent AIHW published report [38] for model prediction comparison. However, for the same reason mentioned above, the predicted rates of histology-confirmed low-grade per 1,000 women screened in women younger than 30 years is likely to be lower than the observed value in Australia.

Figure 7 Predicted age-specific rate of histologically confirmed high grades lesion per 1,000 women screened, compared to the data observed in 2010 in Australia, Victoria and Queensland



The predicted annual cases and age-standardised rate associated with cervical cancer, cervical cancer death deaths, abnormalities detected by cytology and are also consistent with the data observed in Australia, shown in Table 1 below.

Table 1 Model predicted health outcome, compared to data observed in Australia

Health Outcome	Model prediction	Latest observed data
Annual number of cervical cancer cases (0-84 years)	762*	723 (average of 2007-2009, range: 686 - 743)†,††
ASR cervical cancer incidence per 100,000 women**	-	-
20-69 years	9.0	9.2 (average of 2007-2009, range: 9.0 - 9.3) †,††
0-84 years	6.9	6.8 (average of 2007-2009, range: 6.6 - 6.9) †,††
Annual number of cervical cancer deaths (0-84 years)	202*	193 (average of 2005-2007, range: 184 – 198) †,††
ASR cervical cancer mortality per 100,000 women**	-	-
20-69 years	2.1	2.0 (average of 2005-2007, range: 1.9 - 2.0) †,††
0-84 years	1.8	1.8 (average of 2005-2007, range: 1.7 - 1.8) †,††
High grade histology rate per 1,000 women screened in women 20–69 years	7.9	8.4 (in 2011)‡
Number of low-grade cytology abnormalities detected in women 20–69 years	88,121*	84,540 (in 2011)‡
Number of high-grade cytology abnormalities detected in women 20–69 years	30,704*	30,253 (in 2011)‡

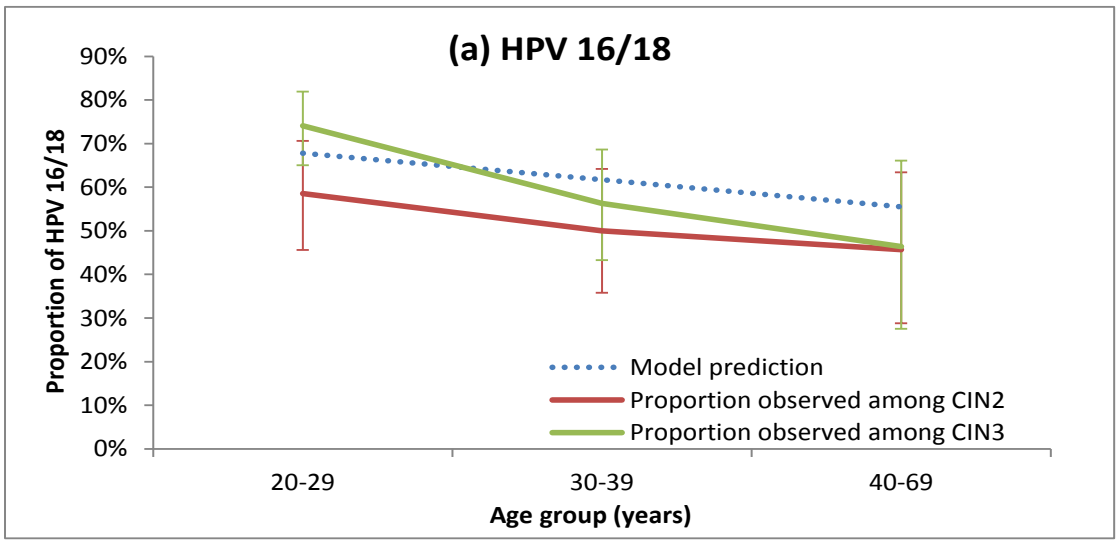
* Assuming Australian female population 2010. ** Using the Australian 2001 population. † At the time of writing, the latest available data for cervical cancer incidence was in 2009 and for cervical cancer deaths was in 2007. †† Data obtained from ACIM (Australian Cancer Incidence and Mortality) Books 2012.[37] ‡ Data obtained from Cervical screening in Australia 2010-2011 [38]

Due to lack of detail for the Australian specific data, the predicted oncogenic HPV type distributions among women with histology confirmed high-grade outcome were calibrated to the data observed New Zealand based on the findings of a recent study conducted by Simonella and colleagues [40]. Figure 8 shows that the model predicted age-group specific proportion of HPV 16/18 infections and

oncogenic HPV (not 16 or 18) infections among women with histology confirmed high-grade are in close agreement with the data observed in New Zealand. The model prediction is also broadly consistent with the age-specific proportion of HPV 16 infections observed among 317 Australian women with CIN3 observed in a study conducted by Brotherton and colleagues [39], shown in Figure 9.

The predicted HPV type distributions among diagnosed cancer cases are shown in Table 1. The model predicted that 77% of cervical cancers were attributed to HPV 16/18 infections. Although this predicted proportion is higher than the findings of IARC review (63%) [44], it is consistent with the conclusion of a systematic review, which estimated that 77.7% of the cervical cancers in Australian were caused by HPV 16/18 infections [45]. It is also consistent with the result of a meta-analyses published in 2007, which found that the HPV 16/18 infections were found in 74-77% of cervical cancer cases in Europe, North America, Australia and that this proportion is higher than the proportion observed in the other region of the world including Africa, Asia and South/Central America [46].

Figure 8 Predicted (a) HPV 16/18 distribution and (b) other oncogenic HPV type (not 18 or 18) distribution among women with histologically-confirmed high-grade lesion, compared to the observed data in New Zealand obtained from the Women and HPV study [40]



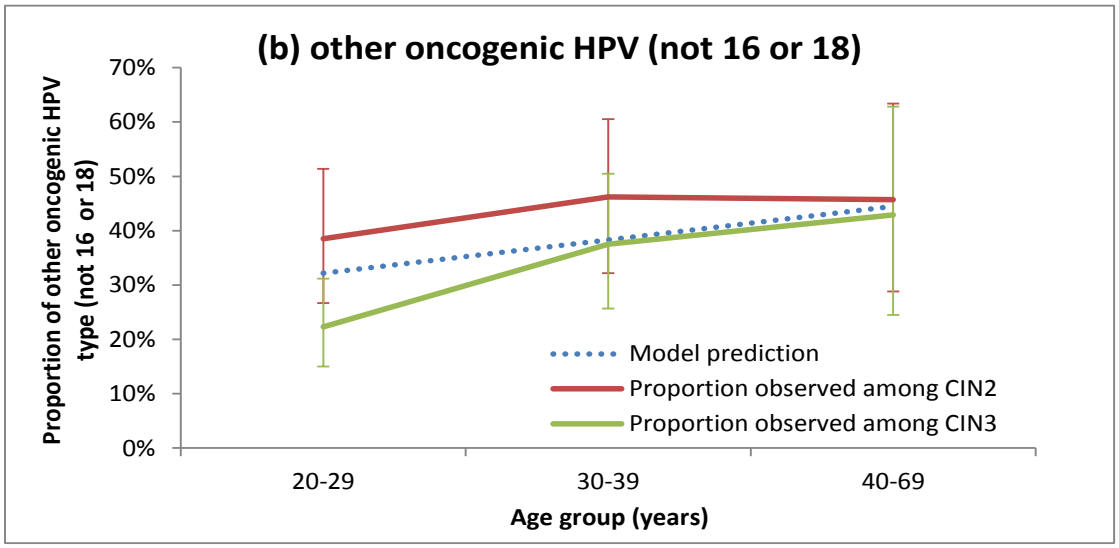
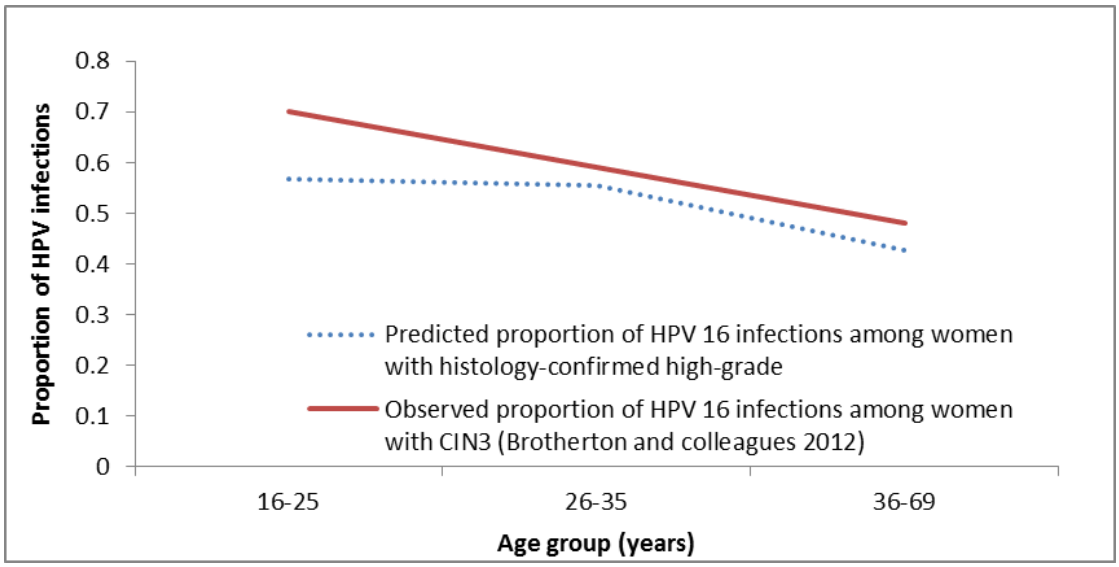


Figure 9 Predicted HPV 16 / 18 distribution among women with histologically-confirmed high-grade lesion, compared with the observed HPV 16 distribution among women with CIN3 in Australia based on the findings of Brotherton and colleagues



Source: [39]

Table 2 Model predicted proportion of cancers caused by the infections of HPV 16, 18 and other high risk types

	HPV 16	HPV 18	Other high risk
Proportion of cervical cancer	61.6%	15.6%	22.8%

Resource utilisation

The model predicted annual number of cytology tests, colposcopy, histology evaluation and treatment for precancerous lesions are summarised in Table 3. The predicted number of cytology tests and histology evaluations performed were consistent with the data observed in Australia in 2010 [38].

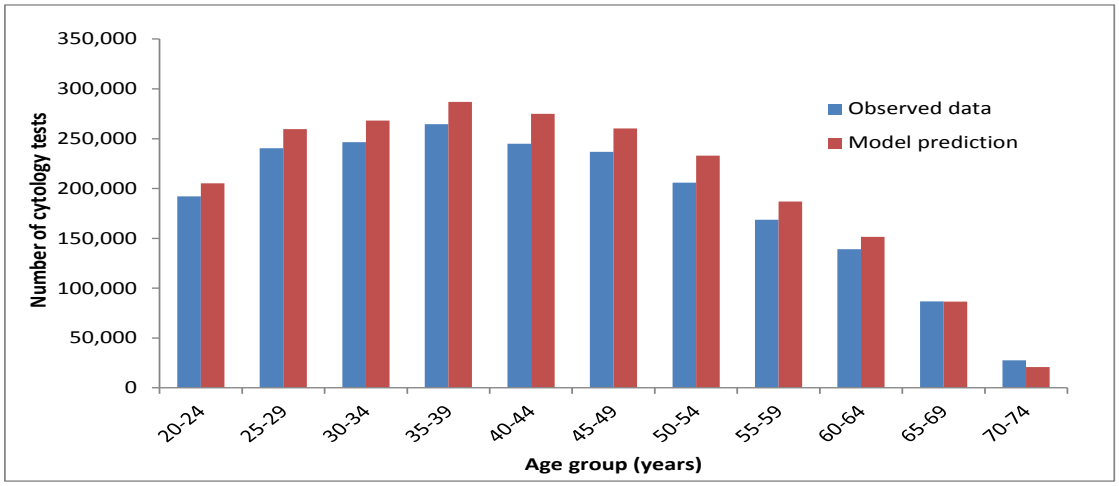
Table 3 Predicted resource utilisation in Australia, compared to the available observed data in Australia in 2010

Procedure	Model predicted*	Latest observed data†
Cytology test		
20-69	2.21 million	2.06 million (in 2011)
All ages	2.27 million	2.15 million (in 2011)
Colposcopy		
20-69	76,600	-
All ages	78,200	-
Histology evaluation (not including multiple biopsies taken at the same colposcopy examination)		
20-69	38,100	37,332 (in 2010)**
All ages	38,700	-
Treatment for precancerous lesion		
20-69	20,100	-
All ages	20,600	-

* Assuming an age structure as observed in Australia in 2010. † Data obtained from *Cervical screening in Australia 2010-2011.*[38] ** Number of cytology followed by a histology test within 6 months

The predicted number of cytology tests by age (assuming 2010 Australian female population) is shown in Figure 10. This representation shows that the number of cytology test as predicted by the model is slightly higher than observed data in 2010 [38].However, there is still good agreement in the age- trend and the overall number of tests performed.

Figure 10 Predicted number of cytology tests by age-group, compared to the observed data in Australia in 2010



Test yield and correlation between high-grade cytology and histology

In order to model the local test performance of conventional cytology in Australia, the assumptions on the conventional cytology test accuracy were derived and calibrated according to the cytological abnormalities rate as well as the correlation between high-grade cytology and histology observed in Australia [38]. Table 4 and Table 5 below show that the model predictions for cytology tests yield in and correlation between high-grade cytology and histology in women age 20-69 years are in close agreement with data observed in Australia.

Table 4 Estimated test yields for base case conventional cytology test characteristics assumption in satisfactory cytology tests from women aged 20-69 years, compared to observed data in Australia in 2011

Estimated outcome versus observed data	Cytology outcome				
	Negative	pLSIL	dLSIL	pHSIL	dHSIL
Estimated outcome	94.5%	2.3%	1.8%	0.7%	0.8%
Observed data†	94.3%	4.2%	4.2%	0.7%	0.8%

† Data obtained from Cervical Screening in Australia 2010-2011 report[47]

Table 5 Modelled correlation between high-grade cytology and histology outcome for conventional cytology in women aged 20-69 years, compared to observed data in Australia in 2010

Estimated outcome versus observed data	Histology outcome		
	Low-grade	CIN 2	CIN 3+
Possible HSIL			
Estimated outcome	21.6%	22.8%	29.5%
Observed data†	21.5%	22.7%	29.3%
Definite HSIL			
Estimated outcome	12.2%	24.1%	52.9%
Observed data†	*12.3%*	*24.0%*	*52.9%*

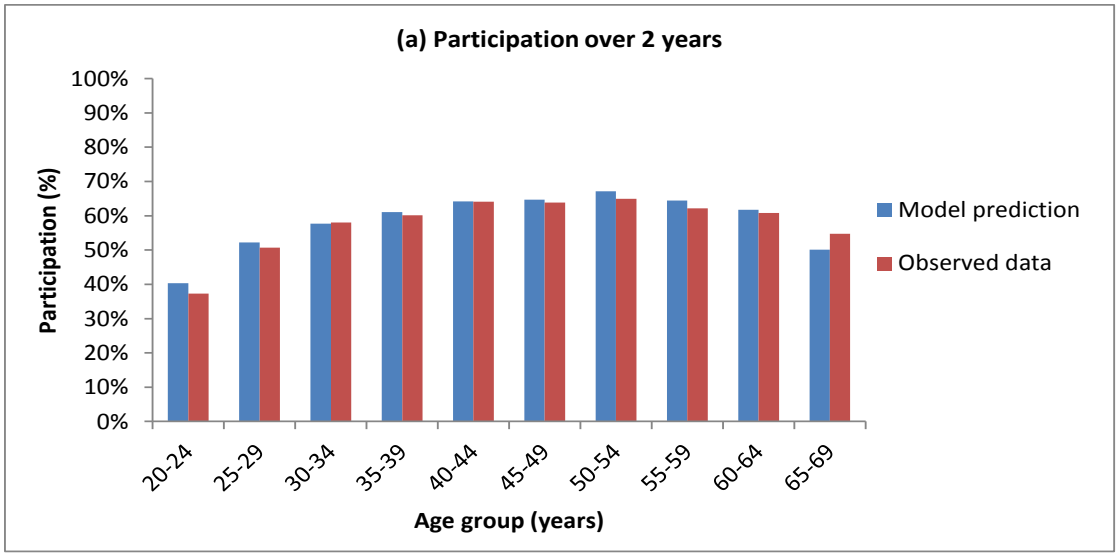
† Data obtained from Cervical Screening in Australia 2010-2011 report [47]

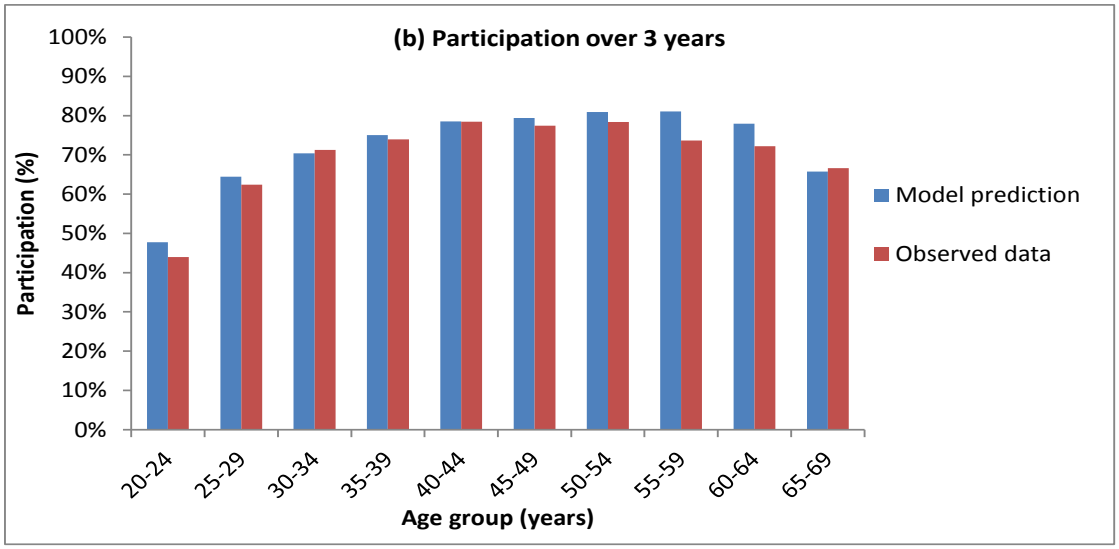
Screening participation

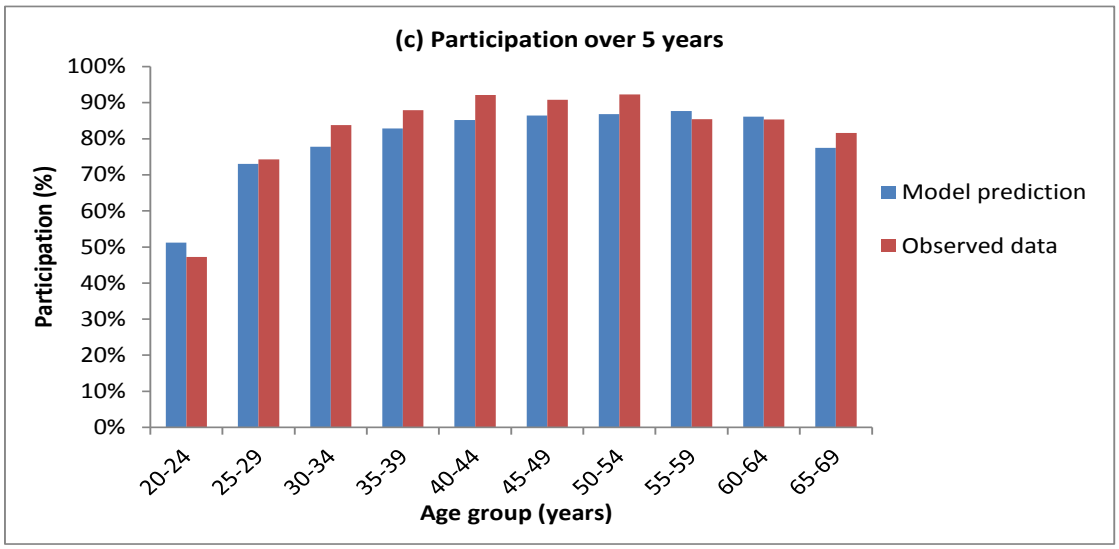
The rescreening probabilities were calculated by using standard cohort analysis methods, taking account of the person-time of follow-up and possible censoring for a cohort starting in 2001. For each index smear, we calculated the earliest of (i) the time to the next smear, (ii) time to death, (iii) 10 years of follow-up or (iv) time to 31 December 2011. The follow-up was stratified by 3-monthly periods, with recalculation of age and period for each stratum of follow-up. We then aggregated the person-time and the number of events to calculate rates, and calculated the interval-specific probabilities of rescreening.

The modelled proportion of women who have had a screening test in the last 2, 3 and 5 years is shown in Figure 11. The observed data is calculated using data provided from the VCCR and re-scaled to match observed Australian participation as reported by the from Cervical Screening in Australia 2009-2010 report [48]. These graphs show that the model is accurately capturing the screening behaviour of women by age group at 2, 3 and 5 years after their last screening test. (Although the AIHW reports national data for observed participation, this data is not calculated in a way that we need – we are performing a cohort analysis and the calculations in AIHW are reported cross-sectionally).

Figure 11 Model predicted screening participation (a) over 2 years, (b) over 3 years and (c) over 5 years, compared to observed data.




(b) Participation over 3 years
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Participation (%)
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
Age group (years)
Model prediction
Observed data


(c) Participation over 5 years
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Participation (%)
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
Age group (years)
Model prediction
Observed data

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