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Models of cervical screening in the era of human papillomavirus vaccination

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Abstract. Epidemiologic and economic evaluation using simulation modelling can support complex policy decisions, and is an important tool in predicting the future interaction between human papillomavirus vaccination and cervical screening. Several categories of screening program evaluation are of interest, including: (1) changes to screening considered over the short term, over which the effects of vaccination should be confined to the youngest age groups (<30 years old); (2) the medium and long-term effect of vaccination on the screening program; and (3) changes to screening in context of vaccination. This review considers some of the policy questions in each category and discusses the modelling implications, with particular focus on the Australian context.

Additional keywords: Australia, Pap smear, simulation modelling.

Introduction

Many developed world countries have implemented human papillomavirus (HPV) vaccination programs, often in the context of existing organised cervical screening programs or high levels of opportunistic screening. The interaction between HPV vaccination and cervical screening is likely to develop in diverse ways in different countries over the next decade and will depend on several factors, including the timing of the implementation of vaccination, the levels of participation in both vaccination and screening, the age range of catch-up vaccination in relation to the age of starting cervical screening, the recommended screening interval and age range, and the technologies used for primary screening and for downstream management of screen-positive women. In Australia, the implementation of the National HPV Vaccination Program in 2007 occurred in context of a highly successful organised screening program. An active interplay between vaccination and screening will occur earlier in Australia than in most countries due to several factors, including relatively early adoption of public HPV vaccination, high coverage rates in both the screening and vaccination programs, and wide and overlapping age ranges in the vaccination catch-up and screening programs.

Simulation modelling can play an important role in understanding the effects of these complex interactions, and in predicting the future outcomes and cost-effectiveness of implementing various options for cervical screening in the context of HPV vaccination. Modelling can be used to integrate clinical evidence garnered from international clinical studies and meta-analyses with local information on population behaviour, risk factors and screening and diagnostic pathways (Fig. 1). It is an important addition or alternative to local clinical trials, and provides a formal framework under which the overall effects and costs of a proposed change can be evaluated, providing the policy decision-maker with a series of snapshots of the resource implications for the screening program over time.

There are four broad categories of epidemiological and cost-effectiveness evaluation that will be of future interest in terms of cervical cancer prevention in Australia: (i) potential changes to the National HPV Vaccination Program (for example, the introduction of male vaccination), which will not be discussed in detail here; (ii) changes to screening recommendations considered over the short term (<5 years), over which the effects of vaccination on the screening program may be assumed to be confined to the youngest age groups (<30 years old); (iii) the medium and long-term effect of vaccination on the screening program, assuming that the current screening recommendations are maintained; and (iv) the evaluation of potential changes aimed at optimising screening in context of vaccination. This review will consider some of the policy and research questions in each category, with particular focus on the Australian context. The modelling issues relevant to these research questions will be discussed.

Evaluation of changes to screening recommendations in the short term

Cervical screening in Australia

HPV vaccination in Australia has been implemented in context of a successful organised screening program. The National Cervical Screening Program has resulted in substantial reductions in cervical cancer incidence and mortality since its inception in 1991.[1,2] The program recommends screening every

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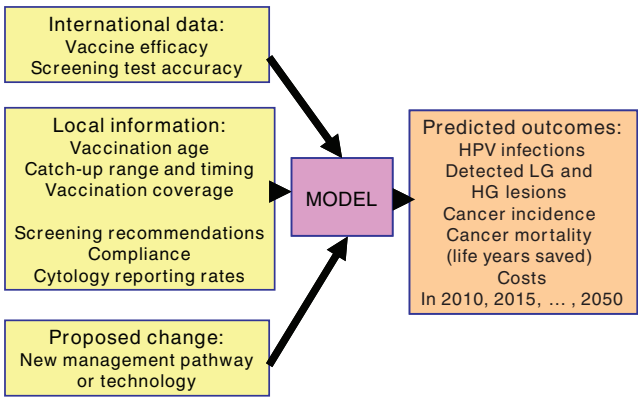

Fig. 1. Role of modelling in integrating evidence and predicting future outcomes for cervical cancer prevention. Models can integrate data from international trials and meta-analyses with local information to predict future HPV infections, detected low and high grade precancerous lesions (LG and HG), and cancer outcomes.

2 years for sexually active women aged 18–20 to 69 years,[3] and achieves high 2-yearly and 3-yearly coverage rates.[1] The most recently available international comparative registry-based incidence data from the International Agency for Research on Cancer (IARC) (as opposed to estimated incidence rates[3,4]) are for the period 1998–2002.[5] Compared with other countries in Europe, North America and Oceania, the Australian states and territories have relatively low rates of cervical cancer, with the age-standardised rate in women aged 20–69 years ranging from 7.9 to 11.8 per 100 000. Lower incidence rates are generally observed only in specific low risk populations in the USA, or in countries with very long established screening programs such as Finland (6.3 per 100 000) and the Netherlands (7.8 per 100 000). Similarly, the most recent comparative mortality data available from the World Health Organization, which are for the year 2003, show that Australia has one of the lower cervical cancer mortality rates in women aged 20–69 years observed in developed countries.[6]

An essential prerequisite for evaluating future changes in the program is to develop a validated model of current practice and its outcomes. Various approaches to modelling aspects of cervical screening in Australia have been taken.[7–9] Several models of cervical cancer screening in other settings have appeared in the literature, and these vary considerably in the complexity of the simulation of natural history (if this is directly modelled) and screening. As an example, this review will use a model of cervical cancer natural history and cervical screening in Australia that has been developed using a Markov cohort approach.[10,11] Cohort models are one of the most commonly used model types for cost-effectiveness evaluations and in the simplest implementation, they simulate a single cohort of people through their lives. Transitions between states occur according to defined probabilities and occur at a defined cycle or update time. A set of possible health states are defined according to the disease and intervention of interest, and cost and quality of life attributes can be attached to each state.[12]

Various approaches have been taken to estimate the transition probabilities for cervical cancer natural history models, including review of the scientific literature on HPV and cervical intraepithelial neoplasia (CIN) progression and regression rates; direct use of data from cohort studies; and/or estimation of transition probabilities using fitting approaches, in which an iterative process is performed to specify the transition rates within a preset range that lead to the best fit to observed data. A variety of fitting methods can be used to select unknown model parameters from within the space of possible parameter sets and fit them to epidemiological data.[13–15] Most modelling approaches have used some combination of these methods, which is a necessary step for dealing with the uncertainty inherent in estimating the natural history transition rates. The uncertainty increases for high grade disease and the probability of progression to invasive cervical cancer, for which only limited evidence is available.[16,17] Iterative fitting processes can potentially be automated using pre-set goodness-of-fit criteria. However, no consensus approach has emerged in the literature with respect to an acceptable minimum specification for the particular fitting targets that should be reported. Although, as a general principle, models should be fitted to as much data as are available, a wide variety of approaches to choosing targets have been taken. Appropriate targets include age- and type-specific rates for HPV infection, age-specific patterns of screen-detected low and high grade abnormalities, and invasive cancer incidence and mortality; but these are not uniformly used. Other aspects of automated fitting approaches that have not yet been well defined include the appropriate criteria for assessing goodness-of-fit, the range of variables that should be included in the analysis, and how the effect of screening and detection should be taken into account when using observed data on rates of precancerous abnormalities. A closely related process is probabilistic sensitivity analysis, in which parameters, (or, more often, in cervical cancer evaluation, a subgroup of parameters) in the model are systematically varied in a multi-way process to assess the effect on outcomes.

In the Australian context, fitting models to multiple sources of observational data is possible due to the ready availability of routinely collected data from the cervical screening program (for detected precancerous abnormalities) and cancer registries (for cancer incidence and mortality). However, there are inevitably some historical constraints inherent in the process of fitting models to observational data. For example, care is required in calibrating models of current screening processes in Australia, because new guidelines for the management of low grade lesions were implemented in 2006[3] and these changes, which result in a change in the number of low grade abnormalities observed in the program, will take time to be fully reflected in the routinely published data.[1,10]

Few models used for screening evaluations have incorporated detailed implementations of post-treatment recurrence rates and the subsequent probability of progression to invasive cancer in women treated for high grade precancerous lesions. However, this can be important for the accurate assessment of the costs and effects of a new screening technology if it is also used in the post-treatment management pathway. For example, analysis of the sensitivity of the cost-effectiveness of HPV triage testing to the cost of the HPV test itself in Australia should take into account that a considerable volume of HPV tests are currently performed as a test-of-cure after treatment.[11] This is because the cost of the test to the health system, at least in Australian context,

is most often standardised and does not depend on where it is used in the screening and management pathway. Therefore, any attempt to assess the influence of test price on cost-effectiveness should take all points in the pathway in which a test is used into account.

Typically, a cost-effectiveness assessment will use a cohort model to calculate the lifetime costs and effects of a particular intervention in relation to a baseline strategy for the cohort, and thus calculate an incremental cost-effectiveness ratio (ICER) for the new strategy. The ICER can be calculated either as a cost per life year saved as a result of the new intervention or, if quality of life weights for model health states are taken into account, as a cost per quality adjusted life year (QALY) saved. The cost per QALY saved measure takes the quality of life decrements (or 'disutilities') associated with some health states into account (for example, having the experience of a screening test, having the experience of treatment for precancer and being diagnosed with and treated for invasive cervical cancer) but the relevance of this measure is strongly influenced by the availability of valid data from well-conducted surveys on the quality of life weights attached to particular health states by women in the population. In the Australian context, there is little information available on quality of life weightings that women attach to cervical screening health states, although one study has examined the disutilities associated with HPV triage testing.[18] Caution should be applied in interpreting QALY findings based on disutility data obtained from studies in other populations, especially if these are not conducted in groups broadly representative of the entire population of women targeted by the screening program.

A limitation of classical Markov models is that they do not incorporate a 'memory' – the proportion of the cohort transitioning from a state at any one time depends only on the proportion in that state during the previous cycle and not on the prior history of transitions into that state. However, semi-Markov implementations which allow the detailed specification of multiple pathways do permit very complex patterns of screening in the population, and screening and management history to be taken into account.[10,11] For complex screening models suitable for addressing questions about the cost-effectiveness of new strategies for screening, the structure of the screening and management pathways in the model should reflect the recommended management of cytology, colposcopy and histology results, taking the relevant history into account. In the Australian context, the current management recommendations are the National Health and Medical Research Council (NHMRC) Guidelines for Cervical Screening.[3] In some instances, the guidelines provide for the discretion of the clinician and, in such cases, the management alternatives as specified in a model are ideally determined by a panel of experts.[10,11] A detailed implementation of current practice is a necessary prerequisite for assessing the effect of changes to screening practice on the lifetime costs and effects of screening in the population.

Screening interval, age range and method of organisation

Even before the advent of HPV vaccination, several issues arose in relation to the potential for further optimising the national screening program in Australia. For example, the recommended 2-yearly screening interval and the relatively wide age range of women targeted by the program means that screening is conducted more intensively in Australia than in most developed countries.[2,19] The IARC recommends that screening start at age 25 years, and that screening is conducted every 3 years in women aged 25–49 years and every 5 years in women aged 50–64 years.[20] Taking these factors into account, the NHMRC in Australia has recommended a review of the screening interval to ensure that it is consistent with international best practice.[3] Given the low cervical cancer incidence and mortality rates currently observed in Australia, and scientific support for the maintenance of cytological screening efficacy with a 3-yearly interval[20–22] and older age of starting screening (at 25 years of age);[23] consideration could be given to changing these aspects of the organised program. Furthermore, evidence from overseas clinical trials suggests that the introduction of HPV DNA testing for primary screening would potentially allow a further extension of the screening interval of up to 5–7 years.[24,25]

One of the main issues to consider in modelling changes to the recommended screening interval is whether or not to take compliance to that recommendation into account, and this determination depends in part on the existing level of compliance. Currently, cervical screening in Australia is organised according to a reminder-based system, in which women who do not attend their screening test are sent a reminder letter 3 or more months after the test is due. An alternative system of organisation is the call-and-recall system as implemented in the UK that comprises several elements: women are proactively sent a letter to attend for screening before the date that their test is due, reminder letters are sent to non-attendees and substantial practitioner incentives based around participation rates are in place. Data from England show that under such a system, very high levels of compliance to the recommended interval can be achieved.[2] Therefore, a simple model of screening, which takes into account age-specific participation rates but not other aspects of population heterogeneity in screening behaviour, can represent cervical cancer outcomes in the UK context with a reasonable level of accuracy.[26] In contrast, there is a greater timing distribution observed for re-screening in Australia[2] (although this distribution is changing somewhat over time because rates of early rescreening are decreasing[1]). In this situation, a model will more accurately represent both behaviour and outcomes if compliance is informed by registry data. Data from the Victorian Cervical Cytology Register for the period 1997–2007 has been used in the Australian context to parameterise a model of screening with 10-year follow-up information on the proportion of women re-screening each year after a negative screening test, the proportion of women attending for cytological follow-up or specialist referral each year after a low grade or high grade cytological abnormality, and the proportion attending for treatment over time, and information on compliance to other management recommendations.[10,11]

Similarly, accurate evaluation of a change to raise the recommended screening starting age to 25 years requires modelling assumptions to be made about the current distribution of the timing of screening initiation in the population. Such assumptions are usefully informed by data

on screening participation in 20–24-year-olds and by survey information on the number of women in each age group who report ever being screened.[1,10,11,27] Potentially, changes to the organisation of screening in Australia could also be considered in order to increase compliance with a longer recommended screening interval and an older age of starting screening, and to mitigate concerns about changes in the recommendations leading to increased levels of underscreening. For modelling purposes, patterns of screening behaviour from other countries are informative. For example, data from England could be used to help inform estimates of likely changes to screening behaviour if call-and-recall were to be introduced in Australia.

New technologies for screening

Various alternatives to conventional cytology screening have emerged, including manually-read liquid-based cytology (LBC), automated image read of LBC (AutoLBC), and the incorporation of HPV DNA testing as a triage for low grade abnormalities or as a primary screening test. LBC and AutoLBC with and without HPV triage testing have recently been evaluated and rejected for public funding in Australia by the Medical Services Advisory Committee (MSAC)[28]. Although MSAC found that the new technologies were safe and at least as effective as conventional cytology, the committee advised that the technology not be supported for public funding because the technologies 'were not cost-effective at the price requested'.[28] One of the factors decreasing the cost-effectiveness of these technologies in the Australian context was found to be the shorter recommended screening interval, leading to a higher frequency of use of the more expensive technologies than would be the case in many other countries.[10,11] Another factor specific to the Australian context was found to be the relatively low rate of unsatisfactory smears currently experienced with conventional cytology,[29] such that the reduction in the unsatisfactory smear rate that could reasonably be achieved with LBC is less than in some other settings.[30]

Various approaches to modelling the test characteristics of cervical cytology, HPV DNA testing, colposcopy and other tests can be used. The simplest approach is to apply estimates of test sensitivity and specificity directly in the model. However, this does not fully specify the relationship between each possible underlying natural history health state at the time of testing and each possible test result. In order to do so, a 'test probability matrix' is required, which gives the probability of each grade of cytological or other test result for each underlying natural history health state specified in the model.[10,11] The test parameters for sensitivity, specificity, positive predictive value and negative predictive value can be derived from the test probability matrix for thresholds at any health state. Where it is available, the test probability matrix should be preferentially populated with data from large scale studies with high quality designs, or from systematic review and meta-analyses of test accuracy.[10,11] The values used also depend on observed cytology abnormality rates in the local context, since these are an indication of the operating sensitivity–specificity trade-off point on the receiver operating characteristic curve for the cytology.

Accurate modelling of the diagnostic process requires characterisation of colposcopy accuracy. Imperfect colposcopic sensitivity for high grade disease leads to lack of confirmation of a small proportion of true screen-positive lesions, and imperfect specificity potentially leads to additional treatments and increased costs. Additionally, modelling the age-specific unsatisfactory rates associated with incomplete visualisation of the original squamocolumnar junction at colposcopy allows the evaluation to take into account the clinical follow-up and treatment processes that occur in this situation.

Evaluation of the effect of vaccination on the existing screening program

Interaction between screening and vaccination in Australia

In countries with both population-based screening and newly implemented HPV vaccination programs, consideration must be given to the interaction between the two programs. However, in some settings, several years will pass before the vaccinated and screened cohorts overlap. For example, in England, the catch-up vaccination program involves females up to the age of 18 years, whereas the recommended age of starting screening is 25 years.[31] In such a situation, no immediate vaccination-related changes to screening policy seem necessary. However, the immediate situation is more complex in Australia, in which vaccinated and screened cohorts have overlapped from the inception of the National HPV Vaccination Program, and in which the degree of overlap will continue to increase year by year as the vaccinated cohorts mature. Australia's implementation of the National HPV Vaccination Program was performed early in international context, in 2007; it has one of the widest reported age ranges for catch-up vaccination, encompassing females aged 12–26 years, and one of the highest levels of base population coverage reported in any country to date, at ~78% in three-dose coverage 12–13-year-old girls.[32] Therefore, Australia is likely to be one of the first settings in which significant numbers of vaccinated women will participate in population-based cervical screening.

The initial impact on the screening program is expected to be that due to catch-up vaccination and confined to the youngest age groups screened (<30 years). The effectiveness of vaccination is expected to be somewhat attenuated in the catch-up cohorts. However, although vaccination has been shown not to affect the duration of HPV infections present at the time of vaccination,[33,34] it has been suggested that there may be some protective effect against re-infection in women who have previously been exposed to, and then apparently cleared, a particular HPV type (i.e. they are seropositive but DNA negative for a type).[35] The short-term effect of catch-up vaccination in Australia on the number of detected abnormalities within the screening program will depend on a complex interplay between the magnitude of this effect, if confirmed, and several other factors including age-patterns of exposure to HPV-16 and -18, the number of co-infections at particular ages and the level of cross-protection against other oncogenic types that is conferred by the vaccine. The median age of sexual debut is 16 years for females in Australia[36] and so within a 5-year period of commencing vaccination, by ~2012, assuming no change to the recommended age of starting screening, the majority of the youngest females entering the screening program at 18–20 years

will have been effectively vaccinated against HPV-16 and -18 infections.

The initial step in estimating the effect of vaccination on the screening program is to model the impact of vaccination on HPV infection rates. This is best done using dynamic transmission models, which incorporate characterisation of the transmission modality of the disease (sexual behaviour for HPV transmission), the probability of an uninfected person becoming infected upon contact with an infected person, the duration of infection and, the duration of naturally acquired immunity to infection.[37,38] Models of HPV transmission in Australia have been developed and parameterised by survey data on sexual behaviour of the Australian population.[36,39] These models can be used to predict the effects over time of HPV vaccination on HPV transmission and, consequently, on infection rates in the population. For example, one model of sexual behaviour and HPV transmission in Australia stratifies the Australian population by sex, 5-year age group and level of sexual activity, incorporating early data on vaccination uptake rates in the national program and data from a review of surveys of sexual behaviour.[36] The output was calibrated to the age-specific prevalence of oncogenic HPV[40] and the model was used to predict the short- and long-term effects of the vaccination program on HPV infections in Australia, finding that if high base coverage rates are maintained for 12- to 13-year-old girls, new infections would be almost halved within a few years of the introduction of the program (by 2010) and reduced by close to 90% by 2050.[36]

In order to model vaccination and screening together, hybrid approaches using dynamic transmission models for HPV transmission and vaccination modelling may be used to calculate future HPV infection rates, and cohort models can be used for modelling precancerous disease, invasive cancer and cervical screening (Fig. 2). However, when modelling the effect of vaccination on precancerous abnormalities and other aspects of the screening program, single cohort models are inadequate to capture the full range of outcomes. There are several major issues that must be borne in mind with the interpretation of findings from single cohort models. First, they do not account for differences in risk or exposure between birth cohorts in the population. For example, the progressive introduction of HPV vaccination with a catch-up phase in Australia means that successive cohorts of females will be at differing risk of HPV infection and this cannot be captured in a single cohort model. A second issue with single cohort models is that they do not provide cross-sectional population outcomes. This can be addressed with multi-cohort implementations that allow the prediction of outcomes for different cohorts, and also calculation of short-, medium- and long-term cross-sectional outcomes and costs in the population.

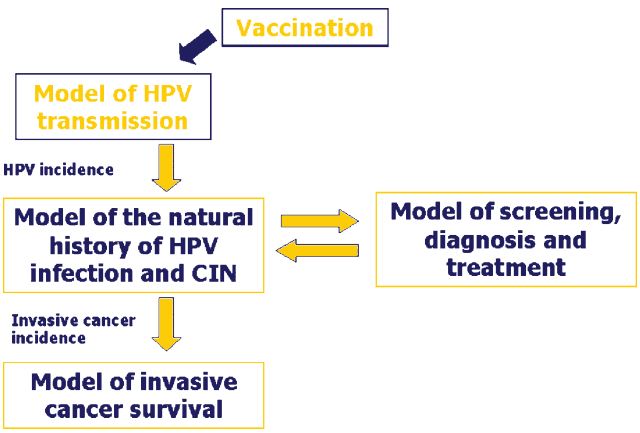

Fig. 2. Hybrid modelling approach for cervical cancer prevention.

Dynamic transmission models can also be built to incorporate full natural history and screening structures, but, in practice, the feasibility of this depends on the desired complexity of screening modelling and the objectives of the research program. For future research questions primarily related to HPV vaccination, such as the role and cost-effectiveness of vaccination in males and the effect of vaccination on genital warts and non-cervical cancers, relatively simpler modelling structures for cervical screening are likely to be adequate. However, research questions related to the relative assessment of the role of particular cervical screening technologies and other changes to screening recommendations or organisation are likely to increase the importance of constructing detailed structures for modelling screening pathways, screening compliance, treatment, colposcopy accuracy and compliance, and post-treatment recurrence and management.[10,11] For example, an evaluation of manually-read LBC in Australia found that even if the technology was available at the same price as conventional cytology, the across-the-board replacement of conventional cytology with LBC would still be associated with significant costs to the health care system, due to the slightly lower specificity of the test and the consequently increased follow-up and management requirements for low grade smears.[10] This effect, and its influence on the subsequent interplay between vaccination and the cost-effectiveness of LBC, can only be captured with a sufficiently detailed model of low grade management pathways.

In the future, the National HPV Vaccination Register in Australia will provide information on HPV vaccination coverage by age, number of doses and geographical area, and this will be useful for more detailed models of population subgroups, and to characterise the relationship between screening and vaccination behaviours in such groups. It will be important to characterise the relationship between screening and vaccination compliance because it is possible that certain high risk groups will be less likely to participate in both the screening and vaccination programs. If this relationship can be well characterised via linkage of screening and vaccination data, future models will be better able to account for differential risks in various population subgroups and, in particular, to characterise risk accurately in socially disadvantaged groups. From the policy perspective, when women reach the recommended age of starting cervical screening, the data from the National HPV Vaccination Register could potentially be used by the cervical screening program to enable targeted invitation letters for screening (and/or vaccination) to be sent to unvaccinated women. This could be done as a supplementary activity to the reminder-based system or as part of a call-and-recall strategy. From a modelling perspective, capturing heterogeneity in screening and vaccination behaviour is likely to require implementation using individual-based

(microsimulation) methods. These methods involve separately modelling the pathways taken by individuals through time; the results are then integrated to capture population level outcomes. Microsimulation models are useful when it is necessary to capture many different possible pathways, as is the case when considerable behavioural differences exist; such behavioural differences can be more difficult to incorporate within a cohort model framework.

Direct protection from vaccine-included HPV types and cross-protection

The vaccine-included HPV types 16 and 18 are involved in ~20–30% and ~50% of low and high grade abnormalities, respectively. In order to consider the effect of depletion of these types on precancerous abnormalities, type-specific models are required to account for the inclusion in the current generation HPV vaccines of some, but not all, oncogenic HPV infections. However, to take HPV vaccine cross-protection into account between HPV-16 and -18, and other oncogenic types, it will also be important to model a range of outcomes. At one end of the spectrum, a slower rate of decrease of precancerous abnormalities will be predicted if it is assumed that HPV-16 and -18 vaccination induces no cross-protection for other oncogenic types; at the other end of the spectrum, the predicted rate of decrease in change in cytological abnormalities will be faster if it is assumed that HPV-16 and -18 vaccination induces close to complete cross-protection against the other oncogenic types.

Evaluation of potential changes to screening in context of HPV vaccination

LBC and AutoLBC

HPV vaccination is expected to reduce the positive predictive value of cytological screening, thus decreasing cytological abnormalities and shifting the distribution of these towards low grade abnormalities. This is because depletion of lesions related to HPV-16 and -18 due to vaccination will reduce high grade cytological abnormalities more than low grade abnormalities. This will eventually affect not only the positive predictive value of abnormal cytology, but also has the potential to influence the intrinsic sensitivity and specificity of cytology-based screening approaches, which have been tailored around detection of HPV-16-related precancerous infections, at least in part.[41] Over time, the effect of vaccination on reducing abnormalities in young women will change the cost-effectiveness of LBC and AutoLBC in relation to conventional cytology. However, whether the cost-effectiveness of these technologies increases or decreases cannot be readily predicted, and will depend on several interacting factors, including the timeframe of the effect of vaccination on the reduction in precancerous abnormalities, the laboratory process efficiencies associated with AutoLBC and the consequent potential for cost savings to the health system, and the effect, if any, of vaccination and consequent HPV-16 depletion in the population on the accuracy of conventional cytology and on LBC-based screening technologies. From the evaluation perspective, obtaining accurate clinical data on these aspects will be critical to modelling the medium- and longer-term interaction between vaccination and cytological screening.

Primary HPV testing

In recent years, there has been the emergence of a body of evidence from several international studies and large randomised controlled trials on primary HPV DNA testing.[24,25,42–48] HPV vaccination has been demonstrated not to affect the clearance of naturally acquired HPV infections.[33,34] Therefore, women who are positive for a particular oncogenic type can be considered to be at similar risk for future development of a high grade precancerous lesion, irrespective of their prior vaccination status. Primary HPV testing could allow population-based screening recommendations to be configured that do not depend on vaccination status but depend on risk assessment for an individual. This is an important consideration because the vaccination status of the population targeted for screening will vary over time as more cohorts vaccinated through the catch-up program reach screening age.

Cervical cancer natural history models reported to date have usually been based on histologically defined health states for precancerous disease, either according to the Bethesda system as low-grade squamous intraepithelial lesion or high-grade squamous intraepithelial lesion,[49] or as CIN1–3.[26] However, for accurate modelling of primary HPV testing, there is likely to be more focus in the future on natural history structures that more directly reflect the infectious course of different HPV types in the cervix, in which low grade disease is viewed as a manifestation of productive HPV infection, with some types being more likely to persist and progress to an immediate precursor of invasive cancer (broadly equivalent to CIN3).[50]

Several technologies for HPV testing are available, and these appear to have differing analytical and clinical sensitivity and specificity. The technology for which the most clinical evidence is available is Hybrid Capture 2 (HC2) (Qiagen Inc., Gaithersburg, MD, USA), for which a rapid-throughput version has recently become available (allowing laboratories to process the large volumes necessary for primary screening). A next generation test (NextGen HC2, Qingen Inc.) with lower levels of cross-reactivity to low risk HPV types[51] may eventually be shown to have higher clinical specificity for CIN2+. Several clinically-positioned polymerase chain reaction based technologies have also become available.[52–54] Various options for the management of HPV positive women have been proposed, including cytological triage, partial typing (i.e. stratifying with respect to whether types 16, 18 and potentially 45 are present),[55] and dual-stained cytology for the molecular markers overexpressed cyclin-dependent kinase inhibitor $p16^{INK4a}$ (p16) and K_i-67.[56] HPV testing with partial typing or assessment of progression markers could allow high volume clinical testing with further risk stratification, allowing the differential (more aggressive) management of women who are exposed to the HPV types most often found in cervical cancer or who are positive for progression markers. However, the role of these technologies, and the optimal and most cost-effective triage strategy, is yet to be fully defined. As has been the case for the assessment of cytologically-based tests, cost-

effectiveness models will need to carefully distinguish between the various available technologies, and incorporate the most current and highest quality evidence on test accuracy. Ultimately, the cost-effectiveness of HPV primary screening in Australia will depend on the particular test characteristics of the HPV test and triage technologies used, as well as several other interacting factors including the direct costs associated with the new technologies and the recommended screening interval associated with the implementation of primary HPV testing.

Conclusions

The implementation of HPV vaccination will eventually change the number of precancerous abnormalities detected with the cervical screening program, which has implications for resource use and for the cost-effectiveness of the existing screening program. In the future, optimising both the effectiveness and cost-effectiveness of screening in the context of vaccination is likely to require changes to the technology used for primary screening. Defining the role of new screening technologies will entail consideration of several issues, including the effect on laboratory processes, the appropriate downstream management of screen-positive women, and the interaction between the screening technology and the optimal screening interval, age range and method of program organisation.

In 2009, the Department of Health and Ageing in Australia announced the renewal of the National Cervical Screening Program, which will aim to 'assess the impact of the HPV vaccine, new technologies, age range, and screening interval on the Program'.[57] Modelling is expected to play an important role in such an assessment. In order to distinguish between future screening options, screening models will need to be detailed enough to distinguish between different technologies for cytology (conventional, LBC and AutoLBC) and for HPV testing (HC2, Next Generation Hybrid Capture and the various other signal-amplified and polymerase chain reaction HPV test technologies), and to capture differences between downstream management options for each of these technologies. Accurate modelling will require incorporation of data from routinely collected datasets, and from international randomised trials and systematic reviews. In the future, suitably validated models will provide policy-makers with predictions of the expected numbers of screening tests, colposcopies and treatments, as well as quantifying costs, cost-effectiveness and the effects on cervical cancer incidence and mortality in the national cervical screening program.

Conflicts of interest

None declared.

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References

1 Australian Institute of Health and Welfare. Cervical Screening in Australia 2006–2007. Report No.: Cat. No. CAN 43. Canberra: Australian Institute of Health and Welfare; 2009.

2 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.

3 National Health and Medical Research Council. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. Canberra: NHMRC; 2005. Available online at: http://www.nhmrc.gov.au/publications/synopses/wh39syn.htm [verified July 2010].

4 International Agency for Research on Cancer. GLOBOCAN 2002. Lyon: IARC; 2005. Available online at: http://www-dep.iarc.fr/ [verified July 2010].

5 Curado MP, Edwards B, Shin HR, Storm H, Frelay J, Heanue M, *et al.* Cancer incidence in five continents, Vol. IX. Report No.: IARC Scientific Publications No. 160. Lyon: IARC; 2007.

6 International Agency for Research on Cancer. WHO mortality database extracted from the World Health Organization (WHO) Databank. Lyon: IARC; 2005. Available online at: http://www-dep.iarc.fr/ [verified July 2010].

7 Neville AM, Quinn MA. An alternative cost effectiveness analysis of ThinPrep in the Australian setting. *Aust N Z J Obstet Gynaecol* 2005; 45: 289–94. doi:10.1111/j.1479-828X.2005.00413.x

8 Anderson R, Haas M, Shanahan M. The cost-effectiveness of cervical screening in Australia: what is the impact of screening at different intervals or over a different age range? *Aust N Z J Public Health* 2008; 32: 43–52. doi:10.1111/j.1753-6405.2008.00165.x

9 Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, *et al*. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. *Sex Health* 2007; 4: 165–75. doi:10.1071/SH07043

10 Medical Services Advisory Committee. Automation assisted and liquid based cytology for cervical cancer screening. MSAC reference 1122, Assessment report. Canberra: MSAC; 2009. Available online at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/2AD0E9BD12315EB9CA2575C5002872A9/$File/1122_MSAC_Assessment_Report.pdf [verified July 2010].

11 Medical Services Advisory Committee. Human papillomavirus triage test for women with possible or definite low-grade squamous intraepithelial lesions. Canberra: MSAC; 2009. Available online at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/8FD1D98FE64C8A2FCA2575AD0082FD8F/$File/39_MSAC_Assessment_Report.pdf [verified July 2010].

12 Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. New York: Oxford University Press; 2005.

13 Kim JJ, Kuntz KM, Stout NK, Mahmud S, Villa LL, Franco EL, *et al*. Multiparameter calibration of a natural history model of cervical cancer. *Am J Epidemiol* 2007; 166: 137–50. doi:10.1093/aje/kwm086

14 van de Velde N, Brisson M, Boily MC. Modeling human papillomavirus vaccine effectiveness: quantifying the impact of parameter uncertainty. *Am J Epidemiol* 2007; 165: 762–75. doi:10.1093/aje/kwk059

15 Goldhaber-Fiebert JD, Stout NK, Ortendahl J, Kuntz KM, Goldie SJ, Salomon JA. Modeling human papillomavirus and cervical cancer in the United States for analyses of screening and vaccination. *Popul Health Metr* 2007; 5: 11. doi:10.1186/1478-7954-5-11

16 McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma *in situ* of the cervix. *Obstet Gynecol* 1984; 64: 451–8.
17 McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, *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* 2008; 9: 425–34. doi:10.1016/S1470-2045(08)70103-7
18 Howard K, Salkeld G, McCaffery K, Irwig L. HPV triage testing or repeat Pap smear for the management of atypical squamous cells (ASCUS) on Pap smear: is there evidence of process utility? *Health Econ* 2008; 17: 593–605. doi:10.1002/hec.1278
19 Dickinson JA. Cervical screening: time to change the policy. *Med J Aust* 2002; 176: 547–50.
20 IARC Working Group on the Evaluation of Cancer. IARC handbooks of cancer prevention volume 10: cervix cancer screening (10th edition). Lyon: IARC Press; 2005.
21 IARC. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. *BMJ* 1986; 293: 659–64. doi:10.1136/bmj.293.6548.659
22 Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer* 2003; 89: 88–93. doi:10.1038/sj.bjc.6600974
23 Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *BMJ* 2009; 339: b2968. doi:10.1136/bmj.b2968
24 Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, *et al*. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer* 2006; 119: 1095–101. doi:10.1002/ijc.21955
25 Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, *et al*. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine* 2008; 26(Suppl. 10): K29–K41. doi:10.1016/j.vaccine.2008.06.019
26 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. doi:10.1038/sj.bjc.6602002
27 Australian Bureau of Statistics (ABS). National Health Survey, summary of results, Australia, 2004–05. Cat. No. 4364.0. Canberra: ABS; 2006.
28 Medical Services Advisory Committee. Completed assessments. 4-1-2010. Canberra: MSAC. Available online at: http://www.health.gov.au/internet/msac/publishing.nsf/content/app1122-1 [accessed February 2010].
29 NPAAC. Performance measures for Australian laboratories reporting cervical cytology. Canberra: Department of Health and Ageing, National Pathology Accreditation Advisory Council; 2006.
30 Williams AR. Liquid-based cytology and conventional smears compared over two 12-month periods. *Cytopathology* 2006; 17: 82–5. doi:10.1111/j.1365-2303.2006.00339.x
31 Cuzick J, Castanon A, Sasieni P. Predicted impact of vaccination against human papillomavirus 16/18 on cancer incidence and cervical abnormalities in women aged 20–29 in the UK. *Br J Cancer* 2010; 102: 933–39. doi:10.1038/sj.bjc.6605528
32 Brotherton J, Deeks S, Campbell-Lloyd S, Misrachi A, Passaris I, Peterson K, *et al*. Interim estimates of human papillomavirus vaccination coverage in the school-based program in Australia. *Commun Dis Intell* 2008; 32: 457–61.
33 Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; 356: 1915–27. doi:10.1056/NEJMoa061741
34 Hildesheim A, Herrero R, Wacholder S, Rodriguez AC, Solomon D, Bratti MC, *et al*. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. *JAMA* 2007; 298: 743–53. doi:10.1001/jama.298.7.743
35 Riethmuller D, for the Quadrivalent HPV Vaccine Investigators. Quadrivalent HPV 6/11/16/18 vaccine efficacy against persistent infection or disease in subjects with prior HPV vaccine HPV type infection. Abstract presented at EUROGIN (SS 3–6). EUROGIN 2010 Meeting, Monte Carlo, Monaco 17–20 February 2010.
36 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. doi:10.1002/ijc.23633
37 Anderson RM, Garnett GP. Mathematical models of the transmission and control of sexually transmitted diseases. *Sex Transm Dis* 2000; 27: 636–43. doi:10.1097/00007435-200011000-00012
38 Garnett GP. An introduction to mathematical models in sexually transmitted disease epidemiology. *Sex Transm Infect* 2002; 78: 7–12. doi:10.1136/sti.78.1.7
39 Regan DG, Philp DJ, Hocking JS, Law MG. Modelling the population-level impact of vaccination on the transmission of human papillomavirus type 16 in Australia. *Sex Health* 2007; 4: 147–63. doi:10.1071/SH07042
40 Garland SM, Brotherton J. The prevalence of human papillomavirus infection in Australia: analysis of data from the Women, Human Papillomavirus prevalence, Indigenous, Non-Indigenous, Urban, Rural (WHINURS) study. Proceedings of the 24th International Papillomavirus Society Conference, Beijing, China; 2007 Nov 9.
41 Schiffman M. Integration of human papillomavirus vaccination, cytology, and human papillomavirus testing. *Cancer* 2007; 111: 145–53. doi:10.1002/cncr.22751
42 Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, *et al*. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007; 357: 1579–88. doi:10.1056/NEJMoa071430
43 Bulkmans NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, *et al*. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet* 2007; 370: 1764–72. doi:10.1016/S0140-6736(07)61450-0
44 Naucler P, Ryd W, Tornberg S, Strand A, Wadell G, Elfgren K, *et al*. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med* 2007; 357: 1589–97. doi:10.1056/NEJMoa073204
45 Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, *et al*. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet* 2003; 362: 1871–6. doi:10.1016/S0140-6736(03)14955-0
46 Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Palma PD, Del MA, *et al*. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol* 2010; 11: 249–57. doi:10.1016/S1470-2045(09)70360-2
47 Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, *et al*. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol* 2009; 10: 672–82. doi:10.1016/S1470-2045(09)70156-1
48 Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, *et al*. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. *Health Technol Assess* 2009; 13: 1–150; iii–iv.

49 Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol* 2000; 151: 1158–71.
50 Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet* 2007; 370: 890–907. doi:10.1016/S0140-6736(07)61416-0
51 Eder PS, Lou J, Huff J, Macioszek J. The next-generation Hybrid Capture High-Risk HPV DNA assay on a fully automated platform. *J Clin Virol* 2009; 45: S85–92. doi:10.1016/S1386-6532(09)70013-7
52 Coutlee F, Mayrand MH, Roger M, Franco EL. Detection and typing of human papillomavirus nucleic acids in biological fluids. *Public Health Genom* 2009; 12: 308–18. doi:10.1159/000214921
53 Day SP, Hudson A, Mast A, Sander T, Curtis M, Olson S, *et al*. Analytical performance of the Investigational Use Only Cervista HPV HR test as determined by a multi-center study. *J Clin Virol* 2009; 45: S63–72. doi:10.1016/S1386-6532(09)70010-1
54 Kurtycz DF, Smith M, He R, Miyazaki K, Shalkham J. Comparison of methods trial for high-risk HPV. *Diagn Cytopathol* 2010; 38: 104–8.
55 Thai H, Rangwala S, Gay T, Keating K, McLeod S, Nazarenko I, *et al*. An HPV 16, 18, and 45 genotyping test based on Hybrid Capture technology. *J Clin Virol* 2009; 45(Suppl. 1): S93–7. doi:10.1016/S1386-6532(09)70014-9
56 Tsoumpou I, Arbyn M, Kyrgiou M, Wentzensen N, Koliopoulos G, Martin-Hirsch P, *et al*. p16(INK4a) immunostaining in cytological and histological specimens from the uterine cervix: a systematic review and meta-analysis. *Cancer Treat Rev* 2009; 35: 210–20. doi:10.1016/j.ctrv.2008.10.005
57 Koukari A. Renewal of the National Cervical Screening Program. Talk at Preventing Cervical Cancer 2009, Melbourne, March, 2009.

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