Gynecologic Oncology 152 (2019) 465–471

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Pathways to a cancer-free future: A protocol for modelled evaluations to maximize the future impact of interventions on cervical cancer in Australia

Louiza S. Velentzis [a,b,*], Megan A. Smith [a,c], Kate T. Simms [a,d], Jie-Bin Lew [a,d], Michaela Hall [a,d], Suzanne Hughes [a], Susan Yuill [a], James Killen [a], Adam Keane [a], Katherine Butler [a], Jessica Darlington-Brown [a], Harriet Hui [a], Julia M.L. Brotherton [b,e], Rachel Skinner [f,g], Alison Brand [h,i], Lara Roeske [e], Stella Heley [e], Jonathan Carter [j], Deborah Bateson [k,l], Ian Frazer [m], Suzanne M. Garland [n,o,p], Rebecca Guy [q], Ian Hammond [r], Paul Grogan [s], Marc Arbyn [t], Philip E. Castle [u], Marion Saville [e,p], Bruce K. Armstrong [c,v], Karen Canfell [a,c,d]

[a] Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia
[b] Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia
[c] School of Public Health, University of Sydney, NSW, Australia
[d] Prince of Wales Clinical School, University of New South Wales, Australia
[e] Victorian Cytology Service Ltd, Carlton, Victoria, Australia
[f] Discipline of Child and Adolescent Health, University of Sydney, Sydney, NSW, Australia
[g] Children's Hospital Westmead, Westmead, NSW, Australia
[h] Discipline of Obstetrics, Gynaecology and Neonatology, Westmead Clinical School, University of Sydney, NSW, Australia
[i] Department of Gynaecological Oncology, Westmead Hospital, Westmead, NSW, Australia
[j] Chris O'Brien Lifehouse, Sydney, NSW, Australia
[k] Family Planning NSW, NSW, Australia
[l] Sydney Medical School, Discipline of Gynaecology & Neonatology, University of Sydney, NSW, Australia
[m] The University of Queensland Diamantina Institute, Queensland, Australia
[n] Department of Microbiology & Infectious Diseases, Royal Women's Hospital, Parkville, Victoria, Australia
[o] Murdoch Children's Research Institute, 50 Flemington Road, Parkville, 3052, Australia
[p] Department of Obstetrics and Gynaecology, University of Melbourne, Parkville 3052, Victoria, Australia
[q] Kirby Institute, University of NSW, Sydney, NSW, Australia.
[r] Division of Obstetrics and Gynaecology, University of Western Australia, Perth, Australia
[s] Cancer Council Australia, Sydney, NSW, Australia
[t] Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium
[u] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, USA
[v] School of Population and Global Health, University of Western Australia, Perth, Australia

HIGHLIGHTS

- *Pathways-Cervix* is a comprehensive approach towards cervical cancer control from prevention to treatment/survivorship.
- The program translates research into action through an implementation process engaging policy-makers and stakeholders.
- *Pathways-Cervix* will generate the best-value investments or "best buys" in cervical cancer control.
- Priority interventions evaluated were selected by a Scientific Advisory Committee in an Australian context.
- The flexibility of the modelling platform can enable application of this program to other settings.

ARTICLE INFO

Article history:
Received 6 August 2018
Received in revised form 5 December 2018
Accepted 21 December 2018

ABSTRACT

Objective. Australia's HPV vaccination and HPV-based cervical screening programs are changing the landscape in cervical cancer prevention. We aim to identify areas which can make the biggest further impact on cervical cancer burden. This protocol describes the first stage of a program of work called *Pathways-Cervix* that aims to generate evidence from modelled evaluations of interventions across the cervical cancer spectrum.

Methods. Based on evidence from literature reviews and guidance from a multi-disciplinary Scientific Advisory Committee (SAC), the most relevant evaluations for prevention, diagnosis and treatment were identified.

* Corresponding author at: 153 Dowling St, Woolloomooloo, NSW 2011, Australia.
E-mail address: louizav@nswcc.org.au (L.S. Velentzis).

https://doi.org/10.1016/j.ygyno.2018.12.019
0090-8258/

Keywords:
Cervical cancer
Health economics
Simulation
Modelling
Cervical cancer prevention
Evaluation

Results. Priority evaluations agreed by the SAC included: increasing/decreasing and retaining vaccination uptake at the current level; vaccinating older women; increasing screening participation; methods for triaging HPV-positive women; improving the diagnosis of cervical intraepithelial neoplasia (CIN) and cancer; treating cervical abnormalities and cancer; and vaccinating women treated for CIN2/3 to prevent recurrence. Evaluations will be performed using a simulation model, *Policy1-Cervix* previously used to perform policy evaluations in Australia. Exploratory modelling of interventions using idealised scenarios will initially be conducted in single birth cohorts. If these have a significant impact on findings then evaluations with more realistic assumptions will be conducted. Promising strategies will be investigated further by multi-cohort simulations predicting health outcomes, resource use and cost outcomes.

Conclusions. Pathways-Cervix will assess the relative benefits of strategies and treatment options in a systematic and health economic framework, producing a list of 'best buys' for future decision-making in cervical cancer control.

1. Introduction

Cervical cancer typically arises after many years of persistent infection of cervical cells with oncogenic human papillomaviruses (HPV) [1]. In the pre-vaccination era, nearly all sexually active women were exposed to HPV infection but most infections are transient or controlled by the immune system. A fraction of women will develop overt, persistent oncogenic HPV infection, a high percentage of which will then progress to precancer [2,3]. A high-percentage of precancer will become invasive cancer if not detected and treated in a timely fashion [4]. Thus, a substantial number of women will develop cervical cancer if they do not receive primary (prophylactic HPV vaccination) and/or secondary (screening for and diagnosis and treatment of precancer) prevention.

In a changing landscape in cervical cancer prevention, diagnosis and treatment, focusing research efforts and resources in areas that can make the biggest impact on its outcomes is a challenge. In Australia, changes have occurred and are continuing to occur in vaccination and screening practices, as outlined below. It is in this context that "*Pathways to a cancer-free future*" ('*Pathways*') was conceived. *Pathways* is a multi-stage program of work that spans the cancer control spectrum, from prevention to treatment and survivorship. Its aims are to synthesise evidence from the literature and thereby generate evidence from targeted modelled evaluations of cancer control interventions that can guide and underpin future research investment and policy implementation. *Pathways* will initially be applied to five major cancers in Australia (cervical, lung, bowel, prostate, and breast cancer). The aim of the current article is to outline the design and objectives of *Pathways-Cervix* and summarise the protocol for modelled evaluations.

2. Background: cervical cancer prevention strategies in Australia

2.1. Cytology based screening

Australia has among the lowest reported cervical cancer age-standardised (world) incidence (5.5 cases per 100,000 women) and mortality rates (1.6 cases per 100,000 women) [5] due to prevention of cervical cancer through its National Cervical Screening Program (NCSP). The NCSP was established in 1991 and, prior to December 2017, recommended 2-yearly cervical screening with conventional cytology for sexually active women aged between 18 and 20 years and 69 years. The proportion of eligible women within the target population participating in the NCSP was 57% over 2 years (2015–2016) and 70% over 3 years (2014–2016) [6]. Since the implementation of the NCSP, incidence and mortality in the target age group of 20–69 years have halved; although, rates have now been stable for around a decade [6,7]. Incidence and mortality are higher, however, in Indigenous Australians than in non-Indigenous Australians (2.2 times and 3.8 times higher respectively), and in women living in socioeconomically disadvantaged areas [6].

2.2. HPV vaccination

Further falls in incidence and mortality are also anticipated due to Australia's publicly-funded National HPV Vaccination Program, which commenced in 2007. This program delivered mostly three doses of quadrivalent vaccine, initially as a catch-up program for all females aged 12–26 years until the end of 2009, then routinely at school to girls aged 12–13 years until 2013, when vaccination was extended to boys aged 12–13 years with a 2-year catch-up in boys aged 14–15 years. National 3-dose vaccination coverage reported by the National HPV Vaccination Program Register was 78.6% and 72.9% for females and males, respectively, turning 15 years of age in 2016 [8]. Although the impact of the vaccination program on the incidence of cervical cancer will not be fully realised for a few more decades, substantial effects on HPV prevalence and cervical pre-cancerous lesions have already been documented. A sentinel surveillance study in family planning clinics found a 78% decrease in the prevalence of vaccine-targeted HPV types in women aged 18–24 years at 4–5 years after the program started (93% reduction in fully-vaccinated women and 35% in unvaccinated women, suggesting herd protection) [9]. Updated data, [10] collected 9 years after the program started now show a reduction of 92% in 18–24 year olds in vaccine targeted types. Furthermore, falls in histologically detected high-grade cervical abnormalities of 65% have been reported nationally in women aged <20 years between 2007 and 2016, with smaller but significant decreases also documented in older women including 40% in women 20–24 years (2010–2016) and 13% in women aged 25–29 years (2013–2016) [6]. It is expected that rates of pre-cancerous lesions will fall further as women who were vaccinated at school, with higher coverage, age as they go through the screening program.

2.3. Move to HPV-based screening

Given the impacts of HPV vaccination, developments in HPV assays, and evidence of greater preventive efficacy of HPV nucleic acid testing than cytology testing [11–14], the NCSP went through a rigorous review process from late 2011 until 2014. A systematic review of the international literature [15], alongside simulation modelling of effectiveness and economic assessment of potential new screening strategies in unvaccinated cohorts and cohorts offered vaccination, were commissioned by Australia's Medical Services Advisory Committee (MSAC) [16]. In April 2014, MSAC recommended 5-yearly screening using primary HPV testing with partial genotyping and reflex liquid-based cytology triage for women aged 25 to 69 years followed by an exit test at 70–74 years of age [17]. Starting at age 25 years (vs. 30 years) with primary HPV screening is feasible in populations with high vaccine uptake and mature vaccination programs [18]. The recommendations were endorsed by the Australian Health Ministers' Advisory Council in August 2014 and the renewed NCSP implemented on the 1st of December

2017, supported by detailed clinical management guidelines developed in 2015–2016 [19].

Compared to the cytology-based NCSP, full implementation of the renewed NCSP over the long term is predicted to result in cervical cancer incidence and mortality reductions of 31% and 36%, respectively, in unvaccinated cohorts, and reductions of 24% and 29%, respectively, in cohorts offered vaccination [20]. We have also estimated a reduction of 13% in the risk of excisional treatment for pre-cancerous lesions in vaccinated women, potentially leading to fewer pre-term delivery and low birth weight events [21]. For the first time, in the renewed program, women 30 years of age or older who have never participated in the NCSP or who are overdue for cervical screening by over two years will be eligible for HPV testing of self-collected samples under the supervision of a healthcare professional [19]. A modelled analysis of the impact of offering self-collected HPV screening to unscreened and underscreened women found that even one round of self-sampling at age 30, 40 or 50 years would prevent a significant number of cervical cancer diagnoses and deaths over the lifetime of these women [7].

2.4. Move to nonavalent HPV vaccination

An additional development that will impact cervical cancer prevention in the long-term is the second-generation nonavalent vaccine (Gardasil-9; Merck, "HPV9") which targets the five next most common oncogenic HPV types (31, 33, 45, 52, and 58) as well as the four most common oncogenic types, which are in the quadrivalent vaccine. It has been estimated that the nonavalent vaccine will protect against HPV types associated with 86.4% of cervical cancers in Australia and an average of 89.9% of cervical cancers worldwide [22,23]. A systematic review of the literature has found the nonavalent vaccine to be safe and effective against vaccine-targeted HPV types and similarly immunogenic to the existing HPV vaccines [24]. The nonavalent vaccine is now in routine use in the National Immunisation Program, with a 2-dose schedule replacing, from 2018, the 3-dose schedule of the quadrivalent vaccine in 12–13 year olds in the school based immunisation program [25,26]. We have estimated that cohorts of women vaccinated with HPV9 will have a further 10 percentage point reduction in lifetime risk of cervical cancer diagnosis and death beyond the 42% reduction in diagnosis and 39% reduction in death expected in females offered the quadrivalent vaccine after transitioning to 5-yearly primary HPV screening from 2-yearly cytology based screening (assuming the management recommended in the 2016 clinical guidelines) [27]. Furthermore, an evaluation of optimal screening strategies in cohorts offered the nonavalent vaccine found that the lifetime number of recommended cervical screens in Australia could be further reduced from ten to between one and four lifetime screens [28].

Given the extent and of promise these changes in Australia's cervical cancer prevention program, the focus of the *Pathways-Cervix* program is to systematically determine whether further possible changes would be likely to add materially to those that are now being implemented.

3. Methods and analysis

3.1. Study design

Pathways has three stages, schematically presented in Fig. 1. Stage 1 is to identify possible further changes in prevention, diagnosis and treatment, and then to use modelling to evaluate the changes in health outcomes they might achieve and their potential cost-effectiveness from an Australian health services perspective. Stage 2 is a consultative phase, where national and international experts, organisations, government, and community representatives, will critically assess the findings of stage 1 and determine their impact on cervical cancer control, taking into account broader political and economic issues around change. The third stage is a decision and investment phase. Its aims are to i) seek policy implementation, when it is justified, through evidence-based advocacy and direct engagement with policy-makers and other stakeholders (e.g. government, non-government not for profit agencies and relevant industries), and (ii) build cooperative relationships in cancer control.

3.2. Scientific Advisory Committee

To guide, critique and validate the work conducted within *Pathways*, national cervical cancer experts in epidemiology, relevant clinical specialities, and policy have been invited to join a multi-disciplinary Scientific Advisory Committee (SAC) for *Pathways-Cervix*. The SAC has representation from a range of Australian states and territories. The role of the SAC is i) to provide guidance and input for identifying potential interventions in cervical cancer control, ii) to review the findings of evaluations of these interventions and iii) critically assess their impact in relation to each other. The first SAC meeting was convened in May 2017. The proposed work plan was presented and endorsed, and dedicated smaller working groups were established to pursue follow-up work and detailed modelling, including members from the advisory committee, systematic reviewers and microsimulation modellers.

3.3. Simulation Model Platform

We will evaluate potential interventions in Stage 1 using a previously developed and validated modelling platform, *Policy-1 Cervix*. It has several elements (see Fig. 2):

a) A dynamic model of sexual behaviour, HPV transmission and HPV vaccination in females and males in the Australian population which tracks individual people through the course of the infection from its acquisition to its progression or resolution, and recovery or death;

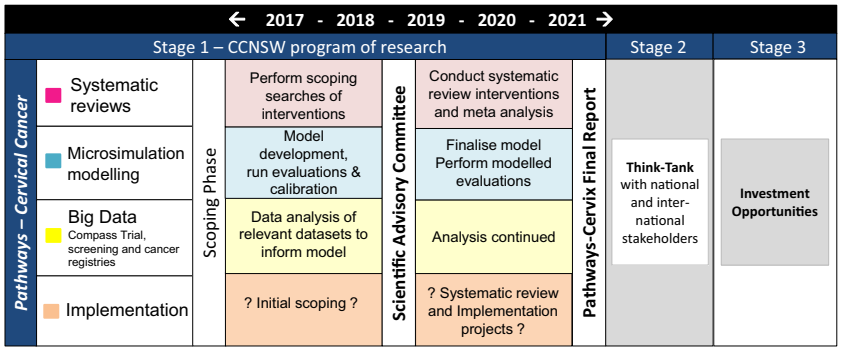
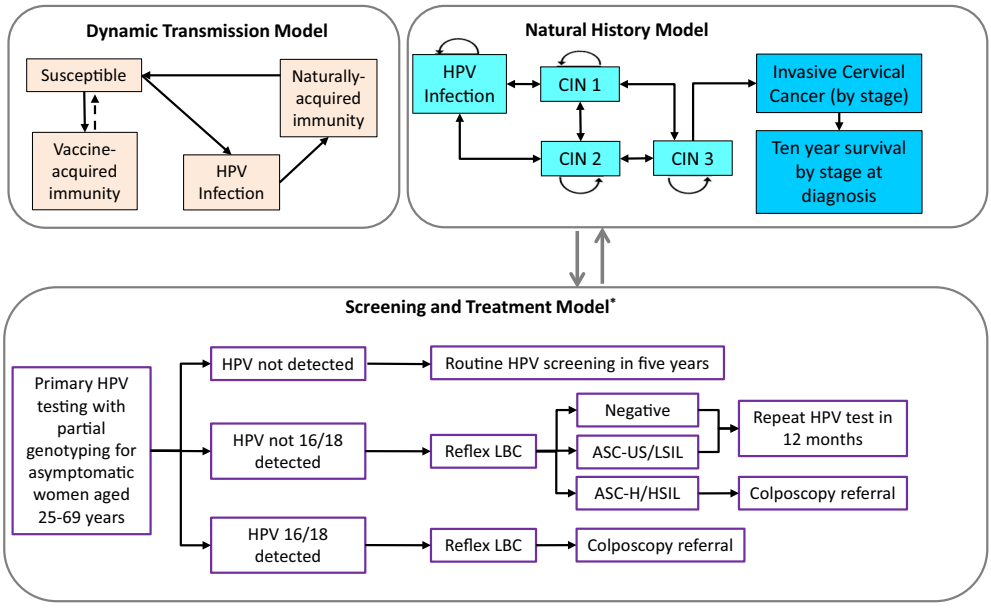


Fig. 1. Diagram of *Pathways-Cervix*.



*Input test probability matrices govern screening and diagnostic outcomes for underlying health states; age-specific compliance assumptions for screening and follow-up management are based on registry data; colposcopy, biopsy and pre-malignancy treatment accuracy and efficacy are explicitly modelled for each health state; a post-treatment natural history module incorporates the probability of recurrence based on systematic reviews; from all health states, age-specific rates for other- cause mortality and for hysterectomy for indications unrelated to cervical cancer are applied.

Fig. 2. Schematic diagram of model platform, *Policy-1 Cervix*. *Input test probability matrices govern screening and diagnostic outcomes for underlying health states; age-specific compliance assumptions for screening and follow-up management are based on Australian registry data; colposcopy, biopsy and pre-malignancy treatment accuracy and efficacy are explicitly modelled for each health state; a post-treatment natural history module incorporates the probability of recurrence based on systematic reviews; from all health states, age-specific rates for other- cause mortality and for hysterectomy for indications unrelated to cervical cancer are applied.

b) A component which simulates the natural history of cervical HPV infection, progression, regression, the development of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer;
c) A model of cervical screening, management, diagnosis and treatment of CIN, and 'test-of-cure' after treatment of high grade CIN;
d) A multiple-cohort implementation model which separately simulates HPV exposure, CIN development, screening, and all downstream processes, for each single year age cohort of females;
e) A population component that applies demographic data to the outputs to estimate cross-sectional results in each age group after the implementation of each potential new strategy or intervention.

The model platform incorporates Australian-specific demographic and health-economic factors; test accuracy; screening compliance; vaccination coverage; and screening, diagnosis and treatment-related costs. Extensive validation of the model has been carried out against a large range of current screening program outputs and other Australian data sources [16,29,30]. *Policy-1 Cervix* has been used previously for a number of HPV vaccination, cervical screening and screening technology evaluations in Australia, New Zealand, England, China and the USA [27–35]. The dynamic model of HPV transmission and vaccination is implemented in C++ (Microsoft Visual Studio C++ Community 2013) and the multi-cohort Markov model is implemented using TreeAge Pro (TreeAge Pro 2014; TreeAge Software, Williamstown, MA, USA). Further details of the model used in this work and its parameterisation can be found online [36]. Data sources, calibration, and validation outcomes, have been described previously [16,27].

3.4. Evaluation processes and analysis

We first performed scoping reviews of the literature to identify potential interventions in cervical cancer prevention, diagnosis and treatment. Evidence from the reviews was presented to the SAC including a list of proposed modelled evaluations. The SAC provided guidance on the selected strategies and interventions and recommendations for full systematic reviews and additional scoping reviews.

A list of agreed intervention evaluations of cervical cancer prevention, diagnosis and treatment was compiled and grouped into two categories. The first category involved interventions focused on obtaining maximum impact from existing approaches (Table 1). Idealised scenarios were modelled to evaluate the relative impact of improving vaccination uptake (e.g. complete coverage), vaccinating older women (≥ 35 years); increasing screening participation (e.g. perfect on-time attendance, no under-screeners, no never-screeners; perfect attendance for surveillance); ensuring quality assurance in screening (impact of use of clinically validated HPV assays); improving the diagnosis of CIN/cervical cancer (e.g. perfect CIN2+ detection, no unsatisfactory colposcopy) and treatments for HPV infections, LSIL and HSIL (e.g. modelling cancer treatments which could increase 5 and 10 year survival by 10%, 50% and 80%). The second category of agreed evaluations involved exploring the potential of new approaches (Table 2). These included tailored screening based on vaccination history and type of HPV vaccine received (quadrivalent or nonavalent), alternative triaging methods (e.g. dual staining with p16 and ki67 or methylation markers for HPV positive self-collected samples), and using the quadrivalent or nonavalent HPV vaccine to prevent CIN2/3 recurrence.

For interventions in Table 1, we will perform exploratory modelling using idealised scenarios in single birth cohorts (cohort size of 100,000 females at age 12) to obtain insight into whether further improvements could be achieved for a specific type of intervention or whether 'ceiling effects' have already been reached, such that increasing efficacy would only have a minimal impact on outcomes. When an idealised scenario is found to have a significant impact on outcomes, further evaluations will be conducted using more realistic assumptions. Promising strategies will be investigated further by conducting multi-cohort simulations predicting cross-sectional outcomes. Findings from these analyses will be reviewed by SAC members and further sensitivity analyses will be conducted as indicated.

Table 1:
Priority evaluations for cervical cancer control recommended by the SAC: obtaining maximum impact[a] from existing approaches.

Evaluation	Approach/broad intervention category[a]
Impact of achieving 100% vaccination coverage compared to current vaccination coverage.	Improving vaccination uptake
Impact of maintaining vaccine coverage in girls and boys at current levels of ~80%.	Improving vaccination uptake
Impact of vaccinating women aged 35+ with HPV4 or HPV9 compared to no adult vaccination.	Vaccinating older women (HPV FASTER)
Impact of increasing attendance for on-time screening to 100% at five years.	Increasing screening participation rates
Impact of all women initiating screening by the age of 30 (no unscreened women).	Increasing screening participation rates
Impact of eliminating under-screening (i.e. the proportion of women who have not attended for screening for ≥7 years).	Increasing screening participation rates
Impact of using HPV assays/HPV genotyping assays that are not clinically-validated.	Ensuring quality assurance in screening
Impact of regular screening using a self-collected samples offered to i) all women and ii) selectively offered to never screened and under-screened.	Increasing screening participation rates
Impact of 100% attendance for women under surveillance for a recent abnormality.	Improving the diagnosis of CIN and cancer
Impact of increasing colposcopy attendance rates to 100% when recommended.	Improving the diagnosis of CIN and cancer
Impact of improving colposcopy performance to 100% sensitivity at CIN2+.	Improving the diagnosis of CIN and cancer
Impact of reduction in colposcopy sensitivity by an absolute magnitude of 20%.	Improving the diagnosis of CIN and cancer
Impact of reducing the rate of unsatisfactory colposcopy procedures.	Improving the diagnosis of CIN and cancer
Impact of improving the effectiveness of treatment for cervical pre-cancer while reducing its harms.	Improving pre-cancer treatment
Impact of HPV16/18 positive women receiving an alternative treatment for HPV-related infection or disease (such as a therapeutic HPV vaccine) after cancer is ruled out.	Treatment for HPV infections, LSIL (CIN1), HSIL (CIN2/3)
Impact of treatment options for women with CIN2/3 and women with HPV/CIN1 separately.	Treatment for HPV infections, LSIL (CIN1), HSIL (CIN2/3)
Impact and threshold costs of a cervical cancer treatment that increases 5 and 10-year survival for each stage (or a specific stage) by reducing cumulative mortality (1-cumulative survival) by 10%, ii) 50% and iii) 80%.	Cervical cancer treatment and guidelines in Australia
Impact of improved quality of life in women being treated for cancer on quality-adjusted life-years saved.	Cervical cancer treatment and guidelines in Australia

Abbreviations: CIN2+: cervical intraepithelial neoplasia grade 2 or higher; HPV4/9: quadrivalent/nonavalent HPV vaccine; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion.
[a] The impact of listed evaluations assessed in terms of health outcomes, resource use and costs.

When evaluating a potential new intervention, we will run a single birth cohort scenario and compare the outcomes of the intervention scenario to a base-case current practice scenario (unless otherwise specified for specific questions). As of December 1st 2017, current practice in Australia is 5-yearly primary HPV screening (with 16/18 genotyping and LBC triage for non-16/18 oncogenic types) starting at age 25 with an exit test between ages 70–74. Because the population has varying levels of exposure to HPV vaccination, evaluations will generally be stratified into results for an unvaccinated cohort, and results for a cohort offered vaccination at age 12 (with uptake as observed in Australia). For scenarios incorporating vaccination, we assume that it was administered at age 12 in 2018 (the first cohort that will receive the nonavalent vaccine as part of the National Immunisation Program) and that completed vaccination (2 doses) is 82.4% in females and 75.5% in males (based on the midpoint between 2- and 3-dose uptake, to reflect the likely uptake that will occur with 2 doses when they are spaced as per current dose 1 and 3). When evaluating scenarios for cohorts offered vaccination, vaccine uptake in earlier birth cohorts (i.e. those offered either 4vHPV or 9vHPV in earlier years than the modelled cohort) will also be modelled, so that evaluations for each cohort offered vaccination will take into account existing indirect/ herd protection due to previous community level vaccination achieved. For all scenarios, we assume females are invited to attend for primary HPV screening from age 25 and were not screened under the previous cytology-based program.

3.5. Primary outcomes

For each scenario, several outcomes will be considered (generally over the lifetime of 100,000 females who enter the cohort at the age of 12 years) including i) health outcomes - lifetime risk of cervical cancer incidence and mortality and lifetime risk of (at least one) pre-cancer treatment; ii) resource use - number of colposcopy procedures (including colposcopies for those under repeat colposcopy surveillance), treatment procedures, and HPV tests; and iii) health-economic outcomes – cost-effectiveness and benefit to cost ratio (threshold value for how much would be beneficial to spend on an intervention for it to remain cost-effective), life-years, QALYs and cost outcomes. Evaluations will be conducted from a health services perspective. Where applicable, costs and life-years over a woman's lifetime (until the age of 85 years) will be calculated with a 5% discount rate, as per the standard approach for economic evaluations in Australia. One-way sensitivity analyses and probabilistic sensitivity analyses will be conducted on selected strategies to assess the effect of changes in selected model parameters on outcomes. Additional secondary outcomes, for example the impact of HPV

Table 2
Priority evaluations for cervical cancer control recommended by the SAC: exploring the potential of new approaches.

Evaluation	Approach
Optimal screening regime for unvaccinated women (based on birth cohort) and vaccinated women based on their vaccination history and type of vaccine received.	Tailored screening based on vaccination status (HPV4 or HPV9)
Longer interval screening schedules following two consecutive negative HPV test results within routine screening.	Tailored screening based on vaccination and screening history.
Impact of partial genotyping for oncogenic HPV types other than 16/18 with direct colposcopy referral for select types compared to cytology triage.	Methods for Triage
Impact of triaging oncogenic HPV positive (non 16/18 types) women with dual-staining (p16 ki67) cytology, compared to LBC.	Methods for Triage
Impact of methylation markers in HPV positive self-collected samples testing compared to clinician-collected cytology test.	Methods for Triage
Impact of vaccinating women treated for CIN2/3 with HPV4/HPV9 if the vaccine reduces recurrence by 50% (for pre-existing HPV types) or 80% (naïve for HPV types).	Vaccine to prevent CIN2/3 recurrence
Impact of vaccinating women treated for CIN2/3 with HPV4/HPV9 if the vaccine prevents or reduces recurrence of CIN2+ after treatment.	Vaccine to prevent CIN2/3 recurrence

Abbreviations: CIN2+: cervical intraepithelial neoplasia grade 2 or higher; CIN2/3: cervical intraepithelial neoplasia grade 2 or 3; HPV4/9: quadrivalent/nonavalent HPV vaccine; LBC: liquid-based cytology.

vaccination on other HPV-related cancers, will be considered at a second stage, later in the program.

3.6. Timeframe

Stage 1 of *Pathways-Cervix* commenced in July 2016. Draft papers for each evaluation will be presented to the SAC for assessment before additional sensitivity analyses are performed. Results of individual evaluations will be submitted for publication in peer-reviewed journals. Overall, the work in Stage 1 will be conducted in three tranches. The first will cover evaluations in HPV vaccination and cervical screening. The second will include evaluations on treatments for HPV infection/CIN1 and treatments for CIN2/3. In the third tranche evaluations for priority populations including Aboriginal and Torres Strait Islander and culturally and linguistically diverse populations will be conducted.

4. Ethics and dissemination

The *Pathways-Cervix* protocol for modelled evaluations has been reviewed and approved by the SAC. No human subjects are involved in this protocol and therefore Human Research Ethics Committee was not required. No deviations from the protocol will be conducted without prior review and approval of the relevant working party leads from the SAC. The findings of the evaluations will be reported in a series of papers in peer-reviewed journals and presented at national and international scientific forums.

5. Discussion

The interventions to be evaluated as part of *Pathways-Cervix* were identified by the SAC as priority interventions. The SAC identified two different evaluation types. The first type examines maximum impact in a particular area by examining a number of aspects in an idealised way which provides an early indication of the most important priority areas. The second type involve a more detailed cost-effectiveness analysis using data from other interventions as carried out in our previous work in cervical screening [20]. Taking colposcopy as an example area, we will be exploring interventions such as the impact of 100% colposcopy attendance rates which is not achievable in practice. However, the evaluation can determine whether the impact of this intervention is substantial and worth pursuing further by identifying barrier and potential interventions that can address them or whether other aspects of colposcopy are more important.

In the Australian context, standardised colposcopy reporting and quality assurance are expected to improve outcomes. Quality assurance in colposcopy will be a new feature of the renewed NCSP after broad agreement that mandatory submission of colposcopy data is important for quality control in colposcopy and treatment [37]. Assessing existing interventions in relation to colposcopy are therefore more likely to have a larger impact than a new intervention, such as for example dynamic spectral imaging colposcopy (DSI). DSI has been shown to be more sensitive for identifying CIN2+ lesions when compared to conventional colposcopy (65% vs 52%) and combining DSI with conventional colposcopy is also more sensitive and cost-effective than conventional colposcopy alone in the whole weighted population (sensitivity 80% vs 52%) [38]. As further evidence accumulates over time for new potential interventions, these will be explored in future work.

Pathways-Cervix has a number of strengths. By modelling the future impact of interventions across the cancer spectrum, considering a range of outcomes including health outcomes, cost-effectiveness, harms through treatments, resource utilisation etc., this program will generate the probable best-value investments or "best buys" in cervical cancer control. Scientists and policy-makers can then come together to determine which interventions should be given priority and how future investment should be directed. In parallel, findings from this program of work will also inform policy change through engagement with government, academia and community partners. The findings may also identify areas where further research is required – for example where an improvement would make an important difference, but there is not yet evidence around how best to achieve it. Furthermore, cervical cancer rates are already very low in Australia, and thus other concerns become more pressing, such as avoiding harms through excessive screening and treatment, and wasting energy and resources in areas which have already attained 'ceiling' effects. Identifying these areas will result in reallocation of resources to more pressing areas of research and reduce harms to women.

The use of simulation modelling is at the core of Phase 1 of *Pathways-Cervix*; however, there are additional elements, unrelated to modelling, that will complement this work by informing parameters of the integrated model. For example, the Compass trial, including the Compass Pilot [39] and the main Compass trial [40] will provide important sources of data on many aspects of the new primary HPV screening program (e.g. HPV-positivity rates; CIN2/3 detection rates; colposcopy referral rates) which in turn will be used to inform evaluations in prevention and diagnosis. Compass is a randomised controlled trial of primary HPV screening every 5 years versus liquid-based cytology screening every 2.5 years [40]. The trial is currently underway nationally in Australia and was set-up as a sentinel experience of the renewed NCSP. Compass-PLUS, a sub-study of Compass which will be initiated in 2019, will provide information on health state preference scores (utilities) used to quantify the quality of life effects associated with cervical screening and subsequent triage and diagnostic pathways in addition to other outcomes. Elements related to informing policy will also be generated from implementation work focused on the Renewed NCSP, as well as the translation of research through the national Centre of Research Excellent (CRE) in Cervical Cancer Control, a four-pronged collaborative initiative in cervical screening, HPV methods, HPV vaccination and global health, funded by the National Health Medical Research Council of Australia.

The current program presents a unique, comprehensive approach to innovation in cervical cancer control. There has been some relevant research in the past, but no prior body of work has assessed the relative benefits of strategies and treatment options across the cervical cancer spectrum in a systematic and health economic framework, producing a list of best buys. Although these best buys are applicable to Australia, which was the first country in the world to implement a publicly-funded HPV vaccination program, they may be similar for other countries with well-established cervical screening and similar vaccination coverage rates. Furthermore, *Pathways-Cervix* is an iterative program of work and once population models are available, evaluations can be performed for specific sub-groups, such as culturally and linguistically diverse populations and Indigenous populations living in Australia. Overall, the flexibility of the modelling platform used in *Pathways-Cervix* allows for changes to be made that can enable the applicability of this program to any other setting in the future, both for developed and developing countries.

Conflict of interest statement

JMLB reports unrestricted investigator initiated grants from MSD (papillomatosis typing study) and Seqirus (cervical cancer typing study) outside the submitted work. IF reports income from the sale of the vaccines as inventor of the technology underlying the HPV vaccines referred to in the paper; this is paid to him as part of his salary from the University of Queensland. SMG reports grants from Merck Investigator initiated research grants [RRP, HPV antibody outcome YFHI], grants from Commonwealth Department of Health and personal fees from Merck and other from Merck Global Advisory Board HPV, outside the submitted work. RS reports non-financial support from Merck, outside the submitted work. MA reports grants from Cancer Council NSW, the 7th Framework Programme of DG Research and Innovation, European Commission and grants from VALGENT. PEC has received cervical cancer screening and diagnostic tests at a reduced or no cost for research from Roche, Becton Dickinson, Arbor Vita Corporation, and Cepheid. KC and MS are co-principal investigators of an investigator-initiated trial of cytology and primary HPV screening in Australia ("Compass"), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity. VCS has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana USA. However neither KC, nor her institution on her behalf (Cancer Council NSW) has received direct or indirect funding from industry for Compass Australia or NZ or any other project. All remaining authors declare there have no conflicts of interest.

Author contribution

KC conceived the overall Pathways programme. SH, SY and HH conducted literature scoping under the guidance of KC and KB who manages the programme. KC, MAS, KTS, JBL, MH, JK and AK produced the initial list of potential modelled evaluations. BKA, MS, JMLB, RK, AB, LR, SH, JC, DB, IF, SMG, RG, IH, PEC, PG, MA and KC as members of the Scientific Advisory Committee selected the priority evaluations and provided guidance for further work. LSV drafted the manuscript with input from KC, MAS, KT and KB. All authors participated in the progress of various stages of the programme, critically reviewed the article and approved the final version.

Acknowledgement

This work was supported by Cancer Council NSW.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.12.019.

References

[1] M. Schiffman, P.E. Castle, J. Jeronimo, A.C. Rodriguez, S. Wacholder, Human papillomavirus and cervical cancer, Lancet 370 (9590) (2007 Sep 8) 890–907.
[2] P.E. Castle, A.C. Rodríguez, R.D. Burk, R. Herrero, S. Wacholder, M. Alfaro, et al., Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study, BMJ 339 (2009) b2569.
[3] S.K. Kjær, K. Frederiksen, C. Munk, T. Iftner, Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence, J. Natl. Cancer Inst. 102 (19) (2010) 1478–1488.
[4] McCredie MR, K.J. Sharples, C. Paul, J. Baranyai, G. Medley, R.W. Jones, et al., Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study, Lancet Oncol. 9 (5) (2008) 425–434http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx, Accessed date: 25 October 2017.
[5] Globocan, Section of Cancer Surveillance 2015, International Agency for Research on Cancer (IARC), 2012.
[6] Australian Institute of Health and Welfare, Cervical screening in Australia 2014–2015, Cancer series no. 105. Cat. no. CAN 104, AIHW, Canberra, 2017.
[7] M. Smith, K. Canfell, Impact of the Australian National Cervical Screening Program in women of different ages, Med. J. Aust. 205 (8) (2016) 359–364.
[8] National HPV Vaccination Program Register, Coverage data. National (Australia) HPV 3 dose vaccination coverage for adolescents turning 15 years of age, http://www.hpvregister.org.au/research/coverage-data, Accessed date: 16 January 2018.
[9] S.N. Tabrizi, J.M. Brotherton, J.M. Kaldor, et al., Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study, Lancet Infect. Dis. 14 (2014) 958–966.
[10] D.A. Machalek, S.M. Garland, J.M.L. Brotherton, D. Bateson, K. McNamee, M. Stewart, et al., Very low prevalence of vaccine human papillomavirus types among 18- to 35-year old Australian women 9 years following implementation of vaccination, J. Infect. Dis. 217 (10) (2018 Apr 23) 1590–1600, https://doi.org/10.1093/infdis/jiy075.
[11] G. Ronco, J. Dillner, K.M. Elfström, et al., the International HPV screening working group, Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials, Lancet 383 (2014) 524–532.
[12] J. Dillner, M. Rebolj, P. Birembaut, et al., Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study, BMJ 337 (2008) a1754.
[13] J.C. Gage, M. Schiffman, H.A. Katki, P.E. Castle, B. Fetterman, N. Wentzensen, N.E. Poitras, T. Lorey, L.C. Cheung, W.K. Kinney, Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test, J. Natl. Cancer Inst. 106 (8) (2014) (pii: dju153).
[14] M. Arbyn, G. Ronco, A. Anttila, C.J. Meijer, M. Poljak, G. Ogilvie, G. Koliopoulos, P. Naucler, R. Sankaranarayanan, J. Peto, Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer, Vaccine 30 (Suppl. 5) (2012) F88–F99.
[15] Australian Government Department of Health, National Cervical Screening Program, AIHW, Medical Services Advisory Committee recommendations, http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/E6A211A6FFC29E2CCA257CED007FB678/$File/Review%20of%20Evidence%20notated%2013.06.14.pdf, Accessed date: 16 January 2018.
[16] J.B. Lew, K. Simms, M.A. Smith, et al., National Cervical Screening Program Renewal: effectiveness modelling and economic evaluation in the Australian setting (assessment report)—MSAC application number 1276, http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/E6A211A6FFC29E2CCA257CED007FB678/$File/Renewal%20Economic%20Evaluation.pdf November, 2013, Accessed date: 16 October 2017.
[17] National Cervical Screening Program, Renewal of the National Cervical Screening Program: partner reference group e-newsletter, http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/52DF583BA30DCAD4CA257CED00801847/$File/PRG%20E-newsletter%2011%20May%202015.pdf May, 2015, Accessed date: 30 November 2017.
[18] K. Canfell, Cervical screening in HPV-vaccinated populations, Climacteric 21 (3) (2018) 227–234.
[19] Cancer Council Australia Cervical Cancer Screening Guidelines Working Party. National Cervical Screening Program: Guidelines for the Management of Screen-detected Abnormalities, Screening in Specific Populations and Investigation of Abnormal Vaginal Bleeding. Sydney: Cancer Council Australia. http://wiki.cancer.org.au/australiawiki/index.php?oldid=167506. (Accessed on the 27 October 2017).
[20] J.B. Lew, K. Simms, M.A. Smith, et al., Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program, Lancet Public Health 2 (2017) e96–107.
[21] L.S. Velentzis, M. Caruana, K.T. Simms, J.B. Lew, J.F. Shi, M. Saville, et al., How will transitioning from cytology to HPV testing change the balance between the benefits and harms of cervical cancer screening? Estimates of the impact on cervical cancer, treatment rates and adverse obstetric outcomes in Australia, a high vaccination coverage country, Int. J. Cancer 141 (12) (2017) 2410–2422, https://doi.org/10.1002/ijc.30926.
[22] J.M.L. Brotherton, S.N. Tabrizi, S. Phillips, J. Pyman, A.M. Cornall, N. Lambie, et al., Looking beyond human papillomavirus (HPV) genotype 16 and 18: defining HPV genotype distribution in cervical cancers in Australia prior to vaccination, Int. J. Cancer 141 (8) (2017) 1576–1584.
[23] L. Zhai, E. Tumban, Gardasil-9: a global survey of projected efficacy, Antivir. Res. 130 (2016) 101–109.
[24] C. Signorelli, A. Odone, V. Ciorba, P. Cella, R.A. Audisio, A. Lombardi, et al., Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence, Epidemiol. Infect. 145 (10) (2017) 1962–1982.
[25] Australian Government Media Release, https://www.pm.gov.au/media/2017-10-08/new-vaccine-strengthen-health-young-australians, Accessed date: 16 January 2018.
[26] Pharmaceutical Benefits Advisory Committee, Australia, http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbacoutcomes/2017-07/positive-recommendations-2017-07.pdf July 2017.
[27] K.T. Simms, J.-F. Laprise, M.A. Smith, et al., Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis, Lancet Public Health 1 (2016) e66–e75.
[28] K.T. Simms, M.A. Smith, J.B. Lew, H.C. Kitchener, P.E. Castle, K. Canfell, Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries, Int. J. Cancer 139 (2016) 2771–2780.
[29] J.B. Lew, K. Simms, M. Smith, H. Lewis, H. Neal, K. Canfell, Effectiveness modelling and economic evaluation of primary HPV screening for cervical cancer prevention in New Zealand, PLoS One 11 (2016), e0151619.
[30] M.A. Smith, D. Gertig, M. Hall, et al., Transitioning from cytology-based screening to HPV-based screening intervals: implications for resource use, BMC Health Serv. Res. 16 (2016) 147.
[31] H. Kitchener, K. Canfell, C. Gilham, 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. 18 (2014) 1–196.
[32] J.F. Shi, J.F. Chen, K. Canfell, et al., Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study, BMC Health Serv. Res. 12 (2012) 123.
[33] J.F. Shi, K. Canfell, J.B. Lew, 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 11 (2011) 239.
[34] K. Canfell, J.F. Shi, J.B. Lew, et al., Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies, Vaccine 29 (2011) 2487–2494.
[35] K. Canfell, J.B. Lew, M. Smith, R. Walker, Cost-effectiveness modelling beyond MAVARIC study end-points, in: H.C. Kitchener, R. Blanks, H. Cubie, M. Desai, G. Dunn, R. Legood, A. Gray, Z. Sadique, S. Moss (Eds.),On Behalf of the MAVARIC Trial Study Group. MAVARIC — A Comparison of Automation-assisted and Manual Cervical Screening: A Randomised Controlled Trial. Health Technology Assessment 2011, p. 15.
[36] Cancer Council NSW, Policy-1 Cervix model documentation, https://www.policy1.org/models/cervix/documentation/policy1-cervix-v1_0.pdf January 2019.
[37] I. Hammond, K. Canfell, M. Saville, A new era for cervical screening in Australia: watch this space! Aust. N. Z. J. Obstet. Gynaecol. 57 (5) (2017) 499–501.
[38] R. Wade, E. Spackman, M. Corbett, S. Walker, K. Light, R. Naik, M. Sculpher, A. Eastwood, Adjunctive colposcopy technologies for examination of the uterine cervix—DySIS, LuViva advanced cervical scan and Niris imaging system: a systematic review and economic evaluation, Health Technol. Assess. 17 (8) (2013) 1–240 (v-vi).
[39] K. Canfell, M. Caruana, V. Gebski, J. Darlington-Brown, S. Heley, J. Brotherton, et al., Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: results of the compass pilot randomised trial, PLoS Med. 14 (9) (2017), e1002388.
[40] K. Canfell, M. Saville, M. Caruana, V. Gebski, J. Darlington-Brown, J. Brotherton, et al., Protocol for Compass: A Randomised Controlled Trial of Primary HPV Testing Versus Cytology Screening for Cervical Cancer in HPV-unvaccinated and Vaccinated Women Aged 25–69 years Living in Australia, BMJ Open, 2017https://doi.org/10.1136/bmjopen-2017-016700.