Gynecologic Oncology 152 (2019) 472–479

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The combined impact of implementing HPV immunisation and primary HPV screening in New Zealand: Transitional and long-term benefits, costs and resource utilisation implications

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HIGHLIGHTS

- Transitioning from cytology to primary HPV cervical screening could avert 149 cancer cases and 45 deaths by 2035.
- Annual primary test volumes will decrease following programme transition, fluctuating with the 5-year screening interval.
- NCSP costs are predicted to reduce by 16% by 2035 due to the effect of HPV vaccination and primary HPV screening.
- Colposcopy referrals following a primary test are predicted to reduce from 2.7% to 2.2% by 2035.
- Findings from this study will be important for planning and communication around the program transition.

ARTICLE INFO

Article history:
Received 25 June 2018
Received in revised form 16 October 2018
Accepted 30 October 2018

Keywords:
Cervical screening
HPV vaccination
HPV testing
Cytology
Cervical cancer

ABSTRACT

Background. In response to emergent evidence, many countries are transitioning from cytology-based to HPV screening. We evaluated the impact of an upcoming transition on health outcomes and resource utilisation in New Zealand.

Methods. An extensively validated model of HPV transmission, vaccination, natural history and cervical screening ('*Policy1-Cervix*') was utilised to simulate a transition from three-yearly cytology for women 20–69 years to five-yearly HPV screening with 16/18 genotyping for women 25–69 years, accounting for population growth and the impact of HPV immunisation. Cervical cancer rates, resources use (test volumes), costs, and test positivity rates from 2015 to 2035 were estimated.

Findings. By 2035, the transition to HPV screening will result in declines in cervical cancer incidence and mortality rates by 32% and 25%, respectively, compared to 2018. A potentially detectable 5% increase in cervical cancer incidence due to earlier detection is predicted for the year of transition. Annual numbers of women screened will fluctuate with the five-year screening interval. Cytology volumes will reduce by over 80% but colposcopy volumes will be similar to pre-transition rates, and program costs will be reduced by 16%. A 9% HPV test positivity rate is expected in the first round of HPV screening (2019–2023), with 2.7% of women referred for colposcopy. Transitioning from cytology to primary HPV cervical screening could avert 149 cancer cases and 45 deaths by 2035.

Conclusion. Primary HPV screening and vaccination will reduce cervical cancer and resources use. A small transient apparent increase of invasive cancer rates due to earlier detection may be detectable at the population level, reflecting the introduction of a more sensitive screening test. These findings can be used to inform health services planning and public communications surrounding program implementation.

1. Introduction

The New Zealand (NZ) Ministry of Health plans to transition the NCSP from three-yearly cytology for women 20–69 years ('current

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https://doi.org/10.1016/j.ygyno.2018.10.045
0090-8258/

practice') to a program involving five-yearly primary HPV screening from age 25–69, partial genotyping for HPV16/18 and LBC triage for non16/18 oncogenic types ('updated NCSP'). This decision was based on international evidence that HPV screening is more effective than cytology. A number of trials and cohort studies, taken together, have established that increased CIN2+ detection at baseline and treatment, leads to decreased CIN3+ longitudinally [1–9] A major pooled analysis of four trials concluded that HPV testing increases protection against the development of invasive cervical cancer. One analysis, for example, found that the cumulative risk of CIN3+ development three years after a negative HPV test is 0.069% versus 0.19% following a negative cytology test [6]. Our previous work predicted that in the long term, reductions in cervical cancer incidence and mortality in NZ of ~12% in cohorts offered quadrivalent (HPV4) vaccination (~16% in unvaccinated cohorts) could be achieved in women offered primary HPV screening from age 25, compared to women under current practice from the age of 20, and also estimated resource utilisation in the context of a primary HPV program [10]. While a growing number of countries are transitioning from existing cytology-based cervical screening programmes to longer-interval HPV-based programmes, there is a need for a greater understanding of not only the population-level health implications of such a transition, but also resource-use estimates for workforce planning and cost analyses for healthcare budgeting [11–13]. Modelling studies from Australia indicate that a rapid transition from shorter-interval cytology (two-yearly cytology in the case of Australia) to five-yearly HPV screening is expected to result in transitional temporal fluctuations in screening and resource utilisation volumes, and health outcomes, for at least the first three rounds of HPV-based screening [14,15]. It is necessary for public communication, safety monitoring, and resource and workforce planning in NZ to derive estimates of the expected health outcomes and resource utilisation during the transitional period from cytology screening to the updated NCSP, in the context of continuing HPV immunisation.

Therefore, the current analysis aims to provide year-by-year estimates for health outcomes and resource use during the period immediately before, during, and after the program transition in NZ, from 2015 to 2035.

2. Materials and methods

We used an established modelling platform for the analysis - *Policy1-Cervix*. Age-specific rates and cases of histologically-confirmed CIN grade 2/3, cervical cancer incidence and mortality were simulated; as well as year-by-year primary and follow-up test volumes, pre-cancer (CIN) treatments and primary and triage test positivity rates. This analysis also provides cost and summary effectiveness analysis outcomes, reporting on life-years, quality-adjusted life-years and total cervical screening programme costs over time. Two scenarios were modelled; the first considers a rapid transition from current practice to the updated NCSP in 2019 (baseline scenario, referred to as 'HPV-based'), and the second (counterfactual scenario, referred to as 'cytology-based') assumes current practice continues indefinitely. The updated NCSP is described in detail in Appendix S1. Both scenarios include the current National HPV Immunisation Programme. This comparison is to quantify the expected success of the updated NCSP relative to current practice, in addition to defining which outcomes are due to screening program change, and which may be attributable to demographic change or reductions in underlying HPV prevalence due to HPV vaccination.

2.1. Modelling of the National Cervical Screening Programme

Policy1-Cervix simulated NZ's planned programmatic transition from current practice to the updated NCSP as occurring in 2019. Briefly, the current NCSP recommends that asymptomatic women aged 20–69 years attend for three-yearly routine screening using LBC, with HPV triage of low-grade cytological abnormalities in women aged 30 + years; women with either a high-grade cytology result or a low-grade cytology result and positive HPV triage test result are referred to colposcopy [16]. The modelled clinical management for routine screening and follow-up were based on existing guidelines and expert advice [10,16]. Screening initiation patterns and age- and interval-specific probabilities that a woman will re-attend for screening are derived from NCSP register data; simulated three- and five-year screening coverage rates are consistent with the observed data. [10,17,18] Detailed descriptions of screening participation, model structure, parameter assumptions and data sources used to model current practice have been described previously [10].

The modelled screening pathway and clinical management assumptions for the updated NCSP during and after transition, were based on updated guidelines for cervical screening in NZ, as released for public consultation [19]. The updated NCSP recommends five-yearly HPV screening with partial genotyping for HPV16/18 for asymptomatic women aged 25–69 years, and LBC triage for women who are screen-positive for non-16/18 oncogenic types. Women positive for HPV 16/18 at primary screening are referred for colposcopy, as are women positive for high risk HPV types not 16/18, whose cytology triage yielded ASC-H/HSIL or worse (Fig. 1, Appendix S1).

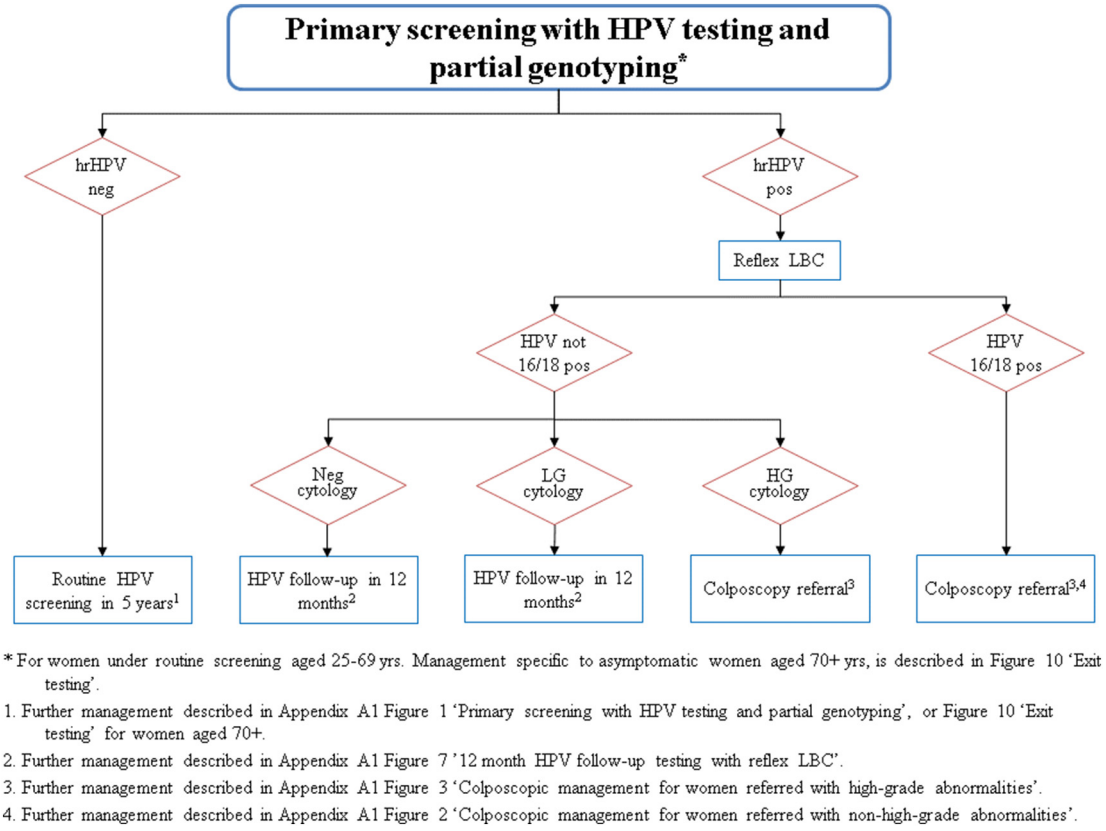
The model assumed the transition to the new programme occurs at the start of 2019. The model assumes that from 2019 onwards, women aged 25 or older attending for a routine screen will receive a HPV test in place of cytology, and henceforth be managed according to the new guidelines; a further assumption was that women under the age of 25 at the time of switchover are ineligible for primary HPV testing, regardless of whether they have already initiated screening, until their 25th birthday. Women attending for follow-up after a previous abnormality (including those aged less than 25 years) would also be managed according to the new guidelines from 2019 [19]. Following the transition, it is assumed that no women initiate screening until 25 years of age, at which time the assumed age-specific uptake rates are such that the proportion of ever-screened women matches that observed under the current program [10]. The modelled screening re-attendance rates in the updated NCSP were derived by assuming that the proportion of women who have early re-screening, on-time screening and late re-screening remains similar to that observed currently in NZ; this modelled screening attendance assumption has been explicitly described elsewhere [10].

2.2. Policy1-Cervix model platform

The platform used in this analysis, *Policy1-Cervix*, consists of a dynamic HPV transmission and vaccination model (implemented in Microsoft Visual Studio C++), overlayed with a semi-Markov model of the natural history of CIN, cervical screening and cervical cancer survival (implemented in TreeAge Pro 2014, TreeAge Software Inc., MA, USA). *Policy1-Cervix* is configurable to different settings and has been used to evaluate various cervical cancer screening strategies in a range of countries. [10,14,20–30] The model platform used in this study has been adapted to the NZ setting and extensively calibrated and validated with observed NZ data, as previously described in detail [10]. The analysis for the current study involved simulation of multiple birth-cohorts for the period 1931–2035 to produce cross-sectional population-level outcomes for calendar years from 2015 to 2035. Each birth cohort was simulated from 10 to 84 years using an annual time step.

2.3. Model parameters, assumptions and data sources

The natural history component of *Policy1-Cervix* incorporates disease progression/regression rates for HPV infections due to types 16 (HPV 16), 18 (HPV 18) and oncogenic HPV (hrHPV) for types other than HPV16/18 (not 16/18). The model parameter assumptions and calibration for NZ have previously been published; this includes a detailed description of NZ-specific screening, diagnosis and treatment costs and



* For women under routine screening aged 25-69 yrs. Management specific to asymptomatic women aged 70+ yrs, is described in Figure 10 'Exit testing'.

1. Further management described in Appendix A1 Figure 1 'Primary screening with HPV testing and partial genotyping', or Figure 10 'Exit testing' for women aged 70+.
2. Further management described in Appendix A1 Figure 7 '12 month HPV follow-up testing with reflex LBC'.
3. Further management described in Appendix A1 Figure 3 'Colposcopic management for women referred with high-grade abnormalities'.
4. Further management described in Appendix A1 Figure 2 'Colposcopic management for women referred with non-high-grade abnormalities'.

Fig. 1. Management of women under the updated NCSP (see Appendix S1 for detailed management flow charts).

QALY (quality-adjusted life year) weights [10]. A dynamic HPV transmission model that has been adapted to the NZ setting was used to estimate the type-specific HPV incidence by single year of age over time in NZ [10]. The transmission model simulated the impact of the National HPV Immunisation Program, which commenced in late 2008, based on published vaccination coverage rate for cohorts born between 1990 and 2002 (uptake rate of all three doses ranges from 38% in the 1990 cohort to 66% in the 2002 cohort) [31]. Uptake in females born after 2003 was assumed to be equivalent to that for those born in 2002. Further detail of the assumptions underlying the modelling of HPV vaccination are described elsewhere [10].

This implementation of *Policy1-Cervix* incorporates further detail with respect to survival assumptions for women diagnosed with cervical cancer than that incorporated in our previous analysis. In our previous analysis, survival rates were applied by year since diagnosis and stage at detection [10]. In this implementation, survival rates by year since diagnosis are applied by both cancer stage at detection (local, regional and distant) and detection modality (screen-detected cervical cancer or symptomatically-detected cervical cancer), as published in recent studies [32–35]. Additional parameter details such as test characteristics, treatment success and compliance to screening and follow-up recommendations have been described in detail elsewhere [10].

2.4. Simulated scenarios and outcomes considered

The modelled analysis simulated two primary scenarios: the first scenario assumed no change to the current NCSP and that current practice continues indefinitely ('cytology-based' counterfactual scenario); the second scenario assumed that the program transitions to the updated NCSP in 2019 ('HPV-based' baseline scenario). Both scenarios are assumed to occur in the context of the National HPV Immunisation Programme. The outcomes of each scenario were predicted for each year in the period between 2015 and 2035 where case numbers, volume estimates and costs are based on Statistics NZ population estimates for 2015–2016 and median population projections for years 2017 onwards [36,37]. The health outcomes considered were case numbers and age standardised rates for each of: histologically-confirmed CIN2/3 detection, incident cervical cancer and cervical cancer death. Estimates are additionally stratified by attributable HPV type group (incident cervical cancer and CIN2/3 detection) and stage at diagnosis (incident cervical cancer). The resource utilisation outcomes considered were the total volumes (all ages) of HPV tests, LBC tests, colposcopies, biopsies, pre-cancer treatments and the total number of women screened. This analysis also reports on primary and triage test positivity rates predicted under the updated NCSP, as well as costs and quality-adjusted life years.

2.5. Model validation

Model validation outcomes are consistent with observed age-specific rates of cervical cancer incidence and mortality, histologically-confirmed low- and high-grade cervical abnormalities and abnormal cytology. These results, in addition to volumes of cervical disease cases and test volumes, are presented in Appendix S2.

2.6. Sensitivity analysis

Our previous modelled analysis for NZ has indicated that HPV test accuracy assumptions and screening compliance assumptions are driving factors behind simulation outcomes [10]; hence these parameters were varied for the sensitivity analysis. Our predictions for health outcomes and resource use were similar across a range of assumptions about HPV test sensitivity and management of post-treatment women (Appendix S3).

3. Results

3.1. Health outcomes

For both the cytology-based (counterfactual) and HPV-based (baseline) scenarios, rates of histologically-confirmed CIN2/3, cervical cancer incidence and cervical cancer mortality are predicted to steadily decline over the period from 2015 to 2035 due to the combined effect of cervical screening and HPV vaccination (Fig. 2). In general, these rates are lower for the HPV-based (baseline) scenario than in the cytology-based (counterfactual) scenario, except for a small transient increase (~5%) in the rate of early cervical cancer detection in the baseline scenario following the introduction of the updated NCSP (due to earlier detection of prevalent disease when the more sensitive test is first introduced). Additionally, small transitional fluctuations in CIN2/3 and cervical cancer detection in-line with the five-year screening interval are predicted following the screening program transition; however, these fluctuations are comparatively minor and dampen quickly after approximately two screening rounds.

Compared to pre-transitional rates (i.e. 2018), the updated NCSP (baseline scenario) is predicted to decrease rates of histologically-confirmed CIN2/3, cervical cancer incidence and cervical cancer mortality by 33% (1.83 per 1000 in 2018; 1.23 per 1,000 in 2035), 32% (7.78 per 100,000 in 2018; 5.26 per 100,000 in 2035) and 25% (2.19 per 100,000 in 2018; 1.64 per 100,000 in 2035), respectively by 2035 (Fig. 2). The reductions in rates of CIN2/3, cervical cancer incidence and mortality under the current NCSP (counterfactual scenario – due only to vaccine impact) are 27% (1.34 per 1000 in 2035), 25% (5.87 per 100,000 in 2035) and 17% (1.82 per 100,000 in 2035), respectively, by 2035 compared to 2018 rates. This equates to HPV-based (baseline) scenario 2035 rates of histologically-confirmed CIN2/3, cervical cancer incidence and cervical cancer mortality being 23%, 31% and 48% lower, respectively, on a relative basis, than the corresponding rates predicted under the cytology-based (counterfactual) scenario.

We predict 2661 cervical cancer cases and 869 deaths over the period from 2019 to 2035 under the updated NCSP (baseline scenario), whereas 2810 cervical cancer cases and 914 deaths are predicted over the same period under the current NCSP (counterfactual scenario). Thus, the transition to primary HPV screening is expected to avert 149 cervical cancer cases and save 45 lives (Fig. 2).

3.2. Resource utilisation outcomes

Fig. 3 shows the estimated annual number of women screened, HPV tests, LBC tests, colposcopies, biopsies, pre-cancer treatments, costs and quality-adjusted life years each year for both the cytology-based (counterfactual) and HPV-based (baseline) scenarios. For the cytology-based (counterfactual) scenario, the number of women screened and primary test (LBC) volumes increase slightly over time, reflecting changes in population demographics (i.e. population increases and ageing). In contrast, in the HPV-based (baseline) scenario, the number of women screened and the primary HPV test volumes decrease sharply after the transition, and then fluctuate in line with the new five-year screening interval; these fluctuations dampen over time. The change in test volumes reflects the shift in the primary test, with a decrease in LBC volumes of ~82% in 2019.

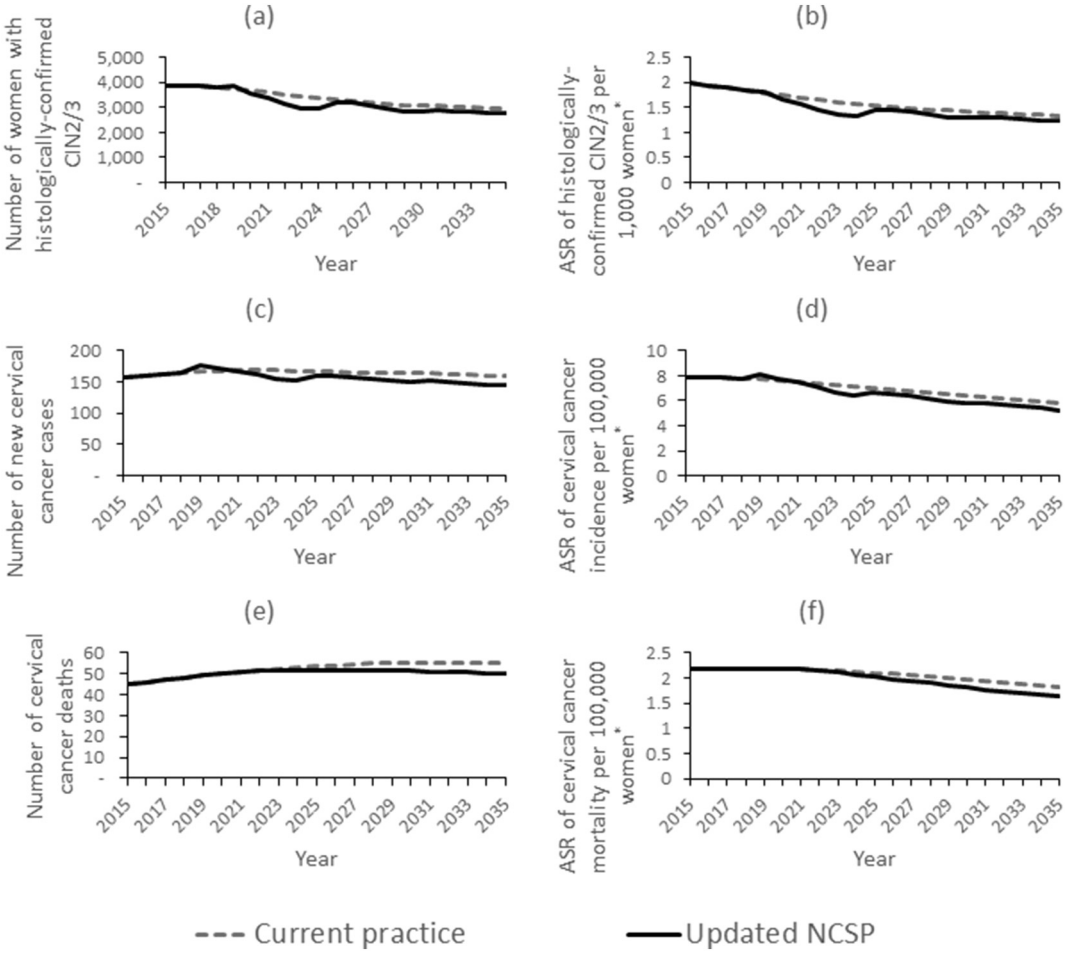


Fig. 2. Estimated cases and age standardised rates of: (a), (b) histologically-detected CIN2/3; (c), (d) cervical cancer diagnosis; and (e), (f) cervical cancer mortality, respectively, for the current NCSP and the updated guidelines taking into account the impact of the HPV Immunisation Program. **Standardised to the Statistics NZ 2001 female population.*

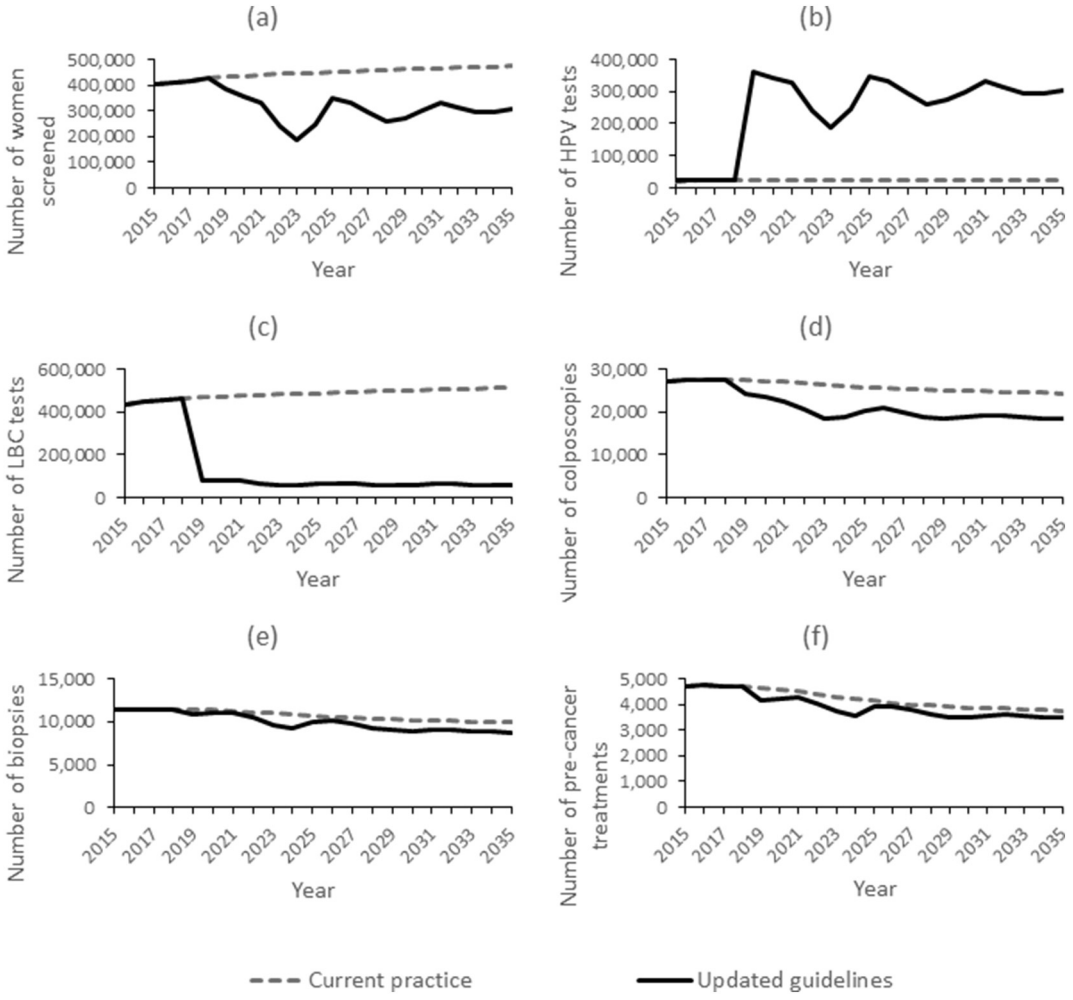


Fig. 3. Year-by-year volumes of (a) women screened, (b) HPV tests, (c) cytology, (d) number of colposcopies, (e) number of biopsies and (f) number of pre-cancer treatments.

Volumes of colposcopies, biopsies and pre-cancer treatments are predicted to generally decline over time after about 2019/2020 in both the cytology-based (counterfactual) and HPV-based (baseline) scenarios. In the cytology-based (counterfactual) scenario, however, the general decline is subject to periodic fluctuations, although these are relatively small and much less pronounced than the fluctuations predicted for the number of women screened and primary test volumes. Colposcopy volumes are predicted to be reduced by 11% in 2019, and to remain well below both pre-transition and counterfactual scenario levels to 2035. This is likely to reflect changes in the guidelines for the updated NCSP clinical management guidelines such as ceasing to recommend a colposcopy in the first year following treatment for HSIL [7], rather than changes in the type of primary test or screening interval.

3.3. Cost analysis outcomes

Total program costs (including the costs of screening, triage, diagnostic test and cancer treatment, but excluding program overheads) are predicted to be NZ$31,784,817 in the year 2018. For the updated NCSP (HPV-based baseline scenario), annual costs will be reduced by 6% in 2019, and 16% in 2035, compared to 2018. On average, program costs are predicted to reduce over time. However, immediately following the transition to the updated NCSP, program costs are expected to fluctuate in line with the five-year screening interval, with fluctuations dampening over two-three screening rounds. This may be contrasted with the programme costs predicted under the counterfactual scenario; here we expect a gradual increase in costs by 0.73% in 2019, and 1.33% by 2035. Total quality-adjusted life-years in NZ women are expected to rise gradually over time, from 2,004,309 in 2018 to 2,337,614 in 2035.

Table 1 displays five-year averages in predicted resource volumes, primary and triage test positivity and cost outcomes.

3.4. Test and referral outcomes

Test results relating to primary screening tests and triage tests following a positive primary screening test are shown in Fig. 4. After an initial peak in primary test positivity following the programme transition, the proportion of primary HPV tests that are predicted to be positive is expected to remain stable from ~2024 onwards, at around 9%. The proportion of all HPV tests positive for HPV16/18 is predicted to only slightly reduce from around 2% after the first round of HPV screening (due to the further impact of vaccination against HPV 16/18), while the proportion positive for non-16/18 types only is predicted to remain around 7% after the first screening round (Fig. 4a). Considering all LBC tests done following a positive primary screening test (including triage tests after a test positive for non-16/18 types only, and tests after a 16/18 positive test done to inform colposcopy), approximately 32% are predicted to have a cytological abnormality (ASC-US+), approximately 24% ASC-US/LSIL and approximately 8% ASC-H+. The proportions with ASC-US/LSIL and ASC-H+ cytology are predicted to be approximately 28% and 17%, respectively, in women positive for HPV 16/18-positive tests, and 23% and 5%, respectively, in women positive for non-HPV16/18 types (Fig. 4). These proportions are predicted to be reasonably stable over time. Considering the results from primary and triage tests, the

Table 1
Predicted annual resources-use volumes, test positivity, costs and effects outcomes under the updated NCSP (HPV-based baseline scenario) averaged over successive five-year screening rounds.

	Updated NCSP (current NCSP)		
	2019–2023	2024–2028	2029–2033
Resource use volumes			
Women screened	299,822 (439,491)	296,007 (453,076)	303,172 (466,826)
HPV tests	292,393 (22,731)	294,633 (22,522)	302,584 (22,104)
LBC tests	71,938 (476,728)	61,008 (490,214)	59,962 (504,441)
Colposcopy visits	21,884 (26,965)	19,709 (25,585)	18,879 (24,831)
Biopsies	10,638 (11,236)	9690 (10,606)	9025 (10,163)
Pre-cancer treatments	4081 (4483)	3763 (4073)	3542 (3859)
Primary HPV test positivity[a]			
HPV-16/18	2.4%	2.1%	1.9%
HPV-not 16/18	6.6%	6.8%	6.9%
LBC triage test positivity in HPV-positive women[a,b]			
ASC-US/LSIL	22.8%	22.7%	22.7%
ASC-H+	5.0%	5.1%	5.1%
Recommendations following primary test[a]			
Colposcopy referral	2.7%	2.5%	2.2%
12-month follow-up	6.3%	6.4%	6.5%
Cost outcomes			
Life years	2,096,745 (2,096,745)	2,202,891 (2,202,889)	2,283,423 (2,283,420)
Quality-adjusted life years (QALYs)[c]	1,850,245 (1,849,873)	1,943,982 (1,943,528)	2,026,716 (2,026,238)
Total program costs[d]	NZ$ 27,997,837 (NZ$ 32,188,368)	NZ$ 27,151,924 (NZ$ 32,129,787)	NZ$ 26,891,838 (NZ$ 32,215,704)

Abbreviations: ASC-US, Atypical squamous cells of undetermined significance; LSIL, Low-grade squamous intraepithelial lesion; ASC-H, Atypical squamous cells where a high-grade squamous intraepithelial lesion cannot be excluded.
[a] Refers to primary HPV screening (i.e. updated NCSP scenario) only.
[b] Following a HPV-not 16/18 positive primary HPV test.
[c] QALY calculations are based on a disutilities set as per published literature, labelled 'QALY weights set 1' as previously published [10].
[d] Total program costs are based on previously published cost assumptions [10].

model predicts that 2.7% of women to be referred for colposcopy in the first screening round (2019–2024); rates of colposcopy referral are predicted to decline slowly over time to ~2% in the 2029–2033 period. In the first screening round, approximately 6.3% of women are predicted to be recommended to return in 12 months for follow-up, with follow-up rates predicted to increase slightly over the period, to 6.5% in the 2029–2033 screening round.

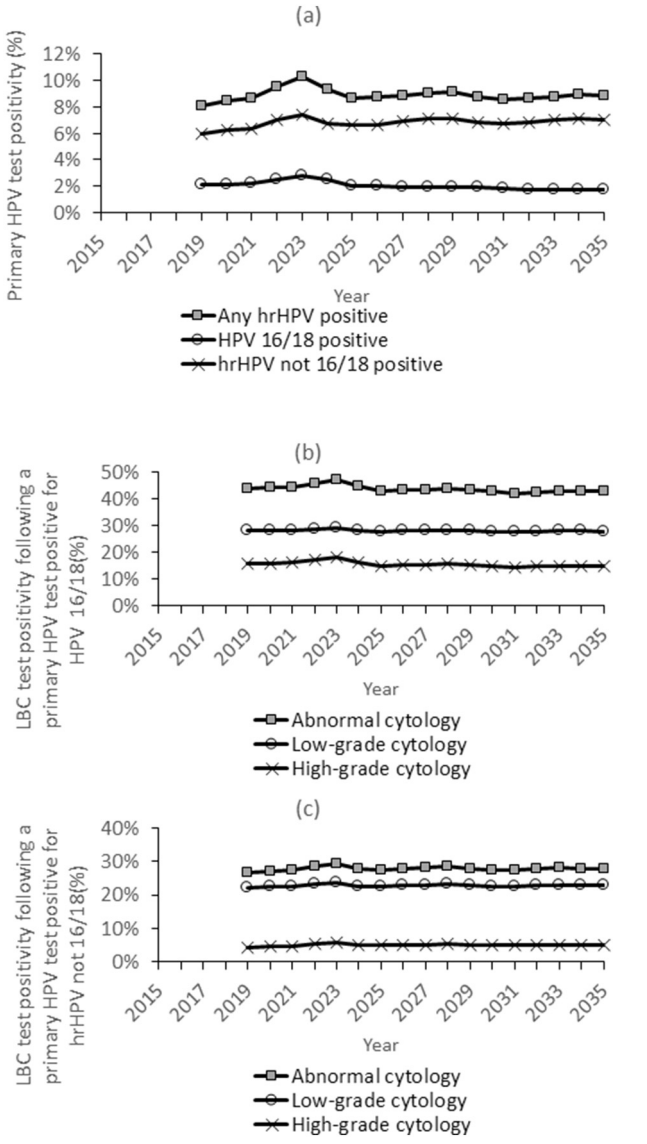


Fig. 4. (a) Primary HPV test positivity and (b) LBC test positivity following a primary HPV test positive for HPV 16/18 and (c) LBC test positivity following a primary HPV test positive for HPV not 16/18.

4. Discussion

This study provides the first comprehensive long-term estimates of the cost, health outcomes, resource utilisation and test outcomes of the NCSP in New Zealand taking into account both the ongoing impact of HPV vaccination and the planned transition to HPV-based screening. Transitioning from 'current practice' (three-yearly LBC) to the 'updated NCSP' (five-yearly HPV testing) would, with exception of minor transitional fluctuations, accelerate the reduction in rates of histologically-detected CIN2/3, cervical cancer incidence and cervical cancer mortality which is already expected to occur as a consequence of HPV vaccination. These reductions are predicted to be 33%, 32% and 25% lower, respectively, in 2035 relative to pre-transitional (2018) rates due to the combined impact of the two interventions. This is 6 (8% relative decrease), 8 (10% relative decrease) and 8 (10% relative decrease) percentage points lower, respectively, than would have occurred due to vaccination impact alone if the current NCSP was maintained. The transition to primary HPV screening is predicted to avert approximately 149 cervical cancer cases and 45 deaths over the period 2015–2035.

The results from this study are broadly consistent with our previous modelled analyses that evaluated the population-level impact of a programmatic transition from shorter-interval cytology screening to five-yearly primary HPV screening in Australia. [14,38] A notable difference between the findings of the Australian study and this analysis is that the magnitude of transitional fluctuations following the transition is predicted to be smaller in NZ than in Australia. This difference may be attributed to the current screening interval being three years in NZ compared to two years in Australia; thus the change in screening interval to five years is less substantial. The final impact of the transition on colposcopy volumes is very limited; the final colposcopy volumes are a function not only of the screening test and triage process, but also of the recommendations for colposcopy at all stages of follow-up and surveillance- thus our modelled outcomes also reflect changes made to these aspects in considering the new recommendations in NZ. It should be noted that the current NCSP recommendations for cytology screening in NZ involve colposcopy referral at more points during surveillance (e.g. for discordant cytology/colposcopy results) than was the case in Australia's cytology program. A change in NZ recommendations around whether or not a post-treatment colposcopy is done appears to have significantly dampened the effect that the programme transition will have on annual colposcopy volumes.

The long-term results of this study, i.e. health and volumes outcomes in the year 2035, are also broadly consistent with the results of our previous single cohort analysis in NZ [10]. In that analysis we predicted that transitioning to a five-yearly primary HPV screening will reduce cervical cancer incidence and mortality by 12–16% and save 4–13% in program costs, compared to three-yearly conventional cytology. In the current analysis, we have estimated that cervical cancer incidence and mortality rates will be ~10% lower by 2035 under the updated NCSP, compared to what rates would have been in 2035 under the current program. Under the updated NCSP we predicted that annual program costs will be ~17% lower under than what they would be under three-yearly cytology. It is important to note that this current study also includes the draft screening management guidelines for the updated NCSP, which were not available at the time of the original policy evaluation, and thus may account for differences in cost reduction [10].

As for any modelled analysis, this study has some limitations. Specifically, we assume compliance to screening is constant (although adjusted for a longer recommended interval), which does not account for the possibility that women may change their behaviour leading up to the screening transition, or alternatively the possibility that women change their screening behaviour due to the perception that HPV vaccination reduces the need for screening. Additionally, the impact of HPV vaccination may be under-estimated, since some vaccine-derived protection may be conferred after two doses (our vaccine uptake assumptions are based on three-dose uptake), and because our analysis assumes continuation of a female-only HPV4 program (in January 2017 the program was extended to boys and adopted the next generation nonavalent vaccine [HPV9]). However, the difference between two- and three-dose uptake in NZ is reasonably small (approximately 5%) and the efficacy of two doses depends on the spacing between the doses, so this small underestimate in coverage is unlikely to have a substantial effect on our results. The inclusion of boys and change to HPV9 will have a greater effect over the long term, however these changes are unlikely to affect predictions over the timeframe we considered. These changes to vaccination would predominantly affect birth cohorts targeted for vaccination from 2017 on, who were generally born in around 2004 or later. Women in these birth cohorts would not enter the screening program until the later years of our simulation, and even in these later years would comprise a relatively small proportion of screened women. In 2031–2035, only 10.6% of screening-age women (25–69 years) will be 25–29 years and thus had been offered HPV9; if ~70% of these girls have been fully vaccinated, then the proportion overall of screened women in this group is ~0.074 (7.4%).

It has recently been announced that NZ will stage its implementation of the new recommendations for screening; firstly, increasing the starting age to 25 from 2019, and then working towards commencing primary HPV screening from 2021 (rather than late 2018, as originally planned) [39,40]. This stepped implementation will slightly impact the timing of the changes predicted here in that transitional effects will be delayed by approximately two years. However, given that both the age of starting screening and the transition to the new screening tests are expected to occur within a relatively short period, we expect no substantial variation on the predictions presented here.

The strengths of this analysis include the use of an extensively calibrated and validated model platform, *Policy1-Cervix*, taking into account detailed observed HPV vaccination coverage and screening compliance rates. Screening and follow-up and surveillance management assumptions in the model are very detailed and incorporate the latest recommendations for the updated NCSP [41]. The work was performed in collaboration with stakeholders and specifically aimed to address important local questions and areas of uncertainty. The findings from this analysis are broadly applicable to settings with similar existing screening policies (three-yearly cytology with HPV triage) and vaccine coverage rates. The transitional increases in disease-detection rates and resource-use observed in this analysis is of the result of utilising a more sensitive screening test, and also expected to be observed during a similar transition in a range of settings. Similarly, we have quantified transitional fluctuations attributable to the change in screening interval, and this is also likely to occur in other settings, since most countries would implement HPV screening at intervals of five years or greater. In particular, we found that these fluctuations are smaller than those predicted following the screening programme transition in Australia; a result which is reassuring for other settings transitioning from three-yearly to five-yearly programme [14]. Further, the predicted primary test positivity rate (9% positive for any high-risk HPV) is comparable to what is currently being observed in Australia, which uses a similar screening algorithm and age-range [42].

The health services research presented in this analysis provides a valuable contribution to the field of gynaecologic oncology. These results are relevant to clinicians, epidemiologists and policy-makers alike as they inform health-services planning, budgets, workforce requirements, quality assurance measures, safety monitoring of the updated NCSP and communication strategies. It is essential for maintaining public confidence in the updated National Cervical Screening Programme that the predicted small transient increase in rates of histological CIN2/3 and cervical cancer detection, if detectable at the population level, are appropriately understood as an indication of program success by bringing forward diagnoses of disease; this increase in early disease detection will result in long-term reductions in invasive cervical cancer incidence and mortality. A new set of results from this study, which were not included in our previous analysis [10], are predictions of primary and triage test positivity rates under the updated NCSP. These will be critical in developing laboratory performance targets and reassuringly, these rates are predicted to be reasonably stable over time in NZ.

Implementing major changes to well-established programs involve many challenges, especially when they occur against a shifting background – as is the case with changes to cervical screening in the context of HPV vaccination. The findings in the current study provide important information to assist in successful implementation of recent screening policy changes, which will provide important benefits for women in New Zealand.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.10.045.

Acknowledgements

We would like to thank the NZ Ministry of Health for their guidance in the development of the clinical management pathways incorporated into the model.

Funding statement

This study was funded by the NZ Ministry of Health. The funder participated in this study by providing cost information and advice on details of the cervical cancer screening and follow-up strategies where draft clinical management guidelines were not explicit.

Competing interest declaration

KC is a co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass') (ACTRN12613001207707 and NCT02328872), which is conducted and funded by the Victorian Cytology Service (VCS) Inc. Ltd., a government-funded health promotion charity. The VCS Inc. Ltd. have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc. USA. She is also a CI on Compass in NZ, ('Compass NZ') (ACTRN12614000714684) which is conducted and funded by Diagnostic Medlab, now Auckland District Health Board. DML received equipment and a funding contribution for the Compass trial from Roche Molecular Systems. However, neither she, nor her institution on her

behalf (Cancer Council NSW) receives direct or indirect funding from industry for Compass Australia or NZ or any other project.

The authors have undertaken other contracted work for the NZ Ministry of Health (modelled policy evaluations, statistical reports).

Author contributions

MAS, HN, MS, GF, JOH and KC conceived and designed the study. MTH, MAS, J-BL and KC contributed to model design and construction. MTH ran the formal analysis. MTH, J-BL, MAS, HN, MS, GF and KC contributed to the interpretation of output data and results. MTH wrote the original manuscript draft. All authors reviewed the final manuscript.

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