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Appendix

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Appendix to: Smith M, Lew JB, Simms K, Canfell K. Impact of HPV sample self-collection for underscreened women in the renewed National Cervical Screening Program. *Med J Aust* 2016; 204: 194. doi: 10.5694/mja15.00912.

Appendix to the article: "*Predicted impact of self-sample HPV testing for underscreened women integrated into a primary HPV screening program in Australia*".

1 Overview of model and parameters varied in sensitivity analysis

The model used in this study has been extensively described in the published report to the Medical Services Advisory Committee (MSAC): "*National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting. MSAC application number 1276 assessment report*" (1). This report is available for download from:

http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1276-public

Information relating to parameters specific to this analysis or model parameters considered in sensitivity analyses are below.

Table 1 Summary of model parameters considered in sensitivity analyses

Parameter	Baseline	Feasible range/ alternative	Reference
Relative accuracy of HPV testing on self-collected samples vs clinician-collected samples	See Table 2	Worst vs best case - see Table 2, section 2.1	(2)
Type of HPV test used on self-collected samples	Broad-spectrum clinical test for any oncogenic type (no partial genotyping)	Clinical test with separate results for HPV 16, 18 and grouped result for other oncogenic types (partial genotyping)	(3)
Accuracy of HPV testing on clinician-collected samples	See Table 3	Worst vs best case - see Table 3, section 2.2	(1, 4)
LBC test accuracy	See Table 4	Worst vs best case - see Table 4, section 2.3	(1, 5)
Colposcopy	See Table 5	Lower positivity vs higher positivity - see Table 5, section 2.4	(1)
Management of women whose self-sample HPV test is negative for HPV16/18 but positive for another oncogenic HPV type and whose LBC triage result is LSIL (possible or definite)	12-month follow-up	Refer for colposcopy	(1, 6)
Compliance with recommended follow-up tests	Perfect (ie women who elected to be screened would complete all recommended tests until they were recommended to return to routine screening (one-lifetime screen scenarios) or until they were discharged from the screening program (join mainstream program scenarios)	Imperfect Compliance with colposcopy: see Table 6, section 3.1 Compliance with recommended surveillance visits – see section 3.2 Compliance re-screening at five years (join program scenarios only): see section 3.3	(1)

Model-predicted outputs have been extensively calibrated and validated against several sources of data including observed reductions in HPV16 in young women soon after the commencement of HPV vaccination (7); age-specific cancer incidence in unscreened populations; age-specific and age-standardised cancer incidence and mortality in Australia; age-specific and age-standardised rates of histologically-confirmed low-grade and high-grade lesions; HPV type distribution within diagnosed cancers, and within histologically-confirmed high-grade abnormalities by age; case numbers for cervical cancer, cervical cancer death, low-grade and high-grade histological abnormalities; cytology test yield and correlation with histological outcome; and numbers of cytology tests, colposcopies and biopsies (1)

2 Characteristics of screening and diagnostic tests

2.1 HPV testing on self-collected samples

Table 2 Modelled sensitivity and specificity for CIN 2+ and CIN 3+ detection of HPV testing on a self-collected sample, relative to a clinician-collected cervical sample

Relative test performance	Disease threshold	
	CIN 2+	CIN 3+
Base case (feasible range)		
Sensitivity	88%	89%
Specificity	96%	96%
Worst case		
Sensitivity	85%	83%
Specificity	94%	94%
Best case		
Sensitivity	91%	96%
Specificity	98%	98%
Data observed (95% CI)†		
Sensitivity	88% (85 – 91%)	89% (83 – 96%)
Specificity	96% (95 – 97%)	96% (93 – 99%)

† Data obtained from a meta-analysis (2).

2.2 HPV testing on clinician-collected samples

Table 3 Modelled sensitivity and specificity for CIN 2+ and CIN 3+ detection of HPV testing on a clinician-collected cervical sample for different clinical applications

Test performance	Primary screening test		Follow-up test of treatment of high-grade CIN	
	CIN 2+	CIN 3+	CIN 2+	CIN 3+
Base case				
Sensitivity	96.4%	98.4%	93.2%	94.0%
Specificity	90.1%	89.6%	80.8%	80.1%
Worst case				
Sensitivity	94.6%	97.0%	85.5%	87.0%
Specificity	88.6%	88.1%	74.1%	73.6%
Best case				
Sensitivity	98.1%	99.0%	97.4%	98.0%
Specificity	93.3%	92.7%	85.6%	84.8%
Data observed (95% CI)†				
Sensitivity	96.0% (95.0-98.0)	98.0% (97.0-99.0)	93.0% (85-97)	N/A††
Specificity	91.0% (90.0-93.0)	N/A††	81.0% (74.0-86.0)	N/A††

† Data obtained from a meta-analysis (4). †† Data not available in the meta-analysis

2.3 Liquid-based cytology

Table 4 Modelled sensitivity and specificity of manually-read LBC for detection of CIN 2+ and CIN 3+ in women aged 20-69 years

Cytology test threshold	CIN 2+		CIN 3+	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Base case	-	-	-	-
pLSIL	77.0	94.7	83.9	94.3
dLSIL	73.8	97.0	80.0	96.6
pHSIL	46.2	99.1	52.0	98.9
Worst case	-	-	-	-
pLSIL	72.2	92.2	79.2	91.9
dLSIL	68.4	95.9	74.2	95.5
pHSIL	42.6	98.2	48.1	98.0
Best case	-	-	-	-
pLSIL	80.7	95.3	86.0	94.9
dLSIL	78.5	97.6	83.0	97.1
pHSIL	50.8	99.7	55.0	99.4

Informed by international meta-analysis data for the relative performance of conventional and manually-read LBC for primary screening (5) and fitted characteristics of conventional cytology in Australia (1). Consistent with data from meta-analyses, specificity results are reported above for the use of LBC as a primary test. As specificity for CIN2+ and CIN3+ depends on underlying disease prevalence, the absolute specificity of LBC would be expected to be different when it was used for triage within a HPV test positive population.

2.4 Colposcopy

A test probability matrix for colposcopy was derived specifying the relationship between each possible underlying natural history health state at the time of testing and the probability of colposcopy result being abnormal/ a biopsy being taken. The baseline estimates were obtained from a large colposcopy dataset (over 21,000 colposcopies) supplied by the Royal Women's Hospital in Victoria (8, 9). An alternative set of test accuracy assumptions with higher rate of having abnormal result at colposcopy evaluation were derived based on the findings of the HPV Sentinel sites study in the UK (10) for sensitivity analysis (Table 5). Another set of test accuracy assumptions assuming colposcopy test positive rate is 10% lower than the base case assumption was also investigated.

Table 5 Modelled test characteristics of colposcopy

Women underlying health state	Probability of having abnormal result/ biopsy taken at colposcopy	
	Base case (%)	Range for sensitivity analysis (%)
Normal	50.2	45.2 - 73.8
HPV	50.2	45.2 - 73.8
CIN1	76.5	68.9 - 79.2
CIN 2+	88.4	79.6 - 90.8

3 Compliance with recommended follow-up tests

3.1 Colposcopy referral

The modelled compliance rate with colposcopy referral was informed by data provided by the Victorian Cytology Service and by the Royal Women's Hospital in Victoria (8, 9). The assumed compliance took into account the age and referring cytology result. We assumed that in scenarios where women are referred to colposcopy with no referral cytology but with a HPV 16/18 positive HPV test result, the compliance with colposcopy is mid-way between the compliance observed in women with a low-grade cytology and women with a high-grade cytology. The colposcopy compliance rates are shown in Table 6.

Table 6 Colposcopy compliance rates

Age group (years)	Women referred with high-grade cytology result	Women referred with low-grade cytology result	Women referred with HPV16/18 positive result
15-29	0.96	0.82	0.89
30-39	0.96	0.86	0.91
40-49	0.95	0.88	0.91
50-59	0.88	0.89	0.89
60-69	0.89	0.92	0.91
70+	0.83	0.86	0.84

3.2 Return for surveillance

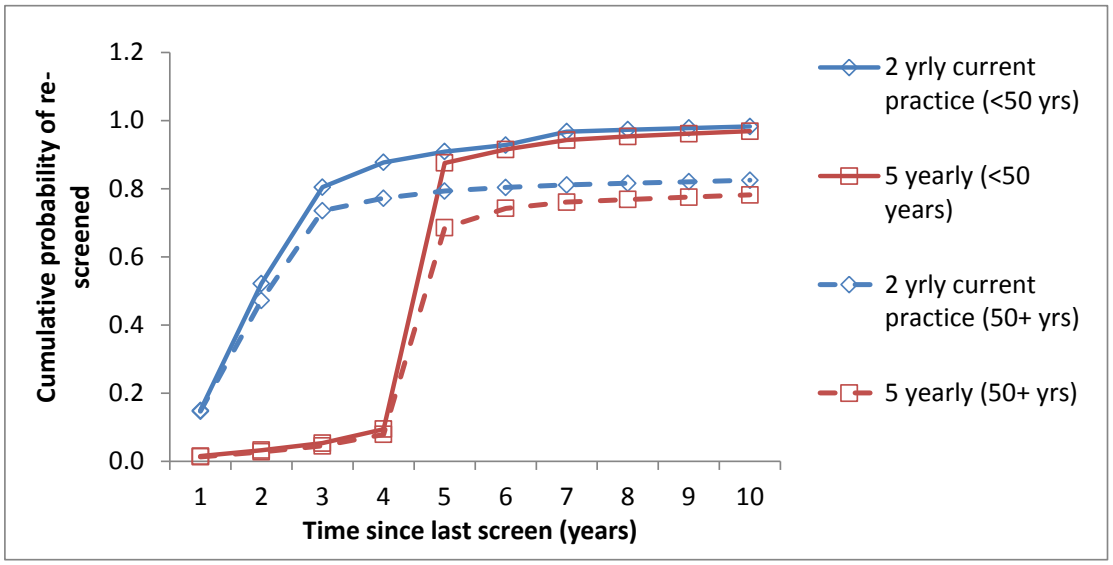
The model incorporated information on compliance with screening and management recommendations obtained via analysis of data from the Victorian Cervical Cytology Register (VCCR), which have previously been described in detail (11-13). Briefly, the probabilities of re-attending for a recommended test were calculated by using standard cohort analysis methods, taking account of

the person-time of follow-up and possible censoring, and stratified according to the index smear result, follow-up recommendation, and whether a woman had had a high-grade histology in the previous 5 years. For each index smear, we calculated the earliest of (i) the time to the next smear, (ii) time to death, (iii) 10 years of follow-up, or (iv) time to 31 December 2007. The follow-up was stratified by 3-monthly periods, with recalculation of age and period for each stratum of follow-up. We then aggregated the person-time and the number of events to calculate rates, and subsequently calculated the age- and interval-specific probabilities of rescreening for 10-year periods after each screening or follow-up investigation. Beyond these 10 year periods, we assumed that each year, among the remaining women who have still not attended any follow-up, 20 per cent of women aged 40-49 years, 10 per cent of women aged 50-59 years and 5 per cent of women aged 60 years or more will finally re-attend.

3.3 Return at the routine interval (join program scenarios only)

Compliance with routine recall (five years) assumed a call-recall system was in place. The behaviour of women under call-and-recall was based on data from England, where a call-recall system was in place. In particular, the proportion of early re-screening and overall participation rate over 5 years is informed by the screening behaviour pattern observed in England, and further adjusted to the current observed screening participation rate in Australia (see Creighton *et al* (2010) (12) for more details on the methods used to derive these probabilities). The re-screening probability curves are shown in Supplementary Figure 1. The observed probability that women recommended to return at two years under the current practice would re-attend is additionally shown, for context.

Supplementary Figure 1 - Cumulative probability that women will have re-attended for screening in the context of a recommendation to return in five years, compared to observed probability of re-attendance under current two-year recommendation in Australia



4 Additional results on number needed to treat

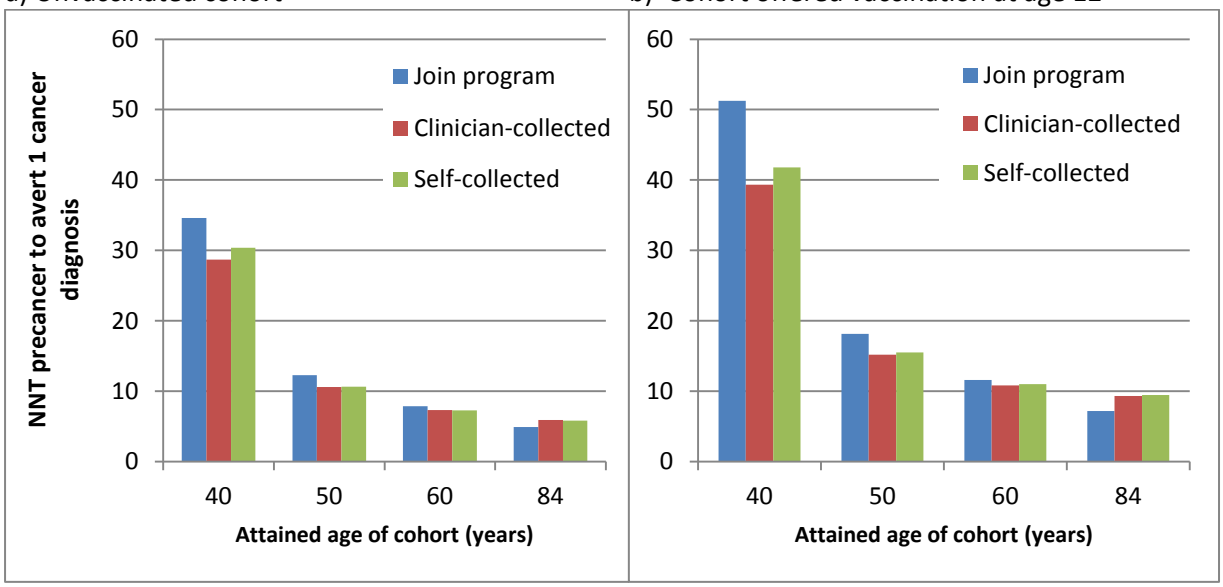
The NNT to avert each cancer case/ death changed over the horizon of time considered. If the time horizon considered was only for 10 years after the decision at age 30, joining the program was associated with the highest NNT to avert a cancer case or death (Supplementary Figure 2). However

as the cohort aged, and benefits continued to accrue more strongly for women who had joined the program, the differences in NNT for different screening decisions at age 30 reduced. By age 60, the differences were very small. Over a lifetime (to age 84), joining the program was associated with the lowest NNT.

Supplementary Figure 2 - Number of women needing to be treated for cervical precancer (NNT) to avert one cancer case and death for different screening decisions at age 30, by exposure to vaccination and attained age of the cohort

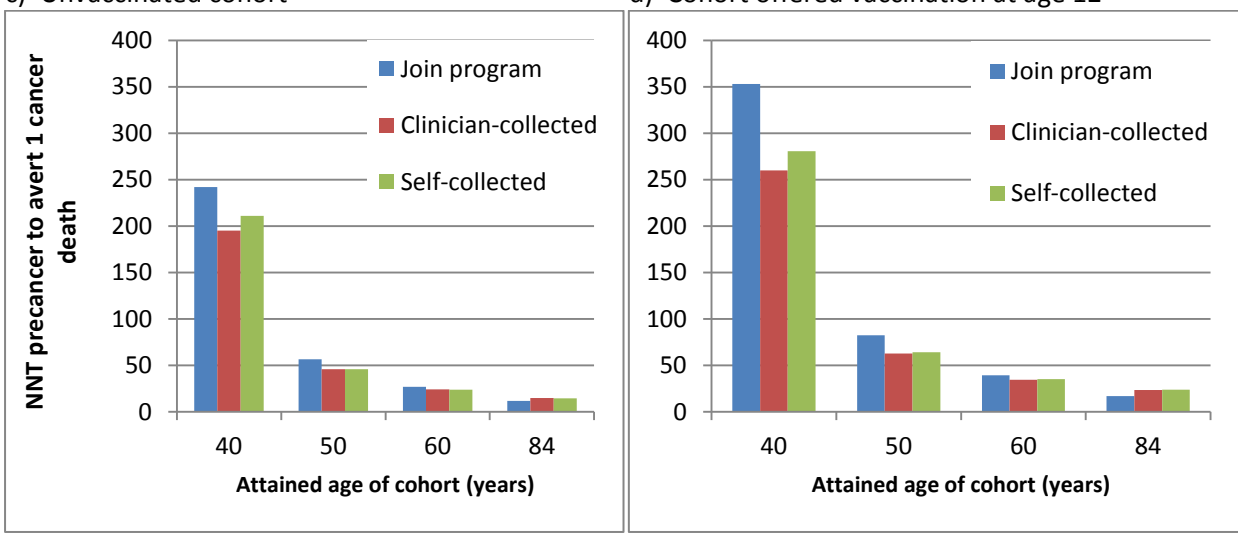
a) Unvaccinated cohort

b) Cohort offered vaccination at age 12



c) Unvaccinated cohort

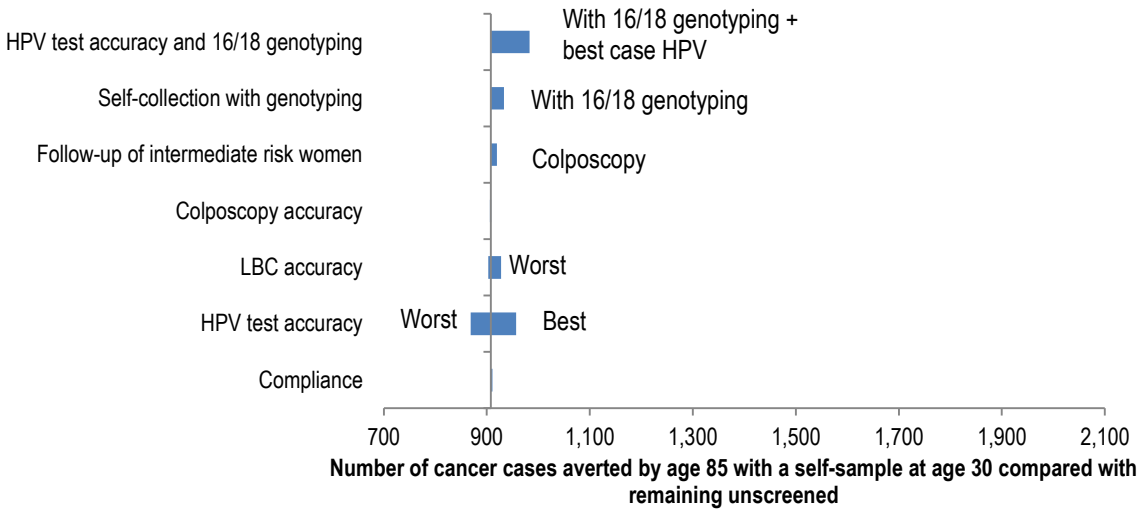
d) Cohort offered vaccination at age 12



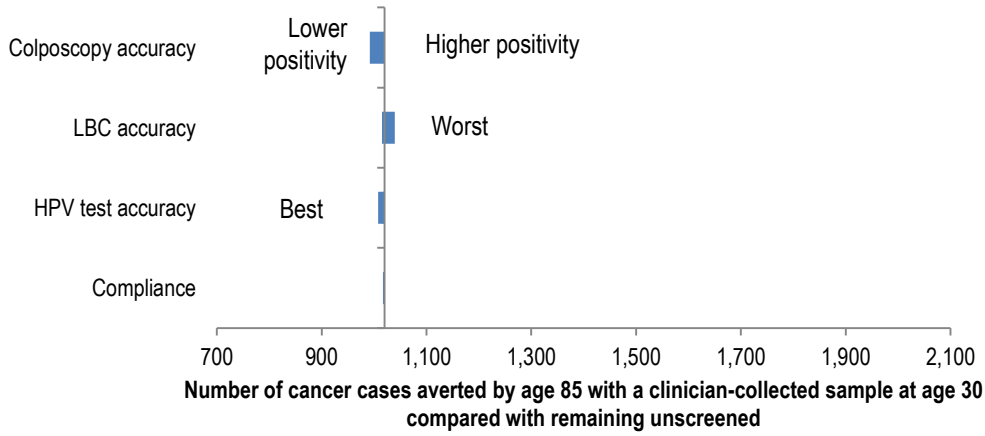
5 Findings of sensitivity analysis

Supplementary Figure 3 - Impact of varying model parameters on cancer cases averted by age 85

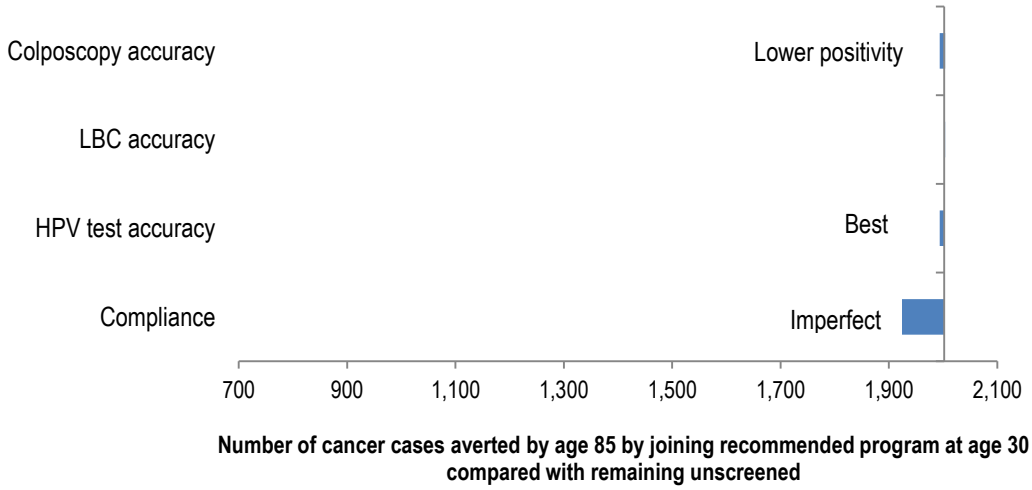
a) 1 x self-sample at age 30



b) 1 x clinician-collected sample at age 30



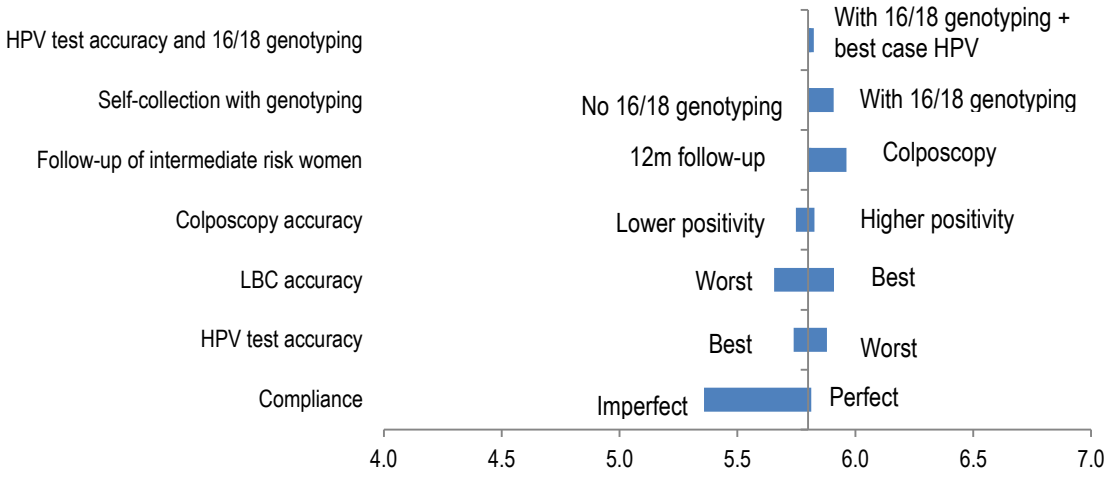
c) Join recommended program at age 30



Intermediate risk women: Those testing positive for HPV types other than 16/18 with triage cytology result of possible/ definite LSIL.

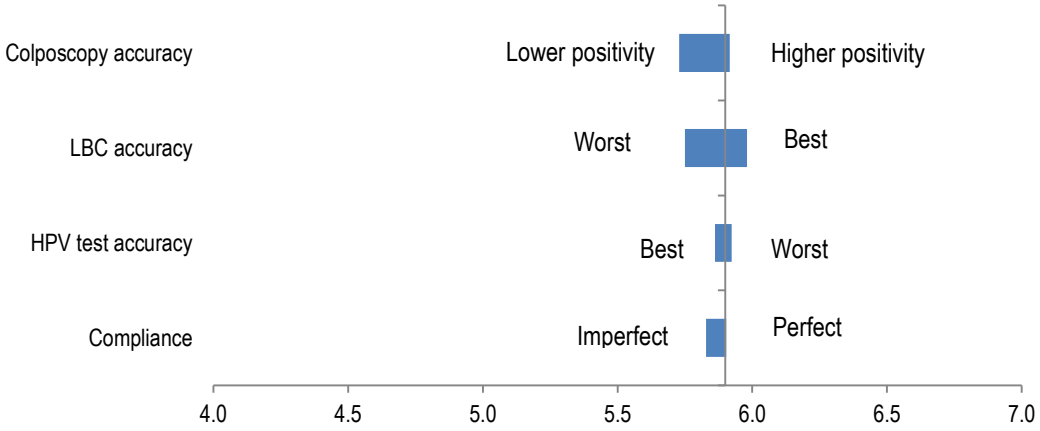
Supplementary Figure 4 - Impact of varying model parameters on number of women needed to treat for precancer to avert a cancer case by age 85

a) 1 x self-sample at age 30



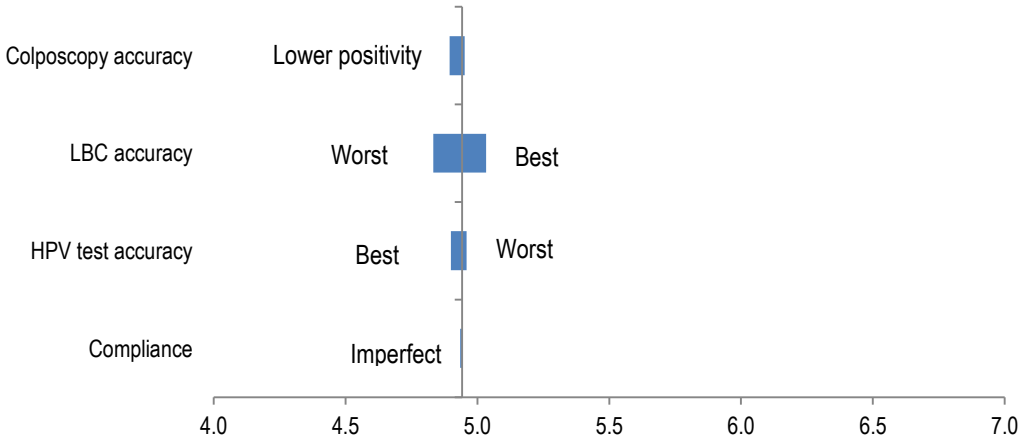
Number of women treated for precancer per cancer case averted by age 85 by a self-sample at age 30 compared with remaining unscreened

b) 1 x clinician-collected sample at age 30



Number of women treated for precancer per cancer case averted by age 85 by a physician-collected sample at age 30 compared with remaining unscreened

c) Join recommended program at age 30



Number of women treated for precancer per cancer case averted by age 85 by joining the recommended programat age 30 compared with remaining unscreened

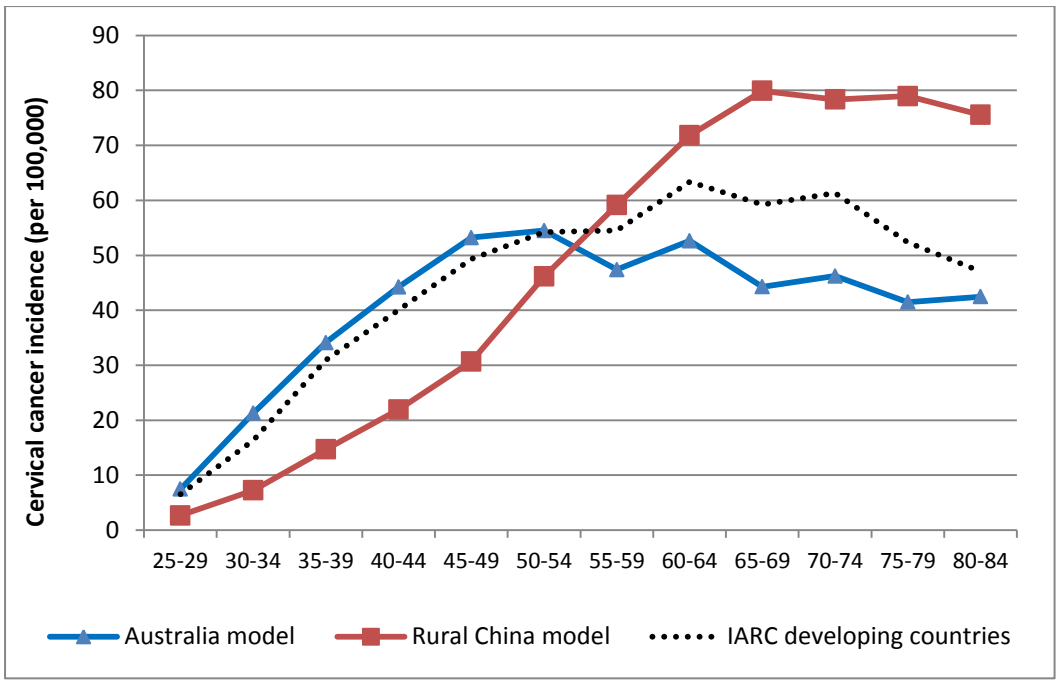
6 Discussion of sensitivity analyses findings

Some results of the sensitivity analysis were counterintuitive - for example, one-lifetime-screen scenarios averted more cancer cases when LBC was less accurate or re-attendance for follow-up tests was imperfect. These findings were driven by the fact that a less specific test and slower attendance at recommended follow-up visits in practice result in a woman remaining in contact with the screening program for a longer time period. This meant there was more opportunity to detect disease which may not have been present at the time of the initial screening test, but which developed later.

7 Discussion of findings for one-lifetime-screen strategies in relation to findings from other settings

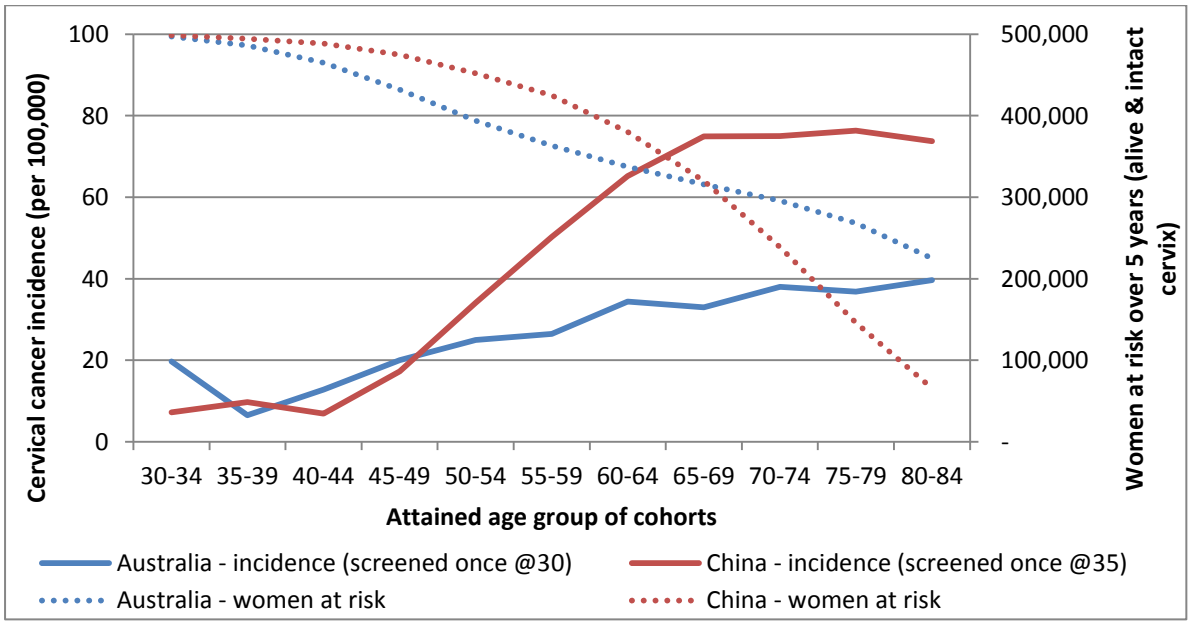
Trial data (14) and other modelling studies (15) support the strong benefits we found from even one lifetime screen; however an earlier modelled analysis we undertook in the context of one-lifetime-screen in rural China suggested a less pronounced reduction is cancer risk than we found here (16). This can be explained by differences in the ways that screening once was modelled, and in the target populations (Australia versus China). The main difference in screening was the perspective of the current analysis in considering the risk reduction in a women who attended for screening and all recommended follow-up visits, versus a population perspective in the modelled analysis for China (with only 71% participation in screening, and imperfect follow-up). Another difference was follow-up management of women following treatment for precancer, who are at high risk for disease recurrence. Australia recommends two rounds of co-testing with cytology and HPV tests, and that women test negative on both tests over two consecutive rounds before they are discharged to routine screening. In contrast, it was assumed that there would be limited follow-up available for treated women in the context of rural China. Some other important differences between women in Australia versus rural China which also drove the differences between the two settings (even in the context of best case assumptions about participation in rural China) included different patterns of age-specific cervical cancer incidence in the absence of screening and differences in the number of women at risk (due to differences in benign hysterectomy and life expectancy).

Supplementary Figure 3 – Age-specific cervical cancer incidence in the absence of cervical screening



In the absence of Australian data on age-specific cervical cancer incidence in unscreened women, the natural history model used (ie without screening) was fitted to incidence observed in other countries without screening from IARC's Cancer Incidence in Five Continents Volume VIII (17)

Supplementary Figure 5 – Cervical cancer incidence and number of women at risk over five-year age groups in a cohort of 100,000 women screened once



Women at risk excludes women who have had a benign hysterectomy or died from causes other than cervical cancer. Incidence rates are not hysterectomy-adjusted, in order to show effect on overall rates of women being alive but no longer at risk. Best case participation assumptions used for China.

8 References

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