An tSeirbhís Náisiúnta Scagthástála
National Screening Service

Estimates for efficacy and likely impact of Irish cancer screening programmes

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Overview

This document contains an independent scientific assessment of the expected benefits of three national population screening programmes (BowelScreen, BreastCheck, CervicalCheck), using international best estimates where available, with appropriate caveats and including critical background where appropriate. The document also explores visual and data-driven methods for conveying this information. The chief aims of this undertaking were as follows:

1. To use international data to model the progression of disease in societies without screening programmes v the progression where screening programmes operate.
2. To base findings, where possible, on data around the cancers for which we have screening programmes in Ireland (cervical, bowel, and breast).
3. To communicate the data in a simple format, eg table or flow diagram / graphic.
4. To show outcomes in a communicable way, whilst also noting the caveats that apply to the outcomes.

Note: This version also contains two additional appendices pertaining to technical aspects of the CervicalCheck screening programme; the first concerning how age profile and HPV vaccination status will likely affect interpretation of future results and the second considering the Irish framework of expedited re-testing of HPV positive results on programme efficacy. Where relevant, results from these analyses have been incorporated into the main text.

Contents

Introduction and report framing

The objective of screening is to identify individuals amongst the ostensibly well who are in fact suffering from disease, so that their condition can be treated before it advances. National and regional screening programmes follow the guidelines laid down by the WHO in 1968 [1], so that maximum efficacy and benefit can be derived. Screening has existed for various diseases for many decades, but organised programmes are a more recent development. The objective of this report is primarily to ascertain the expected impact of screening programmes, using most current international data and best evidence, and how this information might be communicated.

There are a number of caveats to the data presented here - firstly, many screening programmes predate modelling of their efficacy, and this means that in some instances, programmes were initiated before their expected benefit was quantified. In addition, in several programmes, diagnostic approaches and disease treatment have evolved greatly, which confounds simple measures of benefit. In other cases, the epidemiological nature of the disease itself has changed with time. In respective sections, this has been alluded to where relevant.

Finally, the information presented here is provisional, and subject to change as new information becomes available. The rationale for various estimates are given in the relevant sections, but it is important to note that these numbers will likely change as new evidence emerges, and treatment options and the underlying patterns of disease change. Nevertheless, the estimates presented here should remain relatively stable for the foreseeable future, and assumptions and limitations are clearly stated for clarity.

A note on figures and colour coding

All figures in his report are provided as prototypes for conveying screening information, and should be considered illustrative.

Section 1
Cervical cancer screening

Overview

Cervical cancer screening has been incredibly effective at reducing both cervical cancer incidence and associated death rates. While there is great variation in methodology across the world, national screening programmes have reduced cancer mortality rates have reduced by greater than 80% in countries with established national programmes [2-4]. Historically, this has been achieved by cytology-centric methods, such as liquid based cytology (LBC), but the advent of human papilloma virus (HPV) reflex methods have revolutionised cervical cancer screening, allowing for greater stratification of potential cases [5-7].

Cervical cancer itself arises due to uncleared HPV infections by high-risk strains, typically transferred during sexual contact. HPV affects the vast majority of sexually active unvaccinated adults at some point in their life-time, and for most the infection clears itself. For a small minority, this does not occur, and the net result can be cervical cancer. HPV rates vary markedly with age cohort, and younger women are far more likely to have an active infection [8] than older women. Concurrently, HPV vaccination is a relatively new intervention, but one that already has shown dramatic impact at lowering HPV infection rates, with early adopters such as Australia projected to be cervical cancer free by 2040 [9]. This reality means that HPV infection rates and consequently cervical cancer instances should decrease dramatically in vaccinated cohorts, in which case HPV-mediated screening modalities promise improved detection [7].

The natural history of HPV is complicated, and infection rates vary markedly by country and cohort. The Cochrane collaboration estimate that a pooled average of 2% of women screened will have a cervical intra-epithelial neoplasia (CIN) grade 2 or higher, and other estimates suggest that over 8% of the screened population will have an active HPV infection at the time of screening [8]. As there are many different screening modalities possible, this report uses data from the 2018 modelling study from US Preventive Services Task Force [10], validated against the SEER database, applied to the current and previous Irish CervicalCheck screening schema. Potential detrimental effects of over-screening were taken from a recently published model [7] for illustration.

Figure 1: The projected Life-time incidence of cervical cancer in the absence of screening (18.86 cases per 1,000 women), with a cytology-only screening programme akin to the old Irish system (2.34 cases per 1,000 women) and with high-risk HPV strain reflex testing such as in the current system (0.83 cases per 1,000 women)

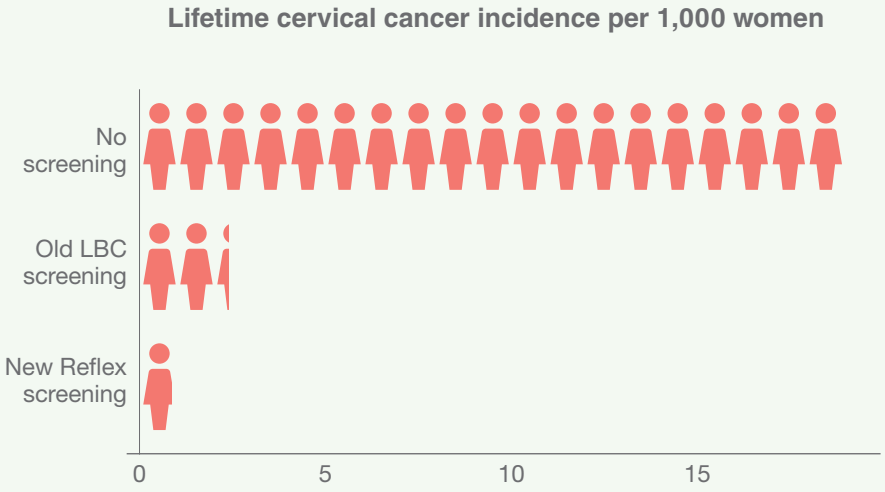


Table I: Estimated Life-time cervical cancer incidence per 1,000 women

Intervention	Life-time cases per 1,000 women	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	NNT (1/ARR)
No screening	18.86	*Reference value*	*Reference value*	*Reference value*
LBC screening	2.34	87.6%	1.6%	61
Reflex screening	0.83	95.6%	1.8%	55

Absolute baseline risk in absence of screening: ~1.87% - Table values rounded to one decimal place

Benefits of screening – reduction in life-time instances of cancer

Table 1 lists the estimated impacts of CervicalCheck on cancer incidence, including calculations of relative and absolute risk reduction (RRR/ARR), as well as number needed to treat (NNT) for no screening, LBC screening, and current Irish reflex screening. Figure 1 depicts this graphically.

Figure 2: The projected Life-time deaths from cervical cancer in the absence of screening (8.34 deaths per 1,000 women), with a cytology-only screening programme akin to the old Irish system (0.76 deaths per 1,000 women) and with high-risk HPV strain reflex testing such as in the current system (0.25 cases per 1,000 women)

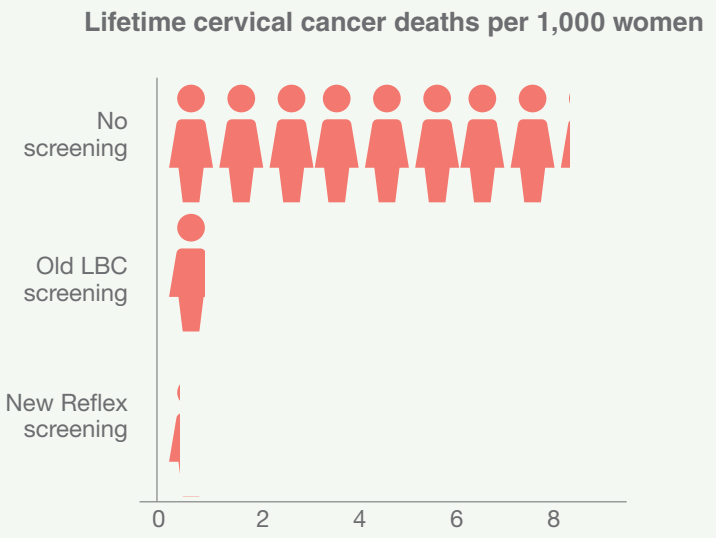


Table 2: Life-time cervical cancer deaths per 1,000 women

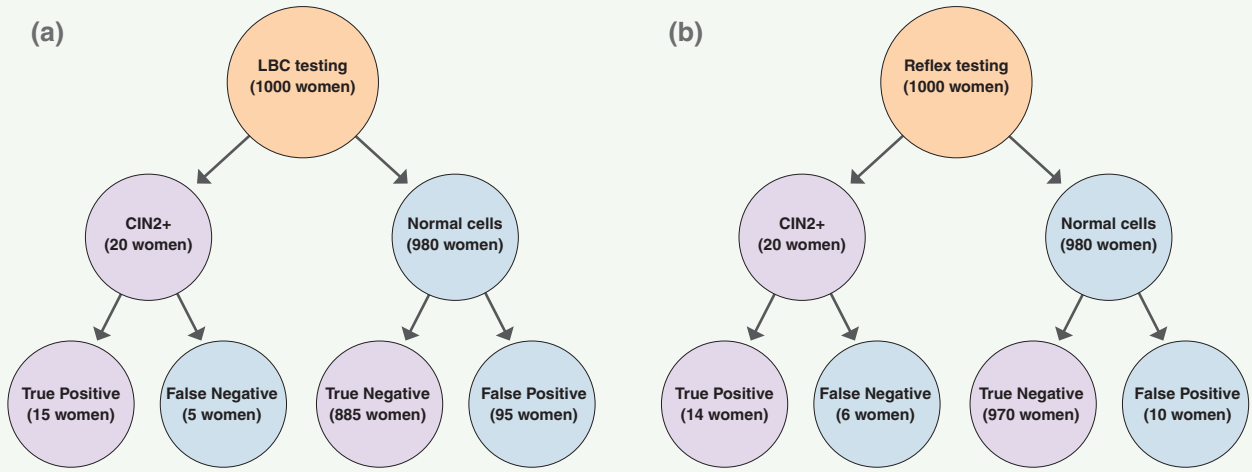
Intervention	Life-time deaths per 1,000 women	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	NNT (1/ARR)
No screening	8.34	*Reference value*	*Reference value*	*Reference value*
LBC screening	0.76	90.9%	0.8%	132
Reflex screening	0.25	97.0%	0.8%	124

Absolute baseline risk in absence of screening: ~0.83% - Table values rounded to one decimal place

Benefits of screening – reduction in cervical cancer deaths

Table 2 lists the estimated impacts of CervicalCheck on cancer deaths, including calculations of relative and absolute risk reduction (RRR/ARR), as well as number needed to treat (NNT) for no screening, LBC screening, and current Irish reflex screening. Figure 2 depicts this graphically.

Figure 3: The expected number of true positive cases (detected abnormalities), false negative cases (missed abnormalities), and false positive cases for 1,000 women with (a) LBC screening (b) HPV testing with LBC reflex. Numbers have been rounded to the nearest whole person here, full details in table III. Note that this diagram only shows general case presuming non-expedited re-testing. See table below and appendices for in depth discussion.



Screening type	False negatives per 1,000 women (95% CI)	False positive (excess colposcopy) per 1,000 women (95% CI)
LBC only	4.9 (3.5 - 6.7)	*95.1 (93.1-97.0)*
HPV test only*	2.0 (1.9 - 2.1)	98.9 (98.0-101.0)
HPV / LBC reflex (no retesting)	6.4 (5.1-8.0)	9.6 (9.4-9.8)
HPV / LBC Co-test*	0.5 (0.3-0.7)	184.4 (181.8-188.0)
CervicalCheck modalities (HPV primary testing with expedited re-testing of HPV+ / LBC- results)		
HPV / LBC reflex (Expedited re-testing, Optimistic HPV clearance rate 70% p/a)	2.2 (2.1-2.3)	28.2 (27.9-28.5)
HPV / LBC reflex (Expedited re-testing, Pessimistic HPV clearance rate 0% p/a)	2.2 (2.1-2.3)	63.5 (63.1-63.8)

* HPV testing is not performed in isolation due to potential over-detection. Co-testing is not recommended due to the high false positive rate. Both included here for completeness and purposes of comparison. The Irish schema for CervicalCheck uses an expedited re-testing framework, where false positives depend on HPV clearance rates; an optimistic (70% HPV clearance per year) and pessimistic (0% clearance) scenario are modelled here. See appendix 2 for further details.

Considerations, caveats, and detrimental impacts of screening

Table 3 depicts the likely detrimental impacts of screening modalities, estimated from recent modelling studies for a typical population [7]. The chief concern of over-screening is needless colposcopies, and to a lesser extent the potential for missed CIN2+ cases. The previous and current Irish schema outcomes are depicted in figure 3. Note that this will also change with age-cohort and HPV vaccination status, as outlined in appendix 1. Ireland also uses an expedited re-testing schema, where HPV positive cases are re-tested on a yearly basis. The false positive rate thus depends on the rate of HPV clearance. This is considered in appendix 2.

Limitations and caveats

The estimates given in this section have a number of limitations that must be considered in usage and extrapolation. These are namely:

- Estimates assume a roughly constant rate of HPV infection, and a steady proportion of CIN2+ cases in the general screening population. This will likely change with time as HPV vaccination rates increase, so these estimates will need to be revised in future as more women are protected from HPV. This is considered in appendix 1.
- These models hinge on a steady state of CIN2+ cases in the general population, in the order of 2%. This varies by subgroup, as indeed does HPV infection. The numbers here only reflect the general case, and caution should be urged in making inferences from this for any particular subgroup. Appendix 1 outlines some of the considerations required.
- US Taskforce data was validated with US SEER data, and there may be some differences in the epidemiology of HPV between Ireland and the USA, and even variations within Ireland. If these are substantial, then estimates might require revision.
- Expedited retesting accuracy depends on the clearance rate of HPV in a given cohort. This is considered in appendix 2 in detail, but it is important to note that this does not affect estimates of false negative results.

Section 2
Advanced colorectal cancer screening

Overview

The chief advantage of colorectal cancer screening is that it has the potential to prevent advanced colorectal cancers (CRCs). This is because the vast majority of CRCs originate from polyps, which if located an be removed via colonic polypectomy before they become malignant.[11-12]. Historically, fecal occult blood tests were used to detect bleeding indicative of polyps in the colon, but these suffered the drawback of having only middling sensitivity and specificity. Accordingly, the Irish programme now uses Fecal Immunochemical Test Screening (FIT), as this offers superior performance without the drawbacks associated with both fecal occult blood tests or the invasiveness of colonoscopy.

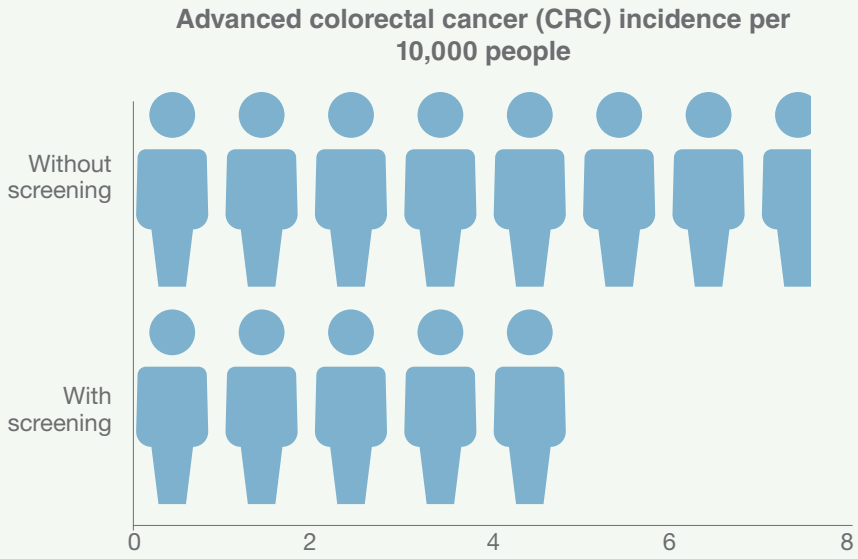
Evidence for the efficacy of colorectal screening is strong, and the US Preventive Services Task Force recommends screening from age 50 to 75 [13]. Taiwan has employed a FIT screening programme since 2004, which has been well studied with ample follow-up [14-16]. In this analysis, we shall use the results of a recent prospective cohort study in Taiwan of nationwide biennial FIT screening, involving 5,417,699 eligible subjects to ascertain likely benefits of screening in terms of lives saved, and advanced CRCs circumvented due to screening [16]. It should be noted that in Taiwan, the programme enrols citizens aged from 50 to 74, whereas Ireland currently screens from 60 to 69 inclusive, though results should be broadly similar, and are discussed overleaf.

Table 4: Life-time incidence of advanced colorectal cancer per 100,000 people

Intervention	Advanced CRC per 100,000	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	NNT (1/ARR)
No screening	75.7	*Reference value*	*Reference value*	*Reference value*
FIT screening	50.0 (48.7-53.0)	34% (30-35.7%)	0.03% (0.02-0.03%)	3891 (3704-4405)

Absolute baseline risk in absence of screening: ~0.076% - Table values rounded to one decimal place (except ARR, to two). Figures given in brackets are calculated 95% confidence intervals for estimates when available.

Figure 3: The projected Life-time incidence of advanced colorectal cancer in the absence of screening (75.7 cases per 100,000 people) and with a FIT screening regimen akin to the existent Irish system (50 cases per 100,000 people). Note that the scale above has been set per 10,000 people for visual clarity.



Benefits of screening – reduction in instances of advanced colorectal cancer

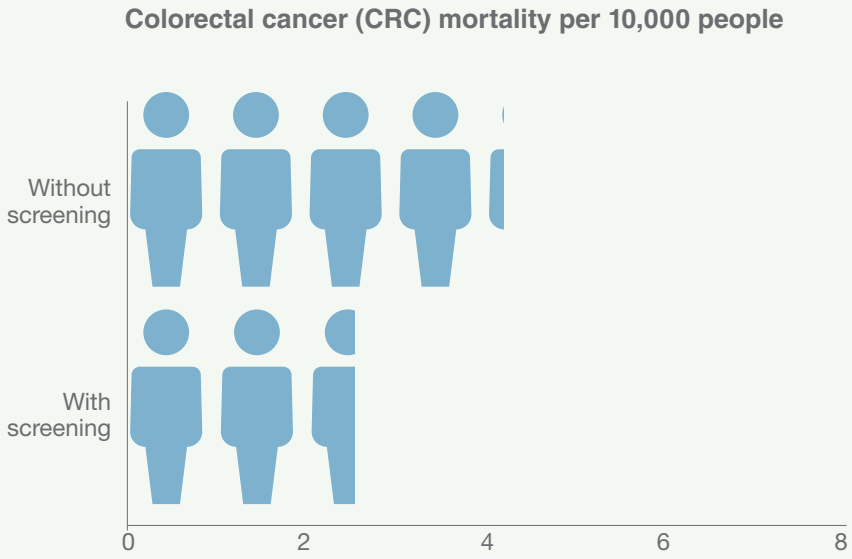
Table 4 lists the estimated impacts of BowelScreen on advanced cancer incidence, including calculations of relative and absolute risk reduction (RRR/ARR), as well as number needed to treat (NNT) for no screening and FIT screening. Figure 4 depicts this graphically.

Table 5: Life-time incidence of advanced colorectal cancer per 100,000 people

Intervention	Advanced CRC per 100,000	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	NNT (1/ARR)
No screening	41.3	*Reference value*	*Reference value*	*Reference value*
FIT screening	24.8 (23.5-26.4)	40% (36.1-43.1%)	0.02% (0.01-0.02%)	6061 (5618-6711)

Absolute baseline risk in absence of screening: ~0.076% - Table values rounded to one decimal place (except ARR, to two). Figures given in brackets are calculated 95% confidence intervals for estimates when available.

Figure 5: The projected mortality of advanced colorectal cancer in the absence of screening (41.3 deaths per 100,000 people) and with a FIT screening regimen akin to the existent Irish system (24.8 deaths per 100,000 people). Note that the scale above has been set per 10,000 people for visual clarity.



Benefits of screening – reduction in instances of advanced colorectal cancer

Table 5 lists the estimated impacts of BowelScreen on deaths due to CRC, including calculations of relative and absolute risk reduction (RRR/ARR), as well as number needed to treat (NNT) for no screening and FIT screening. Figure 5 depicts this graphically.

Limitations and caveats

The estimates given in this section have a number of limitations that must be considered in usage and extrapolation. These are namely:

- The analysis presented here presumes that colorectal cancer rates in Ireland are broadly similar to that in Taiwan. There is significant variation worldwide in how cancer rates are reported, and up-to-date Irish information is not readily available, and this may skew analysis. However, the projected absolute risk reduction ratio will likely be the same, and figures can be readily updated if more recent Irish data becomes available.
- The absolute risk reduction calculated here factors in a Bayesian correction factor for self-selection in the screened and unscreened cohorts. While differences were minimal with the crude rates, this should give a better assessment of the direct impact of screening itself, without the confounding influence of attending versus non-attending.
- It is worth noting however that risk factors for colorectal cancer include diet, and socioeconomic factors likely will play into this, which could further skew the results across different social groups.

Section 3
Breast cancer screening

Overview

Breast cancer screening might be perhaps the best known cancer screening programme in the world, but it has long been contentious [17], and there is ongoing academic debate about its utility [18-19]. There are myriad reasons for this contention, and from an evidence-based medicine perspective, breast screening is surprisingly divisive.

In the last decade, a number of studies have yielded evidence congruent with breast cancer screening reducing breast cancer mortality by upwards of 25% [20-21]. On the face of it, this might seem to suggest a demonstrable efficacy due to breast screening. But there are sources of unavoidable ambiguity. Mammographic techniques have evolved rapidly in the past decades, so too have breast cancer therapies - this leads to a confounding influence that is difficult to untangle, and in reality means that ascertaining the impact of screening as an intervention is surprisingly convoluted, especially as screening does not seem to directly reduce all-cause mortality, a point of contention to critics of the undertaking [22].

Different research groups tend to draw diametrically opposed conclusions – in 2020 alone, several studies [23-26] found evidence suggesting a strong positive impact of screening on mortality due to breast cancer. However, other authors claimed that the ostensible benefit of screening could be entirely explained by the uptake of new adjuvant therapies [27], and even arguments that breast screening should be terminated on that basis. There are known detrimental effects to breast cancer overscreening [22], but similarly polarised conclusions on how drastic these are.

This report cannot hope to make a determination as to the correct interpretation of the available conflicting data. There is also some evidence that the benefits and risks differ greatly by age, and that selective screening of high-risk women might be more beneficial than age-based screening protocols. For the purposes of this report, the most comprehensive, impartial, and thorough source for the assessment of the efficacy of breast cancer screening again comes from the US preventative task force report (2016) [21]. Accordingly, that is the primary data source for the findings listed overleaf.

Figure 6: The projected mortality of breast cancer in a 10-year interval for different age cohorts in the absence of screening (see table 6 for specific cohorts) and with a screening regimen (also consult table 6.). Note that these cohorts do not reflect the Irish screening profile (ages 50-69), which is shown in figure 7 for clarity.

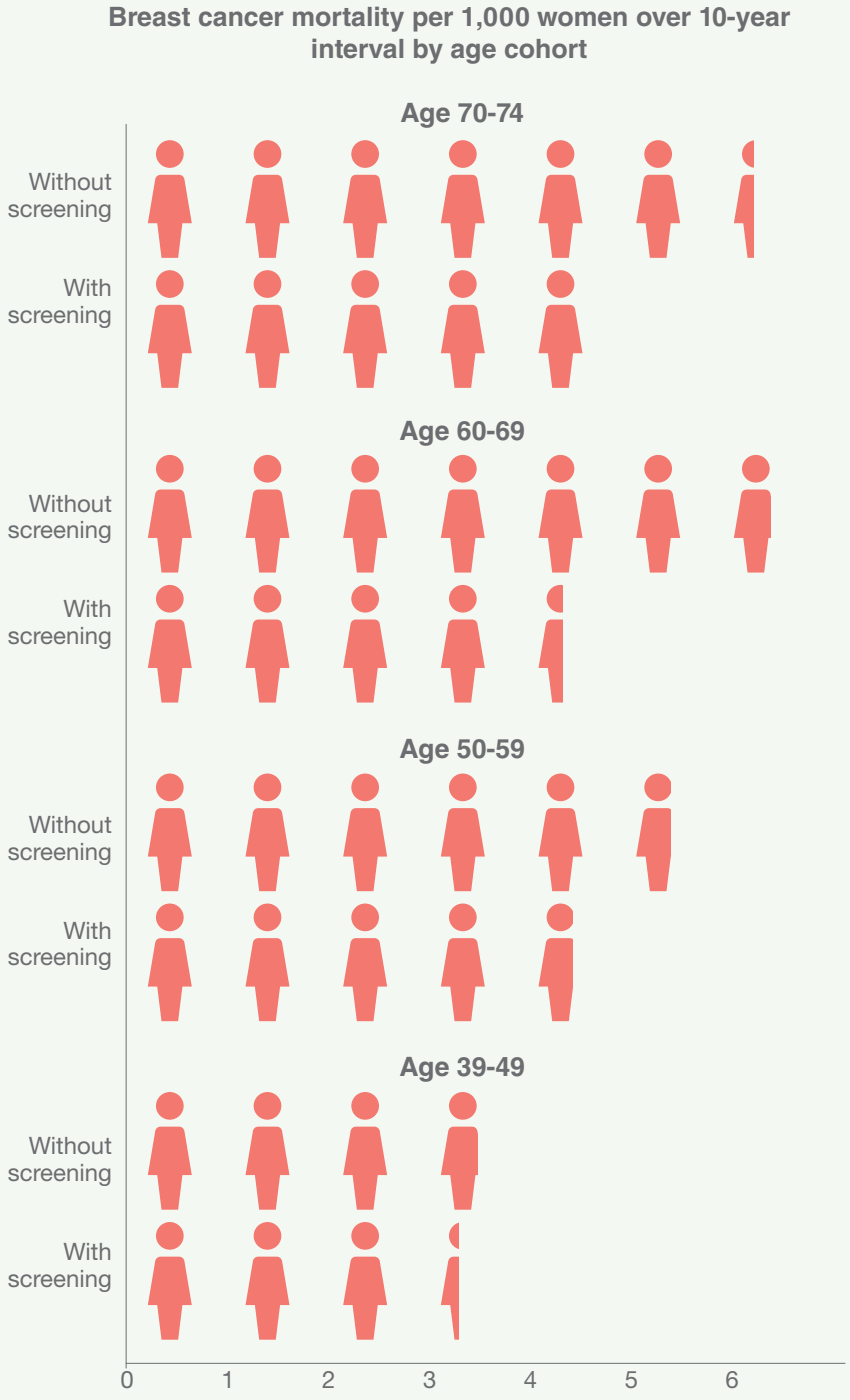
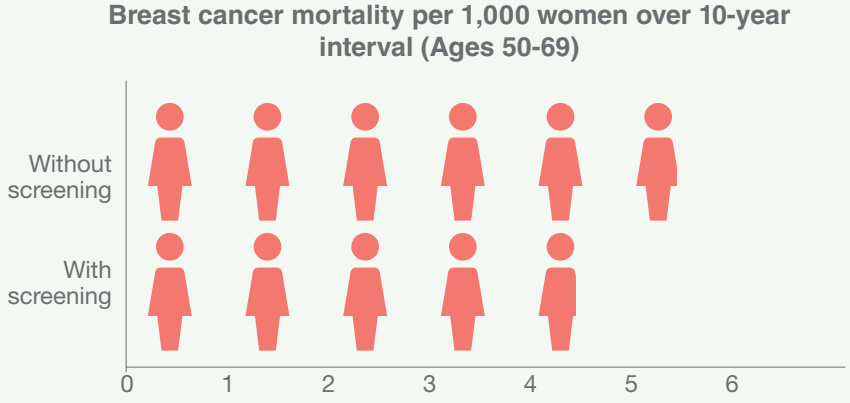


Figure 7: The projected mortality of breast cancer in a 10-year interval for the cohort eligible for screening in Ireland, in both scenarios with an absence of screening (5.8 deaths per 1,000 women over 10 year interval) and with a screening regimen (4.5 deaths per 1,000 women over a 10 year interval).



Benefits of screening – reduction in breast cancer mortality

Figure 6 depicts the mean reduction in mortality with different age cohorts, not all of whom (ages 39-49 and ages 70-74) are applicable to BreastCheck, but are included here for ease of review. It is also worth noting that the relative risk reduction of these two cohorts crosses both sides of unity, which might suggest the intervention is useless or even detrimental, despite the seemingly positive result the figure might imply. Full details are given in table 6, for clarity, including estimates of relative and absolute risk reduction (RRR/ARR), as well as number needed to treat (NNT) for no screening and for mammography.

Figure 7 depicts the reduction in breast cancer mortality for the age cohort relevant to the Irish screening programme (age 50-69), and as can be seen from table 6, the relative risk reduction in this cohort is below unity, implying that screening here is associated with a better outcome for patients. Crucially though, the contentions mentioned in the introduction still apply, and it is difficult to draw a firm inference from this correlation alone, as it may be spurious or associated with improved treatments, as some authors contest.

Limitations and caveats

The estimates given in this section have a number of limitations that must be considered in usage and extrapolation. These are namely:

- As discussed in the section overview, there are hugely conflicting views on breast cancer screening, and it is still unclear whether screening itself is cause of improvement, or whether this is due to improved treatments - or a combination of the two.
- Quoted mortality rates were ascertained using the US Taskforce's "long accrual" method, which counts all breast cancer cases contributing to breast cancer deaths.
- The caveat from the US Taskforce is vital to keep in mind: "Most trials used imaging technologies and treatments that are now outdated, and definitions of advanced breast cancer were heterogeneous. Studies of effectiveness based on risk factors, intervals, or other modalities were unavailable or methodologically limited." Accordingly, caution must be exercised when citing breast cancer screening statistics.

Table 6: Mortality rates from breast cancer in a 10-year interval

Age Cohort	Mortality without screening	Mortality with screening	Relative Risk Reduction	Absolute Risk Reduction (ARR)	Number Needed to Treat
39-49	36 (29-43)	33 (27-36)	8.3% (-2% - 25%)	0.3% (-%0.1 - 0.9%)	333 (111 - Infinity)
50-59	54 (50-58)	46 (37-52)	14.8% (3% - 32%)	0.8% (0.2% - 1.8%)	125 (56 - 617)
60-69	65 (52-81)	44 (35-54)	33% (17% - 46%)	2.1% (1.1% - 3%)	47 (33 - 90)
70-74	62 (48-80)	50 (32-79)	20% (-28% - 49%)	1.2% (-0.2% - 3%)	81 (33 - Infinity)
50-69 (Irish case)	58 (55-62)	45 (39-52)	22% (10%-32%)	1.3% (0.6% -1.9%)	78 (54 - 172)

Table values rounded to one decimal place (except ARR, to two). Figures given in brackets are calculated 95% confidence intervals for estimates when available. Entries in red are not used in Irish screening, but are included solely for completeness.

Section 4
Disclaimer

All data in this report is for guidance only, and should not be taken as legal or medical guidance on its own merit. Estimates in this work are subject to revision as improved data becomes available, and are subject to the limitations discussed herein.

References and sources

1. Wilson JM, Jungner G, World Health Organization. Principles and practice of screening for disease. WHO. 1967
2. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet. 2004 Jul 17;364(9430):249–56.
3. Smith M, Canfell K. Impact of the Australian National Cervical Screening Program in women of different ages. Med J Aust. 2016 Oct 17;205(8):359–64.
4. Smith MA, Edwards S, Canfell K. Impact of the National Cervical Screening Programme in New Zealand by age: analysis of cervical cancer trends 1985–2013 in all women and in Māori women [Internet]. Vol. 28, Cancer Causes & Control. 2017. p. 1393–404. Available from: http://dx.doi.org/10.1007/s10552-017-0967-y
5. Franco EL, Mahmud SM, Tota J, Ferenczy A, Coutlée F. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. Arch Med Res. 2009 Aug;40(6):478–85.
6. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014 Feb 8;383(9916):524–32.
7. Grimes DR, Corry EMA, Malagon T, et al. Modeling Cervical Cancer Screening Strategies with Varying levels of Human Papillomavirus vaccination. JAMA Open. 2021 In Press.
8. Koliopoulos G, Nyaga VN, Santesso N et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database of Systematic Reviews. 2017(8).
9. Hall MT, Simms KT, Lew JB et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. The Lancet Public Health. 2019 Jan 1;4(1):e19-27.
10. Kim JJ, Burger EA, Regan C, Sy S. Screening for cervical cancer in primary care: a decision analysis for the US Preventive Services Task Force. Jama. 2018 Aug 21;320(7):706-14.
11. Hewitson P, Glasziou P, Watson E et al.. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. American Journal of Gastroenterology. 2008 Jun 1;103(6):1541-9.
12. Bernie T, Les I, Paul G, Jan K, David W, Chris S. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. Bmj. 1998 Aug 29;317(7158):559-65.

13. US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. Annals of internal medicine. 2008 Nov 4;149(9):627-37.

14. Chiu HM, Chen SL, Yen AM, Chiu SY, Fann JC, Lee YC, Pan SL, Wu MS, Liao CS, Chen HH, Koong SL. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the O ne M illion T aiwanese Screening Program. Cancer. 2015 Sep 15;121(18):3221-9.

15. Chen RC, Chiu HM, Wang YW, Fann JY, Yen AF, Chiu SH, Chen SS, Lee YC, Wu CY, Jou YY, Chen HH. Reduction of Colorectal Cancer Mortality and Advanced Stage Cancer Incidence After 10 Years of Fecal Immunochemical Test Screening. JCO, 2018

16. Chiu HM, Jen GH, Wang YW, Fann JC, Hsu CY, Jeng YC, Yen AM, Chiu SY, Chen SL, Hsu WF, Lee YC. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. Gut. 2021 Jan 24.

17. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. Cochrane database of systematic reviews. 2013(6).

18. Seely JM, Alhassan T. Screening for breast cancer in 2018—what should we be doing today?. Current Oncology. 2018 Jun;25(Suppl 1):S115.

19. Qaseem A, Lin JS, Mustafa RA, Horwitch CA, Wilt TJ. Screening for breast cancer in average-risk women: a guidance statement from the American College of Physicians. Annals of internal medicine. 2019 Apr 16;170(8):547-60.

20. Broeders M, Moss S, Nyström L, Njor S, Jonsson H, Paap E, Massat N, Duffy S, Lynge E, Paci E. The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. Journal of medical screening. 2012 Sep;19(1_suppl):14-25.

21. US Preventive Services Task Force. Screening for breast cancer: US Preventive Services Task Force recommendation statement. Annals of internal medicine. 2009 Nov 17;151(10):716-236.

22. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. New England Journal of Medicine. 2016 Oct 13;375(15):1438-47.

23. Dunn N, Youl P, Moore J, Harden H, Walpole E, Evans E, Taylor K, Philpot S, Furnival C. Breast-cancer mortality in screened versus unscreened women: Long-term results from a population-based study in Queensland, Australia. Journal of Medical Screening. 2020 Aug 25:0969141320950776.

24. Duffy SW, Tabár L, Yen AM, Dean PB, Smith RA, Jonsson H, Törnberg S, Chen SL, Chiu SY, Fann JC, Ku MM. Mammography screening reduces rates of advanced and fatal breast cancers: Results in 549,091 women. Cancer. 2020 Jul 1;126(13):2971-9.

25. Zielonke N, Gini A, Jansen EE, Anttila A, Segnan N, Ponti A, Veerus P, de Koning HJ, van Ravesteyn NT, Heijnsdijk EA, Heinävaara S. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. European Journal of Cancer. 2020 Mar 1;127:191-206.

26. Duffy S, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith R, Evans A, Blyuss O, Johns L, Ellis I, Sasieni P. Annual mammographic screening to reduce breast cancer mortality in women from age 40 years: long-term follow-up of the UK Age RCT. Health Technology Assessment (Winchester, England). 2020 Oct;24(55):1.

27. Burton R, Stevenson C. Assessment of breast cancer mortality trends associated with mammographic screening and adjuvant therapy from 1986 to 2013 in the state of Victoria, Australia. JAMA network open. 2020 Jun 1;3(6):e208249-.

Appendix 1

Simulated estimation of likely age-related impacts on veracity of cervical screening results

December 9th 2022

Overview

This document contains an independent scientific assessment of how age-related human papillomavirus virus (HPV) infection is likely to impact outcomes of cervical screening. This report also quantifies how wide-spread vaccination against HPV will impact interpretation of screening results. The chief aims of this undertaking were as follows:

1. To use international data to ascertain how HPV infection varies in different age cohorts, and to quantify likely differences in age-mediated HPV prevalence.
2. To ascertain the robustness of the Irish screening modality (HPV primary testing with reflex cytology) to vary levels of cohort baseline HPV infection.
3. To also simulate the impacts of HPV vaccination on screening profiles, and to further ascertain the robustness of future Irish screening in the scenario of high vaccine uptake.
4. To contrast this with alternative modalities, namely co-testing approaches.

Contents of this report

Introduction and report framing

The objective of screening is to identify individuals amongst the ostensibly well who are in fact suffering from disease, so that their condition can be treated before it advances. National and regional screening programmes follow the guidelines laid down by the WHO in 1968 [1], so that maximum efficacy and benefit can be derived. Cervical screening is a lifesaving endeavour, with many possible modalities. All of these have proven hugely successful in saving lives and reducing the burden of disease [2-4]. Maximising the efficacy of screening programmes will save further lives in future.

The natural history of cervical cancer is complex, but almost always stems from the progression of HPV infection. Several factors influence the prevalence of HPV in a population cohort, with age an important consideration. Concurrently, HPV vaccination has proven extraordinarily effective at preventing infection. This report aims to determine how HPV prevalence impacts interpretation of Irish screening, gauging its robustness to differing levels of infection, and future vaccine impacts. There are many caveats to this analysis; the epidemiological nature of cervical disease is complex, changing with time. Available data is often noisy too. In respective sections, this has been alluded to where relevant. Finally, information presented is provisional, subject to change as new information becomes available. Rationales for various estimates are given in the relevant sections, but it is important to note that these numbers will likely change as new evidence emerges. Nevertheless, estimates presented here should remain relatively stable for the foreseeable future, and assumptions and limitations are clearly stated for clarity.

Section 1: Objective and outline

Overview

Programmes of cervical cancer screening have hugely decreased the incidence of cervical cancer in regions with screening programmes, and have consequently reduced associated death rates. In countries with estimated national screening programmes, cervical cancer deaths have dropped by over 80% regardless of methodology implemented [2-4]. These methodologies vary significantly throughout the world; the oldest and most widespread implementations are cytology-centric methods, chiefly liquid based cytology (LBC) approaches. In the last decade, improved methods for detecting human papillomavirus virus (HPV) have proven a huge boon to cervical cancer screening, allowing for greater stratification of potential cases [5-7]. This is chiefly because cervical cancer itself almost always arises due to uncleared HPV infections by high-risk strains, typically transferred during sexual contact.

Before the advent of HPV vaccination, the vast majority of sexually active unvaccinated adults could be expected to endure infection at some point in their life-time. In most instances, infection clears itself, but for a small minority the infection progresses and the net result can be cervical cancer. While vaccination is a relatively new intervention, it has already shown dramatic impact at lowering HPV infection rates, with nations such as Australia projected to be cervical cancer free by 2040 [9]. As HPV infection rates and resultant cervical cancer instances should decrease dramatically in vaccinated cohorts, it has been shown that HPV-mediated screening modalities promise improved detection [7].

A future without cervical cancer is of course the motivating goal of screening and vaccination programmes, but at this juncture it is crucial that screening programmes are robust to trends even in the absence of screening. This is especially important when HPV rates vary markedly with age cohort, and younger women are far more likely to have an active infection [8] than older women. It is therefore important to ascertain how informative results from screening are likely to be as HPV incidence changes. The objective of this short report is to quantify the projected performance of screening in Ireland with varying population age profiles.

Section 2: Methodology

HPV incidence calculations

HPV infection rates vary markedly by country and cohort, and even detection methodology. The evidence to date strongly suggests that HPV infection peaks before 30, though slightly different trends emerge in various data sets. For the purposes of this investigation, we initially restricted analysis to sets prior to widespread coverage of the HPV vaccine. On current estimates from USA and European data, we expect a global average of approximately 8.4% of the total screened population to have active HPV infection at the time of screening [7,8]. For this report, it was crucial to further stratify this figure by age cohort.

This figure varies quite substantially in different reports. Smith et al [10] looked at multiple studies to ascertain the prevalence of HPV in different studies across Europe. Their data, alongside their weighted best fit line, is shown in figure 1, below. It is important to note, however, that there are a number of caveats regarding data inclusion. In this work, studies included not only results from national screening programmes but also specific results from sexual infection clinics and also particular high-risk populations. These results are likely to produce high (or in some cases low) outliers which can skew analysis.

Figure 1: Estimation of HPV prevalence with age derived from multiple Western European studies reproduced from Smith et al [9]. Note that this work included self-reported studies and STI clinic cohorts. See text for details.

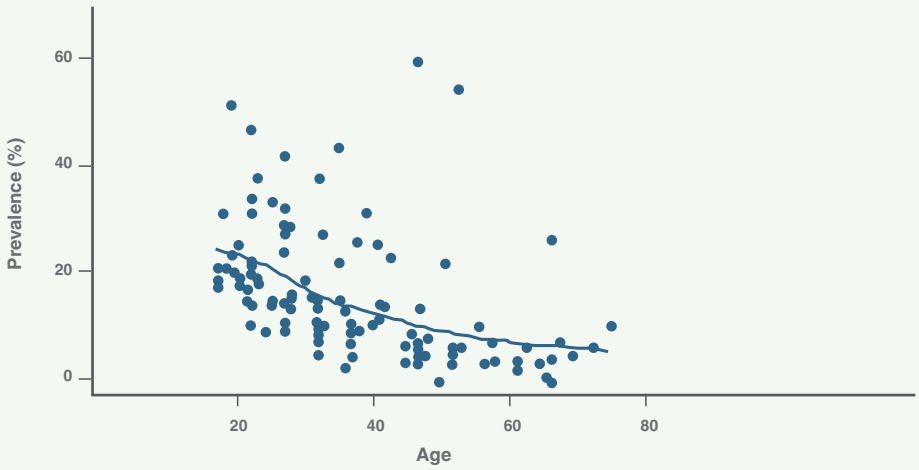
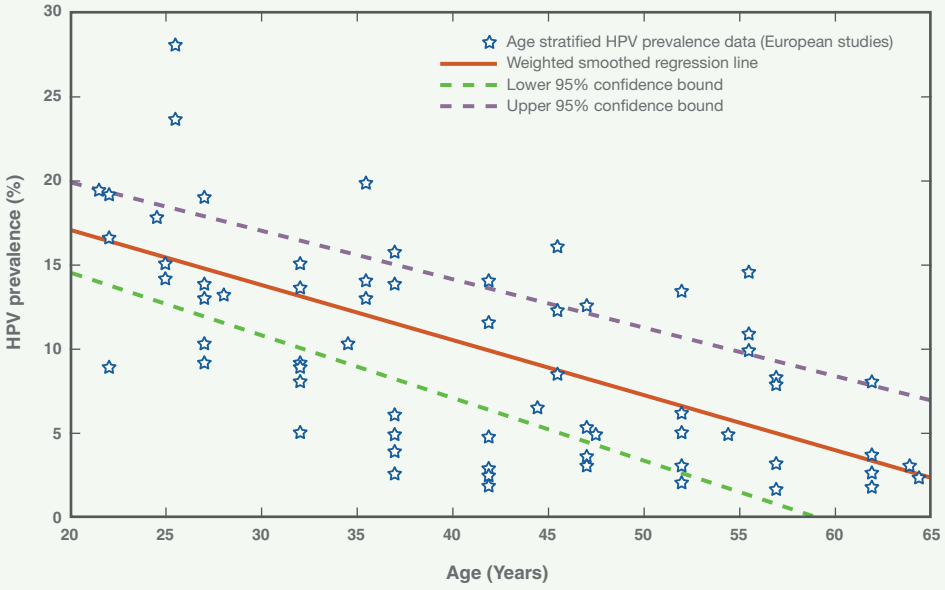


Figure 2: Estimation of HPV prevalence with age derived from 16 Western European screening studies. The red central line depicts a weighted and smoothed linear best fit. See text for details



To try and derive an age-specific HPV incidence rate not unduly skewed by outliers, the inclusion criteria employed involved limiting studies to those taken solely from Europe-based screening programmes. Furthermore, the analysis only considered studies with some degree of age stratification. This resulted in 16 applicable studies [11-27] included to reduce bias and influence of outliers. These studies were undertaken in various cities throughout Belgium, Denmark, France, Italy, the Netherlands, and the United Kingdom between 1992 and 2005. Data from these studies was then taken, and weighted according to the number of study participants and smoothed, so that a linear regression could be fit with 95% confidence intervals.

The raw data points and the resulting best fit line with confidence bounds are depicted above in figure 2. Note that the fit is only phenomenological; it allows bounds estimates, but is not presented as mechanistic. In reality, the true fit is likely more complex but an exact relationship is hard to ascertain due to the noise associated with the raw data. Nevertheless, the approximate linear relationship should suffice for simulation purposes. Stratified HPV prevalence bands by age cohort are given in table 1.

Table 1: Derived estimates of HPV prevalence and 95% confidence intervals used in simulations herein. The bounds are derived from the 95% confidence intervals of the weighted results of the 16 included studies

Age range	Literature range (%)	Simulation value (95% CI)
20-24	8.9 - 19.4	16.6 (13.8-19.3)
24-29	9.1 - 28.0	14.9 (12.0-17.9)
30-34	5.0 - 15.0	13.3 (10.1-16.5)
35-39	2.5 - 19.8	11.6 (8.2-15.0)
40-44	1.8 - 14.0	10.0 (6.4-13.6)
45-49	3.0 - 16.0	8.3 (4.5 -12.1)
50-54	2.0 - 13.4	6.7 (2.7 -10.7)
55-59	1.5 - 14.5	5.0 (0.8 -9.3)
60-64	1.8 - 8.0	3.3 (0.0 - 7.8)

CIN prevalence calculations

In principle, cervical intraepithelial neoplasia (CIN) rates can vary by age. The Cochrane collaboration estimate that a pooled average of 2% of women screened will have a cervical intra-epithelial neoplasia (CIN) grade 2 or higher [8]. The variation of this with age, however, is harder to quantify. CIN grades 2 and 3 can also be identified as High Grade Squamous Intraepithelial Lesion (HSIL) cases. One 2010 review [28] found conflicting results between studies for both CIN2, CIN3, and HSIL identification throughout Europe. The results of this review work for both HSIL and CIN classifications in various European studies are given in figure 3 overleaf to illustrate the spread.

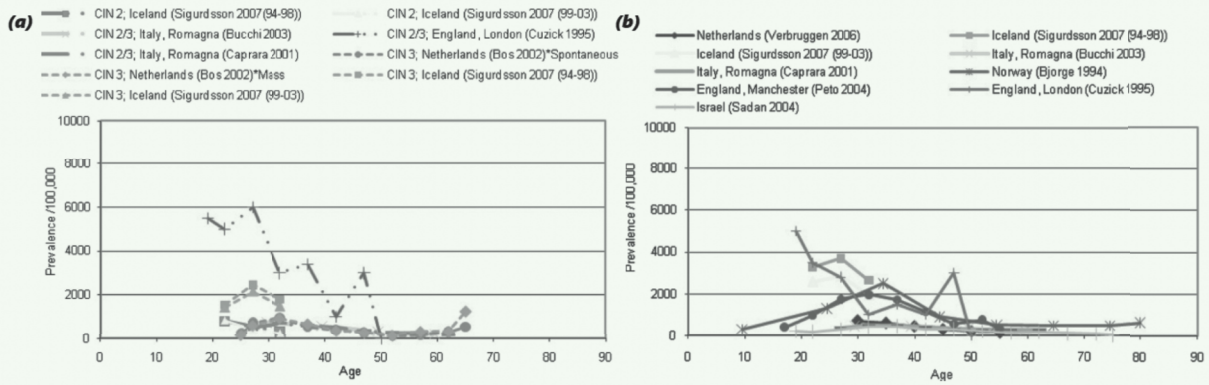
While the data in this review suggests variation in CIN grades 2 and 3, it also includes studies from non-representative cohorts which obscures the data. A more recent review [29] looked at cervical lesions worldwide, stratifying cohorts by under and over the age of 30. There was also high variation in this analysis, and no clear trends. Part of this is the complex nature of HPV's natural history, with lesions more likely to regress in younger women which confounds analysis.

Accordingly, while it is likely that CIN rates differ with age too, the precise trend is hard to ascertain, and is offset by the reality that persistent lesions will be more common in older women, even if they are intrinsically more likely to materialise in younger women. In the absence of clear data on this question, this report makes the simplification of presuming that CIN 2 / CIN 3 incidence is approximately the same in all age cohorts. This is taken as a prevalence of 2%, in line with Cochrane estimates [8]. It is worth noting that increased vaccination will drive this down substantially, but at this juncture we estimate in the absence of vaccination.

Modelling approach

Simulation in this work proceeds with a Markov chain type model previously established in literature [7]. For the basis of comparison, the impact of age-varying HPV infection on false positive / negative detection rates under the Irish CervicalCheck schema (HPV-reflex) were determined in models implemented in MATLAB (2020 release). We then ran the same simulation under the presumption of 80% vaccination to probe future trends. Finally, this was contrasted to a HPV / LBC co-test approach to gauge the robustness of these modalities.

Figure 3: Estimations of (a) CIN2, CIN3, and (b) equivalent HSIL measurements across Europe from TIng et al [28].



Section 3: Results

Simulating the impact of age-specific HPV incidence under CervicalCheck approach

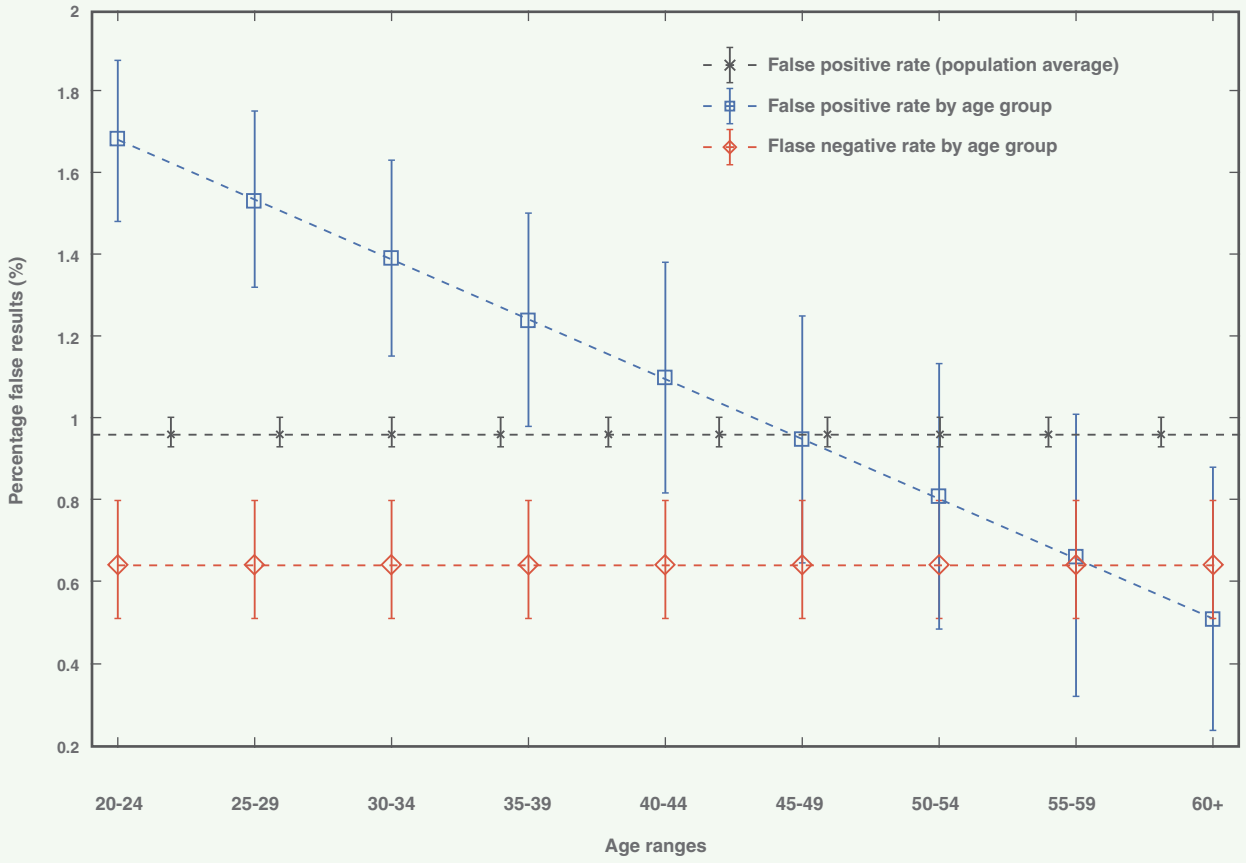
Table 2 gives the estimated number of correct results (both positive and negative), false positives (incorrect detection of CIN grade 2 or 3), and false negatives (missing of CIN 2 or 3) per 1,000 women under the Irish CervicalCheck schema. The percentages of false positive and negative results expected with this modality are given in figure 4 overleaf.

Note that as depicted in figure 4, the false negative rate does not change with HPV / age cohort, and is insensitive to this property. The false positive rate (false detection of CIN2 or CIN3 is slightly sensitive to the age-specific prevalence, as depicted in the blue line above, but this variation is relatively minor; in the cohort with the highest incidence of HPV, the relative risk increase in detecting a false positive compared to global average is 75%, but this translates as an absolute risk increase of only 0.72%. This suggests that the Irish CervicalCheck screening modality is relatively robust to HPV incidence.

Table 2: Derived estimates of HPV prevalence and 95% confidence intervals used in simulations herein. The bounds are derived from the 95% confidence intervals of the weighted results of the 16 included studies.

Age range (In years)	Correctly identified cases per 1,000 women (95% CI)	False positive cases per 1,000 women (95% CI)	False negative cases per 1,000 women (95% CI)
All ages screening	984.1 (982.1-985.6)	9.6 (9.3 - 10.0)	6.4 (5.1 - 8.0)
20-24	976.8 (976.2 - 977.2)	16.8 (14.8-18.7)	6.4 (5.1 - 8.0)
25-29	978.3 (977.5 - 978.9)	15.3 (13.2 - 17.5)	6.4 (5.1 - 8.0)
30-34	979.8 (978.7 - 980.5)	13.9 (11.5 - 16.3)	6.4 (5.1 - 8.0)
35-39	981.2 (980.0 - 982.2)	12.4 (9.8 - 15.0)	6.4 (5.1 - 8.0)
40-44	982.7 (981.2 - 983.9)	11.0 (8.2 - 13.8)	6.4 (5.1 - 8.0)
45-49	984.2 (982.5 - 985.6)	9.5 (6.5 - 12.5)	6.4 (5.1 - 8.0)
50-54	985.6 (983.6 - 987.2)	8.1 (4.9 - 11.3)	6.4 (5.1 - 8.0)
55-59	987.1 (984.9 - 988.9)	6.6 (3.2 - 10.1)	6.4 (5.1 - 8.0)
60-64	988.6 (986.2 - 989.6)	5.1 (2.4 - 8.8)	6.4 (5.1 - 8.0)

Figure 4: False result rates (positive and negative) as a percentage of total screened population, stratified by age cohort. Results suggest that reflex screening is entirely robust to false negative results with HPV prevalence / age cohort, and relatively robust to false positive results with HPV prevalence / age cohort.



Note that as depicted in figure 4, the false negative rate does not change with HPV / age cohort, and is insensitive to this property. The false positive rate (false detection of CIN2 or CIN3 is slightly sensitive to the age-specific prevalence, as depicted in the blue line above, but this variation is relatively minor; in the cohort with the highest incidence of HPV, the relative risk increase in detecting a false positive compared to global average is 75%, but this translates as an absolute risk increase of only 0.72%. This suggests that the Irish cervical screening modality is relatively robust to HPV incidence.

Screening efficacy with HPV vaccination

Results in the prior section assume no vaccination, but this will change as HPV is steadily eradicated by vaccine programmes. Using 29 distinct models of vaccine efficacy [7,30], 80% vaccine uptake corresponds to a reduction in HPV incidence by 93% (95% confidence bounds between 90% and 100% reduction). This can be factored into the simulation to produce table 3.

In this instance, a broadly similar trend appears to that in table 2 and figure 4. Again, the false negative rate remains insensitive to HPV prevalence. The false positive rates have some intrinsic dependence on infection rate by age cohort, but this is even more minimal than previously. The relative risk increase in false positive rates at most is 11.6% relative to baseline, which translates as a minuscule absolute risk increase of 0.05% for false positives. We may conclude that reflex screening (CervialCheck's modality) is robust to even future vaccine trends.

Table 3: HPV reflex test performance at 80% vaccine coverage, derived from multiple models of vaccine efficacy as detailed in the literature [7,30].

Age range (In years) (80% vaccine uptake)	Correctly identified cases per 1,000 women (95% CI)	False positive cases per 1,000 women (95% CI)	False negative cases per 1,000 women (95% CI)
All ages screening	995.2 (994.4-996.3)	4.3 (3.7 - 4.8)	0.5 (0.0 - 0.8)
20-24	994.7 (993.9 -996.3)	4.8 (3.7-5.3)	0.5 (0.0 - 0.8)
25-29	994.8 (994.1 - 996.3)	4.7 (3.7 - 5.1)	0.5 (0.0 - 0.8)
30-34	994.9 (994.3 - 996.3)	4.6 (3.7 - 4.9)	0.5 (0.0 - 0.8)
35-39	995.0 (994.4 - 996.3)	4.5 (3.7 - 4.8)	0.5 (0.0 - 0.8)
40-44	995.1 (994.6 - 996.3)	4.4 (3.7 - 4.6)	0.5 (0.0 - 0.8)
45-49	995.2 (994.8 - 996.3)	4.3 (3.7 - 4.4)	0.5 (0.0 - 0.8)
50-54	995.3 (994.9 - 996.3)	4.2 (3.7 - 4.3)	0.5 (0.0 - 0.8)
55-59	995.5 (995.1 - 996.3)	4.1 (3.7 - 4.1)	0.5 (0.0 - 0.8)
60-64	995.6 (995.2 - 996.3)	4.0 (3.7 - 4.0)	0.5 (0.0 - 0.8)

Contrast with age-specific HPV incidence under HPV / co-testing approaches

For context, it is worthwhile to contrast HPV-reflex screening as used in Ireland to co-testing approaches, such as those used in regions of the United States [7]. For simplicity, we consider a scenario where a positive HPV test is considered grounds for a colposcopy. This is not recommended, but we can quantify how this would impact results to contrast this with Irish results. Pivoting on the assumption of no vaccine uptake, Table 4 showcases this impact.

What is immediately apparent in this table is a marked dependence of test interpretation on screening results under co-testing modalities. The Cochrane review [8] implied that HPV testing resulted in less false negatives than traditional LBC screening, which is true. However, Table 4 showcases why a HPV only or strict co-testing modality [7] is problematic - it results in a large number of women getting unnecessary colposcopies. In the base case, the translates to a relative risk increase of 927% for a colposcopy (absolute risk increase: 8.9%) and this worsens with increasing HPV infection; in the 20-24 cohort, this manifests as an absolute risk increase of over 15.6% relative to HPV reflex screening. This thus illustrates why a simple positive on a HPV test is intrinsically misleading, especially in cohorts with higher infection rates.

Table 4: Co-testing interpretation is largely affected by HPV prevalence

Age range (Co-testing modalities)	False positives per 1,000 women screened	False negatives per 1,000 women screened
All screening	98.6 (97.6-100.6)	2.0 (2.0 - 2.0)
20-24	172.9 (149.4 - 197.5)	2.0 (2.0 - 2.0)
24-29	157.5 (133.1 - 183.9)	2.0 (2.0 - 2.0)
30-34	143.0 (115.9 - 171.2)	2.0 (2.0 - 2.0)
34-39	127.6 (98.8 - 157.6)	2.0 (2.0 - 2.0)
40-44	113.1 (82.5 - 144.9)	2.0 (2.0 - 2.0)
45-49	97.6 (65.3 - 131.3)	2.0 (2.0 - 2.0)
50-54	83.1 (49.0 - 118.5)	2.0 (2.0 - 2.0)
55-59	67.7 (31.8 - 105.8)	2.0 (2.0 - 2.0)
60-64	52.3 (24.6 - 92.2)	2.0 (2.0 - 2.0)

Section 4: Conclusions

The results of this simulation report suggest the following conclusions:

- While higher levels of HPV prevalence in younger cohorts can increase the rate of false positives, the Irish cervical screening reflex approach is quite robust to these impacts, and performs well even under high baseline HPV rates.
- Even in a future with high HPV vaccine uptake, the Irish screening modality should remain robust and screeners can have a high level of confidence in results even as HPV incidence drops substantially. This suggests that the screening approach used in Ireland is both robust and future-proof.
- By contrast, co-testing or HPV only approaches result in an unacceptably high level of false positives, especially in high incidence populations.

Limitations and caveats

The estimates given in this section have a number of limitations that must be considered in usage and extrapolation. These are namely:

- The epidemiology of HPV infection varies hugely in different studies. While a weighed approach was employed here from European data, this may be affected by outliers and ideally Irish screening data could in future be used to improve national estimates.
- These models hinge on a steady state of CIN2+ cases in the general population, in the order of 2%. This is likely to vary by subgroup, but clear trends were impossible to ascertain given the wide-range in HSIL / CIN2 / CIN3 estimates. Accordingly, estimates here must be treated with caution and foreknowledge that divergent CIN rates would impact the analysis.
- Vaccine uptake will also likely different across subpopulations, and will change in younger cohorts first. This has not been simulated for brevity here, but can be included in future analysis if required.

Section 5: Disclaimer

All data in this report is for guidance only, and should not be taken as legal or medical guidance on its own merit. Estimates in this work are subject to revision as improved data becomes available, and is subject to the limitations discussed herein. In the current state, this document is confidential and preliminary, and not designed for public consumption.

References and sources

1. Wilson JM, Jungner G, World Health Organization. Principles and practice of screening for disease. WHO. 1967
2. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet. 2004 Jul 17;364(9430):249–56.
3. Smith M, Canfell K. Impact of the Australian National Cervical Screening Program in women of different ages. Med J Aust. 2016 Oct 17;205(8):359–64.
4. Smith MA, Edwards S, Canfell K. Impact of the National Cervical Screening Programme in New Zealand by age: analysis of cervical cancer trends 1985–2013 in all women and in Māori women [Internet]. Vol. 28, Cancer Causes & Control. 2017. p. 1393–404. Available from: http://dx.doi.org/10.1007/s10552-017-0967-y
5. Franco EL, Mahmud SM, Tota J, Ferenczy A, Coutlée F. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. Arch Med Res. 2009 Aug;40(6):478–85.
6. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014 Feb 8;383(9916):524–32.
7. Grimes, D. R., Corry, E. M., Malagón, T., O'Riain, C., Franco, E. L., & Brennan, D. J. (2021). Modeling Cervical Cancer Screening Strategies With Varying Levels of Human Papillomavirus Vaccination. JAMA Network Open, 4(6), e2115321-e2115321.

8. Koliopoulos G, Nyaga VN, Santesso N et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database of Systematic Reviews. 2017(8).

9. Hall MT, Simms KT, Lew JB et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. The Lancet Public Health. 2019 Jan 1;4(1):e19-27.

10. Smith, J. S., Melendy, A., Rana, R. K., & Pimenta, J. M. (2008). Age-Specific Prevalence of Infection with Human Papillomavirus in Females: A Global Review. Journal of Adolescent Health, 43(4 SUPPL.), S5.e1-S5.e62. https://doi.org/10.1016/j.jadohealth.2008.07.009

11. Baay MF, Smits E, Tjalma WA, et al. Can cervical cancer screening be stopped at 50? The prevalence ofHPV in elderly women. Int J Cancer 2004;108(2):258–61.

12. Vandenvelde C, Scheen R, Van Pachterbeke C, et al. Prevalence of high risk genital papillomaviruses in the Belgian female population determined by fast multiplex polymerase chain reaction. J Med Virol 1992;36(4):279–82

13. Vandenvelde C, Van Beers D. High-risk genital papillomaviruses and degree of dysplastic changes in the cervix: a prospective study by fast multiplex polymerase chain reaction in Belgium. J Med Virol 1993; 39(4):273

14. Baay MF, Tjalma WA, Lambrechts HA, et al. Combined Pap and HPV testing in primary screening for cervical abnormalities: should HPV detection be delayed until age 35? Eur J Cancer 2005; 41(17):2704–8.

15. Kjaer SK. Risk factors for cervical neoplasia in Denmark. APMIS 1998;116(Suppl. 80):5.

16. Kjaer SK, van den Brule AJ, Bock JE, et al. Determinants for genital human papillomavirus (HPV) infection in 1,000 randomly chosen young Danish women with normal Pap smear: are there different risk profiles for oncogenic and nononcogenic HPV types? Cancer Ep- idemiol Biomarkers Prev 1997;6(10):799–805

17. Kruger-Kjaer S, van den Brule AJ, Svare EI, et al. Different risk factor patterns for high-grade and low-grade intraepithelial lesions on the cervix among HPV-positive and HPV-negative young women. Int J Cancer 1998;76(5):613–9.

18. Kjaer SK, van den Brule AJ, Paull G, et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cer- vical squamous intraepithelial lesions in young women: population based prospective follow up study. BMJ 2002;325(7364):572

19. Boulanger JC, Sevestre H, Bauville E, et al. [Epidemiology of HPV infection]. Gynecol Obstet Fertil 2004;32(3):218–23

20. Clavel C, Bory JP, Rihet S, et al. Comparative analysis of human pap- illomavirus detection by hybrid capture assay and routine cytologic screening to detect high-grade cervical lesions. Int J Cancer 1998; 75(4):525–8

21. Levert M, Clavel C, Graesslin O, et al. [Human papillomavirus typing in routine cervical smears. Results from a series of3778 patients]. Gy- necol Obstet Fertil 2000;28(10):722–8

22. Clavel C, Masure M, Bory JP, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. Br J Cancer 2001;84(12):1616–23.

23. Ronco G, Ghisetti V, Segnan N, et al. Prevalence ofhuman papilloma- virus infection in women in Turin, Italy. Eur J Cancer 2005;41(2): 297–305.

24. Jacobs MV, Walboomers JM, Snijders PJ, et al. Distribution of37 mu- cosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. Int J Cancer 2000;87(2):221–7.

25. Cuzick J, Szarewski A, Terry G, et al. Human papillomavirus testing in primary cervical screening. Lancet 1995;345(8964):1533–6.

26. Cuzick J. Human papillomavirus testing for primary cervical cancer screening. JAMA 2000;283(1):108–9

27. Peto J, Gilham C, Deacon J, et al. Cervical HPV infection and neopla- sia in a large population-based prospective study: the Manchester co- hort. Br J Cancer 2004;91(5):942–53

28. Ting, J., Kruzikas, D. T., & Smith, J. S. (2010). A global review of age-specific and overall prevalence of cervical lesions. International Journal of Gynecological Cancer, 20(7), e132. https://doi.org/10.1111/IGC.0b013e3181f16c5f

29. Ting, J., Rositch, A. F., Taylor, S. M., Rahangdale, L., Soeters, H. M., Sun, X., & Smith, J. S. (2015). Worldwide incidence of cervical lesions: a systematic review. Epidemiology and Infection, 143(2), 225–241. https://doi.org/10.1017/S0950268814001356

30. Brisson M, Bénard É, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Health. 2016;1(1):e8-e17. doi:10.1016/S2468-2667(16)30001-9

Appendix 2

Expedited retesting in cervical screening: a modelling analysis

December 9th, 2022

Overview

This document is an analysis of false positive and negative rates in cervical screening considering the effects of expedited retesting on human papillomavirus (HPV) positive patients within the screening cycle. The purpose of this analysis is to ascertain the effective false positive and negative rate per screening cycle, including expedited retesting of HPV positive women.

Contents of this report

Background: cervical cancer screening

Overview

Cervical cancer screening is a powerful tool that has been incredibly effective at reducing both cervical cancer incidence and associated death rates from cervical cancer. There is currently great variation in implementation methodology across the world, and national screening programmes have reduced cancer mortality by greater than 80% in countries with established national programmes [2-4]. Historically, screening for cervical abnormalities was performed with cytology-centric methods, such as liquid based cytology (LBC), but the advent of human papilloma virus (HPV) reflex methods have revolutionised cervical cancer screening, allowing for greater stratification of potential cases [5-7].

This is highly pertinent, as cervical cancer itself arises due to uncleared HPV infections by high-risk strains, typically transferred during sexual contact. While HPV affects the vast majority of sexually active unvaccinated adults at some point in their life-time, for most the infection clears itself. For a small minority, this does not occur, and the net result can be cervical cancer. HPV rates vary markedly with age cohort, and younger women are far more likely to have an active infection [8] than older women. Concurrently, HPV vaccination is a relatively new intervention, but one that already has shown dramatic impact at lowering HPV infection rates, with early adopters like Australia projected to be cervical cancer free by 2040 [9]. This reality means that HPV infection rates and consequently cervical cancer instances should decrease dramatically in vaccinated cohorts, in which case HPV-mediated screening modalities promise improved detection [7].

Typically, a pooled average of 2% of women screened nationally are expected to have a cervical intra-epithelial neoplasia (CIN) grade 2 or higher, and other estimates suggesting over 8% of the screened population will have an active HPV infection at the time of screening [8].Of the many screening modalities possible [10], HPV-reflex screening is currently employed in Ireland. This has several advantages over conventional LBC approaches, as it can drastically reduce false positives by an order of magnitude [7], greatly reducing the number of women who needlessly receive an invasive biopsy. There has been some concerns, however, that such an approach can marginally increase the number of false positives detected, as shown in Table 1.

Figure 1: The expected number of true positive cases (detected abnormalities), false negative cases (missed abnormalities), and false positive cases for 1,000 women with (a) LBC screening (b) HPV testing with LBC reflex. Numbers have been rounded to the nearest whole person here, full details in table I. Figure reproduced from a prior HSE Square Hammer report (June 2021)

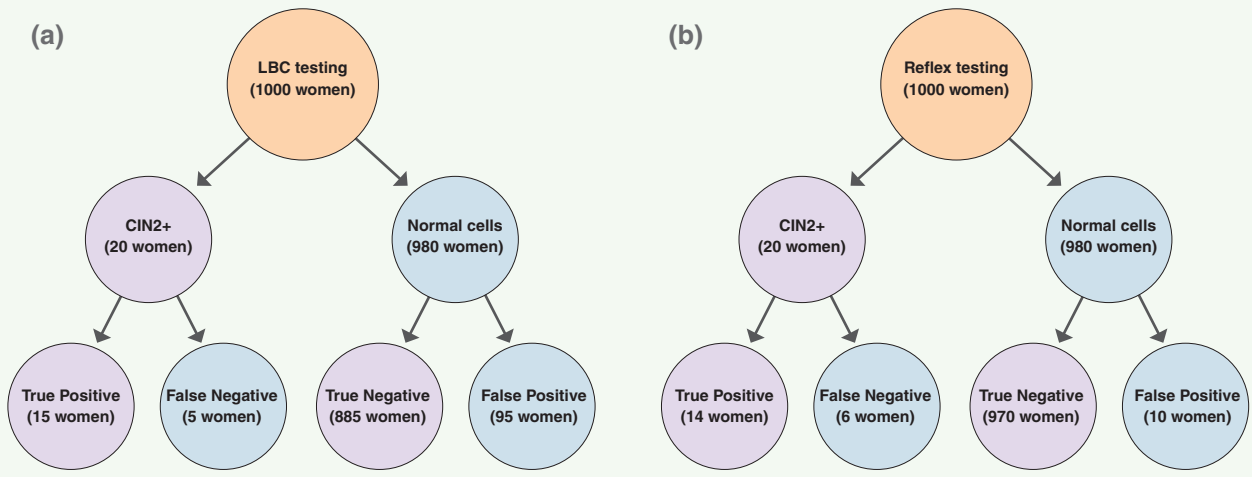


Table I: Test statistics for LBC and HPV-reflex modalities

Screening type	False negatives per 1,000 women (95% CI)	False positive (excess colposcopy) per 1,000 women (95% CI)
LBC only	4.9 (3.5 - 6.7)	95.1 (93.1-97.0)
HPV / LBC reflex	6.4 (5.1-8.0)	9.6 (9.4-9.8)
Change in relative risk between modes	+30.6% (Increase)	-89.9% (Decrease)
Change in absolute risk between modes	0.15% (Increase)	-8.55% (Decrease)

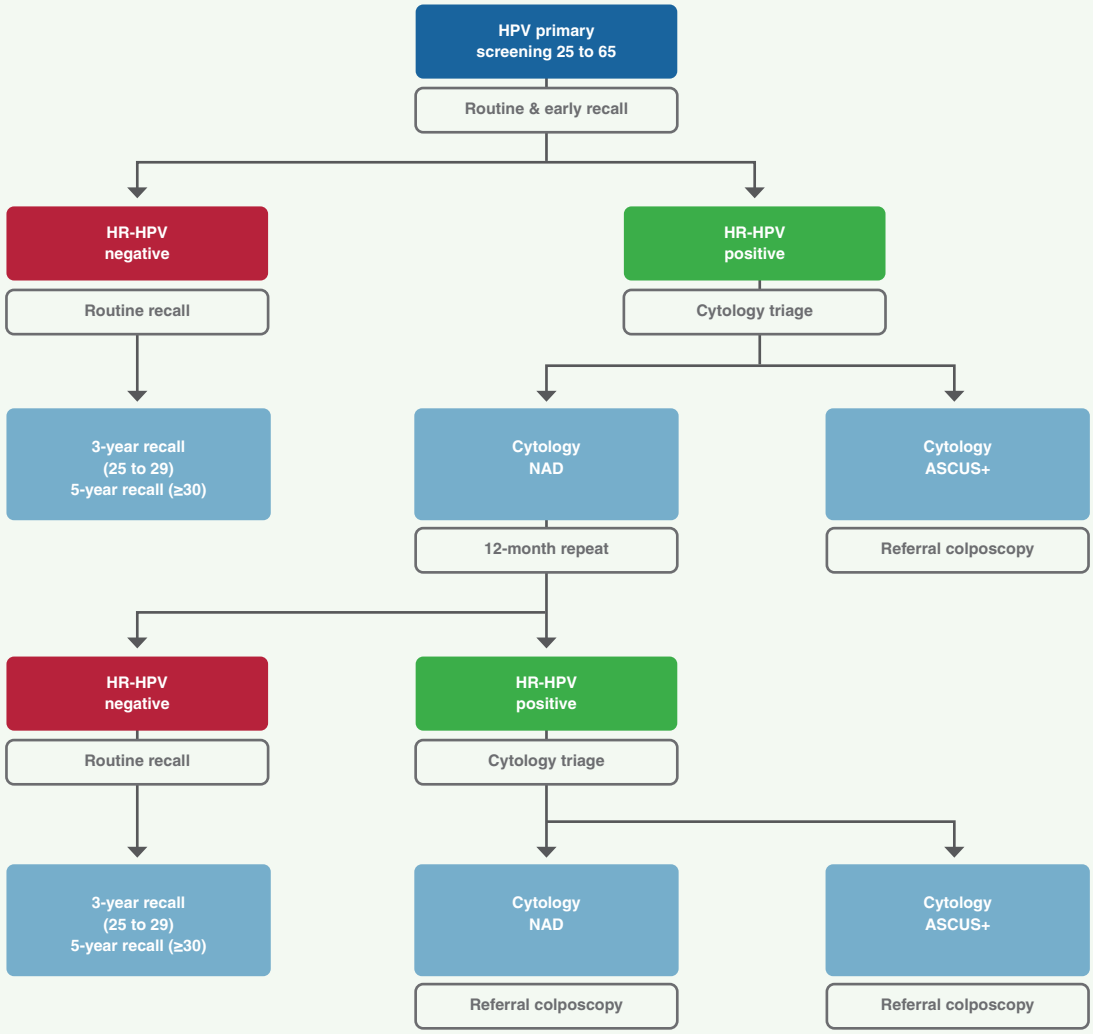
*Table 1: Test statistics in a typical population assuming an HPV incidence of 8.4% and a CIN2+ incidence of 2%. The last two rows yield the relative and absolute risk changes in moving from LBC to HPV-reflex modalities.

Table II: Estimated Life-time cervical cancer incidence per 1,000 women

Intervention	Life-time Cases per 1,000 women	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	NNT (1/ARR)
No screening	*18.86*	*Reference value*	*Reference value*	*Reference value*
LBC screening	2.34	87.6%	1.6%	61
Reflex screening	0.83	95.6%	1.8%	55

Values taken from US Task force report [10]

Figure 2: CervicalCheck screening algorithm



Motivation of this report: Expedited retesting and screening

The screening algorithm is given in figure 2. There is however a subtle nuance to screening that will impact the raw false positive / negative results reported in table 1; expedited retesting. Women who are HPV positive are reflex tested with LBC for CIN2+, with CIN2+ women being biopsied. Women who are HPV positive but negative for CIN2 are invited back for an expedited retest at 12 months, within the screening cycle. The purpose of this report is to estimate how much this will change the CIN2+ detection statistics within a screening cycle.

Section 2: HPV clearance and expedited retesting

HPV infections are typically transient, and the majority regress in time. For expedited retesting, there are several aspects that need to be considered. Firstly, we need to estimate the HPV regression rate for a typical infected woman within 12 months from initial screening. We also need to consider the expedited retest scenario where a woman with CIN2+ tested positive for HPV but initially received a false negative CIN2+. This will reduce the net false negatives per screening cycle, but will also act to increase the net false positive rate per cycle as persistent HPV+ women who have not fully recovered will still require a biopsy. This section lays out the framework for this analysis.

HPV clearance rates

The rate of HPV regression is critical to answering the motivating question of this report. HPV clearance rates vary by patient age and HPV subtype, but we can broadly estimate general cases from literature. Approximately 70% of HPV infections are cleared within one year, and 90% within 2 years [11,12]. In this analysis, we shall use this point estimate for the optimistic scenario, and also consider a pessimistic scenario with 0% HPV clearance after 12 months.

Modelling approach and assumptions

Broadly speaking, the modelling approach employed follows that outlined previously [7] with some important modifications. The required modifications and model assumptions for expedited retesting were as follows:

1. All HPV positive, CIN2- cases were subjected to an additional test 12 months after the initial screening round.
2. In the optimistic scenario, HPV clearance was 70%. In the pessimistic, it was 0%.
3. While missed CIN2+ can and does regress in most cases, in this model the conservative approach was taken by assuming that any initially missed CIN2+ 12 months on remains.
4. A typical population of 1,000 women was assumed, with 2% global CIN2+ incidence and a HPV infection rate of 8.4%. This varies by age group in reality (see square hammer report August 2021) but national averages were employed in this simulation.
5. The model tabulated the net false negatives and false positives per screening cycle (3 years / 5 years depending on age group and all figures are relative to this cycle time.

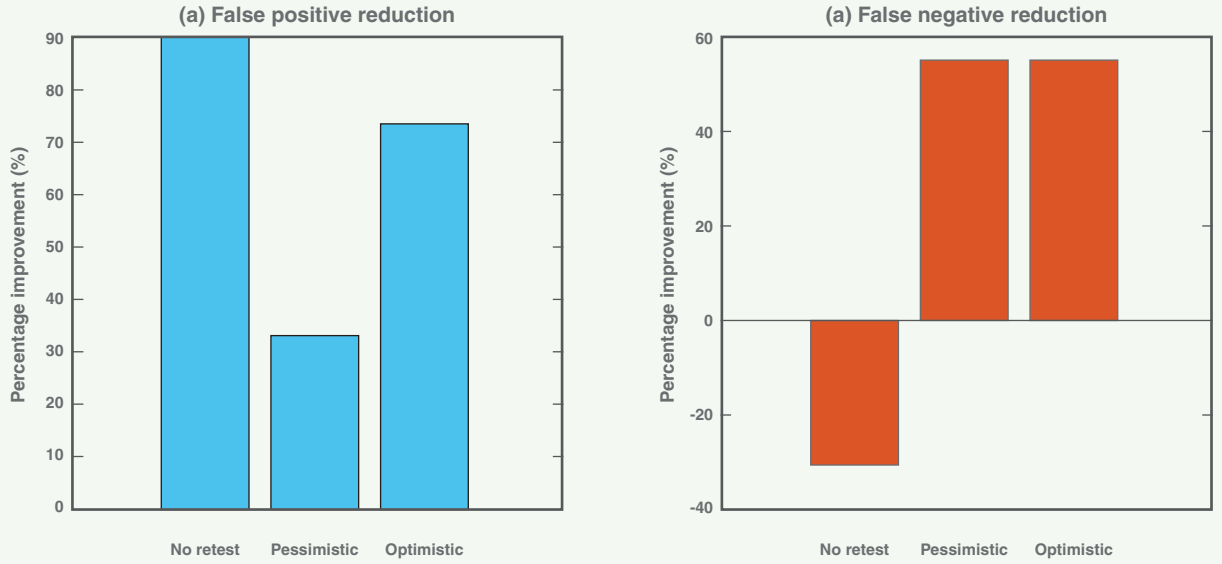
Section 3: Results

Table III shows the projected outcomes for HPV reflex testing with expedited retesting, as well as naive reflex testing. Figure III depicts the percentage improvement relative to LBC baseline.

Table III: Test statistics for LBC and HPV-reflex modalities

Screening type	False negatives per 1,000 women (95% CI)	False positive (excess colposcopy) per 1,000 women (95% CI)	Percentage correct results for patients (%)
LBC Screening (Reference value for comparison)	*4.9 (3.5 - 6.7)*	*95.1 (93.1-97.0)*	*~90.0%*
HPV / LBC reflex (No retesting)	6.4 (5.1-8.0)	9.6 (9.4-9.8)	~98.4%
HPV / LBC reflex (Retesting, Pessimistic: 0% HPV clearance)	2.2 (2.1-2.3)	63.5 (63.1-63.8)	~93.4%
HPV / LBC reflex (Retesting, Optimistic: 70% HPV clearance)	2.2 (2.1-2.3)	28.2 (27.9-28.5)	~96.9%

Figure 3: Percentage improvement (measured as reductions) in (a) false positive results and (b) false negative results of HPV-reflex screening modalities relative to LBC method comparison.



Section 4: Conclusions

- Expedited retesting markedly reduces the rate of false negatives relative both to naive HPV-reflex and to LBC only approaches. For a typical population, the expected false negative rate is an effective 2.2 per 1,000 women screened. This result is agnostic to whether pessimistic (0% HPV clearance) or optimistic (70% HPV clearance) is assumed.
- Expedited retesting does however reduce one of the advantages of naive HPV reflex screening, resulting in a significantly higher false positive rate. This is dependent on the HPV clearance rate, but even under the pessimistic 0% annual clearance assumption, the false positive rate of expedited retesting is still below that of conventional LBC.
- Accordingly, it is reasonable to conclude that expedited HPV screening is superior to LBC in all aspects, superior to naive HPV-reflex screening in terms of false negative rates, and inferior to naive HPV-reflex screening from a false positive rate perspective.
- The current Irish implementation of CervicalCheck is thus expected to have an effective false negative rate rounded to an integer of 2 missed CIN2+ cases per 1,000 women per round of screening, and 18 correctly detected CIN2+ cases per 1,000 women per round of screening presuming a CIN2+ prevalence of 2% in line with international estimates for pool western populations.

Limitations and caveats

The estimates given here have a number of limitations that must be considered in usage and extrapolation. These are namely:

- Estimates assume a mean rate of HPV infection, and a steady proportion of CIN2+ cases in the general screening population. In reality this is likely to vary by subpopulations, but should suffice for the estimates for a national screening population. See prior screening reports on HPV incidence by age for more information.
- These models hinge on a steady state of CIN2+ cases in the general population, in the order of 2%. This varies by subgroup, as indeed does HPV infection. The numbers here only reflect the general case, and caution should be urged in making inferences from this for any particular subgroup.
- If full subgroup data is desired, the appended transition probabilities are appended in the supplementary material at the end of this document, and can be readily updated for any desired population whose infection parameters are known.

Section 5: Disclaimer

All data in this report is for guidance only, and should not be taken as legal or medical guidance on its own merit. Estimates in this work are subject to revision as improved data becomes available, and is subject to the limitations discussed herein.

References and sources

1. Wilson JM, Jungner G, World Health Organization. Principles and practice of screening for disease. WHO. 1967
2. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet. 2004 Jul 17;364(9430):249–56.
3. Smith M, Canfell K. Impact of the Australian National Cervical Screening Program in women of different ages. Med J Aust. 2016 Oct 17;205(8):359–64.
4. Smith MA, Edwards S, Canfell K. Impact of the National Cervical Screening Programme in New Zealand by age: analysis of cervical cancer trends 1985–2013 in all women and in Māori women [Internet]. Vol. 28, Cancer Causes & Control. 2017. p. 1393–404. Available from: http://dx.doi.org/10.1007/s10552-017-0967-y
5. Franco EL, Mahmud SM, Tota J, Ferenczy A, Coutlée F. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. Arch Med Res. 2009 Aug;40(6):478–85.
6. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014 Feb 8;383(9916):524–32.
7. Grimes DR, Corry EM, Malagón T, O'Riain C, Franco EL, Brennan DJ. Modeling cervical cancer screening strategies with varying levels of human papillomavirus vaccination. JAMA network open. 2021 Jun 1;4(6):e2115321-.
8. Koliopoulos G, Nyaga VN, Santesso N et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database of Systematic Reviews. 2017(8).
9. Hall MT, Simms KT, Lew JB et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. The Lancet Public Health. 2019 Jan 1;4(1):e19-27.
10. Kim JJ, Burger EA, Regan C, Sy S. Screening for cervical cancer in primary care: a decision analysis for the US Preventive Services Task Force. Jama. 2018 Aug 21;320(7):706-14.
11. Adebamowo, Sally N., et al. "Clearance of type-specific, low-risk, and high-risk cervical human papillomavirus infections in HIV-negative and HIV-positive women." Journal of Global Oncology 4 (2018): JGO-17.
12. Veldhuijzen, Nienke J., et al. "Factors affecting transmission of mucosal human papillomavirus." The Lancet infectious diseases 10.12 (2010): 862-874.

Supplementary material and legend

A transition markov chain model for expedited retesting with algebraic notation for transition probabilities is available here. The following abbreviations are used in that diagram for clarity.

Parameter	Symbol
Incidence of CIN2+ in a given population	*p*
Incidence of HPV in a given population	h
Proportion of CIN2+ cases attributable to HPV	v
HPV clearance rate (annual)	r
Sensitivity of HPV test for HPV	Snh
Specificity of HPV test for HPV	Sph
Sensitivity of LBC test for CIN2+	Snl
Specificity of LBC test for CIN2+	Spl

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