Appendix: Technical report

Management of intermediate risk women after primary HPV testing for cervical screening: Evaluation of optimal management strategies for the National Cervical Screening Program in Australia

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Abstract

Background: Several countries are currently implementing a transition to HPV testing for cervical screening. Various management options for women who have a positive HPV test result have been proposed. In the Australian National Cervical Screening Program (NCSP), that will transition in 2017 from cytology to primary HPV screening and will involve partial genotyping for HPV 16/18 with direct referral to colposcopy for this higher risk group and HPV-negative women will be recalled at 5 years for routine screening. Intermediate risk women with other oncogenic types (non HPV 16/18: OHR HPV) will be triaged with liquid-based cytology, with high grade cytology referred to immediate colposcopy and normal cytology returned to 12 month surveillance, but the optimal management of OHR HPV with low grade cytology (pLSIL or LSIL, equivalent to ASCUS or LSIL in the Bethesda system) requires evaluation.

Methods: We used a comprehensive dynamic model of HPV transmission, vaccination, natural history and cervical screening, which took into account realistic levels of adherence to follow-up recommendations. We evaluated (1) the 20-year risk of invasive cervical cancer in women with OHR HPV and pLSIL/LSIL who are referred for 12 month follow-up, and compared this to an accepted benchmark risk in Australia which is the risk for women with pLSIL/LSIL, who are currently followed at 12 months; (2) the population-level impact of the whole program, assuming this group are returned to 12 month surveillance vs. immediate colposcopy referral; and (3) the cost-effectiveness of immediate colposcopy compared to 12 month follow-up in this group. Evaluation was performed both for HPV-unvaccinated cohorts and for women offered vaccination through the National HPV Vaccination Program, taking into account observed vaccination coverage (~72% in 12 -13 year old girls).

Results: In women with OHR HPV and pLSIL/LSIL, if 12 month follow-up is implemented the 20 year risk of developing invasive cervical cancer is lower than the risk in women with a screening cytology result of LSIL in the current program (i.e. lower than the accepted benchmark). Referring women who test HPV positive (not 16/18) and LBC pLSIL/LSIL to colposcopy provides an incremental 1-3% reduction in cervical cancer incidence and mortality compared with follow-up at 12 months in this group, but this is in the context of a predicted 24-36% reduction associated with the new HPV screening program compared to the current cytology-based program; considering both unvaccinated cohorts and cohorts offered vaccination. Further, colposcopy referral of this group substantially increases the number of colposcopies, with >650 colposcopies required to avert an additional case of cervical cancer compared to 12 month follow-up in this group. The incremental cost-effectiveness ratio (ICER) for immediate colposcopy compared to 12 month follow-up was estimated to be >A$100,000/LYS, compared to an indicative willingness-to-pay threshold of A$50,000/LYS in Australia. If immediate referral is reserved for women in this group aged 45 and older, the ICER improved to $39,800 (95%CrI: $36,700-$41,900) in unvaccinated cohorts and $40,900/LYS (95%CrI: $38,300-$43,600) in cohorts offered vaccination.

Conclusions: After the introduction of primary HPV screening, referring women with OHR HPV and pLSIL/LSIL for 12 month surveillance is associated with a lesser risk of invasive cancer than a 'benchmark' risk for 12 –month follow-up currently experienced by women with low grade cytology in the current cytology-based program. Although some incremental improvements in cervical cancer rates are expected in the program as a whole, these are limited, and direct referral to colposcopy would be associated with a substantial increase in colposcopy referrals and the associated harms. Furthermore, direct referral of all women in this group is very cost-ineffective, although it becomes more cost-effective if reserved for older women. In conclusion, 12 month surveillance of women

with OHR HPV and low grade cytology appears to provide the best balance of benefits, harms and cost-effectiveness in the new Australian primary-HPV based screening program.

1. Introduction

Several countries are currently evaluating or implementing a transition from cytology to primary HPV testing for cervical screening. HPV-based screening has been shown to provide improved protection against invasive cervical cancer compared to cytology screening.[1] Furthermore, using the HPV test as a primary screening tool allows for development of population-based screening recommendations which take into account the impact of HPV vaccination, since management can be based on individual risk assessment at the time of screening, which is based on the HPV test result, rather than on an individual's HPV vaccination status, which may not be available at the point of screening.[2] Given HPV types 16/18 are associated with the greatest immediate and cumulative risk of CIN 3 or worse,[3-5] screening tests with partial genotyping for HPV 16/18, are expected to improve risk stratification of women who have a positive HPV test result in cervical screening programs.

Australia was the first country to initiate a national public vaccination program in 2007. Female vaccination uptake is approximately 71-72% for 3 dose coverage in 12-13 year old females; catch-up in 18-26 year old females (conducted from 2007-9) achieved coverage rates of the order of 30-50%.[6,7] After the introduction of vaccination, Australia experienced rapid falls in vaccine-included HPV type infections, anogenital warts and histologically confirmed cervical high grade precancerous abnormalities (CIN 2/3). These have now been documented extensively in young females, and reductions in warts has also been seen in heterosexual males due to herd immunity effects. From 2004-6 to 2012, for women aged < 20 years, rates of CIN 2/3 decreased by 53%; for women aged 20-24 years, rates of confirmed CIN 2/3 were stable until 2010, then decreased by 21% in the following year.[8] From 2013, males aged 12-13 have also been vaccinated at school with a two-year catch-up to Year 9 (~15 years). Via herd immunity, male vaccination will also provide incremental benefits to females, and is expected to lead to further reductions in infections with vaccine-included types and high grade cervical abnormalities in females. [2,9]

The implementation and rapid impact of HPV vaccination, together with an accumulation of evidence of primary HPV screening, promoted a review, known as the *renewal*, of the Australian National Cervical Screening Program (NCSP). This commenced with a 2013 evaluation of the evidence, including modelled evidence of the impact of the renewed program in both unvaccinated cohorts and in cohorts offered vaccination, which was performed on behalf of the Australian Government's Medical Services Advisory Committee (MSAC).[10] The MSAC evaluation identified several options for HPV screening in Australia that were predicted to result in improved outcomes, compared with current practice for cytology based screening. The greatest gains in effectiveness were associated with primary HPV testing with partial genotyping for HPV 16/18, in which women with these HPV types are referred directly for diagnostic colposcopic assessment. Based on the findings of the MSAC evaluation, in 2014, Australia announced an upcoming transition from the current cervical screening program, involving 2-yearly conventional cytology in women aged 18-20 to 70 years, to 5-yearly primary HPV-based screening with partial genotyping and direct referral for HPV16/18 positive women, from age 25 years, and discharging HPV-negative women in their early seventies. The target date for implementation of the renewed program is May 1st 2017.

Various management options for women who have a positive HPV test result have been proposed. In the Australian NCSP, a 2017 transition from cytology to primary HPV screening will involve partial genotyping for HPV 16/18 with direct referral to colposcopy for the higher risk group of women positive for HPV 16/18 (with a liquid-based cytology [LBC] sample taken to assist management at colposcopy), and HPV-negative women will be recalled at 5 years for routine screening, or discharged

from screening (if aged 70 or older). Intermediate risk women with other oncogenic types (non HPV 16/18: OHR HPV) will be triaged using liquid-based cytology (LBC), with high grade cytology referred to immediate colposcopy and normal cytology recalled for 12 month surveillance, but the optimal management of OHR HPV with low grade cytology (pLSIL or LSIL, equivalent to ASCUS or LSIL in the Bethesda system) requires evaluation. This evaluation has taken place as part of the process of developing detailed clinical management guidelines for the renewed cervical screening program.

Management of women with a positive 'other oncogenic' HPV test result (not 16/18) and an LBC test report of ASC-US (pLSIL) or LSIL could potentially involve immediate colposcopy referral or a watch-and-wait approach with 12 months surveillance and re-testing for HPV at that time. Although some countries, in the context of HPV triage of low grade cytology, currently recommend colposcopy referral for women with any oncogenic HPV who have low grade cytology,[11] it should be noted that because the higher risk HPV16/18 infections are removed from the pool of women being considered here, that the remaining women are expected to be at lower risk overall. However, there is little direct evidence to inform the assessment of risk in this group.[12] Therefore, we performed a modelled simulation of outcomes given the two management strategies.

The aim of the current study was, in women with OHR HPV infection and low grade cytology (pLSIL or LSIL), to estimate: (1) the 20-year risk of invasive cervical cancer in women with OHR HPV and pLSIL/LSIL who are referred for 12 month follow-up, and compared this to an accepted benchmark risk in Australia which is the risk for women with pLSIL/LSIL, who are currently followed at 12 months; (2) the population-level impact of the whole program, assuming this group are returned to 12 month surveillance vs. immediate colposcopy referral; and (3) the cost-effectiveness of immediate colposcopy compared to 12 month follow-up in this group. Evaluation was performed both for HPV-unvaccinated cohorts and for women offered vaccination through the National HPV Vaccination Program, taking into account observed vaccination coverage.

2. Methods

2.1 Model platform

We used a comprehensive dynamic model of HPV transmission, vaccination, natural history and cervical screening to perform this evaluation. The platform was recently been used to perform the effectiveness modelling and economic evaluation of cervical screening in unvaccinated and cohorts offered vaccination for the MSAC review for the NCSP renewal[10]. It has also been used to evaluate changes to the cervical screening interval in Australia and the United Kingdom,[13,14] the role of alternative technologies for screening in Australia, New Zealand and England,[15-18] the role of HPV triage testing for women with low-grade cytology in Australia and New Zealand,[16,19] the cost-effectiveness of alternative screening strategies, combined screening and vaccination approaches in China[20,21] and for evaluating the cost-effectiveness of primary HPV screening in England.[22]

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 and other high-risk HPV types. The model incorporates information on the age-specific risk of death due to causes other than cervical cancer,[23,24] rate of hysterectomy due to causes other than cervical cancer[25,26] and cervical cancer survival rates by extent of disease at diagnosis.[27]

Validation against observed data for age-specific cervical cancer incidence and mortality, the rate of histologically confirmed high-grade lesions per 1,000 women screened and screening participation

rates has been previously described.[10] 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.[28]

We took a health services perspective and considered aggregate costs for screening, diagnostic and treatment procedures scaled to the year 2013 as described previously.[10]

2.2 Adherence (compliance) assumptions

When modelling the pre-renewed NCSP, the model incorporated data on age-specific screening initiation and compliance with screening and management recommendations in Australian women informed by an analysis of data obtained from Victoria Cervical Cytology Registry (VCCR)). When modelling the renewed NCSP, we assumed on the basis of a call-and-recall system being introduced (with women sent invitations at age 25 years) that the number of women that attend their first screening test at age 25 years (the new initiation age) will be at least equivalent to the number that, under the pre-renewed NCSP, had their first screening test before, or at, the age of 25. For the purposes of this modelled evaluation, we assumed that no screening occurs before the age of 25 years under the renewed NCSP.

Compliance with re-attendance for women in routine screening under the renewed NCSP was evaluated assuming that a call-and-recall screening organisation system was implemented. The behaviour of women under a call-and-recall system was informed by data from England, since a call-recall organisation system has been implemented in this country. Specifically, the proportion of women who attend before or at the recommended screening interval (5-years under the renewed NCSP) is informed by the screening pattern observed in England. However, we assume that the coverage at 7 years is equivalent to what is currently observed under the pre-renewed NCSP– i.e. that changing the recommended screening interval, by itself, will not change behaviour in very under-screened women.

As part of the MSAC evaluation, we previously explored a range of other screening attendance assumptions, including slower screening uptake rates and a less 'efficient' call-recall system (in which there was a higher rate of early re-attendance and a lower rate of on-time attendance). Details of the impact of these screening assumptions can be found in.[10]

We assumed that the probability of attending a follow-up test in the renewed NCSP is equivalent to that currently observed under the pre-renewed NCSP for a given recall timeframe. For compliance with 12 month follow-up, we assumed 80%-90% attendance at 12 months (based on age). Compliance with colposcopy was informed by VCCR data and data from the Royal Women's Hospital in Victoria, and is also imperfect at 85-95% compliance (based on age). We also considered the impact of varying colposcopy compliance by +/-10% and compliance with 12 month follow-up by +/-10% as part of the probabilistic sensitivity analysis (PSA) for the cost-effectiveness outcome.

2.3 Estimating the 20-year risk of invasive cervical cancer in women with OHR HPV and low grade cytology

The guidelines for management of screen-detected abnormalities in the pre-renewed NCSP recommend that women who test pLSIL or LSIL at a routine cytology test should be referred for follow-up with another cytology test in 12 months.[29] An exception is made for women aged 30+ years who have a cytology result of pLSIL or LSIL and who do not have a history of negative cytology in the previous 2-3 years, in that they are recommended to return in 6 months or are referred directly to

colposcopy. Therefore, the risk in women with LSIL who have a recent negative cytology in the last 2-3 years and who have follow-up in 12 months can be considered an acceptable risk benchmark in Australia. We evaluated the risk of invasive cervical cancer over 20 years in this group and considered it as a benchmark when evaluating comparative risks in women testing HPV positive (not 16/18) and LBC pLSIL/LSIL. Specifically, we evaluated the 20 year risk of developing invasive cervical cancer in women of different ages who attend a routine test under the renewed primary HPV screening program, and:

i. Test HPV positive (not 16/18) and LBC p*LSIL,* and return in 12 months for an HPV test; women positive for any HPV type are then immediately referred to colposcopy and HPV-negative women are returned to routine 5-yearly screening

ii. Test HPV positive (not 16/18) and LBC *LSIL*, and return in 12 months for an HPV test; management thereafter as specified above.

iii. Test HPV positive (not 16/18) and LBC *pLSIL or LSIL* and return in 12 months for an HPV test; management thereafter as specified above.

iv. Test HPV positive (not 16/18) and LBC *pLSIL or LSIL at the year of the switch-over* and return in 12 months for an HPV test; management thereafter as specified above , and

v. Test HPV positive (not 16/18) and LBC *pLSIL or LSIL* and attend colposcopy.

For the switch-over scenario, we assessed the risk of disease in women at the year the transition from the pre-renewed NCSP to the renewed NCSP occurs (2017), as distinct from the risk in women who have been managed under the renewed NCSP over a lifetime.

2.4 Estimating the population-level impact

We evaluated the population level impact of adopting a national program utilising primary HPV screening with partial genotyping, compared to current practice for cervical cytology, assuming women testing OHR HPV positive (not 16/18) and LBC pLSIL/LSIL are:

i. Referred for follow-up surveillance in 12 months with an HPV test; or
ii. Referred for immediate colposcopy.

For both options we evaluated population level outcomes for cancer cases, deaths, precancer treatments and colposcopy procedures. These predictions did not consider transitional impacts but were based on long term outcomes. These predictions were also predicated on the overall screening adherence assumptions used for the evaluation.

2.5 Estimating the cost-effectiveness of referring HPV positive (not 16/18) and LBC pLSIL/LSIL to colposcopy compared to 12 months follow-up

We estimated the incremental cost-effectiveness ratios (ICERs) for immediate colposcopy referral versus 12 month follow-up, using standard methods. In the main evaluation we assumed the referral decision applied for women of all ages, but because the relative proportion of high grade abnormalities attributed to OHR HPV vs HPV16/18 increases in older women,[30] it is possible that immediate colposcopy may be more cost-effective in older women. We therefore also assessed strategies which utilised 12 month follow-up for younger women, but then switched to immediate colposcopy for women beyond the age of 35, 45, 55 or 65 years, and we performed probabilistic sensitivity analysis to obtain ranges of uncertainty around the estimates of the ICERs of switching at later ages.

2.6. Supplementary analysis: Follow-up options after 12 month surveillance with HPV testing

As a further exploratory analysis, we evaluated the population-level impact of adopting a national cervical screening program utilising primary HPV screening with partial genotyping, assuming women testing HPV positive (not 16/18) and LBC pLSIL/LSIL are:

- Referred for follow-up in 12 months with an HPV test; women positive for any HPV type are then immediately referred to colposcopy and HPV-negative women are returned to routine 5-yearly screening; or
- Referred for follow-up with HPV testing in 12 months and 24 months, with immediate colposcopy if women are HPV-positive (regardless of type) at either follow-up test, or a return to routine 5-yearly screening if a woman is HPV-negative at both follow-up tests.

Specifically, for both options we evaluated population level outcomes for cancer cases, deaths, precancer treatments and colposcopy procedures as well as the cost-effectiveness of 12 and 24 month follow-up compared to 12 month follow-up only. These predictions did not consider transitional impacts.

We also evaluated the incremental cost-effectiveness of the 12 and 24 month repeat test option, when compared to 12 month follow-up only.

2.7 Sensitivity analysis

Probabilistic sensitivity analysis was performed on the cost-effectiveness outcome to assess the impact of uncertainties in screening attendance rates, screening test accuracy, natural history parameters and costs.

3. Results

3.1 20-year risk of invasive cervical cancer in women with OHR HPV and low grade cytology

The 20-year risk of cancer in women with OHR HPV and low grade cytology who are aged 25, 35, 45, 55 and 65 years, considering various management strategies, is shown in

Further exploratory analysis was done to investigate the cumulative risk of CIN3+ at 24 months after the test result, and compare this to the risk of CIN3+ in women who are LSIL under the current program (shown in Figure 2). For some ages, the risk of CIN3+ is higher in women testing HPV positive (not 16/18) and LBC pLSIL/LSIL when compared to the risk of CIN3+ in women testing LSIL under the pre-renewed NCSP. However, the risk of CIN3+ is higher in women who are referred for immediate colposcopy than in women who are referred for 12 months follow-up, which is likely due to the larger number of women who attend colposcopy (and hence have a diagnosis of CIN3).

Figure 1. The benchmark risk in women testing LSIL (or LSIL with a negative test result in the last 2 years) is also represented. The 20-year risk of cervical cancer in women who tested HPV positive (not 16/18) and LBC pLSIL/LSIL and who are referred to colposcopy is slightly lower than in the group who delayed follow-up by 12 months. However, for each age, the risk in women testing OHR HPV positive (not 16/18) and LBC pLSIL or LSIL under the new guidelines is lower than the benchmark risk for women with LSIL in the pre-renewed program.

Further exploratory analysis was done to investigate the cumulative risk of CIN3+ at 24 months after the test result, and compare this to the risk of CIN3+ in women who are LSIL under the current program (shown in Figure 2). For some ages, the risk of CIN3+ is higher in women testing HPV positive (not 16/18) and LBC pLSIL/LSIL when compared to the risk of CIN3+ in women testing LSIL under the pre-renewed NCSP. However, the risk of CIN3+ is higher in women who are referred for immediate colposcopy than in women who are referred for 12 months follow-up, which is likely due to the larger number of women who attend colposcopy (and hence have a diagnosis of CIN3).

Figure 1: The cumulative risk of developing invasive cervical cancer after 20 years for a range of screening test results. The 20 year risk of cervical cancer in women with LSIL in the pre-renewed NCSP with a negative test in last 2 years (accepted risk under the pre-renewed NCSP) is shown as the horizontal line.

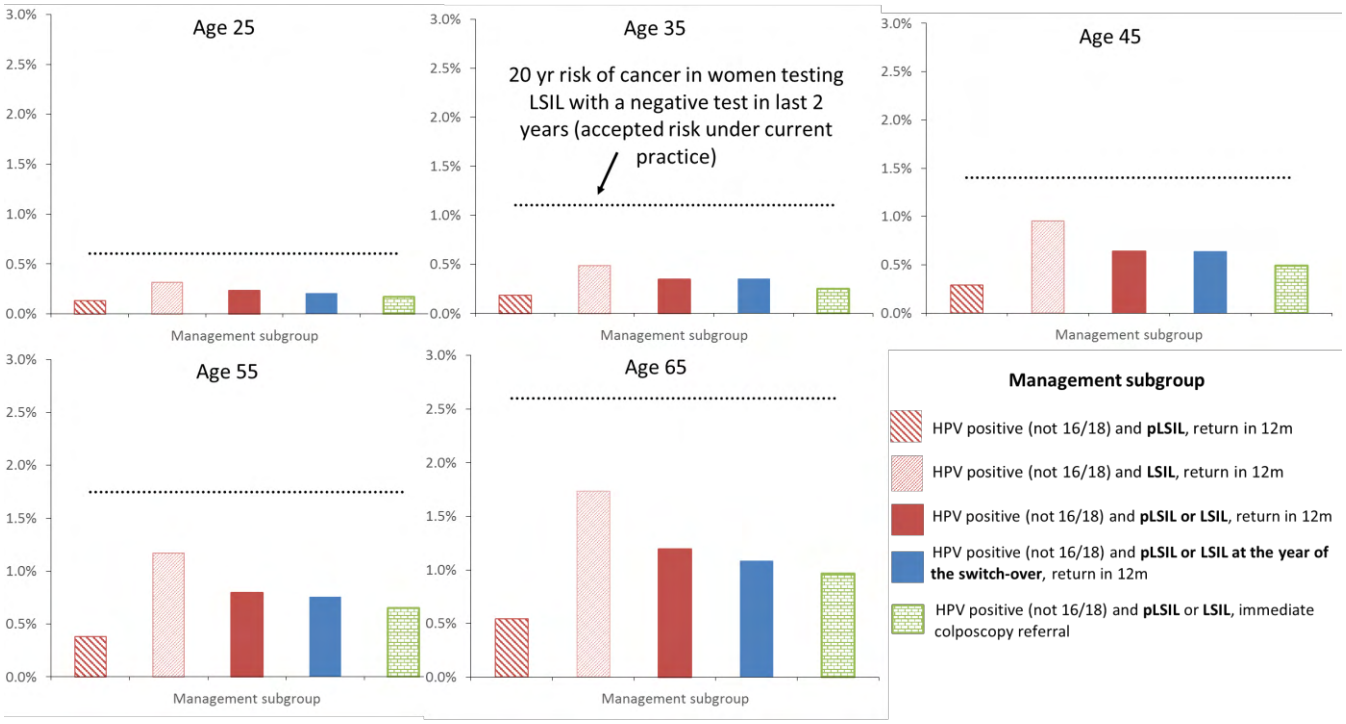
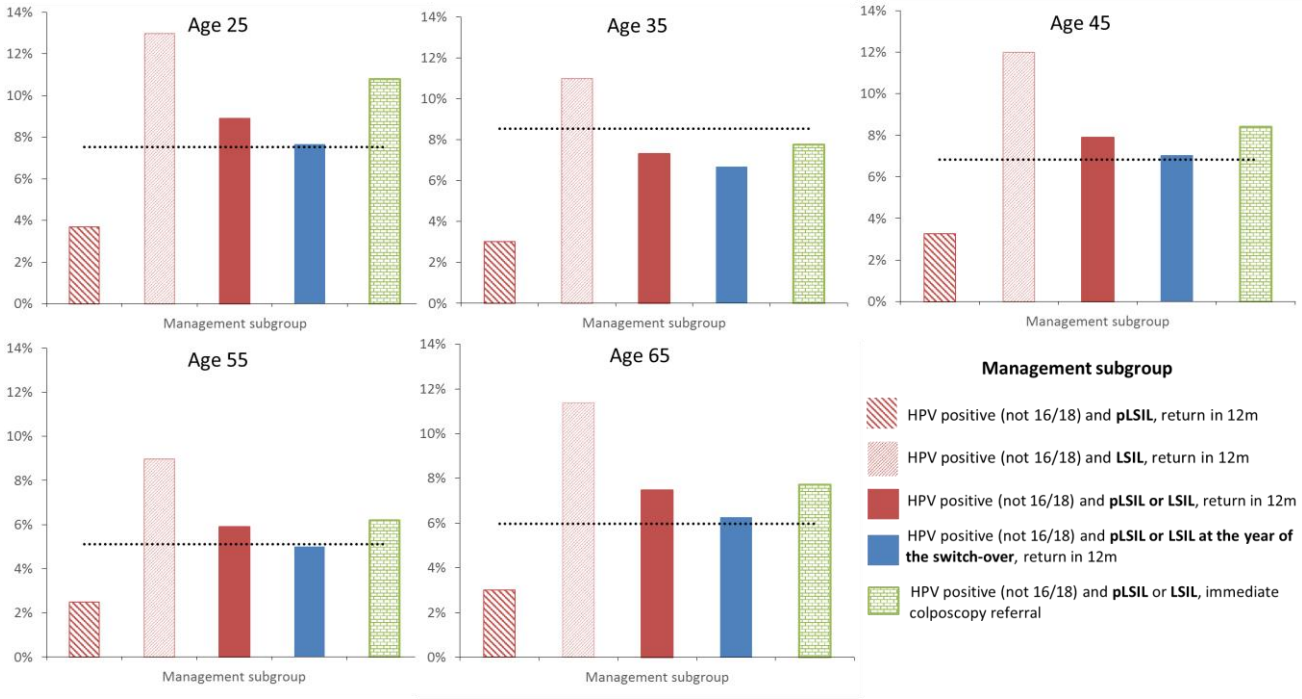


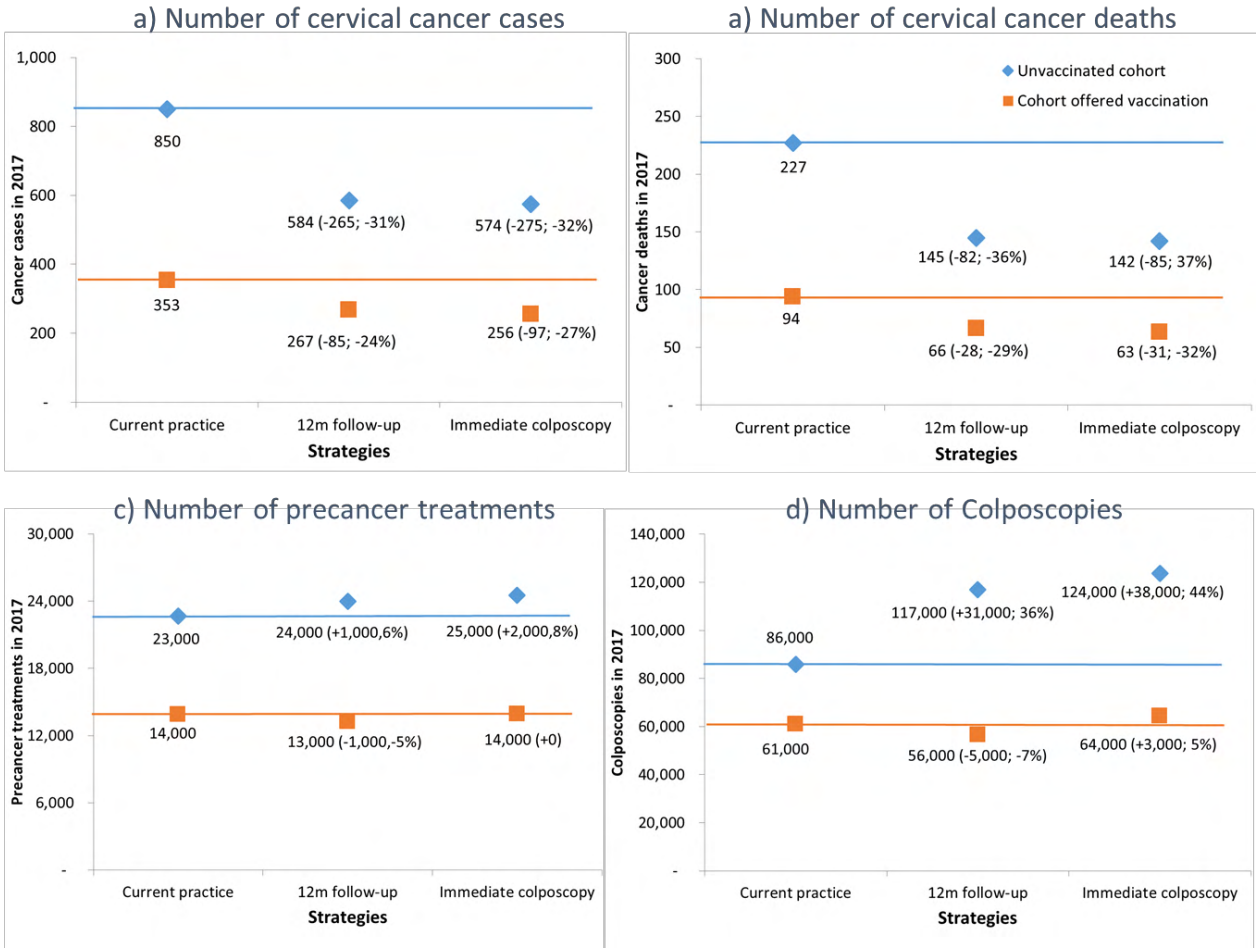
Figure 2: The cumulative risk of CIN3+ 24 months for a range of screening test results. The 24 month risk of CIN3+ in women with LSIL with a negative test in last 2 years under the pre-renewed NCSP is shown as the horizontal line.



3.2 Population-level impact

Figure 3 shows the model predicted number of cervical cancer cases, deaths, histologically-confirmed high-grade lesions and colposcopies for the year 2017 for unvaccinated cohorts and cohorts offered vaccination, given the two alternate management strategies for OHR HPV in the presence of pLSIL/LSIL. All results are shown in relation to current practice for the pre-renewed NCSP.

Figure 3: Model predicted annual number of a) cancer cases, b)cancer deaths, c)precancer (CIN2/3) treatments and d)colposcopies in the for unvaccinated cohorts (blue) and vaccinated cohorts (orange). Numbers indicate case numbers. The difference in case numbers and percentage difference compared to current practice in the pre-renewed NCSP is shown in the brackets.*



*Using female Australian population as predicted for 2017

In the absence of HPV vaccination, cancer cases would be predicted to drop by 31% (265 fewer cases) and 32% (275 fewer cases) given 12 month follow-up and immediate colposcopy management options for women with OHR HPV and p/LSIL, respectively, and to drop by 24% (85 less cases) and 27% (97 less cases) in cohorts offered vaccination, respectively. For unvaccinated cohorts, cancer deaths are predicted to drop by 36% (82 less deaths) and 37% (85 less deaths) under 12 month follow-up and immediate colposcopy options respectively, and drop by 29% (28 less deaths) and 32% (31 less deaths) in vaccinated cohorts. Thus, overall, immediate colposcopy provides an additional 1-3% reduction in cervical cancer cases and deaths when the findings of the whole program are considered at the population level in relation to current screening practice in the pre-renewal NCSP.

For unvaccinated cohorts, colposcopies are predicted to increase substantially by 36% and 44% under 12 month follow-up and immediate colposcopy options respectively, and *decrease* by 7% given 12 month follow-up option in vaccinated cohorts. However, we predict 5% additional colposcopies if immediate colposcopy is implemented when compared to the pre-renewed NCSP. Thus immediate

colposcopy results in an *additional* 8% colposcopies over 12m follow-up in unvaccinated women when compared to the pre-renewed NCSP, and an additional 12% colposcopies in vaccinated cohorts.

Similarly, the number of treatments for CIN2/3 are predicted to increase in unvaccinated cohorts by 6% and 8% under 12 month follow-up and immediate colposcopy options, respectively, but to *decrease* in vaccinated cohorts by 5% and 0% under 12 month follow-up and immediate colposcopy options, respectively.

Therefore, immediate colposcopy referral provides some benefit over 12 month follow-up, but at the cost of a marked increase in colposcopies. An additional 650-700 colposcopies are required to avert a cervical cancer case under immediate colposcopy compared to 12 month follow-up, and an additional 2,300-2,500 colposcopies are required to avert a cancer death.

3.3 The cost-effectiveness of referring HPV positive (not 16/18) and LBC pLSIL/LSIL to colposcopy compared to 12 months follow-up

The estimated cost-effectiveness of immediate colposcopy compared to 12 month follow-up in this group of women is shown in Table 1. The ICER for immediate colposcopy compared to 12 month follow-up was estimated to be >A$100,000/LYS, compared to an indicative willingness-to-pay threshold of A$50,000/LYS in Australia.

If we switch to immediate colposcopy in women from ages 35 years and older, the ICER is estimated to be $59,800/LYS (95%CrI: $55,800-$62,100) in unvaccinated cohorts and $61,600/LYS (95%CrI: $58,300-$64,900) in cohorts offered vaccination. If we switch to immediate colposcopy in women from ages 45 and older, the ICER is $39,800 (95%CrI: $36,700-$41,900) in unvaccinated cohorts and $40,900/LYS (95%CrI: $38,300-$43,600) in cohorts offered vaccination. Therefore, it may be considered cost-effective to utilise immediate colposcopy for women aged 45 and older.

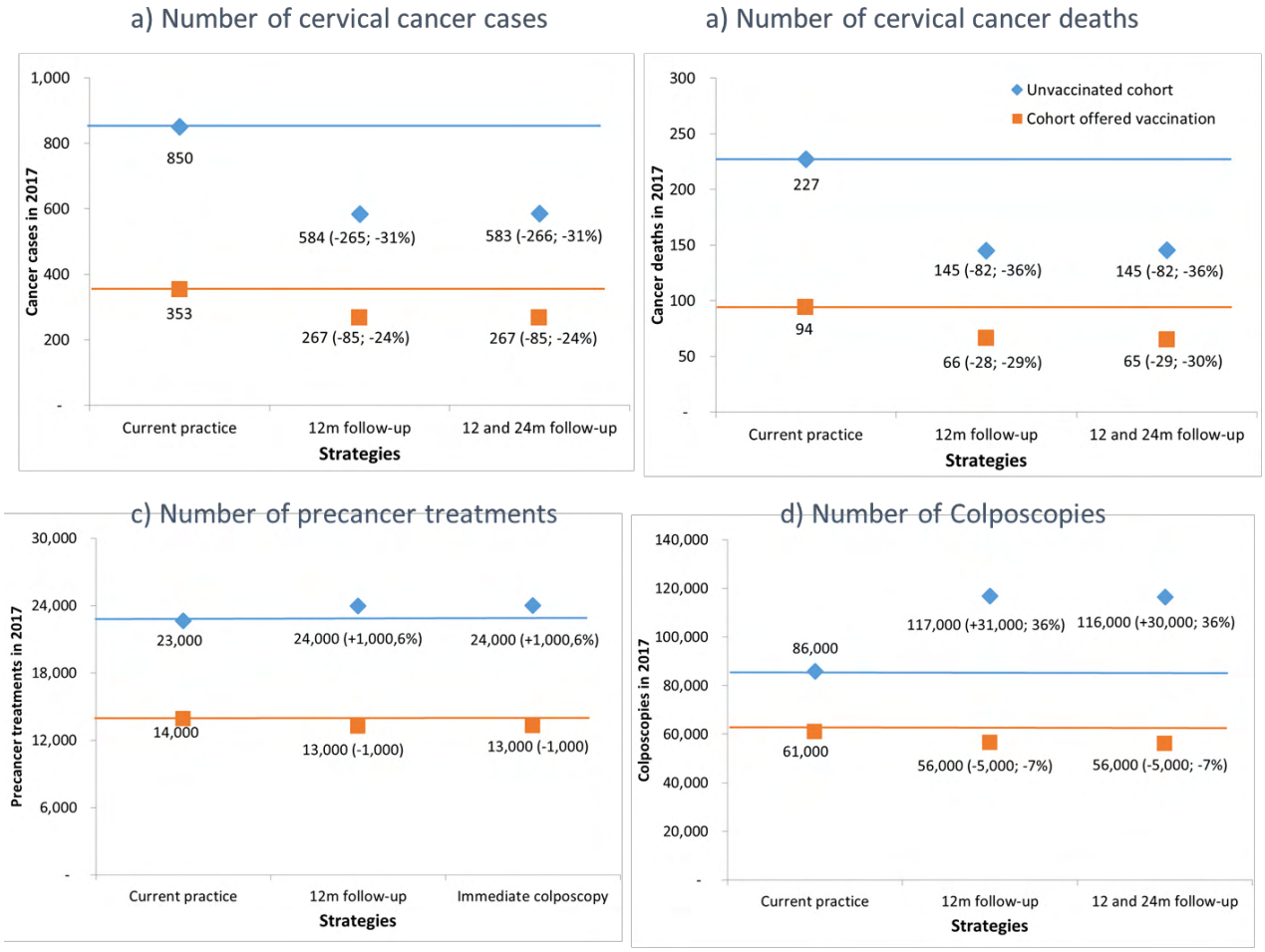
Table 1: The cost-effectiveness of 'Immediate colposcopy' compared to '12m follow-up' in women with OHR HPV and pLSIL or LSIL

	Incremental cost-effectiveness of immediate colposcopy compared to 12m follow-up in women with OHR HPV and pLSIL or LSIL	
	Unvaccinated cohorts	Cohorts offered vaccination
Immediate colposcopy for women of all ages	$154,000/LYS	$158,000/LYS
12m follow-up for women up to age 35, then Immediate colposcopy for women aged 35+	$59,800/LYS (95%CrI: $55,800-$62,100)	$61,600/LYS (95%CrI: $58,300-$64,900)
12m follow-up for women up to age 45, then immediate colposcopy for women aged 45+	$39,800/LYS (95%CrI: $36,700-$41,900)	$40,900/LYS (95%CrI: $38,300-$43,600)
12m follow-up for women up to age 55, then immediate colposcopy for women aged 55+	$40,100/LYS (95%CrI: $36,100-$41,500)	$40,200/LYS (95%CrI: $37,500-$42,900)
12m follow-up for women up to age 65, then immediate colposcopy for women aged 65+	$38,100/LYS (95%CrI: $35,000-$40,500)	$39,400/LYS (95%CrI: $36,600-$42,200)

3.4 Supplementary analysis: Follow-up options after 12 month surveillance with HPV testing

Assuming that women with OHR HPV and pLSIL/ LSIL are returned to surveillance at 12 months, Figure 4 shows the model-predicted number of cervical cancer cases, deaths, precancer treatments and colposcopies for the year 2017 for unvaccinated cohorts and cohorts offered vaccination, given the two scenarios for following these women i.e. either HPV surveillance at 12 months only, or repeat HPV surveillance at 12 months and 24 months if a woman is HPV negative at the first 12 month test.

Figure 4: Model predicted annual number of a) cancer cases, b)cancer deaths, c)precancer treatments and d)colposcopies in the for unvaccinated cohorts (blue) and vaccinated cohorts (orange). Numbers indicate case numbers. The difference in case numbers and percentage difference compared to current practice in the pre-renewed NCSP is shown in the brackets.*



*Using female Australian population as predicted for 2017

For both unvaccinated cohorts and cohorts offered vaccination, the population-level number of cervical cancer cases and deaths is very similar between the 12 month follow-up scenario and the 12 and 24 month follow-up scenarios (<1% difference). The number of CIN2/3 treatments and the number of colposcopies predicted under the two scenarios is also very similar, and there is at most 1% difference between the two scenarios in terms of these outcomes.

The cost-effectiveness of 12 and 24 month follow-up compared to 12m follow-up is shown in Table 2. The ICER for 12 and 24 month follow-up is >$300,000/LYS compared with 12 month follow-up alone. Even if the switch to repeat 12 and 24 month follow-up is confined to women over 55 years, the ICER remains greater than $70,000/LYS. Therefore, repeat 12 and 24 month follow-up is unlikely to be cost-effective in Australia, compared to 12 month follow-up alone.

Table 2: The cost-effectiveness of 12 and 24 month HPV testing follow-up compared to 12m follow-up in women with OHR HPV and P/LSIL.

	cost-effectiveness of 12 and 24m follow-up compared to 12m follow-up	
	Unvaccinated cohorts	Cohorts offered vaccination
12 and 24m follow-up for all ages	$ 405,018	$358,238
12m follow-up for women up to age 35, then 12 and 24m follow-up for women aged 35+	$146,758	$142,886
12m follow-up for women up to age 45, then 12 and 24m follow-up for women aged 45+	$96,744	$ 94,000
12m follow-up for women up to age 55, then 12 and 24m follow-up for women aged 55+	$71,769	$70,823
12m follow-up for women up to age 65, then 12 and 24m follow-up for women aged 65+	Dominated	Dominated

4. Discussion

In this evaluation of potential management strategies for intermediate risk women in the renewed NCSP in Australia, we found that the estimated 20-year risk of developing invasive cervical cancer in women who have other oncogenic HPV (not 16/18) infection and who have a triage LBC low grade (pLSIL/LSIL) result, who then have 12 month follow-up surveillance with HPV testing, is lower than the current risk in women with a screening cytology result of LSIL in the pre-renewed cytology-based screening program. This indicates that the risk of invasive cancer in this group is lower than the accepted benchmark risk for 12-month follow-up in Australia in the current cervical screening program. We also found that the incremental benefit of direct referral to colposcopy for in terms of overall population impact on invasive cancer incidence and mortality, while positive, was relatively modest and that, consequently, the management of these women via direct referral to colposcopy is unlikely to be cost-effective. We also found that such a management strategy would be associated with some harms in the form of additional colposcopy referrals and treatment, with >650 colposcopies required to avert an additional case of cervical cancer and an additional 2,300-2,500 colposcopies to avert a cancer death.

These findings are reflective of the lower risks overall seen in the group of women with OHR HPV infection, once the higher risk groups (those with HPV16/18 infection or cytology results indicative of high grade disease), are removed from the population of interest. In the renewed NCSP, women with HPV16/18 and/or high grade cytology are automatically managed as 'higher risk' and directly referred to colposcopy; thus the risks remaining in those with OHR HPV infection and low grade cytology are reduced. It is likely that in the majority of cases the low grade cytology is reflective of a productive HPV infection with the OHR HPV type. By managing using a follow-up surveillance HPV test, it is possible to check for persistent HPV infection, which has been shown to increase the risk of subsequent disease progression.[12] At the 12 month follow-up, we assumed that women with any HPV detected would at that point be referred for colposcopy, allowing for evaluation. In this way only women with transient infections are not referred to colposcopy; and our findings indicate that this has only a very a modest impact on the risk of developing invasive cervical cancer in the future.

We did find that the cost-effectiveness of direct referral of women with OHR and pLSIL/LSIL increased if such referral is confined to older women (>45 years); this would need to be balanced against any difficulties inherent in implementing differential management recommendations in a specific subgroup according to the age of the woman at testing, and is a policy decision which would need to take into account a range of other factors, such as the number of colposcopies required to avert each additional case, which still exceed 400 for women aged >45.

We found that in the context of performing 12 month follow-up with a single HPV test, adding an additional HPV test at 24 months would be associated with very marginal benefits and would be very cost-ineffective, with an incremental cost-effectiveness ratio of >$300,000/LYS, compared to 12 month follow-up only in this group, and that this intervention remains cost-ineffective even if it confined only to older women. This finding likely reflects the predicted effectiveness of a single HPV test to check for persisting infection at 12 months.

Our evaluation has several strengths. Firstly, we have used a comprehensive and well-validated model of cervical cancer natural history, HPV infection, and cervical screening, which has been validated against many data sources across several countries. We have used local data to take into account realistic levels of adherence to screening and follow-up recommendations, although it should be noted that if the assumed levels of adherence are not achieved the results will not be as predicted. In sensitivity analysis we explored a range of options for adherence with screening recommendations and with compliance with a 12 month follow-up recommendation, and our broad findings remained unchanged across a range of feasible options.

To our knowledge, this is the first detailed evaluation of the management of intermediate risk women with oncogenic (not HPV 16/18) infections in a primary HPV screening program. These findings are currently informing the development of new clinical management guidelines in Australia and will be of broad interest for other countries introducing primary HPV screening, especially in the context of considering the overall benefits of partial genotyping options for primary screening. Although at the current time there is an absence of direct clinical evidence to support our modelled findings, it should be noted that these findings are broadly consistent with known data on the longitudinal risks of serious disease in women with OHR HPV types.[12]

It is notable that an ongoing major clinical trial, *Compass* [Clinicaltrials.gov NCT02328872], is expected to provide direct evidence in the future on the outcomes in this group of women within a primary HPV screening program. Compass is a large scale randomised controlled trial of 5-yearly HPV versus 2.5 yearly image read LBC cytology screening in women aged 25-69 years, and it is being conducted in the state of Victoria, Australia. HPV screening in the trial incorporates the use of partial genotyping and 12 month follow-up for OHR pLSIL/LSIL women, as considered in the current evaluation. Recruitment is stratified according to whether women are in age cohorts that were offered vaccination (i.e. whether aged ~35 years or less in 2015). In HPV-screened women, a secondary randomisation process for intermediate risk women with other oncogenic HPV infections (i.e. not HPV16/18) is implemented, and these women are randomised to be triaged either with LBC or with dual-stained p16/Ki67 cytology (CINtec PLUS, Roche/Ventana). In conjunction with the implementation of the renewed NCSP, Compass will provide emergent evidence both on the performance of LBC triage of women with OHR HPV infections, but also data on new options for management in this group. In the future, this is expected to provide the basis for further review and, if warranted, consideration of the role of other options for management.

In conclusion, in this evaluation, 12 month surveillance of women who have other high risk HPV (not HPV16/18) infections and low grade triage cytology, appears to provide the best balance of benefits, harms and cost-effectiveness in the context of partial genotyping for HPV 16/18 within the new Australian primary-HPV based screening program.

1. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014;383:524-32.
2. HPV Today No 34. HPV Today 2015;34.
3. Castle PE, Glass AG, Rush BB, et al. Clinical human papillomavirus detection forecasts cervical cancer risk in women over 18 years of follow-up. J Clin Oncol 2012;30:3044-50.
4. Gage JC, Duggan MA, Nation JG, Gao S, Castle PE. Comparative Risk of High-Grade Histopathology Diagnosis After a CIN 1 Finding in Endocervical Curettage Versus Cervical Biopsy. J Low Genit Tract Dis 2013.
5. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J NatlCancer Inst 2005;97:1072-9.
6. Gertig DM, Brotherton JML, Saville AM. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. Sexual Health 2011;8:171-8.
7. Brotherton JML, Liu B, Donovan B, Kaldor JM, Saville M. Human papillomavirus (HPV) vaccination coverage in young Australian women is higher than previously estimated: independent estimates from a nationally representative mobile phone survey. Vaccine 2014;32:592-7.
8. Australian Institute of Health and Welfare. Cervical screening in Australia 2011-2012. Cancer series no.82. Cat. no. CAN 79. Canberra: AIHW,; 2014.
9. Smith MA, Canfell K, Brotherton JM, Lew JB, Barnabas RV. The predicted impact of vaccination on human papillomavirus infections in Australia. Int J Cancer 2008;123:1854-63.
10. Lew JB, Simms K, Smith MA, et al. National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting (Assessment Report). MSAC application number 1276. Canberra: Department of Health 2014.
11. National Screening Unit. Guidelines for Cervical Screening in New Zealand: Incorporating the management of women with abnormal cervical smears. Wellington: National Screening Unit, Ministry of Health; 2008.
12. Draft clinical management guidelines for the prevention of cervical cancer. 2016. (Accessed at http://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Prevention.)
13. Canfell K, Sitas F, Beral V. Cervical cancer in Australia and the United Kingdom: comparison of screening policy and uptake, and cancer incidence and mortality. Med J Aust 2006;185:482-6.
14. Creighton P, Lew J, Clements M, et al. Cervical cancer screening in Australia: modelled evaluation of the impact of changing the recommended interval from two to three years. BMC Public Health 2010;10:734.
15. Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. Br J Cancer 2004;91:530-6.
16. Canfell K, Clements M, Harris J. Cost-effectiveness of proposed changes to the national cervical screening program; 2008.
17. Canfell K, Lew JB, Smith M, Walker R. Cost-effectiveness modelling beyond MAVARIC study end-points. In: Kitchener HC, Blanks R, Cubie H, et al., eds. MAVARIC - a comparison of automation-assisted and manual cervical screening: a randomised controlled trial Health Technology Assessment ; Vol 15: No 3; 2011.
18. Medical Services Advisory Committee. Automation Assisted and Liquid Based Cytology for Cervical Cancer Screening. MSAC reference 1122, Assessment report. Canberra: Australian Government Department of Health; 2009.
19. Medical Services Advisory Committee. Human Papillomavirus Triage Test For Women With Possible or Definite Low-Grade Squamous Intraepithelial Lesions. MSAC reference 39, Assessment report. Canberra: Australian Government Department of Health; 2009.

20. Canfell K, Shi JF, Lew JB, et al. Prevention of cervical cancer in rural China: Evaluation of HPV vaccination and primary HPV screening strategies. Vaccine 2011;29:2487-94.
21. Shi JF, Canfell K, Lew JB, et al. Evaluation of primary HPV-DNA testing in relation to visual inspection methods for cervical cancer screening in rural China: an epidemiologic and cost-effectiveness modelling study. BMC Cancer 2011;11:239.
22. C Kitchener H, Canfell K, Gilham C, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess 2014;18.
23. Australian Institute of Health and Welfare (AIHW). ACIM (Australian Cancer Incidence and Mortality) Books. Canberra; 2011.
24. Australian Bureau of Statistics. Deaths, Australia, 2011. Canberra: ABS; 2012.
25. Australian Bureau of S. National Health Survey, Summary of Results, Australia, 2001. Canberra: ABS; 2002.
26. Australian Bureau of S. Deaths, Australia, 2005. Canberra: ABS; 2006.
27. Kang YJ. Patterns of care study and development of a mode of treatment, survival and mortality for invasive cervical cancer: The University of Sydney; 2012.
28. Smith MA, Canfell K. Testing previous model predictions against new data on human papillomavirus vaccination program outcomes. BMC Res Notes 2014;7:109.
29. National Health and Medical Research Council. Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities. Canberra: Commonwealth of Australia; 2005.
30. Simonella L, Lewis H, Smith M, Neal H, Bromhead C, Canfell K. The prevalence of type-specific oncogenic human papillomavirus infection in high grade cervical disease in New Zealand. BMC Infect Dis 2013;13.