



Modelled analysis of hypothetical impacts of COVID-19 related disruptions to the National Cervical Screening Program

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Authors

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Summary

Purpose, Background and Approach

This report was commissioned in March 2020 by the Australian Department of Health and submitted on 1 May 2020 by Cancer Council NSW as part of a rapid response to advising government about potential direct and indirect impacts of COVID-19 on Australia's National Cervical Screening Program. The hypotheses, assumptions and advice in this preliminary report are designed to provide rapid critical guidance to government at a time of major uncertainty and disruption to the health system.

Restrictions in relation to travel and social distancing in response to COVID-19 began to be implemented across Australia from around mid-March 2020. While there was no change in active communication from the National Cervical Screening Program and no explicit restrictions on women accessing cervical screening, some disruptions to participation could be expected due to women being less likely to attend for screening or a reduction in healthcare provider capacity. In both cases this could potentially be due to personal illness, caring for someone with an illness, childcare responsibilities, or a change in work responsibilities or priorities. Additionally, women may be less inclined to visit their provider due to concerns about being exposed to COVID-19 in a healthcare setting.

In mid-March 2020, the National Cervical Screening Program (NCSP) was approximately 27 months into a transition from a 2-year to a 5-year recommended screening interval. The effect of this timing is that fewer women were expected to attend for a routine primary Cervical Screening Test (CST) in Australia in 2020 than in 2019 or earlier years, but also that women who would have attended in 2020 were already overdue for screening (and as a result a higher risk group).

Using a well-established simulation model of human papillomavirus (HPV) natural history and cervical screening, we simulated a range of possible/hypothetical disruption impacts on attendance for a routine primary CST in 2020 (potentially due to a range of factors), and estimated potential impacts of the disruption in attendance on cancer diagnoses (including stage at diagnosis), women screened, and colposcopies. The long-term sequelae of both additional and upstaged cervical cancers diagnosed over 2020-2022 was also considered. Three scenarios were modelled (12-month period with 95% reduction in women attending for a primary test; 9-month period with 75% reduction in women attending for a primary test; 6-month period with 50% reduction in women attending for a primary test). Disruption scenarios also included a temporary change to management of initially intermediate risk women who return for a follow-up test in 2020.

Findings

Under this range of assumptions, an estimated range of 270,378 to 1,027,437 women could potentially miss a routine primary CST in 2020 due to COVID-19-related disruptions.

All three disruption scenarios resulted in an increase in cancer diagnoses among screening-age women over the period 2020-2022 compared to what would have otherwise been expected. The increase over 2020-2022 ranged from 21 - 69 cases (1.1-3.6% increase).

The largest increases in cancer diagnoses would be among women aged 30-39 years and 40-49 years.

Additionally, it is anticipated that interruptions to routine primary screening will lead to some cervical cancers being diagnosed at a later stage, when survival outcomes are less favourable (approximately 6 - 18 cases upstaged from localised to regional; approximately 3 - 9 cases upstaged from regional to distant).

The additional cervical cancers and those which would be diagnosed at a later stage due to disruptions to cervical screening (affecting an estimated 30 – 97 women in total) are expected to lead to approximately 6-20 more deaths from cervical cancer over the longer term.

These predicted outcomes are entirely due to women missing a screening test in 2020, and do not take into account additional cancers, upstaged cancers, or cervical cancer deaths that may result if there is also a reduction in attendance among women who are already under surveillance, or if women with symptoms are less likely to be diagnosed in 2020.

Implications of these findings include that:

- A disruption in screening attendance would reduce demand for colposcopy in 2020, but increase demand in 2021-2022 due to the shift in when women screen. This could both increase the opportunity to reduce colposcopy waiting lists in 2020, but also reduce the opportunity to do so in 2021-2022.
- The women who would have screened in 2020 were already overdue for screening. Catching up these overdue women (and achieving program recovery) will potentially require a broader communications approach than reminder letters. More widespread availability and promotion of self-collection as an option for some women could also assist in this. Consideration could be given to focussing on women aged 30-49 years, who are predicted to have the largest increase in cancers if screening attendance is disrupted (and the effect of the disruption does not vary by age).
- Continued and timely follow-up for women under surveillance or presenting with symptoms remains essential, or the adverse impact is likely to be greater than predicted in this analysis.

In light of some of the findings, limitations, and implications of this preliminary phase of work, potential further areas of work include:

- Explore and model the potential impact of active strategies in 2021-2022 to increase participation among currently under/never-screened women – for example model a range of assumptions for increased participation potentially resulting from more widespread availability and promotion of self-collection.
- More detailed examination of the impact of change in management at 12-month follow-up for initially intermediate risk women - including the implications for resource utilisation, health outcomes, quality-adjusted life-years, and health system costs.
- Quantify the benefits of maintaining attendance by women in follow-up and of transitioning from 2-yearly cytology to 5-yearly primary HPV screening – both of which are likely to have contributed to the relatively small impact on cervical cancer.

- Update estimates to incorporate recent data on colposcopy attendance and capacity
- Explore new policy options to prioritise women for screening and follow-up - for example examination of different triage, follow-up or downstream management options, and/or less frequent screening in vaccinated cohorts, tailored to their needs and allowing focus on reaching higher risk women more frequently.

Background

The COVID-19 pandemic may impact significantly on the delivery of Australia's national cancer screening programs, through disruptions to services and program participation during the immediacy of the crisis response, and over the longer term, as health services readjust and recover after the peak of the pandemic and response.

Restrictions in relation to travel and social distancing in response to COVID-19 began to be implemented across Australia from around mid-March 2020. While there was no change in active communication from the National Cervical Screening Program and no explicit restrictions on women accessing cervical screening, some disruptions to participation could be expected due to women being less likely to attend for screening or a reduction in healthcare provider capacity. In both cases this could potentially be due to personal illness, caring for someone with an illness, childcare responsibilities, or a change in work responsibilities or priorities. Additionally, women may be less inclined to visit their provider due to concerns about being exposed to COVID-19 in a healthcare setting.

The NCSP situation varies from that of the breast and bowel cancer screening programs at the current time, because the NCSP is just over two years into a process of transitioning from a 2-year to a 5-year screening interval. When the NCSP transitioned from cytology-based screening to primary HPV screening on 1st December 2017, women were recommended to attend for their first Cervical Screening Test (CST) in the renewed NCSP two years after their previous cytology test, and a 27-month reminder was sent to women with no record of a CST in this timeframe. As of mid-March 2020, just over 27 months had passed since the NCSP transitioned, and so all women have passed the point when they were due to receive their first CST, and their 27-month reminder letter. Therefore, in the absence of the COVID-19 disruption, women attending in 2020 would either be women returning for surveillance after a previous screen-detected abnormality, or be women returning for a routine screening test who are overdue. Conversely, there should also be a very large number of women who have had their first CST, been screen-negative (ie low risk), and therefore not be due to attend for screening again until at least December 2022. Two implications of this situation are that firstly, many women who are not due for screening until December 2022 or later will be unaffected by disruptions to screening; but secondly, that women who would have attended in 2020 were already overdue for screening, and consequently at higher risk of having underlying cervical abnormalities when they attend for screening.

This report describes findings from preliminary modelling and analysis of potential COVID-19 impacts on the National Cervical Screening Program (NCSP), by simulating, comparing and reporting on multiple scenarios. The overarching goal is to provide information based on modelling to understand the potential impact of the COVID-19 pandemic on the NCSP.

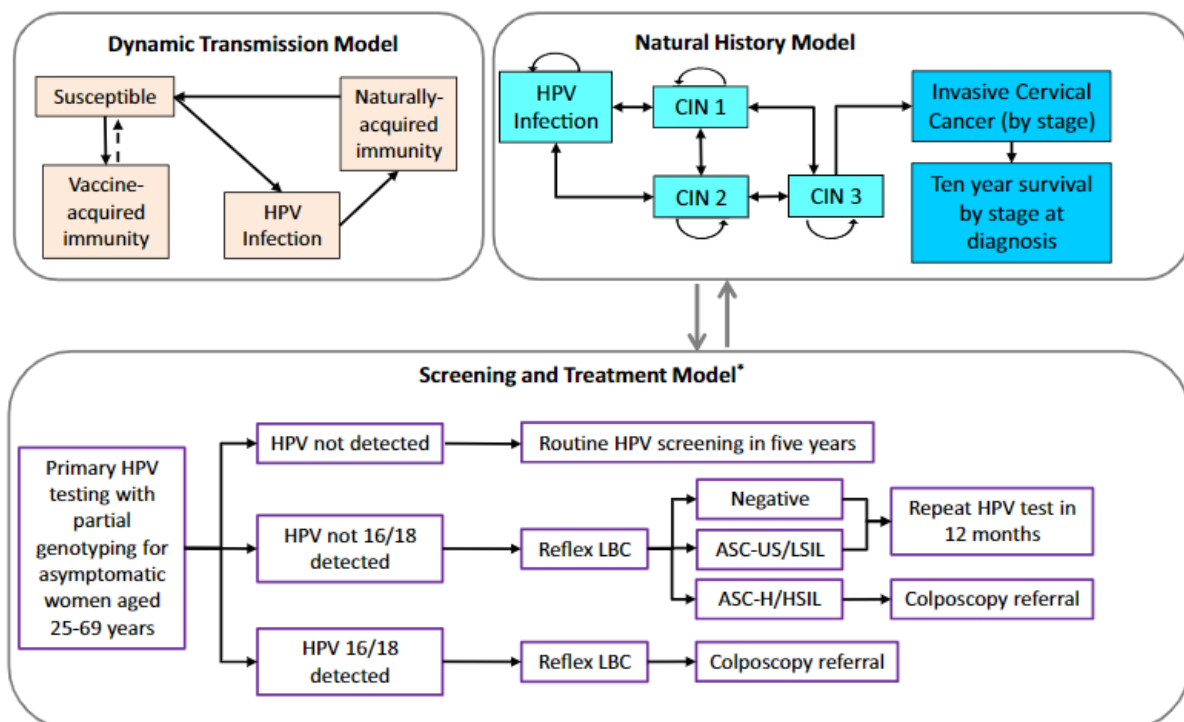
Given the volatility of the COVID-19 situation and anticipated medium- and longer-term considerations, this report presents findings from a preliminary first phase of work, and additionally includes recommendations for follow-up work to support the Australian Government in its COVID-19 response and recovery.

Methods

Model description

Policy1-Cervix is an established model of HPV natural history and vaccination, cervical screening and follow-up management, and cervical cancer treatment and survival (Figure 1). It incorporates a dynamic model of HPV transmission and vaccination (implemented in C++), coupled with a deterministic multi-cohort Markov model of HPV natural history incorporating detailed screening behaviour, and clinical management of screen-detected abnormalities and invasive cervical cancer (implemented using TreeAge Pro 2014). *Policy1-Cervix* has been used for a number of previous policy evaluations in Australia, including the effectiveness and economic evaluation of the NCSP Renewal for the Medical Services Advisory Committee and associated clinical guidelines (1-3); the impact of the NCSP transition on resource utilisation and health outcomes (4, 5); the potential impact of extending self-collection (6), and the impact of the quadrivalent and nonavalent vaccines in Australia (7-9). It has also been used for modelled evaluations in several other settings, including in New Zealand, England, the United States, Japan, China, and globally (10-20).

Figure 1 – Policy1-Cervix model schematic diagram



Outcomes considered

Outcomes considered in Phase 1 work, as agreed with the Commonwealth Department of Health are:

- Cancer diagnoses, by stage
- Cancer deaths
- Number of women screened
- Number of colposcopies

by year, over the period 2020-2022, and among women aged 25-74 yrs¹.

The estimated impact on cervical cancer deaths also takes into account cancer deaths that occur later than 2022, but are attributable to additional or upstaged cancers diagnosed over 2020-2022, and thus are considered to have occurred or been upstaged as a consequence of the COVID-19-related disruption.

Scenarios modelled

Due to the model having a time-step of one year, all modelled scenarios assume that the pre-renewed NCSP (2-yearly cytology for women aged 18-69 years) was in place until the end of 2017, and that the NCSP transitioned to the renewed program (5-yearly primary HPV screening starting at age 25 with an exit test between ages 70-74 years) at the beginning of 2018. Clinical management for women with abnormal screening test results in the model was based on established guidelines (21, 22).

Similar re-screening patterns as in the pre-renewed NCSP were assumed to apply until women have attended for their first Cervical Screening Test (CST) in the renewed NCSP (ie screening behaviour reflects that women are recommended to attend for their first CST two years after their last cytology test). These screening patterns for women's first CST differ slightly from assumed adherence to the 2-yearly interval in the pre-renewed NCSP, in order to directly reflect NCSR data on observed behaviour from December 2017 onwards (see *Data sources*). Re-screening patterns reflecting a recommended 5-yearly interval do not apply to women until after they have attended for their first CST.

Counterfactual – no disruption

The counterfactual scenario assumes there was no disruption to screening in 2020, and women would have continued to re-attend. In the case of routine primary screening, this reflects re-attendance by women whose previous cytology screening test was more than two years ago. Based on data from the NCSR, 38.4% to 64.8% of eligible women have not yet attended for their first CST (results vary by age; see *Data sources* and Appendix Table A1). Re-attendance after the recommended 2-year timeframe reflects data from the pre-renewed NCSP that many women who are late for cervical screening do eventually re-attend, for example by three or five years (23).

Disruption scenarios

Due to timing constraints, this report focuses on results for three disruption scenarios, that are all compared to a counterfactual scenario of no program disruption. Scenarios and

¹ Includes women who turn 74 in 2020 over the whole time period, who will be aged 76 years in 2022.

assumptions were agreed with the NCSP. These aimed to cover a wide range of possibilities.

Disruption scenarios are described in Table 1.

Additionally, the following assumptions were made and applied to all disruption scenarios in the Phase 1 analysis:

- i) There is no change in attendance by women who are already in follow-up for a previous screen-detected abnormality (changes in attendance are assumed to only occur in women who would otherwise attend for routine screening).
- ii) Women with an initial result of Intermediate risk who return for their 12-month follow-up visit in 2020 and who are found to be HPV-positive (non-16/18 types) again on their follow-up test will be managed based on their reflex cytology result. Women with reflex cytology result of possible HSIL or more severe are referred for colposcopy; women with a cytology result of LSIL or less severe are referred for another 12-month follow-up HPV test (ie they are considered to remain at Intermediate risk). If at this third test, women again test positive for non-16/18 HPV types, they will be treated as Higher risk and referred for colposcopy. Women who are HPV-negative at either their 12-month follow-up or at their third (24-month) test are recommended to return to routine 5-yearly screening. This change to the 2017 Guidelines (21) was assumed to be temporary and in place for the period of COVID-19 disruption only.
- iii) To calculate how many cancers were upstaged due to the disruption, we assumed that additional cancers that were diagnosed over 2021-2022 were diagnosed at the localised stage, and that any increase in the number of cancers diagnosed at the distant stage was due to cancers being upstaged from regional to distant. Other changes in the numbers of localised or regional cancers were assumed to be a result of upstaging from localised to regional.

Table 1- Final nominated scenarios

	1. Disruption periods [‡]	2. Attendance for routine screening during disruption	3. Recovery timeframes	Purpose
1	12 months	5% of what it would have been (95% reduction)	Women who would have screened in 2020 instead attend over 2021-2022	Worst case health impact
2	9 months in 2020	25% of what it would have been (75% reduction)	Women who would have screened in 2020 instead attend in 2021	Moderately large surge in resource requirements post-disruption
3	6 months in 2020	50% of what it would have been (50% reduction)	Women who would have screened in 2020 instead attend over 2021-22	Lower estimate of impact on health outcomes and resource requirements

[‡] assumed the disruption covers the whole of 2020, with scaling to reflect different durations of disruption. See Notes.

Notes:

As the model incorporates a 1-year time-step, the disruption will be modelled as occurring from the start of 2020. This has some impact on reflecting women who screened in 2020 prior to the disruption and interpretation of outcomes. This will be addressed as follows:

- In order to reflect the fact that some women will have attended for a Cervical Screening Test (CST) in 2020 prior to the disruption, and that women who have screened since 1 December 2017 will either not be due again until at least December 2022 or be in one of the follow-up categories (which should continue through the disruption), the model reflects NCSR data on all women who have had at least one Cervical Screening Test over the period 1 December 2017-14 January 2020 (the most recent data available in time to commence model runs).
- As the disruption in practise occurred from around late March 2020, rather than at the beginning of the year, model predictions for 2020 would correspond to approximately late March 2020 – late March 2021, and so on for later years.

Data sources

The model and most of the input assumptions used in this preliminary analysis were the same as that used in an earlier modelled analysis to evaluate primary HPV screening in Australia and updated clinical management guidelines undertaken in 2016 (1). Key assumptions used in the current analysis and those which were updated since the previous analysis are described below (Table 2). More detailed descriptions of other parameters and model calibration against observed data are documented in previous publications (1, 2, 24). Briefly, two key assumptions were updated:

- i) Vaccine uptake was updated to reflect more recent data
- ii) Screening participation was updated to reflect observed behaviour since the transition to primary HPV screening in Australia, based on data extracted from the National Cancer Screening Register (NCSR) on 14th January 2020.

Assumptions relating to colposcopy attendance were also reviewed prior to this analysis, but data to directly inform updated model assumptions were not available prior to model runs commencing. To address this, data on colposcopy attendance were requested from Victoria, and these data were compared with the model assumptions used, to give insight into whether model assumptions may have been optimistic or pessimistic.

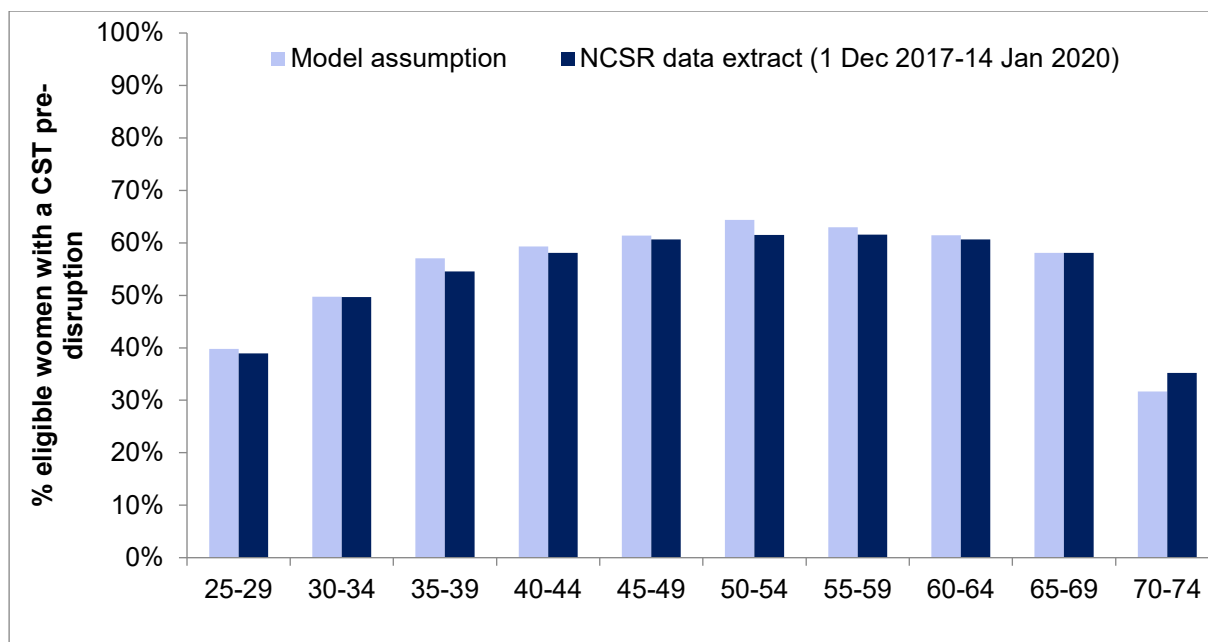
Table 2 – Key model assumptions

Parameter	Description	See
Screening participation (routine)	Phase 1 analyses use a pattern of early, on-time, and late re-screening probabilities based on a previous analysis (1, 2, 24), scaled such that the proportion of eligible women screened at least once prior to the disruption matches the proportion of eligible women screened at least once between 1 Dec 2017 and 14 Jan 2020. A comparison of model assumptions and observed data from the NCSR is shown in Figure 2.	Table A1, Table A2 NCSR data extracted on 14 Jan 2020 in response to <i>ad hoc</i> request AHR200
Screening participation (follow-up)	Phase 1 analyses use the same assumptions as were used in a policy evaluation of primary HPV screening in Australia (1, 2)	
Colposcopy attendance	Phase 1 analyses use the same assumptions as were used in a policy evaluation of primary HPV screening in Australia (1, 2) These assumptions were compared against data extracted from the NCSR for Victoria*	Table A3
Vaccine uptake	All scenarios assume that quadrivalent vaccine is used over 2007-2017, and nonavalent vaccine is used from 2018 on. Uptake in routine target cohorts at age 12 is 82.4% in females and 75.5% in males from 2014 on, with varying uptake in earlier years of the program, based on published data.	Table A5, Table A6 (2, 25-27)

Parameter	Description	See
Cancer survival	<p>Phase 1 analyses use the same assumptions as were used in a policy evaluation of primary HPV screening in Australia (1, 2).</p> <p>Stage-specific survival were based on an analysis of data from the NSW Central Cancer Registry for women diagnosed with cancer over the period 2000-2007 (28).</p>	Table A7

* Aggregated data from NCSR raw data extract (RDE) for Victoria was requested, but due to the timeframe were not available in time to be directly incorporated in the model assumptions for this analysis.

Figure 2 – Comparison of model assumptions of women who had at least one CST prior to COVID-19 disruption with observed participation over 1 December 2017 – 14 January 2020



NCSR data extracted on 14 Jan 2020 in response to *ad hoc* request AHR200; includes CSTs up to 14 Jan 2020

Results

Impact on cancer

The overall predicted impact of the COVID-19-related disruption on cancer diagnoses and deaths are shown in Table 3, and the predicted impact on cervical cancer diagnoses by stage are detailed in Table 4.

All three disruption scenarios that were considered in this analysis predicted an increase in cancer diagnoses among screening-age women over the period 2020-2022 compared to what would have been expected in the absence of any disruption. The increase over 2020-2022 ranged from 21 - 69 cases (1.1-3.6% increase).

Similarly, all three disruption scenarios considered predicted that disruptions to routine primary screening will lead to some cervical cancers being diagnosed at a later stage, when survival outcomes are less favourable. Under the assumptions that all additional cancers were diagnosed at the localised stage, and all additional distant cancers in the disruption scenarios represented upstaging from regional to distant (and not from localised to distant, given the short timeframe), the model predicted 6 - 18 cervical cancers would be diagnosed in 2021-2022 at regional stage, rather than as localised cancers in 2020, and that 3 - 9 cervical cancers would be diagnosed in 2021-2022 at distant stage, rather than at regional stage in 2020 (Figure 3). This equates to 30 – 97 women who are affected by delays in diagnosis due to disruptions to routine screening in 2020. The age groups with the largest number of additional cancers diagnosed were women aged 30-39 years and women aged 40-49 years (Figure 5). These were also the age groups where the percentage increase in cancers was largest (although still relatively small: 1.1 - 4.1% in women aged 30-39 years and 1.2 - 4.3% in women aged 40-49 years). In all three scenarios considered, most (57 - 63%) of the additional cancers were diagnosed among women 30-49 years.

Taking into account both additional cervical cancers and those which were diagnosed at a later stage due to disruptions to cervical screening, 6 - 20 more deaths from cervical cancer are expected to occur over the longer term due to disruptions in routine screening attendance in 2020.

The main results over 2020-2022 include diagnoses and deaths in women who were aged 73-74 years in 2020 (even though in 2021 and/or 2022 these women are outside the recommended screening age range). This was done to ensure that delays in screening women aged 73-74 in 2020 are taken into account. In a secondary analysis, we included only diagnoses and resulting deaths among women aged 25-74 years. This did not change the predicted number of additional cancer cases, upstaged cancers, or cancer deaths, indicating disruptions to screening in 2020 are unlikely to have a substantial effect in women close to exiting cervical screening.

Figure 3 – Total cervical cancers diagnosed among women aged 25-74 years in 2020-2022 under varying scenarios for disruptions to routine screening in 2020, by stage at diagnosis

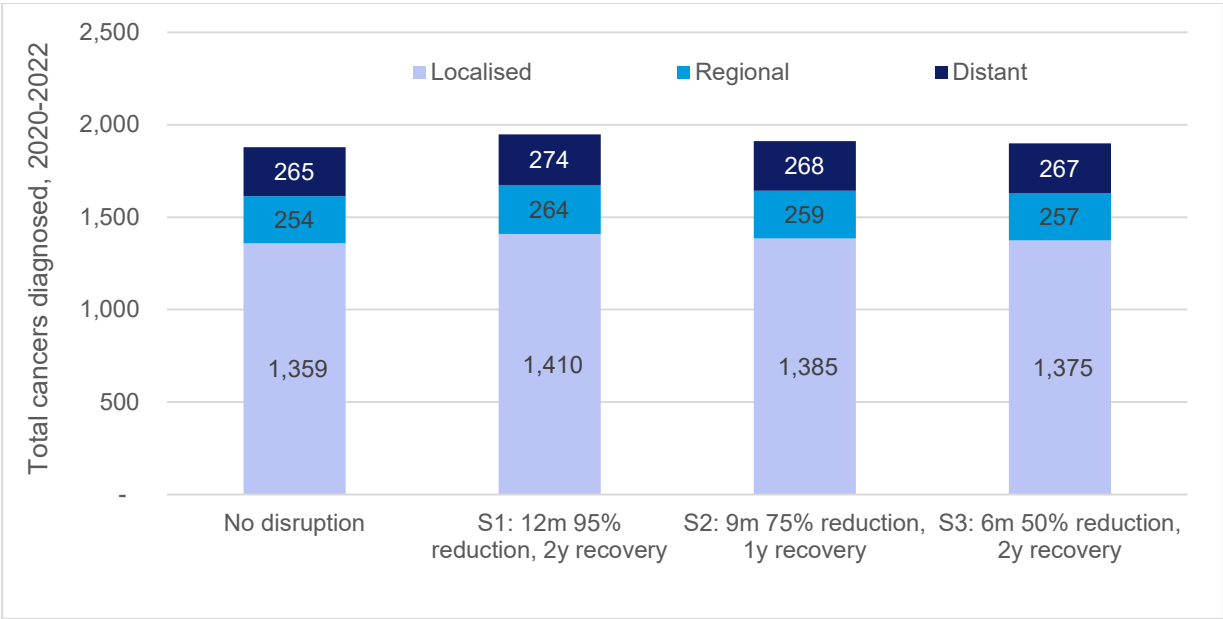
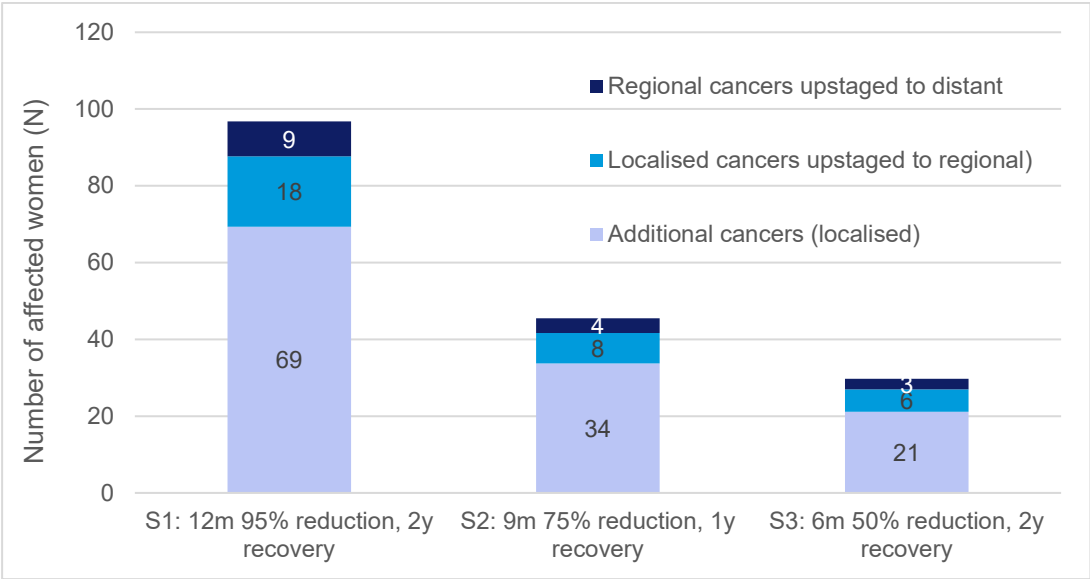
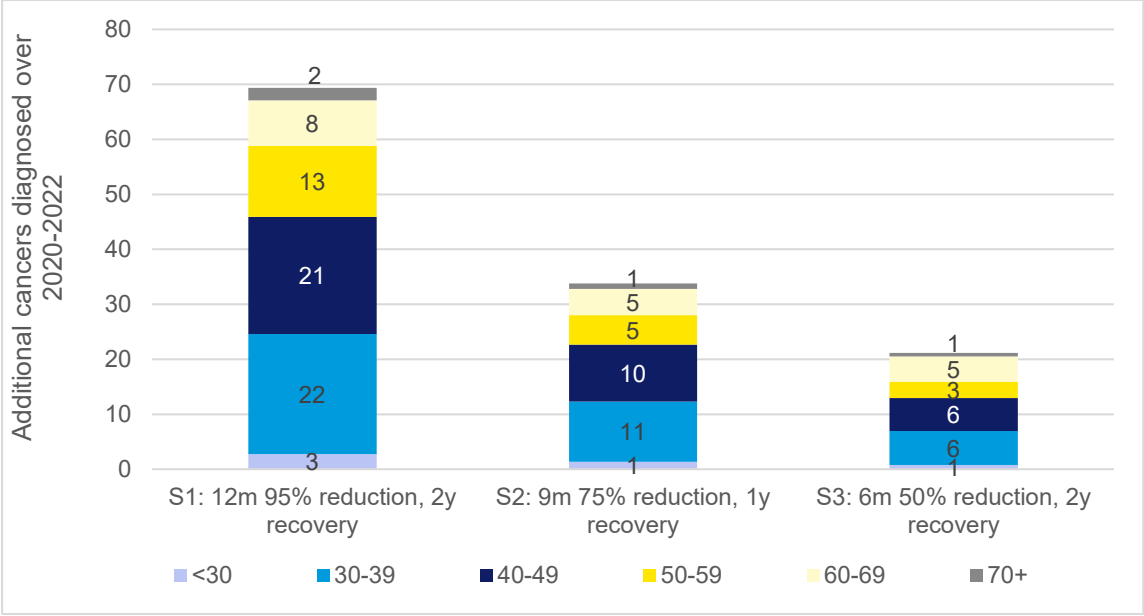


Figure 4 – Number of women affected by delayed cancer diagnosis under varying scenarios for disruptions to routine screening in 2020



Upstaged regional cancers that progressed to distant were calculated by assuming that the difference in numbers of diagnosed distant cancers is due to upstaging from regional only. Upstaged localised cancers that progressed to regional were calculated by assuming that the number of upstaged cancers is equal to the difference in numbers of diagnosed regional cancers, corrected for the number of regional cancers which were upstaged to distant. Some differences between Figures 3 and 4 are due to rounding cases to whole numbers.

Figure 5 – Additional cervical cancers diagnosed among women aged 25-74 years in 2020-2022 under varying scenarios for disruptions to routine screening in 2020, by age at diagnosis



Note: women aged <30 years in 2020 were offered HPV vaccine when aged <17 years; women aged 30-39 years in 2020 were offered HPV vaccination when aged 18-26 years

Table 3 – Impact of disruption on cancer outcomes among women aged 25-74 years, 2020-2022

Scenario	Additional cancers*		Cancers upstaged		Additional deaths due to increase/ upstaged cancers over 2020-2022
	N	% increase	Localised → Regional	Regional → distant	
No disruption	1,878	n/a	n/a	n/a	n/a
S1: 12m 95% ↓	69	3.6%	18	9	20
S2: 9m 75% ↓	34	1.8%	8	4	9
S3: 6m 50% ↓	21	1.1%	6	3	6

Includes outcomes in women aged up to 74 years in 2020, who will be aged up to 76 in 2022. Cancer deaths includes deaths that would be expected to occur outside 2020-2022 but are a result of delayed diagnosis due to the disruption in 2020. * No disruption scenario row shows number expected in that scenario; other rows show difference in relation to the no disruption scenario. Upstaged localised cancers that progressed to regional were calculated by assuming that the number of upstaged cancers is equal to the difference in numbers of diagnosed regional cancers, corrected for the number of regional cancers which were upstaged to distant. Upstaged regional cancers that progressed to distant were calculated by assuming that the number of upstaged cancers is equal to the difference in numbers of diagnosed distant cancers, corrected for the number of distant cancers which resulted in cancer death in the simulated period. Some differences between Tables 3 and 4 are due to rounding cases to whole numbers.

Table 4 – Impact of disruption on cancer outcomes among women aged 25-74 years, by stage at diagnosis, 2020-2022

Scenario	Localised		Regional		Distant	
	N	Difference*	N	Difference*	N	Difference*
No disruption	1,367	n/a	265	n/a	278	n/a
S1: 12m 95% ↓	1,418	51	274	9	287	9
S2: 9m 75% ↓	1,392	26	269	4	282	4
S3: 6m 50% ↓	1,382	15	268	3	281	3

No disruption scenario row shows number expected in that scenario.* difference compared to the no disruption scenario. Negative value indicates fewer cancers diagnosed compared to the no disruption scenario. Some differences between Tables 3 and 4 are due to rounding cases to whole numbers.

Impact on number of women screened and colposcopy demand

The predicted impact of the COVID-19-related disruption on the number of women attending for a CST in each year over the period 2020-2022 is shown in Figure 5 and Table 5.

Model estimates suggest that approximately 1,413,888 million women would have been expected to attend for a screening test in 2020, including those attending for a routine primary test and those attending for surveillance. Under the range of disruption scenarios considered (from 50% reduction in attendance to 95% reduction in attendance for 12 months), it was estimated that between 270,378 and 1,027,437 women would miss their routine primary screening test in 2020. This represents a reduction of 19.1-72.7% in the number of women attending for a CST for any reason in 2020 compared to what would have otherwise been expected. These percent reductions are lower than the percent reductions assumed among women attending for a routine primary test (25-95%), because a proportion of women who have a CST are attending for a follow-up test, rather than a primary screening test.

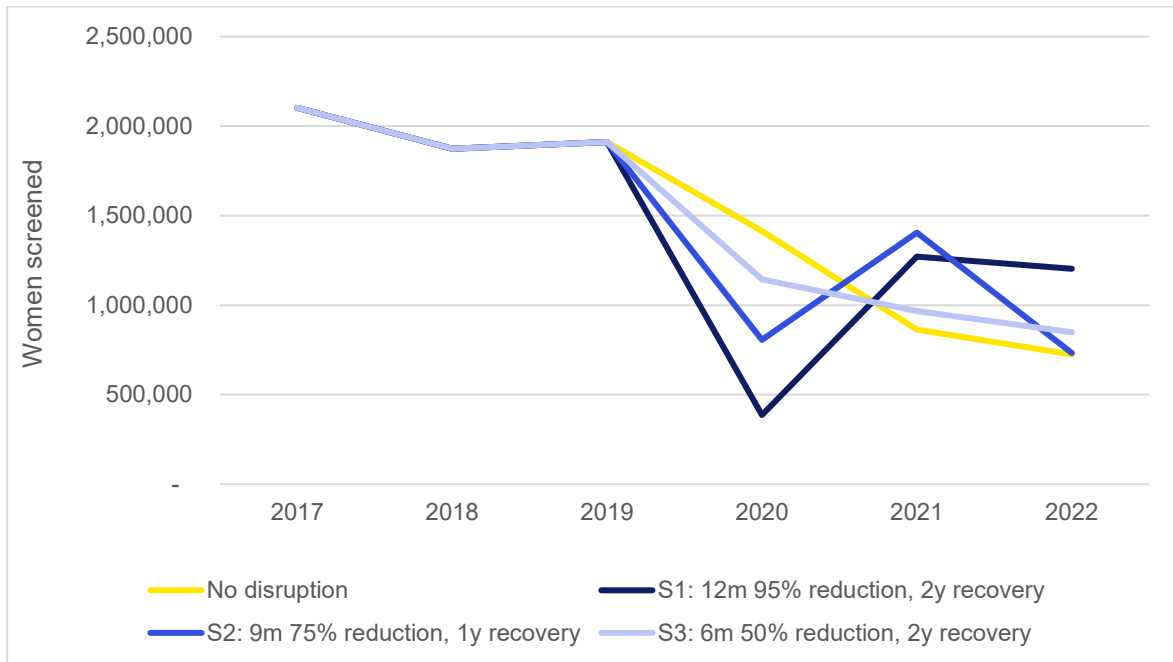
The predicted impact of the COVID-19-related disruption on anticipated colposcopy demand in each year over the period 2020-2022 is shown in Figure 6 and Table 6. Across the range of disruption scenarios considered, it was estimated that there would be 17,680 – 47,868 fewer women attending for a colposcopy in 2020, representing a reduction of 17.4 – 47.2%. As we assumed no change in women attending for a follow-up test in 2020, this would represent a reduction due to women referred as a result of their primary screening or triage test. Note that this estimate excludes any colposcopies that are performed in women with a CST for symptoms potentially suggestive of cervical cancer who are not subsequently diagnosed with cervical cancer. These estimates also do not explicitly take into account colposcopy capacity or waiting lists (as this information was not available), but do incorporate less than perfect adherence to colposcopy (Table A3). Considering the full 3-year period 2020-2022, the disruption is predicted to result in around 12,157-34,175 fewer colposcopies. It should also be noted that as a result of the transition from a 2-year to a 5-year recommended screening interval, the number of colposcopies that were anticipated in each of 2020, 2021, and 2022 differed year to year in the no disruption scenario (Figure 6). This will remain the case in the context of a disruption, but the pattern will vary.

Table 5 – Impact of disruption on number of women expected to attend for a Cervical Screening Test (any purpose)

Scenario	Women screened/ who missed screening*, 2020		Additional women screened: 2021	Additional women screened: 2022
	N	%	N	N
No disruption	1,413,888		n/a	n/a
S1: 12m 95% ↓	1,027,437	72.7%	407,077	479,226
S2: 9m 75% ↓	608,351	43.0%	542,670	7,808
S3: 6m 50% ↓	270,378	19.1%	103,318	123,982

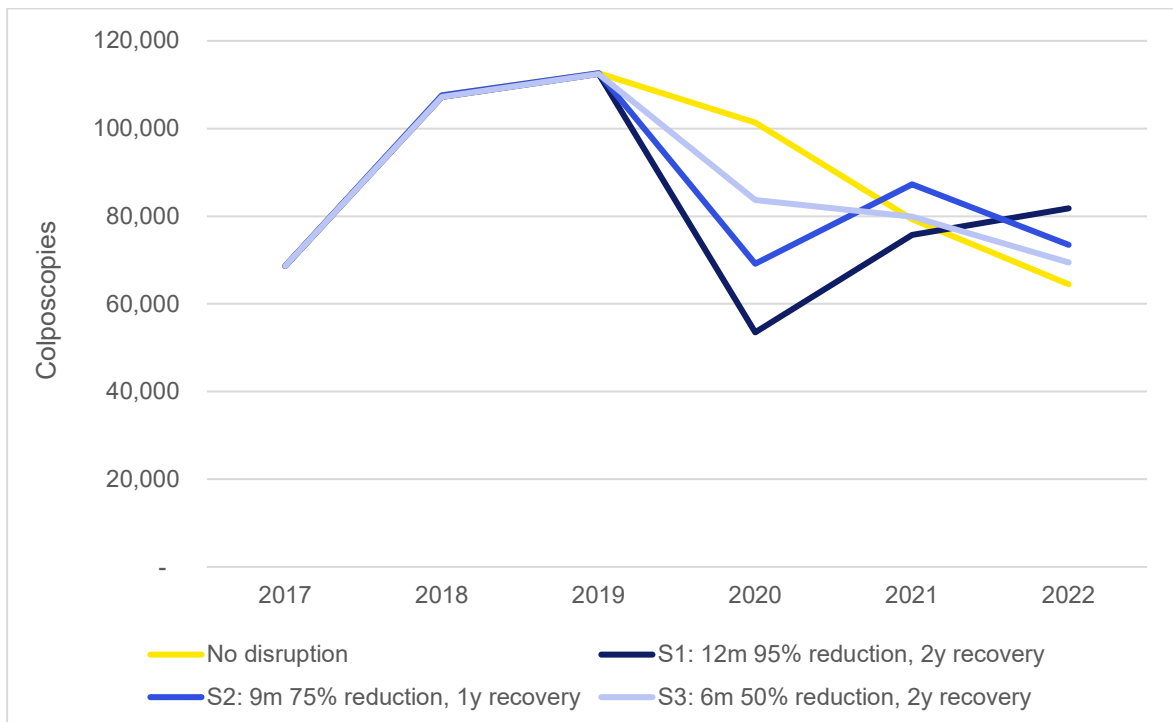
Includes women with a CST for any purpose, including follow-up tests or tests in symptomatic women that result in a cancer diagnosis, but excludes women with a CST for symptoms who are not diagnosed with cervical cancer. * No disruption scenario row shows number expected in that scenario; other rows show difference in relation to the no disruption scenario.

Figure 6 – Predicted number of women aged 25-74 years screened under varying disruption scenarios, by year



Note: Data presented for each year are the total number in that year (existing model structure does not allow for predictions at the level of months)

Figure 7 - Predicted number of colposcopies among women aged 25-74 years under varying disruption scenarios, by year



Note: Data presented for each year are the total number in that year (existing model structure does not allow for predictions at the level of months)

Table 6 – Impact of disruption on expected colposcopy utilisation, 2020-2022

Scenario	Colposcopy difference, 2020		Colposcopy difference, 2021		Colposcopy difference, 2022		Cumulative colposcopy difference, 2020-2022	
	N	%	N	%	N	%	N	%
No disruption*	101,376	n/a	79,476	n/a	64,768	n/a	245,620	n/a
S1: 12m 95% ↓	-47,868	-47.2%	-3,633	-4.6%	17,325	26.8%	-34,175	-13.9%
S2: 9m 75% ↓	-32,208	-31.8%	7,947	10.0%	9,024	13.9%	-15,237	-6.2%
S3: 6m 50% ↓	-17,680	-17.4%	527	0.7%	4,995	7.7%	-12,157	-4.9%

Excludes colposcopies in women with a CST for symptoms who are not diagnosed with cervical cancer. * No disruption scenario row shows number expected in that scenario; other rows show difference in relation to the no disruption scenario.

Discussion

Data obtained from the NCSR for this analysis suggests that 3,652,739 women aged 25-74 years (53.6% of the estimated 6,812,468 eligible women) had their first CST between 1st December 2017 and 14th January 2020. These women either are not due to attend for screening again until at least December 2022, or were already under closer surveillance prior to the impact of COVID-19. This large group of approximately 3.7 million women should be relatively unaffected by COVID-19-related disruptions to screening, provided women who were already under closer surveillance continue their follow-up.

Model estimates suggest that approximately 1.4 million women would have been expected to attend for a screening test in 2020, including those attending for a routine primary test and those attending for surveillance. Note this is fewer than the number who typically attended either prior to the transition to primary HPV screening or in the first two years post-transition (approximately 1.8 million), as a result of the NCSP being just over two years into a process of transitioning women from a 2-year to a 5-year recommended screening interval. Therefore, the number of women affected by disruptions to routine cervical screening during 2020, and the consequences of those disruptions, are likely to be considerably less in the current context than they would have been if Australia still had a 2-yearly cytology-based cervical screening program, or if they had occurred in 2018 or 2019. Consideration of what the impact would have been in Australia in the context of a continued 2-yearly cytology program, and therefore an additional benefit resulting from the transition to primary HPV screening, is a potential subject for future work.

Under the range of disruption scenarios considered (which ranged from a 50% drop in attendance for routine screening lasting six months, to a 95% drop in attendance for 12 months), it was estimated that between around 270,000 and just over one million women would miss their routine primary screening test in 2020. This represents a reduction of 19.1 - 72.7% in the number of women attending for a CST for any reason in 2020 compared to what would have otherwise been expected.

The reduction in women attending for their routine primary screening test is expected to lead to 21 - 69 more diagnoses of cervical cancer over 2020-2022 (Table 3), an increase of 1.1 - 3.6% compared to what would have otherwise been expected. A reduction in women attending for routine primary screening is also expected to lead to upstaging of some cancers that would have otherwise been detected by screening in 2020 – an estimated 6 - 18 cancers being diagnosed as regional rather than localised cancers, and an estimated 3 - 9 cancers being diagnosed as distant rather than regional cancers. Considering the impact of both the additional cancers, and also those which were diagnosed at a later stage over 2020-2022, affecting 30 - 97 women in total, the range of COVID-19-related disruptions considered is predicted to result in 6 - 20 additional cervical cancer deaths over the longer term (these could occur up to 11 years after diagnosis). These predicted outcomes are restricted to women who are age-eligible for screening during 2020-2022, and whose cancers would otherwise have been expected to be detected when they attended for a routine cervical screening test (in the absence of a disruption). It does not include any cervical cancers or deaths that may occur in women outside the age range for routine screening, or cancers that would have been detected due to symptoms in 2020. It was assumed in this analysis that cervical cancers detected symptomatically in 2020 would be unaffected by COVID-19, and that women outside the target age range for routine screening who were being followed up after a previous screen-detected abnormality would also be unaffected. If there are additionally disruptions that affect whether women with symptoms present for clinical

investigation or women with previous screen-detected abnormalities attend for scheduled follow-up, this would likely increase the number of cervical cancers and related deaths that could occur as an indirect result of COVID-19.

The increase in cervical cancer diagnoses predicted to result from a reduction in attendance for routine primary screening is expected to be largest among women aged 30-39 years and 40-49 years, and between 57 - 62% of the additional cancers are expected to be diagnosed among women in these age groups. This may partly reflect the larger numbers of cervical cancers diagnosed in women in this age range compared to other age groups (typically ~46% of diagnosed cases are in women aged 30-49 years (23)); however these age groups also had the largest percentage increase in cancer, as well as the largest number of additional cases. While women aged 30-39 years have previously been offered HPV vaccination, those who received it would have been vaccinated around the age of 17-26 years, when there was a higher chance of prior exposure (for example, model-based predictions suggest that more than half of the women who are eventually diagnosed with cervical cancer acquire the causal HPV infection by the age of 19-23 years (29)). A supplementary analysis indicated that disruptions to screening in 2020 are unlikely to have a substantial effect in women close to exiting cervical screening (aged 73-74 years in 2020), as the number of additional cases, upstaged cases, and consequent deaths was the same regardless of whether or not outcomes in women this age were included or not. These findings related to age are based on the assumption that the percent (relative) reduction in screening attendance does not vary by age (but does take into account that screening participation does vary by age).

Strengths and limitations

The strengths of this analysis include the use of a well-established model of HPV natural history and cervical screening, that is tailored to Australia and reflects a wide range of local data, including data on sexual behaviour, HPV vaccine uptake, screening behaviour, screening and diagnostic test performance, and cancer survival (including variation in survival by clinical stage and mode of diagnosis). The model was also able to incorporate unpublished data from the NCSR on the number of women who had received at least one CST since 1st December 2017, and who therefore are likely unaffected by the disruption, either because they are not due for routine screening in 2020, or are already under closer surveillance.

Given the large number of uncertainties relating to COVID-19 and related disruptions, this analysis deliberately focussed on a high level effect – a wide range of possible reductions in attendance for routine screening in 2020, over different durations of time. In practice these scenarios represent reductions in attendance ranging from 25% (50% reduction for six months) to 95% when averaged over a year. The analysis was agnostic to the cause of the reduction in attendance, and therefore this could reflect any or many of a wide range of possible factors, including changes in women's behaviour and access to screening, reduced capacity of primary care or laboratories to undertake screening, reduced saliency of reminder letters or delays in these being delivered. It could also reflect an overall reduction in participation over multiple periods of disruption rather necessarily a single continuous period.

The model was able to incorporate a change in the management for women with an initial result of intermediate risk who returned for their 12-month follow-up test and who were again found to be HPV-positive (non-16/18 types) again on their follow-up test. This was implemented in the model as a temporary change for women returning during the disruption period in 2020 only, and involved managing women based on their reflex cytology result: women with reflex cytology result of possible HSIL or more severe are referred for colposcopy, while those with a cytology result of LSIL or less severe are referred for another

12-month follow-up HPV test (considered to remain at Intermediate risk). This means that our findings will partly reflect the impact of this change in management, as well as the assumed disruption to routine screening attendance, although unpublished NCSR data provided in early April 2020 suggest that no prevalent cancers would be missed by delaying referral in women with LSIL or less severe cytology at 12 months. This change in management will potentially be a longer term change, extending beyond 2020, and may also not be implemented exactly as modelled here.

One limitation of the current analysis is that data on colposcopy attendance within a year of referral since the NCSP transitioned to primary HPV screening were not available in time to explicitly be included in this analysis. In lieu of this, we have compared the model assumptions for attendance for colposcopy within 12-18 months of a referring test with data from Victoria. The results of this comparison vary by age, and reason for referral, but generally the Victorian data suggested lower attendance for colposcopy than the model had assumed for younger women (aged <50 years), while the data suggested higher attendance for colposcopy than the model had assumed for women aged 70+ years. Longer waiting times for colposcopy have been reported post-transition, and extended delays could lead to fewer women having high grade disease or cancer detected and treated prior to the disruption than was assumed in the model. We were not able to take these delays or capacity constraints on colposcopy explicitly into account in the modelled analysis, as data were not available. This may have affected our estimates of cancers arising in women who would otherwise have attended for routine screening in 2020 if delays in screening are further compounded by delays in colposcopy for these women after the COVID-19 disruption dissipates. There are some limitations on the colposcopy data from Victoria, as they only represent attendance among women whose referring test occurred in 2018 (due to the time required for 12-18 month follow-up data to be available), and they are for one state only, however they are broadly consistent with national data indicating that approximately 85% of women aged 25-74 years have a colposcopy within 12 months of their referring test (NCSR data provided to the authors by the Commonwealth, 28 April 2020).

Another limitation of this analysis is that it does not take into account the opportunity cost of delays in strategies that could otherwise have occurred in 2020-2022 to increase participation among under- and never-screened women. These strategies could have had important effects in reducing cancer and detecting it at an earlier stage, given that so many cervical cancers are diagnosed in under- and never-screened women. As our estimates for the impact on cervical cancer diagnoses, upstaging, and deaths do not take this opportunity cost into account, they are potentially underestimates of overall impact.

How these findings might apply in different states and territories

The model used in this analysis is based on national data and reflects national patterns of HPV vaccine uptake, screening behaviour, screening and diagnostic test performance, and cancer incidence and survival. While national findings could be broken down into indicative numbers for different jurisdictions, this would not take into account factors that vary by jurisdiction and would be expected to affect the outcome in that jurisdiction. This includes not only the extent of COVID-19-related disruption, but also several other factors relating to cervical cancer specifically, including HPV vaccine uptake, screening participation prior to the disruption (and therefore how many women are either low risk or already under surveillance), whether women already under surveillance or presenting with symptoms continue to attend unaffected by COVID-19-related factors, and differences in colposcopy attendance. The flow-on effect to deaths would also depend on patterns of cervical cancer treatment and survival. Table 7 provides an indicative summary of how variation in some of these factors could affect the findings, for example the finding of a 1.1-3.6% increase in cancer diagnoses.

Table 7 – Potential effect of variation in key factors that may vary by jurisdiction

Factor	Potential effect, relative to national findings
HPV vaccine uptake	Additional/ upstaged cancers less likely in younger women in jurisdictions with higher vaccine uptake
Screening behaviour: % of eligible women who have had their first CST	Additional/ upstaged cancers less likely in jurisdictions where a higher proportion of women had already had their first CST, prior to COVID-19 disruption
Extent of COVID-19 disruption on routine screening attendance	Additional/ upstaged cancers less likely in jurisdictions where disruptions are shorter and/or reductions in attendance are smaller
Time to colposcopy	Additional/ upstaged cancers potentially more likely in jurisdictions where a smaller proportion of women are able to receive colposcopy within ~12 months, as this could compound delays in screening
Extent of COVID-19 disruption on attendance for follow-up or investigation of symptoms	Additional/ upstaged cancers more likely in jurisdictions where disruptions additionally reduce attendance for follow-up tests or presentation by women with symptoms
Cancer survival	Flow-on effects from upstaging potentially greater in jurisdictions where stage-specific survival is poorer

Implications

- Women who would have attended for screening in 2020 in the absence of COVID-19 disruptions were all at least three months overdue for screening, and potentially overdue by much longer. These under-screened women, who need to be reached and encouraged to attend in order for the program to recover from the disruption, will potentially be less responsive to reminder letters. ***A broader approach may be required in the recovery, for example communication strategies and more widespread availability and promotion of self-collection as an option for some women².***
- Most (57 – 63%) of the additional cancers that are predicted to occur as a result of disruptions to screening are expected to occur among women aged 30-49 years. ***Consideration could be given to targeting communications to women in this age group during the recovery phase, although all women who are under- or never-screened will benefit from attending for screening.***

² Under the current policy, cervical screening on a self-collected sample is restricted to women aged 30 years or older who are two or more years overdue for screening; at present this would apply to women whose most recent cytology test was four or more years ago.

- Colposcopy demand has exceeded capacity in 2018-2019. Disruptions to attendance for routine primary screening in 2020 will also reduce colposcopy demand in 2020, as will changes to management for initially intermediate risk women attending for their 12-month follow-up test. If women who miss screening do instead attend in 2021-2022, colposcopy demand is likely to return to a level which is similar to or higher than would have been expected in 2021-2022 in the absence of any disruption (noting this demand is lower than in 2018-2019). The larger the disruption in 2020, the more colposcopy demand will increase in 2021-2022, compared to what would have been expected. As a result, **a disruption to primary screening in 2020 may not only provide an opportunity to reduce colposcopy waiting lists, it may also reduce the opportunity to do this in 2021-2022.**
- The adverse impact of COVID-19-related disruptions on cervical cancer and related deaths predicted here result directly from missed primary screening tests in 2020. The impact could be expected to be greater if disruptions also affect attendance for follow-up tests or investigation of symptoms. **Continued and timely follow-up for women under surveillance or presenting with symptoms remains essential or the adverse impact is likely to be greater than predicted here.**

Conclusions & recommendations

Summary of conclusions

While the number of women attending for routine screening was expected to be lower in 2020 than in earlier years (due to the change from a 2-year to a 5-year recommended screening interval), disruptions of the magnitude considered here could result in at least 270,000 women and potentially up to more than one million women missing a screening test in 2020.

All disruption scenarios considered resulted in additional cancer cases (range: 21-69), cancers diagnosed at a later stage (range: 9-27), and additional deaths over the longer term resulting from these delays in diagnosis (range: 6-20). Most of the additional cancer cases are predicted to occur in women aged 30-49 years, if the relative reduction in screening attendance is similar across all age groups.

These predicted outcomes are entirely due to women missing a screening test in 2020, and do not take into account additional cancers, upstaged cancers, or deaths that may result if there is also a reduction in attendance among women who are already under surveillance or if women with symptoms are less likely to be diagnosed in 2020.

Colposcopy demand is expected to reduce as a result of any disruption, but would then be expected to increase in 2021-2022 compared to what would have been expected in the absence of a disruption.

Recommendations for Phase 2 work

Explore and model the potential impact of active strategies in 2021-2022 to increase participation among currently under/never-screened women

The only women affected by disruption were under-screened, so broader strategies may be required to engage them in screening as part of program recovery. We could model a range of assumptions for increased participation potentially resulting from more widespread availability and promotion of self-collection, or other active strategies.

More detailed examination of the impact of change in management at 12-month follow-up for initially intermediate risk women

Phase 1 analysis incorporated this as a temporary change only. The longer term outcomes of this as an ongoing change in management could be examined, including the implications for resource utilisation, health outcomes, quality-adjusted life-years, and health system costs.

Quantify the benefits of maintaining attendance by women in follow-up and of transitioning to primary HPV screening

Each of these factors has likely played an important role in keeping impact on cervical cancer relatively small.

Incorporate updated data on colposcopy attendance

To better reflect the impact of constraints and the potential for colposcopy delays to compound screening delays.

Explore new policy options to prioritise women for screening and follow-up

For example this could include examination of different triage and/ or follow-up options, and/or less frequent screening in vaccinated cohorts tailored to their needs and allowing focus on reaching higher risk women more frequently.

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Appendix

Screening participation

Table A1 – Number and proportion of eligible women with any Cervical Screening Test recorded over 1 Dec 2017-14 Jan 2020, by age

Age group*	Women with CST (any purpose)†	Female population (end 2019) (30)	% with intact cervix (31)	Compass participants	% eligible with CST‡
25–29	371,155	961,043	0.998	6,524	39.0
30–34	468,646	970,344	0.991	17,912	49.7
35–39	471,174	913,832	0.962	15,959	54.6
40–44	427,478	809,934	0.916	6,073	58.1
45–49	440,231	852,043	0.859	6,465	60.7
50–54	390,502	790,858	0.81	6,002	61.5
55–59	371,213	788,129	0.772	5,651	61.6
60–64	318,993	721,631	0.736	5,058	60.6
65–69	258,238	635,533	0.706	4,159	58.1
70–74	135,109	548,979	0.703	2,141	35.2
25-74	3,652,739	7,992,326	6,888,412¶	75,944	53.6§

* age as at end-2019 † NCSR data extracted on 14 Jan 2020 provided by Telstra Health in response to *ad hoc* request AHR200, including CSTs up to 14 Jan 2020. ‡ Method for calculating % of eligible women with a CST is consistent with that used in routine AIHW NCSP monitoring reports, that is the denominator includes the estimated resident population minus women who have had a hysterectomy and minus women enrolled in the Compass trial (31). Estimates of women with an intact cervix are based on the same estimates used in published AIHW NCSP monitoring reports (31). ¶ Estimated number with intact cervix § Crude percentage of eligible women

ABS population estimates are from Series B (mid-range estimates) (30). End-2019 estimates are interpolated from those for mid-2019 and mid-2020.

Table A2 – Proportion of eligible women with any Cervical Screening Test recorded – modelled assumption prior to disruption compared to observed data (1 Dec 2017-14 Jan 2020), by age

Age group	Model assumption (% attended prior to disruption)	Observed data (1 Dec 2017-14 Jan 2020)
25–29	39.3	39.0
30–34	48.5	49.7
35–39	55.4	54.6
40–44	57.7	58.1
45–49	59.9	60.7
50–54	62.6	61.5
55–59	61.4	61.6
60–64	60.5	60.6
65–69	58.0	58.1
70–74	32.0	35.2

Colposcopy attendance

Table A3 – Proportion of women referred for colposcopy who attend within 12 months – model assumptions compared to observed data from Victoria (12-18 months)

Age group (years)	HPV16/18+ OR HPV (non-16/18)+ & pHSIL+*		Persistent HPV (non-16/18)+ †		Referred during test of cure	
	Model assumptions	Observed data (Vic)	Model assumptions	Observed data (Vic)	Model assumptions	Observed data (Vic)
<30	0.9583	0.8197 - 0.8413	0.8906	0.7578 - 0.7874	0.8769	0.7677 - 0.7209
30-39	0.9587	0.8829 - 0.9076	0.9084	0.8711 - 0.9025	0.8211	0.8160 - 0.8527
40-49	0.9459	0.8934 - 0.9019	0.9105	0.8847 - 0.8937	0.5691	0.8288 - 0.8607
50-59	0.8835	0.8974 - 0.9143	0.8864	0.8938 - 0.9120	0.9780	0.8703 - 0.9138
60-69	0.8929	0.8771 - 0.9133	0.9052	0.8709 - 0.9074	0.5145	0.8800 - 0.9024
70+	0.8333	0.9349‡	0.8448	0.9307	0.3858	0.7429 - 0.8333

* consistent with model assumptions and observed data for colposcopy attendance after a cytology result of pHSIL+ in pre-renewed NCSP † midway between model assumptions and observed data for colposcopy attendance after a cytology result of pHSIL+ and observed data for colposcopy attendance after a cytology result of pLSIL/LSIL in pre-renewed NCSP. ‡ range not provided as data for 18 months were too small

Observed data are from NCSR Raw Data Extract (RDE) for Victoria as of 19/03/2020, provided by VCS Population Health in response to an *ad hoc* data request.

Vaccine uptake

All scenarios assume that quadrivalent vaccine is used from 2007-2017, and nonavalent vaccine is used from 2018 on.

Table A4 - Proportion of unvaccinated females who complete a full vaccine course, by age and calendar year

Age	2007	2008	2009	2010	2011	2012 onwards
12	0	0.77	0.76	0.763	0.783	0.824
13	0	0.77	0	0	0	0
14	0	0.765	0	0	0	0
15	0.765	0.76	0	0	0	0
16	0.735	0	0	0	0	0
17	0.675	0	0	0	0	0
18	0.209	0	0	0	0	0
19	0.174	0.232	0	0	0	0
20	0.174	0.209	0.278	0	0	0
21	0.162	0.197	0.244	0	0	0
22	0.162	0.186	0.22	0	0	0
23	0.162	0.186	0.22	0	0	0
24	0.139	0.186	0.209	0	0	0
25	0.145	0.186	0.209	0	0	0
26	0.237	0.29	0.209	0	0	0

Source: National HPV Vaccination Register data (2, 25-27)

Table A5 - Proportion of unvaccinated males who complete a full vaccine course, by age and calendar year

Age	2013	2014	2015	2016 onwards
12	0.750	0.755	0.755	0.755
13	0	0	0	0
14	0.664	0.715	0	0
15	0.316	0	0	0
16	0.01325	0	0	0

Cervical cancer survival

Stage- and interval-specific cancer survival parameters used in the model were based on analysis of data obtained from NSW Central Cancer Registry (28).

Table A6 – Cumulative relative cancer survival assumptions, by time since and stage at diagnosis and mode of detection

Years since diagnosis	<u>Localised</u>		<u>Regional</u>		<u>Distant</u>	
	(scrn-det)	(symptoms)	(scrn-det)	(symptoms)	(scrn-det)	(symptoms)
1	1.0000	0.9195	0.9295	0.8431	0.6266	0.5684
2	0.9895	0.8576	0.8323	0.7115	0.4969	0.4249
3	0.9662	0.8374	0.7983	0.6825	0.4413	0.3773
4	0.9464	0.8203	0.7487	0.6401	0.3563	0.3046
5	0.9337	0.8092	0.7215	0.6169	0.3259	0.2786
6	0.9258	0.8025	0.6976	0.5964	0.2983	0.2551
7	0.9213	0.7986	0.6582	0.5627	0.2838	0.2426
8	0.9186	0.7962	0.6522	0.5576	0.2523	0.2157
9	0.9186	0.7962	0.6427	0.5495	0.2221	0.1899
10	0.9161	0.7940	0.6235	0.5331	0.2221	0.1899
11	0.9080	0.7870	0.6235	0.5331	0.2221	0.1899

Scr-det = cervical cancers detected by screening. Symptoms = cervical cancers detected due to individual presenting with symptoms (not screening). Women who survive for 11 years or more after a diagnosis are assumed to no longer have excess risk of mortality due to cervical cancer.

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