Could HPV Testing on Self-collected Samples Be Routinely Used in an Organized Cervical Screening Program? A Modeled Analysis

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ABSTRACT

Background: Cervical screening on self-collected samples has mainly been considered for targeted use in underscreened women. Updated evidence supports equivalent sensitivity of PCR-based human papillomavirus (HPV) testing on self-collected and clinician-collected samples.

Methods: Using a well-established model, we compared the lifetime impact on cancer diagnoses and deaths resulting from cervical screening using self-collected samples only, with and without the existing restriction in Australia to women aged 30+ years and ≥2 years overdue, compared with the mainstream program of 5-yearly HPV screening on clinician-collected samples starting at 25 years of age. We conservatively assumed sensitivity of HPV testing on self-collected relative to clinician-collected samples was 0.98. Outcomes were estimated either in the context of HPV vaccination ("routinely vaccinated cohorts;" uptake as in Australia) or in the absence of HPV vaccination ("unvaccinated cohorts").

Results: In unvaccinated cohorts, the health benefits of increased participation from self-collection outweighed the worst case (2%) loss of relative test sensitivity even if only 15% of women, who would not otherwise attend, used it ("additional uptake"). In routinely vaccinated cohorts, population-wide self-collection could be marginally (0.2%–1.0%) less effective at 15% additional uptake but 6.2% to 12.4% more effective at 50% additional uptake. Most (56.6%–65.0%) of the loss in effectiveness in the restricted self-collection pathway in Australia results from the requirement to be 2 or more years overdue.

Conclusions: Even under pessimistic assumptions, any potential loss in test sensitivity from self-collection is likely outweighed by improved program effectiveness resulting from feasible levels of increased uptake.

Impact: Consideration could be given to offering self-collection more widely, potentially as an equal choice for women.

See related commentary by Lim, p. 245

Introduction

Testing for oncogenic human papillomavirus (HPV) is the preferred form of cervical screening, across all resource levels (1, 2). In addition to providing strong protection against invasive cervical cancer, HPV-based screening opens the possibility of performing a screening test on a self-collected sample ("self-collection"). Earlier evidence suggested that offering self-collection was an effective way to increase screening participation in under- and never-screened women, but HPV-based screening on a self-collected sample was potentially slightly (∼2%) less accurate than testing on a clinician-collected sample (3–5). In high-income countries, self-collection is usually targeted at women who are overdue for screening or have never been screened, for example, in Australia, the Netherlands, and England (6–8). Updated evidence, however, indicates that the sensitivity of HPV testing on a self-collected sample is similar or equivalent to sensitivity on a clinician-collected sample, provided that PCR-based assays are used [pooled relative sensitivity for $CIN2^+$, 0.99; 95% confidence interval (CI), 0.97–1.02; ref. 9]. This suggests the potential for self-collection to be offered as an option to all women.

In Australia, self-collection was recommended as a means to increase participation rates in never- and underscreened women, as part of a major review ("renewal") of the National Cervical Screening Program (NCSP; ref. 10). Self-collection is only available in the renewed NCSP in Australia in restricted circumstances, specifically to women who are aged 30 years or older and are ≥2 years overdue for cervical screening, and it must be facilitated by a health care professional who also offers cervical screening (6, 11). These restrictions mean that women in Australia who access screening via self-collection are likely to be less well protected than under the "mainstream" NCSP (using clinician-collected samples), albeit much better protected than if not screened (12), not only due to the initially hypothesized loss of sensitivity, but also because of the extended interval (≥7 years, as women must be ≥2 years overdue for 5-yearly screening) and later start age (30 or older) imposed by the current restrictions.

This study, therefore, had two aims, using Australia as an example: (i) to quantify the impact of offering self-collection to all women, taking into account the possibility of trade-offs between a potential

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small loss in test sensitivity and increased screening participation among those who are currently under- or never-screened and (ii) to quantify the difference in effectiveness of screening under the existing restricted self-collection pathway versus the mainstream pathway, and to explore the contribution of each different component of the self-collection pathway (test performance, longer screening interval, and later start age) to the difference in effectiveness.

Materials and Methods

Model platform

We used a well-established model of HPV transmission, natural history, vaccination, cervical screening, and treatment of precancer and cancer, which has been described in detail previously, and validated against age-specific rates of HPV prevalence, screening participation, cytology test results, detected high-grade abnormalities, invasive cancer, and mortality (13–17). Key model parameters are provided in **Table 1**, with further details in Supplementary Data S1 and online (18). Screening pathways were based on published clinical guidelines (6). HPV with partial genotyping for HPV16/18 was the primary screening test; women detected with non-16/18 oncogenic types were triaged with liquid-based cytology (LBC) and women testing either positive for HPV16/18 or positive for a non-16/18 oncogenic type with an LBC result of atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) or worse or glandular abnormalities were referred for colposcopy; and women who were positive for non-16/18 oncogenic HPV types and had an LBC result of low-grade squamous intraepithelial lesion (LSIL) or less were referred for repeat HPV testing in 12 months. Women who were HPV positive again at 12 months were referred for colposcopy. Modeled participation in the mainstream NCSP was based on participation in the cytology-based ("pre-renewed") NCSP, but extended to reflect a longer screening interval and a call-recall system of invitations and reminders (rather than reminders only when overdue, as was the case in the pre-renewed NCSP), using methods described previously (13, 19). Model-based predictions under different screening

Table 1. Baseline values for key model parameters and data sources.

Parameter	Baseline values/assumptions	Data source
HPV test accuracy (for CIN2+)		
Clinician-collected sample	Sensitivity: 96.4%; specificity: 90.1%	Meta-analysis (46)
Self-collected sample[a] (relative to clinician collected)	Relative sensitivity: 0.98; relative specificity: 1.02	Meta-analysis (PCR-based tests; refs. 3, 5)
Self-collected sample[a] (absolute)	Sensitivity: 95.0%; specificity: 93.8%	Meta-analyses (3, 5, 46)
In women being followed up after treatment for CIN2/3	Sensitivity: 93.2%; specificity: 80.8%	Meta-analysis (46)
LBC test accuracy (for CIN2+)		
ASC-US$^+$ threshold	Sensitivity: 77.0%; specificity: 94.7%	Meta-analysis (47); adapted as in Lew and colleagues (13) and Hall and colleagues (15)
ASC-H$^+$ threshold	Sensitivity: 46.2%; specificity: 99.1%	
Screening initiation		
Mainstream NCSP	No women attend before 25. Cumulative proportions of women initiating by the ages of 25, 27, 30, 40, and 69 are 74%, 79%, 85%, 95%, and 98%, respectively, based on data from the pre-renewed NCSP[b].	Data from Victorian Cervical Cytology Registry (assumes cumulative uptake at age 25 years and older as per pre-renewed NCSP)
Restricted NCSP for self-collection	No women attend before 30. Cumulative proportion of women initiating at 30 years and by 40 and 69 years is assumed to be the same as in mainstream NCSP.	Assumption: self-collection with minimal participation changes, to show best-case effectiveness, therefore, minimum value of loss of effectiveness because of delayed start age
Reattendance for a routine test		
Mainstream NCSP	Reattendance rate by 3, 5, and 7 years since last screening was <1%, 86%, and 93%, respectively (ASR; varies by age); very low proportion of early rescreeners and high proportion of on-time screeners, based on call-recall system.	Data from Victorian Cervical Cytology Registry, adapted using methods in Creighton and colleagues (19)
Restricted NCSP for self-collection	No women attend before 7 years. Reattendance rate at 7 years since last screening and cumulative reattendance at 8+ years assumed to be the same as in the mainstream NCSP.	Assumption: self-collection with minimal participation changes, to show best-case effectiveness, therefore, minimum value of loss of effectiveness because of extended interval
Vaccine uptake (routine cohort, born 2006)		National HPV Vaccination Program Register.
Females	82.4%	Midpoint between 2- and 3-dose uptake (as some effectiveness is expected with <3 doses)
Males	75.5%	
Vaccine protection	Lifelong 100% protection against new infections with vaccine-targeted types; no cross-protection against non-targeted types	

Abbreviations: ASC-H, atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; ASR, age-standardized rates; LBC, liquid-based cytology.

[a]Assumes a PCR-based test is used, as required by Australian standards for cervical screening tests (24).

[b]High attendance at 25 years due to invitation sent 3 months prior to women's 25th birthday.

scenarios were produced for a cohort of 100,000 females aged 12 years who were born in 2006 (now aged 14 years), over the course of their lifetime. This cohort was selected for consistency across a range of evaluations within a program of evaluation work across the cervical cancer spectrum (20). Predictions were considered separately for an unvaccinated cohort (approximating women in Australia now aged 40–74 years) and for a cohort of females offered quadrivalent HPV (HPV4) vaccination at age 12 years, with uptake of 82.4% based on the midpoint between recent two- and three-dose uptake data ("routinely vaccinated cohorts;" approximating women in Australia now aged 15–27 years). Vaccine uptake for HPV4 was also modeled in males from 2013, and in females aged 13 to 26 years during 2007 to 2009, to capture indirect protection from the male and catch-up components of the vaccination program (Supplementary Data S1; Supplementary Tables S1 and S2). As this evaluation related to cervical screening, vaccination with nonavalent HPV vaccine (HPV9; included in the routine vaccination program from 2018) was not considered in this analysis, as cohorts offered HPV9 are likely to require far less frequent screening than that recommended in the renewed NCSP (21–23), and will not be eligible for screening until 2031. The accuracy of self-collection was based on the findings of a meta-analysis for the relative accuracy of HPV testing on a self-collected sample, compared with a clinician-collected sample, restricted to PCR-based tests, because Australian standards require that PCR-based HPV tests must be used on self-collected samples (refs. 5, 24; Supplementary Data S1; Supplementary Table S3). A worst case 2% loss in relative test sensitivity was assumed, on the basis of the lower end of the reported CI (5).

Modeled scenarios

Scenarios are described in **Table 2**. For the first component of our analysis, hypothetical scenarios explored the population-level impact of offering self-collection to all women, if it was successful in increasing screening participation (scenarios 1–6). These scenarios assumed that self-collection would increase initiation of screening in previously unscreened women aged ≥30 years (Supplementary Data S1; Supplementary Fig. S1), and also boost participation either specifically in underscreened women (those whose most recent HPV test was ≥7 years ago) or in all women (≥5 years since last HPV test). Participation was boosted by assuming that a proportion of women (15%, 50%, or 80%) who would not otherwise have attended for screening at a given timepoint did attend due to the option of self-collection (population coverage for all scenarios is shown in Supplementary Fig. S2 in Supplementary Data S1). The low-end proportion of 15% (scenarios 1 and 2) was consistent with estimates from international meta-analyses and one of the three studies of self-collection in Australia (uptake of 11.5% and 20.3% among under- and never-screened women, respectively, in response to a mailed-out kit; less comparable with how self-collection is offered in the renewed NCSP, i.e., face to face with clinician support; refs. 4, 25). The high-end proportion of 80% (scenarios 5 and 6) was close to the uptake achieved in two Australian pilot studies of self-collection targeted to specific hard-to-reach groups and delivered in clinic-based settings (as is required in the renewed NCSP; 85.7% and 80.8%; refs. 26, 27). The mid-range estimate of 50% (scenarios 3 and 4) was close to the midpoint of the Australian studies. To explore whether increased participation resulting from offering self-collection may outweigh a possible loss of test performance, these scenarios assumed that all HPV tests were undertaken on self-collected samples (other than "test of cure" tests used to follow-up women treated for CIN2/3, where we assumed a cotest was maintained as per current guidelines). This represents a worst case estimate of the effectiveness of self-collection in the context of a loss in test sensitivity, given that some women are likely to choose screening on a clinician-collected sample when offered the choice between self-collection and clinician collection.

The second component of our analysis examined the difference in effectiveness of being screened under the current restricted self-collected pathway versus the mainstream NCSP pathway (using clinician-collected samples). To separate the impact of different aspects of the current restricted self-collection screening pathway on its overall effectiveness, in addition to examining self-collection as per the current restrictions (scenario 7), we examined hypothetical scenarios, where: there were no additional restrictions on access compared with the mainstream NCSP (impact of test accuracy only; scenario 8); only the first test was restricted, thereafter women could be screened 5-yearly (impact of starting at 30 years of age; scenario 9); and where the only requirement was ≥2 years overdue, with no additional age restriction (impact of longer screening interval and starting at 27 years of age; scenario 10). Because our purpose was to evaluate how the various aspects of accessing screening via self-collection as offered within the NCSP affected the overall effectiveness of this self-collection pathway (rather than to examine the potential effectiveness of self-collection specifically within the subgroup of women who currently do not attend for screening), parameters were varied in each hypothetical scenario in a minimal way to meet the required restrictions.

Effectiveness in each scenario was assessed in terms of cancer cases and deaths over the lifetime of the cohort (to age 84 years), with life-years used as a secondary measure of effectiveness.

Reporting against the HPV-FRAME quality checklist (28) is included in Supplementary Data S2.

Results

Population-level impact of offering self-collection to all women

If self-collection were taken up by 50% of women who would not otherwise attend for screening at a given timepoint, this increased participation would outweigh the hypothetical 2% loss of test sensitivity at the population level, even if all women used self-collection. The overall effectiveness in terms of cancer cases and deaths prevented would increase by 10.3% to 18.5% in unvaccinated cohorts, and by 6.2% to 12.4% in routinely vaccinated cohorts (**Table 3**; **Fig. 1**). If 80% of women who would not otherwise attend for screening at a given timepoint did so because they could access self-collection, cancer cases and deaths would be reduced even further, by 17.6% to 31.2% in unvaccinated cohorts and 12.1% to 23.0% in routinely vaccinated cohorts. For unvaccinated cohorts, increased participation from self-collection would outweigh the possible loss of test accuracy even if only 15% of women who would not otherwise attend took up the offer. In routinely vaccinated cohorts, 15% additional uptake could be marginally less effective at the population level (0.2% / 1%, if available at 5 / 7 years), if there was a 2% loss in relative sensitivity in self-collected tests and all women used self-collection.

Impact of various components of the restricted self-collection pathway on its overall effectiveness

In unvaccinated cohorts, cancer cases and deaths (per 100,000 women) would be 32.7% and 35.9% higher, respectively, if all women were screened under the current restricted self-collection pathway, compared with the mainstream NCSP (**Table 3**). The corresponding increases in incidence and mortality are 20.2% and 21.4% for routinely vaccinated cohorts. In both unvaccinated and routinely vaccinated cohorts, the biggest factor contributing to the loss of effectiveness was

Table 2. Scenarios modeled.

	Scenario number and description	HPV test sample[a]	Earliest screening age (years)	Years since last HPV test when coverage boosted/to access self-collection	Question
	Mainstream NCSP (base participation)	Clinician collected	25	n/a	Comparator
1	Base + 15% women who otherwise would not attend do (from 7 years onward)[b]	Self-collected	30	≥7 (i.e., among women ≥2 overdue)	To what extent does increased participation due to self-collection (with existing restrictions) outweigh loss of performance (low-end uptake)?
2	Base + 15% women who otherwise would not attend do (from 5 years onward)[c]	Self-collected	30	≥5 (i.e., unrestricted)	To what extent does increased participation due to self-collection (unrestricted from age 30 years) outweigh loss of performance (low-end uptake)?
3	Base + 50% women who otherwise would not attend do (from 7 years onward)[b]	Self-collected	30	≥7 (i.e., among women ≥2 overdue)	To what extent does increased participation due to self-collection (with existing restrictions) outweigh loss of performance (mid-range uptake)?
4	Base + 50% women who otherwise would not attend do (from 5 years onward)[c]	Self-collected	30	≥5 (i.e., unrestricted)	To what extent does increased participation due to self-collection (unrestricted from age 30 years) outweigh loss of performance (mid-range uptake)?
5	Base + 80% women who otherwise would not attend do (from 7 years onward)[b]	Self-collected	30	≥7 (i.e., among women ≥2 overdue)	To what extent does increased participation due to self-collection (with existing restrictions) outweigh loss of performance (high-end uptake)?
6	Base + 80% women who otherwise would not attend do (from 5 years onward)[c]	Self-collected	30	≥5 (i.e., unrestricted)	To what extent does increased participation due to self-collection (unrestricted from age 30 years) outweigh loss of performance (high-end uptake)?
					What is loss of effectiveness:
7	Existing restrictions	Self-collected	30[d]	≥2[e]	in women who access screening via self-collection only?
8	No restrictions (participation as in mainstream NCSP)	Self-collected	25	0 (i.e., unrestricted)	due purely to self-collection (rather than enforced longer interval and later start age?)
9	Only restriction age 30+	Self-collected	30[d]	0 (i.e., unrestricted)	in women who access screening via self-collection only, if the only restriction was being initially under-screened?
10	Only restriction ≥2 years overdue	Self-collected	27[f]	≥2[e]	in women who access screening via self-collection only, if the only requirement was ≥2 years overdue?

Note: All scenarios assume no rescreening within 4 years of a negative routine HPV test, consistent with reimbursement restrictions (11). See also Supplementary Figs. S1 and S2.

[a]Utilized by all women.

[b]Assumes participation as per renewed NCSP + 15%/50%/80% women who would not otherwise attend for screening do attend due to self-collection (compatible with existing restrictions to be 2+ years overdue). Initiation boosted from age 30 as shown in Supplementary Data S1; Supplementary Fig. S1.

[c]Assumes participation as per renewed NCSP + an additional 15%/50%/80% women who would not otherwise attend for screening access self-collection from age 30 years (no additional restrictions to be 2+ years overdue). Initiation boosted from age 30 as shown in Supplementary Data S1; Supplementary Fig. S1.

[d]Assumes women who would otherwise initiate screening at ages 25 to 29 years instead initiate at age 30 years; no change to initiation assumptions after age 30 years.

[e]Assumes women who would otherwise attend for screening <7 years after their last routine test instead attend at 7 years; no change to other reattendance assumptions.

[f]Assumes women who would otherwise initiate screening at ages 25 to 26 years instead initiate at age 27 years; no change to initiation assumptions after age 27 years.

Table 3. Outcomes to age 84 years in a cohort of females under different restrictions on self-collection (per 100,000 at age 12 years) compared with 5-yearly primary HPV screening starting at 25 years.

				Each additional cancer case prevented requires[a]:		
	Cancer diagnoses averted	Deaths averted	LYS gained	Women screened	Colposcopies	Women treated for CIN
Renewed NCSP with increased participation due to self-collection:						
Unvaccinated cohorts[b]						
S1: 15% at 7+ years	4 (1.1%)	2 (2.7%)	22 (<0.001%)	2,211	Fewer colposcopies	29.0
S2: 15% at 5+ years	6 (1.4%)	2 (3.0%)	30 (<0.001%)	2,674	Fewer colposcopies	23.1
S3: 50% at 7+ years	41 (10.3%)	10 (17.1%)	301 (0.004%)	1,408	13	8.3
S4: 50% at 5+ years	46 (11.7%)	10 (18.5%)	328 (0.005%)	1,762	25	8.1
S5: 80% at 7+ years	69 (17.6%)	16 (28.3%)	504 (0.007%)	1,461	32	7.5
S6: 80% at 5+ years	80 (20.2%)	17 (31.2%)	552 (0.008%)	1,860	43	7.4
Routinely vaccinated cohorts[c]						
S1: 15% at 7+ years	−1 (−1.0%)	>−0.5 (−0.6%)	−18 (<0.001%)	—	—	—
S2: 15% at 5+ years	−1 (−0.7%)	>−0.5 (−0.2%)	−16 (<0.001%)	—	—	—
S3: 50% at 7+ years	9 (6.2%)	2 (11.0%)	57 (<0.001%)	6,486	Fewer colposcopies	18.1
S4: 50% at 5+ years	10 (7.5%)	2 (12.4%)	67 (<0.001%)	7,645	Fewer colposcopies	17.1
S5: 80% at 7+ years	17 (12.1%)	4 (20.3%)	114 (0.002%)	5,908	17	14.5
S6: 80% at 5+ years	20 (14.4%)	5 (23.0%)	130 (0.002%)	7,231	39	14.2
Self-collection with:						
Unvaccinated cohorts[b]						
S7: existing restrictions[d]	−129 (−32.7%)	−20 (−35.9%)	−1,050 (−0.015%)	Reference	Reference	Reference
S8: no restrictions[e]	−16 (−4.0%)	−3 (−5.5%)	−144 (−0.002%)	2,745	194	19.1
S9: only restriction age 30+[f]	−63 (−15.8%)	−8 (−14.5%)	−714 (−0.01%)	3,081	102	6.6
S10: only restriction ≥2 years overdue[g]	−100 (−25.3%)	−16 (−28.5%)	−665 (−0.01%)	1,861	244	30.7
Routinely vaccinated cohorts[c]						
S7: existing restrictions[d]	−28 (−20.2%)	−4 (−21.4%)	−286 (−0.004%)	Reference	Reference	Reference
S8: no restrictions[e]	−7 (−4.8%)	−1 (−6.9%)	−62 (−0.001%)	11,948	356	46.9
S9: only restriction age 30+[f]	−15 (−10.5%)	−2 (−11.0%)	−183 (−0.003%)	12,417	181	15.1
S10: only restriction ≥2 years overdue[g]	−25 (−17.6%)	−4 (−19.0%)	−208 (−0.003%)	10,066	637	110.2

Note: Scenarios S1–S10 as described in **Table 2**. All scenarios assume accuracy of all HPV tests is as per self-collected samples. Cancer diagnoses and deaths with an absolute value >0.5 and women screened and colposcopies are rounded to whole numbers.

Abbreviation: LYS, life-years saved.

[a]Number of women needing to be screened (once or more), to undergo colposcopy, or to be treated for cervical lesions (once or more) to avert each cancer case compared with self-collection as per current restrictions.

[b]Predicted outcomes in the absence of vaccination (approximating females in Australia now aged 40–74 years).

[c]Cohort offered HPV4 vaccination in 2018 at age 12 years; vaccine uptake 82.4% in females and 75.5% in males (approximating females in Australia now aged 15–27 years).

[d]Assumes no screening before age 30 years or earlier than 7 years after last routine test; other participation assumptions same as renewed NCSP.

[e]Assumes same participation as in renewed NCSP.

[f]Assumes first self-collection test restricted to age 30+, but no additional restrictions on accessing self-collection.

[g]Assumes all women accessing self-collection must be at least 2 years overdue, but no additional restriction on start age (i.e., first test can be accessed at age 27 years).

the extension of the screening interval from at least 5 to at least 7 years (**Fig. 2**). If self-collection was offered without restrictions (i.e., assuming "worst case" different HPV test characteristics, but the same participation patterns as the mainstream NCSP), the loss of effectiveness would be 4.0% to 6.9%, considering both unvaccinated and routinely vaccinated cohorts (**Table 3**). In routinely vaccinated cohorts, the delay in the start age played a relatively smaller role than it did in unvaccinated cohorts, and the impact on cancer cases and deaths of the delay between starting at age 30 versus age 27 years was smaller than or comparable with the impact of using a self-collected test. The impact of the delay in the start age also had a relatively larger impact on effectiveness measured in terms of life-years than it did on effectiveness measured in terms of cancer cases/deaths.

Discussion

Our analysis found that the benefits of increased screening participation by offering self-collection to all women generally outweighed the impact of a potential worst case 2% loss in relative test sensitivity, even if all women elected to be screened with self-collection. An exception was a potential marginal loss in effectiveness in routinely vaccinated cohorts if only 15% of women who would otherwise be under/never-screened were screened as a result of self-collection being available, and all tests were carried out on self-collected samples. We also found that the current self-collection screening pathway within the renewed NCSP is less effective than being screened according to the mainstream pathway based on clinician-collected samples, but that the loss in effectiveness is mostly because of the enforced extended interval of ≥7 years between screens (and to a lesser extent the increase in the start age to 30 years, although this effect is relatively small in cohorts offered HPV4 in Australia). If self-collection were available with no additional restrictions compared with the mainstream NCSP pathway, the increase in cervical cancer incidence and mortality would be much smaller (4%–7%), assuming a worst case (2%) loss in relative test sensitivity (and more likely there would be no increase at all, if test performance is equivalent, as suggested by the updated meta-analysis;

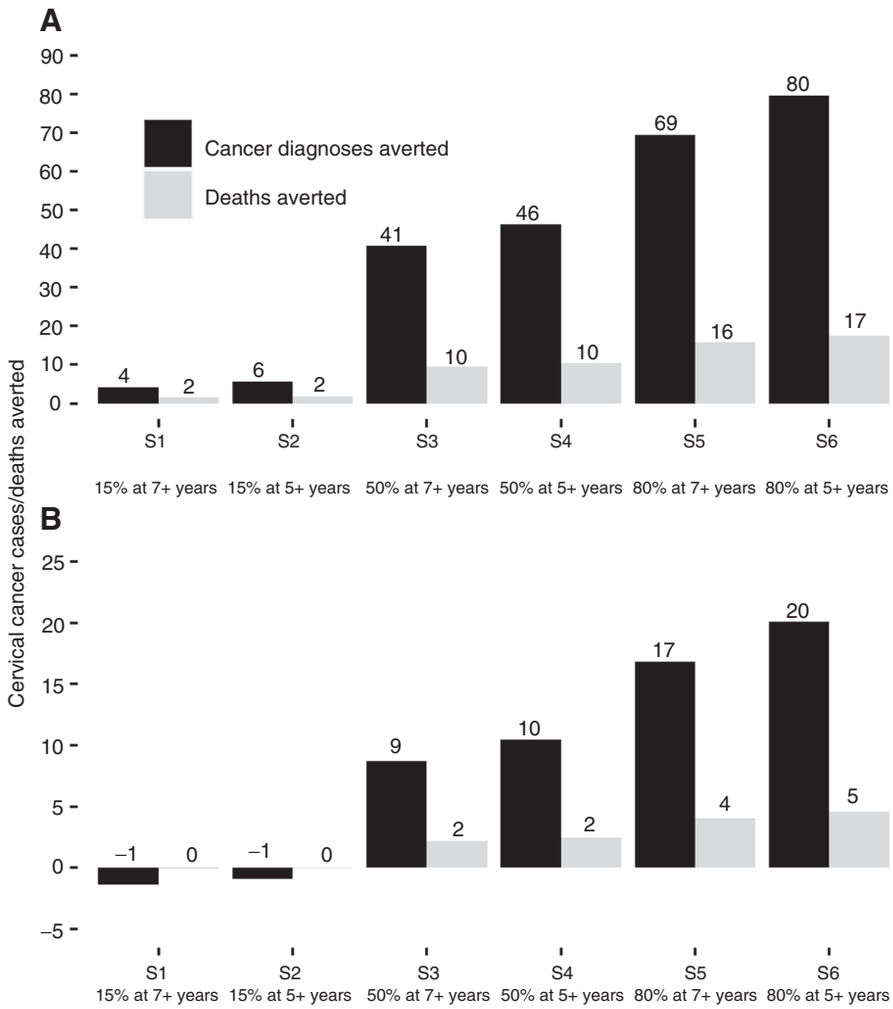

Figure 1.

Cervical cancer cases and deaths averted compared with the mainstream NCSP (5-yearly primary HPV screening starting at 25) in unvaccinated cohorts (**A**) and routinely vaccinated cohorts (**B**), with varying levels of screening participation due to self-collection among women who would not have otherwise attended. Scenarios 1 to 6 as described in **Table 2**. Outcomes are to age 84 years in a cohort of 100,000 females aged 12 years in 2018 (born 2006). Results in unvaccinated cohorts represent outcomes in a cohort in the absence of HPV vaccination (approximating females in Australia now aged 40–74 years). Routinely vaccinated cohort results are for a cohort offered HPV4 vaccination in 2018 when aged 12 years; vaccine uptake 82.4% in females and 75.5% in males (approximating females in Australia now aged 15–27 years).

ref. 9). The impact of the increased start age was smaller in routinely vaccinated cohorts than in unvaccinated cohorts, but somewhat greater on life-years compared with cancer incidence and mortality. This is understandable as the main adverse effect of increasing the start age would be to increase cancer diagnoses in younger women, which would be associated with a greater loss in life-years than cancers that occur in older women. Vaccination would be expected to substantially reduce cancers in younger women in routinely vaccinated cohorts, as cancers in young women are very strongly related to HPV16/18, so the starting age is less critical in these women than in unvaccinated cohorts. Australian data indicate that 86.1% of cervical cancers in women aged 20 to 39 years in Australia are related to HPV16/18 compared with 71.7% across all ages (29). Our findings that a later starting age and extended screening interval have less impact in absolute terms on routinely vaccinated cohorts compared with unvaccinated cohorts are consistent with other modeling studies that have found only marginal differences in cancer prevention between 5-, 7-, and 10-yearly screening in women vaccinated with HPV4 (23). This also suggests the delayed start age may be less critical in Australia, as it only affects women aged younger than 30, and in Australia, women currently aged less than 30 years were offered vaccination as teenagers, so they largely fit into the "routinely vaccinated cohorts" category. However, the delayed starting age is potentially more critical in settings where women aged 25 to 29 years are mostly unvaccinated. It could also be important for women who migrate to Australia in their early 20s from a setting without widespread HPV vaccination, as they would no longer be eligible for HPV vaccination in Australia, and also less likely to have benefitted from herd effects in their home country.

The strengths of this study include that we used a well-established and validated model of HPV natural history and cervical screening. Detailed screening management was modeled on the basis of clinical management guidelines and expert opinion. As this was an exploratory analysis, the first component of our analysis did not assume different attendance for follow-up tests or colposcopy among underscreened women who participated in screening as a result of being offered self-collection. It is possible that underscreened women may be less likely to attend for colposcopy or follow-up tests; however, our assumptions about attending for colposcopy and follow-up are based on data from a state-wide register encompassing both regularly screened and underscreened women. In addition, a recent meta-analysis of self-collection studies reported relatively high attendance (82%) for follow-up tests in women where this was recommended, although this was variable (4). Two studies of self-collection in Australia have also reported relatively high attendance rates for follow-up testing (25, 30).

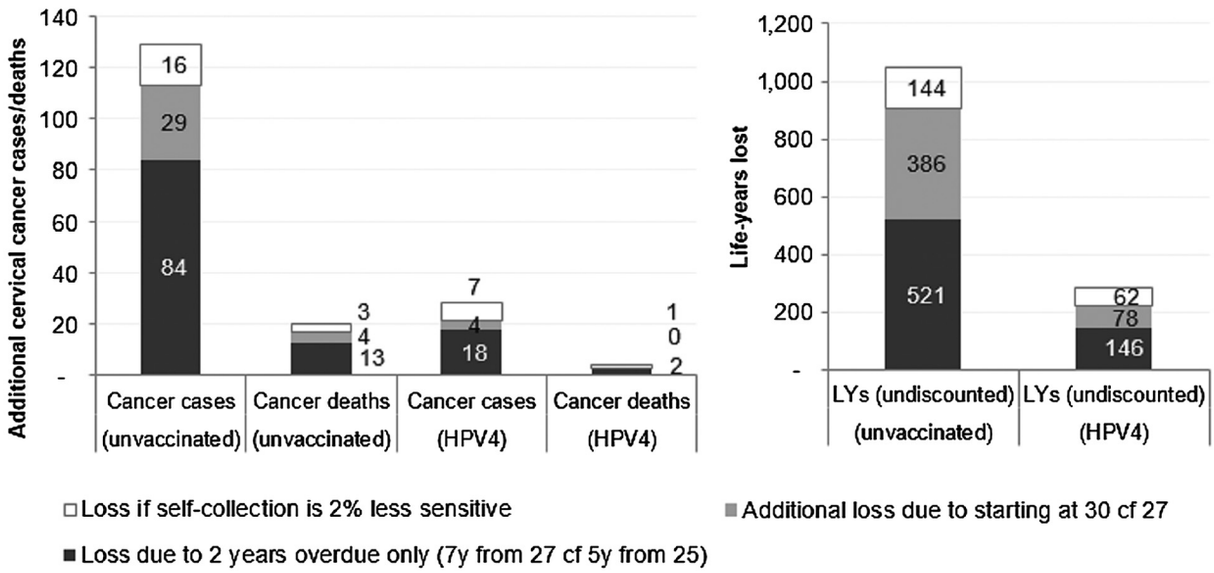

Figure 2.

Components of loss of effectiveness in self-collection with restrictions as in Australia, compared with the mainstream program (5-yearly primary HPV screening from age 25 years), assuming self-collection has a relative sensitivity of 0.98, compared with HPV tests on clinician-collected samples. 7y, 7-yearly; 5y, 5-yearly; HPV4, outcomes in a routinely vaccinated cohort offered quadrivalent vaccination in 2018 when aged 12 years; vaccine uptake 82.4% in females and 75.5% in males on the basis of observed data (approximating females in Australia now aged 15–27 years); LY, life-years; unvaccinated, outcomes in a cohort in the absence of HPV vaccination (approximating females in Australia now aged 40–74 years).

To reflect uncertainty in uptake, we explored a very wide range of possible effects on participation, grounded in local data and an international meta-analysis (9, 25–27). The studies that were clinic-based (most consistent with the delivery model in Australia, which requires the woman to have support from a cervical screening provider) had the highest uptake (∼80%), however, they also included community engagement (26, 27). Clinician-supervised delivery of self-collection could be a limitation on uptake, although this model does not preclude flexible delivery, for example via tele-health or outreach at home, as long as the screening is organized by a screening provider. These two pilots in different populations provide important insight into how success could be achieved. Another potential limitation of our study is that our population-level results assume that differences in cancer risk are driven by screening behavior and not, for example, by the possibility that women who are under- or never-screened may have a higher background risk than other women (this might occur, e.g., if nonattendance for screening was correlated with other risk factors, such as sexual behavior or tobacco use). This likely means that our population-level findings are conservative, as earlier modeling studies have found that if women who attend as a result of self-collection are at a higher background risk, the overall effectiveness of offering self-collection is greater, and the overall effectiveness of the screening program would be maintained even with a higher proportion of women switching from clinician-collected to self-collected samples (31). Other assumptions that we made were also conservative and potentially underestimate the incremental benefits of offering self-collection, including an extreme assumption that all women would switch to self-collection (a conservative estimate for test sensitivity), and relatively high baseline screening participation (based on invitations and reminders for HPV screening starting at age 25 years) that left relatively little room for improvement. Even in the context of these assumptions that were generally unfavorable toward self-collection, we found that benefits from increased participation generally outweighed a potential small loss in test sensitivity. We also assumed in our analysis that the HPV tests used would be PCR based and meet other requirements for tests used on self-collected samples in Australia, including having a cellularity control to detect empty or inadequate samples, and that they are commercially supplied tests meeting an internationally recognized guideline for test performance (24, 32). Currently, no commercial mRNA tests meet these requirements, and a meta-analysis reported lower sensitivity for an amplification-based mRNA test on self-collected compared with clinician-collected samples (9). Therefore, our findings may not apply in settings without these mandatory requirements on tests used on self-collected samples, or in the context of current commercial mRNA tests, although given the clear implications on test performance of using non-PCR–based tests or being unable to distinguish between a sample that is HPV negative versus one that is empty, these requirements would likely apply in many settings with existing organized programs.

The second component of our analysis was intended as an exploration of the impact of the various current restrictions on self-collection and potential differences in test performance on the effectiveness of the self-collection pathway as offered in the NCSP. Consequently, other parameters were varied only minimally in each hypothetical scenario, for example, when the interval was restricted to be no shorter than 7 years, we set participation at 7 years or later to be the same as that under the mainstream NCSP at those timepoints. Therefore, our results for these scenarios cannot be directly interpreted as the likely effectiveness of self-collection, specifically in the subgroup of women who are currently under- or never-screened (we have estimated the benefits and harms of self-collection in never-screened women in a prior analysis; ref. 12).

There is a range of reasons why women do not attend for regular screening, but in some cases the barriers relate to fear, embarrassment, pain, past trauma, or a previous negative experience with screening (rather than logistical or health literacy reasons; ref. 33). In the Victorian pilot of self-collection in underscreened women, 27% of women who agreed to screening with self-collection reported that they would not complete a speculum exam in the future (26), therefore, it is unlikely that all women who agree to be screened using self-collection would thereafter transition to the mainstream NCSP pathway. This is consistent with results from an Italian trial offering self-collection, where offering self-collection increased participation in the round when it was offered, but had no effect on whether women were screened in the subsequent screening round (when only clinician-collected samples were offered; ref. 34). Therefore, while it is likely that self-collection could be expected to increase screening participation in Australia, it will not necessarily increase screening at 5-yearly intervals unless self-collection can be accessed at that frequency. Our results show that the longer interval of 7 or more years is what drives the loss of effectiveness in the self-collection pathway, and not any possible difference in test accuracy, which has a comparatively small effect (and likely no effect at all). To increase the benefits of self-collection, consideration could be given to allowing initially underscreened women to access self-collection at 5-yearly intervals. Our exploratory analysis suggested that if this was possible, and led to a 50% uptake of self-collection by women who would not otherwise have attended, this would improve population-level effectiveness of the program, even in an extreme scenario where all women were to switch to self-collected samples. This level of switching is unlikely in practice, at least in the short term, as previous studies have found that regularly screened women are less accepting of self-collection than those who are never- or underscreened (35). Some women's reservations about self-collection relate to a lack of confidence that they will do it correctly, but this is addressable by appropriate instruction and support, and women who have undertaken self-collection, overwhelmingly report that it is easy (26, 27, 36–39). We also consider it unlikely that a country with a well-established program based on clinician-collected samples would remove the choice from women to continue to have a clinician-collected sample, if this was their preference. Currently, Australia's self-collection policy is under review, and exploring the possibility of giving women the choice of screening on either a self-collected or clinician-collected sample (40). A shorter waiting time to access self-collection is consistent with practice in the Netherlands, where women are able to request this four months after they receive their screening invitation (8). Analysis of data from the renewed NCSP and from the Netherlands could give some insight into whether women who were previously regular screeners appear to be delaying screening to access self-collection. Initial data from 2017 to 2018 suggest that widespread switching has not occurred in the Netherlands, as just 7% to 8% of all HPV tests in the Netherlands were performed on a self-collected sample (41).

Evidence supporting equivalent performance of PCR-based HPV tests on self-collected and clinician-collected samples suggests a new model of care may eventually be appropriate, and is likely to be highly acceptable to both women and providers, whereby all women could be offered self-collection as their initial screen and only HPV-positive women require a speculum examination and clinician collection. This model of care would be particularly useful in the context of COVID-19 restrictions or disruptions to screening attendance, as self-collection could provide opportunities for cervical screening without the need for a clinic visit (e.g., via tele-health), enabling screening to continue while also maintaining social distancing. Offering all women the choice between self-collection and clinician collection would potentially facilitate uptake of self-collection in underscreened women, as this would remove many of the existing barriers in Australia. It would remove the need for providers to confirm eligibility, which is currently difficult to do at the point of care because of delays in providers and women being able to access screening history on the National Cancer Screening Register. Restrictions on eligibility also limit the ability of campaigns and clinics to openly promote self-collection. Unanticipated regulatory hurdles have also meant that currently there are relatively few laboratories that are accredited to process self-collected samples, and for laboratories that cannot yet process samples, there are commercial disincentives to promoting self-collection or facilitating transfer of samples to laboratories that can. There are also limited incentives for laboratories to achieve accreditation while self-collection is a restricted test with lower volumes. Restricting access to self-collection has also led some providers in Australia to believe it is a less reliable test, particularly where it was less readily available from a local laboratory (42), whereas offering the test as an equal choice in routine care would normalize the test. A survey in the first year after the transition to the renewed NCSP found many providers in Australia were not yet confident in offering self-collection nor in their understanding or ability to explain eligibility criteria, but confidence was greater and improved over time in the one state where self-collection was available from the major pathology provider and so was more normalized (42). As a result of these many existing barriers, to date, there has been very limited uptake in Australia, with an estimated fewer than 1% of eligible women having a screening test on a self-collected sample (43), suggesting current restrictions are hindering achievement of the original aim that self-collection increase participation.

Further work is required to examine whether offering self-collection to all women may have unintended consequences and possible flow-on effects, for example, if there is a loss to follow-up for the triage test. Adherence to follow-up in studies of self-collection conducted in underscreened women cannot be directly extrapolated to self-collection in the general community, as it likely reflects difficulties in progressing through the management pathway related to the underscreened group, rather than flowing from the provision of self-collection *per se*. Accurate and efficient triage tests that could be performed on a self-collected sample would facilitate wider offering of self-collection (as some existing or potential triage tests for women who screen HPV positive, such as cytology or dual-stained cytology, cannot be performed optimally on a self-collected sample as cells have not been sampled from the cervical transformation zone). These triage tests could include extended genotyping, as recent research indicates that knowledge of HPV type and how long it has persisted are more informative than cytology, once HPV screening programs are established (44). It could also include methylation markers, which are the subject of many studies, although more insight is needed into the optimal markers, and validated commercial tests suitable for use in population screening programs would be required. Research should be prioritized into identifying better triage tests that can be used in the context of more widespread use of self-collected samples (in both the immediate and longer term), and how they can be successfully implemented. A further focus of future research is to consider how providers would implement a universal offer of self-collection, what supporting information they and women would need, impacts on health care use and costs, and whether other points on the screening pathway could incorporate self-collection (e.g., in posttreatment management, where we assumed a cotest was maintained, as per current guidelines). In addition, there is currently limited evidence on the

capacity of HPV testing on self-collected samples to prevent adenocarcinoma (although this was also a limitation of cytology) and its long-term negative predictive value, due to the smaller number of women screened with this method with long-term follow-up, compared with HPV testing on clinician-collected samples. There is no reason to think PCR-based HPV testing would perform worse on self-collected than on clinician-collected samples, as in both cases, the test detects shedding viral nucleic acid (45), however, these are evidence gaps to be addressed.

In conclusion, self-collection has the potential to reach many women who are currently under- or never-screened (26) and could, therefore, play an important role not only in reducing cervical cancer risk in these women (12), but also in reducing population disparities. While being screened under the current self-collection screening pathway in Australia is predicted to be less effective than the mainstream pathway using clinician-collected samples, this is strongly related to the existing restrictions, especially that which imposes a longer screening interval, rather than any potential loss of test sensitivity. Even if, in the worst-case scenario, there was a small loss in test sensitivity due to self-collection, this would likely be outweighed by improved program effectiveness from feasible levels of increased uptake resulting from offering self-collection to all women. A universal option of self-collection would likely also address the current difficulties for providers in ascertaining whether or not women are eligible for self-collection and in offering it to underscreened women, however, they are likely to need additional support to build confidence in such a change.

Authors' Disclosures

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Disclaimer

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Authors' Contributions

M.A. Smith: Conceptualization, software, formal analysis, supervision, funding acquisition, methodology, writing–original draft. **M.T. Hall:** Software, formal analysis, writing–review and editing. **M. Saville:** Conceptualization, funding acquisition, writing–review and editing. **J.M.L. Brotherton:** Conceptualization, funding acquisition, writing–review and editing. **K.T. Simms:** Conceptualization, software, writing–review and editing. **J.-B. Lew:** Conceptualization, software, writing–review and editing. **D. Bateson:** Conceptualization, writing–review and editing. **S.R. Skinner:** Conceptualization, writing–review and editing. **M. Kelaher:** Funding acquisition, writing–review and editing. **K. Canfell:** Conceptualization, software, funding acquisition, writing–review and editing.

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