The projected timeframe until cervical cancer elimination in Australia: a modelling study

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Summary

Background In 2007, Australia was one of the first countries to introduce a national human papillomavirus (HPV) vaccination programme, and it has since achieved high vaccination coverage across both sexes. In December, 2017, organised cervical screening in Australia transitioned from cytology-based screening every 2 years for women aged from 18–20 years to 69 years, to primary HPV testing every 5 years for women aged 25–69 years and exit testing for women aged 70–74 years. We aimed to identify the earliest years in which the annual age-standardised incidence of cervical cancer in Australia (which is currently seven cases per 100 000 women) could decrease below two annual thresholds that could be considered to be potential elimination thresholds: a rare cancer threshold (six new cases per 100 000 women) or a lower threshold (four new cases per 100 000 women), since Australia is likely to be one of the first countries to reach these benchmarks.

Methods In this modelling study, we used Policy1-Cervix—an extensively validated dynamic model of HPV vaccination, natural history, and cervical screening—to estimate the age-standardised incidence of cervical cancer in Australia from 2015 to 2100. We incorporated age-specific coverage of the Australian National HPV Vaccination Program in girls, including the catch-up programme, and the inclusion of boys into the vaccine programme from 2013, and a change from the quadrivalent to the nonavalent vaccine from 2018. We also modelled the effects of the transition to primary HPV screening. We considered two scenarios for future screening recommendations regarding the cohorts who will be and who have been offered the nonavalent vaccine: either that HPV screening every 5 years continues, or that no screening would be offered to these women.

Findings We estimate that, in Australia, the age-standardised annual incidence of cervical cancer will decrease to fewer than six new cases per 100 000 women by 2020 (range 2018–22), and to fewer than four new cases per 100 000 women by 2028 (2021–35). The precise year of attaining these rates is dependent on the population used for age-standardisation, HPV screening behaviour and test characteristics, the incremental effects of vaccination of men on herd immunity in women, and assumptions about the future frequency of benign hysterectomies. By 2066 (2054–77), the annual incidence of cervical cancer will decrease and remain at fewer than one case per 100 000 women if screening for HPV every 5 years continues for cohorts who have been offered the nonavalent vaccine, or fewer than three cases per 100 000 women if these cohorts are not screened. Cervical cancer mortality is estimated to decrease to less than an age-standardised annual rate of one death per 100 000 women by 2034 (2025–47), even if future screening is only offered to older cohorts that were not offered the nonavalent vaccine.

Interpretation If high-coverage vaccination and screening is maintained, at an elimination threshold of four new cases per 100 000 women annually, cervical cancer could be considered to be eliminated as a public health problem in Australia within the next 20 years. However, screening and vaccination initiatives would need to be maintained thereafter to maintain very low cervical cancer incidence and mortality rates.

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Introduction

In May, 2018, the Director-General of WHO called for a "coordinated action globally to eliminate cervical cancer".[1,2] An elimination threshold in terms of cervical cancer incidence has not yet been defined, but an absolute incidence of cervical cancer could be chosen for such a threshold.

The incidence of cervical cancer and the associated mortality rate in Australia are among the lowest in the world. After the introduction of the National Cervical Screening Program (NCSP) in 1991, cervical cancer incidence in Australia decreased by approximately 50% in women older than 25 years.[3] The NCSP involved cytology-based screening every 2 years, from age 18–20 years to age 69 years. Coverage of this programme, as reported in 2017, was approximately 70·2% over the 3-year period 2013–15, and 83·0% over the 5-year period 2011–15.[4] On Dec 1, 2017, Australia transitioned to the renewed NCSP, a programme that involved primary human papillomavirus (HPV) screening every

Research in context

Evidence before this study

We searched PubMed for studies published in English from Jan 1, 2010, to Sept 24, 2018. The search terms used were "cervical cancer" and "timing OR timeline AND elimination". No previous studies were identified that estimated the time to elimination of cervical cancer in any country. Australia was the first country in the world to initiate a fully funded national human papillomavirus (HPV) vaccination programme and has instituted HPV screening, and therefore is on track to be the first country to use interventional strategies to eliminate cervical cancer as a public health problem.

Added value of this study

We simulated the local HPV vaccination and screening environment in Australia, including the introduction of primary HPV testing in 2017, and the nonavalent HPV vaccine in 2018. We found that the incidence of cervical cancer is likely to decrease below a potential elimination threshold of fewer than four new cases per 100 000 women annually by 2028 (range 2021–35). Because the current cervical screening programme in Australia, which offers HPV testing every 5 years to women aged

25–69 years and exit testing to women aged 70–74 years, is unlikely to be cost-effective for women who have received the nonavalent HPV vaccine as girls, we considered the effects of ceasing cervical screening in these cohorts; an age-standardised annual incidence of fewer than four cases per 100 000 women was still achieved and maintained in this scenario. Screening would continue to be required for older cohorts.

Implications of all the available evidence

The findings of this study offer a valuable insight into the achievability and timeliness of the call to action for cervical cancer elimination. Australia, the global front runner in cervical cancer prevention, is on track to eliminate cervical cancer as a public health problem by 2028 (range 2021–35). However, this population-level finding does not necessarily mean that inequities will not persist in some groups of women. Effective communication strategies will be required to maintain high coverage rates of the HPV vaccine (for younger cohorts) and of cervical screening (for women in older cohorts who were not offered the nonavalent vaccine).

5 years for women aged 25–69 years and exit testing for women aged 70–74 years, with partial genotyping for HPV types 16 and 18 and liquid-based cytology triage for other HPV types.[5] Large-scale clinical trials[6] and detailed modelling[7] suggest that primary HPV screening is more effective at detecting cervical abnormalities and preventing cervical cancer than screening with cytology at shorter intervals.[6,7]

Australia was the first country in the world to initiate a national publicly-funded HPV vaccination programme and to document its effects on intermediate outcomes.[8–11] The Australian National HPV Vaccination Program (NHVP) was rolled out in 2007, and used a quadrivalent vaccine (Gardasil [Merck]) in a three-dose schedule.[12] The quadrivalent vaccine protects against HPV types, 6, 11, 16, and 18; it is of note that HPV types 16 and 18 are implicated in more than 70% of cervical cancers in Australia.[13,14] The NHVP involves routine vaccination of girls aged 12–13 years, and a catch-up programme ran for women aged 14–26 years until 2009. Boys aged 12–13 years were included in the programme from 2013, and a catch-up programme for boys aged 14–15 years ran until the end of 2015.[14] There is increasing medical literature that documents the substantial effects that the NHVP has had on lowering the prevalence of vaccine-included HPV types, anogenital warts, and precancerous lesions in cohorts who have been offered vaccination.[8,15–17] Coverage of the full course of three doses of the vaccine in those turning 15 years in 2016 was reported to be 78·6% in girls and 72·9% in boys.

In 2018, the quadrivalent vaccine was replaced by a two-dose course of the nonavalent vaccine.[18] Based on the underlying HPV type distribution among cervical

cancers in Australia, the nonavalent vaccine will protect against HPV types that are implicated in about 90% of cases of cervical cancer.[13] In Australia, this vaccine is predicted to reduce the lifetime risk of diagnosis with cervical cancer in vaccinated cohorts by 10% compared with those offered the quadrivalent vaccine, and by 52% compared with unvaccinated cohorts, in the context of primary HPV screening.[19] In the future, less frequent screening might be recommended for women who have been offered the nonavalent vaccine as adolescents; potentially, this frequency could be one or two screens in a lifetime.[20,21]

In a 2018 analysis,[22] we estimated the combined effects of a quadrivalent HPV vaccine and a 2018 transition to HPV screening in Australia until 2035, with a focus on the transitional effects. This study is an extension of this previous analysis; we aimed to estimate the incidence of cervical cancer until 2100, explicitly accounting for the implementation of the nonavalent vaccine from 2018, and to estimate the year in which the elimination of cervical cancer as a public health issue will be achieved in Australia. We considered two scenarios for cohorts who are offered the nonavalent vaccine at age 12–13 years: either that HPV screening continues, or that cervical screening is phased out and not offered to these cohorts.

The early adoption of both HPV vaccination and HPV-based cervical screening, high uptake of the vaccine, and high participation in screening position Australia as the first country that is likely to eliminate cervical cancer as a public health issue. We therefore aimed to identify the earliest years by which cervical cancer incidence could decrease below two absolute levels that could be

considered as potential elimination thresholds: a rare cancer threshold (an annual age-standardised incidence of six new cases per 100 000 women, as defined in Europe and Australia)[23,24] and a lower threshold (four new cases per 100 000 women annually).

Methods

Model platform and parameterisation

In this modelling study, we used a well established and validated model platform, Policy1-Cervix.[25] In brief, the platform consists of a dynamic model of HPV transmission, vaccination, natural history, and carcinogenesis, which is overlaid with a model of cervical screening. Further details of the model structure are shown in the appendix (pp 3–4). The model input parameters are also described in the appendix (pp 4–5) and previous work.[22,25]

Vaccination assumptions

Our model assumed use of the nonavalent vaccine from 2018, with a vaccine uptake (defined as a completed course) of 82% in girls and 76% in boys aged 12 years, based on the midpoint of observed two-dose and three-dose coverage from 2017,[18] assuming full efficacy of the vaccine at two doses if appropriately spaced. Observed vaccine uptake in previous years is also explicitly modelled; year-specific and age-specific vaccination coverage is based on published data and have previously been described in detail.[22] The model assumed that vaccination of girls with the quadrivalent vaccine began in 2007, and that this vaccination included girls and women aged 12–26 years during the catch-up programme that ran until December, 2009, followed by ongoing vaccination of girls aged 12 years. The model assumed that vaccination of boys with the quadrivalent vaccine started in 2013, and included catch-up vaccination for boys aged 14–15 years until the end of 2014, followed by ongoing vaccination of boys aged 12 years. Vaccine efficacy was assumed to be 100% against vaccine-included types, and duration was assumed to be lifelong. Cross-protection against non-vaccine included types was not considered. Incomplete courses were assumed to confer no protection.

Modelled scenarios and outcomes

We predicted the age-standardised incidence of cervical cancer and associated mortality rates in Australia each year from 2015 to 2100, considering all women aged up to 84 years. Two screening scenarios were considered. The first screening scenario assumed that screening continues in all cohorts, regardless of whether they were offered the quadrivalent vaccine or the nonavalent vaccine. Assumptions about screening programme management and participation and vaccine coverage in boys and girls have previously been described in detail.[22] The second screening scenario assumed ceasing cervical screening in cohorts offered the nonavalent vaccine as preadolescent
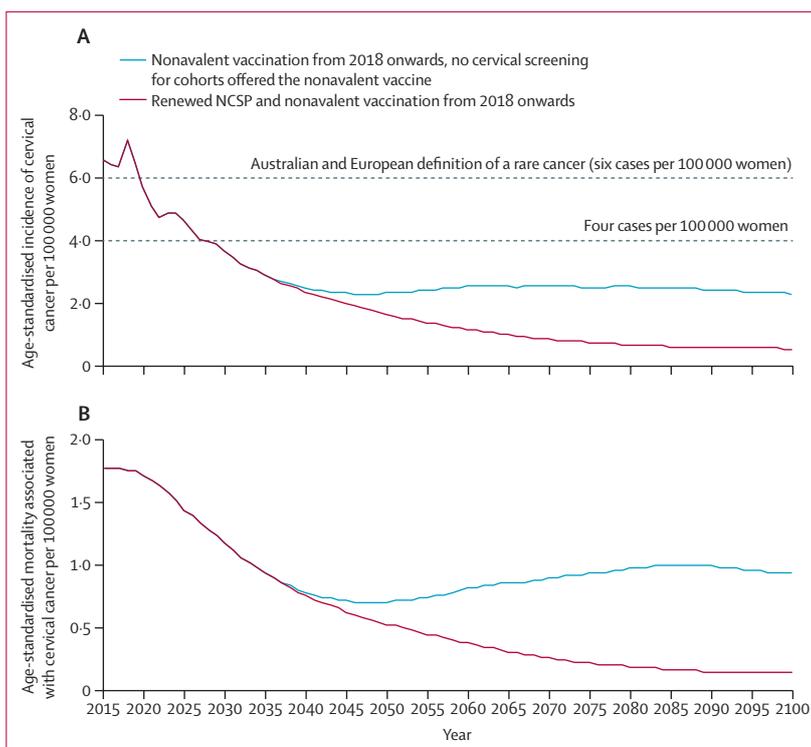

Figure 1: The (A) age-standardised annual incidence of invasive cervical cancer and (B) associated mortality
Data are the model predictions for rates from 2015 to 2100, accounting for the transition to primary human papillomavirus screening in 2017 (the renewed NCSP) and the switch to nonavalent vaccine in 2018. NCSP=National Cervical Screening Programme.

girls (aged 12–13 years), but assumed that HPV screening every 5 years continues for older, unvaccinated cohorts and cohorts offered the quadrivalent vaccine, in accordance with the renewed NCSP. Although we have previously found that two screens per lifetime would remain cost-effective in these cohorts,[20] these two assumptions (no screening vs the renewed NCSP) bounds a wide range of intermediate screening possibilities for cohorts offered the nonavalent vaccine. Because of the herd protection that is provided by the high vaccine coverage in Australia, we did not distinguish between screening assumptions for vaccinated and unvaccinated women within cohorts who had been offered the nonavalent vaccination.

The model simulated cohorts of women in Australia born between 1931 and 2100 to obtain annual estimates of the incidence of cervical cancer and associated mortality from 2015 to 2100. We defined the year of elimination as the first year when the age-standardised annual incidence (ages 0–84 years, standardised to the Australian Standard Population, 2001) decreased to fewer than four new cases per 100 000 women or six new cases per 100 000 women (as appropriate). These thresholds were chosen because an annual incidence of four cases per 100 000 people is two-thirds of the Australian and European definitions of a rare cancer,[23,24] and represents a relative reduction in cervical cancer incidence of more than 70% compared with the global average age-standardised rate, which was
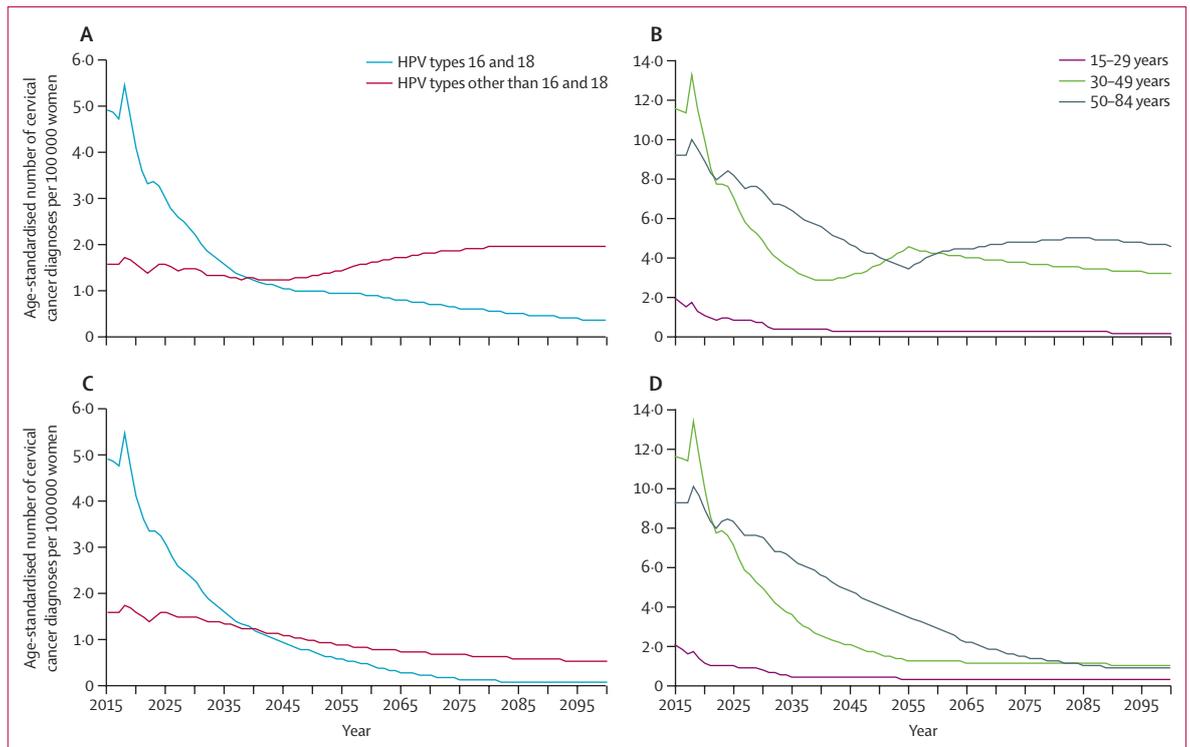
See **Online** for appendix

Figure 2: **Age-standardised number of cervical cancer diagnoses by HPV type and age group under simulated scenarios**
The first scenario assumes vaccination of women with the nonavalent vaccine from 2018 onwards and discontinuation of cervical screening in women offered this vaccination and data are stratified by (A) HPV type and (B) age group. The second scenario assumes continuing vaccination with the nonavalent vaccine and continuation of screening as per the existing National Cervical Screening Program, stratified by (C) HPV type and (D) age group. HPV=human papillomavirus.

14 cases per 100 000 women in 2012. Cumulative lifetime risks of cervical cancer were calculated for individual birth cohorts born between 1971 (the first cohort offered cytology screening every 2 years from age 18–20 years) and 2090. For calculations of mortality rates, we assumed that stage-specific cervical cancer survival was unchanged from the current rate (a conservative assumption)—ie, that mortality improvements were entirely derived from reductions in the incidence of cervical cancer from vaccination, screening, and downstaging due to screening.

Sensitivity analysis
A sensitivity analysis was done to quantify the effects of several factors on the predicted year of elimination. Parameters considered in one-way analysis included: HPV test sensitivity, liquid-based cytology test sensitivity (for reflex testing of HPV-positive women), compliance to routine cervical screening, the frequency of benign hysterectomy, inclusion of boys in the NHVP, and age-standardising population structure assumptions. Parameter assumptions and outcomes of the sensitivity analysis are described in detail in the appendix (p 8).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of

the report. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Results
The base-case estimates for the age-standardised (Australian Standard Population, 2001) annual incidence of invasive cervical cancer and associated mortality from 2015 to 2100 are shown in figure 1; these estimates are shown in the presence and absence of the continuation of screening for cohorts who are offered the nonavalent vaccine at age 12–13 years. Assuming ongoing high coverage of existing vaccination and screening, the rare cancer threshold of six new cases per 100 000 women each year will be achieved in 2020 and cervical cancer elimination (if defined as four new cases per 100 000 women each year) is predicted to occur in 2028. If existing HPV-based screening continues, the incidence of cervical cancer would reach 0·57 cases per 100 000 women in 2100, which is 91% lower than the simulated incidence in 2006 (pre-vaccination; 6·66 new cases per 100 000 women) and 96% lower than the incidence in 1990 (before the introduction of organised cervical screening; 13·5 cases per 100 000 women). In a scenario in which cohorts offered the nonavalent vaccine are not screened, cervical cancer incidence is estimated to be 2·31 cases per 100 000 women in 2100, which is 65% lower

than the incidence in 2006 and 83% lower than the incidence in 1990. Under this scenario the incidence of cervical cancer and associated mortality rates are expected to reach a steady state by 2090.

Mortality from cervical cancer is predicted to decrease to one new case per 100 000 women annually by 2034 and to remain around this rate. If screening continues in the cohorts who are offered the nonavalent vaccine, mortality will continue to decrease to less than 0·15 cases per 100 000 women each year (which equates to fewer than three cases per 1 million women) by 2100 (figure 1). The annual cases of and deaths from cervical cancer for both scenarios are shown in the appendix (pp 6–7).

The age-standardised annual incidence of cervical cancer per 100 000 women, stratified by HPV-type group (16 or 18 *vs* other types) and age are shown in figure 2. Cervical cancer that is attributable to HPV types 16 or 18 is predicted to decrease to fewer than four new cases per 100 000 women by 2021, and the incidence of cervical cancer that is attributable to HPV types other than 16 and 18 is already less than this value. If cohorts who are offered the nonavalent vaccine are not screened, the incidence of cervical cancer that is attributable to HPV types other than 16 or 18 is predicted to increase from 2043 onwards, which is when the first of these cohorts would have entered the screening programme. In the scenario that assumes that all cohorts receive ongoing cervical screening, reductions in the incidence of cervical cancer relative to that in 2100 are estimated to be 91% compared with incidence in 2006 (before the introduction of the quadrivalent vaccine; 0·23 cases per 100 000 women in 2100 *vs* 2·57 cases per 100 000 women in 2006) and 94% compared with incidence in 1990 (ie, before the introduction of organised cervical screening; 4·14 cases per 100 000 women) in women aged 15–29 years; 92% versus 2006 (0·98 cases per 100 000 women in 2100 *vs* 12·25 cases per 100 000 women in 2006) and 96% versus 1990 (21·86 cases per 100 000 women) in those aged 30–49 years; and 91% versus 2006 (0·82 cases per 100 000 women in 2100 *vs* 9·41 cases per 100 000 women in 2006) and 96% versus 1990 (21·38 cases per 100 000 women) in those aged 50–84 years. If cohorts who are offered the nonavalent vaccine are not screened, reductions in the incidence of cervical cancer in 2100 are estimated to be 91% compared with incidence in 2006 and 94% compared with incidence in 1990 in women aged 15–29 years (at an estimated incidence in 2100 of 0·23 cases per 100 000 women); 74% versus 2006 and 85% versus 1990 in those aged 30–49 years (3·23 cases per 100 000 women); and 51% versus 2006 and 78% versus 1990 in those aged 50–84 years (4·64 cases per 100 000 women).

The cumulative lifetime risk of cervical cancer and associated mortality by birth cohort for women born between 1971 and 2090 is shown in figure 3, both in the presence and the absence of continuation of the renewed NCSP for cohorts who are offered the nonavalent vaccine.
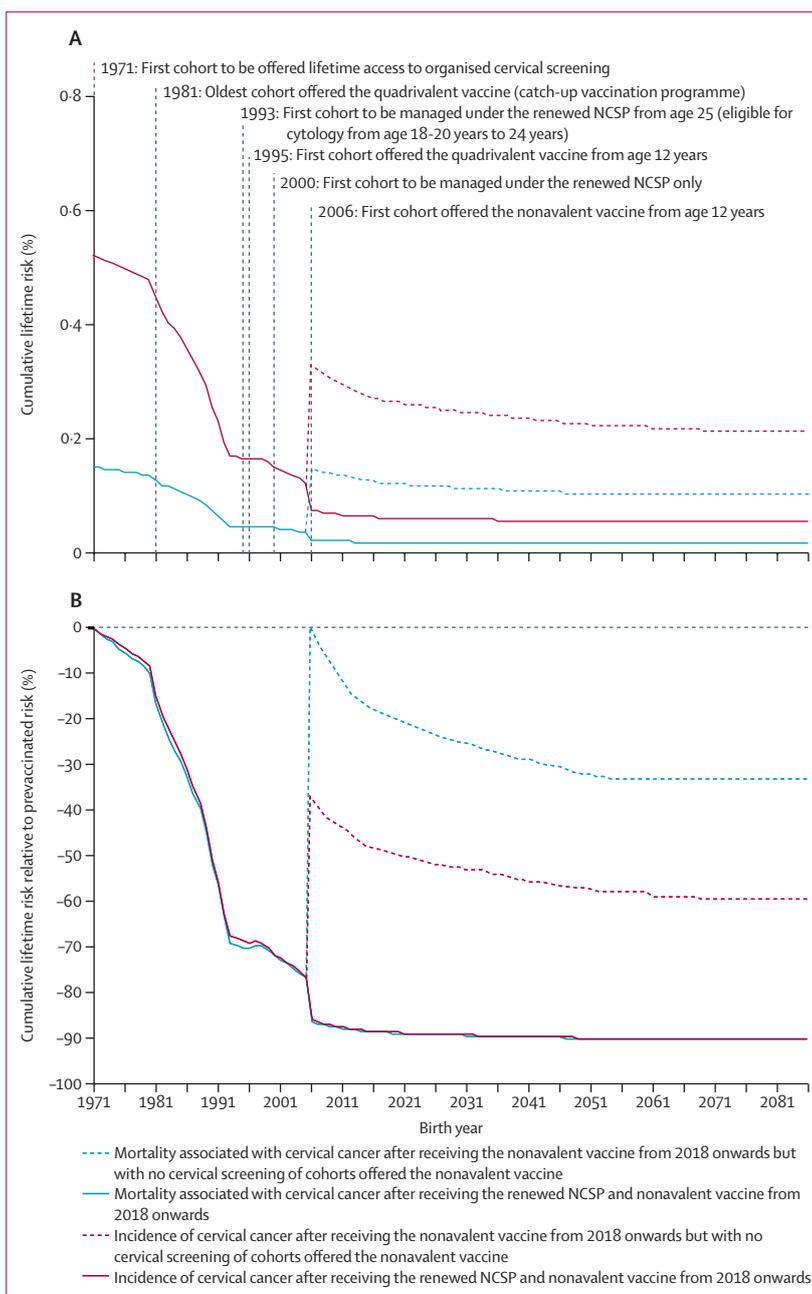

Figure 3: **Cumulative lifetime risk of incidence of invasive cervical cancer and associated mortality in Australian women, by birth year**
Data are (A) cumulative lifetime risk; and (B) cumulative lifetime risk, relative to the prevaccinated risk. The prevaccinated risk refers to the cumulative lifetime risk calculated for the 1971 birth cohort (ie, the first Australian cohort who received organised cervical screening and were not offered human papillomavirus vaccination). NCSP=National Cervical Screening Program.

Each birth cohort is uniquely affected by factors associated with cervical screening and the vaccination programme. Notably, in the scenario where all cohorts are eligible for cervical screening, the cumulative lifetime risk of disease and associated mortality decreases for cohorts born in 2006 or later, which corresponds to the cohorts offered the nonavalent vaccine. In the context of
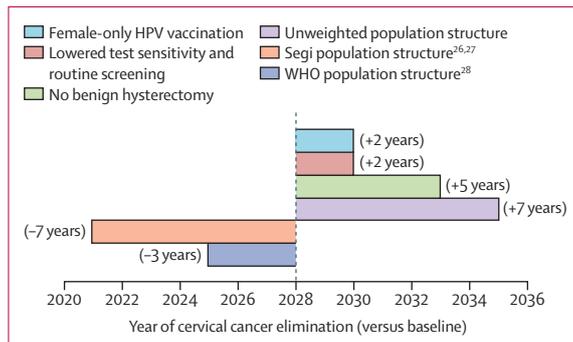
Figure 4: Sensitivity analysis of the factors affecting the likely year of cervical cancer elimination

Data are shown relative to 2028, as per our baseline assumption, if an elimination threshold of four new cases per 100 000 women each year is chosen. HPV=human papillomavirus.

ongoing HPV screening every 5 years for these cohorts, for cohorts born in 2006, the cumulative lifetime risk of cervical cancer is 0·07% and the cumulative lifetime risk mortality is 0·02%. These numbers represent an 89·9% reduction in lifetime risk of cervical cancer diagnosis and 90·0% reduction in lifetime risk of death associated with cervical cancer compared with these risks in the 1971 birth cohort in Australia (vs 0·52% risk of cancer and 0·15% risk of cervical cancer mortality in 1971). In the scenario in which the cohorts who are offered the nonavalent vaccine are not screened, their lifetime risk of cervical cancer and mortality is higher than those who are screened. In the cohort born in 2006 (the first cohort offered the nonavalent vaccine), the lifetime risk of cervical cancer diagnosis is 0·33% and the lifetime risk of death associated with cervical cancer is 0·15% (figure 3). Notably, the lifetime risk of death associated with cervical cancer under this scenario for those born in 2006 is equivalent to that of cohorts born in Australia in 1971, who have been offered screening with cytology since age 20 years and HPV-based screening since age 47 years, but who are unvaccinated. The lifetime risk of cervical cancer diagnosis in cohorts offered the nonavalent vaccine in this scenario would be approximately equal to that for the 1988 cohort, who were vaccinated with the quadrivalent vaccine at age 19 years under the NHVP catch-up in 2007 and who were offered primary HPV screening from 2018 (figure 3).

The findings of this analysis are highly sensitive to the population used for age-standardisation and the frequency of benign hysterectomy in these assumptions change the predicted year of cervical cancer elimination (at the threshold of four new cases per 100 000 women each year) by up to 7 years (figure 4).[26–28] However, parameter assumptions for primary (and triage) screening test sensitivity and screening compliance, and the exclusion of boys from the NHVP had little effect on the predicted year of elimination. Overall, our base-case estimate for the year of cervical cancer elimination was 2028 (if a threshold of four new cases per 100 000 women

each year is used), but a sensitivity analysis indicates that the elimination year could vary from 2021 to 2035.

Discussion

We found that, if the current levels of vaccination and screening coverage are maintained, the annual incidence of cervical cancer in Australia is likely to decrease to fewer than six new cases per 100 000 women by 2020 (range 2018–22) and to fewer than four cases per 100 000 women by 2028 (2021–35). The annual incidence of cervical cancer could decrease to one new case per 100 000 by 2066 (2054–77) if the existing HPV-based screening programme continues in cohorts who are offered the nonavalent vaccine; but if screening is discontinued in these cohorts, the annual incidence will plateau at around three cases per 100 000 women. We estimate that the mortality rates associated with cervical cancer will decrease to less than one case per 100 000 women by 2034 (2025–47). These estimates depend on several factors, including the population used for age-standardisation: incidence will decrease to less than four cases per 100 000 women between 2021 and 2035, depending on these factors.

The incidence of cervical cancer and associated mortality are predicted to decrease steadily following an initial fluctuation after the transition from cytology-based screening every 2 years to primary HPV screening every 5 years, because of the increased effectiveness of screening and the replacement of the quadrivalent vaccine with the nonavalent vaccine in 2018. The annual age-standardised incidence of cervical cancers that are attributable to HPV types 16 or 18 is expected to decrease sharply soon after the transition to primary HPV screening, in response to the differential management of women with HPV types 16 or 18 in the renewed NCSP. Continuing reductions in the incidence of cervical cancer will also result from the introduction of the NHVP programme in 2007. A reduction in the incidence of cervical cancer that is associated with HPV types other than 16 or 18 is predicted to occur more slowly than for those attributed to HPV 16 or 18 because cervical cancer that is attributable to HPV types other than 16 or 18 is more common in older women.[29]

Previous studies[21,30] that evaluated cervical screening in cohorts who have been vaccinated with the nonavalent vaccine in several developed countries found that routine HPV screening every 5 years for women aged 25–74 years might not be cost-effective. It is therefore possible that the frequency of screening in Australia will eventually be reduced for women who have been vaccinated with the nonavalent vaccine. Although it is likely that some form of HPV-based screening will be offered to these cohorts, we simulated an extreme case in which women are not offered any cervical screening. We did not distinguish between vaccinated and unvaccinated women within cohorts being offered the nonavalent vaccine in Australia, because findings suggest that the reduction

in vaccine-preventable infections is high (87%) in unvaccinated women in cohorts who have been offered vaccination; these reductions in infections are similar to those reported for vaccinated individuals in the cohort (94%).[17] Although these findings relate to HPV types included in the quadrivalent HPV vaccine, the herd protection provided by the nonavalent vaccine is anticipated to be at least as substantial as the quadrivalent vaccine, owing to the fact that HPV type 16 (included in the quadrivalent vaccine and the nonavalent vaccine) might be the most difficult type to eliminate.[31] We found that the annual age-standardised incidence of cervical cancer in Australia is predicted to plateau below a potential elimination threshold (at four cases per 100 000 women) if cohorts offered the nonavalent vaccine do not receive cervical screening.

Our medium-term predictions for the incidence of cervical cancer are similar to estimates published for England,[32] which found that primary HPV screening and vaccination with the nonavalent vaccine (with screening coverage and vaccine uptake assumptions in women similar to those that we used in this analysis) is likely to reduce the annual age-standardised incidence of cervical cancer and the associated mortality rate in England by 28% in 2036–40 compared with estimates of incidence over the same time period in which cytology every 3 years and vaccination against only HPV types 16 and 18 were used. Our results are broadly consistent with this finding, since we found that scenarios that assumed a transition to the renewed NCSP showed an age-standardised incidence of cervical cancer that was 33% lower than if the pre-renewed NCSP had been maintained (as previously published).[22] In a sensitivity analysis, we found that, had boys not been included in the NHVP in Australia, the elimination of cervical cancer would have been delayed by 2 years, which is broadly consistent with the findings from Marc Brisson and colleagues' systematic review and meta-analysis,[31] which indicated that the relative reduction in HPV16 prevalence after vaccinating women at 80% coverage increased by only 7% when boys were added to the vaccination programme. The vaccination coverage of girls in Australia is high: the national three-dose coverage for girls turning 15 years in 2016 is 78·6%. In this context, our findings suggest that the addition of vaccination of boys has not substantially affected the timing of elimination in Australia.

There are several strengths to our analysis. To our knowledge, this study represents the first estimation of the time to elimination of cervical cancer at a country level. We separately reported the incidence of cervical cancer and associated mortality rate,[25] in which we simulated the transition to the renewed NCSP in December, 2017, and the introduction of the nonavalent vaccine in 2018. We used a model of HPV transmission, vaccination, HPV natural history, and cervical screening, which has been comprehensively calibrated and validated

in several settings.[22] We considered detailed Australian vaccination coverage and screening compliance rates and herd effects. Management assumptions regarding the renewed NCSP were based on the programme guidelines[5] that were published in 2016, and expert advice. The effectiveness of cervical screening depends on the distribution of underlying health states in the population (for example, whether women are disease-free, HPV-infected, or have cervical pre-cancer or cancer), the characteristics of the screening test used (such as test sensitivity and specificity), and screening behaviour (such as whether women return as recommended for their next test). All these factors are modelled explicitly for each cohort of women with the Policy1-Cervix platform. To determine population-level outcomes, each individual cohort is simulated.

Our study has some limitations. As with any modelling study, the results that we present are dependent on the assumptions made. For example, we assumed no vaccine efficacy at one dose (a conservative assumption for vaccine efficacy). We assumed a vaccine coverage rate with the new two-dose schedule that was halfway between the currently observed two-dose and three-dose coverage for boys and girls; however, if higher coverage is achieved for two-dose course-completion we might have under-estimated the effects of HPV vaccination in Australia. We did not account for immigration effects in the model, which could result in the underestimation of the time to elimination, because 28% of the Australian population in 2015 was born overseas, and not all immigrants have a history of cervical screening or HPV vaccination.[33] A further exploratory analysis (data not shown) found that immigration might delay the timeline to elimination of cervical cancer in Australia by up to 4 years, assuming that 28% of the population do not benefit from HPV vaccination. This finding is likely to be a worst-case scenario, since many immigrants have HPV vaccination programmes in their countries of birth, or they arrive at an age that is young enough for them to be eligible to receive free HPV vaccination in Australia.[2,34,35] Additionally, high female-only coverage by HPV vaccines in Australia has already been shown to have produced herd effects in unvaccinated women, and the level of coverage we have assumed is close to that where modelling studies suggest that vaccine-included HPV types could eventually be eradicated.[17,31] Some immigrants might arrive with an infection that subsequently causes cancer, since these typically are acquired at younger ages, which reinforces the importance of screening.[36]

Our findings imply that the elimination of cervical cancer could be on the horizon for high-income countries, such as Australia. Our findings suggest that continuation of nonavalent vaccination might be sufficient to keep cervical cancer incidence at fewer than four cases per 100 000 women; however, a concurrent national cervical screening programme is necessary for reducing the incidence of cervical cancer even further (such as to less

than one case per 100 000 women each year). Of those adolescents in Australia who turned 15 years in 2016, 79% of girls and 73% of boys are fully vaccinated whereas, in less developed regions, it was estimated that only 2·7% of women aged 10–20 years have been fully vaccinated.[37] Cervical cancer incidence in low-income and middle-income countries could also be substantially reduced through a combination of screening and vaccination; however, major initiatives are required to achieve high coverage of vaccination and cervical screening.

It is important to note that our analysis provides predictions across the entire Australian population, and the findings are not generalisable to specific population subgroups, such as Aboriginal and Torres Strait Islander women, migrants, or disadvantaged subpopulations. Although the effects of HPV vaccination in Australia appear to have been similar in Indigenous and non-Indigenous Australians[15,38] and across areas of different socioeconomic groups,[39] participation in screening differs by Indigenous status and area-level socioeconomic status.[4,40] Indigenous women are 2·5 times more likely to be diagnosed with cervical cancer, and 3·8 times more likely to die of the disease than non-Indigenous women.[41] This discrepancy is, in part, due to lower participation in screening.[41] The new primary HPV screening programme will include the option of self-collection for under-screened women, which could help improve the acceptability of screening for Indigenous Australian women. However, it is likely that if disparities continue to persist, elimination of cervical cancer will be delayed for Indigenous women. To achieve equity for all population subgroups in the elimination of cervical cancer, it will be important to reduce disparities in screening participation between population subgroups and to maintain high coverage by vaccination across all groups.

In conclusion, our analysis has, to the best of our knowledge, been the first study to quantify the timeline to cervical cancer elimination in Australia, the first country that is positioned to achieve it through active control measures. If high-coverage vaccination and screening is maintained, and if an elimination threshold of four cases per 100 000 women is chosen, cervical cancer is on track to be eliminated as a public health problem in Australia within the next 20 years. However, screening and vaccination initiatives would need to be maintained thereafter to continue to achieve very low incidence of, and mortality from, cervical cancer.

References
1 International Papillomavirus Society. IPVS statement: moving towards elimination of cervical cancer as a public health problem. Feb 22, 2018. http://ipvsoc.org/wp-content/uploads/2018/02/IPVs-statement-on-elimination.pdf (accessed May 2, 2018).
2 WHO. WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer. May 19, 2018. http://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/ (accessed May 22, 2018).
3 Smith M, Canfell K. Impact of the Australian National Cervical Screening Program in women of different ages. *Med J Aust* 2016; **205:** 359–64.
4 Australian Institute of Health and Welfare. Cervical screening in Australia 2014–2015. May 25, 2017. https://www.aihw.gov.au/reports/cancer-screening/cervical-screening-in-australia-2014-2015/contents/table-of-contents (accessed March 21, 2018).
5 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. Dec 4, 2017. http://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening (accessed April 6, 2018).
6 Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014; **383:** 524–32.
7 Canfell K. Cervical screening in HPV-vaccinated populations. *Climacteric* 2018; **21:** 227–34.
8 Canfell K, Caruana M, Gebski V, 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 Medicine* 2017; **14:** e1002388.
9 Tabrizi SN, Brotherton JM, Kaldor JM, et al. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis* 2012; **206:** 1645–51.
10 Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med* 2013; **11:** 227.
11 Brotherton JM, Malloy M, Budd AC, Saville M, Drennan KT, Gertig DM. Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: observational cohort of young women in Australia. *Papillomavirus Research* 2015; **1:** 59–72.
12 Department of Health and Ageing. Immunise Australia program: human papillomavirus (HPV). February 14, 2013. http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv (accessed May 9, 2013).

13   Brotherton JML, Tabrizi SN, Phillips S, 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* 2017; **141:** 1576–84.

14   Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. *Int J Cancer* 2011; **128:** 927–35.

15   Smith MA, Liu B, McIntyre P, Menzies R, Dey A, Canfell K. Fall in genital warts diagnoses in the general and Indigenous Australian population following a national HPV vaccination program: analysis of routinely collected national hospital data. *J Infect Dis* 2015; **211:** 91–99.

16   Brotherton JM, Gertig DM, May C, Chappell G, Saville M. HPV vaccine impact in Australian women: ready for an HPV-based screening program. *Med J Aust* 2016; **204:** 184.

17   Machalek DA, Garland S, Brotherton J, 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* 2018; **217:** 1590–600.

18   Office of the Prime Minister of Australia. A new vaccine to strengthen the health of young Australians. Oct 8, 2017. http://parlinfo.aph.gov.au/parlInfo/search/display/display.w3p;query=Id%3A%22media%2Fpressrel%2F5562151%22 (accessed Oct 23, 2017).

19   Simms KT, Laprise JF, Smith MA, 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* 2016; **1:** e66–75.

20   Simms KT, Smith MA, Lew JB, Kitchener HC, Castle PE, Canfell K. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. *Int J Cancer* 2016; **139:** 2771–80.

21   Pedersen K, Burger EA, Nygard M, Kristiansen IS, Kim JJ. Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: the value of stratifying guidelines. *Eur J Cancer* 2018; **91:** 68–75.

22   Hall MT, Simms KT, Lew JB, Smith MA, Saville M, Canfell K. Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017–2035: example from Australia. *PLoS One* 2018; **13:** e0185332.

23   Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011; **47:** 2493–511.

24   Cancer Australia. Rare and less common cancers. March 17, 2014. https://canceraustralia.gov.au/about-us/news/rare-and-less-common-cancers (accessed Sept 5, 2018).

25   Lew JB, Simms K, Smith M, 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* 2017; **2:** e96–107.

26   Segi M, Kurihara M, Matsuyama T. Cancer mortality for selected sites in 24 countries No. 5 (1964–1965). Sendai, Japan: Tohoku University School of Medicine, 1969.

27   Doll R, Payne P, Waterhouse JAH. Cancer incidence in five continents. Geneva: International Union Against Cancer, 1966.

28   Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. 2001. http://www.who.int/healthinfo/paper31.pdf (accessed Sept 26, 2018).

29   Cancer Australia. Cervical cancer statistics. 2016. https://cervical-cancer.canceraustralia.gov.au/statistics (accessed Jan 20, 2017).

30   Simms KT, Laprise JF, Smith MA, 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* 2016; **1:** e66–75.

31   Brisson M, Bénard É, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public Health* 2016; **1:** e8–17.

32   Castanon A, Landy R, Pesola F, Windridge P, Sasieni P. Prediction of cervical cancer incidence in England, UK, up to 2040, under four scenarios: a modelling study. *Lancet Public Health* 2018; **3:** e34–43.

33   Australian Bureau of Statistics. Australia's population by country of birth. 2016. http://www.abs.gov.au/ausstats/abs@.nsf/Previousproducts/3412.0Main%20Features32014-15?opendocument&tabname=Summary&prodno=3412.0&issue=2014-15&num=&view (accessed Sept 8, 2018).

34   Yui Kwan Chow M, Danchin M, Willaby H, Pemberton S, Leask J. Parental attitudes, beliefs, behaviours and concerns towards childhood vaccinations in Australia: a national online survey. *Aust Fam Physician* 2017; **46:** 145–51.

35   Australian Government Department of Social Services. Settlement data reports, January 2017 to 30 June 2017. https://data.gov.au/dataset/8d1b90a9-a4d7-4b10-ad6a-8273722c8628/resource/27adc111-5296-4dc4-884f-3cfbc33b02f3/download/historical-settlement-reports.zip (accessed April 7, 2018).

36   Burger EA, Kim JJ, Sy S, Castle PE. Age of acquiring causal human papillomavirus (HPV) infections: leveraging simulation models to explore the natural history of HPV-induced cervical cancer. *Clin Infect Dis* 2017; **65:** 893–99.

37   Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health* 2016; **4:** e453–63.

38   Ali H, McManus H, O'Connor CC, et al. Human papillomavirus vaccination and genital warts in young Indigenous Australians: national sentinel surveillance data. *Med J Aust* 2017; **206:** 204–09.

39   Smith MA, Liu B, McIntyre P, Menzies R, Dey A, Canfell K. Trends in genital warts by socioeconomic status after the introduction of the national HPV vaccination program in Australia: analysis of national hospital data. *BMC Infect Dis* 2016; **16:** 52.

40   Whop LJ, Garvey G, Baade P, et al. The first comprehensive report on Indigenous Australian women's inequalities in cervical screening: a retrospective registry cohort study in Queensland, Australia (2000–2011). *Cancer* 2016; **122:** 1560–69.

41   Australian Institute of Health and Welfare. Cancer in Aboriginal and Torres Strait Islander people of Australia. Feb 22, 2018. https://www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians/contents/table-of-contents (accessed March 15, 2018).