Name: Megan Smith

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Full Reference:

1. **Smith M,** Killen J, Whop L, O'Farrell X, Nguyen D, Garvey G, Jamieson L, Canfell K. *Expediting elimination in Aboriginal and Torres Strait Islander women: the impact of scaling up prevention measures*. (Oral presentation)
2. **Smith MA**, Killen J, Rimalos K, Canfell K. *Optimising referral to colposcopy in a national HPV screening program.* (Poster)
3. Velentzis LS, **Smith M**, Killen J, Brotherton J, Guy R, Canfell K. Impact of COVID-19 related disruptions to HPV vaccination – a modelled analysis (Poster)

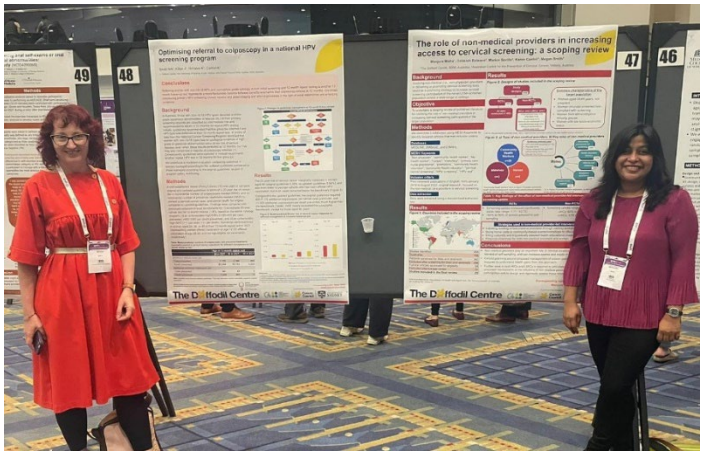
Conference/Meeting Name: International Papillomavirus Conference (IPVC) 2023
https://ipvconference.org/
Location: Washington DC, USA
Dates: 17th – 21st April 2023

Presentation Type: One oral presentation and two posters

In April 2023 I attended the 35th International Papillomavirus Conference (IPVC 2023) in Washington DC, along with almost 1800 others working in the field, from over 100 countries. IPVC is the major international conference for research relating to the human papillomavirus (HPV), which causes more than 700,000 cancers globally each year. The science presented spans basic research, clinical, and public health, with a strong focus on HPV vaccination and screening. The theme of the 2023 conference was "*Coming together for cervical cancer elimination*".

The conference was opened by Dr Jill Biden, the First Lady of the United States, who spoke about how the Biden Cancer Moonshot is working to support cooperation between clinicians, researchers, NGOs, and public health experts across oceans and around the globe, so that – together - we can build a world free of HPV. As a highly preventable cancer, and following the release of the WHO's global strategy to eliminate cervical cancer in 2020, cervical cancer elimination was a focus of many presentations, aligned with the conference theme. We know how to prevent cervical cancer, using HPV vaccination and cervical screening, and many presentations focussed on the inequities that currently exist in cervical cancer, including screening, vaccination and treatment, and how they can potentially be addressed. Presentations considered how inequities relating to income, in Indigenous people, and sexuality and gender minority population, could be addressed. We also continue to learn more about the natural history of HPV infection, vaccination, and screening.

There was exciting new evidence presented at the conference about the durability of protection from just one dose of HPV vaccine. Australia's immunisation schedule changed earlier this year to recognise that one dose provides strong protection, and this evidence reinforces that the protection will be long-lasting. There were also findings from the Anal Cancer–HSIL Outcomes Research (ANCHOR) trial demonstrating that treatment of high-grade anal lesions is effective in reducing the risk of anal cancer. Anal cancer, like cervical cancer, is almost all due to HPV and there are high-grade precursor lesions, but not yet any recommended screening for anal cancer, and previously no clear treatment for high-grade anal lesions. There are still many unanswered questions about screening for anal cancer but this finding was an essential plank in the foundations.



My Daffodil Centre colleague, Dr Monjura Nisha [right], and me presenting our posters. I presented two posters: "*Optimising referral to colposcopy in a national HPV screening program*" and "*Impact of COVID-19 Disruptions to HPV vaccination on HPV-related cancers: a modelled evaluation*".

Visiting the Lincoln Memorial with my close collaborators and colleagues, [clockwise from lower left] Kate, Deb, Julia and Dorothy

I was one of the 90 speakers at the conference, and gave a presentation titled "*Expediting Elimination in Aboriginal and Torres Strait Islander women: the impact of scaling up prevention measures*", as well as presenting two posters. My Daffodil Centre colleagues also presented on a range of topics, including new data from the Compass trial of cervical screening in a vaccinated population, the potential role of non-medical providers in cervical screening, and a range of prevention policy evaluations for Australia, Vietnam, New Zealand, the Federated States of Micronesia and the WHO.

It has been almost 5 years since the last in-person IPVC, and it was wonderful to come together and meet international collaborators, colleagues and friends face to face again – one of the highlights for me. We had great discussions on many active projects and made new contacts with people interested in our work. Around all that science, there was time to see some of DC's icons, including the Washington and Lincoln Memorials, the White House, and many famous faces in the National Portrait Gallery.

Thank you to Sydney Cancer Partners for supporting my travel and this fantastic learning and networking experience.

Optimising referral to colposcopy in a national HPV screening program

Smith MA[1], Killen J[1], Rimalos K[1], Canfell K[1].

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Conclusions

Referring women with non-16/18 HPV and normal/low-grade cytology at both initial screening and 12-month repeat testing to another 12-month follow-up test represents a more favourable balance between benefits and harms than colposcopy referral at 12 months. Countries introducing primary HPV screening should monitor and adapt triaging and referral processes in the light of initial experience and emerging evidence.

Background

In Australia, those with non-16/18 HPV types detected and low-grade squamous abnormalities or less (≤LSIL) at their primary screening episode are classified as intermediate risk and recommended to return in 12 months for repeat HPV testing. Initially, guidelines recommended that this group be referred if any HPV type was detected at their 12-month repeat test. A review of data from the National Cancer Screening Register identified that women with non-16/18 types but no cytological evidence of high-grade or glandular abnormalities were at low risk of serious disease, even when these results persisted at 12 months, but that they also comprised a majority of colposcopy referrals [1]. Consequently, guidelines were updated to instead recommend another repeat HPV test in 12 months for this group [2].

We undertook a modelled evaluation comparing outcomes in women managed according to the updated guidelines compared to those managed according to the original guidelines, as part of program safety monitoring.

Methods

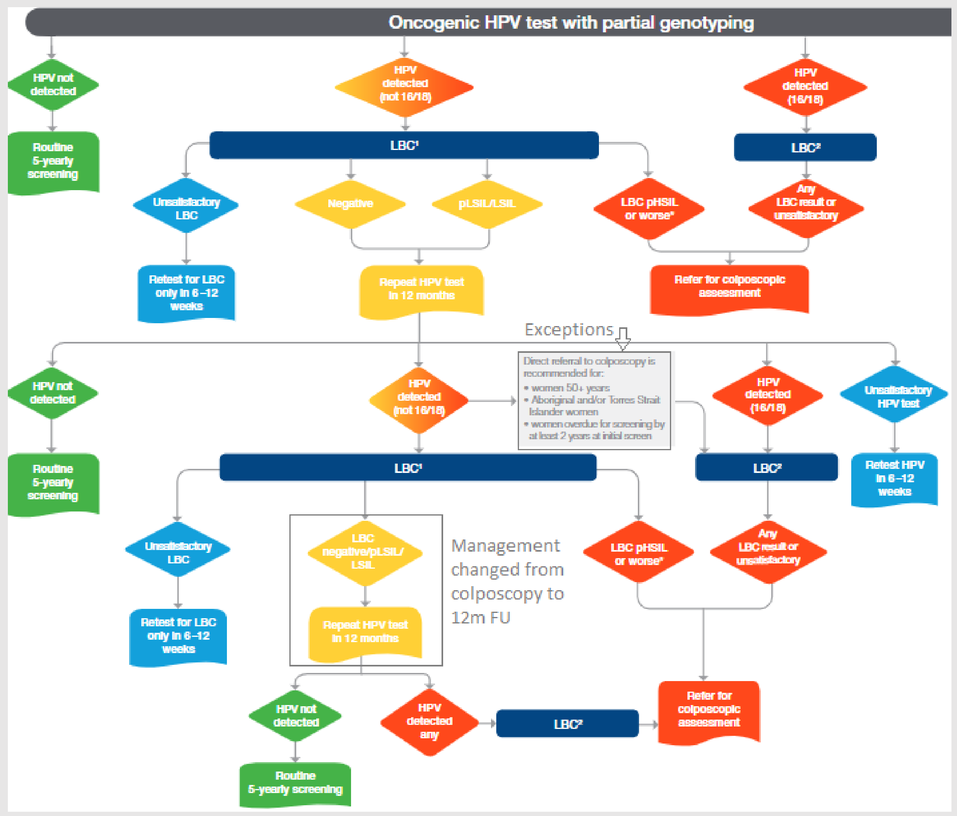
A well-established model (*Policy1-Cervix* [3]) was used to compare original and updated guidelines in terms of i) 20-year risk of cancer; the ii) incremental number of colposcopies needed (INNC); and iii) incremental number of precancer treatments needed (INNT) to prevent a cervical cancer case, and cancer death, for original compared to updated guidelines. Findings were compared with previously established local benchmarks for: i) acceptable 20-year cancer risk for 12-month referral (1.4%; based on the earlier cytology program), ii) an unfavourably high INNC (>340-400 per case prevented; >900-1065 per death prevented), and iii) an unfavourably high INNT (>11 per case; >31 per death). Outcomes were examined in women aged 26, 36, or 46 at their 12-month repeat test in 2021 (representing women offered vaccination at age 12-13; offered vaccination at age 22-23; and not age-eligible for vaccination, respectively).

Table: Model-predicted numbers of colposcopies and precancer treatments required to prevent a cervical cancer case/death for different management at 12-month follow-up test

	Age at 12-month repeat test		
	26 in 2021	36 in 2021	46 in 2021
Additional colposcopies per:			
Case prevented	**7,170**	**2,368**	**605**
Death prevented	**21,304**	**10,704**	**3,024**
Additional precancer treatments per:			
Case prevented	**441**	**89**	4
Death prevented	**1,309**	**403**	21

Bold indicates result favours updated guidelines. Plain text indicates neutral/ potentially supports original guidelines

Figure 1: Changes to guidelines management at 12-month follow-up test

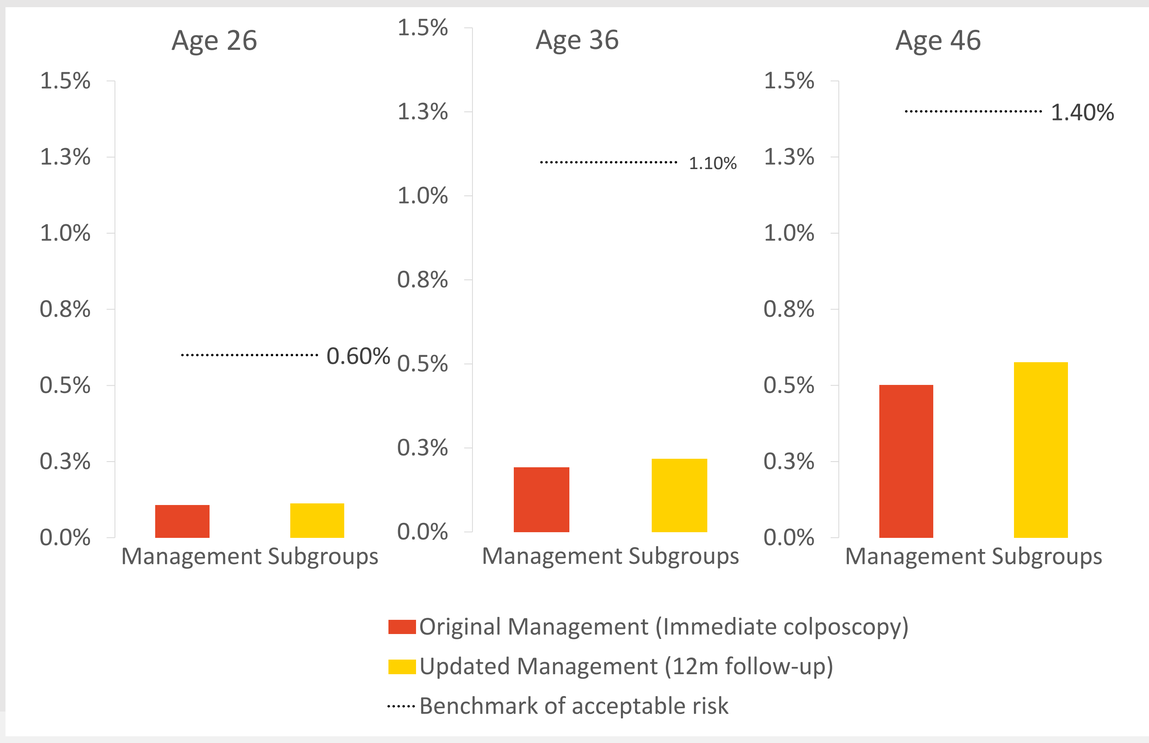


Results

The 20-year risk of cervical cancer marginally increased in women aged 46 (original guidelines 0.50% vs updated guidelines 0.58%), and was even lower in younger cohorts who had been offered HPV vaccination, but in all cases remained below the benchmark (Figure 2).

Compared to the updated guidelines, the original guidelines required 605-7,170 additional colposcopies per cancer case prevented, and >3,000 additional colposcopies per death prevented, much higher than the benchmark (Table). INNT mostly exceeded the acceptable benchmark, except for those aged 46 years.

Figure 2: Model-predicted 20-year risk of cervical cancer diagnosis for different management at 12-month follow-up test



Research funding from the Commonwealth Department of Health. Conference support for Megan Smith was awarded by Sydney Cancer Partners with funding from Cancer Institute NSW (2021/CBG0002).

References

1. Smith *et al*, BMJ. 2022;376:e068582. National experience in the first two years of primary HPV cervical screening in an HPV vaccinated population in Australia: observational study.
2. NCSP Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding https://www.cancer.org.au/clinical-guidelines/cervical-cancer-screening
3. *Policy1-Cervix* technical documentation. www.policy1.org/models/cervix

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Impact of COVID-19-related disruptions to HPV vaccination – a modelled analysis

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Conclusion

Providing that catch-up of missed vaccine doses can be implemented, short-term delays in vaccinating adolescents are unlikely to have substantial long-term effects on HPV-related cancer outcomes.

Background

During the COVID-19 pandemic, physical restrictions disrupted school attendance in many countries, delaying routine adolescent HPV vaccination in some settings. Missed vaccination has the potential to increase the rate and number of preventable HPV-related cancers, and this is in the context that organized screening is not generally available for any of the HPV-related cancers other than cervical cancer.

In Australia, government-funded HPV vaccination is routinely offered through schools, to girls and boys aged 12–13 years. In 2018, a 2-dose course of the 9-valent HPV vaccine (HPV9) replaced a 3-dose course of the quadrivalent vaccine. Catch-up HPV vaccination is also available (from 2023, to age 25 years), and is administered in primary care.

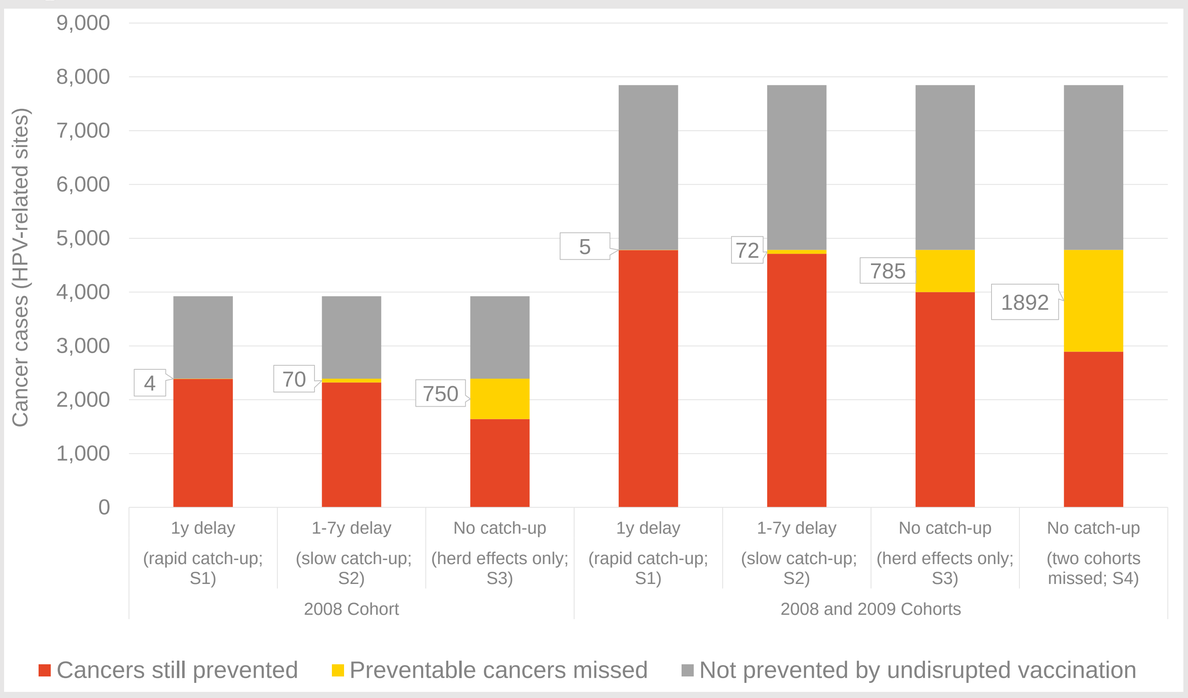
Using a simulation model, we estimated the additional lifetime HPV-related cancer cases in women and men that could be caused by HPV vaccination delays or missed doses due to the pandemic, using Australia as an example.

This work commenced when the impact of the pandemic on vaccination coverage over the short or long-term was not well understood.

Methods

We used the validated *Policy1-Cervix* modelling platform of dynamic HPV transmission and natural history; cervical screening; and cancer treatment and survival.[1] The HPV transmission component incorporates HPV vaccination and was used to estimate age-specific HPV incidence under hypothetical scenarios where vaccination was disrupted, compared to a 'no disruption' scenario. The number of lifetime cervical cancer cases was estimated for potentially affected cohorts, after explicitly modelling cervical screening (5-yearly HPV screening starting from age 25).[2]

Figure 1: Estimated lifetime HPV-related cancer cases from HPV



S: scenario; y: year.

HPV incidence estimated by the transmission model was used in a separate incidence-based model to project the lifetime number of non-cervical HPV-related cancers in both sexes.[3,4]

Compared to no disruption (HPV9 vaccine uptake at age 12 as in Australia: 82.4% [females]; 75.5% [males]), additional lifetime HPV-related cancer cases were calculated for the following:

Three disruption scenarios affecting one birth cohort (2008):
S1: 1-year delay (rapid catch-up);
S2: 1 to 7-year delay (slow catch-up);
S3: no catch-up (one cohort missed; herd effects only).

A fourth scenario assumed no catch-up for two cohorts (2008, 2009).

Results

In the baseline no disruption scenario, we estimate 2,391 HPV-related cancer cases would be prevented in the 2008 cohort due to HPV vaccination, equating to 61% of all HPV-related cases. A 1-year delay (rapid catch-up) could result in ≤0.3% more HPV-related cancers (n=4) but the increase would be greater if catch-up was slower (5%; n=70), and especially if there was no catch-up (49%; n=750) (Table 1, Figure 1).

Additional cancers were most commonly cervical (23% for a single missed cohort), oropharyngeal (males:20%) or anal (females:16%).

In the worst-case scenario of two birth cohorts missing vaccination (without catch-up), 62% more HPV-related cancers would be diagnosed compared to undisrupted vaccination (n=1,892). More than a third (37%) of HPV-related cancers would still be prevented, however, due to herd effects.

Table 1: Estimated number of cancer cases in modelled scenarios according to sex and cancer type.

Modelled scenarios	Total Cases (additional compared to no disruption)*	Females, N (additional compared to no disruption)					Males, N (additional compared to no disruption)		
		Anal	Cervical	Oropha-ryngeal	Vaginal	Vulvar	Anal	Oropha-ryngeal	Penile
2008 cohort									
No vax	3,923	489	788	185	162	729	389	911	271
No disruption	1,532	100	62	86	61	580	74	423	146
S1	1,537 (4)	101 (1)	63 (1)	86 (0)	61 (0)	580 (0)	75 (1)	424 (1)	146 (0)
S2	1,603 (70)	114 (14)	74 (12)	90 (4)	64 (3)	586 (6)	85 (11)	440 (17)	150 (4)
S3	2,282 (750)	236 (136)	250 (188)	121 (35)	96 (35)	632 (52)	175 (101)	593 (170)	180 (34)
2008 and 2009 cohorts									
S4	4,954 (1,893)	544 (345)	588 (463)	260 (88)	211 (89)	1,291 (131)	404 (256)	1,278 (433)	378 (86)

* Sum of cases and the number of additional cases presented in the table do not always match the difference between case figures stated for individual scenarios, due to rounding.

No vax: assuming no HPV vaccination in cohort(s);
No disruption: HPV vaccination in males and females at age 12
Scenario 1: 1-year delay,
Scenario 2: slow catch-up: 1 to 7-year delay;
Scenario 3: no catch-up (herd effects only 2008 cohort missed);
Scenario 4: no catch-up (herd effects only; 2008 and 2009 cohorts missed).

1. Policy1-Cervix. www.policy1.org/models/cervix
2. Smith et al. Impact of disruptions and recovery for established cervical screening programs across a range of high-income country program designs, using COVID-19 as an example: A modelled analysis. Prev Med. 2021; 151:106623.
3. Kim et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. PLoS Med. 2021;18(3):e1003534.
4. Velentzis and Smith et al. Impact of COVID-19 related disruptions to HPV vaccination – a modelled analysis. Submitted to eLife (20-12-2022-SR-eLife-85720).

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