Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study

Kate T Simms, Sharon J B Hanley*, Megan A Smith*, Adam Keane, Karen Canfell*

Summary

Background Funding for human papillomavirus (HPV) vaccination in Japan began in 2010 for girls aged 12–16 years, with three-dose coverage initially reaching more than 70%. On June 14, 2013, 2 months after formal inclusion in Japan's national immunisation programme, proactive recommendations for the HPV vaccine were suspended following reports of adverse events since found to be unrelated to vaccination, but which were extensively covered in the media. Vaccine coverage subsequently dropped to less than 1% and has remained this low to date. We aimed to quantify the impact of this vaccine hesitancy crisis, and the potential health gains if coverage can be restored.

Methods In this modelling study, we used the Policy1-Cervix modelling platform. We adapted the model for Japan with use of data on HPV prevalence, screening practices and coverage, and cervical cancer incidence and mortality. We evaluated the expected number of cervical cancer cases and deaths over the lifetime of cohorts born from 1994 to 2007 in the context of the vaccine hesitancy crisis. We assessed a range of recovery scenarios from 2020 onwards, including a scenario in which routine coverage is restored to 70%, with 50% catch-up coverage for the missed cohorts (aged 13–20 years in 2020). To estimate the impact of the vaccine crisis to date, we also modelled a counterfactual scenario in which 70% coverage had been maintained in 12-year-olds from 2013 onwards.

Findings The vaccine crisis from 2013 to 2019 is predicted to result in an additional 24 600–27 300 cases and 5000–5700 deaths over the lifetime of cohorts born between 1994 and 2007, compared with if coverage had remained at around 70% since 2013. However, restoration of coverage in 2020, including catch-up vaccination for missed cohorts, could prevent 14 800–16 200 of these cases and 3000–3400 of these deaths. If coverage is not restored in 2020, an additional 3400–3800 cases and 700–800 deaths will occur over the lifetime of individuals who are 12 years old in 2020 alone. If the crisis continues, 9300–10 800 preventable deaths due to cervical cancer will occur in the next 50 years (2020–69).

Interpretation The HPV vaccine crisis to date is estimated to result in around 5000 deaths from cervical cancer in Japan. Many of these deaths could still be prevented if vaccination coverage with extended catch-up can be rapidly restored.

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*Contributed equally

Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia (K T Simms PhD, M A Smith PhD, A Keane PhD, K Canfell DPhil); **Department of Obstetrics and Gynaecology, Hokkaido University, Sapporo, Japan** (S J B Hanley PhD); **School of Public Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia** (K T Simms, M A Smith, A Keane, K Canfell); **and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia** (K Canfell)

Correspondence to: Dr Karen Canfell, Cancer Research Division, Cancer Council NSW, Sydney, NSW 2011, Australia **karen.canfell@nswcc.org.au**

Introduction

Human papillomavirus (HPV) causes cervical cancer and cancers at other anogenital and oropharyngeal sites in both women and men, resulting in an estimated total of 630 000 HPV-related cancers globally in 2012.[1] With an estimated 570 000 new cases and 311 000 deaths due to cervical cancer in 2018, the global burden of cervical cancer represents a major public health problem.[2] Modelling has shown that effective integration of HPV immunisation programmes, HPV-based screening, and access to high-quality cancer treatment and palliative care services has the potential to eliminate cervical cancer as a public health problem in 78 low-income and lower-middle-income countries over the course of the next century.[3,4] We also previously found that elimination could be achieved in most countries in the world if rapid scale-up of HPV vaccination and cervical screening were implemented.[5] On May 19, 2018, the WHO Director-General issued a global call to action to end avoidable suffering and deaths caused by cervical cancer.[6] In January, 2019, WHO also listed vaccine hesitancy as one of the top ten threats to global health.[7]

First-generation quadrivalent and bivalent HPV vaccines have been available since 2006 and 2007, respectively. These vaccines induce high-level antibody responses to HPV types 16 and 18, responsible for about 70% of cervical cancer cases globally.[8] Three recent population-based studies have also shown some sustained cross-protection against HPV types 31/33/45/52 with the bivalent vaccine,[9–11] which could prevent a further 17% of cervical cancer cases globally.[12] A second-generation nonavalent HPV vaccine, which became available in 2014, provides direct protection against HPV 16/18/31/33/45/52/58, responsible for approximately 90% of cervical cancers globally (as well as protection

Research in context

Evidence before this study

Human papillomavirus (HPV) causes cervical cancer and cancers at other anogenital and oropharyngeal sites in both women and men; globally, cervical cancer represents the largest burden of HPV-related cancer. HPV vaccination of girls and young adolescent females prevents infections with vaccine-targeted types and the development of cervical precancerous abnormalities. Although the HPV vaccine is still included in the Japanese national immunisation programme and is provided free of charge for girls aged 12–16 years, the Japanese Government suspended proactive recommendations for the vaccine in June, 2013, after unconfirmed reports of adverse events following immunisation appeared in the media. Vaccine coverage declined rapidly from more than 70% to less than 1%. Despite a large amount of evidence supporting the safety of HPV vaccination, the suspension of proactive recommendation has now continued for more than 6 years, and has not only negatively impacted vaccine confidence within Japan, but might also have influenced the perception of the vaccine in other countries, such as Denmark, Ireland, and Colombia. In January, 2019, WHO listed vaccine hesitancy as one of the top ten threats to global health.

We searched PubMed for studies published from Jan 1, 2007, to Aug 8, 2019, with the search terms "HPV vaccine", "hesitancy", and "modeling" OR "modelling" OR "model" OR "prediction". We restricted the search to publications in English. Our search found no other studies that have estimated the detailed health impact of HPV vaccine hesitancy in terms of quantifying the number of cases and deaths directly attributable to declines in HPV vaccination coverage due to vaccine hesitancy.

Added value of this study

To the best of our knowledge, the impact of the HPV vaccine crisis in Japan has not been quantified to date. We used a well validated modelling platform to quantify the additional cervical cancer cases and deaths that will occur because of the vaccine crisis. We found that the ongoing crisis since 2013 is predicted to result in an additional 24 600–27 300 cases and 5000–5700 deaths due to cervical cancer over the lifetime of cohorts born from 1994 to 2007, compared with the numbers that would have been expected if coverage had remained at around 70%. If coverage is not restored in 2020, an additional 3400–3800 cases and 700–800 deaths will occur over the lifetime of individuals who are 12 years old in 2020 alone; over the next 50 years (2020–69), if the crisis continues, it will result in more than 9000 avoidable deaths. However, rapid restoration of the programme with catch-up for missed cohorts has the potential to avert many of these additional deaths.

Implications of all the available evidence

The vaccine crisis in Japan to date will result in around 5000 deaths due to cervical cancer alone, and this number will increase by around 700–800 for each year that the crisis continues. Most of the additional cervical cancers and deaths are still preventable if vaccination coverage is quickly restored. However, even if vaccination coverage is restored, cervical screening initiatives should also be prioritised, especially for women in cohorts who missed vaccination due to the crisis, and for older unvaccinated women.

against HPV types 6 and 11, which cause anogenital warts).[13] As of December, 2019, 124 countries and territories had included HPV vaccines in their national immunisation programmes.[14] With more than 12 years of real-world use, and more than 270 million doses delivered worldwide since 2006, HPV vaccines have an established record of effectiveness and safety against vaccine-type HPV infection and related disease.[15–18]

According to GLOBOCAN 2018, 13 276 new cases of cervical cancer and 4088 deaths occurred in Japan in 2014 across all ages (equivalent to an annual age-standardised incidence of 18·8 per 100 000 women using the World Standard Population for ages 10–84 years).[2] This incidence is about twice that of countries with high cervical screening coverage, such as Australia.[2] Cervical cancer incidence and mortality have been increasing in Japan since the mid-1990s, especially in women of reproductive age (15–39 years), with an annual percentage change in incidence of 4·4% between 1994 and 2011 and in mortality of 1·9% between 1994 and 2014.[19,20] These increases raise concerns over the effectiveness at the whole-population level of current screening initiatives for cervical cancer in Japan, which achieve coverage of around 30–40%,[21] and suggest that the long-term relative impact of a national HPV immunisation programme on cervical cancer has the potential to be greater in Japan than in other high-income countries with greater screening coverage.

Bivalent and quadrivalent vaccines were licensed in Japan in 2009 and 2011, respectively. In December, 2010, a temporary fund was established for the HPV vaccine, whereby the national government committed to paying 50% of the total vaccine cost for girls aged 12–16 years if regional governments paid the remaining 50%. From April 1, 2013, both HPV vaccines were introduced into the Japanese national immunisation programme and were provided free for girls aged 12–16 years. However, soon after the announcement that the vaccine would be included in the national programme, unconfirmed reports of adverse events following immunisation began to appear in the media and emotive images of girls having difficulty walking or controlling their movements were broadcast extensively on news programmes.[21,22] Despite the publication of a position paper endorsing HPV vaccine safety by the Global Advisory Committee of Vaccine Safety on June 13, 2013, one day later the Japanese Ministry of Health, Labour, and Welfare announced that, although the vaccine would remain in the national immunisation programme and would be free for

12–16-year-old girls, all proactive recommendations for it would be suspended. As of January, 2020, the situation remains unchanged, with the vaccine still available for free to the target age group but not being proactively recommended.[21] From December, 2010, until suspension of proactive recommendations, uptake of the first dose was around 80% nationally,[23] and data from Hokkaido indicated that three-dose coverage was more than 70%.[21] After the suspension of proactive recommendations, vaccination uptake decreased sharply, with less than 1% of eligible females vaccinated in April, 2013.[21] Coverage has remained at less than 1% since that date.[23] In this report, we refer to this period of low coverage from 2013 to 2019 (and ongoing) as the vaccine crisis.

Given the long latency period between HPV infection and the diagnosis of invasive cancer, the long-term impact of the vaccine crisis to date, in terms of morbidity and mortality due to cervical cancer and other HPV cancers, will not be seen for decades. Mathematical disease simulation models can estimate this impact by predicting preventable cancer diagnoses and deaths decades into the future. Therefore, we aimed to quantify the impact of the crisis to date on affected cohorts (assuming they are not eventually offered catch-up vaccination); the ongoing impact for every year that coverage remains low; and the potential impact of restoration of 70% vaccination coverage from 2020 onwards (with and without a possible catch-up for those cohorts that missed the opportunity to be vaccinated due to the crisis, including the possibility of using the nonavalent vaccine as part of the catch-up).

Methods

Model platform and calibration

Policy1-Cervix, an extensively validated dynamic model of HPV transmission, vaccination, type-specific natural history, cancer survival, screening, diagnosis, and treatment,[24–29] was used to evaluate the impact of the vaccine crisis in Japan. The model has been calibrated and validated across a range of settings, including Australia,[26,28] New Zealand,[27] England,[25,29] and China,[30] and has been used to directly inform policy in several of these settings. The model has also been used to evaluate the timeline to elimination of cervical cancer globally[5] and as part of a comparative modelling analysis for 78 low-income and lower-middle-income countries to support the WHO cervical cancer elimination strategic planning process.[3,4]

The model simulates HPV infection, which can persist or progress to cervical intraepithelial neoplasia grades 1, 2, and 3 (CIN1, CIN2, and CIN3); CIN3 can then progress to invasive cervical cancer. Progression and regression rates between states are modelled separately for types HPV 16, HPV 18, other high-risk types covered by the nonavalent vaccine (31/33/45/52/58), and high-risk types not covered by the nonavalent vaccine. The model platform captures the increased risk of CIN2+ recurrence in women successfully treated for CIN2 or CIN3 (compared to the baseline risk of CIN2+ in the population). Reporting is done according to HPV-FRAME standards for models evaluating HPV vaccination and cervical screening (appendix pp 2–4).[31]

See Online for appendix

We adapted the model for Japan by taking into account the following national data: life expectancy from the Ministry of Health, Labour, and Welfare,[32] HPV prevalence in women with normal cytology,[33,34] HPV prevalence in invasive cervical cancer,[35,36] current practice for screening every 2 years with cytology, assuming coverage of 30–40%,[21,37,38] cervical cancer incidence and mortality from National Registry data and GLOBOCAN 2018 estimates,[2,19] cancer survival by stage, and stage distribution at diagnosis.[39] A proportion of cervical cancers are known to have been misclassified as uterine cancers in Japan registry data;[40] however, we took a conservative approach and did not explicitly calibrate to a scaled cervical cancer rate, although the scaled version is shown in addition to the national rates (scaled rates increase the age-standardised rate by 12%; appendix p 1). Final model outputs accurately reflected age-specific HPV prevalence by HPV type, rates of detected CIN2 or CIN3, cervical cancer incidence and mortality, stage distribution at diagnosis, and HPV types in cancer (figure 1; appendix p 1).

Vaccination assumptions and scenarios

To estimate three-dose HPV vaccine coverage in Japan, we used national one-dose HPV coverage rates by birth cohort and year from the Ministry of Health, Labour, and Welfare,[23] and adjusted by the proportion of those who complete all three doses as reported in Hokkaido (around 70% three-dose coverage).[21] Coverage assumptions by birth cohort are shown in figure 2. Consistent with previous evaluations,[24,42] we assumed that prophylactic HPV vaccines are 95% effective against vaccine-targeted HPV types in females without a current infection and that efficacy is lifelong (or that appropriate boosters are delivered if efficacy is shown to wane), and we also considered a shorter duration of effectiveness (20 years) in sensitivity analyses. Because Japan had primarily delivered the bivalent vaccine in cohorts vaccinated from 2008 to 2013 (as of November, 2018, more than 7 million doses of bivalent vaccine had been administered compared with just under 2 million doses of the quadrivalent vaccine), and cross-protection has been shown for the bivalent vaccine,[9,11] we considered a level of cross-protective efficacy as well as direct efficacy. We estimated base-case results as a range for two potential scenarios for cross-protective efficacy: (1) 71·9% protection against types 31, 45, and 52 (based on published Japanese data,[11] effectively protecting against an additional 8·6% of cervical cancers in Japan) lasting 20 years, consistent with at least 7 years of protection reported to date from population-level data from

For more on **the Policy1-Cervix model** see https://www.policy1.org

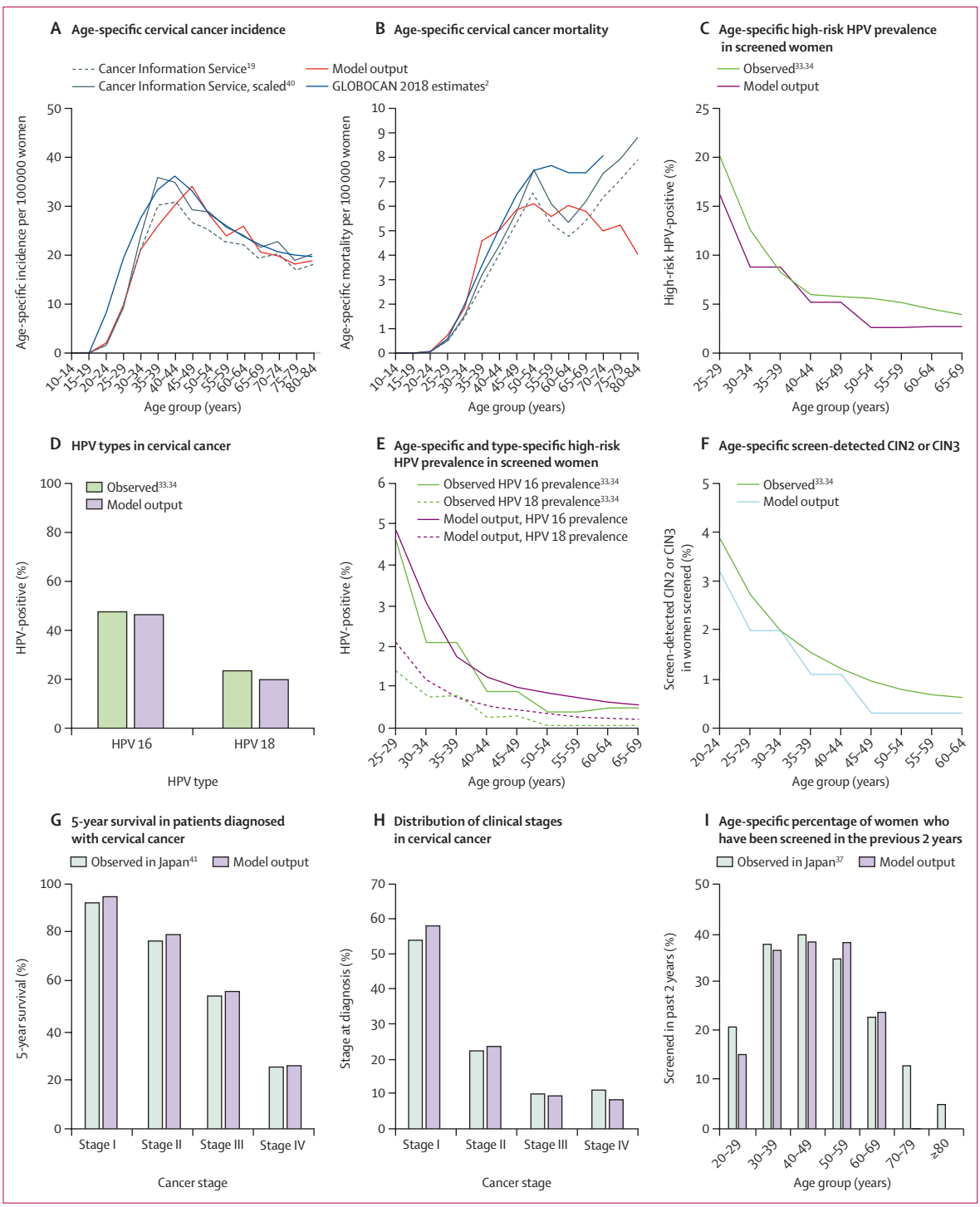

Figure 1: **Comparisons between observed data and model outputs**
Scaled cancer incidence and mortality are based on the estimated proportion of women who are misclassified as having uterine cancer in Japanese registry data (appendix p 1).[40] CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus.

Scotland;[7] and (2) a worst-case assumption of absolutely no cross-protection. In our base-case, we considered herd effects from vaccination based on a dynamic transmission model, which assumed a median age of sexual debut of 16–17 years for women and men, and a median lifetime number of sexual partners of four for women and seven for men. These assumptions are consistent with a study in Japan showing that 50·3% of

women have 2–5 sexual partners in their lifetime, and 54% have sex for the first time before the age of 19 years,[11,43] and another study in Japan showing that 31·1% of female university students had 3–4 lifetime partners and a further 28·4% had five or more partners.[44] No recent Japanese data were available for men, although other settings indicate that the number of lifetime partners in men is higher than in women. For instance, in the UK Natsal-2 (1999–2001) study of adults aged 16–44 years, men had 1·9-times more partners than women, and in the Natsal-3 (2010–12) study, men had 1·5-times more.[45] In our sensitivity analysis, we considered a scenario with no herd effects.

We assessed the longer-term impacts of four potential recovery scenarios, in which vaccine coverage in 12-year-olds was as follows: (1) coverage stays at 2013–19 levels of less than 1% indefinitely (denoted as crisis, no recovery); (2) coverage gradually reaches 70% over the period 2020–25 (crisis, gradual restoration); (3) coverage increases to 70% in 2020 (crisis, rapid restoration); and (4) coverage increases to 70% in 2020, with a 50% uptake with catch-up vaccination in 13–20-year-olds for 2020 only (denoted as crisis, rapid restoration plus catch-up, or crisis, rapid restoration plus catch-up with nonavalent vaccine if the nonavalent vaccine is used from 2020). When modelling catch-up, we assumed that 50% of 13–20-year-old unvaccinated women were vaccinated in 2020, in addition to the small level of uptake in some cohorts when they were eligible (figure 2). To estimate the impact of the crisis to date, and also of vaccination delivered to date, two additional counterfactual scenarios were modelled: 70% coverage maintained in 12-year-olds from 2013 onwards (no crisis); and no vaccination at all (no vaccination).

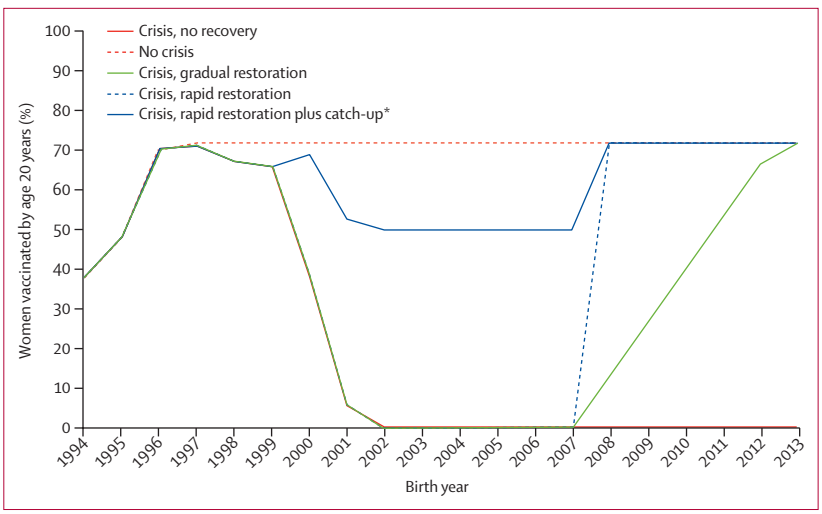

Figure 2: **Vaccine coverage at age 20 years by birth cohort in five scenarios**
*50% uptake achieved for females aged 13–20 years in 2020, some of whom might already be infected; for these cohorts, vaccination is given to them in the year 2020 only.

Outcomes

We considered two sets of outcomes. Firstly, we made a conservative estimate restricted to cervical cancer cases and deaths occurring over the lifetime of cohorts who were eligible for vaccination during the period 2010–19, considering vaccination of girls aged up to 16 years (the birth cohorts born from 1994–2007). The range of birth cohorts considered includes cohorts not affected (or minimally affected) by the crisis (women born from 1994 to 2000) and those impacted substantially by the crisis (women and girls born from 2001 to 2007). Secondly, we estimated total cervical cancer cases and deaths over the 50-year period 2020–69 that additionally took into account the impact on later birth cohorts, assuming the crisis continues. We also estimated age-standardised incidence and mortality each year to 2095. When calculating age-standardised rates, we used the World Standard Population developed in 2001 for ages 10–84 years.

Screening assumptions

We assumed the use of cytology-based screening at 2-year intervals in women aged 20–75 years, and we assumed that women with abnormal squamous cells of undetermined significance or worse are referred for colposcopy.[35] We assumed that 70% of women will be screened at least once during their lifetime, and 40% of these women will be screened every 2 years (selected randomly from the pool of 70% who are screened at least once in their lifetime). These behavioural assumptions are similar to published data, as shown in figure 1, and result in an estimated 30–40% 2-yearly screening coverage, which is in accordance with previously published estimates.[21,37] We additionally assumed that 20% of women were lost to follow-up after referral to colposcopy or repeat surveillance testing. Screening-related behavioural assumptions were assumed to be independent of vaccination status. Model outputs based on these screening assumptions were similar to observed data across a range of outcomes, including the proportion of detected CIN2 or CIN3 by age, cervical cancer incidence and mortality by age, and cervical cancer stage distribution at diagnosis (figure 1).

Sensitivity analysis

To assess the robustness of the predicted impact of the vaccine crisis to date, we varied key parameters in a sensitivity analysis. We considered the impact of the crisis to date if vaccine protection were 20 years (instead of lifelong); if cervical cancer burden were reduced by 25% (as a proxy for other initiatives to reduce burden, such as increasing screening coverage); and if vaccination provided no herd protection at all (a highly conservative assumption for estimating the impact of vaccination, given extensive evidence for herd protection in many countries).[17]

Role of the funding source

The funders 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

	Cervical cancer cases	Cervical cancer deaths	Difference versus no vaccination, cases	Difference versus no vaccination, deaths	Difference versus no crisis, cases	Difference versus no crisis, deaths	Difference versus crisis, no recovery, cases	Difference versus crisis, no recovery, deaths
No vaccination	97 500	19 900	..	..	..	..	..	..
No crisis	52 900–57 500	10 800–11 800	40 000–44 600	8100–9100	..	..	..	..
Crisis, no recovery*	80 200–82 100	16 500–16 800	15 400–17 300	3100–3400	24 600–27 300	5000–5700	..	..
Crisis, gradual restoration†	78 400–80 500	16 200–16 600	17 000–19 100	3300–3700	23 000–25 500	4800–5400	1600–1800	200–300
Crisis, rapid restoration	77 300–79 500	15 900–16 200	18 000–20 200	3700–4000	22 000–24 400	4400–5100	2600–2900	600–600
Crisis, rapid restoration plus catch-up	64 000–67 300	13 100–13 800	30 200–33 500	6100–6800	9800–11 100	2000–2300	14 800–16 200	3000–3400
Crisis, rapid restoration plus catch-up with nonavalent vaccine	59 900–61 800	12 400–12 700	35 700–37 600	7200–7500	4300–7000	900–1600	20 300–20 300	4100–4100

Cases and deaths are counted over the lifetime of cohorts (up to age 84 years) born 1994–2007. Unless otherwise stated, we assume the bivalent or quadrivalent vaccines are used in recovery scenarios. Ranges represent model outputs under different assumptions of cross-protective efficacy against non-vaccine-included HPV types, with no cross-protection giving the lower range of vaccine impact, and cross-protection (based on data for the bivalent vaccine) giving the higher range of vaccine impact. Numbers of cases and deaths are rounded to the nearest 100. Numbers might not add up across cells due to rounding. *This scenario assumes that cohorts who missed vaccination in these years will not receive vaccination later in life. †Restoration occurs gradually over 2020–25.

Table 1: **Model predictions of cervical cancer cases and deaths over the lifetime of cohorts born from 1994 to 2007**

	Cumulative cancer cases during 2020–69	Cumulative cancer deaths during 2020–69	Difference versus no vaccination, cases	Difference versus no vaccination, deaths	Difference versus no crisis, cases	Difference versus no crisis, deaths	Difference versus crisis, no recovery, cases	Difference versus crisis, no recovery, deaths
No vaccination	434 500–434 500	93 700–93 700	..	..	..	..	..	..
No crisis	350 900–361 000	78 000–79 700	73 500–83 600	14 000–15 700	..	..	..	..
Crisis, no recovery*	414 600–416 800	88 800–89 000	17 700–19 900	4700–4900	55 800–63 700	9300–10 800	..	..
Crisis, gradual restoration†	377 700–384 800	83 400–84 600	49 700–56 800	9100–10 300	23 800–26 800	4900–5400	32 000–36 900	4400–5400
Crisis, rapid restoration	371 000–379 000	81 700–83 000	55 500–63 500	10 700–12 000	18 000–20 100	3300–3700	37 800–43 600	6000–7100
Crisis, rapid restoration plus catch-up	361 300–370 300	80 200–81 900	64 200–73 200	11 800–13 500	9 300–10 400	2200–2200	46 500–53 300	7100–8600

We assume the bivalent or quadrivalent vaccines are used in recovery scenarios. Ranges represent model outputs under different assumptions of cross-protective efficacy against non-vaccine-included HPV types, with no cross-protection giving the lower range of vaccine impact, and cross-protection (based on data for the bivalent vaccine) giving the higher range of vaccine impact. Numbers of cases and deaths are rounded to the nearest 100. Numbers might not add up across cells due to rounding. Cases and deaths are those in all birth cohorts (including those not yet affected by the crisis) over the next 50 years. *This scenario assumes that cohorts who missed vaccination in these years will not receive vaccination later in life. †Restoration occurs gradually over 2020–25.

Table 2: **Model predictions of cumulative cervical cancer cases and deaths over the period 2020–69**

access to all the data and had final responsibility to submit for publication.

Results

Over the lifetime of cohorts who have already received HPV vaccination in Japan, the vaccine is expected to prevent 15 400–17 300 cervical cancer cases and 3100–3400 deaths; this is a conservative estimate based on 1994–2007 birth cohorts only (table 1). Compared with if coverage remained at 70%, the vaccine crisis (assuming missed cohorts remain unvaccinated) is predicted to result in 24 600–27 300 cervical cancer cases and 5000–5700 deaths in 1994–2007 birth cohorts alone (table 1). If the crisis continues into 2020 with no restoration of coverage, 3400–3800 cases of cervical cancer and 700–800 deaths will occur over the lifetime of individuals who are 12 years old in 2020 alone that could have been prevented if vaccination coverage was 70%. If coverage is restored rapidly in 2020, and catch-up vaccination is offered to cohorts who missed vaccination between 2013 and 2019 (50% uptake in catch-up cohorts), 9800–11 100 cases and 2000–2300 additional deaths are predicted over the lifetime of women born from 1994 to 2007, compared with the numbers that would have occurred if coverage remained at 70%. Therefore, of the 24 600–27 300 additional cases and 5000–5700 additional deaths experienced over the lifetime of affected cohorts without recovery from the crisis, rapid restoration with catch-up vaccination would prevent 14 800–16 200 cases (59–60%) and 3000–3400 of deaths (60–60%). If the nonavalent vaccine is used from 2020 onwards (including catch-up for missed cohorts in 2020), 20 300–20 300 cases (74–83%) and 4100–4100 deaths (72–82%) could be averted compared with the scenario in which the crisis continues.

The long-term impact of the vaccine crisis on cervical cancer cases and deaths is shown in table 2, over the 50-year period from 2020 to 2069. If the crisis continues, an additional 55 800–63 700 cases and 9300–10 800 deaths are predicted over the period 2020–69, compared with what would have occurred without the crisis. Most of these additional cases are still preventable; a

rapid restoration of coverage in 2020 would prevent 37 800–43 600 (68–68%) of these cases and 6000–7100 (65–66%) of these deaths. Additionally implementing catch-up for missed cohorts with 50% uptake would prevent 46 500–53 300 (83–84%) of these cases and 7100–8600 (76–80%) of these deaths. Gradual restoration of coverage would prevent 32 000–36 900 (57–58%) cases and 4400–5400 (47–50%) deaths over the period 2020–69 compared with if the vaccine crisis continues.

If the vaccine crisis is not resolved, and assuming no changes to screening uptake, age-standardised cervical cancer incidence will remain above 15 cases per 100 000 women for most of the rest of the century (figure 3A). By contrast, age-standardised incidence will reduce to 7–8 cases per 100 000 women by the end of the century under most vaccine recovery scenarios. Incidence declines fastest in the scenario in which rapid restoration is achieved by 2020 and catch-up vaccination with the nonavalent vaccine with 50% uptake for women and girls aged up to 19 years is also achieved in 2020; in this situation, the benefits of the second-generation vaccine used for ongoing vaccination of young cohorts leads to the largest reductions in incidence and mortality. Age-standardised cervical cancer mortality shows similar patterns of decline in the various recovery scenarios (figure 3B).

The effect of a range of parameters on the predicted impact of the vaccine crisis in cohorts born from 1994 to 2007 were assessed in a sensitivity analysis (table 3). If vaccine protection lasts only 20 years (rather than being lifelong), an ongoing vaccine crisis is predicted to result in 16 200–19 000 additional cervical cancer cases and 3400–4000 deaths over the lifetime of these cohorts compared with the numbers of cases and deaths if coverage had remained at 70%. If the burden of disease is reduced by 25% (eg, due to improvements in screening), then the impact of an ongoing vaccine crisis is similarly reduced, with 18 500–20 500 additional cases and 3700–4300 additional deaths compared with if coverage had remained at 70%. If herd effects are not considered, then an ongoing vaccine crisis is predicted to result in an additional 21 400–23 500 cases and 4400–5000 deaths compared with if coverage had remained at 70%. In all sensitivity analyses considered, restoration of coverage plus catch-up would prevent at least 9800 cases and 2100 deaths over the lifetime of affected cohorts.

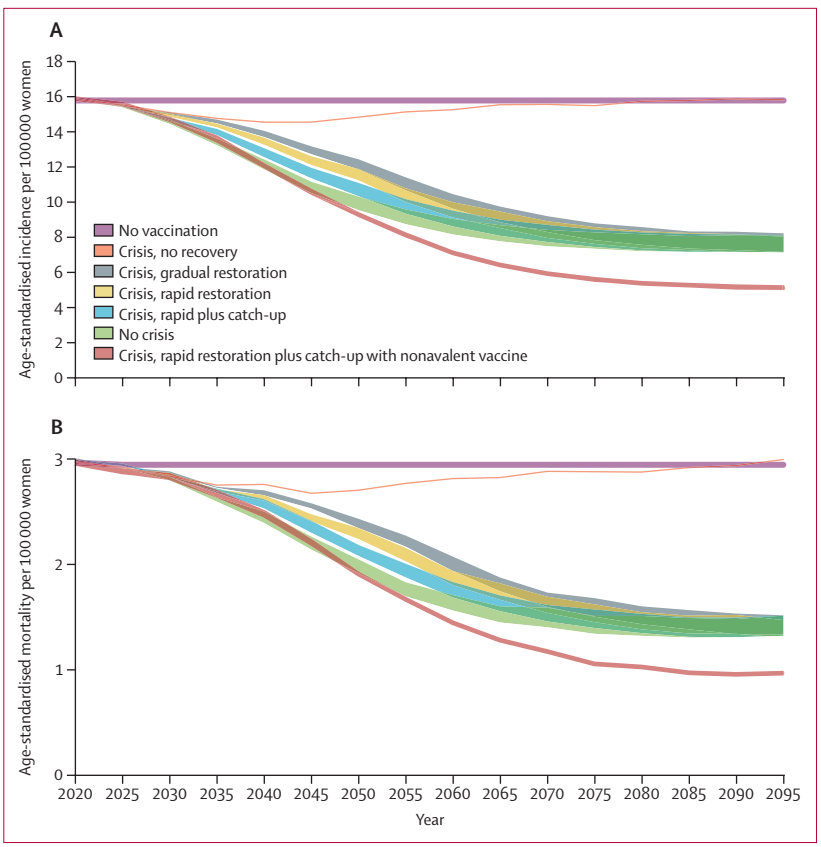

Figure 3: **Impact of the vaccine crisis and potential recovery scenarios from 2020 to 2095 on age-standardised cervical cancer incidence (A) and cervical cancer mortality (B)**
Unless otherwise stated, we assume the bivalent or quadrivalent vaccines are used in recovery scenarios. Age-standardisation was calculated using the World Standard Population for ages 10–84 years. Shaded areas represent variation depending on assumptions of cross-protective efficacy against non-vaccine-included HPV types, with the lower range showing cross-protection (on the basis of data from the bivalent vaccine) and the higher range showing zero cross-protection.

Discussion

In this analysis of the health impact of the HPV vaccine crisis in Japan, we found that the sharp decline in vaccine coverage in Japan from 2013 to 2019 will result in 24 600–27 300 preventable cases of cervical cancer and 5000–5700 deaths due to cervical cancer over the lifetime of cohorts born from 1994 to 2007 if the crisis continues without recovery in 2020, compared with the numbers of cases and deaths that would have been expected if the vaccine crisis had not occurred. If the crisis continues without recovery in 2020, it will result in an additional 3400–3800 cases and 700–800 deaths over the lifetime of individuals who are 12 years old in 2020 alone. Restoration of coverage in 2020, including multi-age catch-up vaccination for missed cohorts with 50% catch-up coverage, could prevent 59–60% of the additional cases and 60% of the additional deaths, and if the nonavalent vaccine is used from 2020 onwards, 74–83% of the additional cases and 72–82% of the additional deaths could be averted, thereby mitigating much of the health impact of the vaccine crisis. The benefit of coverage restoration is greater still when considering the impact on future cohorts, and not only those already affected by the crisis; if the crisis continues, compared with the scenario in which no crisis occurred, 55 800–63 700 additional cases of cervical cancer and 9300–10 800 additional deaths will occur over the 50-year period from 2020 to 2069. Rapid restoration of coverage with catch-up vaccination for missed cohorts using the bivalent or quadrivalent vaccines could prevent more than 76% of these cases and deaths over the 50-year

	Cervical cancer cases	Cervical cancer deaths	Difference versus no vaccination, cases	Difference versus no vaccination, deaths	Difference versus no crisis, cases	Difference versus no crisis, deaths	Difference versus crisis, no recovery, cases	Difference versus crisis, no recovery, deaths
Vaccine protection lasts only 20 years against vaccine-preventable HPV types								
No vaccination	97 600	19 900	..	..	..	..	..	..
No crisis	70 300–75 000	14 400–15 300	22 500–27 300	4600–5500	..	..	..	..
Crisis, no recovery*	89 300–91 200	18 400–18 700	6300–8300	1200–1500	16 200–19 000	3400–4000	..	..
Crisis, gradual restoration†	86 700–88 800	17 900–18 300	8700–10 900	1600–2000	13 800–16 400	3000–3500	2400–2700	400–500
Crisis, rapid restoration	86 200–88 500	17 700–18 100	9000–11 400	1800–2200	13 500–15 900	2800–3300	2700–3200	600–700
Crisis, rapid restoration plus catch-up	78 000–81 400	16 000–16 600	16 100–19 600	3300–3900	6400–7700	1300–1600	9800–11 300	2100–2400
Burden of disease reduced by 25%								
No vaccination	73 100	14 900	..	..	..	..	..	..
No crisis	39 700–43 100	8100–8900	30 000–33 400	6000–6800	..	..	..	..
Crisis, no recovery*	60 200–61 600	12 400–12 600	11 500–12 900	2300–2500	18 500–20 500	3700–4300	..	..
Crisis, gradual restoration†	58 800–60 400	12 200–12 500	12 700–14 300	2400–2700	17 300–19 100	3600–4100	1200–1400	100–200
Crisis, rapid restoration	58 000–59 600	11 900–12 200	13 500–15 100	2700–3000	16 500–18 300	3300–3800	2000–2200	400–500
Crisis, rapid restoration plus catch-up	48 000–50 500	9 800–10 400	22 600–25 100	4500–5100	7400–8300	1500–1700	11 100–12 200	2200–2600
No herd effects								
No vaccination	97 500	19 900	..	..	..	..	..	..
No crisis	58 700–64 100	12 000–13 100	33 400–38 800	6800–7900	..	..	..	..
Crisis, no recovery*	81 900–85 500	17 300–17 500	12 000–13 800	2400–2600	21 400–23 500	4400–5000	..	..
Crisis, gradual restoration†	81 900–85 500	17 300–17 500	12 000–13 800	2400–2600	21 400–23 500	4400–5000	0–0	0–0
Crisis, rapid restoration	81 900–85 500	17 300–17 500	12 000–13 800	2400–2600	21 400–23 500	4400–5000	0–0	0–0
Crisis, rapid restoration plus catch-up	71 800–74 500	14 700–15 200	23 000–27 500	4700–5200	10 400–11 600	2100–2400	11 000–11 900	2300–2600

Cases and deaths are counted over the lifetime of cohorts (up to age 84 years) born 1994–2007. We assume the bivalent or quadrivalent vaccines are used in recovery scenarios. Ranges represent model outputs under different assumptions of cross-protective efficacy against non-vaccine-included HPV types, with no cross-protection giving the lower range of vaccine impact, and cross-protection (based on data for the bivalent vaccine) giving the higher range of vaccine impact. Numbers of cases and deaths are rounded to the nearest 100. Numbers might not add up across cells due to rounding. *This scenario assumes that cohorts who missed vaccination in these years will not receive vaccination later in life. †Restoration occurs gradually over 2020–25.

Table 3: **Sensitivity analysis of model predictions of cervical cancer cases and deaths over the lifetime of cohorts born from 1994 to 2007**

period from 2020 to 2069. If uptake greater than 50% could be achieved in catch-up vaccination, more lives could be saved and the damage from the crisis potentially mitigated further.

Even if vaccination coverage is effectively restored, it is likely that more effective and culturally acceptable strategies for cervical screening are needed, especially for women in those cohorts that missed vaccination due to the crisis, and for older unvaccinated women. Primary HPV screening, either as a standalone primary test or with cytology (co-testing), is not yet recommended in Japan. Internationally, there is strong evidence for the efficacy of HPV-based screening, including a pooled analysis of four randomised controlled trials reporting that HPV-based screening significantly increases protection against the development of invasive cervical cancer compared with cytology-based screening.[46] The consolidated evidence of the effectiveness of HPV-based cervical screening, supplemented by modelled analyses indicating that longer-interval HPV testing is more effective and generally less costly than cytology-based screening, has prompted major changes in several countries, including Australia, Italy, and the Netherlands, and the USA now has recommendations supporting primary HPV screening as well as co-testing.[28,47] HPV testing also allows for self-sampling collection methods, which have been shown to be highly acceptable in Japanese women.[48] HPV testing was reviewed by the Japanese Advisory Committee on Cancer Screening, but they did not recommend HPV testing in their 2009 guidelines.[49] A second review in 2013 by an expert panel commissioned by the Japanese Ministry of Health, Labour, and Welfare[50] concluded that scientific evidence generated in Japan was necessary (as opposed to relying on international evidence) to evaluate the benefits versus harms of an HPV-based screening programme in Japan.

Our estimates of preventable cervical cancer cases and deaths due to the vaccine crisis are conservative for several reasons. Firstly, we did not take into account the effect of female-only vaccination on non-cervical HPV-related cancers in both women and men (via herd effects), including cancers of the anus, penis, vulva, vagina, and oropharynx. Non-cervical HPV-related cancers are estimated to account for 10% of all HPV-related malignancies globally,[2] and are predominantly caused by the vaccine-preventable type, HPV 16. Secondly, we took a

conservative approach to the estimated burden of disease in Japan, given that registrations for cervical cancer have probably been underestimated[40] and that cervical cancer incidence and mortality have been increasing in 15–39-year-old girls and women in Japan.[19,20] Thirdly, we did not consider potential changes to the Japanese national immunisation programme that could increase effective vaccine coverage beyond 70%. For example, other countries have now adopted a two-dose schedule in individuals aged 14 years or younger (as recommended by WHO), which is expected to have reduced loss to follow-up due to requiring fewer doses.[51] We also did not consider the potential for increased herd effects via vaccination of adolescent boys. Previous modelling studies have found that at low coverage of girls (<50%), including boys into the programme can improve programme effectiveness.[52] However, these same studies also found that increasing coverage in adolescent girls consistently results in greater population-level effectiveness than adding boys to a programme.

The model platform we used is a comprehensive dynamic model of HPV transmission, vaccination, and cervical screening, that captures herd effects and detailed screening management, and has been used to perform evaluations across a range of settings, including to support the elimination targets for cervical cancer set by WHO.[6] Although by necessity our analysis had some limitations and simplifying assumptions, whenever possible we were conservative in our estimates. We assumed high levels of vaccine effectiveness at three doses and lifetime duration of protection, which is supported by evidence showing more than 95% effectiveness in HPV-naive individuals, and evidence suggesting that vaccine duration of protection will be very long or lifelong.[53] The HPV vaccine has already been observed to provide more than 10 years of sustained protection against vaccine-preventable types, and evidence of vaccine efficacy at two doses, or even one dose, is mounting. However, we evaluated a scenario in which the vaccine provides only 20 years of protection against vaccine-included types in a sensitivity analysis. Both the impact of the crisis and the number of cases still preventable if coverage were to be restored were reduced in this scenario, but they remained substantial. Our main analysis considered a degree of cross-protection with a 20-year duration, based on strong evidence of at least 7 years of cross-protection in Scotland[9] and data from Japan indicating high cross-protective effectiveness of the bivalent vaccine to types 31, 45, and 52;[9] however, our main results also considered the possibility of no cross-protection at all (a very conservative assumption).

We assumed that vaccination provides some herd protection, on the basis of evidence from other countries. In Australia, reductions in vaccine-targeted HPV types have been observed in unvaccinated women aged 18–35 years (adjusted prevalence ratio in unvaccinated women 0·13 [95% CI 0·02–0·91] and adjusted prevalence ratio in vaccinated women 0·06 [0·01–0·24])[54] and in Australian-born heterosexual men of a similar age during the female-only period of vaccination (adjusted prevalence ratio 0·37 [95% CI 0·22–0·60]).[55] Evidence of herd effects has been synthesised in a meta-analysis of HPV vaccination effectiveness,[17] and was reported in a retrospective population study of cervical disease in vaccinated and unvaccinated cohorts from Scotland, with higher coverage associated with larger impact.[16] Herd effects in both unvaccinated women and men in Japan would be expected if high coverage vaccination was maintained. However, we also considered a scenario in which no herd protection is experienced in Japan; in this scenario, we found that the vaccine crisis to date will still result in 21 400–23 200 cancer cases and 4400–5100 deaths over the lifetime of affected cohorts. Finally, we assumed that screening rates would remain unchanged in the future. The proportion of women receiving cervical screening is low in Japan, and if coverage could be increased, cervical cancer incidence and mortality might be reduced further, which would compensate in part for missed vaccination. However, the government target for cervical screening coverage remains at 50%.[19] In a sensitivity analysis, we assessed the scenario in which the burden of disease in missed cohorts was decreased by a further 25%, which could be observed if screening coverage were to increase substantially. In this scenario, the crisis to date would still result in an additional 18 500–20 500 cancer cases and 3700–4300 deaths over the lifetime of affected cohorts.

Because of the instant and wide-ranging influence of the internet and social media, suspension of proactive recommendations for the HPV vaccine not only resulted in the crisis in Japan, but also probably contributed to vaccine hesitancy crises in other countries, notably Denmark, Ireland, and Colombia.[56–58] Despite negative media coverage, the Danish and Irish governments continued to proactively promote HPV vaccination, and various medical and non-medical organisations formed an alliance to actively advocate for HPV vaccination.[56,59] A turnaround in uptake was seen in both countries.[56,59] An appropriate and timely response to reports of adverse events following immunisation is essential to sustain and rebuild public trust; the governments in Denmark and Ireland acted quickly to regain control of the narrative. The HPV vaccine has been shown to be extremely safe, and has been reviewed by the Global Advisory Committee on Vaccine Safety several times since the vaccine became available in 2006.[18] Our results show the intermediate-term and long-term cost of vaccine hesitancy in Japan, but they also indicate that much of the negative health impact could be mitigated if high-level political support for HPV vaccination were restored and proactive recommendations reinstated.

In May, 2018, the Director-General of WHO announced a call to action for the elimination of cervical cancer as a public health problem. We have previously reported

that, if an elimination threshold of 4 cases per 100 000 women were chosen, cervical cancer could be eliminated in Australia within the next 8–15 years,[26] and in most countries globally by the end of the 21st century if 80–100% uptake of the HPV vaccine were achieved in 12-year-old girls, along with two lifetime HPV screens at the ages of 35 and 45 years.[5] We have also found that, for 78 low-income and lower-middle-income countries, the elimination targets proposed by WHO would result in elimination of cervical cancer as a public health problem for all countries considered, and would prevent 74 million cervical cancer cases and 62 million deaths over the next 100 years if targets for vaccination, screening, and cancer treatment were implemented.[3,4] One of our previous analyses included Japan, which we found could eliminate cervical cancer as a public health problem by 2055–60 if both screening and vaccination coverage were substantially increased by 2020.[5] When considering the potential for cervical cancer elimination, the choice of standard population is important. In the main analysis of this study, we used the World Standard Population for ages 10–84 years, which leads to long-term estimates of age-standardised cervical cancer incidence of 7–8 per 100 000 women in 2095 if vaccination is scaled up. If we use the recommended population for elimination calculations,[5] the 2015 World Population for ages 0–99 years, the age-standardised incidence in 2100 would be 6–7 per 100 000 (or 4–5 per 100 000 if the nonavalent vaccine is used from 2020 onwards). In either scenario, we predict that vaccination alone will not lead to an incidence of less than 4 per 100 000 women by the end of the century—the proposed elimination threshold. Thus, our analysis also highlights that increasing vaccination coverage alone, although critical to saving lives over the long term, is not sufficient for achieving elimination of cervical cancer in Japan. 5-year survival for cervical cancer is already high in Japan: 92% at stage I, 77% at stage II, 54% at stage III, and 25% at stage IV.[41] In addition to restoring vaccination coverage, increasing cervical screening coverage will also be required; this combination of factors, in the context of access to cancer treatment services, will be critical to achieving elimination and maximising impact in terms of averted cervical cancer deaths.

The events relating to HPV vaccination in Ireland and Denmark show that it is possible to reverse rapid declines in HPV vaccine coverage due to vaccine hesitancy and successfully address safety concerns reported in the media. Strong support from government is required and is most effective when there is cooperation across multiple sectors. This study shows the importance and urgency of increasing HPV vaccination coverage in Japan, and the substantial health gains that could be made if the vaccine hesitancy crisis were to be addressed.

Contributors

KTS contributed to the study design, model evaluation, data analysis, data interpretation, figure and table creation, and the write-up. SJBH contributed to the study design and data analysis, collected additional required data specific to Japan, provided policy-relevant insight into the situation in Japan, and contributed to data interpretation and the write-up. MAS contributed to the study design, data analysis, data interpretation, figure and table creation, and the write-up. AK contributed to the data analysis, data interpretation, figure and table creation, and the write-up. KC oversaw all aspects of study design, model evaluation, data analysis, data interpretation, figure design, and the write-up.

Declaration of interests

SJBH reports grants from the Japan Society for the Promotion of Science during the conduct of the study. MAS reports grants from the National Health and Medical Research Council and from Cancer Institute New South Wales (NSW). KC is co-principal investigator of an unrelated investigator-initiated trial of cytology and primary human papillomavirus screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity. In 2013, the VCS Foundation received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana. However, neither KC nor her institution (Cancer Council NSW) receives direct funding from industry for this trial or any other project. All other authors declare no competing interests.

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