THE IMPACT AND COST-EFFECTIVENESS OF CERVICAL SCREENING STRATEGIES IN PORTUGAL

Diana Mendes

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy of the
University of London

April 2019

Department of Infectious Disease Epidemiology

Faculty of Epidemiology & Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded by Fundação para a Ciência e a Tecnologia (FCT), Portugal

Research group affiliation: Modelling & Economics Unit, PUBLIC HEALTH ENGLAND

Declaration

I, Diana Mendes, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: 

Date: 27 June 2018

Abstract

Despite having a similar healthcare system, Portugal has almost 50% higher cervical cancer incidence than the United Kingdom and twice that of its neighbouring country Spain. This disparity is particularly noteworthy in the European context, where countries who have invested in organised screening have seen significant reductions of the burden of cervical cancer and have started the transition to a molecular-based assessment of risk for progression to cancer enabled by technologies like HPV testing.

The overall aim of this thesis was to evaluate the clinical impact and cost-effectiveness of alternative cervical screening strategies in Portugal. This was achieved by (i) identifying the key factors determining burden of cervical cancer in Portugal, (ii) reviewing the literature on model-based evaluations of cervical screening, (iii) parameterising, adapting, and calibrating an existing mathematical model of HPV infection and progression to cervical cancer to Portuguese sexual behaviour, HPV prevalence and cervical cancer incidence, and (iv) evaluating the clinical impact and cost-effectiveness of alternative screening protocols.

The first analysis found that cervical cancer incidence and mortality in Portugal would likely have declined more sharply had screening been organised, based on a comparison on burden and risk factors for cervical cancer in England. The review of the literature on modelling cervical screening showed that model calibration to country-specific data is not standard practice yet and that there was only one cost-effectiveness analysis concerning Portugal, which did not investigate the utility of the currently relevant technologies.

In the analysis of the impact of alternative screening protocols, our mathematical model predicts that primary HPV DNA screening as part of an organised programme is likely more effective than cytology-based strategies preventing cervical cancer cases. The economic evaluation showed that HPV primary screening with extended interval may be cost-effective but this is highly dependent on the unit cost of HPV DNA testing relative to cytology.

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Acknowledgements

I would like to thank everyone who helped me throughout this adventure. Firstly, to my supervisors Prof. Mark Jit and Dr. Marc Baguelin who gave me the opportunity to join their team to learn and attempt modelling infectious disease. Mark, thank you for all the time you made available to me and this project, and for your knowledge and guidance throughout. Marc, thank you for your sensible observations and critical appraisal of the work.

I am immensely grateful to Dr. Iren Bains for all the sharing, teaching, and close support along this steep learning curve. My sincere thank you to Prof. John Edmunds, who welcomed me at the School, for his crucial direction in the initial stages of the PhD. I am also obliged to Dr. Angela Pista for sharing data and knowledge and for her fundamental guidance in my investigations of the Portuguese context. In the Infectious Disease Epidemiology Department at LSHTM, I am also thankful to Dr. Emilia Vynnycky and Prof. Judith Glynn for their inspiration and wise advice. Also at the School, I owe to Andrea for his superb wit and always positive outlook on life, and to Lori, Chris, Bindu, Maud, Andreia, and Frank for their fellowship and support. My gratitude also goes to Tazio for pivotal talks preceding the start of my PhD.

At Public Health England, I am grateful to Dr. Tendai Mugwagwa for the helpful discussions on modelling and beyond. Thank you for your great support. I am also obliged to Dr. Sheeja Krishnan and Mr. Norman Hansen for their critical help in the final stages of this PhD. I must also thank Dr. Peter White and Dr. Yoon Choi for having me at the modelling unit where I had the gratification of sharing these years also with Alicia, Perrine, Nathan, Timo, Koen, Esther, AJ, Gayle, and many other whose help I could not have done without. I am also grateful to the colleagues in the medical statistics unit as Stephano, Nikos, Ross, and a specific thank you to Tom Nichols for helpful discussions.

In Portugal, I would also like to thank Dr. Nuno Miranda and Dr. Cristina Portugal for key information on cervical screening programmes, as well as to the regional coordinators of the screening programmes, in particular to Dr. Fernando Tavares whose advice was fundamental to this thesis. I also owe to Dr. Jose Salvatore for his clinical practice perspective and I thank FCT for funding my studies and making this thesis viable.

Finally, I am forever grateful to my dear Joao, for your uplifting sense of humour, restless companionship, and your moral support throughout this PhD. I also thank my mum, dad, Fernanda, and Jose for all their support and care particularly in the final run of this thesis. I dedicate this thesis to Gabriela who was born during this PhD and has since transformed my life as I could not have imagined.

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List of Abbreviations

ADC	Adenocarcinomas
AIDS	Acquired immunodeficiency syndrome
APC	Annual percentage change
ARTISTIC	A Randomised Trial In Screening To Improve Cytology
ASCH	Atypical squamous cells cannot exclude HSIL
ASCUS	Atypical squamous cells of undetermined significance
BSCC	British Society for Clinical Cytology
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CFR	Case-fatality risk
CIN	Cervical intraepithelial neoplasia
CLEOPATRE	Cervical Lesions Observed by Papillomavirus Types – A Research in Europe
CVG	Cost per vaccinated girl
DNA	Deoxyribonucleic acid
EASR	European age-standardised rate
FIGO	International Federation of Gynecology and Obstetrics
HC	Hybrid capture
HIC	High-income countries
HIV	Human immunodeficiency virus
HPRU	Health Protection Research Unit
HPV	Human papillomavirus
HRQoL	Health-related quality of life
HSIL	High-grade squamous intraepithelial lesion
ICER	Incremental cost-effectiveness ratio
INFARMED	Portuguese National Authority of Medicines and Health Products
IQR	Inter-quartile range
LBC	Liquid-based cytology
LMIC	Low and middle-income countries
LSIL	Low-grade squamous intraepithelial lesion
LY	Life year
MCMC	Markov Chain Monte Carlo
MLE	Maximum likelihood estimator
mRNA	Messenger ribonucleic acid
NHS	National Health Service
NIHR	National Institute for Health Research
NS	no screening
OPP	Opportunistic screening
ORG	Organised screening
PHE	Public Health England
POBASCAM	Netherlands using Population-Based SCreening study Amsterdam
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSRF	Potential scale reduction factor
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RHA	Regional health administration
SCC	Squamous cell carcinomas
SS	Self-sampling
STIs	Sexually Transmitted Infections
UK	United Kingdom
USA	United States of America
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugol's iodine
WHO	World Health Organization
ZIP	Zero-inflated Poisson

1. Chapter1. Introduction

1.1.Background

1.1.1. Human papillomavirus infection and cervical cancer

Human papillomavirus (HPV) infection is a major cause of infection-related cancer worldwide, with approximately 83% of HPV-associated cancers being that of the *cervix uteri*.[1] In 2012, cervical cancer was the second most common malignancy and cancer-related deaths among women aged 15 to 44 years old worldwide.[2] This was the case in Portugal and Europe as well that year where the age-standardised (European 1976 standard population) mortality of cervical cancer was 4.9 per 100,000 women-years, and incidence was 10.8 and 13.4 per 100,000 women-years, respectively.[3]

The causal association of HPV infection with cervical cancer is currently well established, with more than 95% of cervical cancer biopsies containing high-risk HPV genomes.[4] Over seventy per cent of invasive cervical cancer was HPV16 and/or 18 positive in all world regions except Asia.[5] In Portugal, the three most prevalent high-risk HPV types in invasive cervical cancer cases are 16 (71%), 18 (10%), and 33 (9%).[6]

HPV infection is ubiquitous and sexually transmitted. Prevalence of high-risk HPV in women aged under 25 with normal cytology was 23.9 (21.4 – 26.6 95% confidence interval, CI) and 27.6 (26.9 – 28.3 95%CI) in Portugal and Europe in 2015, respectively.[7] Most infections are benign and transient, naturally cleared by immune response; however, persistent infections have higher probability of progression to invasive carcinoma.[8] The major steps of the natural history of cervical disease are HPV infection, persistence, progression to cervical precancerous lesions, and malignant cells invasion.[9]

1.1.2. Current approaches to cervical cancer prevention in high-income settings

Vaccination

Three prophylactic HPV vaccines are currently available having demonstrated safety and immunogenicity against infection by the two most carcinogenic types (HPV16 and 18). The bivalent vaccine confers protection against types 16 and 18, the quadrivalent vaccine protects additionally against HPV 6 and 11 (responsible for 90% of external genital warts in men and women), and the nonavalent vaccine immunises as well against cervical cancer high-risk types 31, 33, 45, 52, and 58.

Both bi- and quadrivalent vaccines demonstrated over 90% efficacy in HPV-naïve women (aged 15-25) at the prevention of new infections and a range of precancerous endpoints. They were also shown to induce partial cross-protection against a limited number of non-vaccine types.[10][11] The nonavalent vaccine is expected to prevent over 90% of cervical cancer cases as it has shown similar immunogenicity to the quadrivalent vaccine (regarding HPV 6, 11, 16, and 18), as well as efficacy against infection and disease by the additional 5 high-risk HPV types in women aged 16-26 years.[12]

Duration of protection has not yet been established; however, antibody persistence up to 10, 12, and 6 years has been demonstrated for three-dose schedules of the two-, four-, and nine-valent vaccines, respectively.[12–14]

High-coverage vaccination programmes are likely to considerably reduce HPV prevalence and therefore significantly impact the need to screen.[15] However, long-term efficacy monitoring is needed. The only study of the early impact of HPV vaccination of girls on cervical high-grade lesions shows significant reduction in girls aged 15-19 but no effect on those aged over 19. Also, mathematical modelling studies suggest that HPV vaccination of girls is highly cost-effective in most countries, but short-term vaccine-conferred protection could result in a delay and not a decrease in cancer incidence.[16][17]

Given the evidence of non-inferior immunogenicity for two-dose compared to three-dose schemes, the World Health Organisation currently recommends a two-dose schedule at 6 or 12 months for girls under 15 years, and several countries (including Portugal) have adopted it.[18] One-dose schedules alone or alongside screening are also being investigated as simple vaccination schemes are likely more effective.[19]

Screening

The purpose of screening for cervical cancer is to reduce its related morbidity and mortality by early detection and treatment of precancerous lesions likely to progress to cancer. For that purpose, a large number of asymptomatic individuals at risk of cancer are tested for precancerous lesions that only rarely progress to cancer. Test results determine then further diagnosis and treatment. Considering that tests are prone to error (there is always a proportion of false-positive and of false-negative results), when choosing a screening test or designing a screening strategy, the decision maker must consider the accuracy of the tests available and face the trade-off between the potential benefits and harms of screening. In cervical cancer screening, this trade-off is mainly related to the consequences of not detecting all cancer cases and to those of having a large number of false-positives or of over-diagnosing and treating naturally regressive precancerous lesions. Additionally, decision makers need to

understand the resource use and costs implied in a screening programme, which may involve a formal assessment of the programme opportunity cost (e.g. cost-effectiveness analysis).[20,21]

Cytology-based screening programmes are recognized for having significantly reduced cervical cancer incidence and mortality in countries such as Japan, Sweden, and the United Kingdom, as screening allows diagnosing and treating high-grade or persistent pre-cancerous lesions, and therefore reducing the incidence of invasive cervical cancer.[22]

Despite the introduction of vaccination programmes in some high-income countries, screening remains highly relevant worldwide. Most women at risk of cervical cancer have not been vaccinated, particularly in countries with higher burden of cervical cancer, and it will take many years before all women in screening ages are vaccinated.[23] Moreover, the bi- and quadri-valent vaccines available before 2015 confer nearly full protection against a few high-risk HPV types only (accountable for about 70% of cervical cancer).[24] Besides the demonstrated high efficacy (over 95% for CIN3) in women without prior exposure who adhered to all aspects of the trials' protocol, the intention-to-treat cohorts (including women with prior exposure to HPV) showed lower efficacy (about 45% for CIN3).[10,25]

Vaccination is expected to reduce the incidence of pre-cancerous lesions and therefore to reduce the positive predictive value of cytology or any other screening technology as well, implying a reassessment of screening strategies.[24] The timing of such reassessment depends on the age of vaccinated girls (mainly the oldest catch-up cohort and its coverage) and the starting age for screening. Moreover, as efficacy in pre- and early-adolescents, currently the primary targets for vaccination, has not been demonstrated (trials in this age group would require longer follow-up), screening has also be used to assess the impact of vaccination and gather evidence on changes in prevalence of the several HPV types.[10,15,26]

Screening technologies and strategies

The selection of a particular screening test depends ultimately on the existing evidence of its clinical utility for a given role as part of a screening strategy, i.e. its impact on improving patients' health outcomes in the relevant population, compared to a comparator strategy (current best standard practice).[27,28] Provided evidence of its clinical utility, other characteristics of the screening test are considered before recommendation of its integration in a screening strategy, namely its cost-effectiveness and its broader impact in society (e.g. acceptability and feasibility of implementation).

Screening for cervical cancer aims at early detection of a rare preventable life-threatening disease. Hence, a highly sensitive test is preferred to detect as many people with progressive

precancerous lesions as possible (minimising the number of false negatives, in contrast with a scenario of high prevalence of a deadly disease where a highly specific test would be preferable aiming at minimising the number of false positives, as not to treat women without cervical cancer).

As an ideal precursor of cervical cancer (only present in women that will develop the disease) has not been found yet, none of the available screening tests distinguishes perfectly women that will develop cervical cancer from those that will not. Currently used precursors and biomarkers are present in both groups of women in overlapping levels and test results depend on the threshold established for that particular test (e.g. cytological abnormal outcomes occur in women who will and will not develop cancer and the current threshold for diagnosis referral varies from atypical squamous cells of undetermined significance (ASCUS) to high-grade intraepithelial lesion (HSIL)).

Therefore, the selection of a technology for cervical screening entails a trade-off between sensitivity and specificity where the lower the threshold, the more sensitive the test becomes (larger number of true positives) and less specific the test is in identifying as negative women who will not develop cervical cancer (larger number of false positives as well). So that this later group of women, who will not develop cancer despite testing positive at a primary screening stage, are not referred to diagnostic testing (by colposcopy – an expensive medical procedure of visual inspection of the cervix with a colposcope that can cause discomfort and anxiety[29]), a triage screening test can be performed to reduce the proportion of false-positive results or to help interpreting ambiguous results, as to distinguish those who are at greater risk of cancer from those who are not and select only the first for further testing.[21]

Cervical cytology, using the Papanicolaou test, or Pap smear is the most commonly used screening procedure in high-income countries, broadly consisting of the microscopic analysis after staining of collected cells to detect epithelial cell abnormalities or malignancy.[30] The conventional method is still widely used in Portugal and involves a sample collected with a spatula which was smeared onto a glass slide and then fixed.[31,32]

Cytology accuracy is highly variable as it depends on the availability of adequately collected samples and well-trained cytotechnicians, leading to high rates of false negatives. Its sensitivity is on average 53% (ranging from around 20% to 75%), and its average specificity is 97%. [33] Cytology is based on the subjective interpretation of morphological cellular alterations, and the repetitive nature of work leads to errors of interpretation. Given its low sensitivity, women are asked to repeat cytology frequently before they can be safely followed according to an extended screening schedule.[24]

In liquid-based cytology (LBC), the cervical sample is put in a fluid medium which contains fixative and the cells are then selected and fixated onto a slide producing a more homogeneous preparation of cervical cells.[32] Compared with conventional cytology, LBC results in a lower proportion of unsatisfactory smears, enables faster interpretation, and allows repeated smears from the sample and the application of other techniques (e.g. HPV DNA testing) to that same sample. LBC has therefore made processing cellular samples easier compared with conventional cytology by improving sample adequacy and laboratory productivity. However, LBC has not demonstrated to be more sensitive than the conventional cytology, and thus this limitation remains.[24,34,35]

Following the discovery of a causal relationship between persistent high-risk HPV infection and cervical cancer, several technologies have been developed to detect HPV DNA and other biomarkers in smear samples, aiming at overcoming the current limitations of cytology. These relate mainly to its subjectivity, its variable sub-optimal accuracy in detecting precancerous lesions most likely to progress, and its costs.[22,36] As a technique dependent on the interpretation of a highly trained cytotechnician that uses qualitative criteria to identify cells with altered morphology, cytology reproducibility and accuracy is highly variable. Some molecular-based tests are thought to have the potential to improve cytology's accuracy and reproducibility (e.g. p16 immunostaining), while other are thought to be promising alternatives to cytology (e.g. HPV DNA, p16/ki-67 dual immunostaining, or methylation markers) as they can be subject to automated quantification. However, only HPV DNA testing (with or without genotyping) is currently used in clinical practice.[37–39]

High-risk HPV DNA testing has been diversely integrated in different cytology-based algorithms: for triage of minor cytological abnormalities (e.g. in Canada, and Catalonia, Spain), as an adjunct test to cytology screening (i.e. co-testing in the USA and Spain), and as test of cure after treatment in the UK. In Portugal, LBC with HPV triage has been introduced gradually with the implementation of regional organised cervical screening programmes.[31]

More recently, HPV DNA testing has been adopted as primary screening test by several countries, such as the Netherlands and Sweden,[40][41] following robust evidence of its greater sensitivity to CIN3 and cancer compared to cytology, lower risk of precancer for HPV-negative women (compared to cytology-negative) allowing for extension of the screening interval, and efficiency in improving screening coverage when offered as self-sampling. [42] [43]

The introduction of HPV DNA testing in primary screening for cervical cancer entails introducing a strategy for the management of HPV-positive women, given the potential over screening and treatment of women with temporary infections. Most countries where HPV DNA

testing has been introduced as primary test have selected cytology alone for triage of HPV-positive women, whereas a few chose to use HPV 16/18 genotyping as well (e.g. Australia and New Zealand) with immediate colposcopy of HPV 16/18 positives.[41]

There is extensive evidence of the clinical validity of cytology in triage of high-risk HPV-positive women from European randomised controlled trials, and that its use in triage of HPV-positive women can safely reduce the high colposcopy referral rates expected with HPV primary screening.[42] However, cytology triage is still reliant on subjective morphological assessment which entails inter-site performance variation and permanent investment on quality assurance and training of specialist technicians, and it is not applicable to self-sampling.

Using HPV 16/18 genotyping to triage high-risk HPV-positive women is based on their high prevalence in cervical cancer (65% and 17% for HPV 16 and 18, respectively) and increased risk of precancer and cancer for women infected by these HPV subtypes.[44] [43] HPV 16/18 genotyping has shown higher sensitivity and similar positive predictive value for CIN3+ as cytology ASCUS+ in triage of HPV-positive women, while necessarily entailing over referral to colposcopy and potential over screening and over treatment.[45][46]

Other potentially useful tools for triage of HPV-positive women with some evidence of superior clinical performance compared to cytology alone or combined with HPV 16/18 genotyping include p16/Ki-67 dual stained cytology, and viral and host methylation markers.[47][48][49][50] Methylation biomarkers would additionally enable to primary screen and triage self-collected samples. However, evidence from large head-to-head comparisons of biomarkers is needed to fully assess their utility as part of HPV primary screening algorithms.[51]

Novel programmes are expected to move towards a comprehensive and integrated approach to screening and vaccination, including the transition to HPV primary testing and appropriate triage, the expansion of self-sampling, and exploring options for screening vaccinated cohorts.[52][41]

Mathematical modelling

Mathematical models have been widely used to assess the impact of one or several of the multiple technologies available in distinct roles within strategies for the prevention of cervical cancer.[53][54] The range of options for preventing cervical cancer has rapidly increased, making the process of determining optimal algorithms for cervical screening increasingly complex. Mathematical models have allowed synthesising evidence from an extensive range of sources and simulating setting-specific scenarios that would be unfeasible or unethical in

clinical practice. Often assumptions are incorporated to overcome particular limitations of the evidence available and sensitivity analysis is used to explore their impact on model results.

Recent examples of epidemiological and economic modelling used to help inform policy decisions concerning cervical screening include cost-effectiveness analyses of HPV primary screening and can comprise vaccinated cohorts besides unvaccinated ones.[55][56] Recently revised screening policies in Australia and New Zealand, for instance, where HPV primary screening with partial genotyping for both unvaccinated and vaccinated women has been introduced, made use of mathematical models to study the epidemiologic and economic impact of primary HPV protocols compared to cytology-based ones.[56–58] Cost-effectiveness analyses of integrated approaches to cervical cancer prevention have found vaccination and HPV primary screening with cytology triage of HPV-positive women optimal compared to cytology-based approaches and likely to allow for a prolonged screening interval in vaccinated cohorts.[59]

Although screening based on vaccination status is likely more cost-effective than a uniform strategy (given the lower risk of cervical cancer of vaccinated cohorts than unvaccinated ones), the accurate identification of who has been vaccinated will be challenging and dependent on the linkage of screening and vaccination registries. A uniform screening strategy may be the only possible option or may become cost-effective as the number of vaccinated women of screening age and the subsequent herd immunity effect increase over time. Primary HPV screening will facilitate the monitoring of HPV 16/18 prevalence among unvaccinated women and mathematical models have been used to identify the level of herd immunity at which reducing the screening intensity of unvaccinated women may be safe and cost-effective.[60]

1.2.Thesis outline

1.2.1. Rationale

Despite having a similar healthcare system, Portugal has almost 50% higher cervical cancer incidence than the United Kingdom and twice that of its neighbouring country Spain.[61] This disparity is particularly noteworthy in the European context, where countries who have invested in organised screening have seen significant reductions of the burden of cervical cancer and have started the transition to a molecular-based assessment of risk for progression to cancer enabled by emergent technologies, with growing concern for women at high risk of cervical cancer who do not regularly participate in screening programmes.[62][38]

In 2008, thirty years after the introduction of opportunistic screening in Portugal, HPV vaccination of girls was included in the National Immunization Plan and the implementation of regional cytology-based organised programmes with distinct protocols began. Since then,

efforts towards the expansion of the existing protocols and their merger into a uniform national programme (including Lisbon and Tagus Valley where organised screening has just been introduced in some areas) have been made.[31]

The emerging pertinence of adopting HPV DNA testing for primary cervical screening was highlighted in the last report by the Portuguese Directorate-General of Health, and HPV 16/18 genotyping with cytology triage of positive results for other high-risk HPV types (being piloted in the North region) has recently been endorsed as primary test by the Portuguese Ministry of Health.[31,63] HPV primary screening can enable the extension of the screening interval, tailoring screening protocols to women's risk of cervical cancer (increasingly relevant as the first vaccinated cohorts reach the age of first screen), and improving attendance of women who do not usually engage with screening via self-sampling.[23,64]

The outstanding burden of cervical cancer in Portugal alongside the current transition from the regional diversity of regimes and protocols for cervical screening to a joined HPV-based approach calls for an investigation of the potential impact of a uniform well-organised programme.

Hence, it is timely to investigate the key factors driving the relatively high burden of cervical cancer in Portugal and the potential effectiveness of alternative screening strategies, including an evaluation of their economic implications.

1.2.2. Aims and objectives

The overall aim of this thesis was to evaluate the cost-effectiveness of alternative cervical screening strategies in Portugal. For this purpose, the following intermediate main objectives were set:

1. To characterise the current state of HPV infection and cervical cancer epidemiology in Portugal and identify the key factors determining the disease burden

2. To identify existing evaluations based on mathematical models of cervical screening in Portugal and review the methods currently used to model cervical screening in distinct settings

3. To investigate the impact of distinct screening policies in Portugal, via the adaptation of an existing mathematical model of HPV infection and disease progression to the Portuguese context

4. To evaluate the cost-effectiveness of alternative cervical screening protocols in Portugal

These objectives were met by undertaking the research described in the individual chapters of this thesis.

1.2.3. Structure of the thesis

Chapter 2 meets objective 1 of this thesis providing a comparative analysis of the time trends of the burden of cervical cancer, risk factors, and preventive interventions in Portugal and England. While investigating the epidemiology of cervical cancer in Portugal (aiming at characterising it as best as one could in the parameterisation of our mathematical model) and adapting a model originally developed for the English context, England emerged as a pertinent comparator given its successful experience with organised screening in reducing the burden of cervical cancer. Hence, evidence from a range of data sources was gathered to analyse the elements that could have affected cervical cancer incidence and mortality in both countries.

Chapter 3 presents the results of a systematic review of the literature on mathematical models of cervical screening conducted to address objective 2. It gives a comprehensive overview of model-based effectiveness and cost-effectiveness analyses of cervical screening strategies, covering epidemiological and economic studies of the full range of technologies available in different settings, including screening of vaccinated populations.

Chapter 4 gives a detailed description of the adaptation of an existing mathematical model of HPV infection and progression to cervical cancer, including the analyses performed for model parameterisation, calibration, and to assess the effectiveness of distinct screening algorithms. This piece of work meets objective 3.

Chapter 5 provides a cost-effectiveness analysis of cervical screening protocols in Portugal, addressing objective 4. It includes a comparison of the impact of cervical screening strategies in terms of predicted cost, cancers prevented, and life years and quality-adjusted life years saved, together with details on the methods used for the economic analyses performed and a discussion of the results obtained.

Chapter 6 discusses the main findings of the work presented in all previous chapters and areas of further research.

1.2.4. Contribution of the candidate to the thesis

The candidate conducted the investigations involved in the four research papers presented in this thesis, including literature review, analysis, and preparation of all drafts. Hence, the candidate is the first author of the four research papers. The first two have already been published and the last two are in preparation for submission. The co-authors' contribution to the manuscripts is detailed at the start of each chapter of this thesis, consisting mostly of comments on the drafts prepared by the candidate.

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2. Chapter 2. Determinants of burden of cervical cancer in Portugal and England

2.1.Preamble to research paper 1

As the introduction chapter indicates, identifying the key drivers for the relatively high burden of cervical cancer in Portugal was motivated by two reasons: (i) to better understand current cervical cancer epidemiology in Portugal, as well as identify factors driving current morbidity and mortality, and (ii) to gather the best available evidence to properly parameterise a mathematical model used to investigate the impact of alternative screening policies in Portugal.

A comparison of cervical cancer epidemiology between Portugal and England was conducted, motivated by the need to adapt an existing mathematical model developed by Bains and colleagues (detailed in the Appendix to this thesis) to help inform decisions on cervical screening policies in England, to the Portuguese context.

The burden of cervical cancer among Western European countries has been higher in the North than in the South[1]. Portugal and England were exceptions to this trend, so comparing them allowed identifying the country-level differences that caused Portugal and England to differ from each other as well as from their regional counterparts.

Research paper 1 demonstrates how the 20-year time lag in the adoption of widespread organised cervical screening is highly likely to be the key driver of these differences. Key lessons for cervical cancer surveillance and prevention relevant throughout Europe can also be drawn from this investigation.

Data for a wider region such as England and Wales, Great Britain, or the United Kingdom was used when data for England only was not available. Despite the existing differences in HPV prevalence[2]and cervical screening policies[3-6] between the different nations of the UK, cervical cancer incidence has been similar over time in the 4 constituent countries, and at 8.2, 9.6, 11.1, and 12.1 cases per 100,000 women (EASR) in 2007 in England, Northern Ireland, Wales, and Scotland, respectively[7].

The overall crude HPV prevalence among women with normal cytology in England and the UK was 0.12 [0.09-0.15] and 0.12 [0.10-0.14], respectively[2]. Nonetheless, Wales had the lowest crude estimate 7% [95% CI 6.5-7.5%] and Northern Ireland had the highest 13% [95% CI 12-14%], with 12% [5-22%] in Scotland[2].

Screening policies have also differed slightly in target ages and frequency over time between UK nations[3-6]. Although a centrally organised NHS Cervical Screening Programme and a

national call/recall system were introduced in England and Wales since 1988 (where women aged 20-64 years were invited for cervical screening at least once every 5 years), Cervical Screening Wales was formed in 1999 and introduced its own programme targeting women aged 20-64 every 3 years. In Northern Ireland, by 1993 all women aged 20-64 were invited every 5 years as part of a call/recall system, and in Scotland, women aged 20-60 years were invited for cervical screening at least once every 3 to 5 years since 1989. In 2004, the age range and frequency of cervical screening changed to 3 yearly from age 25 and 5 yearly from age 50 to 64 in England ,and this policy was adopted only more recently by Northern Ireland (2011), Wales (2013), and Scotland (2016).

Despite these policy differences, 5-year cervical screening coverage in England and Wales (women aged 25-64), and Scotland (aged 20-60) has been similar and slightly decreasing over time - from 80% to 77% in England and 79% to 78% in Wales (2005-2015), and 84% to 77% in Scotland (2006-2015), whilst in Northern Ireland 5-year coverage increased from 69% in 2000 to 77% in 2011[3-6].

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2.2.Research paper 1.

Understanding differences in cervical cancer incidence in Western Europe: comparing Portugal and England

Diana Mendes,[1,2] David Mesher,[3] Angela Pista,[4] Marc Baguelin,[1,2] Mark Jit [1,2*]

[1] Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom

[2] Modelling and Economics Unit, Public Health England, London, United Kingdom

[3] HIV and STI Department, Public Health England, London, United Kingdom

[4] National Institute of Health, Lisbon, Portugal

Publication status: Published in *The European Journal of Public Health*, 2017, doi: 10.1093/eurpub/ckx176

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Student	Diana Mendes
Principal Supervisor	Mark Jit
Thesis Title	The impact and cost-effectiveness of cervical screening in Portugal

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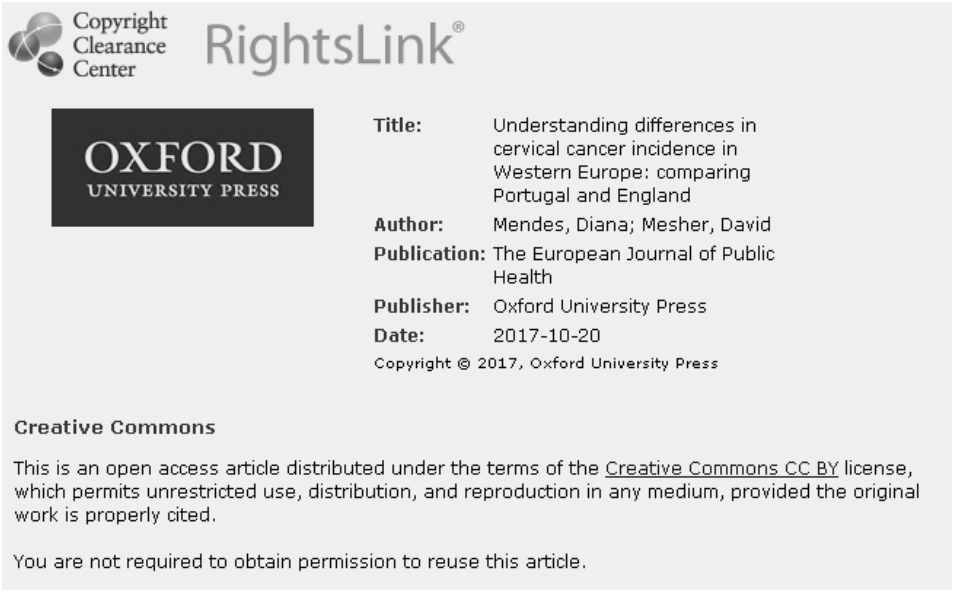

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Title: Understanding differences in cervical cancer incidence in Western Europe: comparing Portugal and England

Author: Mendes, Diana; Mesher, David

Publication: The European Journal of Public Health

Publisher: Oxford University Press

Date: 2017-10-20

2.2.1. Abstract

Background: Cervical cancer incidence has decreased over time in England particularly after the introduction of organised screening. In Portugal, where opportunistic screening has been widely available with only slightly lower coverage than that of the organised programme in England, rates of cervical cancer have been higher than in England. We compared the burden of cervical cancer, risk factors, and preventive interventions over time in both countries, to identify elements hindering the further decline in incidence and mortality in Portugal.

Methods: We used joinpoint regression to identify significant changes in rate time-trends. We also analysed individual-level Portuguese data on sexual behaviour and human papillomavirus prevalence, and recent aggregate data on organised and opportunistic screening coverage. We compared published estimates of survival, risk factors, and historical screening coverage for both countries.

Results: Despite stable incidence, cervical cancer mortality has declined in both countries in the last decade. The burden has been 4 cases and 1 death per 100,000 women annually higher in Portugal than in England. Differences in human papillomavirus prevalence and risk factors for infection and disease progression do not explain the difference found in cervical cancer incidence. Significant mortality declines in both countries followed the introduction of different screening policies, although England showed a greater decline than Portugal over nearly 2 decades after centralising organised screening.

Conclusion: The higher rates of cervical cancer in Portugal compared to England can be explained by differences in screening quality and coverage.

Keywords: human papillomavirus; cervical cancer; screening; incidence trends; mortality trends

2.2.2. Introduction

Portugal has had higher burden of cervical cancer than England. Several multi-country comparisons have shown that European countries with poor cervical screening coverage have a higher cervical cancer burden[1–4]. Reasons for the difference are not obvious because cervical cancer development is multi-factorial and depends on infection with high-risk human papillomavirus (HPV), the rate of progression of pre-cancerous lesions, and the existence of preventive interventions such as screening and vaccination[5].

Opportunistic screening has reduced cervical cancer mortality in some countries; however, it is characterised by unnecessarily frequent screening, heterogeneous quality, and poor coverage of underserved women who may be at highest risk. Well organised programmes enable high coverage of the target population, adequate follow-up, and equity of access with more efficient resource use but has yet to be implemented in many European countries[6].

Like most western European countries, England has seen a decline in the burden of cervical cancer following the introduction of cytological screening in 1964, particularly since screening was centrally organised in 1988[6].

In Portugal, cervical screening was introduced in 1978 but only on an opportunistic basis, although more recently regional organised programmes with varying coverage have been initiated. Each mainland regional health administration (RHA) and the regional health systems of Azores and Madeira are autonomously responsible for the provision of any programme. Partially-organised screening was introduced in 1990 in the Centre region. Fully-organised programmes have been introduced post-2008 with varied regional coverage in Alentejo, Algarve, Azores, and the North. Lisbon and Tagus Valley and the Autonomous Region of Madeira have not implemented such a programme yet[7].

Here we investigate the extent to which screening and other factors may have driven differences in cervical cancer incidence between Portugal and England by analysing estimates and time-trends in multiple data sets including HPV prevalence, cervical cancer incidence and mortality, screening coverage, sexual behaviour and other potential risk factors. We then explore the implications of our results for policy making across Europe.

2.2.3. Methods

Cervical cancer incidence and mortality

European age-standardised rates (EASR) were estimated using the 1976 European Standard Population. Age-standardised incidence was estimated from individual case data provided for 1998-2010 by all four Portuguese population-based regional registries (Azores, Centre, North, and South), covering 100% of the population. National estimates were pooled by weighting the regional age-specific number of cases by the respective proportion of the population. For the UK, we used estimates from EUREG and national statistics databases[8,9].

Cervical (and other uterine) cancer mortality and female population sizes for both countries were obtained from the WHO mortality database[10] and Statistics Portugal[11]. Inaccuracies in death certification were adjusted by reallocating deaths from non-otherwise specified uterine cancers to cervical cancer[1].

We performed segmented regression to analyse rate trends and identify trend joinpoints (i.e., calendar years where the slopes of two linear trends changed). The annual percentage change (APC) was estimated for each segment fitting a log-linear model with the Joinpoint software[12].

Case-fatality risk

Annual case-fatality risk (CFR) was calculated from incidence and mortality estimates, as its complement (1-Mortality/Incidence) has been considered a valid approximation of the 5-year relative survival for most cancers[13]. The two-proportion z-test was used to test whether these populations' risks differ significantly.

Cervical cancer survival

We used published 5-year survival estimates from the CONCORD-2[14] and the EUROCARE[15] studies based on cancer registries data.

HPV prevalence

We estimated age-standardised prevalence of 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) from the CLEOPATRE Portugal study which recruited 2,165 unvaccinated women aged 18-64 attending National Health Service

(NHS) gynaecology, obstetrics, and sexually transmitted disease services in 2008/9.[16] Age-specific and overall crude prevalence estimates of high-risk HPV in women attending cervical screening in England were sourced from a systematic review and meta-analysis of the main pre-vaccination studies.[17]

Sexual behaviour

Behavioural risk indicators for HPV infection were estimated from individual-level data of the 2007 survey on sexual behaviour and HIV/AIDS in mainland Portugal[18] (1,860 valid questionnaires from sexually active women aged 16-65 years). We compared these estimates with those published from the British National Surveys of Sexual Attitudes and Lifestyles (Natsal-2 in 1999-2000 16-44 years old, and Natsal-3 in 2010-2012 16-74 years old).[19] Definitions were standardised across the two surveys (additional information is available on request).

Other risk factors

Published estimates were obtained for risk factors for HPV infection acquisition, persistence, and cervical cancer progression: smoking[20], contraception use[21], fertility[22], male circumcision[23] and other sexually transmitted infections (STIs)[24,25]. We compared outcomes from European Union surveillance of human immunodeficiency virus (HIV), chlamydia, syphilis, and gonorrhoea in both countries. Data on these risk factors were only found for the UK.

Cervical screening

Cervical screening coverage in Portugal prior to the introduction of organised programmes (2008) was obtained from the literature[26,27]. Coverage post-2008 was estimated from aggregate data provided by RHAs in mainland Portugal. Coverage of opportunistic screening was derived from the number of conventional cytology tests reimbursed to contracted laboratories in 2010-2014. For England, we used published screening coverage estimates[28].

2.2.4. Results

Cervical cancer incidence

Annual incidence of cervical cancer in Portugal in 1998-2010 ranged from 11.6 (10.8-12.5) to 14.3 (13.4-15.3) per 100,000 women; the negative linear trend over that time period was not significant (Supplementary Table 2-1 and Figure 2-1). In England over the same period, incidence varied between 8.0 (7.7-8.3) and 9.7 (9.4-10.1) and was similarly stable in the 2000s. We estimated a positive APC in 1977-1988 followed by a negative APC in 1988-1998, but no evidence of a change in incidence in 1999-2011.

In England, the peak age of cervical cancer incidence has shifted from after 45 years in the early 1980s to around 30-45 years in the late 1990s. In Portugal, it peaked at 40-49 year olds in 1998-2010 (Supplementary Figure 2-1).

Cervical cancer mortality

For Portugal (1955-2013), we estimated 2 joinpoints in cancer mortality at 1970 and 1982. There was no evidence of a change in mortality until 1970, with a decline thereafter (Figure 2-1 and Supplementary Table 2-1). Three trend periods were estimated for England with joinpoints in 1964, 1988, and 2006. The APC has declined since 1950, with the steepest decline in 1988-2006.

In 1998-2010, average cervical cancer incidence in Portugal exceeded that in England by 4 cases per 100,000 women. However, cervical cancer mortality was similar between countries (on average 1 more death per 100,000 women annually in Portugal than in England). Both countries show a period-specific effect as age-specific rates declined similarly in consecutive periods and birth cohorts across all age groups apart from the youngest (20-29 and 30-39 years old) (Supplementary Figure 2-2 and 2-3).

Case-fatality risk and survival

Cervical cancer CFR was higher in England (mean 0.33, range 0.24-0.40, 1998-2010) compared to Portugal (mean 0.30, range 0.25-0.34, 1998-2010) but the difference was not statistically significant ($p>0.5$ every year) (Supplementary Figure 2-4). Also, CFR declined in England throughout 1996-2011 but not in Portugal (Supplementary Table 2-1).

Allemani and colleagues[14] found that 5-year net survival improved from 54% (50-58%) to 62% (60-63%) in Portugal (1998-2009) and from 58% (57-59%) to 60% (59-62%) in England (1995-2009) (Supplementary Table 2-2). Similarly, the EUROCARE database shows a greater improvement of 5-year relative survival in Portugal [from 56.5 (54.4-58.5) to 61.3 (59.5-63.1)] than in England [from 59.1 (58.6-59.6) to 59.6 (58.7-60.5)] between 1995-1999 and 2000-2007[15].

Although similar estimates were found for both countries, slightly greater survival improvement was reported for Portugal in both EUROCARE and CONCORD-2 studies, while we found a steeper decline in CFR for England (Supplementary Table 2-1). Given that population-based survival estimates from high data quality are available, our CFR estimates must be considered cautiously and their complement should not be used instead of 5-year relative survival estimates.

Human papillomavirus prevalence

High-risk HPV prevalence among unvaccinated women with normal cytology was 5.5% (95% CI: 3.6-8.9%) in Portugal and 10.4% (4.5-18.7%) in the UK. The age distribution was similar in both countries, with peak prevalence at 20-24 years of age, followed by a decline until age 40 (Supplementary Figure 2-5). The overall crude high-risk HPV prevalence was similar in England and the UK.

Sexual behaviour

Women's median age of first heterosexual intercourse was higher in Portugal (19 years) than in Great Britain (17 years) (Supplementary Table 2-3). The age difference between partners at start of the relationship was smaller in Portugal compared with that in Great Britain, with 76% and 63% being ≤5 years, respectively.

Portuguese women had fewer lifetime partners than British women, but the number of partners over the last year and the proportion of women with ≥1 new partner last year were similar in both countries. Portuguese women reported 8% of relationships lasting less than 1 month, whereas in Great Britain these account for 51% of the relationships. In both countries, over 30% of reported relationships overlapped.

Overall, Portuguese women were at lower behavioural risk of acquiring HPV from their partners given their later sexual debut, fewer number of lifetime partners per year and fewer short-term relationships.

Other risk factors

Smoking, the number of full-term pregnancies, the use of oral hormonal contraceptives, and exposure to other STIs have been associated with cervical cancer. Conversely, there is robust evidence of inverse association between male circumcision and HPV acquisition and consequent development of cervical cancer[5].

Both Portugal and the UK have shown a decreasing trend in tobacco use over the last decade[20], with the prevalence of smoking lower in Portugal than in the UK (Supplementary Table 2-4). The Portuguese fertility rate was lower in the early 2000s than in the UK[22]. However, Portugal has higher hormonal contraceptive use, lower condom use and lower prevalence of male circumcision compared to the UK [21,23].

The UK has higher gonorrhoea and syphilis incidence, whilst Portugal has higher HIV incidence [24,25]. Portugal has no organised Chlamydia surveillance system so Chlamydia prevalence cannot be compared with the UK[25].

Cervical screening

Cervical screening in Portugal and England differ both in quality and coverage. There is a 20-year lag between countries in the introduction of fully-organised programmes (Figure 2-2).

In Portugal, cervical screening remains mainly opportunistic with lower coverage than in England (Figure 2-3). The proportion of eligible women aged 25-64 screened between 2012 and 2014 in Portugal was lower than in England between 1995 and 2015 (average 3-year coverage 60% *versus* 69%, respectively). Despite the introduction of organised screening post-2008 in Portugal, 3-year coverage of resident women in 2012-2014 (55%) was lower than in 2002-2003 (58%). In England, 5-year coverage also decreased over time.

Organised programmes in Portugal 2012-2014 covered at most for 40% of resident women aged 25-64; however, the proportion of eligible women invited for screening via a call/recall system varied from 6% (the North) to 60% (Alentejo), assuming 10% of

resident women are excluded for clinical reasons[7] (Supplementary Table 2-5).Over the same period, the English NHS Cervical Screening Programme was available to all resident women aged 25-64, all eligible women (94% of resident) were invited to participate, and 91% of these were adequately screened.[28]

Prior to 2008, in both countries, younger women had the lowest participation rates among women eligible for cervical screening (aged from 20/25 to 60/64, depending on the country) (Supplementary Figure 2-6).

2.2.5. Discussion

Since 1998, cervical cancer incidence and mortality has declined in both Portugal and England, but has been consistently higher in Portugal[1,29] despite lower prevalence for high-risk HPV and risk factors for cervical cancer (such as sexual activity, smoking and other STIs besides HIV) in Portugal. Indeed, HPV prevalence in England exceeds that in Portugal, with the age distributions of HPV prevalence in the two countries resembling those for Southern and Northern Europe in 1995-2009[30]. HPV vaccination was introduced in both countries too recently to have had an effect on cervical cancer incidence as the first vaccinated cohorts reached the screening age of 25 in 2015. Hence, the higher incidence in Portugal can only be explained by differences in screening.

Cervical cancer survival in England is similar to that in Portugal, despite lower incidence. This may be due to screening selectively preventing the less invasive cancers and to differences in access and effectiveness of cancer treatment between countries[31].

Registration inaccuracies have hindered trend analyses of cervical cancer[29]. More recently, Allemani and colleagues[14] used individual patient data from all four Portuguese regional cancer registries (1998-2009) who reported 100% coverage of the national population and higher overall quality compared to the European average. We assumed similar quality for the data available to us (1998-2010). We corrected for inaccuracies in deaths certification following Arbyn and colleagues' approach[1]. We reproduced their results for Portugal, the Netherlands, and the UK, and extended the analysis to 2013. The reliability of these adjustments is debatable, particularly for Portugal where the Netherlands have been used as reference country, and further

methodological research is needed. Consequently, our mortality (and CFR) estimates for Portugal may be underestimates, and the gap between countries could be even greater. These data limitations highlight the importance of high-quality registry data (which may reduce the number of deaths classified as being from uterine cancer not otherwise specified) and effective collaboration between cancer and screening registries to enable monitoring and evaluating the effectiveness of preventive interventions.

Our findings support existing recommendations for investment in well-organised cervical screening programmes[6]. Opportunistic screening may have somewhat reduced cervical cancer mortality in Portugal but not to the extent seen in England. Time-trends suggest cervical cancer rates in Portugal would have declined more sharply had screening been organised. In the UK, incidence and mortality only declined post-central organisation of screening. England (in contrast to Portugal) has seen reductions in the peak age of cervical cancer incidence[32].

These findings are likely generalizable to other European countries – most of which have or are implementing organised programmes, as previous studies showed that the increasing cohort-specific risk of cervical cancer in Europe (after the 1930-40s) was overridden earlier and more pronouncedly in Northern Europe by the decreasing period-specific risk due to effective screening[2]. Encouraging trends are seen in the Baltic countries where organised screening has been initiated and incidence is stabilising, whilst in Bulgaria and Romania (where screening is fairly opportunistic) incidence trends are still increasing[33].

Widespread opportunistic screening might also be hindering the extension of coverage of the recently implemented programmes in Portugal[6,7]. Other European countries also in transition to organised screening (including Belgium, France, Greece, Italy, Spain and many Eastern European countries) may face similar challenges. Hence, countries with no screening yet (eg. Albania, Azerbaijan) may benefit from thorough planning and implementation of organised programmes.

2.2.6. Acknowledgments

We thank the help of Pedro Moura Ferreira at the Social Sciences Institute Portugal; Nuno Miranda and Cristina Portugal at the National Programme for Oncological

Disease, General-Directorate for Health, Portugal; Tereza Lopes, Filomena Horta Correia, Fernanda Loureiro, Ana Dinis, and Fernando Tavares at the regional health administrations of Alentejo, Algarve, Centre, Lisbon and Tagus Valley, and North; Gonçalo Forjaz, Joana Bastos, Ana Filipa Gonçalves, and Alexandra Mayer-da-Silva at the cancer registries of Azores, Centre, North, and South.

DM was funded by the Foundation for Science and Technology (individual PhD studentship SFRH/BD/84974/2012) on behalf of the Portuguese Ministry of Education and Science and the Human Potential Operational Programme of the National Strategic Reference Framework, within the European Social Fund of the European Commission's 7th Framework Programme. MJ was part funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England (PHE) (grant HPRU-2012-10096). The views expressed are those of the authors and not necessarily those of the NHS (England), the NIHR, the Department of Health (England), Public Health England or NIH Portugal.

2.2.7. Conflicts of interest

None declared.

2.2.8. Key points

- Cervical cancer incidence and mortality have been higher in Portugal than in England.
- High-risk HPV prevalence, sexual behavioural risk, and the prevalence of other risk factors for cervical cancer, such as smoking and other STIs (apart from HIV), have been lower in Portugal than in England.
- Differences in cervical screening are likely to explain the higher burden of cervical cancer in Portugal compared to England.
- Cervical cancer rates in Portugal are likely to have declined more rapidly had cervical screening been organised earlier.

2.2.9. References

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2.2.10. Figures

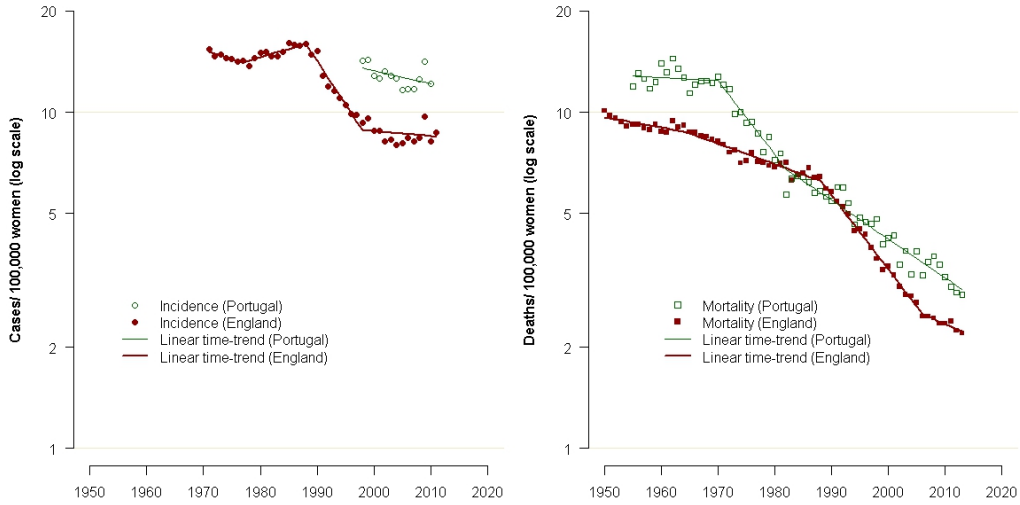

Figure 2-1. Age-standardized Cervical Cancer Incidence and Mortality by calendar period, EASR.

EASR, European age-standardised rate using the 1976 European Standard Population; dots represent annual incidence estimates; squares represent annual mortality estimates; solid lines represent lines represent linear time-trends obtained by joinpoint regression; dashed lines represent 95% confidence intervals; *Incidence data pertain to England and mortality data pertain to England and Wales

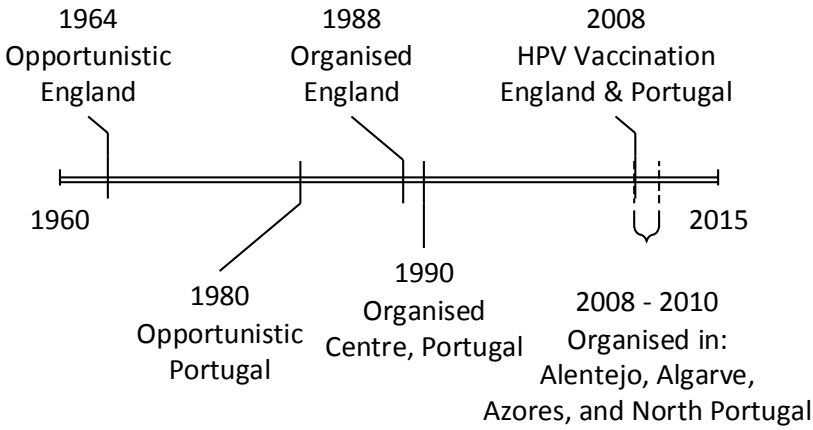

Figure 2-2. Timeline of main cervical cancer preventive interventions in Portugal and England.

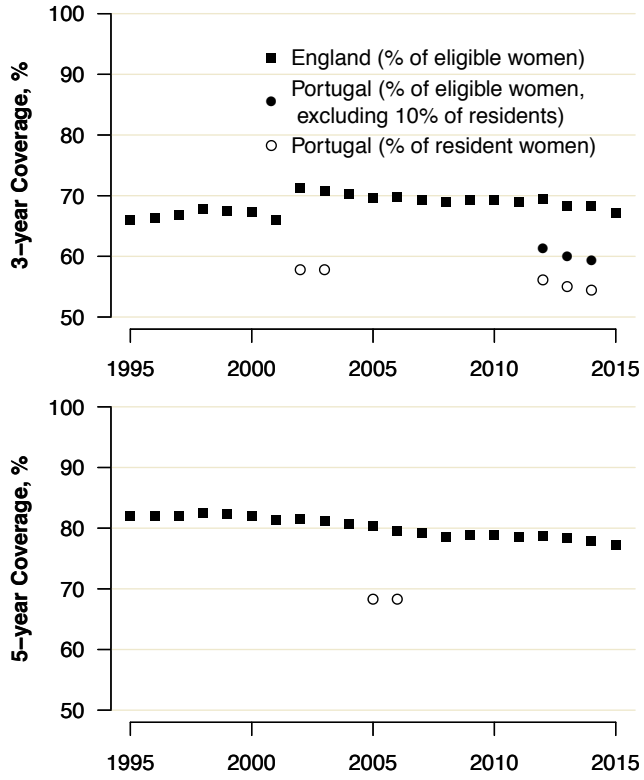

Figure 2-3. Screening coverage in women aged 25-64 in Portugal[26,27]and England[28].

For England, coverage is defined as the proportion of eligible women aged 25-64 who were screened adequately within the previous 3.5 or 5 years. For Portugal, white dots represent coverage as the proportion of resident women aged 25-64 screened within the previous 3 or 5 years, and black dots represent coverage as the proportion of eligible women aged 25-64 screened within the previous 3 years (assuming 10% of resident women are excluded for clinical reasons[7]).

2.3.Supplementary material

Supplementary Table 2-1. Joinpoints and annual percentage changes in cervical cancer incidence and mortality over time, EASR

Country (Time period)	Joinpoint(s) (95%CI)	Trend period(s)	APC (95%CI)
Incidence			
Portugal (1998-2010)	None	1998-2010	-0.9 (-1.9; 0.2)
England (1971-2011)	1977 (1973-1991)	1971-1977	-1.1 (-2.9; 0.7)
	1988 (1985-2001)	1977-1988	1.2 (0.4; 2.0)
	1998 (1994-2008)	1988-1998	-5.7 (-6.8; -4.7)
		1998-2011	-0.3 (-1.2; 0.5)
Mortality			
Portugal (1955-2013)	1970 (1966-1973)	1955-1970	-0.2 (-1.0; 0.5)
	1982 (1975-1985)	1970-1982	-4.9 (-6.1;-3.8)
		1982-2013	-2.6 (-2.9; -2.4)
England & Wales	1964 (1958-1971)	1950-1964	-0.7 (-1.1;-0.3)
(1950-2013)	1988 (1987-1990)	1964-1988	-1.4 (-1.6;-1.2)
	2006 (2002-2009)	1988-2006	-5.0 (-5.2; -4.7)
		2006-2013	-1.7 (-2.8; -0.6)
Case-fatality risk			
Portugal (1998-2010)	None	1998-2010	-1.4 (-2.9; 0.1)
England (1998-2010)	1989 (1984-1993)	1971-1989	-1.6 (-2.0;-1.2)
	1996 (1991-2001)	1989-1996	0.9 (-1.6;3.4)
		1996-2011	-3.1 (-3.8;-2.4)

APC, annual percentage change; EASR, European age-standardised rate using the 1976 European Standard Population; 95% CI, 95% confidence interval (the range of values within which the population mean may lie with 95% confidence level)

Sources:
Regional Cancer Registries from Azores, Centre, North, and South of Portugal:
[Registo Oncologico Regional Norte] Regional Cancer Registry North - RORENO [Internet]. Available from: http://www.roreno.com.pt/; [Registo Oncologico Regional Centro] Regional Cancer Registry Centre - ROR-Centro [Internet]. Available from: http://www.rorcentro.com.pt/; [Registo Oncologico Regional Sul] Regional Cancer Registry South [Internet]. Available from:http://www.ror-sul.org.pt/ContactosLinks/Pages/default.aspx; [Registo Oncologico Regional Acores] Regional Cancer Registry Azores - RORA [Internet].Available from: http://estatistica.azores.gov.pt/conteudos/Relatorios/lista_relatorios.aspx?idc=29&idsc=3570&lang_id=1
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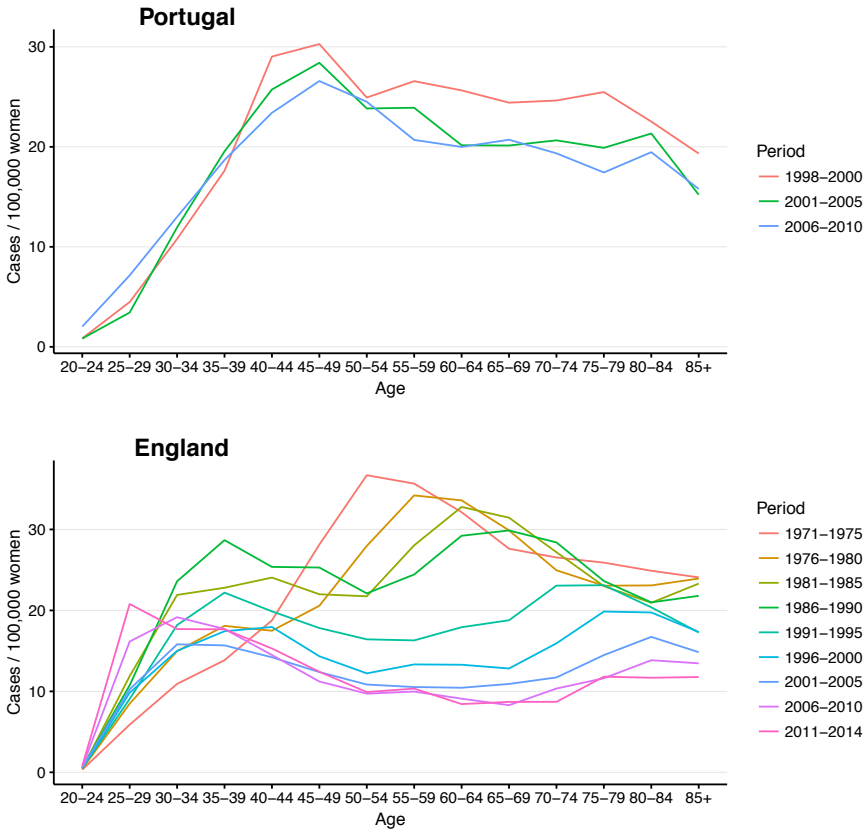

Supplementary Figure 2-1. Age-specific cervical cancer incidence in Portugal and England, EASR

Sources:
Regional Cancer Registries from Azores, Centre, North, and South of Portugal;
National Cancer Registration and Analysis Service, Number of new cervical cancer cases by year and age group in England 1971-2014, Public Health England, 2016;
Office for National Statistics. Population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-1971 to mid-2014, 2015,
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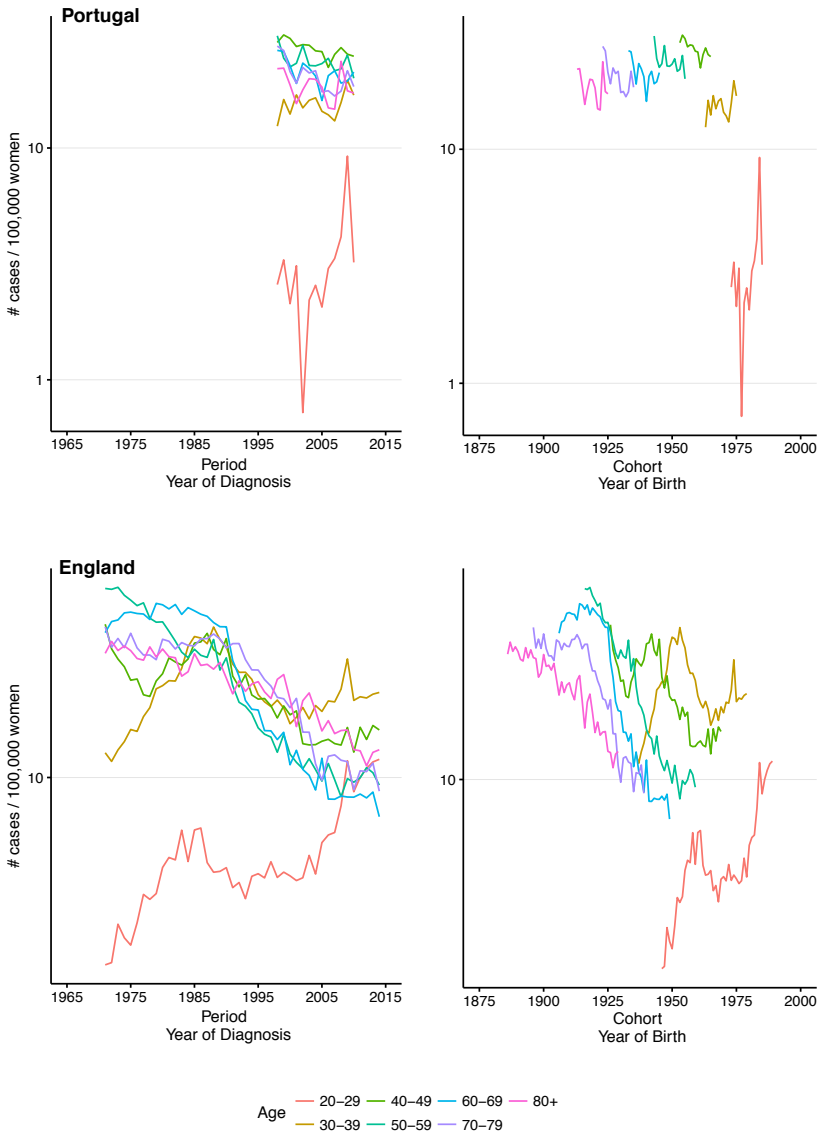
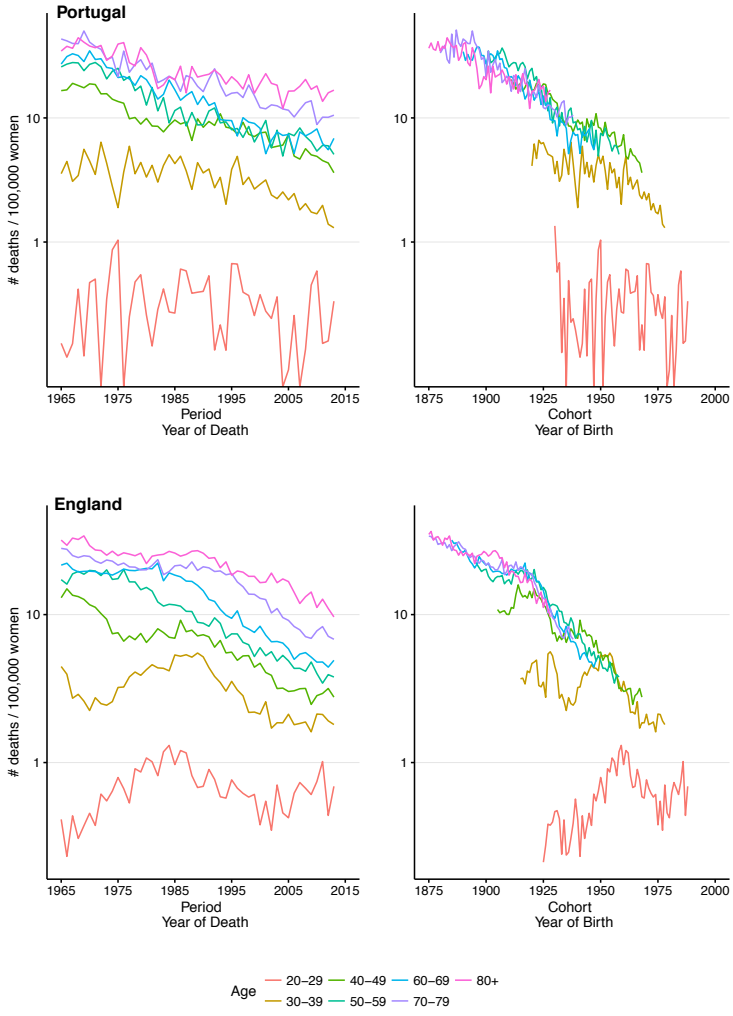


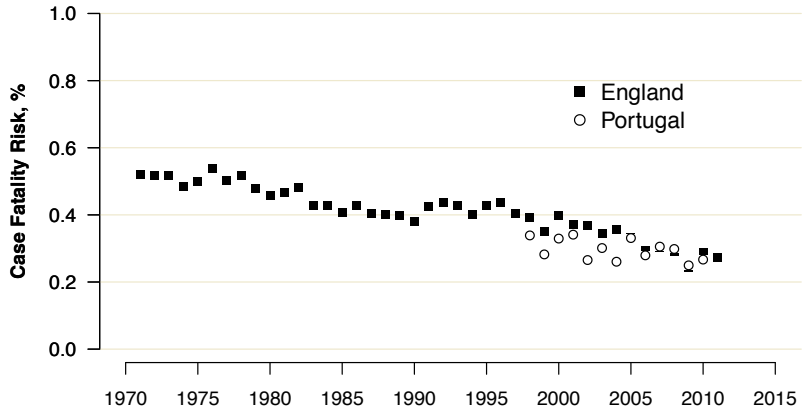
Supplementary Figure 2-2. Age-specific incidence by period and birth cohort, EASR

Sources:
Regional Cancer Registries from Azores, Centre, North, and South of Portugal;
National Cancer Registration and Analysis Service, Number of new cervical cancer cases by year and age group in England 1971-2014, Public Health England, 2016;
Office for National Statistics. Population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-1971 to mid-2014, 2015,
http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/index.html



Supplementary Figure 2-3. Age-specific mortality by period and birth cohort, EASR

Source: World Health Organization. WHO Mortality Database [Internet]. [cited 2015 Oct 29]. Available from: http://apps.who.int/healthinfo/statistics/mortality/whodpms/



Supplementary Figure 2-4. Case-fatality risk, %

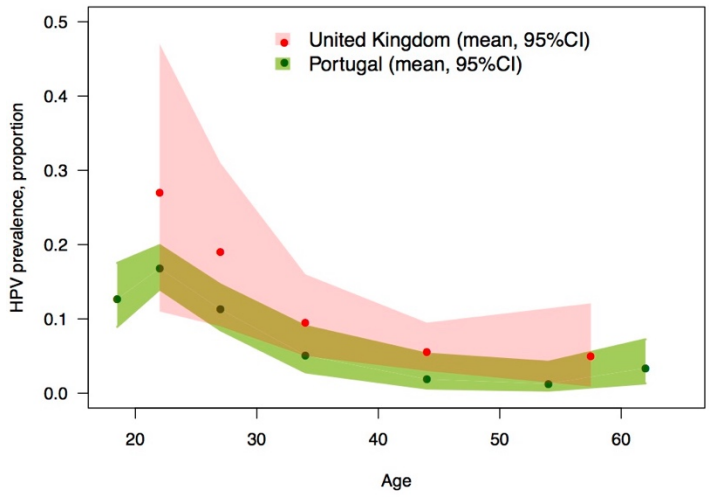
Sources: Regional Cancer Registries from Azores, Centre, North, and South of Portugal
Office for National Statistics. Cervical Cancer Incidence, mortality and survival, England, 1971-2011 [Internet]. 2011 [cited 2016 Apr 21]. Available from: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/sty-cervical-cancer.html
Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, et al. European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe [Internet]. 2012 [cited 2016 Apr 25]. Available from: http://eco.iarc.fr
World Health Organization. WHO Mortality Database [Internet]. [cited 2015 Oct 29]. Available from: http://apps.who.int/healthinfo/statistics/mortality/whodpms/
Instituto Nacional de Estatistica, IP [Statistics Portugal] [Internet]. [cited 2016 Apr 15]. Available from: www.ine.pt

Supplementary Table 2-2. Cervical cancer survival by country

		England	Portugal
5-year age-standardised Net Survival*, %[95%CI][14]			
	1995-99	58.2[57.2-59.1]	54.0[50.0-58.0]
	2000-04	59.2[58.2-60.2]	60.3[58.4-62.1]
	2005-09	60.4[59.4-61.5]	61.5[59.7-63.2]
5-year age-standardised Relative Survival*, %[95%CI][15]			
	1990-94	60.8[59.8-61.9]	54.4[48.2-61.4]
	1995-99	59.1[58.6-59.6]	56.5[54.4-58.5]
	2000-07	59.6[58.7-60.5]	61.3[59.5-63.1]

*For adults (aged 15-99 years) after diagnosis with cervical cancer; using the International Cancer Survival Standard age distributions; Net survival, cumulative probability that the cancer patients would have survived a given time after diagnosis in the hypothetical situation that the cancer was the only possible cause of death; Relative survival, ratio of the measured survival of patients to the expected survival in the general population

Sources: [14]Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet [Internet]. Allemani et al. Open Access article distributed under the terms of CC BY; 2015;385(9972):977–1010. Available from: http://dx.doi.org/10.1016/S0140-6736(14)62038-9; [15] EUROCARE. EUROPEAN CANCER REGISTRY BASED STUDY ON SURVIVAL AND CARE OF CANCER PATIENTS [Internet]. [cited 2016 Oct 17]. Available from: http://www.eurocare.it/Database/tabid/77/Default.aspx



Supplementary Figure 2-5. Age-specific high-risk HPV prevalence in the UK and Portugal

Dots- mean estimates, shaded areas-95%CI; Sources: Pista A, Oliveira C, Cunha MJ, Paixão T, Real O, Group CPS. Prevalence of Human Papillomavirus Infection in Women in Portugal - The CLEOPATRE Portugal Study. Int J Gynecol Cancer [Internet]. 2011;21(6):1150–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21792018; Anderson L, O'Rorke M, Jamison J, Wilson R, Gavin A. Prevalence of Human Papillomavirus in Women Attending Cervical Screening in the UK and Ireland: New Data From Northern Ireland and a Systematic Review and Meta-Analysis. J Med Virol [Internet]. 2013;85:295–308. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jmv.23459/abstract

Supplementary Table 2-3. Sexual behaviour indicators

	Great Britain, Natsal 2 (1999-2000)	Great Britain, Natsal 3 (2010-2012)	Portugal, 2007
Age of sexual debut, years, median[IQR][1,2]			
All ages	17 [16-18]	17 [15-22]	19 [17-21]
16-17	17 [15-18]	nr	14.79[14-16.36]
18-19	16 [15-18]	nr	16[15-17]
20-24	16 [15-18]	nr	18[16-19]
16-24	nr	16 [15-18]	17 [16-18]
25-34	17 [16-18]	17 [15-18]	18 [17-20]
35-44	17 [16-19]	17 [16-19]	19 [17-21]
45-54	nr	17 [16-19]	19 [18-22]
55-64	nr	18 [17-20]	20 [18-24]
65-74	nr	19 [17-21]	na
Age difference of the new partner, years, mean [95%CI][3]			
All ages	2.0 [1.8;2.1]	nr	0.9 [-9.7;10.0]
16-24	nr	nr	1.9 [-2.4;11.3]
25-34	nr	nr	1.3 [-5.0; 10.6]
35-44	nr	nr	0.6 [-8.7;9.9]
45-54	nr	nr	-0.5 [-23.1;17.2]
55-64	nr	nr	-0.0 [-7.9;10]
Age difference with partner, % [95%CI] of new partnerships: [2]			
Male 5+ years older than female	24.9 [21.6 – 28.6]	nr	15.4 [12.4-18.3]
Male within 5 years of female's age	62.8 [59.2 – 66.2]	nr	76.4 [73.0-79.9]
Male 5+ years younger than female	12.3 [10.3 – 14.6]	nr	9.3 [6.9-11.7]
Number of lifetime partners, % [95%CI] [1,2,4]			
0	5.3 [nr]	4.2 [3.8-4.6]	2.2 [1.5-3.1]
1	18.3 [nr]	22.4 [21.3-23.5]	53.9 [51.3-56.5]
2	10.9 [nr]	11.1 [10·3–11·9]	15.8 [13.9-17.8]
3-4	19.6 [nr]	19.2 [18·2–20·2]	16.0 [14.1-18.0]
5-9	26.5 [nr]	23.2 [22·2–24·3]	8.7 [7.3-10.3]
>=10	19.4 [nr]	19.9 [19·0–20·9]	3.4 [2.5-4.5]
Mean [SD], Median [IQR][2, 4]			
All ages	6.5 [9.7], 4 [39]†	7.1 [32.1], 4 [1-8]	2.6 [4.6], 1 [1-3]
16-17	1.8 [11.6], 1 [16]†	nr	1.8[1.6],2[1.7-
18-19	4.9 [41.1], 3 [30]†	nr	2.2]
20-24	6.4 [78.5], 4 [33]†	nr	2.3[2.4],2[1-3]
16-24	nr	5.2 [8.1], 3 [1-7]	3.1[5.7],2[1-3]
25-34	7.3 [94.4], 5 [42] †	8.9 [17.2], 5 [2-10]	2.9 [5.1], 2 [1-3]
35-44	6.8 [115.8], 4 [41] †	8.5 [19.7], 5 [3-10]	3.0 [4.7], 2 [1-4]
45-54	nr	6.8 [11.8], 4 [2-7]	2.6 [4.1], 1 [1-3]
55-64	nr	6.1 [38.3], 3 [1-5]	2.3 [4.1], 1 [1-3]
65-74	nr	6.3 [73.9], 2 [1-4]	2.2 [5.4], 1 [1-1]
			na
Number of partners in past year, %[95%CI][1,2]			
0			
All ages	10.7 [nr]	22.3 [21·3–23·3]	18.2 [16.2-20.3]
16-17	50.0 [nr]	nr	20.7[18.6-22.9]
18-19	17.4 [nr]	nr	8.3[6.9-9.9]
20-24	10.1 [nr]	nr	8.1[6.8-9.7]
16-24	nr	23.0 [21.0-25.1]	8.4 [7.0 – 10.0]
25-34	5.3 [nr]	8.2 [7.0-9.5]	8.0 [6.7-9.6]
35-44	8.4 [nr]	9.2 [7.5-11.2]	10.3 [8.8-12.0]
45-54	nr	15.0 [13.1-17.2]	22.1 [20.0-24.4]
55-64	nr	36.3 [33.0-39.6]	42.0 [39.4-44.6]
65-74	nr	57.9 [54.0-61.7]	na
1			
All ages	76.0 [nr]	68.4 [67·2–69·5]	75.8 [73.5-78.0]
16-17	33.7 [nr]	nr	50.0[47.3-52.6]
18-19	50.8 [nr]	nr	67.5[65.0-69.9]
20-24	65.9 [nr]	nr	70.3[67.8-72.7]

16-24	nr	50.3 [47.8 – 52.7]	69.2 [66.7-71.6]
25-34	83.0 [nr]	79.1 [77.1-80.9]	85.2 [83.2-86.9]
35-44	84.3 [nr]	82.9 [80.5-85.1]	85.7 [83.8-87.5]
45-54	nr	80.5 [78.1-82.6]	74.8 [72.5-77.1]
55-64	nr	62.3 [58.9-65.5]	58.0 [55.4-60.6]
65-74	nr	41.4 [37.7-45.3]	na
≥2			
All ages	13.3 [nr]	9.3 [8·7–10·0]	6.0 [4.9-7.4]
16-17	16.3 [nr]	nr	29.3[27.0-31.8]
18-19	31.8 [nr]	nr	24.4[22.0-26.6]
20-24	24 [nr]	nr	21.6[19.5-23.8]
16-24	nr	26.7 [24.5-29.0]	22.3 [20.2-24.6]
25-34	11.6 [nr]	12.8 [11.3-14.3]	6.9 [5.7-8.4]
35-44	7.2 [nr]	7.9 [6.5-9.6]	4.0 [3.0-5.1]
45-54	nr	4.5 [3.5-5.8]	3.0 [2.2-4.1]
55-64	nr	1.5 [0.9-2.3]	0 [0-0.3]
65-74	nr	0.7 [0.3-1.7]	na
At least 1 new partner last year, % [95%CI][1]			
All ages	nr	14.5 [13·8–15·4]	10.4 [8.8-12.1]
16-24	nr	38.3 [35.9-40.7]	39.4 [36.9-42.1]
25-34	nr	19.6 [17.9-21.5]	14.3 [12.5-16.3]
35-44	nr	11.2 [9.5-13.2]	7.3 [6.0-8.8]
45-54	nr	8.9 [7.4-10.8]	2.8 [2.0-3.9]
55-64	nr	4.4 [3.3-5.9]	0 [0-0.3]
65-74	nr	2.1 [1.2-3.6]	na
Number of occasions of sexual intercourse in past 4 weeks,			
Mean [SD], Median [IQR] [1,2,4]	6.5 [6.6], 4 [28]†	4.0 [4.9], 3 [1–6]	8.4 [12.2], 5 [3-10]
All ages	nr [nr], 0 [0-3]	nr	na
16-17	nr [nr], 4 [0-10]	nr	na
18-19	nr [nr], 4 [1-10]	nr	na
20-24	nr	5.8 [6.6], 4 [1-8]	10.5 [22.5], 5 [2-12]
16-24	nr [nr], 4 [2-8]	4.9 [5.1], 4 [1-7]	9.5 [8.2], 8 [4-12]
25-34	nr [nr], 4 [1-8]	4.0 [4.6], 3 [1-5]	9.5 [13.1], 6 [4-12]
35-44	nr	3.5 [4.2], 2 [1-5]	6.6 [5.6], 5[3-9.2]
45-54	nr	2.5 [3.4], 2 [0-4]	3.8 [3.1], 3 [1.5-5]
55-64	nr	1.4 [2.3], 1 [0-2]	na
65-74			
Proportion of relationships lasting < 1 month, %[95%CI][5]	50.5 [nr]	nr	7.5 [5.0-10.2]
Proportion overlap between last two relationships, %[95%CI][6]	35 [nr]	nr	31.1 [25.8-36.8]

na, not applicable; nr, not reported; † 99th percentile; Sources: [1] Mercer CH, Tanton C, Prah P, Erens B, Sonnenberg P, Clifton S, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet [Internet]. Mercer et al. Open Access article distributed under the terms of CC BY; 2013 Nov 30 [cited 2014 Dec 12];382(9907):1781–94. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3899021&tool=pmcentrez&rendertype=abstract [2] Erens B, McManus S, Prescott P, Field J, Johnson A, Wellings K, et al. Natsal - The National Survey of Sexual Attitudes and Lifestyles [Internet]. 2003 [cited 2016 Apr 12]. Available from: http://natsal.ac.uk/natsals-12/results-archived-data.aspx; [3] Mercer CH, Copas AJ, Sonnenberg P, Johnson AM, McManus S, Erens B, et al. Who has sex with whom? Characteristics of heterosexual partnerships reported in a national probability survey and implications for STI risk. Int J Epidemiol [Internet]. 2009 Feb [cited 2014 Dec 12];38(1):206–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19001667; 4 Johnson A, Mercer C, Erens B, Copas A, McManus S, Wellings K, et al. Sexual behavior in Britain: Partnerships, practices, and HIV risk behaviours. Lancet. 2001;358:1835–42. [5] Althaus C. Transmission of Chlamydia trachomatis through sexual partnerships: a comparison between three individual-based models and empirical data. J … [Internet]. 2011 [cited 2014 Dec 12];(June 2011):136–46. Available from: http://rsif.royalsocietypublishing.org/content/early/2011/06/03/rsif.2011.0131.short; [6] Schmid B V, Kretzschmar M. Determinants of sexual network structure and their impact on cumulative network measures. PLoS Comput Biol [Internet]. 2012 Jan [cited 2014 Dec 12];8(4):e1002470. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3343090&tool=pmcentrez&rendertype=abstract

Supplementary Table 2-4. Risk factors for HPV infection and cervical cancer progression

Risk Factor		Portugal	United Kingdom*
Age-standardised smoking prevalence among women aged ≥15 years, %[95%CI][21]			
	2000	15.7 [10.8-20.9]	28.9 [22.7-35.1]
	2005	14.9 [10.6-19.4]	24.7 [20.5-29.8]
	2010	14.2 [9.4-18.5]	21.4 [17.1-26.5]
Percentage of women using contraception among those aged 15 to 49 who are married or in union [22]		*2005/06*	*2008/09*
	i. Oral contraceptive	58.9	28
	ii. Male Condom	11.2	27
Total fertility rate, births per woman[23]			
	1990	1.6	1.8
	2000	1.6	1.6
	2007	1.4	1.9
	2008	1.4	1.9
	2009	1.3	1.9
	2010	1.4	1.9
	2011	1.4	1.9
	2012	1.3	1.9
	2013	1.2	1.8
Proportion of circumcised men aged 15–64 years (2015),%[24]		0.61	20.1
Number of HIV cases per 100,000 population**[25]**			
	2005	21.2	13.1
	2006	21.6	12.3
	2007	20.6	12.0
	2008	21.2	11.7
	2009	19.3	10.7
	2010	18.3	10.2
	2011	15.9	9.8
	2012	15.2	9.8
	2013	14.0	9.4
	2014	8.8	9.5
Number of Gonorrhoea cases per 100,000 population[26]			
	2004	0.3	37.2
	2005	0.5	31.9
	2006	0.5	31
	2007	0.7	30.5
	2008	0.6	26.7
	2009	1.1	28.5
	2010	0.8	29.9
	2011	1.1	37
	2012	1.1	45.3
	2013	1.1	50.7
Number of Syphilis cases per 100,000 population[26]			
	2004	1	4.9
	2005	1	5.8
	2006	1.2	5.8
	2007	1.1	5.8
	2008	0.9	5.4
	2009	1.4	5.1
	2010	1.7	4.7
	2011	1.5	5.2
	2012	2.5	5.2
	2013	1.8	5.6

*****data not reported exclusively for England; Sources: [21] United Nations, Department of Economic and Social Affairs PD. World contraceptive use 2011 [Internet]. 2011. Available from: http://www.un.org/esa/population/publications/contraceptive2011/wallchart_front.pdf ; [22] The World Bank.

World Bank Data [Internet]. [cited 2016 Apr 11]. Available from: http://data.worldbank.org/indicator/SP.DYN.TFRT.IN; [23] Morris BJ, Wamai RG, Henebeng EB, Tobian AAR, Klausner JD, Banerjee J, et al. Estimation of country-specific and global prevalence of male circumcision. Popul Health Metr [Internet]. Population Health Metrics; 2016;14(1):1–4. Available from: http://dx.doi.org/10.1186/s12963-016-0080-6; [24]Amato-Gauci AJ, Donoghoe M, Emiroglu N, Rodier G, Lazdina V, Catchpole M, et al. HIV/AIDS surveillance in Europe 2013 [Internet]. 2014. Available from: http://ecdc.europa.eu/en/publications/publications/hiv-aids-surveillance-report-europe-2013.pdf; [25]European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2013. 2015.[26]World Health Organization. World Health Survey - Portugal [Internet]. 2003. Available from: http://www.who.int/healthinfo/survey/en/

Supplementary Table 2-5. Opportunistic and organised cervical screening in mainland Portugal, 2010-2014

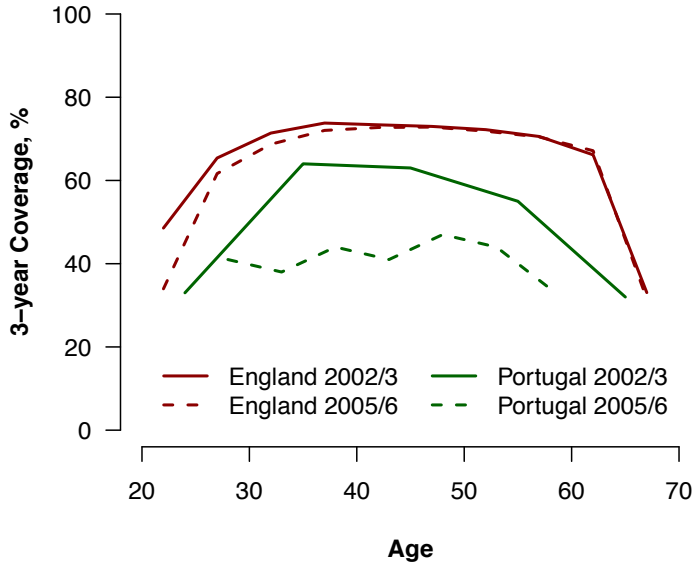
	Region	Screening	2010-2012	2011-2013	2012-2014
Proportion of women registered with the NHS aged 25-64 who were screened, %	Alentejo	Opportunistic	3.6	1.8	0.9
		Organised	44.6	46.5	41.0
	Algarve [a]	Opportunistic	36.5	31.6	25.4
		Organised	11.7	16.7	16.5
	Centre	Opportunistic	12.1	10.1	8.6
		Partly-organised	41.3	47.7	46.8
	Lisbon & Tagus Valley [b]	Opportunistic	33.9	33.9	33.9
		Organised	0	0	0
	North	Opportunistic	67.2	62.7	64.3
		Organised	5.5	5.5	4.7
	Portugal (mainland)	Opportunistic	42.9	40.5	40.7
		Organised	13.3	14.5	13.7
Proportion of eligible[c] women invited by letter within programme,%	Alentejo	Organised	60.5	63.5	60.0
	Algarve		17.4	27.5	25.4
	Centre		0	0	0
	Lisbon & Tagus Valley		0	0	0
	North		6.9	7.1	6.4

Opportunistic cervical screening in Portugal consists of eligible women being invited by their general practitioner (GP) when they visit their practice for any reason. Women who accept the invite undergo a conventional Pap smear cytology and are asked to take the smear to a contracted laboratory in their residential area and to bring back the result once available.
Partly-organised cervical screening in the Centre means that eligible women are invited for screening opportunistically by their GP who performs the smear and sends it for analysis to a regional reference laboratory that informs the GP back when results become available. Based on the cytological result, women are notified by phone or letter of their following screening appointment.
Organised or fully-organised cervical screening means that all eligible women are invited under a call/recall system by their GP who performs the smear and sends it for analysis to a regional reference laboratory that informs the GP back when results become available.
[a] Algarve did not report on the proportion opportunistically screened; this was estimated assuming same overall coverage as Alentejo (RHA with lowest coverage among regions with organised screening); likely to be an underestimate as in 2005/6 5-year coverage was 30% and 70% in Alentejo and Algarve, respectively. [28]

[b] Lisbon and Tagus Valley RHA reported 33.93% of women aged 25-64 who had cytology within last 3 years (opportunistic screening, 2013); source: Administração Regional de Saúde de Lisboa e Vale do Tejo [Regional Health Administration Lisbon and Tagus Valley]. Relatório anual de atividades 2013 [Annual Activity Report].2014. 1-130 p. Available from: http://www.arslvt.min-saude.pt/uploads/document/file/1478/Relat_rio_de_Atividades_2013__07_07_2014_.pdf

[c] assuming 10% of resident women would be excluded (non-eligible) for clinical reasons[4]

Sources: Regional health administrations with fully-organised (Alentejo, Algarve, and North) or partly-organised (Centre) screening programmes provided the number of women aged 25-64 years registered with the NHS, invited for screening by letter (except Centre), and who attended screening within the implemented programmes. Opportunistic screening data provided by Alentejo, Centre, and North.



Supplementary Figure 2-6. Age-specific 3-year screening coverage (%) of women aged 25-64 in Portugal and 20-69 in England, 2002/3 and 2005/6

Sources:

World Health Organization. World Health Survey - Portugal [Internet]. 2003. Available from: http://www.who.int/healthinfo/survey/en/

Couceiro L, Alves I, Almendra R. Plano Nacional de Saúde em Foco - Doenças Oncológicas em Portugal - Boletim Informativo no. 4 [National Health Plan under focus - Cancer Diseases in Portugal - Informative Bulletin nr.4]. Alto Comissariado da Saúde [High Commissariat for Health Portugal]. 2009.

Health and Social Care Information Centre. Cervical Screening Programme, England 2004-2005 [Internet]. 2005. [cited 2016 Apr 15]. Available from: http://content.digital.nhs.uk/article/2021/Website-Search?productid=1481&infotype=13367&sort=Title&size=10&page=7

Supplementary Table 2-6. Type-specific high-risk HPV prevalence among invasive cervical cancer cases in Portugal and the UK

	HPV Prevalence, % (95%CI)	
High-risk HPV types	**Portugal**	**UK**
16	71.4 (64.2-77.7)	61.4 (59.7-63.1)
18	10.1 (6.4-15.6)	17.6 (16.3-19.0)
31	0.9 (0.2-5.1)	3.6 (3.0-4.3)
33	9.3 (5.1-16.2)	3.9 (3.3-4.7)
35	1.9 (0.5-6.5)	1.0 (0.7-1.4)
39	0.0 (0.0-3.4)	1.2 (0.9-1.7)
45	3.7 (1.4-9.1)	4.4 (3.7-5.2)
51	1.6 (0.3-8.3)	0.8 (0.5-1.2)
52	0.9 (0.2-5.1)	2.1 (1.6-2.7)
56	1.9 (0.5-6.5)	0.5 (0.3-0.8)
58	2.8 (0.9-7.9)	1.1 (0.7-1.5)
59	0.9 (0.2-5.1)	1.0 (0.7-1.5)

Sources: Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Portugal. Summary Report 10 December 2018. [Accessed 05/02/2019] Available from http://www.hpvcentre.net/statistics/reports/PRT.pdf; Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the United Kingdom. Summary Report 10 December 2018. [Accessed 05/02/2019] Available from http://www.hpvcentre.net/statistics/reports/GBR.pdf

3. Chapter 3. Systematic review of model-based cervical screening evaluations

3.1. Preamble to research paper 2

Chapter 1 introduced the key role that mathematical and economic models play in synthesising evidence from epidemiological studies to project long-term outcomes of a range of potential choices about cervical screening.

Previous model-based studies on cervical screening provided useful insights towards the main aim of this thesis, i.e. the evaluation of the effectiveness and cost-effectiveness of alternative cervical screening strategies in Portugal.

The literature on cervical screening models has grown rapidly and several reviews have been conducted in this field. Since 2005, two systematic reviews were conducted and both focused on model-based economic studies of primary HPV screening[1,2]. Other (non-systematic) reviews also concentrated on a particular technology[3,4] or on particular settings[5]. However, the full range of epidemiological and economic studies using mathematical models to quantify the impact and cost-effectiveness of cervical screening (with any technology) had never been systematically reviewed.

Research paper 2 is the first systematic review of the literature to provide an overview of (i) how model-based studies (both epidemiological and economic) have informed cervical screening policy in distinct settings, (ii) what methods have been applied and how they have evolved alongside the development of cervical screening technologies, and (iii) what the current trends and gaps are to address present and emergent challenges in this field.

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3.1.Research paper 2

Systematic review of model-based cervical screening evaluations

Diana Mendes,[1,2*] Irenjeet Bains,[2] Tazio Vanni,[3] Mark Jit [1,2]

[1] Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, Bloomsbury, London, WC1E 7HT, United Kingdom

[2] Modelling and Economics Unit, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, United Kingdom

[3] Brazilian Ministry of Health, Esplanada dos Ministérios Bloco G, Brasília-DF, CEP: 70058-900, Brasil

Publication status: Published in BMC Cancer, 2015, doi: 10.1186/s12885-015-1332-8

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Student	Diana Mendes
Principal Supervisor	Mark Jit
Thesis Title	The impact and cost-effectiveness of cervical screening in Portugal

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	MJ conceptualised the review and supervised the data analysis and the writing of the manuscript. All authors read and approved the final manuscript and agreed on its inclusion in this thesis.

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3.1.1. Abstract

Background: Optimising population-based cervical screening policies is becoming more complex due to the expanding range of screening technologies available and the interplay with vaccine-induced changes in epidemiology. Mathematical models are increasingly being applied to assess the impact of cervical cancer screening strategies.

Methods: We systematically reviewed MEDLINE®, Embase, Web of Science®, EconLit, Health Economic Evaluation Database, and The Cochrane Library databases in order to identify the mathematical models of human papillomavirus (HPV) infection and cervical cancer progression used to assess the effectiveness and/or cost-effectiveness of cervical cancer screening strategies. Key model features and conclusions relevant to decision-making were extracted.

Results: We found 153 articles meeting our eligibility criteria published up to May 2013. Most studies (72/153) evaluated the introduction of a new screening technology, with particular focus on the comparison of HPV DNA testing and cytology (n = 58). Twenty-eight in forty of these analyses supported HPV DNA primary screening implementation. A few studies analysed more recent technologies - rapid HPV DNA testing (n=3), HPV DNA self-sampling (n=4), and genotyping (n=1) - and were also supportive of their introduction. However, no study was found on emerging molecular markers and their potential utility in future screening programmes. Most evaluations (113/153) were based on models simulating aggregate groups of women at risk of cervical cancer over time without accounting for HPV infection transmission. Calibration to country-specific outcome data is becoming more common, but has not yet become standard practice.

Conclusions: Models of cervical screening are increasingly used, and allow extrapolation of trial data to project the population-level health and economic impact of different screening policy. However, post-vaccination analyses have rarely incorporated transmission dynamics. Model calibration to country-specific data is increasingly common in recent studies.

Keywords: systematic review; human papillomavirus; cervical cancer; screening; mathematical models; economic evaluations

3.1.2. Background

Cytological screening for cervical cancer is recognized as having substantially reduced cervical cancer incidence and mortality in many high-income countries (HIC). However, recent technological developments are prompting a paradigm shift in cervical cancer prevention.[1] Human papillomavirus (HPV) DNA testing has greater sensitivity for high-grade lesions than cytology when used as a primary screening method,[2] while a panoply of other biomarkers, such as p16, Ki-67, mRNA, and methylation markers, have been investigated for their potential role in primary screening, triage of borderline cytological outcomes, and triage of HPV-positive results that could enable a fully molecular-based approach to screening.[3] Moreover, where introduced, HPV vaccination is expected to eventually reduce the incidence of cervical cancer and therefore reduce the absolute impact of existing screening programmes, necessitating their reassessment for future unvaccinated and vaccinated cohorts.[4]

Hence the choice of optimum cervical screening strategies in future will be highly complex due to the number of technological choices available, combined with epidemiological changes in the target population. Mathematical models offer a way to combine different types of evidence about the choices available (together with their associated uncertainty) to predict the impact of alternative prevention strategies unlikely to be tested in clinical trials due to the enormous time and resource requirements.[5] However, the type of analysis used, the health technologies assessed, and the modelling methods applied may have an important impact on decision-making.

This is the first systematic review encompassing all model-based effectiveness and/or cost-effectiveness analyses of cervical cancer screening strategies. Initial reviews in this area [6, 7] only examined cervical cancer models analysing exclusively cytology-based strategies, while those published after 2005[5, 8–10] focused only on economic (and not epidemiological) models. There have been three reviews of HPV DNA testing and cytology for primary screening,[8–10] but only two[9, 10] were systematic. Other reviews have also examined HPV DNA testing as triage for equivocal cytological outcomes in high-income settings and visual inspection in low-resource countries,[5] as well as a range of technologies in the USA and in low-resource settings.[11] The limited geographical scope of these reviews and the recent technological development justify a systematic review of the literature, including epidemiological evaluations, over the full range of technologies available in any kind of setting.

The aims of this review are to (i) provide an overview of results from all model-based evaluations of cervical screening, in order to inform comprehensive policy making on secondary prevention of cervical cancer, and (ii) identify trends and gaps in these models in order to inform future work.

3.1.3. Methods

Search strategy

This review was conducted following guidance of the Centre for Reviews and Dissemination for systematic reviews[12] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] We searched the following electronic databases for studies published up to May 2013: MEDLINE®; Embase; Web of Science®; EconLit; the Health Economic Evaluations Database; and The Cochrane Library including the NHS Economic Evaluation Database and the Health Technology Assessment database using the searches strategies in Additional material 1.

Selection criteria

We included original research articles that met the following criteria:

1. Based on mathematical modelling of HPV infection and/or cervical disease progression
2. Estimated the impact of at least one cervical screening technology/strategy
3. Estimated either clinical outcomes alone (epidemiological models) or both clinical and economic outcomes (economic models)

Studies modelling women of any age at risk of infection, infected, or who had been previously infected with HPV were included, as well as studies on women with concomitant infections (e.g. human immunodeficiency virus (HIV)) or who had been treated for cervical lesions. We included models of HPV vaccination where different cervical screening strategies are compared to each other. Economic evaluations (specifically cost-effectiveness analyses, cost-utility analysis, and cost-benefit analyses) were included if they reported both costs and benefits expected for each strategy of the analysis. Full texts for abstracts and conference presentations identified as potentially relevant in searches were sought, including initiating contact with the corresponding authors when details were otherwise unobtainable. Research articles published in any language in peer-reviewed journals; and abstracts or conference presentations from 2012 onwards published with sufficient details to allow full completion of the pre-established data extraction form were included.

Studies only comparing the costs of different strategies were excluded, as well as publications that were neither (i) archived by the British Library[14] nor (ii) published in a journal included in the Thompson Reuters Impact Factor list.[15]

Study selection

Study selection was performed independently by two reviewers (DM and IB). Initially, the titles and abstracts of the references retrieved in the searches were screened according to the inclusion criteria defined above to identify potentially relevant studies. All titles and abstracts were screened by at least one reviewer; 20% were independently screened by both reviewers. Where initial assessments differed, reviewers' decisions and disagreements were compared and discussed. Full papers of references identified as potentially relevant in the initial screening were then assessed for eligibility (ten per cent independently assessed by both reviewers). The reviewers again compared results and discussed any differences. A third reviewer (MJ) was consulted where consensus was not reached in any of the screening stages.

Data Extraction

Data extracted included name of first author, year of publication, country of study, type of analysis, type of model, calibration method, strategies/technologies assessed, and main findings. Additional material 2 provides a list of the data extracted. The included studies were grouped by World Health Organization (WHO) region [16] and level of income of the analysed countries, as per the World Bank 2014 income levels.[17] Studies referring to their region of interest as 'developing countries' were assumed to relate to all WHO regions.

3.1.4. Results

The searches conducted identified 2,644 studies that potentially met the inclusion criteria set out above. A PRISMA[13] flow diagram of the selection of the included studies is given below (Figure 3-1) and a completed PRISMA checklist is provided as Additional material 3 . From screening titles and abstracts, 392 records were retrieved for full screening, and 153 articles met the inclusion criteria.

Seventy-eight of the 153 publications included in this review explicitly acknowledged that they were adaptations or alternative applications (i.e. without changes to the model assumptions) of previously published models.

The main characteristics of the studies included are summarised in Figure 3-2 and are discussed further below. Greater detail is provided in Additional materials 4 and 5 that present the characteristics of studies that focused on screening alone and on combined screening and vaccination interventions, respectively, by year of publication.

Countries

Most included studies (n=135) were based on a single country. Additional material 6 shows the number of single- and multiple-country studies by country. Forty-five countries were addressed individually (either in single- or multiple-country publications), ten of which – Argentina, Barbados, Belgium, Chile, France, Finland, France, Iceland, Ireland, Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe - were only analysed as part of multiple-country studies. Figure 3-3 shows the distribution of the included single-country studies on the world map. Over half (80/153) of the studies focused on either the USA (n=44), the UK (n=14), the Netherlands (n=13), or Canada (n=9). The Americas, Europe, and/or Western Pacific regions accounted for 86% of the studies.

Most studies focused exclusively on HIC (n=117), whereas 35 studies analysed low- and/or middle-income countries, with 28 analysing only middle-income settings and only 2 studies focusing entirely on low-income ones.[18, 19] One study analysed 6 regions of different income-level.[20]

Type of Analysis

Most studies (n=129) included a cost-effectiveness analysis. Of these, 10 presented health outcomes in terms of disease-specific measures only, 79 in terms of lives saved or life years gained, and 40 in terms of the generic health utility measure quality-adjusted life years (QALYs). Quality-adjusted life years were particularly common among studies assessing vaccination alongside screening compared to those which assessed screening alone (42% compared to 21%). There were no cost-benefit analyses (i.e. studies in which both costs and outcomes were expressed in monetary terms).

Figure 3-4 shows the distribution of studies by year according to the type of analysis outcome (epidemiological or economic) and the type of prevention strategies assessed (screening alone or screening combined with vaccination). Post-vaccination economic analyses have become more common in the last decade and economic analyses in general have become dominant compared with studies analysing health outcomes only.

Type of intervention

The included studies estimated the incremental effectiveness or cost-effectiveness of three types of interventions: (a) introduction of a new screening programme where none existed before (n=34), (b) changes to existing screening algorithms without the introduction of a new technology (n=47), and (c) introduction of a new screening technology (n=72).

a) Studies on the impact of introducing a new screening programme (n=34) were mostly economic evaluations (n=30). Most were set in middle-income (n=14) or high-income (n=13) countries. Several (n=12) investigated screening strategies post-HPV vaccine introduction. All 34 studies recommended introducing screening.
b) Studies exclusively analysing changes to existing screening programmes examined alternative cytology-based strategies (n=47, 42 in HIC). Most (18/23) studies making recommendations on screening intervals or frequency endorsed an interval of 3 years or more. Recommended starting ages ranged between 20-35 years old, while recommended stopping ages ranged between 60-73 years old. Three studies looked at rescreening cytology negative outcomes, and had mixed results. One study examined follow-up of women post-hysterectomy and recommended against screening women over 40 years.[21]
c) Seventy-two studies analysed the introduction of a new screening technology to an existing programme. All compared the new technology to cytology apart from one study that compared visual inspection with acetic acid (VIA) to HPV DNA testing. The findings of these comparisons are detailed in the following subsections.

Technologies assessed

Publications focused on cytology (n=150), HPV DNA (n=77), and VIA (n=12). Overall, the studies analysed 8 screening techniques: cytology (n=150, of which 34 referred to liquid-based cytology (LBC)), cytology automated reading (e.g. Papnet© and AutoPap©, n=7), speculoscopy as adjunct to cytology (n=1), HPV DNA (n=76), self-sampled HPV DNA testing (n=4), HPV 16/18 genotyping (n=1), and VIA (n=12).

The main technological comparisons made were between (a) alternative cytology-based strategies (n=77), (b) HPV DNA *versus* cytology (n=69), (c) VIA *versus* cytology and/or HPV DNA (n=11). Additional material 7 summarises the findings on comparisons of technologies.

Alternative cytology-based strategies

Liquid-based cytology was recommended in 18/26 economic analyses and in one epidemiological analysis comparing it with conventional cytology. The remaining studies recommended conventional cytology (8/27) or were equivocal (1/27).

Automated reading of cytological results was found to be cost-effective when compared to manual reading in all (n=6) economic studies. One epidemiological study on adding automated reading to LBC concluded that evidence was still insufficient to recommend it relative to manual reading.[22] One economic analysis found the addition of speculoscopy to biennial

conventional cytology cost saving and health improving compared with annual conventional cytology alone.[23]

HPV DNA testing *versus* cytology alone

Several studies examined replacing cytology with HPV DNA testing as the primary screening technique (n=17) and 15/17 studies found HPV DNA more cost-effective. Twenty-four studies compared co-testing with cytology and HPV DNA (n=17), or with cytology primary screening only (n=7). Co-testing was supported in 6/7 studies comparing it with cytology; however, HPV DNA testing was the most supported technology among studies comparing it with co-testing and cytology (10/17), whilst 8/17 were favourable to co-testing, and 6/17 to cytology alone for primary screening (some studies supported more than one technology). Overall, HPV DNA primary screening was supported in 26/34 studies comparing it to cytology alone and/or co-testing.

The introduction of HPV DNA testing to triage minor cytological abnormalities was supported in 9/10 studies comparing it with repeat cytology and immediate referral to colposcopy (7/8), immediate treatment (1/1), or co-testing (1/1) in high- and middle-income countries.

Rapid and relatively-inexpensive HPV DNA testing (careHPV™, n=3) was found cost-effective in China compared with VIA[24] or cytology,[25] as well as when performed twice a lifetime alongside vaccination compared with once a lifetime, provided affordable vaccination cost.[26]

Most (3/4) economic analyses of post-treatment screening[21, 27–29] investigated the introduction of HPV DNA testing. Two of these recommended its introduction,[27, 28] whereas one study found conventional cytology the most cost-effective approach compared to HPV DNA testing or LBC.[29]

The introduction of self-sampled HPV DNA primary screening instead of clinic-based HPV DNA testing or conventional cytology was found cost-effective in 2/4 studies that looked at it.

One study on HPV 16/18 genotyping found it cost-effective in the USA for triage of equivocal results of co-testing (HPV DNA and LBC) compared with co-testing alone, HPV DNA with LBC triage, LBC with HPV DNA triage, or LBC alone.[30]

VIA *versus* HPV DNA and/or cytology

All studies comparing VIA with HPV DNA and/or cytology for primary screening (n=11) were economic analyses and most comparing HPV DNA testing and VIA(6/9)recommended HPV DNA testing (n=2)[19, 31] or either (n=4)[18, 20, 32, 33].

One study compared VIA with HPV DNA, cytology, and self-sampling in South Africa and concluded that 1-visit HPV DNA testing was the most effective strategy, slightly more costly than 1-visit VIA.[32]

One study only comparing VIA and HPV DNA testing found the latter cost-effective in low resource settings,[19] and all studies comparing VIA with cytology only (n=2) supported VIA in MIC,[33, 34] with one finding cytology cost-effective to screen women over 50 years old every 5 years in Thailand.[35]

Screening and vaccination

Studies analysing screening strategies in vaccinated populations (n=35) assessed (a) the introduction of screening strategies where non-existent (n=12), (b) changes to existing cytology-based screening strategies (n=12), and (c) the introduction of new screening technologies in existing programmes (n=11).

a) Introducing screening (using any technology) alongside vaccination was preferred over screening alone by 10/12 studies (8 regarding low- and/or middle-resource settings).
b) Most studies analysing changes to existing cytology-based screening alongside vaccination (10/12, 10 in high- and 2 in middle-income countries) recommended combined screening and vaccination interventions. Half of these studies highlighted the importance of high coverage of screening and immunization programmes. Recommendations on cytology screening target age and interval varied among HIC studies (n=4).
c) Studies on the introduction of screening technologies post-vaccination looked largely at HPV DNA testing and cytology (9/11, 2 in low and middle income countries (LMIC)). HPV DNA testing alone was found more cost-effective than cytology in 5/5 studies focused on primary screening with these technologies alone. Studies comparing these with co-testing as well (n=3) concluded favourably regarding co-testing.[36–38] One study explored only the introduction of HPV DNA in triage of cytological results, and supported it in the Netherlands, Taiwan, and USA, but not in Canada or the UK.[39]

Table 3-1 summarises the findings and recommendations of the studies included in this review.

3.1.5. Modelling methods

The modelling approaches used in the included studies were classified according to the following dimensions:[40]

(a) Randomness (stochastic *versus* deterministic): In deterministic models, events such as HPV acquisition and clearance occur at a pre-determined rate. Stochastic models incorporate

randomness (stochasticity) in the occurrence of these events, so the outcomes of a model are not exactly the same each time it is run.

(b) Level (individual *versus* aggregate): Individual-based models simulate and record the events that occur in each modelled individual's lifetime, so that each individual has unique characteristics. In contrast, aggregate models group individuals with similar characteristics into compartments, eliminating their variability within each compartment. Hence individual-based models capture population heterogeneity more easily.

(c) Interaction (static *versus* dynamic): If the rate at which people get infected with HPV (i.e. the force of infection) is likely to change, such as following population-based vaccination, then herd immunity (i.e. indirect protection of susceptible individuals by a significant proportion of immune individuals in the population) is likely to affect the model results greatly. Dynamic models account for herd immunity as the risk of infection is modelled as dependent on the number of infectious individuals rather than assumed to be constant over time (static models).

The models found were mainly static (149/153), deterministic (113/153) and aggregate (113/153); all aggregate models were deterministic. Only 4 studies were dynamic and all of these were deterministic and modelled individuals at an aggregate level. Three of the four dynamic models found were used to assess screening strategies alongside vaccination. Similarly to models of screening interventions alone, the models used for post-vaccination analyses were mainly static (32/35), and deterministic aggregate (19/35). Stochastic individual-based models were more common among post-vaccination analyses (16/35; 46%) than amid those analysing screening interventions alone (24/118; 20%).

Many models require values of parameters that are difficult to measure directly, such as the rate of progression from CIN3 to invasive cancer. Such values can be estimated by calibrating the model, that is, adjusting its internal parameters until model outputs (such as cancer incidence) match observational data. The extent to which the outputs can match data is often quantified using a goodness-of-fit measure. Commonly used quantitative goodness-of-fit measures and tests include the sum of squared residuals, the chi-squared statistic and the likelihood of the model parameters given the data. [41]

Most studies (n=83) did not report having calibrated their models at all. Of those that reported calibration (n=70), 21 did not specify the goodness-of-fit measure used and 30 only assessed model fit to data visually without using any quantitative goodness-of-fit measure. The remaining studies (n=19) explicitly reported using a formal goodness-of-fit measure. A greater proportion of models used for the assessment of screening strategies alongside vaccination

were calibrated (23/35; 66%) compared with those of models only assessing screening strategies (47/117; 40%).

3.1.6. Discussion

Many studies addressing a wide range of questions met our inclusion criteria compared to that in other cervical cancer-related reviews.[42, 43] This may reflect the substantial global burden of cervical cancer, the recent development of new screening methods and technologies, as well as the role mathematical modelling has played regarding context-specific policy questions that only very large long term trials would address.[43, 44]

Results from model-based evaluations of cervical screening

Most studies included a cost-effectiveness analysis (129/153) and investigated the introduction of new screening technologies (72/153), with fewer focusing exclusively in alternative strategies using already-adopted technologies (47/153), and even fewer on the introduction of screening programmes where non-existent (34/153). Evaluations of the introduction of a screening technology were generally favourable to its adoption, with LBC recommended *over* conventional cytology (18/27), HPV DNA recommended *over* cytology for primary screening (15/17), rapid HPV DNA (3/3) or self-sampling (2/4) recommended for primary screening, and HPV DNA (9/10) or genotyping (1/1) recommended for triage of equivocal results.

Overall, our findings are in line with those of previous reviews of cost-effectiveness analyses[5, 8–11] and post-vaccination analyses in the context of developed countries with existing screening programs[40], which mostly recommend the introduction of HPV DNA primary screening in high-resource settings and the revision of screening policies towards the introduction of HPV DNA primary testing.

As Nahvijou and colleagues also found,[10] there is a discrepancy between guidelines and model-based evaluations regarding more recent technologies. Generally, current HIC screening guidelines (Summary of cervical screening guidelines provided in Additional material 8) are aligned with the overall findings of evaluations of cytology-based strategies; however, most concluded lacking sufficient evidence on the effectiveness of HPV DNA testing for primary screening to support its implementation,[45] with only a few countries, such as Australia, the Netherlands and the USA, recommending it at the moment.

Trends and gaps identified

Most of the global cervical cancer burden lies in low- and middle-income countries without organised screening programmes [46] However, as noted in previous reviews, [5, 11] only a

small proportion of studies in our review (34/153) addressed these settings, with the vast majority (33/34) supporting the existence of a screening programme. Indeed, over half the studies (80/153) were set in just 4 HIC – the USA, the UK, the Netherlands, or Canada. More evaluations focused on the regions with the greatest cervical cancer burden may have greater influence in driving adoption of screening technologies where they are most needed.

Currently several molecular biomarkers are being investigated for their potential to be integrated alongside cytology and HPV DNA testing in screening algorithms. However, no model-based study was found in this review on these emerging screening technologies. Only a few studies analysed more recent technologies as rapid HPV DNA testing, self-sampled HPV DNA testing, or HPV 16/18 DNA genotyping. No study on rapid HPV DNA testing was found in a low-income setting either.

Some molecular-based tests are thought to have the potential to improve cytology's accuracy and reproducibility (e.g. p16 immunostaining), while other are thought to be promising alternatives to cytology (e.g. HPV DNA testing, HPV mRNA testing, p16/ki-67 dual immunostaining, or methylation markers) as they can be subject to automated quantification.[47] The clinical utility of HPV DNA testing has been shown,[2] and it has recently been introduced in primary screening in a few HIC, e.g. the Netherlands and Ontario.[48] These recent developments in screening technologies may suggest a transition to a fully molecular-based screening approach. However, the population-level effectiveness and cost-effectiveness behind many of the molecular technologies is still unexplored. For most biomarkers there is currently only cross-sectional evidence of their potential accuracy.[3] HPV mRNA testing for instance was approved by the U.S. Food and Drug Administration for screening women over 30 years in combination with cytology, despite there being no evidence at that time from longitudinal trials of its improved accuracy compared to primary cytology or co-testing for HPV DNA in the detection of CIN2+ lesions who do not regress.[49] Mathematical models are a key tool to allow results from trials and observational studies of these technologies to be extrapolated to explore their long-term impact in population-based screening programmes.

Another aspect of research that can be explored via mathematical modelling is the interaction between vaccination and screening. Vaccinating adolescent girls has been found likely to be cost-effective even in settings with existing screening programmes.[40, 50] However, vaccination is expected to decrease the incidence of cervical abnormalities and eventually cancer.[51] Hence the positive predictive value of cytology will decrease, as will the effectiveness of most screening modalities. [43, 52] In order to assist in population level policy making, future analyses in settings with vaccination will need to account for its impact on

existing and prospect screening programmes. This is particularly true if a 9-valent HPV vaccine is successful in trials, as it is projected to ultimately prevent 90% of invasive cervical cancers.[53]

Also, most models of screening in post-vaccination settings relied on a static infection structure. This may be suitable for comparing alternate screening strategies in a setting in which disease prevalence is constant, but would not capture the long-term changes in HPV prevalence, in settings with successful national HPV vaccination programmes[54] such as the UK, Australia and Portugal. Dynamic transmission models are particularly important now that a 9-valent HPV vaccine has shown high immunogenicity and efficacy in clinical trials.[55] This will have further implications on cervical screening since vaccinated girls will have a very low risk of infection with an oncogenic HPV type and hence risk of cervical cancer. The few dynamic models compared alternative cytology-based strategies[56, 57] or strategies with rapid HPV DNA testing *versus* vaccination only or alongside vaccination.[26] Their overall results were consistent with those of static models in that screening strategies alongside vaccination maximise health outcomes. However, it can take many years for the direct and indirect impact of vaccination to be observed in surveillance data, so dynamic models will be increasingly important to explore changes to screening as the first vaccinated cohorts enter the age of screening eligibility.

Model calibration to observed setting-specific data has become more common; however it is still not routinely used. As most natural history parameters governing the progress of cervical abnormalities are very difficult to measure directly, model calibration enables their estimation based on observable outcomes such as abnormal screening results. This is generally a more reliable approach than making assumptions on parameters based on limited studies, often in unrepresentative populations.[41, 58] Even the studies reporting having calibrated these parameters to outcome data often gave few details about the goodness-of-fit measure used and very rarely provided details on other aspects of calibration, such as the selection of calibration targets, parameter search strategies, and convergence criteria used. Detailed reporting of the calibration process should be common practice for reproducibility purposes.[59] Also, there should be an indication of uncertainty in the parameter estimates used and how it is incorporated to judge the sensitivity of model predictions to the data sources used.

This review is subjected to limitations. We focused on models used to assess the impact of alternative screening strategies, and excluded model-based studies assessing vaccination strategies, including those modelling screening strategies alongside vaccination that did not compare different screening strategies. Because of the volume and diversity of the relevant

modelling literature, we did not critically appraise the quality of individual studies, but instead focused on providing an overview of the main approaches and conclusions of the models. Further work is needed to critically review modelling literature that addresses specific questions (such as the choice between cytological and DNA-based screening methods) in more detail. The main strength of our work lies in providing a broad overview of the vast literature over a long time period, and in identifying key conclusions that are common across models as well as gaps in the methodology and scope of current models.

3.1.7. Conclusions

The main questions addressed over time by models used to assess cervical cancer screening strategies focused on high-income settings analysing matters relevant to LMIC as well, such as the introduction of HPV DNA testing and more recently the most appropriate post-vaccination screening strategy. Despite the increasingly large number of publications, few studies investigated the utility of HPV DNA self-sampling and genotyping in future screening programmes, and none explored the potential role of emergent molecular markers. Transmission dynamics have rarely been incorporated and model calibration is not standard practice yet. Dynamic models fitted to country-specific data could be helpful tools to investigate future post-vaccination screening strategies.

3.1.8. Abbreviations

DNA – deoxyribonucleic acid, HIC - high-income countries, HIV - human immunodeficiency virus, HPV - human papillomavirus, LBC - liquid-based cytology, LMIC – low- and middle-income countries, mRNA – messenger ribonucleic acid, PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QALY - quality-adjusted life year, UK – United Kingdom, USA – United States of America, VIA - visual inspection with acetic acid, WHO - World Health Organization

3.1.9. Competing interests

The authors declare that they have no competing interests.

3.1.10. Author's contributions

DM conducted the literature searches, selected the studies, extracted and analysed the data, and drafted the manuscript. IB also selected the studies and extracted data, participated in the conceptualisation of the review, and supported data analysis. TV contributed to the conceptualisation of the review and the validation of study selection. MJ conceptualised the

review and supervised the data analysis and the writing of the manuscript. All authors read and approved the final manuscript.

3.1.11. Acknowledgements

We thank John Edmunds for helpful comments.

DM was funded by the Foundation for Science and Technology (individual PhD studentship SFRH/BD/84974/2012) on behalf of the Portuguese Ministry of Education and Science and the Human Potential Operational Programme of the National Strategic Reference Framework, within the European Social Fund of the European Commission's 7th Framework Programme.

MJ was part funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England (PHE). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR the Department of Health or Public Health England.

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3.1.13. Figures

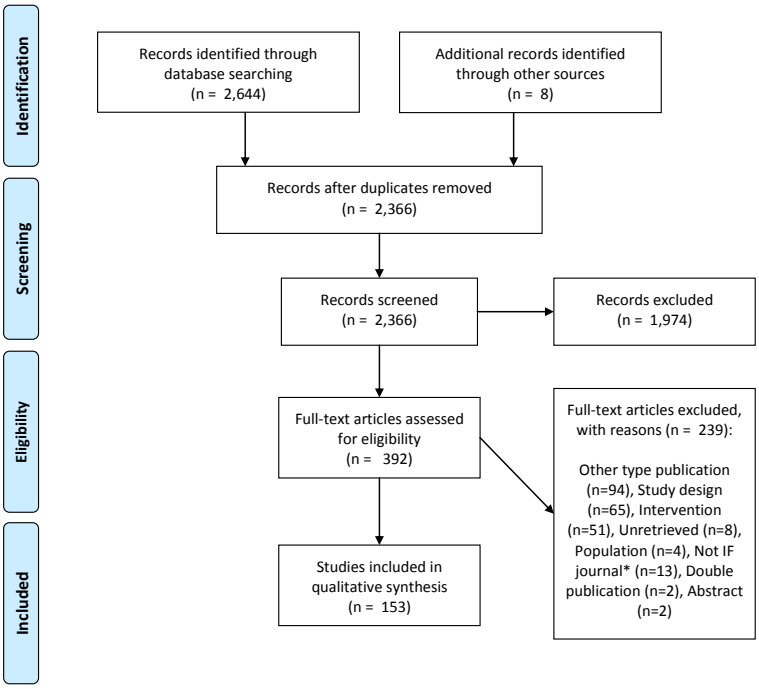

Figure 3-1. PRISMA Flow diagram of study selection process

*Articles published in journals not included in the British Library catalogue or Thompson Reuters Impact Factor (IF) list

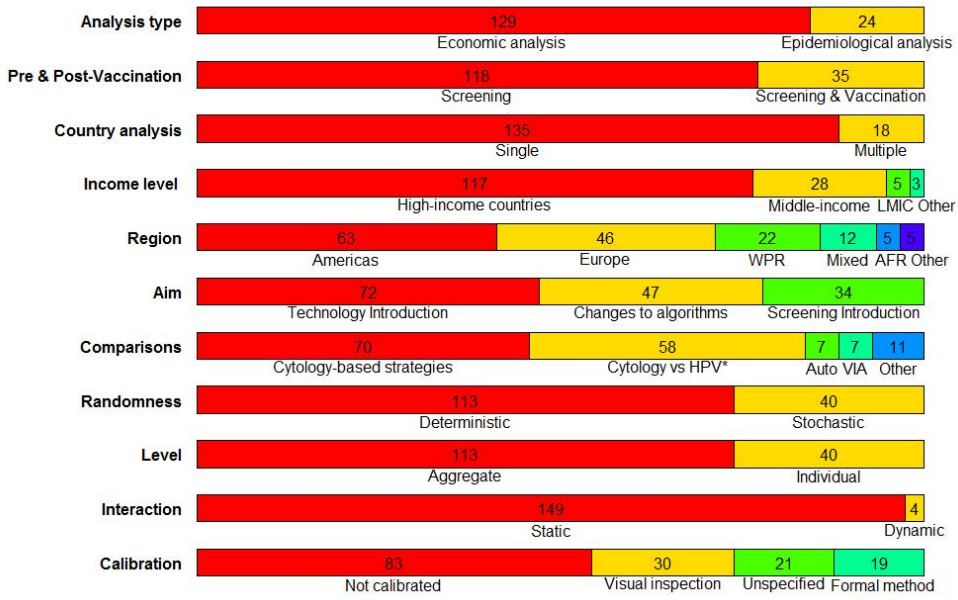

Figure 3-2. Characteristics of included studies

*exclusively these technologies; AFR, African Region; Auto; automated cytology; HPV, HPV DNA testing; LMIC, low and middle income countries; VIA, VIA vs HPV DNA testing and cytology ; WPR, Western Pacific Region

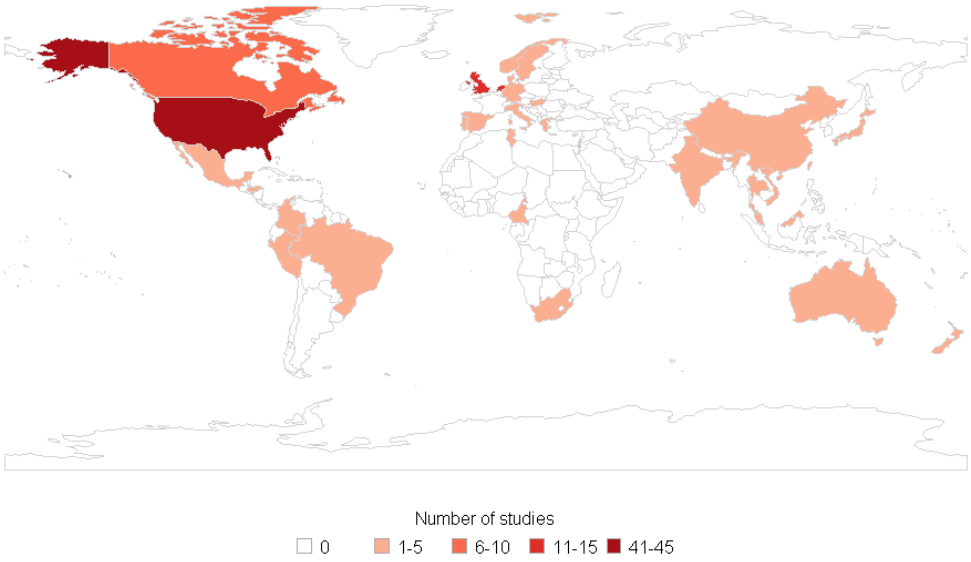

Figure 3-3. Number of single-country studies per country

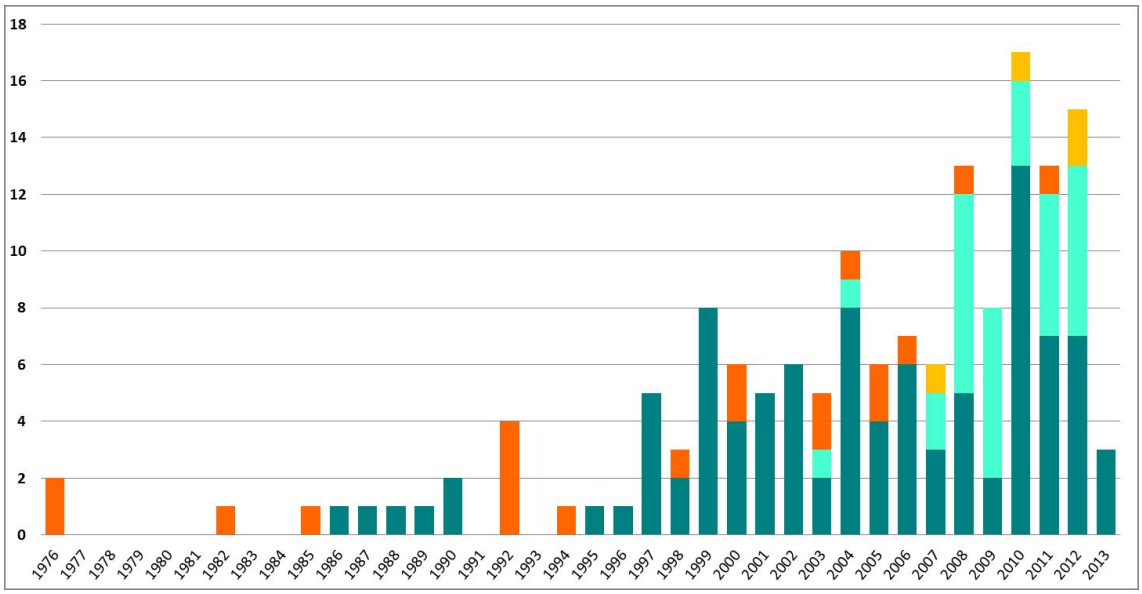

Figure 3-4. Number of studies by analysis and prevention type over time

Dark blue, Economic Screening; Light blue, Economic Screening & Vaccination; Orange, Epidemiological Screening; Yellow, Epidemiological Screening &Vaccination

Table 3-1. Summary of findings and recommendations

Type of intervention

- Screening should be introduced (34/34, 100%)
- Cytology-based screening should have screening intervals ≥3 years (18/23, 78%), starting age ≥25 years old (9/10, 90%), and stopping age ≥60 years old (5/5, 100%)
- No post-hysterectomy screening follow-up should be given to women >40 years old (1/1, 100%)

Technologies assessed

- Liquid-based cytology is recommended over conventional cytology (18/27, 67%)
- Automated reading should be introduced (6/7, 86%)
- HPV DNA testing for primary screening is more cost-effective than cytology (15/17, 88%)
- Co-testing is more cost-effective than cytology in HIC (6/7, 86%)
- HPV DNA testing is supported over co-testing and cytology alone (10/17, 59%)
- HPV DNA to triage minor cytological abnormalities is endorsed over (i)repeat cytology and immediate colposcopy (7/8), (ii)immediate treatment (1/1), or (iii)co-testing (1/1) (9/10, 90%)
- HPV DNA testing for post-treatment screening should be introduced (2/3, 67%)
- Rapid HPV DNA testing should be introduced in China (3/3, 100%)
- Self-sampled HPV DNA testing as primary screening in HIC is cost-effective *versus* clinic-based HPV DNA or conventional cytology alone(2/2, 100%); however, in upper-middle income countries, it is not cost-effective *versus* other technologies, such as clinic-based HPV DNA (2/2, 100%)
- HPV 16/18 genotyping should be introduced for triage of equivocal results of co-testing *versus* co-testing alone, HPV DNA with LBC triage, LBC with HPV DNA triage, or LBC alone (1/1, 100%)
- HPV DNA is more cost-effective than VIA in LMIC (1/1; 100%)
- VIA is more cost-effective than cytology in LMIC (2/2; 100%)

Screening and Vaccination

- Screening should be introduced even in a post-vaccination setting (10/12, 83%)
- Screening should be continued after vaccination is introduced (10/12, 83%)
- Post-vaccination HPV DNA primary screening is cost-effective compared to cytology alone in HIC (5/5, 100%)

Figures in parentheses show the proportion (x/y) and percentage (%) of relevant studies supporting each recommendation.

3.2.Additional Material

3.2.1. Additional material 1.

Supplementary Table 3-1. Search strategies for each database consulted

Database and search date	Search strategy
Medline 1946 to May Week 5 2013 (OvidSP) 11/06/2013 (updated - extended headings)	1. exp Uterine Cervical Dysplasia/ or exp Uterine Cervical Diseases/ or exp Cervical Intraepithelial Neoplasia/ or exp Uterine Cervical Neoplasms/ 2. (cervix or cervical or cervico*) (tw) 3. cancer* (tw) or carcinoma.mp. or adenocarcinoma.mp. or neoplas* (tw) or dysplas* (tw) or dyskaryos* (tw) or squamous (tw) or CIN (tw) or CINII* (tw) or CIN2* (tw) or CINIII* (tw) or CIN3* (tw) or SIL (tw) or HSIL (tw) or H-SIL (tw) or LSIL (tw) or L-SIL (tw) or ASCUS (tw) or AS-CUS (tw) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 4. 2 and 3 5. 1 or 4 6. HPV.mp. or Tumor Virus Infections/ or Papillomavirus Infections/ or Oncogene Proteins, Viral/ or Papillomaviridae/ or human papilloma.mp. or Alphapapillomavirus/ 7. (cytolog* or liquid based cytology) (tw) 8. (hybrid capture or (HC2 or HCII or HC 2 or HC II)).mp. 9. (pap or papanicolaou or vagina* or cervical or cervix or cervico*) (tw) or Vaginal smears/ 10. smear*.mp. or test (tw) or tests (tw) or testing (tw) or tested (tw) or swab*.mp. or scrap*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 11. 9 and 10 12. Early Detection of Cancer/ 13. DNA, Viral/ 14. PCR.mp. or Polymerase Chain Reaction/ 15. colposcopy.mp. or Colposcopy/ or visual inspection.mp. 16. (oncogene mRNA or methylation or proliferation or integration).mp. or immunohistochemistry/ or Tumor Markers, Biological/ or Ki-67 Antigen/ or ki67.mp. or Tumor Suppressor Protein p53/ or Antibodies, Monoclonal/ or Cyclin-Dependent Kinase Inhibitor p16/ or p16.mp. or E6.mp. or E7.mp. or 3q.mp. or 5p.mp. or MCM?.mp. or Top2A.mp. or CDC6.mp. or DAPK1.mp. or CADM1.mp. or RARB.mp. 17. Enzyme-Linked Immunosorbent Assay/ 18. antibod*.mp. or Antibod*/ 19. models, theoretical/ or models, biological/ or exp models, statistical/ or likelihood functions/ or linear models/ or logistic models/ or exp models, economic/ or nomograms/ or proportional hazards models/ or nonlinear dynamics/ or Cost-Benefit Analysis/ or Epidemiologic methods/ or mathematical concepts/ or health care evaluation mechanisms/ 20. 5 or 6 21. 7 or 8 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 22. screen*.mp. or Mass Screening/ or Triage/ or management.mp. or follow up.mp. or marker.mp. or biomarker.mp. 23. 21 or 22 24. 19 and 20 and 23

	25. limit 24 to humans
Embase Classic+Embase 1947 to 2013 May 9 (OvidSP) 10/05/2013	1. papilloma*.mp. or exp Papilloma virus/ or HPV.mp. or Wart virus/ or alphapapillomavirus/ 2. cervical cancer.mp. or exp uterine cervix carcinoma in situ/ or exp uterine cervix tumor/ or exp uterine cervix cancer/ or exp uterine cervix dysplasia/ or exp uterine cervix hypertrophy/ or exp uterine cervix disease/ or exp uterine cervix carcinoma/ or ((cervic*.mp. or exp cervix/) and (exp squamous cell carcinoma/ or exp cancer/ or exp carcinoma/ or exp neoplasia/ or exp neoplasm/ or exp dysplasia/)) or CIN.mp. or SIL.mp. or ASCUS.mp. 3. exp vagina smear/ or exp uterine cervix cytology/ or exp Papanicolaou test/ or cervical cancer screening.mp. 4. screen*.mp. or Mass Screening/ or triage.mp. or management.mp. or follow up.mp. or marker.mp. or biomarker.mp. 5. DNA/ or PCR.mp. or Polymerase Chain Reaction/ or colposcopy.mp. or Colposcopy/ or Visual inspection.mp. or (oncogene mRNA or methylation or integration or proliferation).mp. or immunohistochemistry/ or Tumor Markers, Biological/ or Ki-67 Antigen/ or ki67.mp. or Tumor Suppressor Protein p53/ or Antibodies, Monoclonal/ or Cyclin-Dependent Kinase Inhibitor p16/ or p16.mp. or E6.mp. or E7.mp. or 3q.mp. or 5p.mp. or MCM?.mp. or Top2A.mp. or Enzyme-Linked Immunosorbent Assay/ or CDC6.mp. or DAPK1.mp. or CADM1.mp. or RARB.mp. or antibod*.mp. or Antibod*/ 6. computer model/ or statistical model/ or stochastic model/ or loglinear model/ or biological model/ or theoretical model/ or process model/ or hidden Markov model/ or mathematical model/ or proportional hazards model/ or population model/ or compartment model/ 7. 1 or 2 8. 3 or 5 9. 4 and 8 10. 6 and 7 and 9 11. limit 10 to human
Econlit 1961 to April 2013 (OvidSP) 10/05/2013	1. cervi*.mp. [mp=heading words, abstract, title, country as subject] 2. HPV.mp. [mp=heading words, abstract, title, country as subject] 3. papilloma*.mp. [mp=heading words, abstract, title, country as subject] 4. (papanicol* or smear or cytolog* or liquid?based cytolog*).mp. [mp=heading words, abstract, title, country as subject] 5. (screen* or test* or inspection or colposcop* or DNA or triage or biomarker* or RNA or methilation or integration or proliferation or p16 or antibod*).mp. [mp=heading words, abstract, title, country as subject] 6. 1 or 2 or 3 7. 4 or 5 8. 6 and 7 9. model*.mp. [mp=heading words, abstract, title, country as subject] 10. 8 and 9
HEED 10/05/2013	AX= 'HPV' AX= 'CERVICAL' Or 'CERVICAL-CANCER' Or 'CERVICAL-CANCER-SCREENING' Or 'CERVICAL-VAGINAL' Or 'CERVICAL/VAGINAL' Or 'CERVICO-VAGINAL' Or 'CERVICOVAGINAL' AX= 'SCREEN' Or 'SCREEN-ALL' AX= 'MODEL' Or 'MODEL-BASED' Or 'MODEL-CALCULATED' Or 'MODEL-DERIVED' Or 'MODEL-ESTIMATED' Or 'MODEL-GENERATED' Or 'MODEL-PREDICTED' Or 'MODEL-PROJECTED' Or 'MODEL-SIMULATED' Or 'MODELLING-TECHNIQUES' Or 'MODELLING/DECISION-ANALYTIC' Or 'MODELLING' Or 'MODELS-STATISTICAL' CS= 1 OR 2 CS= 3 AND 4 AND 5
Cochrane Library (all databases apart from CENTRAL, no limits) 10/05/2013	ID Search #1 MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees #2 MeSH descriptor: [Papillomaviridae] explode all trees #3 HPV #4 MeSH descriptor: [Mass Screening] explode all trees

	#5 model* #6 {or #1-#3} #7 {and #4-#6}
Web of Science 14/05/2013	Topic=(Cervi*) AND Topic=(cancer or carcinoma or neoplas*or dysplas* or tumor or tumour or hypertrophy or disease or squamous or CIN or SIL or ASCUS) OR Topic=(HPV or human papilloma*) AND Topic=(screen* or test*) AND Topic=(smear or pap* or cytology or visual inspection or VIA or marker or DNA or colposcopy or RNA or methylation or integration or proliferation or immunohistochemistry or Ki-67 antigen or p53 or antibod* or p16 or E6 or E7 or 3q or 5p or MCM? or Top2a or CDC6 or DAKP1 or CADM1 or RARB) AND Topic=(model*) AND Topic=(math* or computer or statistic* or likelihood or linear or logistic or economic)

3.2.2. Additional material 2.

Supplementary Table 3-2. List of the types of data extracted and categorisation used

Administrative variables	
RefID	*Reference identification number*
Status	*Retrieved; unretrieved*
PubType	*Journal article; review; comment*; *Reviewer's*
Reviewer	*name*
Decision	*Include; exclude; unclear*
Reviewer comments	
Variables	
Author	*First author*
Year	
Title	
Language	
Country	
Population	*Gender, age, comorbidities*
HIV	*y/n*
Technologies	
Intervention	*Strategies assessed*
Comparator	*Baseline strategy*
Model type	
Study Aim	
Outcomes	
Results	*Main conclusion (1-2 sentences)*
Calibration	

Form drop-down lists by category

Technologies	**Study Aim**
Unspecified	Effectiveness of screening strategies/interventions
Cytology	Effectiveness of vaccination strategies/vaccines
- Conventional cytology	Effectiveness of treatment strategies/interventions
- LBC	Cost-effectiveness of screening strategies/interventions
- Automated reading	Cost-effectiveness of vaccination strategies/vaccines
HPV DNA	Cost-effectiveness of treatment strategies/interventions
Self-sampled HPV DNA	Parameter estimation
VIA	Other
VILI	
Colposcopy	**Outcomes***
Vaccine	HPV Prevalence
	Number of cervical cases
Model type	Number of deaths avoided
Deterministic	Cost per cervical case
Stochastic	Cost per death avoided
Aggregate	Cost per life year gained
Individual-based	Cost per QALY gained
Static	Cost per DALY averted
Transmission dynamic	Incidence of cervical cases
Hybrid	Net Benefit
Compartmental/state transition/Markov	Cost and Lys
Decision tree	Cost per vaccinated girl (CVG)
	Number of tests/repeats
Calibration	Life years saved
Not reported	Smears per LYG
Visual inspection	DALYs averted
Least squares	Risk reduction
Chi-squared	
Likelihood	
Other	
Unspecified method	

3.2.3. Additional material 3.

Supplementary Table 3-3. Completed PRISMA 27-item checklist for current systematic review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 and Additional material 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Additional material 2

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Counts and proportions
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Additional material 4 and 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Additional material 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Additional material 6 and 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

3.2.4. Additional material 4.

Supplementary Table 3-4. Main characteristics of studies focused on screening interventions alone (n=118)[1]

First Author	Year	Country	Econ/ Epid	Aim	Technologies	Main findings	Type of model	Calibration
Agorastos[1]	2010	Greece	Econ	TechIntro	Cyt vs HPV	HPV/(Cyt&Colp)+	Static, Deterministic, Aggregate	Not reported
Anderson[2]	2008	Australia	Econ	Algorithm	Cyt vs Cyt	Current 2y(20-69);25-; 74-;1y-;3y?	Static, Deterministic, Aggregate	Visual inspection
Andres-Gamboa[3]	2008	Colombia	Econ	TechIntro	Cyt vs HPV	HPV/Pap5y+	Static, Deterministic, Aggregate	Not reported
Atashili[4]	2011	Cameroon	Epid	ScreenIntro	Cyt vs Cyt	HAART+Cyt1x+	Static, Deterministic, Aggregate	Not reported
Balasubramanian [5]	2010	USA	Econ	TechIntro	Cyt vs HPV vs SS	OrgScreen+;HPV-; SS/LBC3y+	Static, Deterministic, Aggregate	Not reported
Berkhof[6]	2006	Netherlands	Econ	TechIntro	Cyt vs HPV	ConvC-, LBC/HPV+	Static, Deterministic, Aggregate	Not reported
Berkhof[7]	2010	Netherlands	Econ	TechIntro	Cyt vs HPV	HPV/Pap+	Static, Stochastic, Individual	Formal method
Bidus[8]	2006	USA	Econ	TechIntro	Cyt vs HPV	LBC/HPV2y+	Static, Deterministic, Aggregate	Unspecified method
Bistoletti[9]	2008	Sweden	Econ	TechIntro	Cyt vs HPV	OrgPap+, Pap/HPV9y+	Static, Deterministic, Aggregate	Not reported
Boyd[10]	1989	UK	Epid	Algorithm	Cyt vs Cyt	OrgScreen+, >=3y+	Static, Stochastic, Individual	Formal method
Brown[11]	1999	USA	Econ	TechIntro	Cyt vs Auto	ConvC&Auto3y+	Static, Deterministic, Aggregate	Not reported
Burger[12]	2012	Norway	Econ	TechIntro	Cyt vs HPV	HPV/LBC >=34+	Static, Stochastic, Individual	Formal method
Campos[13]	2012	USA	Econ	TechIntro	Cyt vs HPV	LBC/LBC-, LBC/Colp(<21, >25)+, LBC/HPV(21-24)+	Static, Deterministic, Aggregate	Not reported
Canfell[14]	2004	UK	Epid	Algorithm	Cyt vs Cyt	3y(25-50)5y(50-64)+	Static, Deterministic, Aggregate	Visual inspection

Chow[15]	2010	Taiwan	Econ	TechIntro	Cyt vs HPV	HPV/Cyt5y+	Static, Deterministic, Aggregate	Not reported
Chuck[16]	2010	Canada	Econ	TechIntro	Cyt vs HPV	Pap/HPV/Pap(>30)+; LBC-	Static, Deterministic, Aggregate	Unspecified method
Coppleson[17]	1976	USA	Epid	Algorithm	Cyt vs Cyt	Screen(34-73)10x+	Static, Deterministic, Aggregate	Not reported
Coupe[18]	2007	Netherlands	Econ	TechIntro	Cyt vs HPV	HPV6mth + HPV&Pap24mth+	Static, Deterministic, Aggregate	Not reported
Creighton[19]	2010	Australia	Econ	Algorithm	Cyt vs Cyt	3y+	Static, Deterministic, Aggregate	Unspecified method
de Bekker-Grob[20]	2012	Netherlands	Econ	TechIntro	Cyt vs HPV	LBC>ConvC +/-	Static, Stochastic, Individual	Visual inspection
de Kok[21]	2012	European Union	Econ	TechIntro	Cyt vs HPV	HPV/Cyt+	Static, Stochastic, Individual	Not reported
Dewilde[22]	2004	UK, USA, Australia, Japan	Econ	Algorithm	Cyt vs Cyt	3y+	Static, Deterministic, Aggregate	Visual inspection
Eddy[23]	1987	USA, Canada, Europe	Epid	Algorithm	Cyt vs Cyt	3y+	Static, Deterministic, Aggregate	Visual inspection
Fennessy[24]	2002	Australia	Econ	TechIntro	Cyt vs Cyt	LBC-	Static, Deterministic, Aggregate	Not reported
Fetters[25]	2003	USA	Econ	Algorithm	Cyt vs Cyt	ScreenPostHyst-	Static, Deterministic, Aggregate	Not reported
Flores[26]	2011	Mexico	Econ	TechIntro	Cyt vs HPV vs SS	HPV+;HPV&Cyt+; SS-	Static, Deterministic, Aggregate	Unspecified method
Frame[27]	1998	Europe and North America	Epid	Algorithm	Cyt vs Cyt	IncCov+;>=3y+; IncFreq-	Static, Deterministic, Aggregate	Not reported
Goldie[28]	2004	USA	Econ	TechIntro	Cyt vs HPV	ConvC-, LBC+, LBC/HPV=HPV&LBC(>30)3y+	Static, Deterministic, Aggregate	Visual inspection
Goldie[29]	2001	USA	Econ	TechIntro	Cyt vs HPV	HPV&Cyt+	Static, Deterministic, Aggregate	Not reported
Goldie[30]	2005	India, South Africa, Kenya,	Econ	ScreenIntro	Cyt vs HPV vs VIA	Pap-, HPV+, VIA+	Static, Deterministic, Aggregate	Visual inspection

		Peru, Thailand						
Goldie[31]	2001	South Africa	Econ	ScreenIntro	Cyt vs HPV vs SS vs VIA	VIA+, 1-visit HPV+, SS+vsNoScreen	Static, Deterministic, Aggregate	Unspecified method
Goldie[32]	1999	USA	Econ	Algorithm	Cyt vs Cyt	HIV:Cyt1y+	Static, Deterministic, Aggregate	Unspecified method
Gustafsson[33]	1992	Sweden, Canada, USA, UK, Barbados	Epid	Algorithm	Cyt vs Cyt	OrgScreen+; (30-60)or (31-67)5x+	Static, Deterministic, Aggregate	Not reported
Gutierrez-Aguado[34]	2011	Peru	Econ	ScreenIntro	Cyt vs Cyt	ScreenAlone+	Static, Deterministic, Aggregate	Not reported
Gyrd-Hansen[35]	1995	Denmark	Econ	ScreenIntro	Cyt vs Cyt	4y(25-59)+	Static, Deterministic, Aggregate	Unspecified method
Hadwin[36]	2008	UK	Econ	Algorithm	Cyt vs Cyt	Pap/Colp(1mth)+	Static, Deterministic, Aggregate	Not reported
Helfand[37]	1992	USA	Epid	Algorithm	Cyt vs Cyt	Improve Pap quality+ (reduce false-negative rate)	Static, Deterministic, Aggregate	Not reported
Hughes[38]	2005	USA	Econ	TechIntro	Cyt vs HPV	LBC+, LBC/HPV+	Static, Deterministic, Aggregate	Not reported
Hutchinson[39]	2000	USA	Econ	TechIntro	Cyt vs Auto	ConvC-, Auto+, LBC+	Static, Deterministic, Aggregate	Unspecified method
Karnon[40]	2004	UK	Econ	TechIntro	Cyt vs Cyt	LBC+	Static, Deterministic, Aggregate	Not reported
Kim[41]	2004	Hong Kong	Econ	ScreenIntro	Cyt vs Cyt	LBC+, OrgScreen+	Static, Deterministic, Aggregate	Not reported
Kim[42]	2013	USA	Econ	Algorithm	Cyt vs Cyt	>=3y+	Static, Stochastic, Individual	Formal method
Kim[43]	2005	UK, Italy, Netherlands, France	Econ	TechIntro	Cyt vs HPV	Cyt_HPV&Cyt>30+, Cyt/HPV+	Static, Deterministic, Aggregate	Visual inspection
Kim[44]	2002	USA	Econ	TechIntro	Cyt vs HPV	LBC+, LBC/HPV+	Static, Deterministic, Aggregate	Unspecified method
Knox[45]	1976	UK	Epid	Algorithm	Cyt vs Cyt	25-;30-;(35-80)10x+	Static, Deterministic, Aggregate	Not reported
Koong[46]	2006	Taiwan	Econ	ScreenIntro	Cyt vs Cyt	3y+	Static, Stochastic, Individual	Not reported

Koopmanschap[47]	1990	Netherlands	Econ	ScreenIntro	Cyt vs Cyt	OrgPap+, every6y+,37-73	Static, Stochastic, Individual	Visual inspection
Koopmanschap[48]	1990	Netherlands	Econ	ScreenIntro	Cyt vs Cyt	OrgPap+, (37-73)6y+	Static, Stochastic, Individual	Not reported
Krahn[49]	2008	Canada	Econ	TechIntro	Cyt vs HPV	Pap=LBC, HPVtriage+	Static, Deterministic, Aggregate	Formal method
Kulasingam[50]	2006	USA	Econ	TechIntro	Cyt vs HPV	LBC/HPV+	Static, Deterministic, Aggregate	Not reported
Kulasingam[51]	2006	USA	Econ	Algorithm	Cyt vs Cyt	(<30)2-3y(>30)3y+	Static, Deterministic, Aggregate	Not reported
Kulasingam[52]	2009	Canada	Econ	TechIntro	Cyt vs HPV	HPV/Cyt>25+	Static, Deterministic, Aggregate	Unspecified method
Kulasingam[53]	2013	USA	Econ	TechIntro	Cyt vs HPV	Cyt3y_HPV&Cyt5y>30+	Static, Deterministic, Aggregate	Not reported
Lazaar[54]	2010	Tunisia	Econ	Algorithm	Cyt vs Cyt	3y-;5y-;10y+	Static, Deterministic, Aggregate	Not reported
Legood[55]	2012	UK	Econ	TechIntro	Cyt vs HPV	HPVtestCure+	Static, Deterministic, Aggregate	Visual inspection
Legood[56]	2006	UK	Econ	TechIntro	Cyt vs HPV	LBC&HPV>35+	Static, Deterministic, Aggregate	Not reported
Levin[57]	2010	China	Econ	ScreenIntro	Cyt vs HPV	LBC+, CareHPV+	Static, Deterministic, Aggregate	Unspecified method
Mandelblatt[58]	2002	Thailand	Econ	ScreenIntro	Cyt vs HPV vs VIA	OrgScreen+, VIA5y(35-55)+,Pap&HPV5y(20-70)+	Static, Deterministic, Aggregate	Visual inspection
Mandelblatt[59]	1997	USA	Econ	Algorithm	Cyt vs Cyt	ERscreen+	Static, Deterministic, Aggregate	not reported
Mandelblatt[60]	2002	USA	Econ	TechIntro	Cyt vs HPV	HPV&Pap2y+	Static, Stochastic, Individual	Visual inspection
Mandelblatt[61]	1988	USA	Econ	Algorithm	Cyt vs Cyt	Screen1x(>65)+	Static, Deterministic, Aggregate	not reported
Mandelblatt[62]	2004	USA	Econ	TechIntro	Cyt vs HPV	HPV&Pap2y+	Static, Deterministic, Aggregate	Not reported
Matsunaga[63]	1997	Japan	Econ	ScreenIntro	Cyt vs Cyt	Pap+	Static, Deterministic, Aggregate	Not reported
Maxwell[64]	2002	USA	Econ	TechIntro	Cyt vs HPV	LBC+, LBC/HPV+	Static, Deterministic, Aggregate	Not reported
McCrory[65]	1999	USA	Econ	TechIntro	Cyt vs Auto	LBC+/-Auto3y+	Static, Deterministic, Aggregate	Visual inspection
Melnikow[66]	2010	Canada	Econ	TechIntro	Cyt vs HPV	Pap+, LBC-, HPV-	Static, Deterministic, Aggregate	Visual inspection
Mittendorf[67]	2003	Germany	Econ	TechIntro	Cyt vs HPV	HPV/Colp+, HPV&Cyt+	Static, Deterministic, Aggregate	Not reported
Montz[68]	2001	USA	Econ	TechIntro	Cyt vs Cyt	LBC+	Static, Deterministic, Aggregate	Not reported

Myers[69]	2000	USA	Epid	Algorithm	Cyt vs Cyt	n.a.	Static, Deterministic, Aggregate	Not reported
Myers[70]	2000	USA	Econ	Algorithm	Cyt vs Cyt	IncFreq-; IncSE&SP+	Static, Deterministic, Aggregate	Not reported
Neville[71]	2005	Australia	Econ	TechIntro	Cyt vs Cyt	LBC+	Static, Deterministic, Aggregate	Not reported
Novoa-Vazquez[72]	2004	Portugal	Econ	ScreenIntro	Cyt vs Cyt	LBC+, OrgScreen+	Static, Deterministic, Aggregate	Not reported
Ostensson[73]	2010	Sweden	Econ	TechIntro	Cyt vs HPV	Pap/HPV+	Static, Deterministic, Aggregate	Not reported
Ostensson[74]	2013	Sweden	Econ	TechIntro	Cyt vs SS	SS(>35)5y+, ConvCyt<35+	Static, Deterministic, Aggregate	Visual inspection
Parkin[75]	1985	UK	Epid	Algorithm	Cyt vs Cyt	Screen+	Static, Stochastic, Individual	Not reported
Parkin[76]	1986	UK	Econ	Algorithm	Cyt vs Cyt	<35-;(>35)5y+	Static, Stochastic, Individual	Not reported
Perkins[77]	2010	Honduras	Econ	ScreenIntro	Cyt vs VIA	VIA+, Pap-	Static, Deterministic, Aggregate	Not reported
Philips[78]	2001	UK	Econ	TechIntro	Cyt vs HPV	Pap = Pap/HPV; EarlyWithdrawal-	Static, Deterministic, Aggregate	Unspecified method
Raab[79]	1999	USA	Econ	TechIntro	Cyt vs Cyt	Pap+, newTech-	Static, Deterministic, Aggregate	Not reported
Raab[80]	1997	USA	Econ	Algorithm	Cyt vs Cyt	PapRescreen+/-	Static, Deterministic, Aggregate	Not reported
Raab[81]	1999	USA	Econ	Algorithm	Cyt vs Cyt	PapRescreenHigh-risk+	Static, Deterministic, Aggregate	Not reported
Raab[82]	1998	USA	Econ	Algorithm	Cyt vs Cyt	ASCUS: Colp-,Treat-, Pap1y+	Static, Deterministic, Aggregate	Not reported
Radensky[83]	1998	USA	Econ	TechIntro	Cyt vs Auto	Auto+	Static, Deterministic, Aggregate	Not reported
Raffle[84]	2003	UK	Epid	Algorithm	Cyt vs Cyt	SceenIntro+	Static, Deterministic, Aggregate	Not reported
Sato[85]	1999	Japan	Econ	ScreenIntro	Cyt vs Cyt	ScreenIntro+	Static, Deterministic, Aggregate	Not reported
Sawaya[86]	2003	USA	Epid	Algorithm	Cyt vs Cyt	30-64:1-3y-;1-1-3y-;1-1-1-3y+	Static, Deterministic, Aggregate	Not reported
Schechter[87]	1996	USA	Econ	TechIntro	Cyt vs Auto	Auto+,2y+	Static, Deterministic, Aggregate	Not reported
Sheriff[88]	2007	Germany	Econ	TechIntro	Cyt vs HPV	Pap/HPV+, Pap/Pap-, Pap/Colp-	Static, Deterministic, Aggregate	Not reported
Sherlaw-Johnson[89]	2004	UK	Econ	TechIntro	Cyt vs HPV	LBC+, HPV&LBC5y+	Static, Deterministic, Aggregate	Not reported

Sherlaw-Johnson[90]	2000	Eastern Europe	Econ	TechIntro	Cyt vs HPV	HPV/Colp+	Static, Stochastic, Individual	Unspecified method
Sherlaw-Johnson[91]	1997	Developing countries	Econ	ScreenIntro	Cyt vs HPV	HPV1x(30-59)+	Static, Stochastic, Individual	Unspecified method
Sherlaw-Johnson[92]	1999	UK	Econ	Algorithm	Cyt vs HPV	Stop50,55,60-;65+, HPV&Cyt=Cyt	Static, Stochastic, Individual	Unspecified method
Sherlaw-Johnson[93]	1994	Latin America, Finland, Iceland	Epid	Algorithm	Cyt vs Cyt	ASCUS:Colp-Cyt6mth+;IncCov+	Static, Stochastic, Individual	Not reported
Shi[94]	2011	China	Econ	ScreenIntro	HPV vs VIA	CareHPV+, VIA-	Dynamic, Deterministic, Aggregate	Not reported
Shun-Zhang[95]	1982	Canada	Epid	ScreenIntro	Cyt vs Cyt	Screen+; Pap(25-52)3y OR (25-40)3y+(40-60)5y+	Static, Deterministic, Aggregate	Not reported
Siebert[96]	2006	Germany	Epid	Algorithm	Cyt vs Cyt	2y+	Static, Deterministic, Aggregate	Visual inspection
Smith[97]	1999	USA	Econ	TechIntro	Cyt vs Auto	Auto+	Static, Deterministic, Aggregate	Not reported
Sroczynski[98]	2011	Germany	Econ	TechIntro	Cyt vs HPV	HPV/Cyt2yOlder+	Static, Deterministic, Aggregate	Visual inspection
Stout[99]	2008	USA	Epid	TechIntro	Cyt vs HPV	LBC/HPV+_HPV/LBC(>30)+	Static, Stochastic, Individual	Formal method
Straughn[100]	2004	USA	Econ	TechIntro	Cyt vs HPV	LBC/HPV2y+	Static, Deterministic, Aggregate	Not reported
Suba[101]	2001	Vietnam	Econ	ScreenIntro	Cyt vs Cyt	ScreenIntro+	Static, Deterministic, Aggregate	Not reported
Taylor[102]	2000	USA	Econ	TechIntro	Conv+/-Spec	2y+	Static, Deterministic, Aggregate	Not reported
van Ballegooijen[103]	2000	UK, Italy, Netherlands, Germany, France, Spain, Portugal, Greece, Denmark, Finland,	Epid	Algorithm	Cyt vs Cyt	n.a.	Static, Stochastic, Individual	Not reported

		Sweden, Belgium, Ireland						
van Ballegooijen[104]	1992	Netherlands	Epid	ScreenIntro	Cyt vs Cyt	OrgScreen+,Pap(30-60)5y+	Static, Stochastic, Individual	Not reported
van Ballegooijen[105]	1997	Netherlands	Econ	TechIntro	Cyt vs HPV	HPV&Pap = Pap	Static, Stochastic, Individual	Not reported
van den Akker-van Marle[106]	2002	Netherlands	Econ	Algorithm	Cyt vs Cyt	>=3y+	Static, Stochastic, Individual	Visual inspection
van Oortmarssen[107]	1992	Canada	Epid	Algorithm	Cyt vs Cyt	Pap(35-64)5y+	Static, Deterministic, Aggregate	Unspecified method
van Rosmalen[108]	2012	Netherlands	Econ	TechIntro	Cyt vs HPV	LBC-, Pap_HPV/Pap(>32)+	Static, Stochastic, Individual	Visual inspection
Vanni[109]	2011	Brazil	Econ	TechIntro	Cyt vs HPV	HPV/Cyt1y+	Static, Deterministic, Aggregate	Formal method
Vanni[110]	2011	Brazil	Econ	TechIntro	Cyt vs HPV	Cyt/HPV(>30)+	Static, Deterministic, Aggregate	Formal method
Vijayaraghavan[111]	2009	South Africa	Econ	TechIntro	Cyt vs HPV	HPV/Pap+	Static, Deterministic, Aggregate	Not reported
Vijayaraghavan[112]	2010	Canada	Econ	TechIntro	Cyt vs HPV	Pap-, Pap/HPV+, HPV/Pap+, HPV&Pap+	Static, Deterministic, Aggregate	Not reported
Vijayaraghavan[113]	2010	USA	Econ	TechIntro	Cyt vs HPV vs GT	HPV&LBC/GT+	Static, Deterministic, Aggregate	Visual inspection
Voko[114]	2012	Hungary	Econ	Algorithm	Cyt vs Cyt	Improve Cov+	Static, Deterministic, Aggregate	Visual inspection
Willis[115]	2005	UK	Epid	TechIntro	Cyt vs Auto	Cyt+, Auto-	Static, Stochastic, Individual	Not reported
Woo[116]	2007	China	Econ	ScreenIntro	Cyt vs Cyt	4y+	Static, Deterministic, Aggregate	Not reported
Woo[117]	2005	Hong Kong	Epid	ScreenIntro	Cyt vs Cyt	OrgScreen+	Static, Deterministic, Aggregate	Visual inspection
Wu[118]	2011	Hong Kong	Econ	TechIntro	Cyt vs HPV	HPV&Cyt3y+	Static, Stochastic, Individual	Visual inspection

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3.2.5. Additional material 5.

Supplementary Table 3-5. Main characteristics of studies focused on screening interventions alongside vaccination (n=35)

First Author	Year	Country	Econ/Epid	Aim	Technologies	Main findings	Type of model	Calibration
Accetta[1]	2010	Italy	Econ	TechIntro	Cyt vs HPV	HPV/Cyt5y +/-Vac+	Static, Deterministic, Aggregate	Formal method
Campos[2]	2012	Kenya, Eastern Africa, Mozambique, Tanzania, Uganda, Zimbabwe	Econ	TechIntro	HPV vs VIA	HPV3x+, Vac&HPV+	Static, Stochastic, Individual	Formal method
Canfell[3]	2011	China	Econ	ScreenIntro	HPV vs HPV	Vac&CareHPV2x(30-59)+	Dynamic, Deterministic, Aggregate	Visual inspection
Chen[4]	2011	Taiwan	Econ	TechIntro	Cyt vs HPV	Pap+; HPV&Cyt+	Static, Stochastic, Individual	Not reported
Coupe[5]	2012	Netherlands	Econ	TechIntro	Cyt vs HPV	Vac&HPV/Cyt+	Static, Stochastic, Individual	Visual inspection
Coupe[6]	2009	Netherlands	Econ	TechIntro	Cyt vs HPV	Vac&HPV/Cyt=Vac&Cyt/HPV>30	Static, Stochastic, Individual	Unspecified method
Coupe[7]	2009	Netherlands	Econ	Algorithm	Cyt vs Cyt	Vac&Cyt+	Static, Stochastic, Individual	Formal method
Crowcroft[8]	2012	Canada	Epid	Algorithm	Cyt vs Cyt	Vac&Cyt+	Static, Deterministic, Aggregate	Not reported
de Blasio[9]	2012	Norway	Epid	Algorithm	Cyt vs Cyt	Vac&Screen+; 30-;59-; 5y-; (25-69)3y+	Dynamic, Deterministic, Aggregate	Visual inspection
Diaz[10]	2008	India	Econ	ScreenIntro	Cyt vs HPV vs VIA	Vac&2visitHPV3x(35,40,45)+	Static, Stochastic, Individual	Formal method
Diaz[11]	2010	Spain	Econ	ScreenIntro	Cyt vs HPV	Screen+; Vac&HPV/Cyt>30+	Static, Stochastic, Individual	Formal method
Ezat[12]	2010	Malaysia	Econ	Algorithm	Cyt vs Cyt	Screen&QVvac+	Static, Deterministic, Aggregate	Not reported
Ginsberg[13]	2012	Sub-Saharan Africa, South East Asia	Econ	ScreenIntro	Cyt vs HPV vs VIA	Vac-, Cyt or VIA+	Static, Deterministic, Aggregate	Not reported
Ginsberg[14]	2009	EMRO, SEARO, AMRO, WPRO, AFRO, Eastern Europe	Econ	ScreenIntro	Cyt vs HPV vs VIA	HIC:Vac&anyScreen+; LMIC:Vac&Pap3or5y+	Static, Deterministic, Aggregate	Not reported
Ginsberg[15]	2007	Israel	Econ	ScreenIntro	Cyt vs HPV vs VIA	HPV-, VIA-, Vac&Pap5y+	Static, Deterministic, Aggregate	Not reported
Goldhaber-Fiebert[16]	2008	USA	Econ	TechIntro	Cyt vs HPV	HPV/Cyt(>30)+Cyt/HVP(<30)+/-Vac+	Static, Stochastic, Individual	Formal method
Goldhaber-Fiebert[17]	2007	USA	Epid	Algorithm	Cyt vs Cyt	Vac&Screen+; (18-70)5y+	Static, Stochastic, Individual	Formal method

Goldie[18]	2004	USA	Econ	TechIntro	Cyt vs HPV	Vac&ConvC(>25)3y+	Static, Deterministic, Aggregate	Unspecified method
Goldie[19]	2011	USA	Econ	TechIntro	Cyt vs HPV	Vac&HPV/Cyt>30+	Static, Stochastic, Individual	Unspecified method
Goldie[20]	2008	Latin America, Caribbean (Argentina, Chile, Colombia, Mexico, Peru)	Econ	ScreenIntro	Cyt vs HPV	Vac&2-visit HPV3x(>30)+	Static, Stochastic, Individual	Formal method
Goldie[21]	2007	Brazil	Econ	ScreenIntro	Cyt vs HPV	Vac&Cyt+	Static, Stochastic, Individual	Formal method
Goldie[22]	2008	Developing countries	Econ	ScreenIntro	Cyt vs HPV	Vac&HPV+	Static, Stochastic, Individual	Not reported
Gutierrez-Delgado[23]	2008	Mexico	Econ	TechIntro	Cyt vs HPV	Vac&HPV&Cyt+	Static, Deterministic, Aggregate	Not reported
Kim[24]	2008	Vietnam	Econ	ScreenIntro	Cyt vs HPV	Vac&HPV5y+	Static, Stochastic, Individual	Visual inspection
Kim[25]	2009	USA	Econ	TechIntro	Cyt vs HPV	Vac>30-; HPV&Cyt-; HPV-	Static, Stochastic, Individual	Formal method
Kulasingam[26]	2003	USA	Econ	Algorithm	Cyt vs Cyt	Vac&Screen(>24)2y+;3-5y-;18-	Static, Deterministic, Aggregate	Not reported
McLay[27]	2010	USA, Western Europe	Epid	Algorithm	Cyt vs Cyt	Vac&Screen+; >3y+	Static, Deterministic, Aggregate	Visual inspection
Praditsitthikorn[28]	2011	Thailand	Econ	ScreenIntro	Cyt vs VIA	VIA(30-45)Pap(50-60)5y+	Static, Deterministic, Aggregate	Not reported
Reynales-Shigematsu[29]	2009	Mexico	Econ	Algorithm	Cyt vs Cyt	Vac+, Vac&Cyt-	Static, Deterministic, Aggregate	Visual inspection
Rogoza[30]	2008	Canada, Netherlands, Taiwan, UK, USA	Econ	TechIntro	Cyt vs HPV	Vac&Cyt/HPV-;Vac&Cyt+	Static, Deterministic, Aggregate	Unspecified method
Sharma[31]	2012	Thailand	Econ	ScreenIntro	Cyt vs HPV vs VIA	Vac&HPV5x(>35)+	Static, Stochastic, Individual	Formal method
Sopina[32]	2011	New Zealand	Econ	Algorithm	Cyt vs Cyt	Vac&Screen(30-60)5y+; 20-; 69-; 3y-	Static, Deterministic, Aggregate	Not reported
Tully[33]	2012	Canada	Econ	Algorithm	Cyt vs Cyt	CatchUp+; 25+; 18-;21-	Dynamic, Deterministic, Aggregate	Visual inspection
Wong[34]	2009	Australia	Econ	Algorithm	Cyt vs Cyt	Vac-;LBC-;ConvCyt 1y+	Static, Deterministic, Aggregate	Not reported
Yamamoto[35]	2012	Japan	Econ	Algorithm	Cyt vs Cyt	Vac&Cyt+	Static, Deterministic, Aggregate	Unspecified method

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3.2.6. Additional material 6.

Supplementary Table 3-6. Number of single- and multiple-country studies per country

Country	Single-country studies	Multiple-country studies	Total
Argentina	-	1	1
Australia	5	1	6
Barbados	-	1	1
Belgium	-	1	1
Brazil	3	-	3
Cameroon	1	-	1
Canada	9	3	12
Chile	-	1	1
China	4	-	4
Colombia	1	1	2
Denmark	1	1	2
Germany	4	1	5
Greece	1	1	2
France	-	2	2
Finland	-	2	2
Honduras	1	-	1
Hong Kong	3	-	3
Hungary	1	-	1
Iceland	-	1	1
India	1	1	2
Ireland	-	1	1
Israel	1	-	1
Italy	1	2	3
Japan	3	1	4
Kenya	-	2	2
Malaysia	1	-	1
Mexico	3	1	4
Mozambique	-	1	1
Netherlands	13	3	16
New Zealand	1	-	1
Norway	2	-	2
Peru	1	2	3
Portugal	1	1	2
South Africa	2	1	3
Spain	1	1	2
Sweden	3	2	5
Taiwan	3	1	4
Tanzania	-	1	1
Thailand	3	1	4
Tunisia	1	-	1
Uganda	-	1	1
UK	14	5	19
USA	44	5	49
Vietnam	2	-	2
Zimbabwe	-	1	1

3.2.7. Additional material 7.

Supplementary Table 3-7. Summary of findings on comparisons of screening technologies

Intervention/ Comparison	No. of studies, Type of analysis	Recommended technology (no. of studies, country)
Cytology		
Conventional Cytology vs LBC	27 (26 Economic, 1 Epidemiological[59])	LBC (n=18; Australia[60], China[25], Hong Kong[61], Netherlands[62, 63], Portugal[64], UK[65–67], USA[68–75, 59]) Conventional (n=8, Australia[76][77]†, Canada[29, 78], Netherlands[79], Sweden[80], USA[81, 82]†) Conventional or LBC (n=1, Canada)[78]
Cytology +/- Automation	7 (6 Economic, 1 Epidemiological[22])	Automated cytology (n= 6, USA)[74, 75, 81, 83–85] Cytology alone (n=1, UK)[22]
Cytology +/- Speculoscopy	1 Economic	Cytology + Speculoscopy (n=1, USA)[23]
HPV DNA		
Cytology vs HPV	17 Economic	HPV (n=15; Brazil[86][a], Canada[87], Caribbean and Latin America[88]†, Colombia[89], unspecified developing countries[90, 91]†, Eastern Europe[92], European Union[93], Italy[94]†, Netherlands[79]† [95]†, Norway[96], USA[97]†[98]†, Vietnam[99]†) HPV/cytology triage or Cytology/HPV triage ≥30y (n=1, Netherlands)[100] Cytology (n=1, Canada)[101]
Co-testing vs Cytology vs HPV	17 (16 Economic, 1 Epidemiological[59])	HPV (n= 6; Canada[102], Germany[103, 104], Netherlands[105], Taiwan[106], USA[59]) Co-testing (n=2; USA[107], Mexico[36]†) Co-testing or HPV (n=3, UK[66], South Africa[108], USA[38]†) Co-testing or Cytology (n=2, UK, Italy, Netherlands, and France[109], Taiwan[37]†) Co-testing or HPV or Cytology (n=1, Netherlands)[110] Cytology (n= 3; Brazil[111]†, Sweden[112], Spain[113]†)
Co-testing vs Cytology	7 Economic	Co-testing (n=6; Hong Kong[114], UK[67], USA[115–117] [82][a] Cytology/HPV triage (n=1, USA)[118]
Triage of cytological abnormalities		
Repeat Cytology vs HPV vs Co-testing	1 Economic	HPV triage (n=1, Netherlands)[62]
Repeat Cytology vs HPV vs Immediate treatment	1 Economic	HPV triage (n=1,Germany[119])

Repeat Cytology vs HPV vs Immediate colposcopy	8 Economic	Colposcopy with biopsy (n=1, Sweden)[120] HPV triage (n=7; Brazil[121], Canada[78], UK[122], USA[39, 71, 123, 124], Netherlands and Taiwan[39]†) Cytology triage(n=1, Canada and UK)[39]†
Rapid HPV		
Rapid HPV(2x) vs Rapid HPV (1x)	1 Economic	Rapid HPV (2x) (n=1, China)[26]
Rapid HPV vs VIA	1 Economic	Rapid HPV (25-49, triennial; 50-64, quinquennial)(n=1, China)[24]
Rapid HPV vs HPV vs Cytology	1 Economic	Rapid HPV (3x) (n=1, China)[25]
Self-sampling		
Cytology vs HPV vs SS vs VIA	1 Economic	VIA or HPV; SS vs No screening (n=1, South Africa) [32]
Cytology vs HPV vs Co-testing vs SS	1 Economic	HPV alone or Co-testing (n=1, Mexico)[125]
Cytology vs HPV vs SS	1 Economic	SS (n=1, USA)[126]
Cytology vs SS	1 Economic	SS (≥35y) and cytology (<35y) (n=1, Sweden)[80]
HPV 16/18 genotyping		
Cytology vs HPV vs Co-testing vs Co-testing+Genotyping	1 Economic	Co-testing with HPV 16/18 genotyping triage (n=1, USA)[30]
VIA		
Cytology vs HPV vs SS vs VIA	1 Economic	VIA or HPV (n=1, South Africa)[32]
Cytology vs HPV vs VIA	7 Economic	VIA or HPV (n=2, India[18]†, Kenya, Peru, Thailand, and South Africa)[33] VIA or Cytology (n=1, Sub-Saharan Africa and South East Asia)[127]† VIA or Co-testing (n=1, Thailand)[128] VIA in LMIC, any in HIC (n=1, developing countries)[20]† HPV (n=1, Thailand[31]†) Cytology (n=1, Israel)[129]†
Cytology vs VIA	2 Economic	VIA (n=1, Honduras)[34] VIA (30-45y) and Cytology (50-60y) (n=1, Thailand)[35]†
HPV vs VIA	1 Economic	HPV (n=1; Kenya, Mozambique, Tanzania, Uganda, Zimbabwe[19]†)

[a]HIV-positive women; †screening & vaccination study; Co-testing, combined cytology and HPV DNA testing; HPV, HPV DNA testing; LBC, liquid-based cytology; SS, self-sampling HPV DNA testing; VIA, visual inspection with acetic acid; y, years; 1x, once a lifetime; 2x, twice a lifetime

3.2.8. Additional material 8.

Supplementary Table 3-8. Summary of cervical screening guidelines

Country and Year of publication	Recommendation for primary screening
Australia 2015[130]	Currently, conventional cytology 2-yearly for women aged ≥18 or 20, or 1-2 years after sexual debut, whichever is later. In 2016, HPV DNA testing 5-yearly to women aged 25-74
Canada 2013[45]	Cytology[a] 3-yearly to women aged 25-69
Ireland 2011[131]	LBC 3-yearly to women aged 25-44; 5-yearly to women aged 45-60
Japan 2010[132]	Cytology[a] recommended 2-yearly to women aged ≥20 Free screening offered 5-yearly to women aged 20–40
Latvia 2009[133]	Cytology[b] 3-yearly to women aged 25-69
Netherlands 2011[134]	Conventional cytology 5-yearly to women aged 30-60 In 2016, HPV DNA testing 5-yearly to women aged 30-60
New Zealand 2010[135]	Cytology [a] 3-yearly to women aged 20-69
Norway 2005[136]	Cytology [a] 3-yearly to women aged 25–69 Planning to start introducing HPV DNA primary screening for women aged 34 – 69 in four counties in 2015[137, 138]
Portugal 2014[139]	Cytology[a] 3-yearly to women aged 25-65 or HPV DNA primary testing 5-yearly for women aged 30-65
Singapore 2010[140]	Cytology[a] 3-yearly to women aged 25–69
South Korea 2012[141]	Cytology[a] yearly to women aged 20–70
Sweden 2010[142]	LBC 3-yearly to women aged 23-49; 5-yearly to women aged 50-60
Switzerland 2004[143]	Conventional cytology yearly from sexual debut
Taiwan 1995[144]	Conventional cytology yearly to women aged ≥30
UK 2012 [145][146]	*England, Northern Ireland and Wales:* LBC to 25-64; 3-yearly to women aged 25-49; 5-yearly to 50-64 *Scotland:* LBC 3-yearly to women aged 20-60 In 2016, to change to same schedule as rest of UK
USA 2012[147]	Cytology[a] 3-yearly to women aged 21-65 Optional, Co-testing 5-yearly to women aged 30-65

[a] Conventional or liquid-based; [b] Giemsa stain in Leishman modification; Co-testing, combined cytology and HPV DNA testing; LBC, liquid-based cytology

4. Chapter 4. Model-based evaluation of the effectiveness of primary HPV testing versus cytology-based cervical screening in Portugal

4.1. Preamble to research paper 3

In research paper 1[1], the burden of cervical cancer, risk factors, and preventive interventions in place in Portugal were characterised. Its findings suggest that the incidence of cervical cancer is likely to decrease with improvements on screening coverage and quality.

The overall aim of this thesis was to investigate the effectiveness and cost-effectiveness of distinct screening policies in Portugal. The systematic review of previous model-based evaluations of cervical screening (research paper 2[2], Chapter 3) demonstrated how similar mathematical models have yielded insight in other countries. The two studies[3,4] found on Portugal analysed the impact of cytology-based strategies in the 2000s. Since then, HPV vaccination has been introduced in the Portuguese National Immunisation Plan[5], organised screening has been introduced in several Portuguese regions[6], and primary HPV testing has proven its superiority to prevent cervical cancer compared to primary cytology in large European clinical trials[7]. The questions to address in this context now concern mainly the integration of primary HPV screening into a countrywide organised programme, including the appropriate triage of HPV positive women.

In order to investigate how alternative screening protocols are likely to impact cervical cancer incidence in Portugal, we adapted an existing model of HPV acquisition and progression to cervical cancer to Portugal. Research paper 3 in this chapter shows how we parameterised the model using Portuguese data and the methods applied to circumvent data constraints to predict the effectiveness of cytology- and HPV-based protocols.

While research paper 1[1] facilitated identifying crucial data sources for the parameterisation of our model, research paper 2[2] improved our understanding of the methodology used in the field and showed that model calibration to country-specific data is rarely but increasingly conducted to more robustly characterise the setting regarding parameters non-directly measurable.

We used individual-patient data from the latest Portuguese population-based sexual health survey[8] to parameterise the HPV acquisition component of our model and calibrated it to Portuguese age- and type-specific HPV prevalence[9] and incidence of cervical cancer[10]. The characterisation of opportunistic screening was based on the Portuguese National Health

Survey 2005/6 individual-patient data[11], before the introduction of regional organised programmes in 2008.

Research paper 3 provides the first model-based evaluation of primary HPV screening in Portugal and shows that such a nationwide organised programme is likely more effective in the prevention of cervical cancer than cytology-based protocols.

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4.2.Research paper 3.

Model-based evaluation of the effectiveness of primary HPV testing versus cytology-based cervical screening in Portugal

Mendes, D[1,2]; Bains, I[2]; Baguelin, M[1,2]; Jit, M[1,2]

[1] Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, United Kingdom

[2] Modelling and Economics Unit, Public Health England, United Kingdom

Publication status: in preparation

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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SECTION A – Student Details

Student	Diana Mendes
Principal Supervisor	Mark Jit
Thesis Title	The impact and cost-effectiveness of cervical screening in Portugal

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The European Journal of Cancer
Please list the paper's authors in the intended authorship order:	Diana Mendes, Iren Bains, Marc Baguelin, Mark Jit
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The candidate had the idea for this research paper and developed a proposal for funding of this thesis with MJ. The research questions were refined in collaboration with MJ. IB developed the original model that the candidate adapted to this research paper. The candidate liaised with the necessary parties to acquire the data sources used. The candidate

	analysed the data, parameterised and calibrated the model with IB's supervision. The candidate adapted parts of the model to accommodate particularities of the setting analysed in this research paper in close consultation with IB, MB, and MJ. MB advised on methodology used. The candidate wrote the manuscript and incorporated the comments of MB and MJ.

Student Signature: [redacted] **Date:** 25 June 2018

Supervisor Signature: _____ **Date:** 26 June 2018

4.2.1. Abstract

Background: Portugal has shown higher incidence of cervical cancer than England, despite its relatively low overall prevalence of human papillomavirus (HPV) and behavioural risk factors for HPV infection prior to the introduction of HPV vaccination. Publicly-funded opportunistic cervical screening is ubiquitous and recently implemented organised regional programmes vary in coverage, protocols, and technologies used. Primary HPV screening is being piloted in preparation for a uniform countrywide organised approach, but this has not been formally assessed. Our aim was to compare the effectiveness of alternative cervical screening strategies in Portugal.

Methods: We projected the effectiveness of possible cervical screening strategies in Portugal using a static, stochastic, individual-based mathematical model of HPV infection and cervical disease progression adapted to the Portuguese context. The acquisition of HPV infection was parameterised with data from a population-based Portuguese sexual health survey. Rates of HPV acquisition and clearance were fitted to pre-vaccination HPV prevalence from a population-based cross-sectional Portuguese study, and disease progression to national cervical cancer incidence. Screening currently in place was characterised based on published estimates of cytology uptake and data from the organised programmes. The calibrated model was used to quantify the impact of alternative cervical screening strategies.

Results: Our results indicate that opportunistic screening has decreased cervical cancer incidence by over 30% and organised screening may lead to a further 35% reduction. Protocols incorporating HPV triage of minor abnormalities detected during cytological screening would require fewer tests while detecting similar numbers of cervical intraepithelial neoplasia (CIN) 2+ lesions compared to repeat cytology. However, as part of a national coordinated strategy, primary HPV DNA testing every 3 years is likely to prevent more cervical cancer cases with fewer tests than most primary cytology-based strategies. Extending the screening interval to 5 years would achieve comparable reduction in cervical cancer incidence as 3-yearly strategies and require fewer tests, with an average annual number of tests similar to what is predicted for opportunistic screening.

Conclusions: A countrywide organised HPV-based cervical screening programme with a 5-year screening interval may help identify a substantial number of neoplasias and potentially prevent more cervical cancers without increasing the burden of testing.

4.2.2. Introduction

Cytology-based cervical screening has reduced cervical cancer incidence more pronouncedly where organised programmes have been implemented, as shown by several time trend and age-period-cohort analyses of incidence and mortality in Europe[1–3] and worldwide[4]. For instance, in England and Wales, opportunistic screening had reduced cervical cancer deaths by 40% in young women by 1987[5] and a further decline in mortality to less than a third projected was seen in the decade following the organisation of a national screening programme[3].

Several countries with organised programmes (e.g. the Netherlands and Australia) are now transitioning from using cytology to using human papillomavirus (HPV) DNA testing as the primary screening[6,7] on the basis of the emergent evidence of greater protection against high-grade pre-malignant lesions and invasive cervical cancer and safe extension of the screening interval conferred by HPV DNA testing compared to cytology as primary screening test. The higher sensitivity and slightly lower specificity to high-grade precancerous lesions of HPV testing compared to cytology (whether used for primary testing alone or as adjunct to cytology-based screening) has been demonstrated in several European and North American split-sample studies[8] and randomised controlled trials (RCTs)[9–13]. The lower incidence of cervical cancer following primary HPV screening compared to cytology was shown in the follow-up analysis of four large European RCTs as well as the safety of prolonging the screening interval to at least 5 years[14]. Several large trials in Europe[14,15] and North America[16–18] also demonstrated the lower risk of cervical cancer following a negative HPV result compared to that after a negative cytology, with Gage and colleagues' analysis[17] of Kaiser Permanente North California data (largest and longest experience with routine HPV screening) estimating a lower risk of high-grade precancer with 5-yearly HPV screening than with 3-yearly cytology.

Other advantages of HPV-based screening include the high reproducibility and better quality assurance of an automated test, its potential to improve coverage of non-attenders with implementation of self-sampling, and its potential to be less affected by the foreseen reduction on prevalence of cervical lesions due to vaccination than cytology[19].

Primary HPV screening entails effective management of HPV-positive results given the greater sensitivity of primary HPV DNA testing compared to primary cytology. As cytology has been widely used in cervical screening and is more specific for cervical intraepithelial neoplasia (CIN)2+ than HPV testing[20], it can safely reduce the high colposcopy referral rates expected when used in triage of HPV-positive women compared to immediate referral of HPV-positives for colposcopy[21]. Alternative triage tests have not yet been approved[19].

Portugal is likely to benefit from improvements in screening quality and coverage conveyed by organised screening to reduce incidence and mortality of cervical cancer further[22]. Publicly-funded opportunistic cervical screening is ubiquitous but has recently been supplemented by organised cytology-based regional programmes that have extended screening to different populations, with distinct protocols and technologies[23]. Additionally, the Portuguese Ministry of Health now recommends HPV testing for primary screening of women aged 25-60 every 5 years[24]. There may be benefits in moving to a HPV-based uniform countrywide organised approach, but this has not been formally assessed.

Mathematical models of HPV infection and cervical disease progression have been widely used internationally to inform cervical screening policies. While large long-term trials are necessary to collect primary evidence on the impact of screening protocols on cancer incidence in a particular context, mathematical models are a useful tool to combine the existing evidence and predict the impact of different screening algorithms involving alternative technologies in varied populations from those in trials[25].

Given the mix of screening efforts currently in place, we investigated the impact of the transition from an exclusively opportunistic approach using conventional cytology to an organised programme using liquid-based cytology (LBC) or HPV DNA testing as primary screening technology.

4.2.3. Methods

We adapted an existing model of HPV acquisition and progression of cervical disease previously developed by Bains and colleagues (described in the Appendix to this thesis). Our main aim was to compare the effectiveness of alternative screening protocols in Portugal in terms of cervical cancer cases and related deaths prevented.

The static, stochastic, individual-based model developed by Bains and colleagues consists of three main components: (1) acquisition of HPV infection, (2) natural progression to cervical cancer in HPV-positive women, and (3) detection and treatment of cervical high-grade lesions and cancer.

In Bains and colleagues' model, HPV type-specific acquisition is simulated accounting for individuals' age and level of sexual activity. HPV-positive women can then develop cervical lesions which may progress to cancer or regress spontaneously at any stage of disease progression. We used country-specific inputs for each component and calibrated Bains and colleagues' model to Portuguese data on HPV prevalence and cervical cancer incidence. Subsequently the impact of alternative screening strategies was predicted by overlaying a

screening component to the natural history of the disease. Figure 4-1 provides a schematic diagram of our adaptation of the Bains and colleagues model.

Infection acquisition model

We parameterised Bains and colleagues' model of infection acquisition with Portuguese data to generate a modelled cohort of women representative of Portuguese women in terms of age- and type-specific HPV prevalence. Details on the parameterisation and calibration of the HPV acquisition component of the model are provided in Supplementary material 4.3.1.

In Bains and colleagues' model of HPV infection, the number of infected women over time was determined by their risk of acquisition and clearance of HPV infection. Women were assumed to become susceptible after clearing the infection, given the unclear protection from re-infection conferred by naturally acquired immunity[26,27]. The risk of HPV acquisition was modelled as a function of women's sexual behaviour, the number of infectious male partners, and the transmissibility of HPV. The probability of sexual contact with an infected partner by age and activity level was determined by HPV male prevalence and the age mixing matrix. HPV infection acquisition was dependent on the number of sex acts and the transmissibility per sexual act rate. Eight types of HPV were modelled: 16, 18, 31, 33, 45, 51, 52, 58. Simultaneous infections by multiple HPV types were assumed independent.

We modified this model by characterising Portuguese women's sexual behaviour with distributions for age of sexual debut, partner acquisition rate, age of new partner, duration of relationship, and frequency of sex acts obtained from individual-patient data of a 2007 Portuguese population-based sexual health survey[28].

The number of infectious male partners was assumed constant over the lifetime of each modelled cohort of women. We derived age- and type-specific male HPV prevalence in Portugal from Portuguese female HPV prevalence adjusted by the ratio of male and female HPV prevalence in England (Supplementary material 4.3.1).

Women's HPV type-specific clearance parameters and transmissibility per sexual act, and men's seroconversion and clearance rates were calibrated by fitting the model's predicted pre-vaccination HPV type-specific prevalence to data from the population-based cross-sectional Cervical Lesions Observed by Papillomavirus Types – A Research in Europe (CLEOPATRE) study in Portugal[29,30]. The posterior distributions for the fitted parameters, used to run our analyses, were found via an adaptive Metropolis algorithm using Markov Chain Monte Carlo simulation implemented in R[31]. We incorporated deviance of the model output to the observed HPV prevalence (-2*log(likelihood)) in Bains and colleagues' functions to measure goodness-of-fit, using the likelihood function of the binomial distribution. We used the priors

defined by Bains and colleagues for male and female HPV clearance rates, and non-informative priors for transmissibility per sexual act and male seroconversion rate.

Disease progression model

Bains and colleagues modelled progression from HPV infection to pre-malignant cervical lesions via a set of conditional probability functions, where cytological outcomes are interdependent, generating time-dependent HPV type-specific probabilities of the different cytological outcomes (described in the Appendix to this thesis). Progression rates for cytological outcomes fitted to English data on LBC and HPV DNA test outcomes by Bains and colleagues were used for Portugal, based on the assumption that disease progression following HPV infection is independent from women's country of origin and the performance of cytology is comparable between the two countries (Supplementary material 4.3.2). Consequently, the eight most prevalent high-risk HPV types in England were modelled: 16, 18, 31, 33, 45, 51, 52, and 58. We also used Bains and colleagues' estimates for the probabilities of the distinct colposcopy outcomes conditional on women's cytological outcome (based on data from the cervical screening programme in England), assuming the same diagnostic performance for colposcopy in both countries. Our model uses the British Society for Clinical Cytology terminology for cytological outcomes (normal, borderline change, low-grade dyskaryosis (mild), high-grade dyskaryosis (moderate), or high-grade dyskaryosis (severe)) adopted in England for histological results[32].

Bains and colleagues modelled the incidence of HPV type-specific cervical cancer as a function of time since HPV infection (detailed in the Appendix to this thesis). Progression from HPV infection to cervical cancer was modelled independently for squamous and adenocarcinomas. For squamous cell carcinomas, time since infection to cancer clinical detection was modelled as a function of time since infection to cancer onset and time since cancer onset to its clinical detection, whereas time since infection to clinical diagnosis of adenocarcinomas was modelled unabridged using a gamma distribution. Like Bains and colleagues, we used a gamma distribution to model time since infection to onset of squamous cell carcinomas for Portugal; however, we assumed that time from cancer onset to clinical detection followed a lognormal distribution, as it fitted the observed incidence better that the exponential distribution used for England.

Posterior distributions for these non-directly measurable cancer-related parameters were calibrated to cervical cancer incidence in Portugal[33–38]. We limited the fitting target to incidence in women under 50 years of age as our model cannot capture the cohort effects reflected in the observed incidence for older age groups[39]. For HPV 16 and 18 squamous cell

carcinomas, we assumed that the gamma parameters modelling time to cancer onset were uniformly distributed. We ran the model with several sets of values for the gamma and the lognormal parameters and selected the best fitting set by visual inspection of the fit. For the remaining HPV types and for adenocarcinomas, we selected among Bains and colleagues' posterior distributions for England those that visually better fit type-specific incidence in Portugal.

Age-at-diagnosis-specific mortality rates for cervical cancer were derived from survival data reported by the Portuguese cancer registry of the North region[40] and applied for 5 years after diagnosis to women with detected cancer, whose survival was assumed to be the same as in the general population from then onwards[41]. Further details on disease progression model and its parameterisation and calibration are given in Supplementary material 4.3.2.

Screening model

For each screening strategy, the model was run for 5 cohorts of 10,000 women from age 10 and followed over their lifetime. The occurrence of events, such as HPV acquisition or attendance of a screening appointment, was modelled in months. To capture the uncertainty in the fitted parameters, the model was run with 1,000 distinct combinations of parameter values randomly drawn from their distributions.

The screening component was originally structured by Bains and colleagues (in the Appendix to this thesis) to model screening frequency as a function of the individual's age and previous screening attendance history. Given the lack of data on Portuguese women's screening attendance, we restructured the screening component to model women's probability of attending subsequent screens and the waiting time to their next screen independently from their previous attendance.

Decision trees for each strategy were developed specifically for the Portuguese context and incorporate the mapping between the Bethesda system used in Portugal (normal, atypical squamous cell of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL) and that of the British Society for Clinical Cytology[42,43] (detailed in Supplementary material 4.3.3). We also adapted the relevant model functions to accommodate opportunistic screening and repeat cytology triage (which were not modelled for England).

A no screening strategy and several cervical screening protocols were modelled independently. Table 4-1 summarises the characteristics of the cervical screening protocols modelled. Strategy 1 is intended to represent the widespread opportunistic conventional cytology-based screening in Portugal (prior to the introduction of organised programmes and still

predominant), where ASCUS is triaged at 6 months with repeat cytology (strategy 1). We also modelled the introduction of HPV testing to immediately triage ASCUS and LSIL (strategy 2).

We then simulated fully organised cytology-based primary screening with repeat cytology (strategy 7) and HPV triage (strategy 3), assuming screening frequency and compliance under a country-wide organised programme in Portugal would be the same as in the organised cervical screening programme in England.

The screening algorithms recommended by the Portuguese Society of Gynaecology[44] for the opportunistic and organised approach were used to characterise strategies 1- 3 and 7. We also modelled HPV triage in an organised system following the English cervical screening programme protocol[45] (strategy 6), under the same screening frequency and compliance assumptions as strategy 3.

Finally, we modelled the adoption of HPV DNA testing for primary screening following the management algorithm by the English cervical cancer screening programme for HPV primary screening pilot protocol using a screening interval of 3 and 5 years in strategies 4 and 5, respectively[46].

Opportunistic and organised screening were recreated in our model via use of alternative data and assumptions for the proportion of women never screened, the age at first screen, time to next screen, and compliance with referrals for colposcopy and screen or post-treatment follow-up.

Screening frequency under opportunistic screening (i.e. the proportion of women never screened, the age at first screen, and time to next screen) was characterised using individual-patient data from the Portuguese National Health Survey 2005/6[47]. The probability of a women being lost to follow up was assumed to be 0.50, as this is slightly below the lowest compliance rate to screening invitation reported in organised programmes in 2013 (55%). Compliance to repeat cytology referral was assumed to be 100% as 99% was reported in the Centre region, the only region where repeat cytology has been in place. Compliance with colposcopy referral was assumed to be 0.75, the mid-point of 10-40% estimates of non-adherence to referral by Khanna and Phillips[48], e.g. 40% lost to follow-up in Nottingham, England before introduction of an organised programme in 1984, due to lack of Portuguese data to inform this parameter.

To characterise organised screening in Portugal, we assumed that screening frequency would be similar to that in England under a similarly organised call-recall cervical screening programme; hence we used Bains and colleagues' model of age at first screen for women aged over 24.5 years in England, and the distribution of time since last adequate test reported

for women aged 25-64 in the NHS Cervical Screening Programme, England (2012-2013)[49]. We also assumed 10% of women would never be screened based on a population-based study on cytology attendance in the Manchester Health Authority Area (2004)[50].

As the average screening attendance in Portuguese regional organised programmes was 82% (range: 55-86% in Algarve and Alentejo, respectively) in 2013, we assumed that 20% of women are lost to follow-up following identification of a cytological lesion, under organised screening. Colposcopy attendance was assumed to be 88%, the average in Portugal organised programmes (range: 59-92%, in Alentejo and North, respectively).

Conventional cytology is the primary screen used in Portugal in areas not covered by an organised programme. For our analyses, we assumed conventional cytology and LBC had equivalent performance based on Arbyn and colleagues' meta-analysis[51]. Potential advantages of LBC compared to conventional cytology, such as reduction of unsatisfactory samples and inter-laboratory discordance, are not accounted for in out model. The performance of the screening tests modelled was implicitly captured by our disease progression rates. The number of treatments performed in each strategy was estimated assuming that all CIN2+ cases were treated. The parameterisation of the screening model for each of these strategies is described in detail in Supplementary material 4.3.3.

4.2.4. Results

The predicted age-specific crude incidence of squamous cell carcinomas and adenocarcinomas in women undergoing the different strategies is shown on Figure 4-2. Under a hypothetical scenario of no screening performed, cervical cancer incidence would be 11.7 and 11.0 per 100,000 women using the 1976 and 2013 European Standard Population, respectively.

If entirely cytology-based opportunistic screening had continued in place in the same way as prior to 2008 (strategy 1), the predicted annual European age-standardised incidence (EASR) of squamous cell carcinoma and adenocarcinoma attributable to the modelled high-risk HPV types would be 7.5 and 7.2 per 100,000 women (EASR 1976 and 2013, respectively). In Portugal between 1998 and 2010, annual cervical cancer incidence varied between 11.6 and 14.3 cases per 100,000 women (EASR 1976, including all HPV and histological types)[22] and we estimate 8.9-11.0 cases attributable to the modelled high-risk HPV types per 100,000 women (EASR 1976). For squamous cell carcinoma, our predicted 5.5 incident cases per 100,000 women attributable to the 8 high-risk HPV types modelled with opportunistic cytology-based screening (strategy 1) is just under our estimated 6.6 incidence per 100,000 women (EASR 1976) based on data from the National Cancer Registry (2001-2010)[33–38].

An opportunistic programme with HPV triage of equivocal cytological results (strategy 2) is predicted to reduce cancer incidence similarly to strategy 1 (repeat cytology), whereas organised cytology- or HPV-based programmes (strategies 3-7) would reduce incidence to 3.6-3.8 cases per 100,000 women (EASR 2013).

Table 4-2 presents our model results in terms of number of tests and cervical cancer cases predicted, assuming the 2016 Portuguese population aged 10-89. The number of tests by age group is shown in Figure 4-3. The average annual 640,000 primary cytologies predicted for opportunistic screening with repeat cytology (strategy 1) is comparable to our estimate of 675,000 and 630,000 primary tests if 65% the Portuguese 2016 female population aged 20-64 and 25-64, respectively, were screened every 3 years. Our estimates for the proportion of women never screened [35.5%, 95%CI 33.8%- 37.2% and 23.3% (95%CI 7.4%, 39.2%) aged over 20 and 25-64, respectively] from data of the Portuguese National Health Survey 2005/6 are similar to Oliveira and colleagues estimates[52].

We predict that current practice (strategy 1) has prevented 30% of cervical cancer cases (220 cases per year) compared to no screening at a cost of 680,000 annual cytologies and 20,000 colposcopies. A fully organised programme with repeat cytology (strategy 7) would reduce an additional 34% of cases compared to no screening requiring over 50% more tests than opportunistic repeat cytology.

An opportunistic programme with HPV triage of ASCUS and LSIL approach with lesions followed by annual co-testing (strategy 2) would reduce a similar number of cancer cases to opportunistic repeat cytology despite 45% fewer colposcopies, given the greater proportion of cervical intraepithelial neoplasias among colposcopies performed in strategy 2 compared to strategy 1. Overall, HPV triage would involve 4% more tests due to a greater number of additional HPV DNA tests despite the fewer cytologies (3% of the total number of cytologies) and colposcopies required, but substantially lower burden for women by averting unnecessary colposcopies.

If an organised strategy was adopted instead of an opportunistic strategy, then the greatest proportion of cervical intraepithelial neoplasias detected would occur among 25-29 year olds instead of among 35-39 year olds (Figure 4-3).

A fully-organised HPV- or cytology-based screening programme (strategies 3 to 7) would reduce cancer cases by over 65% compared to no screening. On average, primary HPV screening every 3 years with cytology triage of HPV positive women (strategy 4) was the most effective protocol in reducing the incidence of cervical cancer and would entail similar total number of tests as a less follow-up intensive organised HPV triage programme (strategy 6),

and about 10% less than intense follow-up cytology-based strategies 3 and 7 compared to opportunistic repeat cytology (strategy 1). Primary 3-yearly HPV testing (strategy 4) would detect a similar number of CIN2+ cases with 38% fewer colposcopies, given the greater proportion of severe outcomes among colposcopies with strategy 4 (0.45 no CIN, 0.15 CIN1, and 0.41 CIN2+) than strategy 3 (0.65 no CIN, 0.12 CIN1, and 0.24 CIN2+).

Extending the interval of primary HPV screening to 5 years (strategy 5) would lead to a similar reduction of cervical cancer incidence compared to organised programmes with a 3-yearly interval screening. However, strategy 5 would yield 34% fewer tests than HPV primary every 3 years (strategy 4) and 40% less than the most screening intense programme (organised repeat cytology, strategy 7).

Our model also shows that at age 35-39 the proportion of CIN2+ lesions detected was greatest under opportunistic cytology-based screening (strategies 1 and 2). The proportion of CIN2+ detected was higher in younger age groups with HPV triage (strategy 2) than with repeat cytology (strategy 1), and with organised screening (strategies 3 ,6, and 7) the proportion of CIN2+ lesions detected was greatest 10 years earlier (age 25-29).

4.2.5. Discussion

Primary HPV screening with cytology triage of HPV-positive women is likely to be more effective reducing cervical cancer incidence than most cytology-based strategies modelled. However, primary HPV testing with a 5-year screening interval would involve fewer tests than organised programmes based on 3-yearly screening and similar numbers of tests to that with opportunistic screening protocols despite the higher coverage, lesions follow-up, and adherence to screening.

Our findings on the average effectiveness of HPV-based programmes relative to cytology primary screening are consistent with the lower rates of cervical cancer with primary HPV than cytology in four large European randomised clinical trials[14], and also support the safe extension of the screening interval to 5 years.

We also found that introducing HPV triage testing of ASCUS and LSIL would require fewer colposcopies than repeat cytology while preventing a similar number of cancers. Although the HPV triage protocol (triage referral for ASCUS or LSIL) involved more triage tests than repeat cytology (triage referral for ASCUS), the proportion of HPV-positive women would be smaller than that of women with repeat cytological result of ASCUS or worse, and the severity of lesions among women referred to colposcopy after HPV triage greater than among those referred after repeat cytology. Berkhof and colleagues[53] also predicted HPV triage of borderline or mild lesions (with immediate referral of HPV-positive women to colposcopy) to

require fewer cytologies and colposcopies than repeat cytology but preventing slightly more cancers, in their economic evaluation for the Netherlands.

Our analysis predicts a change in the ages at which the detection of CIN2+ lesions is most frequent towards younger age groups with the transition from opportunistic to organised screening. A similar shift was found for the age of cervical cancer incidence in England between the early 1980s and the late 1990s, where age-at-diagnosis decreased accompanying the decline in incidence[22,54].

Strengths and limitations

Our model strengths include the integrated microsimulation of HPV infection and progression to cervical cancer with calibration to Portuguese age- and type-specific HPV prevalence and cervical cancer incidence, which provides a detailed representation of the population at risk of HPV infection and cervical cancer. The simulation of individual women eligible for screening over a lifetime also facilitates a thorough characterisation of the screening eligible population (e.g., capturing the heterogeneity of screening attendance patterns), and it would have allowed investigating as well the impact of additional protocols targeting particular risk groups, such as that of self-sampling HPV testing, shown to be superior to re-invitation in attracting typical non-attendees[55]. For instance, we could have incorporated screening attendance dependent on women's previous screening history, where the time to next screen would be a function of the time between previous screens. However, the limited data available on screening participation and outcomes of Portuguese women has hindered our use of the model full potential. Several methodological and data-driven limitations must be kept in mind.

We modelled HPV types 16, 18, 31,33,45,51,52, and 58 because these were the types for which age-specific disease progression was available from the model fitted by Bains and colleagues to English data; hence, we are possibly missing some of the most prevalent types for cervical cancer in Portugal. According to the latest meta-analysis by the International Agency for Research on Cancer[56] (which included 3 studies of Portuguese women with invasive cervical cancer, n=168), we may be missing 3.8% of cases due to HPV types 35 and 56 (more prevalent than HPV 31,51, and 52 which were present in 3.6% of cases). A more recent retrospective study of 714 samples (1928-2005)[57] suggests that HPV 35 and 39 are more prevalent than HPV 51, which account in total for 2.6% of cases, 1.5% and 1.3%, respectively.

Because of the lack of data on screening and colposcopy outcomes in Portuguese women, we used Bains and colleagues' distributions for progression rates from HPV infection to precancerous lesions and for the distribution of colposcopy outcomes by cytological outcome, assuming disease progression and test performance to be independent of the

population/setting studied. However, Portuguese and English women may differ in exposure to risk factors for pre-malignant lesions. We found that Portuguese women are likely at lower risk for progression to cervical cancer than their English counterparts, e.g. in terms of smoking and contraception prevalence[22]. Hence, a slower progression to precancerous lesions among Portuguese women is likely. Also, we are possibly overestimating the performance of screening tests; particularly for cytology as the objective nature and automation of HPV DNA testing makes its inter-laboratory reproducibility more likely than for cytology. Although similar performance for conventional and LBC has been found in a meta-analysis[51] and two more recent randomised clinical trials in Italy[58] and the Netherlands[59], cytology's performance varied noticeably among 15 European countries[60]. Ronco and colleagues' analysis of key performance indicators showed that the performance of cytology-based screening programmes can vary substantially between settings and is generally better where screening has been organised for longer given the long-term monitoring and quality assurance[60]. Our model also does not capture potential benefits from using LBC compared to conventional cytology, such as faster interpretation and greater reproducibility[61].

Our characterisation of opportunistic screening in Portugal was restricted by the scarcity of available data on screening frequency and attendance. The distribution for age of first screen and proportion of women never screened were estimated from the Portuguese National Health Survey 2005/6 data[47] (when cervical screening was exclusively opportunistic). However, given the lack of data on the actual time interval between screens, we also used data on the self-reported year of last cytology from the Portuguese National Health Survey 2005/6 to derive age-specific screening intervals, by assuming that women's next screen occurred within the year that followed the survey; hence, our average screening interval of 2.97 (95% CI 0.83, 3.08) years under opportunistic screening is likely an overestimate. We also lacked the data to characterise long-term attendance patterns, as the time to next screen has been reported dependent on the previous screen interval in England (Bains and colleagues in Appendix to this thesis).

We took a pragmatic but potentially suboptimal approach to calibrate the progression to cancer model to the observed incidence of cervical cancer in Portugal. For HPV 16 and 18, we only explored a narrow range of the parameter space with a limited number of proposed parameter values selected based on the posterior distributions found by Bains and colleagues for England. We also did not use an optimization algorithm to search for parameter values nor used an objective statistical measure of goodness-of-fit for the selection of the best fitting parameter sets. Instead of visually inspecting the fit of each proposal and using this to choose the next one, we could have used an automated method to more effectively search the

parameter space and objectively identify sets of values that better fit the target[62]. For instance, for the calibration of the HPV acquisition model, we used an adaptive Metropolis algorithm to search the parameter space and identify those that better match the target based on their likelihood to result in output that best fits the observed incidence. This approach would have led to a better match between predicted and observed incidence, more accurate estimates of the fitted parameters, and more reliable model outcomes, as illustrated by Morina and colleagues study of the impact of alternative calibration methods[63].

For the remaining HPV types and for adenocarcinomas, we attempted to approximate the predicted incidence to the observed data by selecting the best matching posterior distributions fitted by Bains and colleagues for England. However, our predicted incidence overestimates the observed incidence of adenocarcinomas in Portugal. Hence, re-calibration with more efficient methods would be necessary to obtain appropriate country-specific estimates of these unmeasurable parameters and a better representation of the Portuguese setting.

Type-specific HPV prevalence in Portuguese men was derived from prevalence in Portuguese women using Bains and colleagues' models for English male seroprevalence and seroconversion, as we did not find Portuguese male prevalence estimates in the literature. We adjusted for differences in sexual behaviour between populations by applying the age- and type-specific HPV prevalence ratios between English and Portuguese women to men. Previous static models[64,65] modelled HPV incidence (the rate at which women become infected per unit of time) as a function of age but not of sexual activity or HPV prevalence over time, thus not capturing the heterogeneity in sexual behaviour (and subsequent risk of HPV acquisition) across women in a population.

Parsimoniously, we did not explicitly model natural immunity to re-infection. Despite evidence of modest naturally acquired immunity (of unknown duration) to subsequent HPV infections in seropositive women[26,66], other modelling studies[67,68] have assumed an SIS structure. Baussano and colleagues'[69] model-based estimation of the probability of developing life-long immunity after clearance suggests this is a likely pattern for HPV 16 (responsible for the majority of cervical cancers) but may not be valid for the remaining types.

We modelled an unvaccinated population, and so do not capture the indirect protection conferred by vaccinated individuals to unvaccinated ones. Vaccination of girls is expected to diminish the incidence of HPV infection and cervical lesions in future screening cohorts, as vaccinated women are not susceptible to the vaccine HPV-types and not infectious to susceptible men. Also, the reduction in prevalence of precancerous lesions is also expected to diminish substantially the positive predictive value of cytological screening tests. Primary HPV DNA screening with cytology triage of HPV-positive women is then likely to be a more

adequate approach as the prevalence of high-risk cytological lesions will be higher among HPV-positive women and hence so will the positive predictive value of cytology be.[70] HPV vaccination was introduced for thirteen-year old girls in Portugal in 2008 with a catch-up campaign for 17-year olds, who have now reached the age of screening. However, older cohorts of women have not been vaccinated, so our model results provide important evidence to inform screening algorithms for those cohorts.

Moreover, we have not exhaustively explored all the alternative strategies for screening that are currently available in Portugal. A particularly relevant alternative is HPV16/18 genotyping. The impact of strategies where women positive to HPV16/18 are immediately referred to colposcopy should be investigated, as this is the most recent recommendation from the Portuguese Ministry of Health and is being piloted in the North of Portugal.

Policy implications

Our findings support the adoption of primary HPV screening with cytology triage of positive results under a well organised programme with high coverage and adherence similar to those in the English Cervical Screening Programme. Widespread screening is one of the main challenges to the successful implementation of organised programmes[71,72] and such transition will require the creation an effective invitation system, the adjustment of services and integration of information systems between primary care centres and hospitals, as well as between screening and cancer registries, with intensive monitoring and high-quality assurance in the different stages of the screening process[60,73,74].

In the context of an organised HPV-based programme, HPV testing offers additional advantages for cervical cancer prevention compared to cytology, such as the potential to deploy self-collected HPV testing in parallel to the clinic-based programme to improve adherence of under-screened women, necessarily at higher risk of cervical cancer.

As more women vaccinated for HPV 16 and 18 become screening eligible in Portugal, it is important to also note that prevalence monitoring can be facilitated by primary HPV testing and used to adapt future screening protocols[75].

Although our model was parameterised and calibrated to Portugal, the main findings of this study are likely generalisable to other European countries, such as Spain and France, with similar cervical cancer epidemiology and who are also transitioning from opportunistic to organised primary HPV screening.

4.2.6. Acknowledgements

We are thankful to Tom Nichols at Public Health England; Angela Pista at the National Institute of Health, Portugal; Pedro Moura Ferreira at the Social Sciences Institute Portugal; Nuno Miranda and Cristina Portugal at the National Programme for Oncological Disease, General-Directorate for Health, Portugal; Tereza Lopes, Filomena Horta Correia, Fernanda Loureiro, Ana Dinis, and Fernando Tavares at the regional health administrations of Alentejo, Algarve, Centre, Lisbon and Tagus Valley, and North; Gonçalo Forjaz, Joana Bastos, Ana Filipa Gonçalves, and Alexandra Mayer-da-Silva at the cancer registries of Azores, Centre, North, and South. DM was funded by the Foundation for Science and Technology (individual PhD studentship SFRH/BD/84974/2012) on behalf of the Portuguese Ministry of Education and Science and the Human Potential Operational Programme of the National Strategic Reference Framework, within the European Social Fund of the European Commission's 7th Framework Programme.

4.2.7. References

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4.2.8. Tables

Table 4-1. Main characteristics of the screening strategies modelled

	Strategy 1	**Strategy 2**	**Strategy 7**	**Strategy 3**	**Strategy 6**	**Strategy 4**	**Strategy 5**
Screening system	Opportunistic	Opportunistic	Organised	Organised	Organised	Organised	Organised
Primary test	Cytology	Cytology	Cytology	Cytology	Cytology	HPV DNA	HPV DNA
Triage test	Repeat cytology	HPV DNA	Repeat cytology	HPV DNA	HPV DNA	Cytology	Cytology
- threshold for referral (assumed wait time for triage)	- ASCUS (6 months)	- ASCUS or LSIL (immediate)	- ASCUS (6 months)	- ASCUS or LSIL (immediate)	- ASCUS or LSIL (immediate)	- HPV positive (immediate)	- HPV positive (immediate)
Diagnosis test	Colposcopy	Colposcopy	Colposcopy	Colposcopy	Colposcopy	Colposcopy	Colposcopy
- threshold for referral following primary test	>=LSIL	HSIL	>=LSIL	HSIL	HSIL		
triage test	>=ASCUS	>=ASCUS	>=ASCUS	>=ASCUS	>=ASCUS	HPV positive & >=ASCUS	HPV positive & >=ASCUS
- follow-up test for normal colposcopy	Cytology	Co-testing*	Cytology	Co-testing*	Cytology	HPV DNA	HPV DNA
Treatment	Conisation	Conisation	Conisation	Conisation	Conisation	Conisation	Conisation
- threshold for referral	- CIN2+ - Persistent CIN1 (24 months) - Post-treatment CIN1+	- CIN2+ - Persistent HSIL (12 or24 months) - Post-treatment CIN1+	- CIN2+ - Persistent CIN1 (24 months) - Post-treatment CIN1+	- CIN2+ - Persistent HSIL (12 or24 months) - Post-treatment CIN1+	- CIN2+	- CIN2+	- CIN2+
- follow-up test	Cytology & Colposcopy	Cytology & Colposcopy	Cytology & Colposcopy	Cytology & Colposcopy	Cytology	HPV DNA	HPV DNA
Proportion of women never screened	0.355 [α]	0.355 [α]	0.1[50]	0.1[50]	0.1[50]	0.1[50]	0.1[50]
Screen age range, minimum – maximum	19-66 (85 if follow-up)	19-66 (85 if follow-up)	24-66 (85 if follow-up)	24-66 (85 if follow-up)	24-66 (85 if follow-up)	24-66 (85 if follow-up)	24-66 (85 if follow-up)
Age at first screen, median, mean (IQR) years	33.00, 32.37 (28.88, 36.67)[α]	33.00, 32.37 (28.88, 36.67)[α]	26.12, 28.09 (25.18, 28.29)[β]	26.12, 28.09 (25.18, 28.29)[β]	26.12, 28.09 (25.18, 28.29)[β]	26.12, 28.09 (25.18, 28.29)[β]	26.12, 28.09 (25.18, 28.29)[β]

Screening frequency, [θ] median, mean (IQR) years	1.67, 2.97 (0.83, 3.08)[α]	1.67, 2.97 (0.83, 3.08)[α]	2.08, 3.02 (1.00, 3.42)[δ]	2.08, 3.02 (1.0, 3.42) [δ]	2.08, 3.02 (1.0, 3.42) [δ]	2.08, 3.02 (1.0, 3.42) [δ]	4.08, 4.72 (2.33, 6.25) [σ]
Probability of loss to follow-up of cytological abnormality or treatment	0.5	0.5	0.2	0.2	0.2	0.2	0.2
Probability of complying with repeat cytology referral	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Probability of complying with colposcopy referral	0.75	0.75	0.88	0.88	0.88	0.88	0.88
Probability of complying with treatment referral	0.97	0.97	0.97	0.97	0.97	0.97	0.97
Lesions follow up waiting time, months							
Post-triage:							
- ASCUS & normal cytology	6 (for 1 yr)	-	6 (for 1 yr)	-	-	-	-
- ASCUS & HPV-negative	-	routine	-	routine	routine	-	-
- HPV-positive & normal cytology	-	-	-	-	-	12 (for 2 yrs)	12 (for 2 yrs)
Post-colposcopy:							
- normal colposcopy	6 (for 1 yr)	12 (for 2 yrs**)	6 (for 1 year)	12 (for 2 yrs**)	routine (minor) /12 (high-grade)	routine	routine
- CIN1	6 (for 2 yrs)	12 (for 2 yrs)	6 (for 2 yrs)	12 (for 2 yrs)	12	12 (for 2 yrs)	12 (for 2 yrs)
Post-treatment	6 (for 2 yrs, annually afterwards)	12 (for 2 yrs, routine afterwards)	6 (for 2 yrs, annually afterwards)	12 (for 2 yrs, routine afterwards)	6 (once, routine afterwards)	12 (for 2 yrs, routine afterwards)	12 (for 2 yrs, routine afterwards)

Note: Recommended screening ages & interval by the Portuguese Society of Gynaecologists: 20-64 every 3 years (opportunistic cytology-based strategies), 25-64 every 3 years (organised cytology-based strategies), 30-64 every 5 years (organised HPV-based strategies alongside cytology every 3 years for women aged 25-29)[44] n.a., not applicable; *Co-testing corresponds to testing with cytology and HPV DNA testing ; **follow-up of LSIL/HPV-negative or normal colposcopy following ASCUS/HPV-positive or HSIL results at 12 and 24 months, or follow-up of normal colposcopy following LSIL at 12 and 36 months; [α] individual patient data from the Portuguese National Health Survey 2005/6[47]; [β] obtained using Bains and colleagues[76] model of age at first screen derived from NHS CSP England data; [δ] derived

from NHS CSP England report (2012-2013)[49]; [σ] assumed 2 additional years for each age category of the distribution reported by NHS CSP England (2012-2013)[49] where women aged 25-49 and 50-64 are invited for screening every 3 and 5 years, respectively. [θ] Screening frequency in England was based on cross-sectional data on time since last screen, rather than actual screen interval data. Consequently, the organised screening strategies modelled have a shorter median interval than that expected (for 3-yearly strategies, 2.1 years versus 3 years, respectively), being effectively simulations of 2-yearly and 4-yearly organised screening strategies. This error – to be corrected in subsequent publication - has affected the health outcomes predicted for each strategy and the results of this analysis.

Table 4-2. Predicted total number of tests and cancers by strategy, mean (95%CI)

	No Screening	S1 (OPP Repeat Cytology)	S2 (OPP HPV triage)	S5 (ORG HPV 5y)	S6 (ORG HPV triage ENG)	S7 (ORG Repeat Cytology)	S3 (ORG HPV triage PT)	S4 (ORG HPV 3y)
Primary cytologies	-	639000 (632000; 646000)	639000 (630000; 649000)	-	901000 (893000; 908000)	969000 (961000; 978000)	913000 (906000; 920000)	-
Triage cytologies	-	17900 (13500; 22500)	-	33600 (32500; 34500)	-	27000 (21300; 32200)	-	41600 (40300; 42700)
HPV DNA tests	-	0 (0; 0)	50000 (41000; 60000)	592000 (587000; 597000)	50000 (43000; 57000)	0 (0; 0)	83000 (72000; 98000)	909000 (901000; 917000)
Colposcopies	-	19800 (16100; 23800)	10800 (9200; 13100)	11700 (11300; 12100)	14300 (12000; 16800)	47000 (40100; 54500)	23100 (20000; 27000)	14300 (13900; 14800)
Treatments	-	2200 (1900; 2600)	2700 (2500; 3000)	5000 (4700; 5300)	4800 (4500; 5400)	4600 (4100; 5500)	5500 (5200; 6000)	5900 (5600; 6300)
Total tests	-	676000 (664000; 689000)	700000 (685000; 715000)	637000 (631000; 642000)	965000 (955000; 976000)	1043000 (1024000; 1062000)	1019000 (1002000; 1040000)	965000 (957000; 974000)
SCC	501 (256; 747)	329 (267; 419)	325 (265; 405)	172 (132; 220)	153 (115; 200)	148 (108; 195)	146 (110; 191)	145 (109; 189)
Screen-detected SCC	-	69 (47; 97)	67 (44; 93)	58 (37; 84)	49 (31; 70)	46 (27; 68)	44 (27; 63)	45 (27; 65)
Clinically-detected SCC	501 (256; 747)	260 (209; 330)	259 (208; 324)	115 (86; 148)	104 (77; 135)	102 (74; 137)	102 (77; 133)	101 (73; 132)
ADC	134 (20; 341)	96 (33; 222)	87 (29; 208)	62 (17; 156)	60 (17; 146)	62 (18; 158)	54 (13; 144)	52 (14; 132)
Total cancers	634 (309; 999)	425 (328; 566)	413 (322; 553)	234 (167; 337)	213 (153; 308)	210 (144; 308)	199 (141; 297)	197 (139; 287)
Cancer reduction*, %	-	33	35	66	66	67	69	69
Total tests change, %**	-	-	4	-6	43	54	51	43

For the 2016 Portuguese female population aged 15-89; * compared to no screening; ** compared to strategy 1

4.2.9. Figures

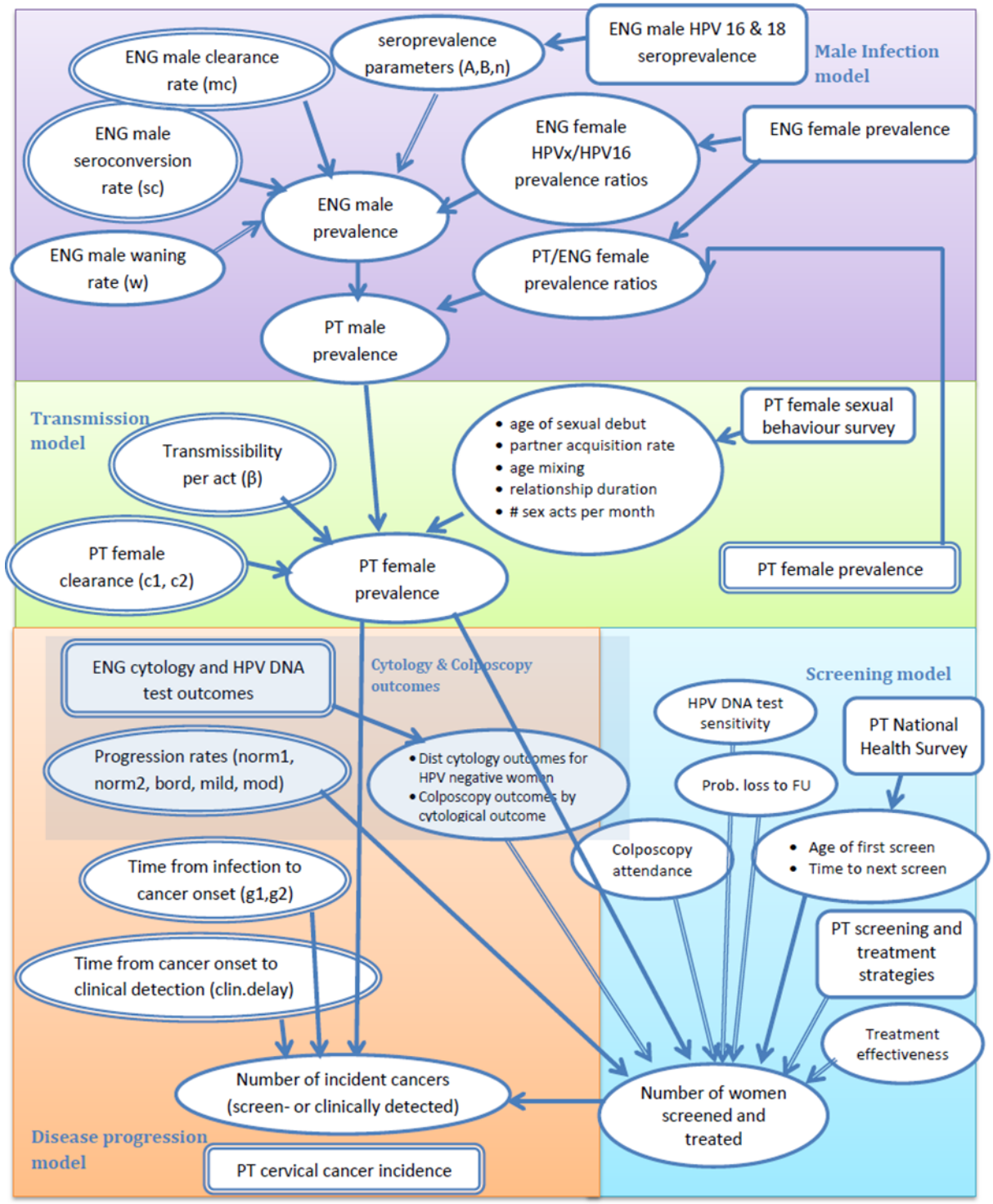
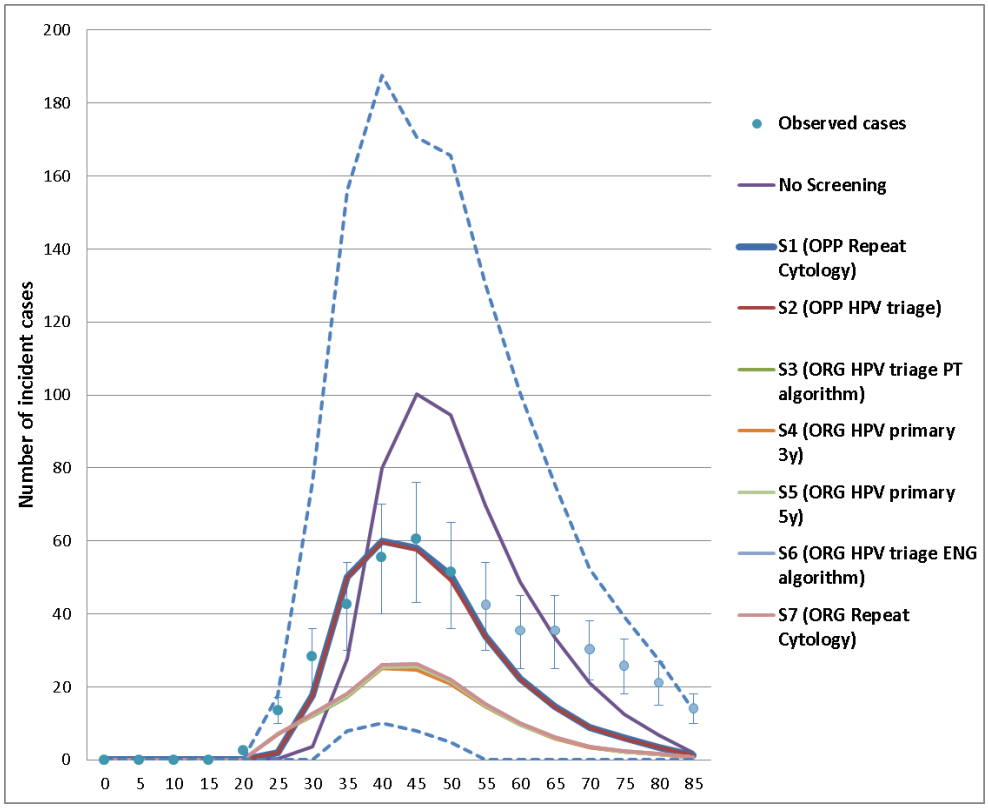


Figure 4-1. Diagram of model components, data, and parameters

Double and simple arrows indicate deterministic and stochastic relationships, respectively
Ellipses indicate variables, rectangles indicate data
Double and single circled ellipses indicate unknown or known parameter, respectively
Double and single lined rectangles indicate calibration target or parameterisation data, respectively

A



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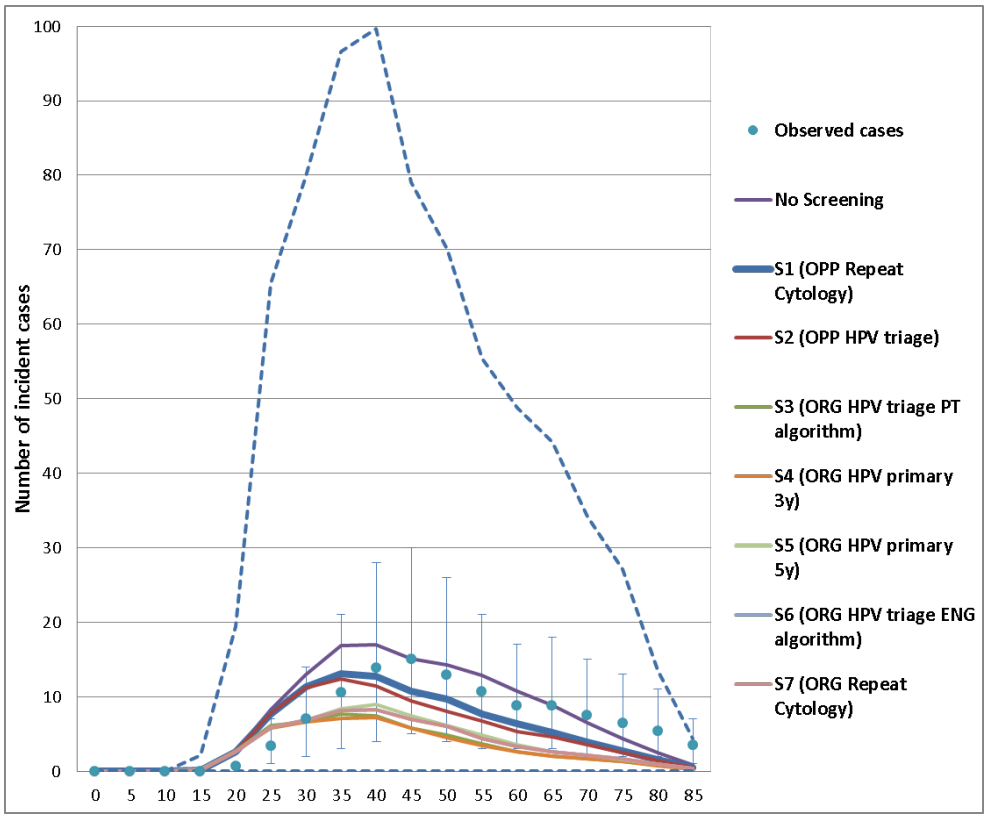


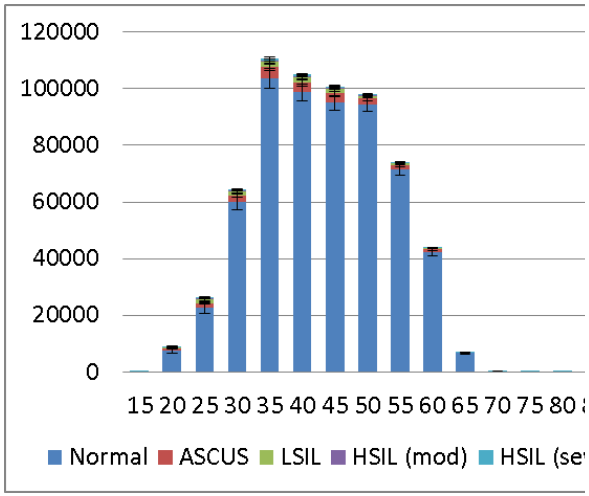
Figure 4-2. Predicted and observed age-specific crude incidence of squamous cell carcinomas (A) and adenocarcinomas (B)

Dots and error bars represent the mean and 95%CI of observed incidence, respectively (fitting target in blue and non-targeted in light blue); blue thick line and dotted lines correspond to the mean and 95%CI incidence for strategy 1 (fitted to observed incidence); remaining lines correspond to the mean incidence predicted for no screening and strategies 2 to7.

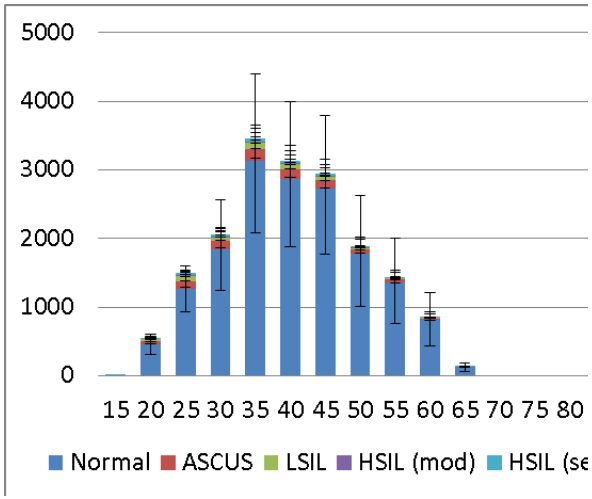
Figure 4-3. Age-specific number of tests per strategy, mean and 95%CI

Strategy 1 – Opportunistic repeat cytology

Cytology primary test



Cytology triage test



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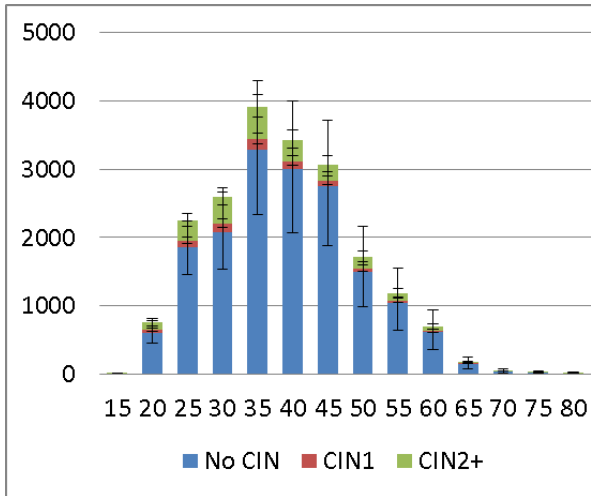
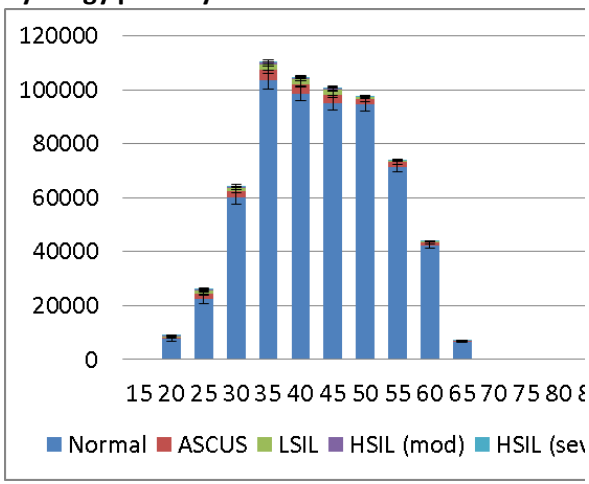
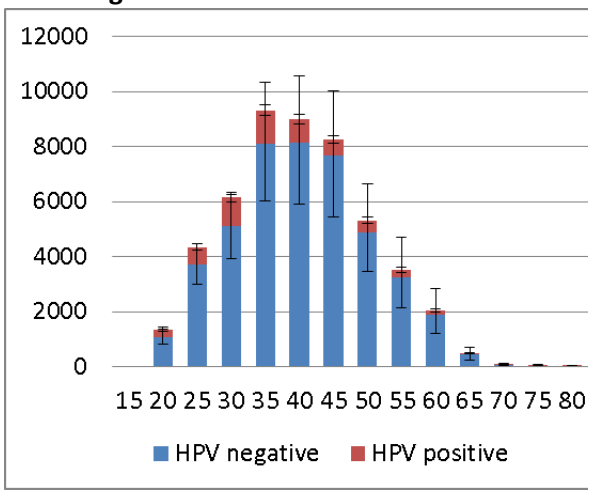


Strategy 2 – Opportunistic HPV triage of ASCUS

Cytology primary test



HPV Triage test



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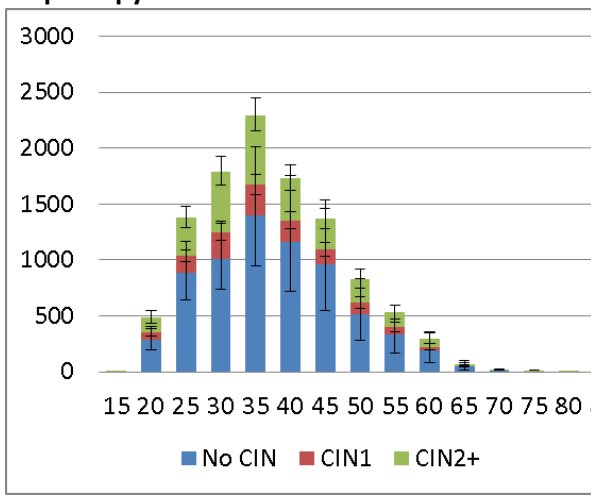
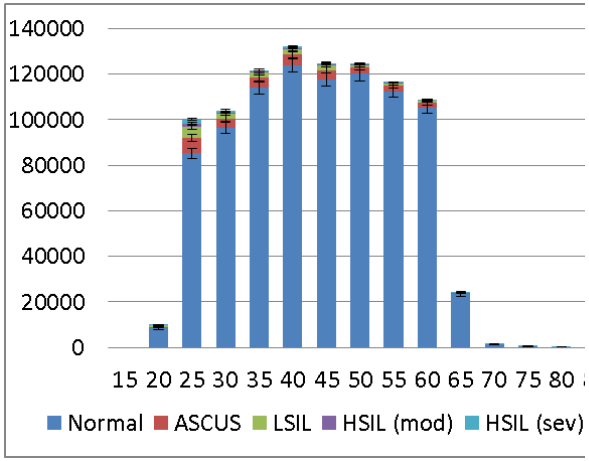
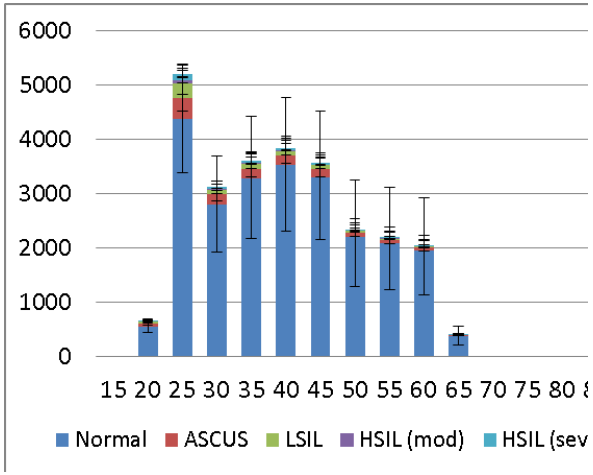


Strategy 7 – Organised repeat cytology

Cytology primary test



Cytology triage test



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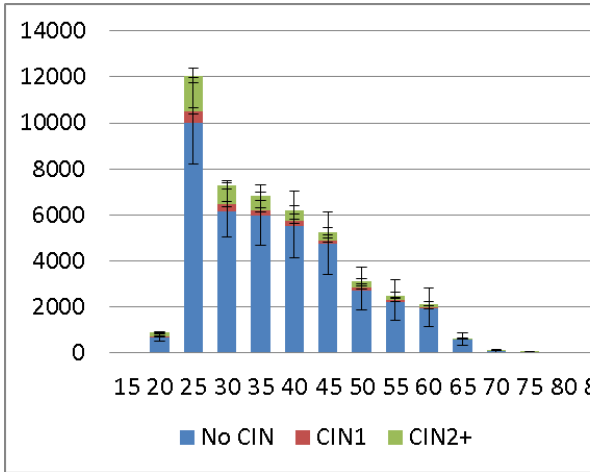
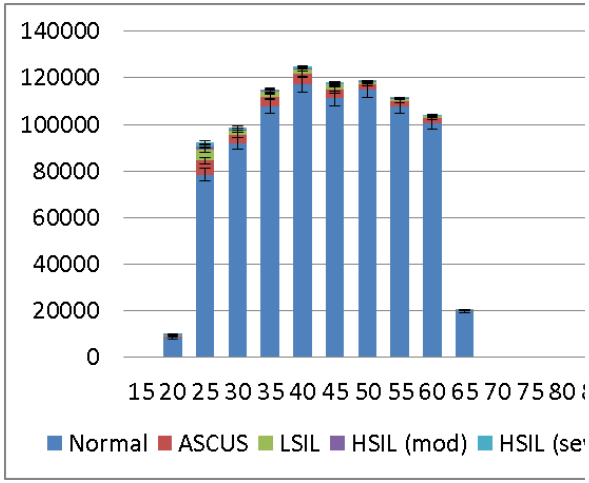
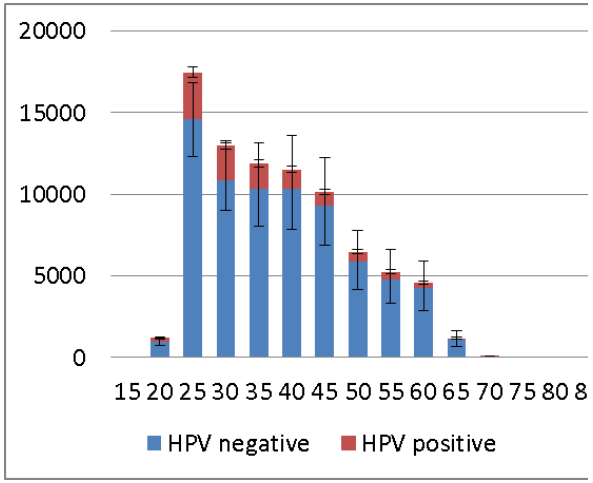


Strategy 3 – Organised HPV triage of ASCUS and LSIL – Portuguese Society of Gynaecology protocol

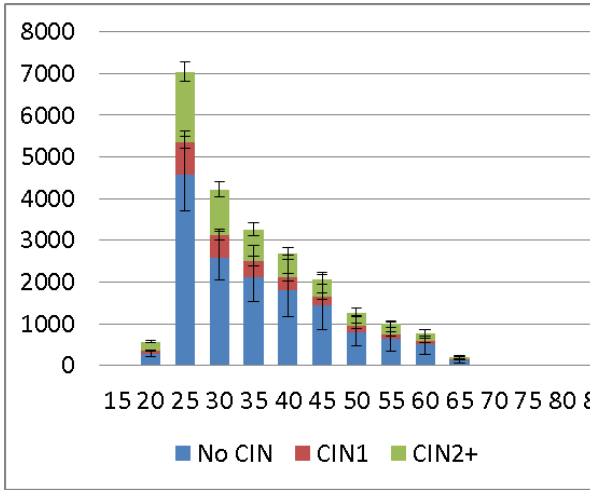
Cytology primary test



HPV Triage test

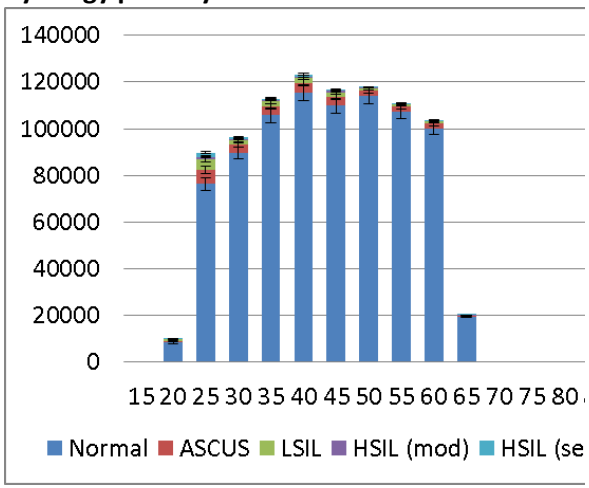


Colposcopy

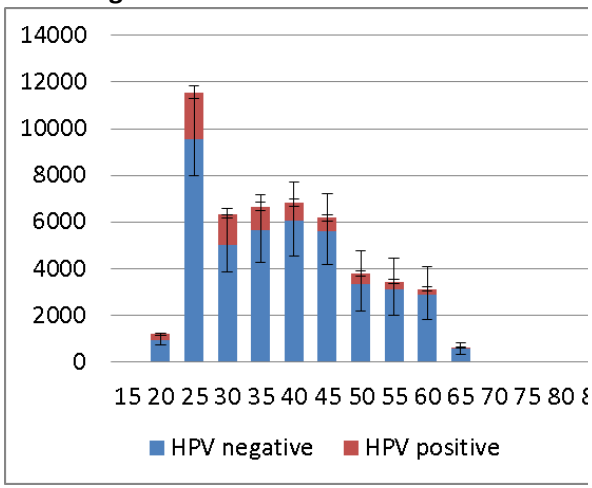


Strategy 6 – Organised HPV triage of ASCUS and LSIL – NHS CSP England protocol

Cytology primary test



HPV Triage test



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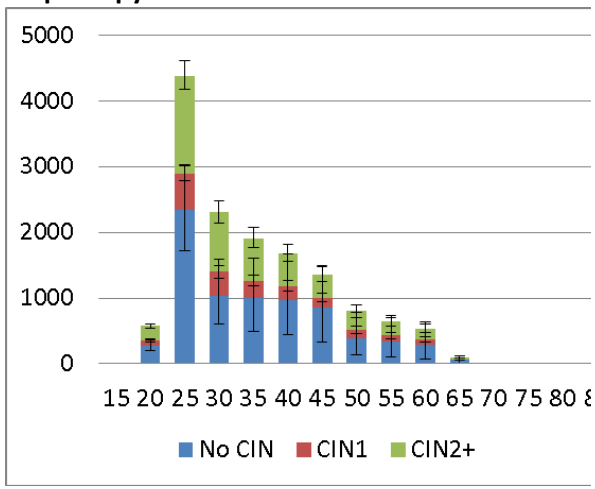
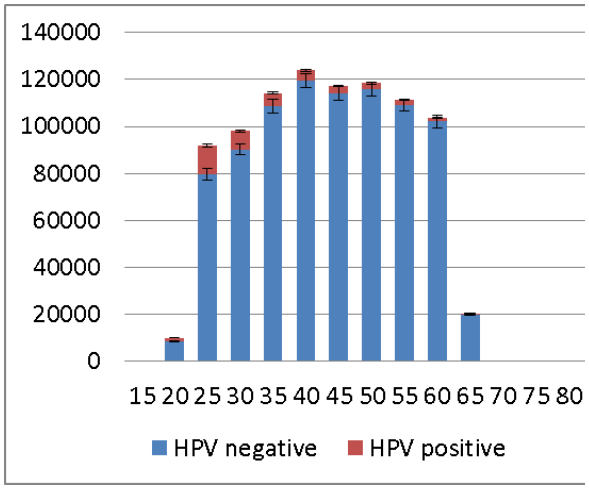
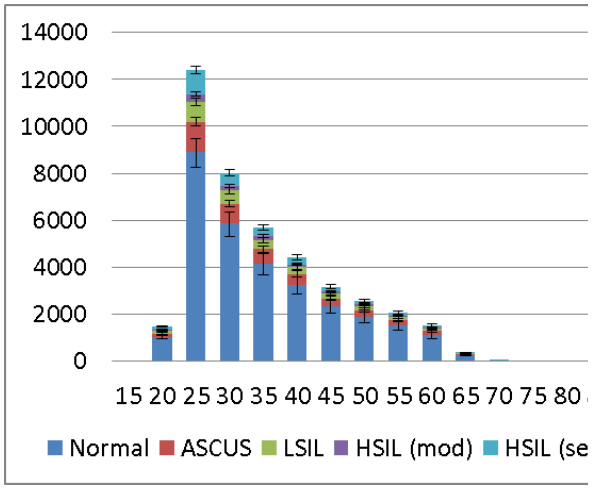


Strategy 4 – Organised Primary HPV screening every 3 years

HPV primary test



Cytology Triage test



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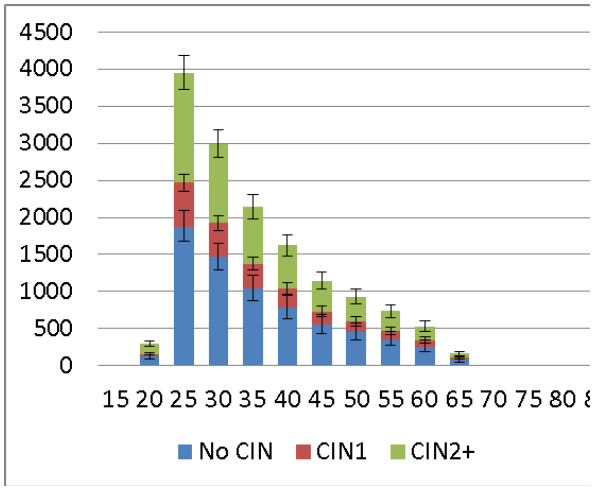
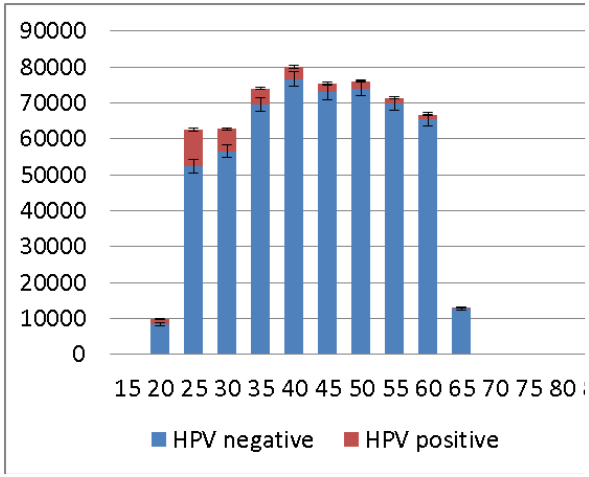
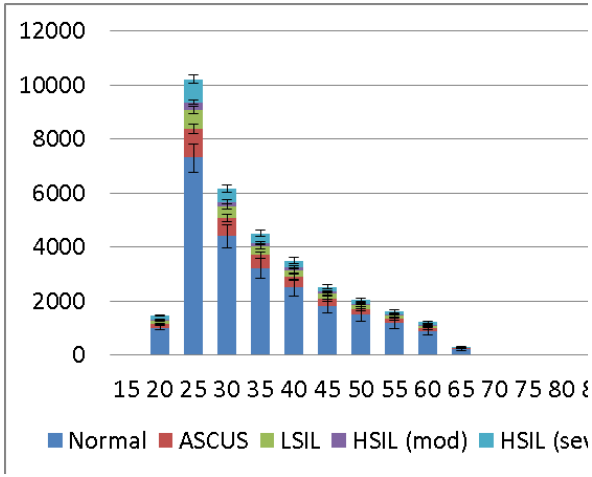


Strategy 5 – Organised Primary HPV screening every 5 years

HPV primary test



Cytology Triage test



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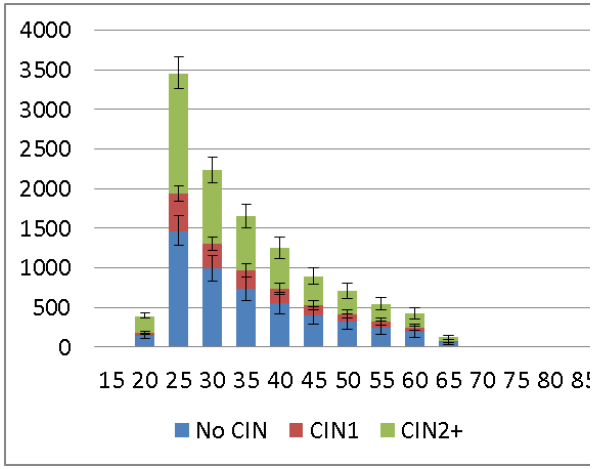


4.3.Supplementary Material

4.3.1. HPV acquisition model

We re-parameterised the transmission component of Bains and colleagues model (described in the Appendix to this thesis) to generate Portuguese age- and type-specific HPV prevalence among the modelled women, i.e. the number of infected women over time.

In Bains and colleagues' model, prevalence of HPV infection is determined by the risk of acquisition of HPV infection and its persistence. The risk of HPV acquisition is a function of (a) women's sexual behaviour, (b) the number of infectious male partners, and the (c) transmissibility of HPV, and the persistence of HPV infection depends on (d) women's natural clearance of the infection. We used a susceptible-infected-susceptible model of HPV infection in women, where the possible naturally acquired immunity to cervical HPV is not explicitly modelled.

This unusual approach of including sexual behaviour in a static model developed to evaluate the impact of screening-only strategies taken by Bains and colleagues has the advantage of capturing the heterogeneity in behavioural risk for the acquisition of HPV infection.

Herein we present the derivation of parameter values used in the HPV acquisition component for the Portuguese context: those estimated directly from data on (a) sexual behaviour and (b) male prevalence, and (c) not directly observable parameters that were derived by model fitting to observed data, namely HPV transmissibility per sex act, female clearance shape parameter and rate parameters, male seroconversion rate, and male clearance rate.

4.3.1.1. Sexual behaviour

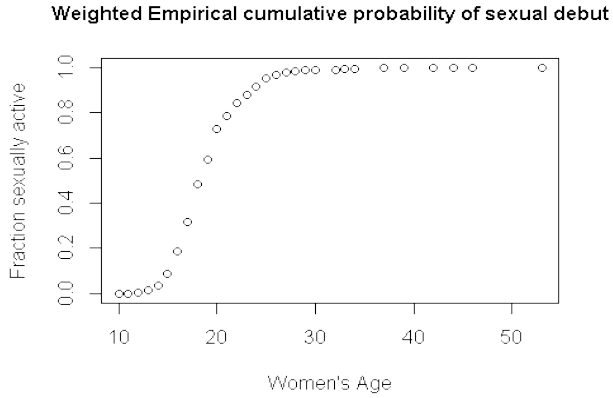
The HPV acquisition component of the model requires estimates of the following parameters on sexual behaviour that determine women's risk of acquiring HPV from infected partners:

1. Age of sexual debut
2. Partner acquisition rate
3. Age of the new partner
4. Duration of the relationship
5. Frequency of sex acts

We derived distributions for these parameters from individual-level data of the 2007 survey on sexual behaviour and HIV/AIDS in mainland Portugal (1,860 valid questionnaires from sexually active women aged 18-65 years)[2].

1. Age of sexual debut

In the model, the age of sexual debut for each individual woman is randomly sampled from the empirical cumulative density function of the reported age of sexual debut by Portuguese women[2] (Supplementary Figure 4-1), which determines the transition from unsusceptible to susceptible to HPV infection.

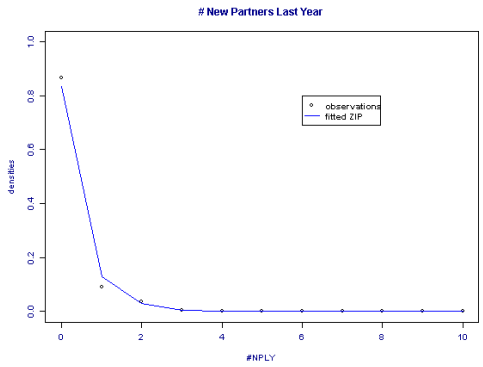


Supplementary Figure 4-1. Empirical cumulative probability of sexual debut

2. Partner acquisition

The modelled time to the next partnership is determined by the rate of acquisition of a new partner, which was derived from the number of new partners last year. The number of new partners is not part of the data collected in the Portuguese survey, hence an approximation was estimated from the reported total number of partners last year and reported first time sex dates for the last 2 most recent partnerships. For participants reporting more than 2 partners last year and providing consistent dates for these relationships, the number of new partnerships last year was assumed to be the same as the total number of partners in that time period. For those reporting concurrency in last 5 years, we assumed one long-term relationship and subtracted that from the total number of partners last year.

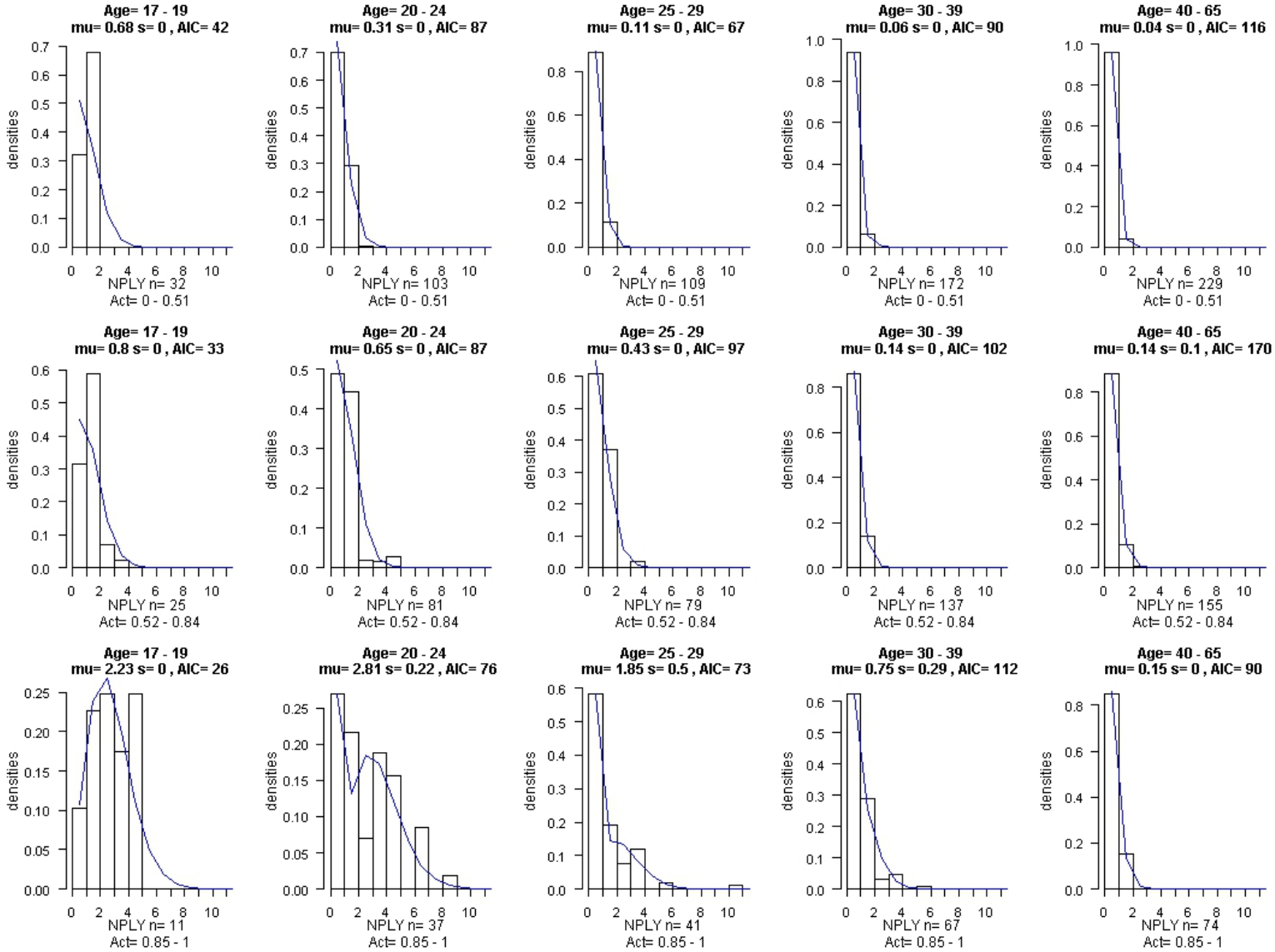
We tested the fit of some statistical models to the number of new partners - Poisson, negative binomial, geometric - using the gamlss package (allows estimating parameters using the maximum likelihood method for a wide family of distributions) and the zero-inflated Poisson (ZIP) model showed lower global deviance (Supplementary Figure 4-2). The ZIP model is a mixture of two components: a Binomial distribution, with the value 0 with probability sigma, and the Poisson distribution with probability 1-sigma. It lends itself to the interpretation of the probability of women being available or not to a new sexual partnership, and among those available there is a rate of partner acquisition that follows a Poisson distribution, expressing the probability of a given number of new partners last year.



Supplementary Figure 4-2. Women's number of new partners last year (observed and modelled)

According to this model, the baseline proportion of women not available for a new sexual partnership is approximately 0.55. For those available, some do not have a new sexual partner (0.16), most have 1 new partner (0.30) and the remaining have 2 or more (0.54). The annual rate of partner acquisition decreases by approximately 9% with each year of age and the average annual rate of partner acquisition for 20-year old women is just over 1 partner per year (1.12).

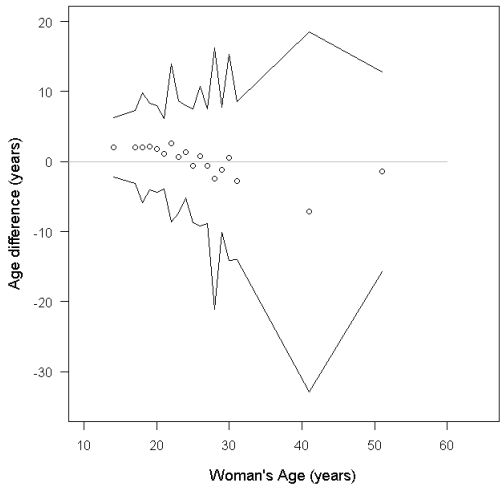
We stratified risk of infection by age and activity level. We fitted the ZIP model to different activity level thresholds and age bands and the best goodness-of –fit (lowest deviance) was obtained using 5 age bands [17-19, 20-24, 25-29, 30-39, 40-65] and 3 activity levels [0-0.51,0.52-0.84,0.85-1] (Supplementary Figure 4-3).



Supplementary Figure 4-3. Number of new partners last year by age group and activity level (observed and modelled)

3. New partner age

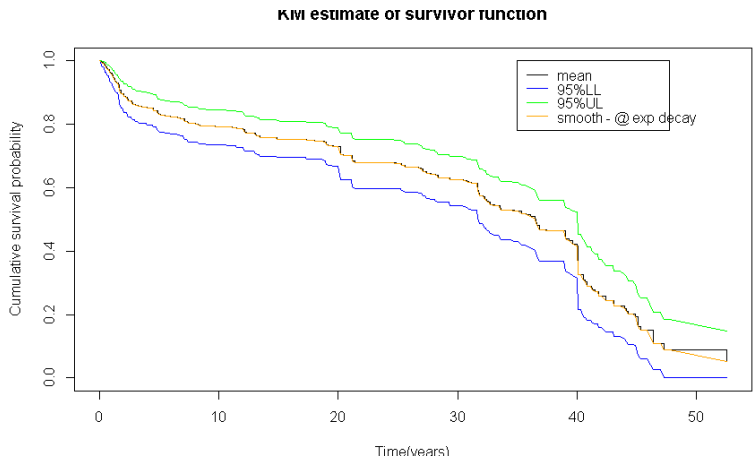
The age mixing matrix used in the model is based on the partners' age difference and provides the cumulative probability distribution of a partner's age for each woman's sexually active year of age. Partners' age difference was derived from women's reported age of most recent partner and women's own age at first time sex with the most recent partner (partners' ages at start of the relationship). Women's own age at first time sex with the most recent partner was estimated from the difference between the reported year of birth and the reported year of first time sex with most recent partner. We assumed the partner's age difference follows a Normal distribution and estimated the mean and standard deviation by woman's year of age (Supplementary Figure 4-4).



Supplementary Figure 4-4. Partner's age difference by women's age, years

4. Partnership duration

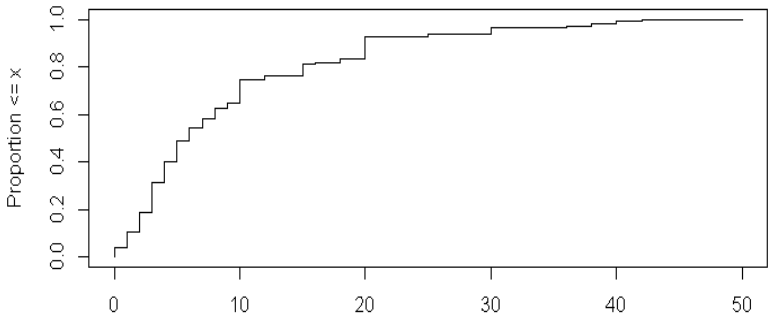
Relationship duration in the model is randomly generated using the fraction of occasional relationships (0.036, n=1,275 relationships) and the mean cumulative probability of relationship survival (Supplementary Figure 4-5). Estimates of partnership duration were derived from reported year and month of first time and last time sex with previous most recent partner, and year and month of first time sex with most recent partner. Last time sex with most recent partner was derived from reported categorical question (defining complete relationship as last sexual act more than 3 months ago) and the interview date. The interview date was not available for each individual, so we used the reported first interview date for each borough for right-censoring the data.



Supplementary Figure 4-5. Cumulative probability of relationship survival

5. Frequency of sex acts

The number of sex acts per month is randomly generated at each model iteration using the respective cumulative probability distribution of x acts (P(X<=x)) obtained from the Portuguese survey data (Supplementary Figure 4-6). We used the reported number of sexual acts last month by women in an active relationship (defined as less than 3 months since last sexual contact).



Supplementary Figure 4-6. Empirical cumulative probability of x number of sex acts

4.3.1.2. Male prevalence

In Bains and colleagues model, the type-specific HPV infection status of partners for women of each sexually active age is pre-generated using the age mixing matrix and male prevalence curve (Bains and colleagues in the Appendix to this thesis). For each model simulation, a male prevalence curve (number of infected men by age) is randomly generated using a male infection model developed by Bains and colleagues (male prevalence as a function of age, seroprevalence, seroconversion rate, clearance and immunity waning rate, and female inter-type and inter-country HPV prevalence ratios). The predicted English and Portuguese male type-specific HPV prevalence and details of our adaptation are provided herein.

Male infection model

In Bains and colleagues' model, male HPV prevalence in England is calculated using a seroconversion HPV male infection model developed and fitted to the English population by Bains and colleagues (in the Appendix to this thesis). English age-specific male HPV 16 and 18 prevalence is modelled as a function of seroprevalence, seroconversion, clearance, and waning rates using a susceptible-infectious-recovered-susceptible model. Immunity waning rate was fixed at 0.05 per month for all HPV types (Bains and colleagues in the Appendix to this thesis).

We used the seroconversion model developed by Bains and colleagues to obtain age- and type-specific HPV prevalence in English men. We then derived HPV prevalence for Portuguese men from Portuguese female prevalence using our estimates of inter-type and inter-country HPV prevalence ratios.

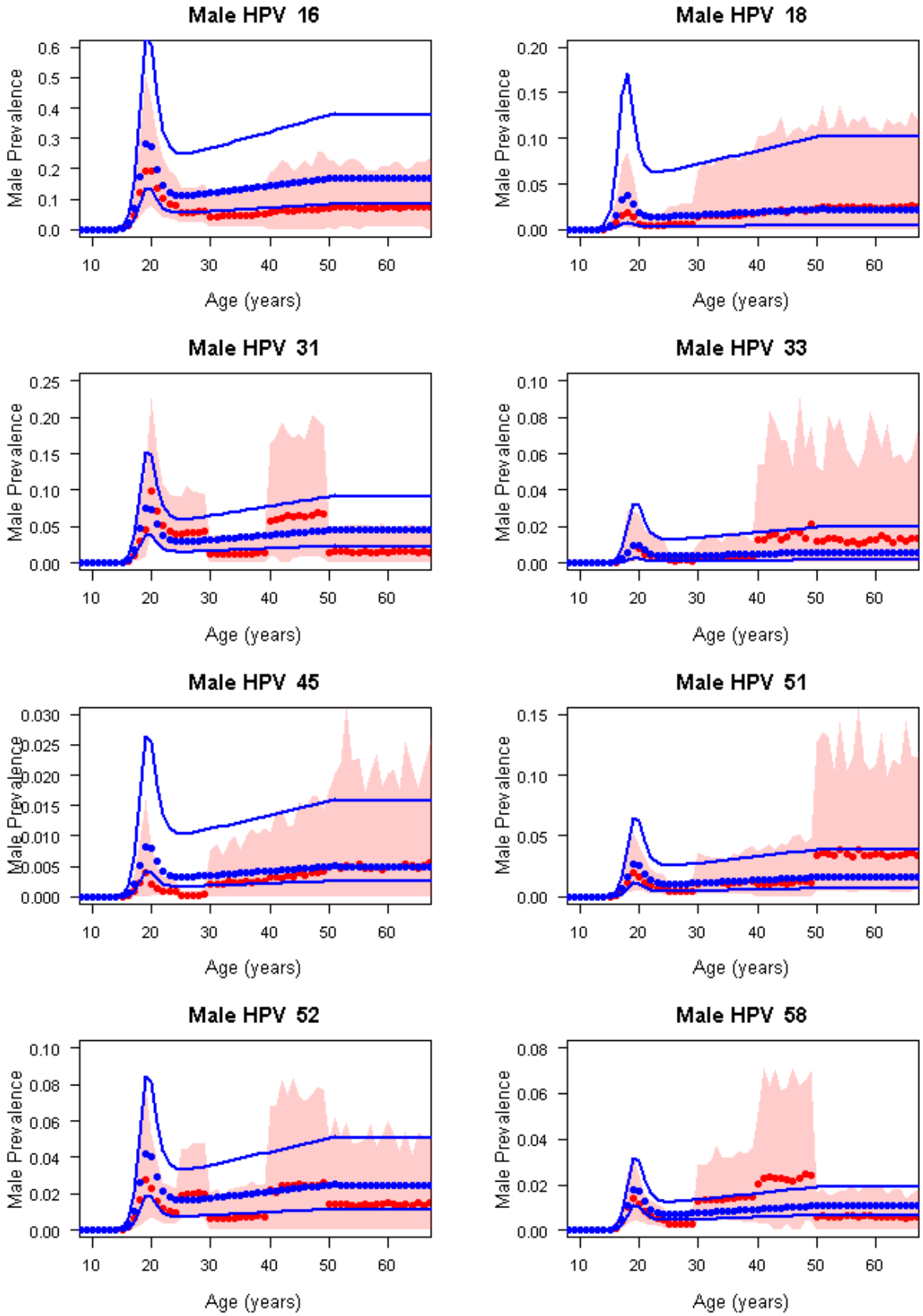
In Bains and colleagues' model of male infection, HPV 16 and 18 prevalence among English men is calculated using their seroconversion model from the seroprevalence function. The observed seroprevalence in English men[3] is assumed to follow the following hill function:

$\text{Seroprevalence (t)} = \frac{B*t^{n+1}}{A^{n+t^n}}$, with A=18.2117869, B=0.1793239, n= 19.9999864 for HPV 16,and A=16.56897610, B=0.06720027, n=19.99995364 for HPV18, and male prevalence over 50 years old was assumed constant (Bains and colleagues in the Appendix to this thesis).

We used Bains and colleagues' model to obtain England male HPV 16 and 18 prevalence and derived English male prevalence for the remaining HPV types from that for HPV 16 using inter-type HPV prevalence ratios in English women, assuming the same ratios would be found among men (presented below). We also applied the inter-country female prevalence ratios to estimate male prevalence in Portugal from male prevalence in England, as outlined in the following equations:

$Prev_{ijM}^{E} = Prev_{iM}^{E16} \times \frac{Prev_{ijF}^{E}}{Prev_{iF}^{E\,16}}$, where $Prev_{ijM}^{E}$ is the prevalence of HPV type j in age group i in males (M) in England (E), $Prev_{iM}^{E16}$ is that for HPV type 16, and F for females; and

$Prev_{ijM}^{P} = Prev_{ijM}^{E} \times \frac{Prev_{ijF}^{P}}{Prev_{ijF}^{E}}$, where (P) corresponds to Portugal.



Supplementary Figure 4-7. Type-specific predicted male HPV prevalence in Portugal and England

Predicted prevalence for England and Portugal in blue and red, respectively

Dots and lines or shaded areas represent mean and 95th percentile, respectively

Inter-type HPV prevalence ratios

English male prevalence of the remaining HPV subtypes was derived by applying bootstrapped HPVx/HPV16 prevalence ratios among English women (Supplementary Table 4-1) to HPV 16 male prevalence.

Supplementary Table 4-1. Summary of the HPVx/HPV16 prevalence ratio distributions (yearly 16-39 & 5-yearly 40-64)

Age	HPV 31	HPV 33	HPV 45	HPV 51	HPV 52	HPV 58
16	0.061 (0;0.458)	0.115 (0;0.59)	0.343 (0.026;1.22)	0.566 (0.123;1.74)	0.241 (0;0.83)	0.353 (0.033;1.297)
17	0.448 (0.051;1.491)	0.255 (0;0.718)	0.302 (0;1.066)	0.669 (0.148;3.066)	0.314 (0;1.12)	0.586 (0.071;2.822)
18	0.345 (0.02;1.169)	0.2 (0;0.585)	0.251 (0;0.879)	0.596 (0.171;1.505)	0.379 (0.059;1.039)	0.198 (0;0.753)
19	0.383 (0.015;1.809)	0.162 (0;0.736)	0.296 (0;1.601)	0.541 (0.074;2.044)	0.286 (0;1.144)	0.581 (0.124;1.938)
20	0.401 (0.054;1.612)	0.105 (0;0.877)	0.164 (0;1.194)	0.606 (0.119;1.889)	0.295 (0;1.222)	0.346 (0;1.415)
21	0.352 (0.014;2.059)	0.183 (0;0.841)	0.197 (0;1.068)	0.415 (0;1.178)	0.492 (0.015;1.876)	0.256 (0.009;1.067)
22	0.354 (0;2.967)	0.597 (0;9.081)	0.348 (0;2.844)	0.769 (0;4.942)	0.3 (0;3.8)	0.47 (0;4.242)
23	0.445 (0;2.935)	0.21 (0;1.679)	0.506 (0;3.076)	0.57 (0;4.459)	0.952 (0.066;5.471)	0.281 (0;1.395)
24	0.067 (0;0.53)	0.069 (0;0.952)	0.528 (0;4.85)	0.423 (0;3.207)	0.595 (0;3.295)	0.082 (0;0.724)
25	0.375 (0.027;3.222)	0.228 (0.001;0.861)	0.542 (0;4.304)	0.593 (0.052;4.626)	0.444 (0;4.847)	0.443 (0;1.013)
26	0.273 (0.024;1.121)	0.166 (0;1.145)	0.643 (0;4.375)	0.997 (0.093;6.236)	0.797 (0;5.76)	0.972 (0.024;5.763)
27	0.42 (0.034;3.459)	0.278 (0.001;4.101)	0.542 (0;4.159)	0.162 (0;0.822)	0.086 (0.005;0.525)	0.082 (0;0.618)
28	0.134 (0;0.56)	0.258 (0.001;1.243)	0.092 (0;0.449)	0.585 (0;5.441)	0.156 (0;0.912)	0.128 (0;2.145)
29	0.348 (0.019;1.816)	0.308 (0.001;1.553)	0.641 (0;7.928)	0.884 (0;8.237)	0.164 (0;1.082)	1.234 (0;9.489)
30	1.804 (0.062;16.3)	0.587 (0;7.471)	0.149 (0;1.143)	0.556 (0;6.571)	0.854 (0;8.859)	1.395 (0.001;13.14)
31	0.227 (0;1.058)	0.231 (0;0.999)	0.709 (0;6.28)	1.575 (0;9.659)	0.624 (0;6.556)	0.171 (0;0.775)
32	0.661 (0.008;11.9)	0.241 (0;6.765)	0.029 (0;0.392)	0.05 (0;0.757)	0.203 (0;0.937)	0.208 (0;0.949)
33	0.674 (0;15.18)	0.017 (0;0.501)	0.319 (0;11.85)	0.267 (0;1.492)	0.621 (0;19.54)	0.07 (0;1.568)
34	0.156 (0;1.994)	0.138 (0;2.612)	0.776 (0;17.9)	0.499 (0;12.42)	0.423 (0;9.822)	0.083 (0;1.532)
35	0.399 (0;5.116)	0.538 (0;1.839)	0.059 (0;0.856)	1.246 (0;17.17)	0.277 (0;2.816)	1.987 (0;22.43)
36	3.752 (0;179.9)	0.895 (0;25.51)	0.503 (0;16.42)	1.265 (0;53.01)	0.73 (0;8.503)	0.672 (0;31.13)
37	0.166 (0;3.39)	0.024 (0;0.737)	0.045 (0;1.28)	1.042 (0;19.58)	0.677 (0;21.42)	0.579 (0;13.48)
38	1.933 (0.001;15.18)	0.128 (0;0.811)	0.446 (0;2.154)	0.447 (0;3.456)	0.002 (0;0.196)	0.125 (0;1.507)
39	0.49 (0.001;3.959)	0.265 (0;2.448)	0.08 (0;0.628)	2.511 (0;32.88)	0.158 (0;2.521)	0.378 (0;2.516)
40-44	0.556 (0.094;2.175)	0.089 (0.007;0.343)	0.39 (0.016;1.657)	0.368 (0.019;1.941)	0.663 (0.09;3.654)	0.23 (0;2.077)
45-50	0.486 (0.078;2.244)	0.254 (0;1.857)	0.817 (0.062;4.111)	0.836 (0.087;4.052)	0.628 (0.036;3.188)	0.643 (0.018;3.931)
55-60	0.587 (0.028;2.791)	0.145 (0.001;1.126)	0.319 (0.001;1.549)	0.236 (0.02;1.402)	0.283 (0.014;1.736)	0.483 (0.016;2.505)
60-64	0.666 (0.002;9.747)	0.045 (0;0.526)	0.012 (0;0.193)	0.342 (0;6.194)	0.564 (0.001;12.46)	0.965 (0.034;10.67)

Inter-country HPV prevalence ratios

We used bootstrapped type-specific HPV prevalence ratios between Portuguese and English women to derive the Portuguese HPV male prevalence from that in England (Supplementary Table 4-2). We assumed the same age- and type-specific proportions would be found between men.

Portugal/England prevalence ratios were randomly generated from prevalence among women in both countries, assuming prevalence follows a binomial distribution of probability p obtained for each age group by maximum likelihood estimation from the country-specific prevalence data available. Maximum likelihood estimates were adjusted using the Wilson method to relocate central estimates when prevalence mle(p) is very close to zero (some age groups over 40 or less prevalent HPV subtypes)[4]. Also, the binomial distribution was truncated to the 95%CI when the randomly sampled English prevalence was zero (less prevalent HPV subtypes age groups over 50) to prevent infinite ratios.

Supplementary Table 4-2. Portugal/ England HPV female prevalence ratios, mean (95%CI)

HPV type	Age group					
	18-19	20-24	25-29	30-39	40-49	50-64
HPV 16	0.681 (0.338;1.149)	0.69 (0.482;0.945)	0.51 (0.308;0.761)	0.351 (0.071;0.725)	0.406 (0;1.129)	0.432 (0.087;0.974)
HPV 18	0.498 (0.185;0.922)	0.285 (0.114;0.517)	0.403 (0.079;0.88)	0.908 (0;2.323)	0.998 (0;2.93)	1.081 (0;2.921)
HPV 31	0.618 (0.117;1.444)	1.347 (0.785;2.149)	1.377 (0.706;2.36)	0.372 (0;0.906)	1.554 (0.272;3.585)	0.343 (0;1.004)
HPV 33	0.964 (0.142;2.647)	0.795 (0.332;1.52)	0.371 (0.062;0.88)	0.69 (0;2.013)	2.685 (0;9.524)	2.102 (0;8.034)
HPV 45	0.473 (0;1.263)	0.239 (0.046;0.522)	0.095 (0;0.257)	0.602 (0;1.776)	0.775 (0;2.241)	1.015 (0;3.213)
HPV 51	0.707 (0.256;1.365)	0.634 (0.364;1.004)	0.413 (0.161;0.741)	0.917 (0.275;1.83)	0.795 (0;2.344)	2.169 (0.402;5.624)
HPV 52	0.636 (0.124;1.489)	0.57 (0.306;0.929)	1.192 (0.586;2.052)	0.368 (0;1.035)	1.053 (0;2.689)	0.56 (0;1.674)
HPV 58	0.847 (0.248;1.82)	0.657 (0.298;1.194)	0.342 (0.105;0.666)	1.643 (0.566;3.179)	2.305 (0.331;5.926)	0.566 (0;1.506)

4.3.1.3. Calibration of the transmission model

HPV type-specific posterior distributions of the following not directly observable parameters were estimated by calibration of the model to age- and type-specific HPV prevalence in the Portuguese population:

- HPV transmissibility per sex act *transprob*
- female clearance shape parameter *clearance1* and rate parameter *clearance2*
- male seroconversion rate *maleseroC*
- male clearance rate *maleclear*

We used the modMCMC function of FME package to implement a Markov Chain Monte Carlo (MCMC) simulation using an adaptive Metropolis algorithm in R[5]. Sixty parallel chains of the

model were set to run with different initial parameter values for 20,000 iterations for each HPV type.

To find the best fitting set of parameter values, at each iteration, a new proposal set of parameter values was compared with the observational estimates of HPV prevalence using the likelihood function of the binomial distribution (i.e. the probability of obtaining the observational outcomes given that set of parameter values).

The fitting algorithm determined the computational steps to find the values for each set of parameters which were likely to result in output that best fits the data, i.e. those with which the deviance (-2*log(likelihood)) of the model output to the observed HPV prevalence was smallest.

The adaptive Metropolis algorithm was used aiming at a more efficient process by updating the proposal distribution every 1,000 iterations tuning it to the target distribution based on the process information so far.

The coda package was used for analysis of the MCMC chains.[6] We visually inspected how the accepted values varied within the parameter space over the iterations for each parameter and each individual chain. We selected the chains that presented good exploration of the parameter space and removed auto-correlation within each chain by thinning with an interval of 50 iterations (i.e. discarding all but the 50^{th} accepted value).

Convergence was diagnosed using the (1) Geweke test statistic, defining convergence when the z-score for the difference in the means of the first 10% of the chain and the final 50% is within -2 and 2, and the (2) Gelman diagnostic, that compares the variance of each parameter within each chain to its pooled variance (in all chains) and provides an estimate of the potential scale reduction factor (PSRF) (i.e. how much variance could be reduced by running chains longer) for each parameter and a multivariate PSRF for multivariate chains , defining convergence when the upper limit is close to 1.

Priors

We used a Bayesian framework to ensure that different sources of evidence were appropriately incorporated. In Bayesian statistics, data and prior information of the parameters are combined using Bayes' rule into a posterior distribution which update the prior knowledge using information from the data. In this framework, heterogeneous data sources can be easily combined to refine parameter estimation. This allows an optimal use of the different data sources and a rigorous treatment of the uncertainty.

We used the priors defined by Bains and colleagues (in Appendix to this thesis). A non-informative prior was used for parameters that are not well defined, specifically the probability of transmission of HPV per sexual contact and for the male seroconversion rate. The rate of HPV infection clearance in men was assumed to be lognormally distributed based on the assumption of a median time to clear of 6 months (i.e. mean log rate 0.134 and variance of 0.2 of the mean log rate).[7]

The duration of HPV infection was assumed to follow a Weibull distribution with shape and scale parameters (*clearance1* and *clearance2*, respectively). The probability of clearance of HPV infection is thought to be initially high, but decreasing over time and right-skewed. Hence, the shape parameter (*clearance1*) was assumed to be less than 1 and follow a beta distribution with Beta [2,1] and the rate parameter (*clearance2*) is in the same unit as time (months) was assumed follow a lognormal distribution, ranging from 0 to +∞. The type-specific prior for the rate parameter was generated using the median annual clearance rates of initial infection predicted by Johnson and colleagues.[8]

Calibration Target

As calibration target we estimated the observed type-specific HPV prevalence from individual patient data from the Cervical Lesions Observed by Papillomavirus Types – A Research in Europe (CLEOPATRE) Portugal study, a cross-sectional study where smears from 18 to 64-year-old unvaccinated women eligible for screening across the 5 RHAs were taken for LBC and HPV DNA genotyping.[9]

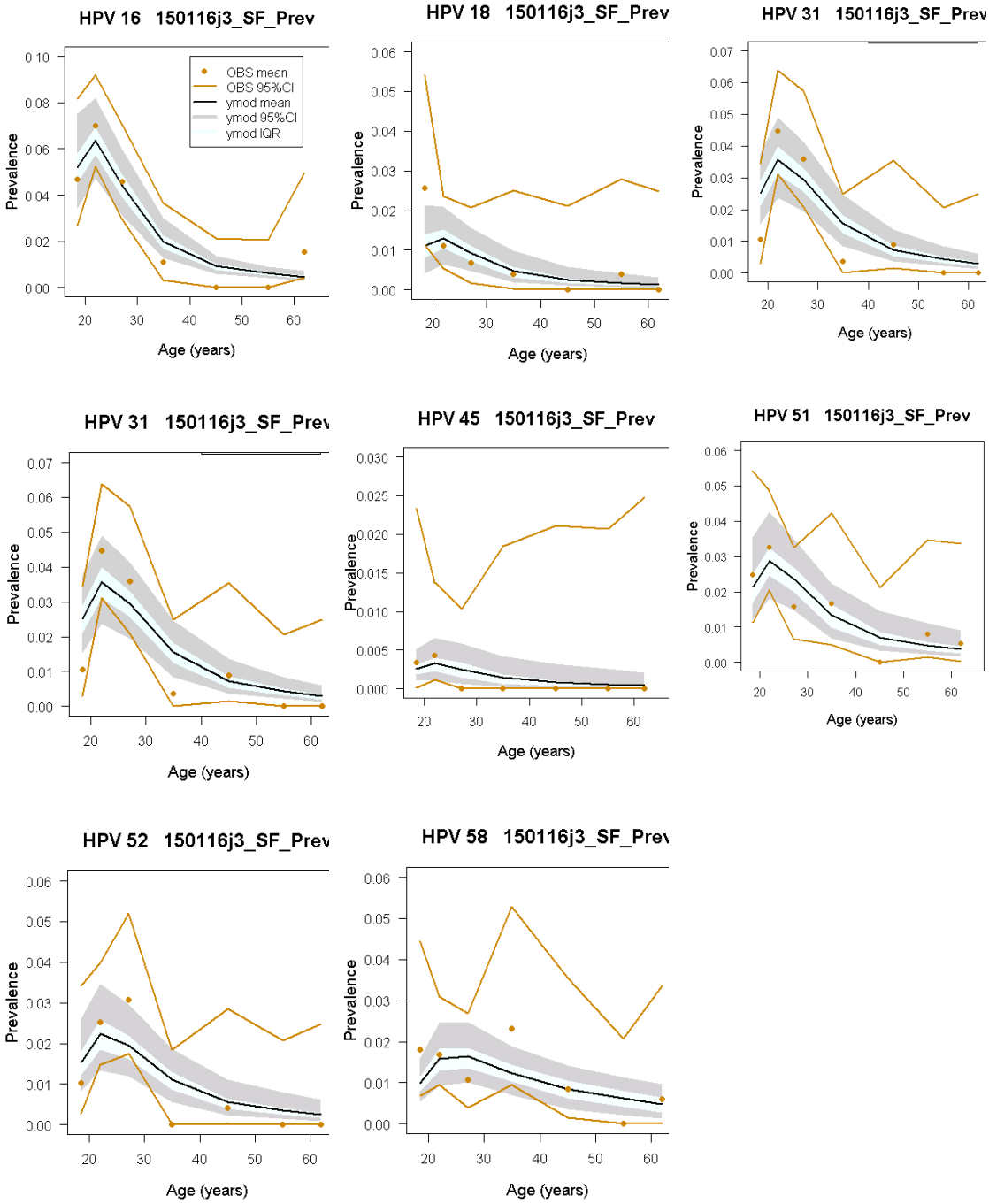
Results

The sets of parameters that provide best model output fit to the observed data were used to run the effectiveness analyses. The posterior distributions found for the fitted parameters (summarised in Supplementary Table 4-3, their pairwise densities, and correlation coefficients are presented in Supplementary Figure 4-9.

Our model predicted prevalence and estimates of the observed age- and type-specific prevalence are shown in Supplementary Figure 4-8.

Supplementary Table 4-3. Summary of the posterior distributions of fitted parameters by HPV type, mean (95%CI)

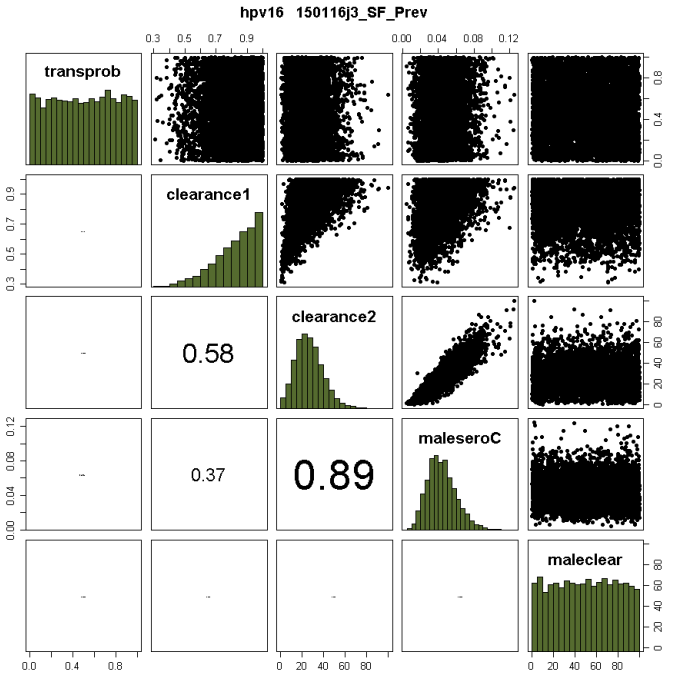
	Transmissibility, β	Clearance shape, c1	Clearance scale, c2	Male seroconversion	Male clearance	Fraction infected at 12mths	Fraction infected at 24mths	Median time to clear (months)
HPV 16	0.49 (0.028;0.974)	0.817 (0.491;0.993)	25.941 (3.632;50.759)	0.043 (0.019;0.076)	42.195 (2.063;96.601)	0.559 (0.176;0.767)	0.374 (0.085;0.611)	16.796 (1.761;33.859)
HPV 18	0.512 (0.025;0.975)	0.771 (0.396;0.993)	26.907 (1.345;79.924)	0.19 (0.022;0.521)	50.131 (3.596;97.098)	0.487 (0.019;0.818)	0.331 (0.001;0.689)	16.586 (0.694;49.455)
HPV 31	0.5 (0.022;0.969)	0.828 (0.511;0.993)	46.737 (12.442;88.407)	0.019 (0.008;0.032)	50.334 (3.011;97.417)	0.695 (0.375;0.859)	0.538 (0.23;0.744)	30.257 (6.754;59.649)
HPV 33	0.486 (0.019;0.965)	0.775 (0.361;0.99)	34.403 (2.579;87.184)	0.384 (0.07;0.873)	48.185 (1.827;96.344)	0.569 (0.081;0.848)	0.41 (0.024;0.729)	21.253 (0.949;55.728)
HPV 45	0.494 (0.031;0.977)	0.719 (0.239;0.988)	24.673 (1.936;82.465)	0.639 (0.156;0.984)	50.132 (3.859;97.211)	0.466 (0.038;0.805)	0.314 (0.006;0.682)	14.288 (0.496;48.44)
HPV 51	0.499 (0.022;0.982)	0.76 (0.372;0.989)	38.379 (3.843;90.627)	0.258 (0.072;0.515)	49.566 (1.013;97.168)	0.61 (0.186;0.848)	0.455 (0.092;0.73)	23.84 (1.701;58.678)
HPV 52	0.492 (0.027;0.976)	0.814 (0.436;0.992)	50.941 (11.651;94.351)	0.132 (0.055;0.25)	50.731 (2.12;97.214)	0.703 (0.362;0.864)	0.553 (0.228;0.754)	32.613 (5.68;62.261)
HPV 58	0.587 (0.05;0.97)	0.519 (0.042;0.957)	62.58 (9.125;98.452)	0.133 (0.071;0.218)	49.354 (1.341;96.687)	0.628 (0.336;0.86)	0.531 (0.267;0.751)	29.431 (0.006;63.229)

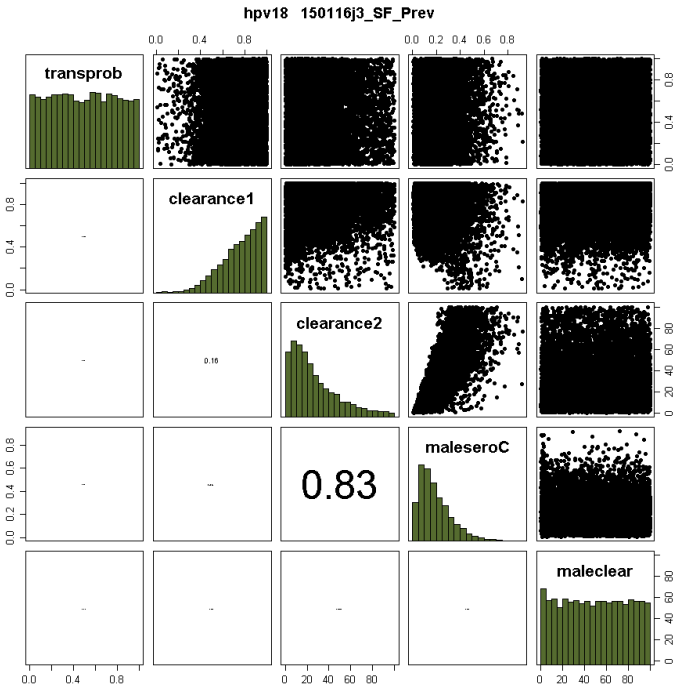


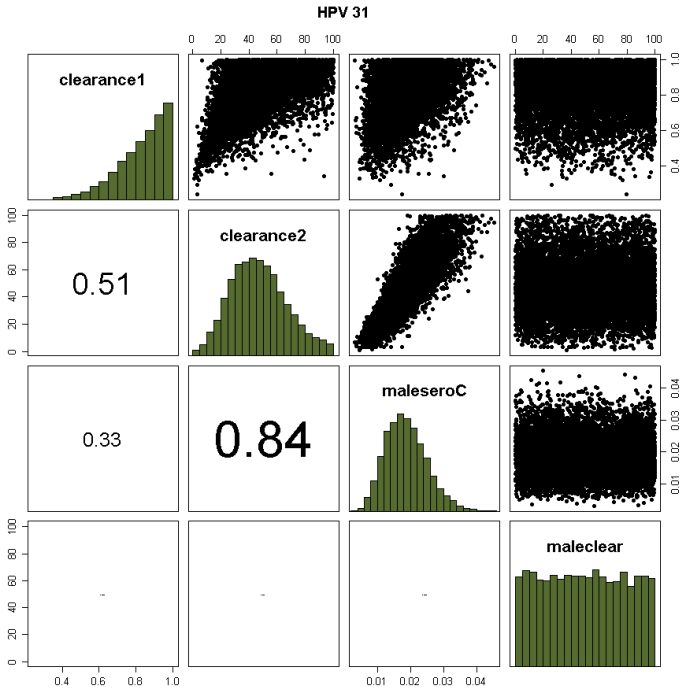
Supplementary Figure 4-8. Age- and type-specific HPV prevalence (modelled and observed)

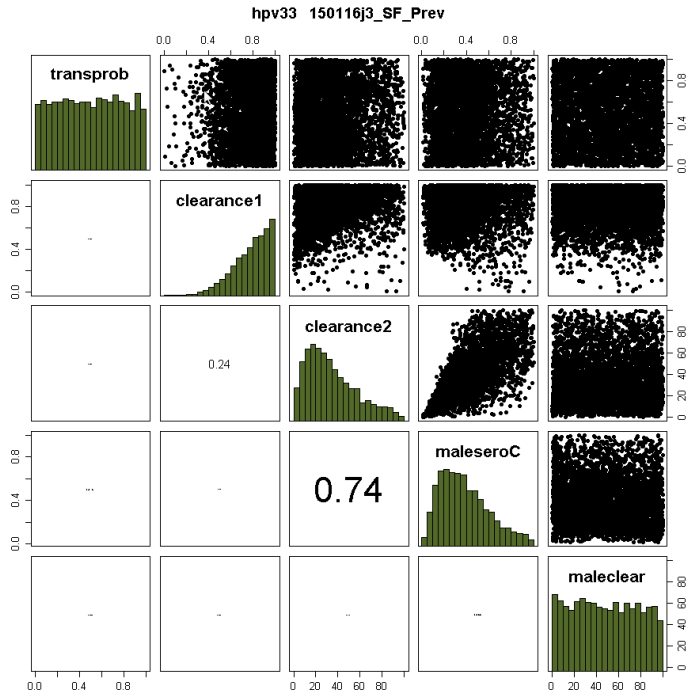
Observed prevalence in orange (dots and lines correspond to mean and 95%CI, respectively); modelled prevalence in black and shaded areas (black line, light blue area, and light grey area correspond to mean, IQR and 95th percentile, respectively)

Supplementary Figure 4-9. Posterior distributions used for calibrated parameters of the transmission model






HPV 31
clearance1
clearance2
0.51
maleseroC
0.33
0.84
maleclear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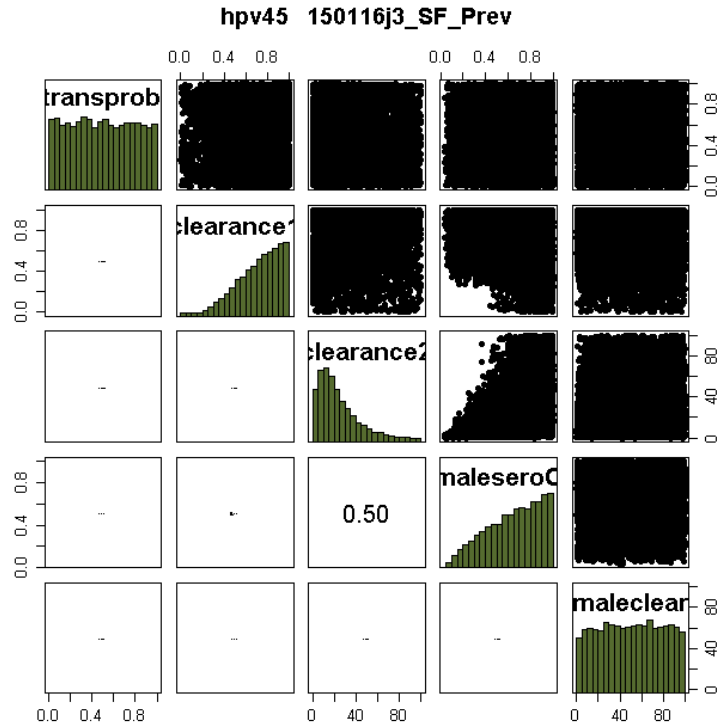
transprob
clearance1
clearance2
0.24
maleseroC
0.74
maleclear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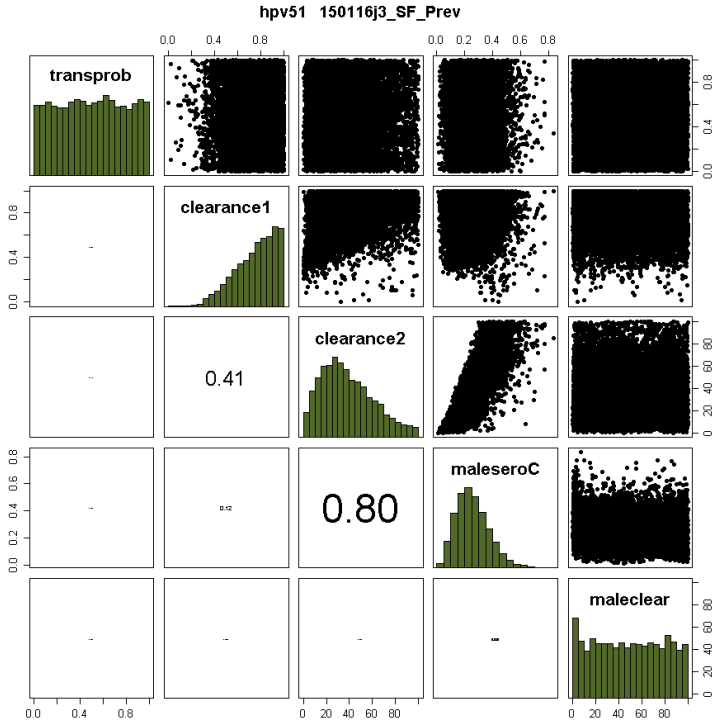
transprob
clearance1
clearance2
0.50
maleseroC
maleclear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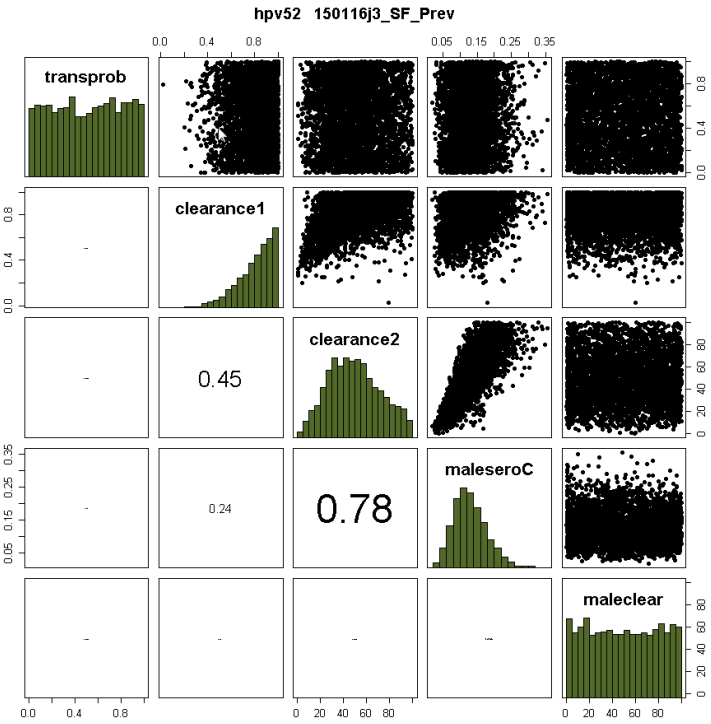
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0.45
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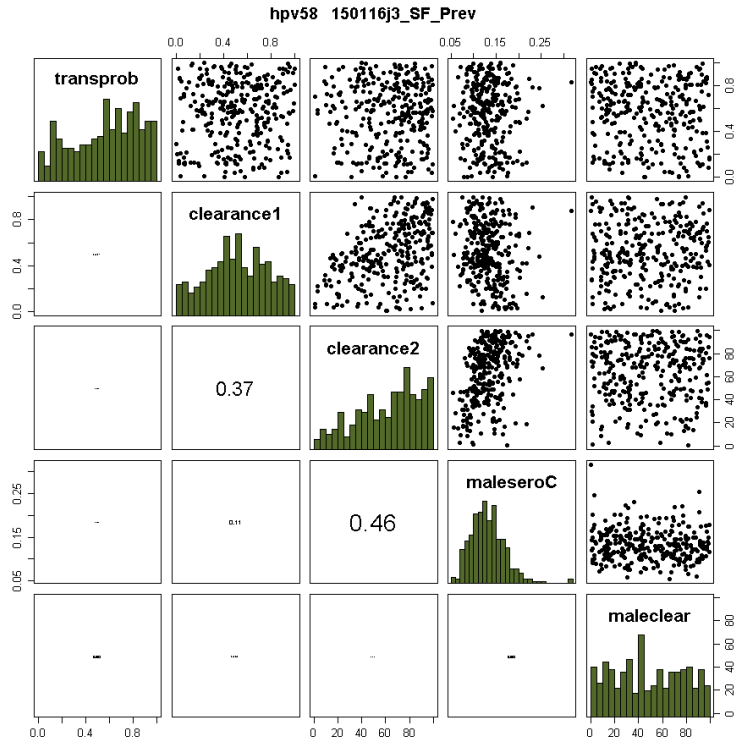
hpv58 150116j3_SF_Prev
transprob
clearance1
clearance2
maleseroC
maleclear
0.37
0.46

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4.3.2. Disease progression

4.3.2.1. Progression to pre-malignant cervical lesions

Several classification criteria have been used to report cytological and histological results (Supplementary Table 4-4 provides a summary of these terminologies).

Both Portugal and England have adopted the cervical intraepithelial neoplasia (CIN) terminology for histological results as per European guidelines;[1][2]however, different systems are used for cytology reporting. While Portugal has implemented the Bethesda System, England has used the terminology by the British Society for Clinical Cytology (BSCC).[3]

Our model uses the BSCC terminology for cytology outcomes (Bains and colleagues in Appendix to this thesis); hence, we adapted the screening decision algorithms to map between systems for Portugal (described in detail in Supplementary material 4.3.3).

Supplementary Table 4-4. Terminologies used for cytological and histological reporting (adapted from IARC 2005 and Schiffman and Wentzensen 2013) [4] [5]

	Histology			Cytology	
Natural history model	Papanicolaou class system (Papanicolaou 1954)	World Health Organisation (WHO) (Riotton *et al.*1973)	CIN (Richart 1968,1973)	Bethesda System (Solomon *et al.* 2002)	BSCC (1986,2013)
	Class I	Negative	Negative	Within normal limits	Negative
Infection	Class II	Squamous atypia	Squamous atypia	Benign cellular changes ASCUS ASCH	Borderline change
Precancer	Class III	Mild dysplasia	CIN1	Low-grade SIL (LSIL)	LD (mild)
		Moderate dysplasia	CIN2		HD (moderate)
		Severe dysplasia	CIN3	High-grade SIL (HSIL)	HD (severe)
Cancer	Class IV	Carcinoma *in situ*			
	Class V	Microinvasive carcinoma Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	HD/?invasive squamous carcinoma

ASC, atypical squamous cells; CIN, cervical intraepithelial neoplasia; HD, high-grade dyskaryosis; LD, low-grade dyskaryosis; SIL, squamous intraepithelial lesions

Cytological outcomes for HPV-positive women

Bains and colleagues modelled the development of pre-malignant lesions for HPV-positive women as a function of time since acquisition of HPV infection (detailed in the Appendix to this thesis). HPV type-specific progression parameters fitted by Bains and colleagues and their time-dependent probability model of the different cytological outcomes were used to randomly generate cytological outcomes as a function of time since infection. The probability of a normal outcome was thought to decrease exponentially over time since infection and to be less than *norm2* at time of cancer onset. Given an abnormality, the probability of a severe outcome was modelled to increase over time since infection while the probability of the remaining abnormalities was modelled to decrease exponentially over time since infection (Bains and colleagues in Appendix to this thesis).

$$P\ (normal\ , t) = (1 - norm2) \times e^{-norm1 * t} + norm2$$

$$P\ (borderline, t) = (1 - P\ normal) \times e^{-bord1 * t}$$

$$P\ (mild, t) = (1 - P\ normal) \times \left(1 - e^{-bord1 * t}\right) \times e^{-mild1 * t}$$

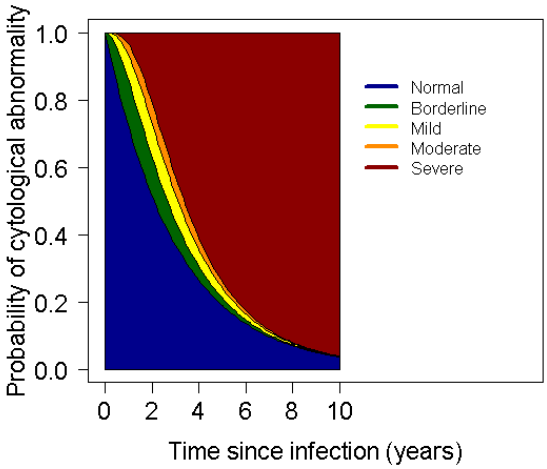
$$P\ (moderate, t) = (1 - P\ normal) \times \left(1 - e^{-bord1 * t}\right) \times \left(1 - e^{-mild1 * t}\right) * e^{-mod1 * t}$$

$$P\ (severe, t) = 1 - Pnormal - Pborderline - Pmild - Pmoderate$$

Bains and colleagues' posterior distributions of the five progression parameters used for each HPV type are summarised in Supplementary Table 4-5 and the probability of any given cytological outcome over time since infection is shown in Supplementary Figure 4-10.

Supplementary Table 4-5. Posterior distributions of cytological outcomes parameters, by HPV type, mean (95%CI) (Bains and colleagues in Appendix to this thesis)

	norm1	norm2	bord1	mild1	mod1
HPV 16	0.334 (0.0798,1.5738)	0.0006 (0,0.0037)	0.723 (0.0912,1.9066)	0.6576 (0.0456,1.9122)	0.7366 (0.0484,1.906)
HPV 18	1.3812 (0.2335,1.9815)	0.0052 (0,0.0377)	1.0985 (0.1296,1.9441)	0.8482 (0.0448,1.9388)	0.9542 (0.0571,1.9387)
HPV 31	0.1869 (0.0179,0.9381)	0.0003 (0,0.0007)	0.5748 (0.03,1.911)	0.6058 (0.023,1.8928)	0.8446 (0.0368,1.9475)
HPV 33	0.4209 (0.1212,1.6706)	0.0003 (0,0.0028)	0.4507 (0.103,1.6846)	0.1234 (0.0214,0.4913)	0.8384 (0.0647,1.9446)
HPV 45	0.0505 (0.0059,0.2027)	0.001 (0,0.0068)	0.9098 (0.0387,1.9282)	0.8605 (0.031,1.9451)	0.9369 (0.0468,1.9392)
HPV 51	0.144 (0.0278,0.4301)	0.0008 (0,0.0045)	0.6778 (0.0388,1.9007)	0.6771 (0.021,1.9159)	0.8406 (0.0363,1.9422)
HPV 52	0.144 (0.0278,0.4301)	0.0008 (0,0.0045)	0.6778 (0.0388,1.9007)	0.6771 (0.021,1.9159)	0.8406 (0.0363,1.9422)



Supplementary Figure 4-10. Probability of the different cytological outcomes by time since infection (Bains and colleagues in Appendix to this thesis)

Cytological outcomes distribution for HPV-negative women

For HPV-negative women, Bains and colleagues modelled the probability of a given cytological outcome as a function of age at time of screen. We used their estimates for 3 age categories derived from the National Health Service Cervical Screening Programme England data (Supplementary Table 4-6) (Bains and colleagues in Appendix to this thesis).

Supplementary Table 4-6. Cytological outcomes for HPV negative women, by age group (Bains and colleagues in Appendix to this thesis)

Cytological outcome	Age group		
	25-29	30-49	50+
Normal	0.86767990	0.946778133	0.9714036878
Borderline	0.06160168	0.031433627	0.0199242190
Mild	0.04808784	0.015740005	0.0066748133
Moderate	0.01224573	0.003267666	0.0010578025
Severe	0.01038485	0.002780570	0.0009394774

Colposcopy outcomes

We used the probabilities of the different colposcopy outcomes by cytological outcome for HPV-positive women under cytology-based and HPV primary screening derived by Bains and colleagues from National Health Service Cervical Screening Programme England data (Supplementary Table 4-7) (Bains and colleagues in Appendix to this thesis).

Supplementary Table 4-7. Probability of colposcopy outcomes, by cytological outcome and primary screening technology (Bains and colleagues in Appendix to this thesis)

	Colposcopy outcome		
Cytology primary	Normal	CIN1	CIN2+
- Borderline/Mild	0.4437	0.2805	0.2759
- Moderate/Severe	0.0259	0.0518	0.9223
HPV DNA primary			
- Borderline/Mild	0.5883	0.1758	0.2359
- Moderate/Severe	0.0192	0.0392	0.9415

4.3.2.2. Progression to cervical cancer

Bains and colleagues modelled the incidence of HPV type-specific cervical cancer as a function of time since HPV infection (Bains and colleagues in Appendix to this thesis). Squamous cell carcinomas and adenocarcinomas were modelled independently. Clinical detection of squamous cell carcinomas was modelled as a combination of (1) time since infection to cancer onset and (2) time from cancer onset to clinical detection. The first is assumed to follow a gamma distribution with shape and rate parameters, and the later an exponential distribution with a clinical detection delay rate decreasing with time. For adenocarcinomas, time since infection to clinical detection modelled using a single gamma distribution with shape and rate parameters, as cervical screening has proven inefficient in their detection and subsequent prevention[6]. Incidence of squamous cell carcinomas was modelled separately for screen-detected and clinically-detected cancers, so that incident squamous cancers are clinically detected if not yet detected by screening.

Cancer incidence was modelled as a function of women's infection history and all-cause mortality, where being alive and persistent infection were necessary conditions for cancer incidence (Bains and colleagues in Appendix to this thesis). Women's time of death was randomly pre-generated from the cumulative probability function derived from Portuguese age-specific mortality (1981-2060)[7].

We obtained distributions of HPV type-specific time to cancer-related parameters by calibration of our model predicted incidence to the observed annual incidence of cervical cancer in Portugal.

Calibration target

We estimated HPV type-specific incident squamous and adenocarcinoma cases by 5-year age group to use as calibration target of this component of the model (Supplementary Table 4-8 and Supplementary Table 4-9, respectively). These estimates were derived from (1) the number of incident cases, (2) the histological distribution of cervical cancers, and (3) HPV type-specific prevalence in cervical cancers.

The proportion of HPV 16 and HPV 18 is 68% and 11% of squamous cases and 52% and 37% of adenocarcinoma cases, similar to the proportions reported by Tjalma and colleagues.[8] The total number of incident cases and their distribution by histological type and age group obtained (Supplementary Table 4-10) is also in line with the data reported by the Portuguese National Cancer Registry[9–14], e.g. the total squamous and adenocarcinoma cases account on average for 65% and 16% of the total number of cases.

Supplementary Table 4-8. Number of HPV type-specific incident SCC cases by age group, mean(95%CI) Portugal

	HPV 16	**HPV 18**	**HPV 31**	**HPV 33**	**HPV 45**	**HPV 51**	**HPV 52**	**HPV 58**
0-4	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
5-9	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
10-14	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
15-19	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0.1 (0.1 ; 0.1)	0 (0 ; 0)	0.1 (0 ; 0.1)	0 (0 ; 0)
20-24	1.8 (1.4 ; 2.1)	0.3 (0.2 ; 0.3)	0.1 (0 ; 0.1)	0.1 (0 ; 0.1)	0.9 (0.6 ; 1.1)	0.1 (0.1 ; 0.1)	0.3 (0.2 ; 0.4)	0.3 (0.2 ; 0.3)
25-29	5.8 (4.2 ; 7.7)	1.8 (1.2 ; 2.3)	0.7 (0.5 ; 0.9)	0.8 (0.6 ; 1)	1.5 (1.1 ; 1.9)	0.1 (0.1 ; 0.1)	0.5 (0.3 ; 0.6)	0.5 (0.3 ; 0.6)
30-34	20.7 (14.6 ; 25.8)	3 (2.1 ; 3.8)	1.3 (0.9 ; 1.6)	1.8 (1.3 ; 2.3)	1.9 (1.4 ; 2.5)	0.2 (0.1 ; 0.2)	0.7 (0.5 ; 0.9)	0.6 (0.4 ; 0.7)
35-39	30.1 (21.6 ; 37.7)	5.1 (3.7 ; 6.5)	1.5 (1 ; 1.8)	2.3 (1.6 ; 2.9)	2.9 (2.1 ; 3.6)	0.3 (0.2 ; 0.3)	1.3 (0.9 ; 1.6)	1 (0.7 ; 1.3)
40-44	40 (28.6 ; 50.3)	6.6 (4.7 ; 8.3)	2.6 (1.8 ; 3.2)	2.7 (1.9 ; 3.3)	3.2 (2.2 ; 4)	0.3 (0.2 ; 0.3)	1.5 (1.1 ; 1.9)	0.8 (0.6 ; 1)
45-49	35.5 (25.1 ; 44.7)	6.9 (4.9 ; 8.7)	2.3 (1.6 ; 2.9)	2.9 (2.1 ; 3.7)	3.2 (2.2 ; 4)	0.2 (0.2 ; 0.3)	1.3 (0.9 ; 1.6)	0.8 (0.6 ; 1)
50-54	35.1 (25.1 ; 44)	6 (4.3 ; 7.6)	2.3 (1.7 ; 2.9)	2.8 (2 ; 3.5)	1.9 (1.4 ; 2.4)	0.2 (0.1 ; 0.2)	0.9 (0.6 ; 1.1)	0.6 (0.5 ; 0.8)
55-59	27 (18.9 ; 33.6)	4.1 (2.9 ; 5.2)	1.8 (1.3 ; 2.2)	2.3 (1.6 ; 2.9)	1.7 (1.2 ; 2.1)	0.1 (0.1 ; 0.2)	0.8 (0.5 ; 0.9)	0.4 (0.3 ; 0.5)
60-64	21.6 (15.3 ; 27.2)	3.9 (2.8 ; 4.9)	1.7 (1.2 ; 2.1)	1.9 (1.3 ; 2.3)	1.9 (1.3 ; 2.4)	0.2 (0.1 ; 0.2)	0.8 (0.6 ; 1)	0.7 (0.5 ; 0.8)
65-69	27.5 (19.5 ; 34.8)	4 (2.9 ; 5.1)	1.4 (1 ; 1.8)	2.2 (1.6 ; 2.8)	1.5 (1.1 ; 1.9)	0.1 (0.1 ; 0.2)	0.5 (0.4 ; 0.7)	0.4 (0.3 ; 0.5)
70-74	20.7 (14.7 ; 25.8)	3.3 (2.4 ; 4.2)	1.8 (1.3 ; 2.3)	1.9 (1.3 ; 2.4)	1.4 (1 ; 1.7)	0.1 (0.1 ; 0.1)	0.6 (0.4 ; 0.7)	0.4 (0.3 ; 0.5)
75-79	18.4 (13.2 ; 23)	2.5 (1.8 ; 3.2)	1.2 (0.8 ; 1.5)	1.5 (1 ; 1.8)	1.2 (0.9 ; 1.5)	0.1 (0.1 ; 0.1)	0.4 (0.3 ; 0.5)	0.3 (0.2 ; 0.4)
80-84	20.2 (14.6 ; 25.2)	1.4 (1 ; 1.8)	1 (0.7 ; 1.2)	1.4 (1 ; 1.7)	0.7 (0.5 ; 0.9)	0.1 (0 ; 0.1)	0.2 (0.1 ; 0.3)	0.2 (0.1 ; 0.2)
85+	9.5 (7 ; 11.9)	1.7 (1.2 ; 2.1)	0.5 (0.3 ; 0.6)	0.8 (0.6 ; 1)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
Total	314 (223.8 ; 393.7)	50.8 (36.2 ; 64)	20 (14.3 ; 25.2)	25.2 (17.8 ; 31.7)	23.9 (17.1 ; 30.1)	2 (1.4 ; 2.5)	9.8 (6.9 ; 12.3)	6.9 (4.9 ; 8.7)

Supplementary Table 4-9. Number of HPV type-specific incident ADC cases by age group, mean(95%CI)Portugal

	HPV 16	HPV 18	HPV 31	HPV 33	HPV 45	HPV 51	HPV 52	HPV 58
0-4	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
5-9	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
10-14	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
15-19	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
20-24	0.5 (0 ; 1)	0.2 (0 ; 0.4)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0.1)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
25-29	2.1 (0.5 ; 4.1)	1.5 (0.4 ; 3)	0 (0 ; 0)	0 (0 ; 0.1)	0.2 (0.1 ; 0.4)	0 (0 ; 0.1)	0 (0 ; 0)	0 (0 ; 0)
30-34	3.3 (1 ; 6.2)	3.2 (1.1 ; 6.3)	0.1 (0 ; 0.2)	0.1 (0 ; 0.2)	0.6 (0.2 ; 1.3)	0.1 (0 ; 0.2)	0 (0 ; 0)	0 (0 ; 0)
35-39	6.5 (2.1 ; 12.9)	4.4 (1.5 ; 8.6)	0.1 (0 ; 0.2)	0.1 (0 ; 0.3)	0.8 (0.2 ; 1.6)	0.1 (0 ; 0.2)	0 (0 ; 0)	0 (0 ; 0)
40-44	6.9 (2.1 ; 13.9)	4.4 (1.5 ; 8.6)	0.1 (0 ; 0.3)	0.2 (0.1 ; 0.4)	1.3 (0.4 ; 2.6)	0.1 (0 ; 0.3)	0 (0 ; 0)	0 (0 ; 0)
45-49	9.2 (3.1 ; 18.1)	5.8 (1.9 ; 11.6)	0.1 (0 ; 0.3)	0.2 (0.1 ; 0.4)	1 (0.3 ; 1.9)	0.2 (0.1 ; 0.3)	0 (0 ; 0)	0 (0 ; 0)
50-54	5.6 (1.6 ; 11.3)	4.2 (1.1 ; 8.2)	0.1 (0 ; 0.2)	0.1 (0 ; 0.2)	1.3 (0.4 ; 2.5)	0.2 (0 ; 0.3)	0 (0 ; 0)	0 (0 ; 0)
55-59	5 (1.6 ; 9.8)	4.1 (1.1 ; 8.2)	0.1 (0 ; 0.3)	0.1 (0 ; 0.3)	0.7 (0.2 ; 1.3)	0.1 (0 ; 0.3)	0 (0 ; 0)	0 (0 ; 0)
60-64	3.8 (1 ; 7.3)	2 (0.7 ; 3.7)	0.1 (0 ; 0.2)	0.1 (0 ; 0.2)	0.6 (0.2 ; 1.1)	0.1 (0 ; 0.2)	0 (0 ; 0)	0 (0 ; 0)
65-69	4.9 (1.6 ; 9.8)	3.6 (1.1 ; 7.1)	0.1 (0 ; 0.2)	0.1 (0 ; 0.2)	0.8 (0.3 ; 1.6)	0.1 (0 ; 0.2)	0 (0 ; 0)	0 (0 ; 0)
70-74	4 (1 ; 7.8)	1.9 (0.7 ; 3.7)	0.1 (0 ; 0.1)	0.1 (0 ; 0.2)	0.6 (0.2 ; 1.1)	0.1 (0 ; 0.2)	0 (0 ; 0)	0 (0 ; 0)
75-79	3.7 (1 ; 7.3)	3 (1.1 ; 6)	0.1 (0 ; 0.1)	0.1 (0 ; 0.1)	0.4 (0.1 ; 0.9)	0.1 (0 ; 0.2)	0 (0 ; 0)	0 (0 ; 0)
80-84	2.9 (1 ; 5.7)	2.1 (0.7 ; 4.1)	0.1 (0 ; 0.1)	0.1 (0 ; 0.1)	0.3 (0.1 ; 0.6)	0.1 (0 ; 0.1)	0 (0 ; 0)	0 (0 ; 0)
85+	1.4 (0.5 ; 2.6)	1.6 (0.4 ; 3.3)	0 (0 ; 0.1)	0 (0 ; 0.1)	0.3 (0.1 ; 0.6)	0 (0 ; 0.1)	0 (0 ; 0)	0 (0 ; 0)
Total	59.9 (18.1 ; 118)	42 (13.4 ; 82.9)	1.2 (0.4 ; 2.4)	1.4 (0.4 ; 2.8)	8.9 (2.7 ; 17.6)	1.4 (0.4 ; 2.7)	0 (0 ; 0)	0 (0 ; 0)

1) Number of incident cases

We estimated the annual total number of incident cervical cancer cases (Supplementary Table 4-10) from the total number of incident cases (ICD-10 code C53 – Malignant neoplasm of cervix uteri[18]) and total number of women by 5-year age bands from National Cancer Registry data for 2001, 2005, 2006, 2007, 2008, and 2010.[9–14] The age-specific annual rate of invasive cervical cancer in the Portuguese population was estimated fitting a Poisson distribution to the data.

Supplementary Table 4-10. Number of incident cases and women by age group and histological category, Portugal

Age group	Total number of cervical cancer cases (mean, 95%CI)	Squamous carcinoma cases (mean, 95%CI)	Adenocarcinoma cases (mean, 95%CI)	Number of women (mean, 95%CI)
0-4	0 (0 ; 3.7)	0 (0 ; 0)	0 (0 ; 0)	257258.2 (250919.7 ; 263596.7)
5-9	0 (0 ; 3.7)	0 (0 ; 0)	0 (0 ; 0)	265435 (258814.3 ; 272055.7)
10-14	0 (0 ; 3.7)	0 (0 ; 0)	0 (0 ; 0)	270559.7 (268169.9 ; 272949.5)
15-19	0 (0 ; 3.7)	0 (0 ; 0)	0 (0 ; 0)	290800.8 (276755.2 ; 304846.5)
20-24	4 (1.1 ; 10.2)	2.6 (2 ; 3)	0.7 (0 ; 1)	324572.7 (298279.1 ; 350866.3)
25-29	21 (13 ; 32.1)	13.6 (10 ; 17)	3.4 (1 ; 7)	374194.2 (354475.9 ; 393912.5)
30-34	44 (32 ; 59.1)	28.4 (20 ; 36)	7.1 (2 ; 14)	408155.8 (392381.3 ; 423930.3)
35-39	66 (51 ; 84)	42.5 (30 ; 54)	10.6 (3 ; 21)	399400 (388100.3 ; 410699.7)
40-44	86 (68.8 ; 106.2)	55.5 (39 ; 70)	13.8 (4 ; 27)	392457.7 (380169.8 ; 404745.5)
45-49	94 (76 ; 115)	60.6 (43 ; 76)	15.1 (5 ; 30)	379612.7 (363698.6 ; 395526.8)
50-54	80 (63.4 ; 99.6)	51.5 (36 ; 65)	12.9 (4 ; 26)	355066.5 (341817.6 ; 368315.4)
55-59	66 (51 ; 84)	42.5 (30 ; 53)	10.6 (3 ; 21)	334738.8 (318213.1 ; 351264.6)
60-64	55 (41.4 ; 71.6)	35.4 (25 ; 45)	8.8 (3 ; 18)	309607 (297364.5 ; 321849.5)
65-69	55 (41.4 ; 71.6)	35.4 (25 ; 45)	8.9 (3 ; 18)	285553.8 (281699.7 ; 289408)
70-74	47 (34.5 ; 62.5)	30.3 (22 ; 38)	7.6 (2 ; 15)	273568.7 (264761.1 ; 282376.2)
75-79	40 (28.6 ; 54.5)	25.8 (18 ; 32)	6.4 (2 ; 13)	240000.5 (232715.8 ; 247285.2)
80-84	33 (22.7 ; 46.3)	21.3 (15 ; 27)	5.3 (2 ; 11)	172872.3 (166290.3 ; 179454.2)
85+	22 (13.8 ; 33.3)	14.2 (10 ; 18)	3.5 (1 ; 7)	134678.3 (124192.2 ; 145164.3)
Total	713 (538.8 ; 944.7)	459.5 (325 ; 579)	114.8 (35 ; 229)	5468532.5 (5258818.3 ; 5678246.7)

2) Histological distribution of cervical cancer cases

The proportion of each histological type was derived from the type-specific annual total number of squamous, adeno, and other type of cervical carcinoma cases reported for 2001, 2005, 2007, 2008, and 2010.[9,10,12–14] We fitted a Dirichlet-Multinomial distribution to the data to estimate the maximum likelihood estimator (MLE) of the probability of having squamous cell carcinoma (SCC), adenocarcinoma (ADC), or other histological type (Supplementary Table 4-11).

Supplementary Table 4-11. Maximum likelihood estimators for histological type-specific probability of cancer

Histological type	p (SE)
squamous carcinoma	0.645 (0.0413)
adenocarcinoma	0.161 (0.0336)
other	0.194 (0.0311)
theta	0.036 (0.0159)

3) HPV type-specific prevalence in cervical cancer cases

The proportion of each modelled HPV type was derived from estimates of high-risk HPV prevalence among women with high grade CIN or invasive cervical cancer by histological diagnosis from two studies: (i) a meta-analysis of data (n= 2,715 ICC) from17 European countries between 2001 and 2008 and (ii) a cross-sectional study of Portuguese women with CIN2+ lesions or cervical cancer (n=64 ICC) attending NHS obstetrics/gynaecology services.[8,19] We combined both studies data and fitted a Dirichlet –multinomial distribution to obtain the MLE of the probability of infection in incident cases for each HPV type by histological category (Supplementary Table 4-12).

Supplementary Table 4-12. Maximum likelihood estimators for HPV type-specific probability of infection by cancer histological type

HPV type	**Squamous carcinoma p (SE)**	**Adenocarcinoma p (SE)**
16	0.658 (0.01)	0.511 (0.0267)
18	0.106 (0.0065)	0.369 (0.0258)
31	0.04 (0.0041)	0.011 (0.0057)
33	0.053 (0.0047)	0.011 (0.0057)
35	0.012 (0.0023)	-
39	0.012 (0.0023)	0.011 (0.0057)
45	0.049 (0.0046)	0.074 (0.014)
51	0.004 (0.0013)	0.011 (0.0057)
52	0.02 (0.0029)	-
56	0.01 (0.0021)	-
58	0.014 (0.0025)	-
59	0.006 (0.0017)	-
66	0.002 (0.0009)	-
68	0.014 (0.0025)	-
Theta	0 (0)	0 (0)

Calibration

We tried obtaining posterior distribution for time to cancer-related parameters using MCMC simulation and the adaptive Metropolis algorithm method used to calibrate the HPV acquisition component of the model to Portuguese HPV prevalence (described in Supplementary material 4.3.1). We used Bains and colleagues' type-specific distributions for England as priors (in Appendix to this thesis) and introduced the Poisson likelihood function to calculate the deviance between predicted and observed incidence used to measure goodness-of-fit. The model was run for HPV 16 and 18 with alternative sets of starting values, lower and upper bounds, jumps (proposal covariance matrix), and weights for the prior distributions. However, many attempts failed to explore the parameter space and none of those reached convergence.

We then took on a manual approach to fit progression to squamous cell carcinomas attributable to HPV 16 and 18 based on the assumption that the gamma distribution parameters used to model time from infection to cancer onset follow a uniform distribution. We also changed Bains and colleagues' model of time to clinical detection by using a lognormal distribution with location and shape parameter as it seemed to fit Portuguese incidence better. Alternative several value sets for these distributions parameters were chosen to run the model with, based on the posterior distributions reported by Bains and colleagues for progression to cancer in English women and the output of attempts to fit the model using MCMC simulation. The best fitting set of parameter values were selected by visual inspection of the fit to the observed incidence. For HPV 16, we used the "L-BFGS-B" optimisation method of the optim function in R stats package[15] - to refine the fit of the three best visually fitting parameter sets and selected the one with least sum of squared residuals to run our model with.

For HPV 18, we assumed the gamma shape and rate parameters for time to squamous cell carcinoma onset were uniformly distributed and ran the model using different ranges for these parameters (minimum and maximum values for those uniform distributions). We selected the best fitting set of values by visual comparison of the fit. For squamous cell carcinomas caused by the remaining HPV types and for adenocarcinomas, we used Bains and colleagues' posterior distributions of gamma parameters for England (in Appendix to this thesis), selecting for each HPV type the distribution that visually better fit its incidence in Portugal.

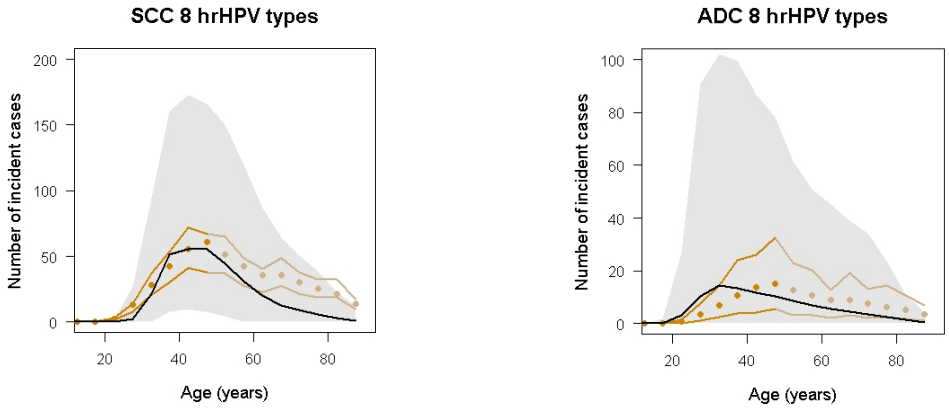
We used as calibration target the observed incidence of cervical cancer under 50 years of age as our model does not capture incidence in older women. This difference between predicted

and observed incidence in older age groups has been described for England and it is likely explained by cohort effects as in practice older women did not benefit from cervical screening available in the more recent decades to younger women and this is not captured in our model[16].

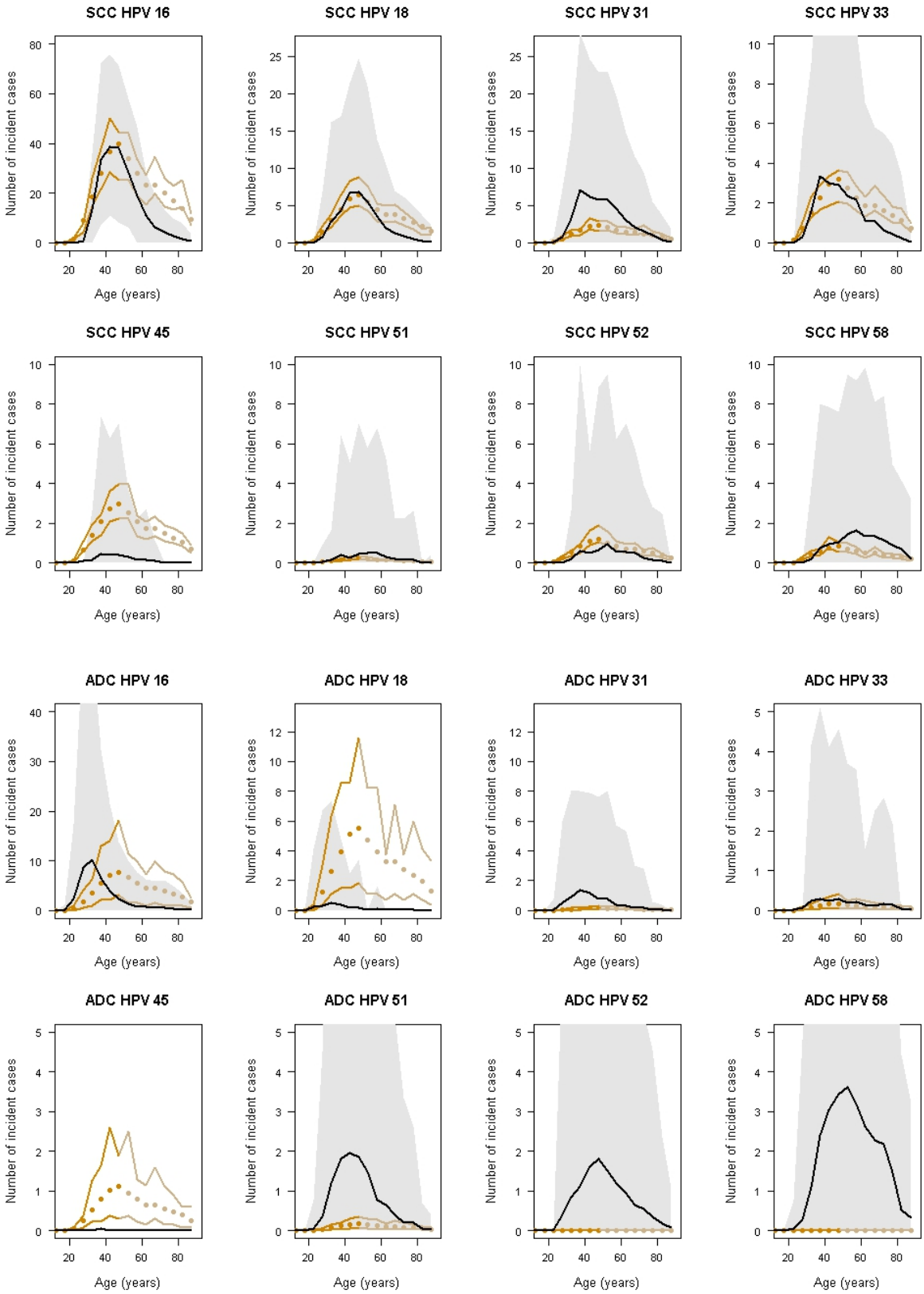
Supplementary Table 4-13 summarises the distributions used for our cancer-related parameters and observed and model predicted age- and type-specific incidence is shown in Supplementary Figure 4-11 and Supplementary Figure 4-12.

Supplementary Table 4-13. Posterior distributions of fitted parameters by HPV type

	Squamous carcinomas				Adenocarcinomas	
	Gamma shape min – max / mean (95%CI)	**Gamma rate min – max / mean (95%CI)**	**Lognormal location**	**Lognormal shape**	**Gamma shape min – max / mean (95%CI)**	**Gamma rate min – max / mean (95%CI)**
HPV 16	205.04	1.29	5.086	0.477	6.049 (4.1,7.9)	0.012 (0.008,0.015)
HPV 18	30-60	0.1-0.3	5.406	0.385	6.777 (2.896,38.832)	0.017 (0.003,0.119)
HPV 31	6.222 (2.896,34.483)	0.015 (0.003,0.112)	5.086	0.477	5.194 (3.943,8.115)	0.005 (0.003,0.011)
HPV 33	5.298 (2.7,12.9)	0.015 (0.003,0.055)	5.086	0.477	5.194 (3.943,8.115)	0.005 (0.003,0.011)
HPV 45	5.298 (2.7,12.9)	0.015 (0.003,0.055)	5.086	0.477	5.194 (3.943,8.115)	0.005 (0.003,0.011)
HPV 51	45.338 (4.082,175.676)	0.008 (0.003,0.026)	5.086	0.477	44.952 (4.102,175.676)	0.007 (0.003,0.026)
HPV 52	45.338 (4.082,175.676)	0.008 (0.003,0.026)	5.086	0.477	5.194 (3.943,8.115)	0.005 (0.003,0.011)
HPV 58	5.229 (3.943,8.115)	0.005 (0.003,0.011)	5.086	0.477	5.194 (3.943,8.115)	0.005 (0.003,0.011)



Supplementary Figure 4-11. Age-specific cervical cancer incidence (modelled and observed) for squamous cell carcinomas and adenocarcinomas (total, all HPV types modelled)



Supplementary Figure 4-12. Age- and HPV type-specific cervical cancer incidence (modelled and observed) for squamous cell carcinomas and adenocarcinomas

SCC, squamous cell carcinomas; ADC, adenocarcinomas; Observed incidence in orange (the fitting target in dark orange and incidence in women >50 years in light orange), dots and lines correspond to mean and 95%CI, respectively; modelled incidence in black and grey shaded area correspond to mean and 95th percentile, respectively.

4.3.2.3. Cervical cancer survival

Cervical cancer survival was derived from survival data reported by the Portuguese cancer registry of the North region[17]. A model assuming survival exponentially decreasing over time was calibrated to age-group specific 1- and 5-year net survival of patients diagnosed in 2007/8 (Supplementary Table 4-14). The fitted yearly rates were used to predict post-treatment survival in our model. Age-at-diagnosis-specific mortality rates (1-survival) were applied for 5 years after diagnosis to women with detected cancer, whose survival was assumed to be the same as in the general population from then onwards.

Supplementary Table 4-14. Cervical cancer survival

Survival (%), 1year, 5 year	Mean	Sources
15-44	93.3, 80.8	IPO Porto[17]
45-54	88.9, 76.0	
55-64	91.7, 65.2	
65-74	87.5, 62.2	
75+	72.5, 32.2	

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4.3.3. Screening

This component simulates implementing a screening strategy alongside the natural disease progression, where women can be tested to detect cervical pre-malignant lesions or cancer and be referred to follow-up screen, colposcopy, or treatment according to the severity of the screening test outcome. The screening strategies modelled are defined by their target age groups, screening frequency, technologies used, and thresholds for lesions follow-up, colposcopy, or treatment referral.

The screening component of Bain and colleagues' model was developed and parameterised to inform decisions for the National Health Service Cervical Screening Programme England (in Appendix to this thesis). It was structured so that screening frequency was modelled as a function of the individual's age and previous screening attendance history. Given the lack of data on Portuguese women's screening attendance, we restructured the screening component of the model. We modelled women's probability of attending subsequent screens and the waiting time to their next screen independently from their previous attendance.

4.3.3.1 Description of the screening model developed by Bains and colleagues (detailed in the Appendix to this thesis)

In Bains and colleagues model, the probability of an individual woman being ever screened is randomly generated by sampling with replacement in each model iteration. For those who ever get screened, a month of first screen is randomly generated from the cumulative distribution function of first screen age. The month of first screen is hence determined by vector of 10,000 months of age at first screen that is updated thereafter at each screen with the age at next screen for that particular individual.

If the date of screen is over the maximum screening age of 66 then no screen occurs. Otherwise, the woman's cytological and HPV infection status at date of screen are assigned (based on the infection history of the individual) as well as whether cancer is detected at that screen. The outcome of each screen for a given woman depends on her current screening recall status and the cytological outcome and HPV status. The recall status determines the applicable primary and triage tests and whether there's referral to immediate colposcopy or not before the next screen based on the cytological and HPV status.

The cytological outcome is extracted from previously randomly generated vectors of outcomes according to time since infection at date of screen or according to the woman's age if HPV negative (detailed in Supplementary material 4.3.2. Disease progression). For each infection persistent at that particular screen, time since infection is normalised to a period of10 years

waiting time to cancer, proportional to the waiting time to cancer for that infection. The worse cytological outcome among the existing infections is then assigned.

Squamous cell carcinomas are detected by screening if there's a persistent infection and the current date of screen is at or after the onset date of cancer and before the date of clinical detection. If detection occurs at that screen, that individual's age at screen detection is updated for all existing infections.

The outcome of referral to colposcopy depends on the HPV infection status and worse cytological outcome. The probability of attending colposcopy varies according to the cytological outcome. If the HPV status is negative (false referral), the colposcopy outcome is normal, if attended. If there's an HPV infection, the colposcopy outcome depends on the cytological outcome (Supplementary material 4.3.2).

A new screening recall status is assigned to the individual based on the cytological, triage, and colposcopy results. If the colposcopy appointment was missed, the woman is assumed to go back to the standard recall status.

The waiting time to next screen is then assigned based on the new recall status. If she goes back to standard recall, the date of next screen is dependent on the woman's age and the previous screen waiting time. If cancer is detected, there's no further screens (the next screen for that individual is set over the maximum screening age). If not, the woman is assumed to attend the follow-up visit at the scheduled waiting time, provided she is not lost to follow up. If she does miss her appointment, her next time of screen is assigned based on her previous screening waiting time.

If the woman is treated, the infection history record for that individual is updated depending on whether the lesion and/or the HPV infection were successfully treated/ cleared. If treatment was unsuccessful in treating the lesion, the individual's infection record remains unchanged. If both lesion and HPV infection are treated, the age at end of infection is updated for all current infections that have not yet progressed to cancer to the current date of screen. If the lesion was treated but HPV infection remains, the date of infection is updated to the current date of screen, the age at cancer onset updated to the current date of screen plus a randomly extracted time to cancer, and the age at clinical detection updated to increase by the same amount that the age at cancer was delayed.

4.3.3.2 Adaptation of the screening model to Portugal

We developed decision trees for each strategy modelled for the Portuguese context based on Bains and colleagues design and adapted all the relevant model functions to accommodate opportunistic screening and repeat cytology triage (not modelled for England). We also adapted the functions involved in summarising the screening strategies output.

Women's waiting time to next screen was modelled as dependent on women's age but not on women's previous screening history, given the lack of Portuguese data.

The maximum screening age of 66 used by Bains and colleagues for standard routine screening was adopted as well and the maximum screening age of 85 for follow-up of cytological abnormalities or treatment was introduced.

Due to the paucity of data on screening and colposcopy attendance, we assumed the probability of attending colposcopy did not vary according to the cytological outcome, and that women who miss their appointments for lesions follow-up have the same probability of attending a next screen at the next scheduled screening age as women of that age attending standard routine screens.

4.3.3.2.3. Screening strategies

Flowcharts for each strategy are shown in Supplementary Figure 4-13 and the decision trees used for the different strategies and respective recall waiting times to next screen are shown in section 4.3.3.2.4. The mapping between the Bethesda system used in Portugal and that of the British Society for Clinical Cytology is incorporated in the decision trees, where borderline changes, low-grade dyskaryosis (mild), and high-grade dyskaryosis (moderate or severe) are followed-up according to the recommendations for atypical squamous cell of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL), respectively. Atypical squamous cells cannot exclude HSIL (ASC-H) in Portugal are followed up as HSIL just as borderline changes, high-grade dyskaryosis not excluded are managed as high-grade dyskaryosis in England. Despite the general overlap of the two terminologies, our model does not account for the fact that borderline changes may include low-grade squamous intraepithelial lesions and some moderate dyskaryosis can be read as LSIL in Portugal[1,2].

Opportunistic screening in Portugal has been based on conventional cytology until the present day. Liquid-based cytology was introduced in 2008 (alongside HPV DNA testing for triage of ASCUS and LSIL lesions) and has been confined to areas where organised programmes have been implemented. We assumed the same performance for conventional and liquid-based cytology in our analyses[3].

The different cervical screening strategies studied in this thesis were selected based on discussions with the co-ordinators of screening programmes for the mainland Regional Health Administrations at the Portuguese General-Directorate for Health. It is important to note that many other possible strategies with varying screening intervals, screening ages, and pathways were not included.

Strategies 1 and 2 simulate different management protocols deployed opportunistically (the same screening frequency and compliance parameters were applied to these strategies), whereas strategies 3- 7 model alternative protocols implemented as part of a fully call-recall organised programme. The data and assumptions used to characterise these programmes are detailed in Parameterisation below.

Strategy 1

In Strategy 1, we assumed women were screened and followed up according to the Portuguese Gynaecology Society guidelines, where ASCUS were triaged by repeating cytology at 6 months and LSIL+ lesions were referred to immediate colposcopy (Supplementary Figure 4-13A). Those with abnormal triage cytology were referred to immediate colposcopy and those with normal triage cytology were followed up in 6 months.

Normal colposcopy results were also followed up by cytology at 6 months. If normal cytology at 6 months, the next cytology was at 12 months, and given both results were normal, women went back to standard routine screening. If any abnormality was detected they were referred to immediate colposcopy and followed up accordingly. CIN1 lesions were followed by cytology and colposcopy 6-monthly until 24 months if normal or CIN1. If normal at 24 months, women went back to standard routine screening. Persistent CIN1 at 24 months or any CIN2+ detected were referred to immediate treatment.

Post-treatment follow up consisted of cytology and colposcopy 6-monthly for 2 years. CIN1+ lesions were referred to immediate treatment. If normal for 2 years women entered a yearly follow-up with cytology. Cytology abnormalities were checked by immediate colposcopy. Normal colposcopy results were followed up in 12 months, whereas CIN1+ were referred to immediate treatment.

Strategy 2

Strategy 2 replicates the introduction of HPV DNA testing to triage ASCUS and LSIL lesions at 12 months and yearly co-testing with cytology and HPV DNA testing to follow-up <CIN1 lesions, as per the Portuguese Gynaecology Society guidelines (Supplementary Figure 4-13B). Women with normal cytology or ASCUS HPV-negative went back to standard screening. LSIL HPV-negative women were followed up with co-testing at 12 months and went back to standard

routine screening if normal. HPV-positive or HSIL women were referred to immediate colposcopy.

Normal colposcopy results after ASCUS were followed by co-testing at 12 months and went back to standard routine screening if normal cytology & HPV-negative. Normal colposcopy results after LSIL were followed by co-testing at 12 months and 36 months and went back to standard routine screening if normal cytology & HPV-negative. Normal colposcopy results after HSIL and any CIN1 colposcopy were followed by co-testing at 12 months and 24 months and went back to standard routine screening if normal cytology & HPV-negative. CIN2+ results were referred to immediate treatment.

After treatment, women were followed up at 6, 12, and 24 months. At 6 months, all women had cytology and colposcopy. If normal colposcopy, they had co-testing with cytology and HPV DNA at 12 months, and HPV-positive women or women with abnormal cytology had colposcopy and were followed accordingly (as described above). Women with normal cytology and HPV negative at 12 months had co-testing of cytology and HPV DNA at 24 months and were sent to standard routine screening if all negative, whereas HPV-positive or women with any abnormalities had colposcopy and were followed accordingly.

Strategies 3 and 7

Strategy 3 and 7 used the same decision trees for management of lesions as strategies 2 and 1, respectively (Supplementary Figure 4-13). Hence, both approaches were simulated under organised screening using the age at first screen and screening interval reported for women in the NHS Cervical Screening Programme, England (Bains and colleagues, Appendix in this thesis).

Strategy 6

We also modelled HPV triage in an organised system following the National Health Service Cervical Screening Programme England protocol[4] (Strategy 6, Supplementary Figure 4-13D), under the same screening frequency and compliance assumptions as Strategy 3.

The main differences between the lesions management algorithm used in strategy 6 compared to the one used for strategies 2 and 3 are:

- Women with normal colposcopy after ASCUS or LSIL go back to standard recall (instead of followed in 12 months)
- HPV-negative women after LSIL go back to standard recall (instead of followed in 12 months)
- 12 months lesions follow-up is done by cytology alone with HPV triage of ASCUS & LSIL (instead of co-testing everyone)

- At co-testing at 12 months follow-up, women with normal cytology or HPV-negative with ASCUS/LSIL go back to standard recall (instead of only HPV-negative women with normal cytology (both negative) go back to standard recall; everyone else has colposcopy in S2 & S3).
- Post-treatment 6 months follow-up by co-testing normal/ASCUS/LSIL. HSIL are referred to immediate colposcopy (instead of cytology & colposcopy to everyone). HPV-negative women with normal/ASCUS/LSIL go back to routine recall (instead of normal colposcopy with normal/ASCUS/LSIL go to 12 month follow-up by co-testing). Post-treatment Normal colposcopy with HSIL go back to standard recall and CIN1 (any cytology outcome) are followed up by cytology in 12 months (instead of everyone with HSIL or CIN1 post-treatment being referred to treatment again).

Strategy 4

In strategy 4, HPV DNA test was the primary screening test and HPV-positive women were triaged with cytology (Supplementary Figure 4-13C). HPV-positive women with normal triage cytology were referred to HPV testing in 12 months. If negative at 12 months, they went back to standard routine screening, whereas if HPV positive, cytology was used for triage and any cytological abnormality resulted in referral to colposcopy. HPV-positive women with normal cytology were followed-up in 12 months. HPV-positive women at 12 months had cytology triage and referred to colposcopy regardless of the cytological outcome.

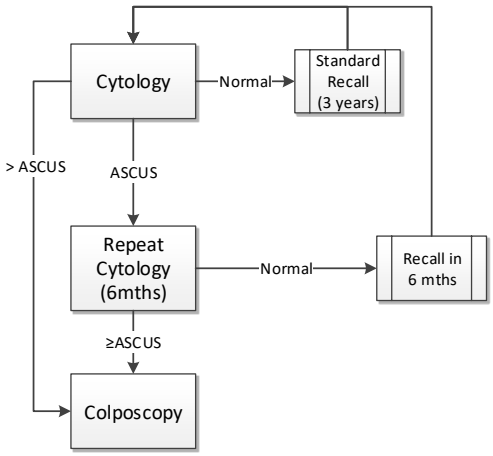
Women with normal colposcopy went back to standard routine screening. Those with CIN1 were followed up at 12 and 24 month, those with CIN2+ were referred to immediate treatment.

Post-treatment follow-up with HPV DNA testing occurred at 6 months. HPV negative women went back to routine screening, while HPV positive results were triaged by cytology and referred to colposcopy regardless of the cytological outcome. Colposcopy results were managed accordingly.

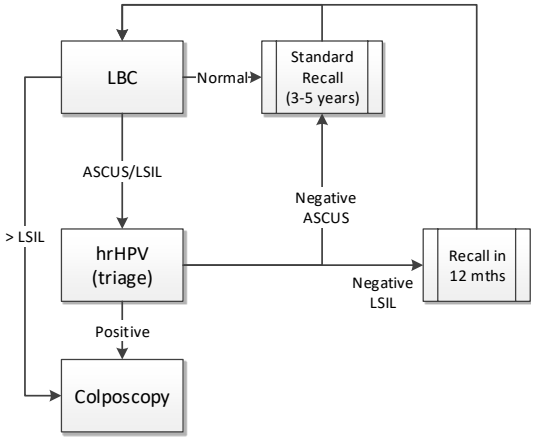
Strategy 5

We used the same decision trees for strategy 4 and 5, but assumed an extended screening interval of 5 years for the latter.

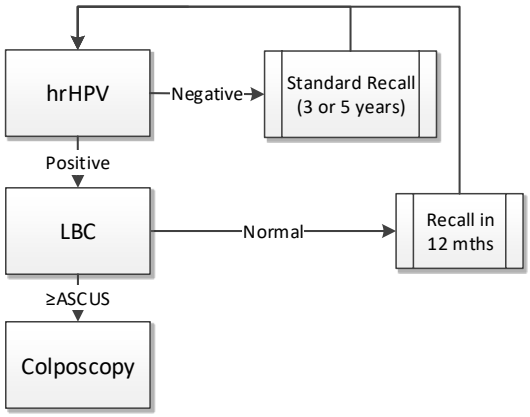
A) Strategies 1 & 7 – Repeat cytology



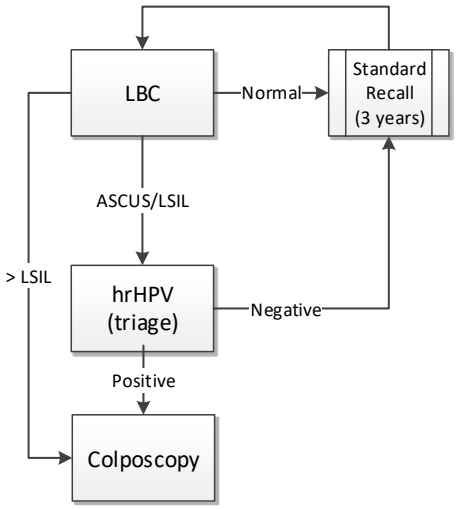
B) Strategies 2 & 3 – HPV triage (PT algorithm) [5]



C) Strategies 4 & 5 – Primary HPV testing



D) Strategy 6 – HPV triage (EN algorithm)[4]



Supplementary Figure 4-13. Screening strategies flowcharts

4.3.3.2.4. Decision trees

Supplementary Table 4-15. Decision Trees and assumed time to next screen

Decision tree	Decision tree description	Time to next screen (months)
Strategy 1 and 7		
1	Standard routine	36
2	Normal colposcopy 6 months follow-up	6
3	Post-treatment 6 months follow-up	6
4	Normal colposcopy 12 months follow-up	6
5	CIN1 6 months follow-up	6
6	CIN1 12 months follow-up	6
7	CIN1 18 months follow-up	6
8	CIN1 24 months follow-up	6
9	Post-treatment 12 months follow-up	6
10	Post-treatment 18 months follow-up	6
11	Post-treatment 24 months follow-up	6
12	Post-treatment >24 months follow-up	12
Strategy 2 and 3		
21	Standard routine	36
22	LSIL&HPV-negative or Normal colposcopy 12 months follow-up	12
23	Post-treatment 6 months follow-up	6
24	Post-treatment 12 months follow-up	12
25	Post-treatment 24 months follow-up	12
26	LSIL 12 months follow-up	12
27	LSIL 36 months follow-up	24
28	HSIL 12 months follow-up	12
29	HSIL 24 months follow-up	12
30	CIN1 12 months follow-up	12
31	CIN1 24 months follow-up	12
Strategy 4 and 5		
41	Standard routine	36
42	HPV-positive normal cytology 12 months follow-up	12
43	Post-treatment 6 months follow-up	6
44	HPV-positive normal cytology 24 months follow-up	12
45	CIN1 12 months follow-up	12
46	CIN2 24 months follow-up	12
Strategy 6		
61	Standard routine	36
62	CIN1 and HSIL/Normal colposcopy follow-up	12
63	Post-treatment 6 months follow-up	6

Supplementary Table 4-16. Strategies 1 and 7 – Repeat conventional cytology algorithm

1

C	CT	H	K	A
1	0	0	0	1
2	1	0	0	2
2	2	0	1	2
2	2	0	2	5
2	2	0	3	3
2	3	0	1	2
2	3	0	2	5
2	3	0	3	3
2	4	0	1	2
2	4	0	2	5
2	4	0	3	3
2	5	0	1	2
2	5	0	2	5
2	5	0	3	3
3	0	0	1	2
3	0	0	2	5
3	0	0	3	3
4	0	0	1	2
4	0	0	2	5
4	0	0	3	3
5	0	0	1	2
5	0	0	2	5
5	0	0	3	3

2

C	CT	H	K	A
1	0	0	0	4
2	0	0	1	2
2	0	0	2	5
2	0	0	3	3
3	0	0	1	2
3	0	0	2	5
3	0	0	3	3
4	0	0	1	2
4	0	0	2	5
4	0	0	3	3
5	0	0	1	2
5	0	0	2	5
5	0	0	3	3

4

C	CT	H	K	A
1	0	0	0	1
2	0	0	1	2
2	0	0	2	5
2	0	0	3	3
3	0	0	1	2
3	0	0	2	5
3	0	0	3	3
4	0	0	1	2
4	0	0	2	5
4	0	0	3	3
5	0	0	1	2
5	0	0	2	5
5	0	0	3	3

3

C	CT	H	K	A
1	0	0	1	9
1	0	0	2	3
1	0	0	3	3
2	0	0	1	9
2	0	0	2	3
2	0	0	3	3
3	0	0	1	9
3	0	0	2	3
3	0	0	3	3
4	0	0	1	9
4	0	0	2	3
4	0	0	3	3
5	0	0	1	9
5	0	0	2	3
5	0	0	3	3

5

C	CT	H	K	A
1	0	0	1	6
1	0	0	2	6
1	0	0	3	3
2	0	0	1	6
2	0	0	2	6
2	0	0	3	3
3	0	0	1	6
3	0	0	2	6
3	0	0	3	3
4	0	0	1	6
4	0	0	2	6
4	0	0	3	3
5	0	0	1	6
5	0	0	2	6
5	0	0	3	3

6

C	CT	H	K	A
1	0	0	1	7
1	0	0	2	7
1	0	0	3	3
2	0	0	1	7
2	0	0	2	7
2	0	0	3	3
3	0	0	1	7
3	0	0	2	7
3	0	0	3	3
4	0	0	1	7
4	0	0	2	7
4	0	0	3	3
5	0	0	1	7
5	0	0	2	7
5	0	0	3	3

7

C	CT	H	K	A
1	0	0	1	8
1	0	0	2	8
1	0	0	3	3
2	0	0	1	8
2	0	0	2	8
2	0	0	3	3
3	0	0	1	8
3	0	0	2	8
3	0	0	3	3
4	0	0	1	8
4	0	0	2	8
4	0	0	3	3
5	0	0	1	8
5	0	0	2	8
5	0	0	3	3

8

C	CT	H	K	A
1	0	0	1	1
1	0	0	2	3
1	0	0	3	3
2	0	0	1	5
2	0	0	2	3
2	0	0	3	3
3	0	0	1	5
3	0	0	2	3
3	0	0	3	3
4	0	0	1	3
4	0	0	2	3
4	0	0	3	3
5	0	0	1	3
5	0	0	2	3
5	0	0	3	3

9

C	CT	H	K	A
1	0	0	1	10
1	0	0	2	3
1	0	0	3	3
2	0	0	1	10
2	0	0	2	3
2	0	0	3	3
3	0	0	1	10
3	0	0	2	3
3	0	0	3	3
4	0	0	1	10
4	0	0	2	3
4	0	0	3	3
5	0	0	1	10
5	0	0	2	3
5	0	0	3	3

10

C	CT	H	K	A
1	0	0	1	11
1	0	0	2	3
1	0	0	3	3
2	0	0	1	11
2	0	0	2	3
2	0	0	3	3
3	0	0	1	11
3	0	0	2	3
3	0	0	3	3
4	0	0	1	11
4	0	0	2	3
4	0	0	3	3
5	0	0	1	11
5	0	0	2	3
5	0	0	3	3

11

C	CT	H	K	A
1	0	0	1	12
1	0	0	2	3
1	0	0	3	3
2	0	0	1	12
2	0	0	2	3
2	0	0	3	3
3	0	0	1	12
3	0	0	2	3
3	0	0	3	3
4	0	0	1	12
4	0	0	2	3
4	0	0	3	3
5	0	0	1	12
5	0	0	2	3
5	0	0	3	3

12

C	CT	H	K	A
1	0	0	0	12
2	0	0	1	11
2	0	0	2	3
2	0	0	3	3
3	0	0	1	11
3	0	0	2	3
3	0	0	3	3
4	0	0	1	3
4	0	0	2	3
4	0	0	3	3
5	0	0	1	3
5	0	0	2	3
5	0	0	3	3

The first row indicates the number of the decision tree; Column names: C, primary cytology; CT, repeat cytology (triage); H, HPV test; K, colposcopy; A, action (next follow-up decision tree); each row represents a set of potential outcomes in a given follow-up path (columns C, CT, H, and K) and the number of the decision tree for the next follow-up (column A); Cytological outcomes: 1, normal; 2, borderline; 3, mild; 4, moderate; 5, severe dyskaryosis; HPV test outcomes: 1, negative; 2, positive; Colposcopy outcomes: 1, normal; 2,CIN1; 3, CIN2+; 0, represents test not performed.

Supplementary Table 4-17. Strategies 2 and 3 – Primary liquid-based cytology and HPV triage algorithm as per Portuguese guidance[5]

21				
C	CT	H	K	A
1	0	0	0	21
2	0	1	0	21
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	0	22
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	0	1	28
4	0	0	2	30
4	0	0	3	23
5	0	0	1	28
5	0	0	2	30
5	0	0	3	23

22				
C	CT	H	K	A
1	0	1	0	21
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

23				
C	CT	H	K	A
1	0	0	1	24
1	0	0	2	23
1	0	0	3	23
2	0	0	1	24
2	0	0	2	23
2	0	0	3	23
3	0	0	1	24
3	0	0	2	23
3	0	0	3	23
4	0	0	1	23
4	0	0	2	23
4	0	0	3	23
5	0	0	1	23
5	0	0	2	23
5	0	0	3	23

24				
C	CT	H	K	A
1	0	1	0	25
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

25				
C	CT	H	K	A
1	0	1	0	21
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

26				
C	CT	H	K	A
1	0	1	0	27
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

27				
C	CT	H	K	A
1	0	1	0	21
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

28				
C	CT	H	K	A
1	0	1	0	29
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	23
4	0	1	2	23
4	0	1	3	23
5	0	1	1	23
5	0	1	2	23
5	0	1	3	23
4	0	2	1	23
4	0	2	2	23
4	0	2	3	23
5	0	2	1	23
5	0	2	2	23
5	0	2	3	23

29				
C	CT	H	K	A
1	0	1	0	21
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	23
4	0	1	2	23
4	0	1	3	23
5	0	1	1	23
5	0	1	2	23
5	0	1	3	23
4	0	2	1	23
4	0	2	2	23
4	0	2	3	23
5	0	2	1	23
5	0	2	2	23
5	0	2	3	23

30				
C	CT	H	K	A
1	0	1	0	31
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

31				
C	CT	H	K	A
1	0	1	0	21
1	0	2	1	22
1	0	2	2	30
1	0	2	3	23
2	0	1	1	22
2	0	1	2	30
2	0	1	3	23
2	0	2	1	22
2	0	2	2	30
2	0	2	3	23
3	0	1	1	26
3	0	1	2	30
3	0	1	3	23
3	0	2	1	26
3	0	2	2	30
3	0	2	3	23
4	0	1	1	28
4	0	1	2	30
4	0	1	3	23
5	0	1	1	28
5	0	1	2	30
5	0	1	3	23
4	0	2	1	28
4	0	2	2	30
4	0	2	3	23
5	0	2	1	28
5	0	2	2	30
5	0	2	3	23

The first row indicates the number of the decision tree; Column names: C, primary cytology; CT, repeat cytology (triage); H, HPV test; K, colposcopy; A, action (next follow-up decision tree); each row represents a set of potential outcomes in a given follow-up path (columns C, CT, H, and K) and the number of the decision tree for the next follow-up (column A); Cytological outcomes: 1, normal; 2, borderline; 3, mild; 4, moderate; 5, severe dyskaryosis; HPV test outcomes: 1, negative; 2, positive; Colposcopy outcomes: 1, normal; 2,CIN1; 3, CIN2+; 0, represents test not performed.

Supplementary Table 4-18. Strategies 4 and 5 – Primary HPV testing with liquid-based cytology triage algorithm

41

H	H	CT	K	A
1	0	0	0	41
2	0	1	0	42
2	0	2	1	41
2	0	2	2	45
2	0	2	3	43
2	0	3	1	41
2	0	3	2	45
2	0	3	3	43
2	0	4	1	41
2	0	4	2	45
2	0	4	3	43
2	0	5	1	41
2	0	5	2	45
2	0	5	3	43

?

42

H	H	CT	K	A
1	0	0	0	41
2	0	1	0	44
2	0	2	1	41
2	0	2	2	45
2	0	2	3	43
2	0	3	1	41
2	0	3	2	45
2	0	3	3	43
2	0	4	1	41
2	0	4	2	45
2	0	4	3	43
2	0	5	1	41
2	0	5	2	45
2	0	5	3	43

?

43

H	H	CT	K	A
1	0	0	0	41
2	0	1	1	41
2	0	1	2	45
2	0	1	3	43
2	0	2	1	41
2	0	2	2	45
2	0	2	3	43
2	0	3	1	41
2	0	3	2	45
2	0	3	3	43
2	0	4	1	41
2	0	4	2	45
2	0	4	3	43
2	0	5	1	41
2	0	5	2	45
2	0	5	3	43

44

H	H	CT	K	A
1	0	0	0	41
2	0	1	1	41
2	0	1	2	45
2	0	1	3	43
2	0	2	1	41
2	0	2	2	45
2	0	2	3	43
2	0	3	1	41
2	0	3	2	45
2	0	3	3	43
2	0	4	1	41
2	0	4	2	45
2	0	4	3	43
2	0	5	1	41
2	0	5	2	45
2	0	5	3	43

45

H	H	CT	K	A
1	0	0	0	41
2	0	1	0	46
2	0	2	1	41
2	0	2	2	45
2	0	2	3	43
2	0	3	1	41
2	0	3	2	45
2	0	3	3	43
2	0	4	1	41
2	0	4	2	45
2	0	4	3	43
2	0	5	1	41
2	0	5	2	45
2	0	5	3	43

46

H	H	CT	K	A
1	0	0	0	41
2	0	1	0	41
2	0	2	1	41
2	0	2	2	45
2	0	2	3	43
2	0	3	1	41
2	0	3	2	45
2	0	3	3	43
2	0	4	1	41
2	0	4	2	45
2	0	4	3	43
2	0	5	1	41
2	0	5	2	45
2	0	5	3	43

The first row indicates the number of the decision tree; Column names: H, HPV test; CT, cytology (triage); K, colposcopy; A, action (next follow-up decision tree); each row represents a set of potential outcomes in a given follow-up path (columns C, CT, H, and K) and the number of the decision tree for the next follow-up (column A); Cytological outcomes: 1, normal; 2, borderline; 3, mild; 4, moderate; 5, severe dyskaryosis; HPV test outcomes: 1, negative; 2, positive; Colposcopy outcomes: 1, normal; 2,CIN1; 3, CIN2+; 0, represents test not performed.

Supplementary Table 4-19. Strategy 6 - Primary liquid-based cytology and HPV triage algorithm as per NHS CSP, England[4]

61					62					63				
C	CT	H	K	A	C	CT	H	K	A	C	CT	H	K	A
1	0	0	0	61	1	0	0	0	61	1	0	1	0	61
2	0	1	0	61	2	0	1	0	61	1	0	2	1	61
2	0	2	1	61	2	0	2	1	61	1	0	2	2	62
2	0	2	2	62	2	0	2	2	62	1	0	2	3	63
2	0	2	3	63	2	0	2	3	63	2	0	1	0	61
3	0	1	0	61	3	0	1	0	61	2	0	2	1	61
3	0	2	1	61	3	0	2	1	61	2	0	2	2	62
3	0	2	2	62	3	0	2	2	62	2	0	2	3	63
3	0	2	3	63	3	0	2	3	63	3	0	1	0	61
4	0	0	1	62	4	0	0	1	62	3	0	2	1	61
4	0	0	2	62	4	0	0	2	62	3	0	2	2	62
4	0	0	3	63	4	0	0	3	63	3	0	2	3	63
5	0	0	1	62	5	0	0	1	62	4	0	0	1	61
5	0	0	2	62	5	0	0	2	62	4	0	0	2	62
5	0	0	3	63	5	0	0	3	63	4	0	0	3	63
										5	0	0	1	61
										5	0	0	2	62
										5	0	0	3	63

The first row indicates the number of the decision tree; Column names: C, primary cytology; CT, repeat cytology (triage); H, HPV test; K, colposcopy; A, action (next follow-up decision tree); each row represents a set of potential outcomes in a given follow-up path (columns C, CT, H, and K) and the number of the decision tree for the next follow-up (column A); Cytological outcomes: 1, normal; 2, borderline; 3, mild; 4, moderate; 5, severe dyskaryosis; HPV test outcomes: 1, negative; 2, positive; Colposcopy outcomes: 1, normal; 2,CIN1; 3, CIN2+; 0, represents test not performed.

4.3.3.2.5. Parameterisation

Individual patient data from the Portuguese National Health Survey 2005/6[6] was used to parameterise our model on screening frequency under opportunistic screening. The variables of interest were derived from the self-reported year of last cytology and the year the survey was taken (n=3,368 valid answers).

To characterise screening frequency in the context of organised screening, we used an Bains and colleagues model for the distribution of age at first screen derived from data of the NHS CSP, England (2011/12) (Bains and colleagues, Appendix in this thesis). We also used the distribution of time since last adequate test reported for women aged 25-64 in the NHS Cervical Screening Programme, England (2012-2013)[7], and an estimate of loss to follow-up from a population-based study on cytology attendance in the Manchester Health Authority Area (2004)[8].

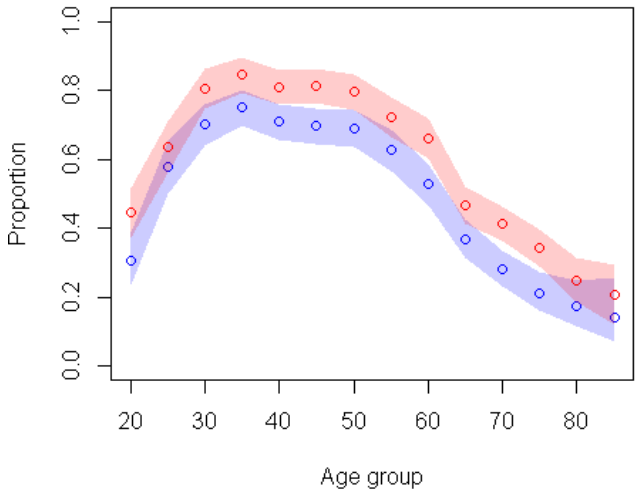
Proportion never screened

Under opportunistic screening (strategies 1 and 2), 35.5% of women never attend screening over a lifetime. Out of the 3,368 valid answers, 1,588 women reported never having been screened (47.15% (95%CI 45.5%, 48.9%) and 35.5% (95%CI 33.8%, 37.2%) crude and weighted estimate, respectively).

For organised screening strategies, we assumed 10% of women were never screened based on an analysis of screening records in the Manchester Health Authority Area estimating that 11% of women aged 30-64 (n=72,613) never attended NHS screening[8].

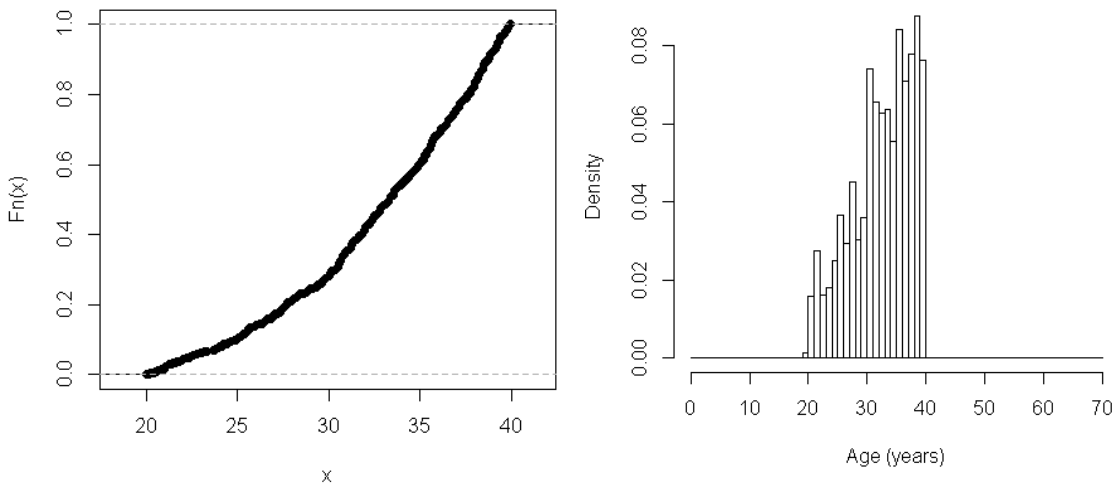
Age at first screen

To model opportunistic screening, we derived the age at first screen from the proportion of women ever screened stratified by age group, as the actual age at first screen was not reported in the Portuguese National Health Survey 2005/6. The probability of having been screened at a given age was obtained by fitting a binomial distribution by maximum likelihood estimation. The maximum age at first screen was then assumed to be the last year within the age group with highest probability of having been screened, i.e. 39 years old Supplementary Figure 4-14).



Supplementary Figure 4-14. Proportion of women ever screened by 5-year age group

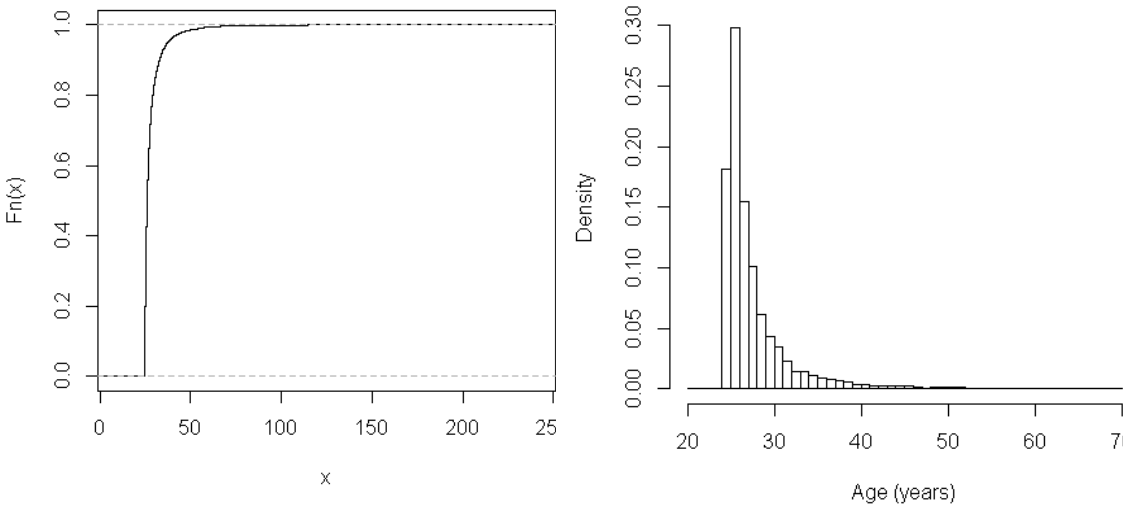
As the individual age at the survey participants was not available, we assume they were evenly distributed across the age group and randomly sampled the individual years and months of age. The empirical cumulative distribution function of first screen age was then used to randomly sample the age at first screen from for each individual woman modelled (Supplementary Figure 4-15), mean 32.58,median 33.42, 95%CI [21.25, 39.67]).



Supplementary Figure 4-15. Predicted age at first screen (opportunistic screening), cumulative probability distribution (left) and histogram (right)

To model organised screening, we used Bains and colleagues' distribution function of age at first screen for women aged over 24.5 years in England, where the age at first screen is assumed to be at least 24.5 years of age plus a lognormally distributed time interval whose logarithm has mean and standard deviation of 0.47389 and 1.26237, respectively (Appendix in this thesis). Supplementary Figure 4-16 shows the predicted age at first screen distribution used for modelled strategies of organised screening (mean 28.09, median 26.13, 95%CI [24.64, 43.54]).

Age at first screen ~ 24.5 + LogNormal[0.47389, 1.26237]



Supplementary Figure 4-16. Predicted age at first screen (organised screening), cumulative probability distribution (left) and histogram (right)

Time to next screen

To model opportunistic screening, we derived time since last cytology from individual-patient data of the Portuguese National Health Survey 2005/6 by subtracting the self-reported year of last cytology from the reported year of the survey data. For each year of age, we sampled the time since last cytology of the respective age group with replacement and added a randomly generated month within a year, assuming the time of next cytology to be within a year's time from completion of the survey. Supplementary Table 4-20 shows the summary statistics for the reported time since last cytology and for our modelled screening interval under opportunistic screening.

Supplementary Table 4-20. Time since last cytology and opportunistic screening interval by age group

Age group	Time since last cytology mean, median (IQR), years	Screening interval mean, median (IQR), years
20-24	1, 1.19 (0, 2)	1.42, 1.8 (0.67, 2.58)
25-29	1, 1.4 (0, 2)	1.42, 1.69 (0.75, 1.92)
30-34	1, 1.71 (0, 2)	1.33, 2.04 (0.58, 2.25)
35-39	1, 1.94 (0, 2)	1.42, 2.39 (0.67, 2.75)
40-44	1, 2.36 (0, 3)	1.67, 2.69 (0.92, 3.33)
45-49	1, 2.31 (0, 2)	1.58, 2.2 (0.83, 2.67)
50-54	1, 2.83 (1, 3)	1.75, 3.38 (1, 3.42)
55-59	2, 3.08 (1, 4)	2, 3.46 (0.92, 4.5)
60-64	3, 5.44 (1, 9)	3.17, 6.15 (1.33, 10.17)
65-69	4, 7.9 (1, 10)	3.92, 7.4 (1.75, 10.5)
70-74	5, 9.18 (2, 13)	5.25, 9.18 (2.17, 12.92)
75-79	8, 12.38 (2, 20)	7.5, 12.62 (4.83, 20.42)
80-84	10, 10.39 (3, 16)	5.92, 8.84 (1.83, 10.92)

For organised screening, we used the distribution of time since last adequate test reported for women aged 25-64 in the NHS Cervical Screening Programme, England (2012-2013), assuming similar screening frequency would take place in Portugal under a similarly organised call-recall cervical screening programme.[7] The proportion of women who had their last adequate test within a given period of time was used (categories: <1.5 , 1.5-3, 3-3.5, 3.5-5, 5-10,10-15, 15-20 years). We sampled the time since last cytology with replacement (in months) for each year of age, assuming this variable was uniformly distributed within each time category.

For the extended screening interval of 5 years (strategy 5), we used the organised screening distribution of time to next screen but added 2 years to each category: <3.5 , 3.5-5, 5-6.5, 6.5-7, 7-12, 12-17, 17-22 years.

Supplementary Table 4-21 summarises the primary screen intervals used as inputs to model screening strategies under opportunistic and organised regimes.

Supplementary Table 4-21. Screening interval by age group, mean, median (IQR), years

Age group	Opportunistic screening (3 yearly)	Organised screening (3 yearly)	Organised screening (5 yearly)
20/25-65	1.67, 2.97 (0.83, 3.08)	2.08, 3.02 (1, 3.42)	4.08, 4.72 (2.33, 6.25)
20-24	1.42, 1.8 (0.67, 2.58)	-	-
25-29	1.42, 1.69 (0.75, 1.92)	2.08, 3.03 (1, 3.42)	4.08, 4.7 (2.33, 6.25)
30-34	1.33, 2.04 (0.58, 2.25)	2.08, 3.02 (1, 3.42)	4.08, 4.69 (2.33, 6.17)
35-39	1.42, 2.39 (0.67, 2.75)	2.08, 3.01 (1, 3.42)	4.08, 4.72 (2.33, 6.25)
40-44	1.67, 2.69 (0.92, 3.33)	2.08, 3.03 (1, 3.5)	4.08, 4.74 (2.33, 6.33)
45-49	1.58, 2.2 (0.83, 2.67)	2.08, 3.02 (1, 3.42)	4.08, 4.71 (2.33, 6.17)
50-54	1.75, 3.38 (1, 3.42)	2.08, 3.02 (1, 3.5)	4.08, 4.73 (2.25, 6.25)
55-59	2, 3.46 (0.92, 4.5)	2.08, 3.02 (1, 3.42)	4.08, 4.73 (2.33, 6.25)
60-64	3.17, 6.15 (1.33, 10.17)	2.08, 3 (1, 3.42)	4.08, 4.73 (2.33, 6.33)
65-69	3.92, 7.4 (1.75, 10.5)	2.08, 2.98 (1, 3.42)	4.08, 4.73 (2.33, 6.33)
70-74	5.25, 9.18 (2.17, 12.92)	2.08, 3.02 (1, 3.5)	4.08, 4.72 (2.33, 6.25)
75-79	7.5, 12.62 (4.83, 20.42)	2.08, 3.03 (1, 3.42)	4.08, 4.71 (2.25, 6.27)
80-84	5.92, 8.84 (1.83, 10.92)	2.08, 3.02 (1, 3.42)	4.08, 4.71 (2.25, 6.25)

Compliance with follow-up, diagnostic, and treatment referrals

Opportunistic screening

The probability of a women being lost to follow up of a cytological abnormality (including vigilance of minor abnormalities and post-treatment follow-up) was assumed to be 0.50, as this is slightly under the lowest compliance to screening invitation reported by one of the Regional Health Administrations in 2013 (55%).

Compliance to repeat cytology referral was assumed to be 100% as 99% was reported in the Centre region, where repeat cytology has been in place.

Compliance with colposcopy referral was assumed to be 0.75, the mid-point of 10-40% estimates of non-adherence to referral by Khanna and Phillips[9], e.g. 40% loss FU in Nottingham pre-1984 when screening was opportunistic.

Organised screening

For organised screening strategies, we assumed only 20% of women being lost to follow-up of a cytological lesion given the 82% (range: 55-86%, in Algarve and Alentejo respectively) average attendance to screening reported in organised programmes (2013).

Colposcopy attendance was assumed to be 88%, the average in Portugal organised programmes (range: 59-92%, in Alentejo and North, respectively).

We assumed 100% compliance to referrals to treatment of CIN2+ lesions and that only 24-month persistent CIN1 lesions were treated, for both opportunistic and organised screening strategies.

Treatment effectiveness

As per Bains and colleagues (in the Appendix to this thesis), in our model, the proportion of lesions successfully treated was 95% and the probability of treatment successfully clearing HPV infections was 88.4%, as 16% of all women treated are HPV positive.[10]

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5. Chapter 5. Economic evaluation of primary HPV DNA screening in Portugal

5.1.Preamble to research paper 4

The systematic review of previous model-based evaluations of cervical screening in research paper 2[1] (Chapter 3) showed that cost-effectiveness analyses have become more common in this area than studies of effectiveness only. The economic impact of screening interventions has been proposed as a key criteria for the comprehensive evaluation and selection of screening strategies for clinical practice[7,8].

Over two thirds of the studies reviewed in research paper 2[1] quantified health outcomes only in terms lives or life-years saved and a third in quality-adjusted life-years (QALYs) gained (particularly common among analyses of vaccination and screening). In research paper 4, we performed a cost-effectiveness evaluation, measuring economic efficiency in terms of life-years and QALYs in the base-case analysis and health-related quality of life in scenario sensitivity analyses.

One[2] of the two studies[2,3] previously published on modelling screening in Portugal included economic outcomes taking the perspective of the health care system on costs to analyse the cost-effectiveness of organised primary screening with conventional cytology or liquid-based cytology compared to opportunistic screening in euros (€) per life-year gained over an horizon of 10 years.

In research paper 4, the cost-effectiveness of organised programmes with conventional or liquid-based cytology was compared to opportunistic screening (which is still commonly practiced in parts of Portugal) as well as to no screening and strategies including HPV DNA testing, either as a primary screening test or as triage of minor cytological lesions. The economic implications of extending the screening interval under organised primary HPV screening were also investigated. Health and economic outcomes were estimated over the lifetime of screened women and a partial societal perspective on costs was adopted, as per Portuguese guidelines on economic evaluations of medicines[4], by including the direct costs of providing health care for the National Health Service and the indirect costs of paid productivity loss by women due to cervical cancer. Other direct and indirect costs to society, e.g. costs to patients for attending screening, have not been included though. Cost-utility analysis was also performed in two scenarios with alternative assumptions on the impact of cervical cancer and cervical screening on women's health-related quality of life.

The overall aim of this thesis was accomplished with the work presented in research paper 4 as it presents a fully incremental analysis of the cost-effectiveness of cytology- and HPV-based protocols compared to no screening.

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5.2.Research paper 4.

Economic evaluation of primary HPV DNA screening in Portugal

Mendes, D[1,2]; Bains, I[2]; Baguelin, M[1,2]; Jit, M[1,2]

[1] Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, United Kingdom

[2] Modelling and Economics Unit, Public Health England, United Kingdom

Publication status: in preparation

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student	Diana Mendes
Principal Supervisor	Mark Jit
Thesis Title	The impact and cost-effectiveness of cervical screening in Portugal

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Gynecological Oncology
Please list the paper's authors in the intended authorship order:	Diana Mendes, Iren Bains, Marc Baguelin, Mark Jit
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The candidate had the idea for this research paper and developed a proposal for funding of this thesis with MJ. The research questions were refined in collaboration with MJ. IB developed the original model that the candidate adapted to this research paper. The candidate liaised with the necessary parties to acquire the data sources used. The candidate

	parameterised and adapted parts of the model to accommodate particularities of the setting analysed in this research paper with MJ's supervision. MB advised on methodology used. The candidate wrote the manuscript and incorporated the comments of MB and MJ.

Student Signature: [redacted] **Date:** 25 June 2018

Supervisor Signature: _____ **Date:** 26 June 2018

5.2.1. Abstract

Background: Portugal is moving towards a nationwide organised HPV-based cervical screening programme. Opportunistic screening is currently still predominant in most parts although organised regional programmes have gradually expanded since 2008. A unified organised programme is likely to reduce the incidence of cervical cancer more effectively; however, the cost-effectiveness of primary HPV- and cytology-based organised cervical screening in Portugal has yet to be evaluated.

Methods: We adapted a static, stochastic, individual-based mathematical model of HPV acquisition and cervical disease progression to Portugal, and calibrated it to type-specific Portuguese HPV prevalence and incidence of cervical cancer. The cost-effectiveness of alternative opportunistic and organised cervical screening strategies, including repeat conventional cytology for triage of ASCUS, liquid-based cytology with HPV DNA triage of ASCUS and LSIL, and primary HPV DNA testing with liquid-based cytology triage of HPV-positive women was compared to no screening. Opportunistic screening was characterised using data on screening attendance from the Portuguese National Health Survey 2005/6. Organised screening in Portugal was assumed to have the same screening participation, frequency, and follow-up of lesions as the organised call-recall programme in England. A partial societal perspective was adopted by including direct medical costs to the National Health Service and paid productivity loss to patients due to cervical cancer.

Results: Primary HPV screening every 5 years may be cost-effective at a willingness-to-pay of just under €18,000 per life-year saved compared to no screening, assuming the unit cost of HPV DNA testing was half of that of liquid-based cytology, followed by organised repeat cytology with an additional cost of €33,210 per life-year saved compared to 5-yearly primary HPV screening. Probabilistic sensitivity analysis revealed substantial uncertainty in our findings with several protocols under organised screening having similar probability of being cost-effective over a willingness-to-pay of €20,000 per life-year saved. Organised repeat conventional cytology is likely optimal over €44,000 per life-year saved given its lower cost in Portugal and assumed similar performance to liquid-based cytology in England, with no screening having the highest probability of being cost-effective below that threshold.

Conclusions: A national HPV-based organised cervical screening programme is likely more effective than cytology-based protocols and may be cost-effective if the screening interval is extended to 5 years. However, the cost-effectiveness of primary HPV screening is highly dependent on the unit cost of HPV DNA testing relative to cytology.

5.2.2. Introduction

Cervical cancer is the second most common cause of cancer mortality in women aged 15-45 in Portugal.[1] Opportunistic cervical screening has been offered as part of the National Health Service (NHS) in Portugal since 1978, but incidence of cervical cancer has remained stable between 1998 and 2010, despite a significant decline in mortality due to cervical cancer since the early 1980s.[2]

Age-period-cohort models[3,4] and time trend analyses[5] have shown a greater decline in the burden of cervical cancer in areas with high-coverage of organised cytological screening than where screening is largely opportunistic. Organised screening can also ensure equity of access, improved screening quality and more effective use of resources[6]. In Portugal, the implementation of regional fully-organised cervical screening programmes began in 2008[7], when human papillomavirus (HPV) vaccination of 13-year-old girls was introduced in the National Immunisation Plan[8].

The Portuguese universal, tax-financed NHS is provided by 5 regional health administrations (RHAs) each responsible for its own population health strategy and direct management of primary care centres, as well as for the implementation of national health programmes and the coordination of the several levels of health care provision[9]. On behalf of the Portuguese Ministry of Health, the Central Administration of the Health System manages the financial and human resources of the Portuguese NHS and is responsible together with the RHAs for contracting with hospitals and private care providers for the NHS patients, including services implied in cervical cancer prevention.

Opportunistic cervical screening in Portugal has relied on private providers to examine smears collected in NHS primary care centres as part of conventional cytological screening and brought in for analysis by patients. The Centre region has offered semi-organised screening since the 1990s. In this region, women are offered conventional cytology in primary care centres opportunistically, but the transportation and examination of conventional cytology samples has been part of the RHA contract with the regional central public hospital. In other regions of the country, opportunistic conventional cytological screening coexists alongside fully organised programmes where women are offered liquid-based cytology and HPV testing is used to triage equivocal cytological results. These organised regional programmes include a call-recall invitation system and the transportation and examination of smears are part of the contract with the regional central public hospitals.

National price lists for institutions and services integrated in the Portuguese NHS are based on diagnosis-related groups (DRGs) and include the unit costs of services charged to subsystems

and private insurers[10] or paid to private care providers assisting the NHS by the Central Administration of the Health System[11]. In 2018, the unit cost for all screening, diagnosis, and treatment activities to support RHAs on cervical cancer prevention became uniform nationally as part of contracts with public hospitals[12,13].

Since 2008, the geographical coverage of existing regional organised cervical screening programmes has increased, with the aim of ultimately attaining a centrally coordinated nationwide single screening strategy[7]. The implementation of primary HPV screening has recently been endorsed by the Portuguese Ministry of Health and HPV 16/18 genotyping with cytology triage of women positive to other HPV types is being piloted in the North region of Portugal since September 2017[7,12].

Other countries where HPV vaccination has also been implemented are evaluating possible HPV-based screening protocols[14]. HPV DNA testing has shown to be more sensitive to high-grade precancerous lesions than cytology while enabling the safe extension of the screening interval to at least 5 years[15]. This objective automated test is also more reproducible, reliable, and likely more robust to the anticipated impact of vaccination on HPV prevalence and cervical lesions than cytology, offering as well the compatibility with self-sampling[16]. Primary HPV screening may result in unnecessary referral for colposcopy though, if adequate triage is not conducted, given its lower specificity to high-grade cervical intraepithelial neoplasia than cytology. The variety of triage algorithms of HPV-positive women recommended for or applied in different countries reflects the uncertainty in identifying the optimal approach for risk stratification.

Mathematical models have been helpful in making projections to assist decision making based on epidemiological and economic evidence concerning alternative screening technologies and algorithms [17]. These models have been used to predict the lifetime health benefits and costs associated with different screening protocols and assess the effectiveness and cost-effectiveness of different options, in vaccinated and unvaccinated cohorts[18,19].

In this study, we aimed at estimating the expected health effects and costs of alternative cervical screening strategies in unvaccinated Portuguese women and their relative cost-effectiveness. To our knowledge, this is the first cost-effectiveness analysis of HPV- and cytology-based cervical screening protocols in Portugal.

5.2.3. Methods

We adapted an existing mathematical model (described in Bains and colleagues in the Appendix to this thesis) to simulate HPV acquisition and progression to cervical cancer in Portugal. The model was calibrated to Portuguese HPV prevalence and incidence of cervical cancer (detailed in research paper 3, Chapter 4) and its effectiveness outcomes together with Portuguese cost data were used to project the health and economic outcomes associated with alternative screening protocols presented in this chapter.

We compared the approaches currently available in the Portuguese National Health Service: (i) conventional cytology-based screening, the predominant opportunistic countrywide protocol also currently available in the partly-organised programme of the Centre region, and (ii) organised liquid-based cytology with HPV triage of equivocal cytological results, in place in Alentejo, Algarve, and the North region; with alternative primary HPV DNA testing strategies and no screening. For each strategy, health outcomes (such as the number of deaths due to cervical cancer, life-years lost, and quality-adjusted life years lost due to screening and cervical cancer) and costs (in 2018 euros, €) were projected over the lifetime of the screened women. Incremental cost-effectiveness ratios (ICERs, i.e. additional cost (€) per additional life-year saved) were calculated to evaluate the relative cost-effectiveness of the distinct strategies. We adopted a partial societal perspective and discounted future health and costs annually by 5%, as recommended in Portugal[20]. Indirect costs to cervical cancer patients due to paid productivity loss were included, but other societal costs such as those related to attending screening were not. The robustness of our findings to parameter and scenario uncertainty was investigated in sensitivity analysis.

Model structure

We adapted an existing static, stochastic, individual-based model developed to assist decisions for the National Health Service Cervical Screening Programme in England (described in detail by Bains and colleagues in the Appendix to this thesis). The acquisition and clearance of infection by 8 HPV types - 16, 18, 31, 33, 45, 51, 52, and 58 - were simulated over women's lifetime in monthly steps. The risk of acquisition was modelled as a function of their age, sexual behaviour, the number of infectious men in that cohort of the population, and HPV transmissibility per sexual act. The number of infectious men was constant over the cohort lifetime. The development of HPV type-specific precancerous lesions and cancer was modelled for HPV-positive women depending on the time since acquisition and clearance of the infection. Cervical cancer remained undiagnosed if not detected via screening or clinical symptoms.

Portuguese data were used to parameterise the distinct components of the model, where available. Data from the Portuguese 2007 population-based sexual behaviour and HIV/AIDS survey[21] was used to simulate the behavioural risk of HPV acquisition among Portuguese women. Type-specific HPV clearance and transmissibility rates were among the parameters obtained by calibration to Portuguese age- and type-specific HPV prevalence[22]and cervical cancer incidence[23]. Age-specific cervical cancer survival was derived from data reported by the Portuguese cancer registry of the North region[24], and mortality from other causes from Portuguese life tables (1981-2060)[25].

The performance of the screening tests modelled was implicitly captured by the progression rates to precancerous lesions used in our model. Given the lack of Portuguese data on cytological outcomes, we used the lesions progression rates fitted by Bains and colleagues for England on liquid-based cytology (LBC) and HPV DNA test outcomes, as well as their estimates for the probabilities of the distinct colposcopy outcomes conditional on women's cytological outcome (based on data from NHS CSP England), assuming progression of cervical lesions to be independent of women's country of origin and the same performance for screening and diagnostic tests in both countries. Also, as conventional cytology is the primary test used in Portugal in areas not covered by an organised programme, we assumed conventional cytology and LBC had equivalent performance[26]. The number of treatments performed in each strategy was calculated assuming that all grade 2 or above cervical intraepithelial neoplasia (CIN2+) cases were treated.

Details of the parameterisation and calibration of the model can be found in Chapter 4 of this thesis.

Screening strategies

The characteristics of the strategies modelled for cervical screening of unvaccinated women are summarised on Table 5-1 (tabulated in greater detail in Research paper 3 Table 4-1, Chapter 4). We compared 7 screening protocols to a no screening approach, including the currently prevalent opportunistic conventional cytology-based screening with repeat cytology for triage of ASCUS (strategy 1) and an organised analogous programme (strategy 7).

Liquid-based cytology with HPV triage of low-grade lesions (ASCUS and LSIL) was modelled under (i) opportunistic screening (strategy 2), and (ii) organised screening according to protocols recommended by the Portuguese Society of Gynaecology[27] (strategy 3) and (iii) organised screening according to the English National Health Service Cervical Screening Programme protocol[28] (strategy 6).

An organised programme with primary HPV screening and cytology triage of HPV-positive women was also modelled with a screening interval of 3 and 5 years (strategies 4 and 5, respectively).

Screening attendance under opportunistic screening was characterised based on individual-patient data from the Portuguese National Health Survey 2005/6[25], when screening was exclusively opportunistic in Portugal. For organised screening, we assumed the screening attendance in Portugal would be similar to that of the organised call-recall National Health Service Cervical Screening Programme England[29].

Cost-effectiveness analysis

We conducted a cost-effectiveness analysis based on the guidelines for the economic evaluation of medicines by the Portuguese National Authority of Medicines and Health Products (INFARMED)[21]**.** Table 5-2 below summarises the methods used.

Health outcomes were estimated in terms of number of cervical cancers and deaths, life-years (LY) lost, and quality-adjusted life years (QALY) lost due to screening and cancer. For each screening strategy, the accumulated health outcomes and costs (in 2018 euros, €) were estimated for each simulated individual over her lifetime. Future costs, LY, and QALY losses were discounted at a rate of 5% per year, according to the guidelines[21]**.**

We adopted a partial societal perspective on costs and resource use, including direct costs for the Portuguese National Health Service to provide screening, follow-up, diagnosis, and treatment for precancerous lesions and cervical cancer as well as indirect cost due to cervical cancer patients' productivity loss. Paid productivity costs were calculated by applying the workforce engagement rate among women aged 20 to 64 years and the net monthly average wage reported for women in mainland Portugal[]25] to the number of life-years lost due to cervical cancer. Other direct and indirect costs to social care services, patients, and family, such as out-of-pocket fees and productivity loss due to attending screening, were not included.

The relative cost-effectiveness of the strategies analysed was estimated in terms of incremental cost-effectiveness ratios (ICER). Strategies were ranked by increasing cost and the incremental costs averted, as well as life-years or QALY saved were calculated relative to the immediately less expensive strategy. Strategies that were both less effective and more costly were left out of the analysis as these are dominated by the next more effective strategy. The ICER for the dominant strategies was then estimated and extendedly dominated strategies (with larger ICER than the subsequent more costly strategy) were ruled out as well before the final recalculation of the ICER[30].

Scenario and univariate sensitivity analyses were performed to explore the impact of alternative input data sets and assumptions on our model results. The model stochasticity and the Bayesian method of inferring the transmission parameters inherently enabled estimating the impact of joint parameter uncertainty, also known as probabilistic sensitivity analysis.

Health-related quality of life

We searched PubMed for studies measuring the impact of screening, diagnosis, and treatment of precancerous lesions or cervical cancer on the health-related quality of life (HRQoL) of women attending screening or cervical cancer patients using the EQ-5D. The search terms used were "EQ-5D cervical cancer screening" and "utility scores cervical cancer screening".

No study was found on Portuguese women and only one study in the Netherlands provided utility scores for all health states related to cervical screening derived from data reported directly by women attending screening and cervical cancer patients using the EQ-5D with preference elicited[31]. De Kok and colleagues[31] found no significant association with disutility from screening itself, only from cervical cancer and that post-treatment disutility held for at least 10 years after diagnosis.

Among the studies found, a survey by Simonella and colleagues[32] was conducted specifically to estimate utility scores for primary HPV screening and subsequent triage and management for use in an economic evaluation of primary HPV screening in England by Kitchener and colleagues[33]. Simonella and colleagues[32] measured preferences for hypothetical health states using a two-stage standard gamble in a sample of women from the general population targeted for cervical screening who ranked an HPV-positive result below a low-grade cytological outcome.

We built two scenarios to explore the effect of alternative assumptions on the impact of cervical screening of women's HRQoL on our cost-effectiveness results. In scenario 1, we assigned no disutility to screening events, accounting only for the impact of cervical cancer diagnosis and treatment, and assumed lifetime post-treatment disutility as per de Kok and colleagues[31]. In scenario 2, disutility from screening, colposcopy, and treatment for CIN2+ was incorporated, as well as that from cervical cancer, similarly to the approach taken by Kitchener and colleagues[33] in their economic evaluation of primary HPV screening in England. Women surviving cancer for at least 5 years were assumed to recover to full health in this scenario[33].

Table 5-3 below summarised the utility estimates used as inputs. Disutility for each health state was calculated by subtracting the utility score (drawn from a beta distribution) for that

health state from that of the general population (scenario 1) or from 1 (scenario 2). We assumed utility scores to follow a beta distribution.

The distribution of cervical cancer cases by stage reported for the largest oncology hospital in the North region (2010-2014, Table 5-4) was used to apply stage-specific disutility from cancer, based on the age at which the cancer was diagnosed[34].

Costs and resource use

In our systematic review of model-based studies of cervical screening strategies[18] (Chapter 3), we found one cost-effectiveness analysis of cervical screening in Algarve, Portugal by Novoa-Vazquez[35]. We accounted for similar resource use and used the latest Portuguese NHS price lists[10,11,13], assuming that these prices are a reasonable approximation of the opportunity cost of health-care resources in Portugal; however, list prices may not capture the actual underlying cost of resources.

Similarly to Novoa-Vazquez[35], we added the cost of sampling to the laboratory examination cost of each primary screening test (conventional cytology, liquid-based cytology, or HPV DNA testing) and the cost of a gynaecological visit to each colposcopy. The sampling cost for liquid-based cytology was also used for HPV DNA testing.

The unit cost of conventional cytology varied per strategy. For strategy 1, it included the examination cost (€5.42) paid by the Portuguese NHS to private providers and the patient's co-payment (€3.00)[11] used for the opportunistic screening currently in place throughout the country, whereas in strategy 7, representing an organised programme based on repeat conventional cytology (resembling that in place in the Centre region), the unit cost of conventional cytology consisted of the examination cost (€15.20) charged to the Portuguese NHS subsystems[10]. These are list prices for the Portuguese NHS. They are assumed to be a reasonable approximation of the opportunity cost of cytology in Portugal.

We also assumed that 35% of colposcopies involved biopsy[35], that all CIN2+ lesions were treated by conisation [27,35], and 97% compliance with treatment referral as per data from the organised cervical screening programme in Alentejo (2011-2013)[RHA, personal communication].

The unit cost for an HPV DNA test without genotyping is not catalogued in the Portuguese national price lists[10]; however, the unit cost of HPV DNA genotyping is listed as €64.40. In England, the unit cost of an HPV DNA test is approximately half of that for liquid-based cytology[33]. The relatively high cost of HPV DNA testing in Portugal is likely due to it depending on in house specialist technology; hence we assumed that as part of an organised programme with the subsequent economies of scale, the cost ratio seen in England would

apply to Portugal. This assumption was varied in a scenario where HPV DNA was assumed to cost the same as liquid-based cytology.

A scenario analysis was also conducted to reflect the recent NHS national contract with public hospitals to support RHAs on screening activities (2018)[13] by using the unit cost of €67.50 for the examination of any cervical screening sample (applicable to primary cytology or HPV test and subsequent triage test) by public hospitals.

The unit costs and resource use applied in our model are presented on Table 5-5 below and were assumed lognormally distributed in our model.

5.2.4. Results

Cancer cases and life-years lost

Table 5-6 presents the predicted annual number of cervical cancer cases, deaths, and years of life lost, as well as the total annual number of tests and cost (differentiating screening, treatment, and productivity cost) for each simulated strategy.

Organised programmes based on cytology or HPV DNA testing (strategies 3-7), which are likely to achieve higher coverage and improved follow-up of women with positive screening results, prevented more cancer cases and saved more life years than protocols in opportunistic screening (strategies 1 and 2), and no screening yielded the greatest health loss. Protocols under organised 3-yearly screening would have over 70% and 20% of their annual cost due to screening activities and productivity losses due to cancer deaths, respectively, whilst nearly 50% of the annual cost of opportunistic repeat cytology screening is predicted to be due to productivity loss.

On average, primary HPV screening every 3 years (strategy 4) was the most effective protocol in preventing more cancer cases and subsequent cancer-related deaths and life-years saved; however, its effectiveness is not significantly different from the other HPV- and cytology-based protocols under organised screening (strategies 3,5,6,and 7).

Primary HPV screening every 5 years (strategy 5) was as effective as protocols based on 3-year screening intervals, reducing cancer incidence by nearly twice as much than opportunistic repeat cytology (strategy 1) relative to no screening, and was the strategy involving the fewest tests (on average), similar to those under opportunistic screening (strategies 1 and 2).

Cost-effectiveness analysis

Opportunistic repeat cytology was the least expensive protocol, in terms of discounted lifetime cost per woman, as the sampling and examination cost of conventional cytology (€7.50 and €5.42 plus €3.00 user charge, respectively) is about half of that for liquid-based cytology or HPV DNA testing (€15.00 and €15.20, respectively), in the Portuguese national price list[10]. The cheaper sampling cost of conventional cytology also contributed to organised conventional-cytology based screening (strategy 7, with sampling and examination cost of €7.50 and €15.20, respectively) being similarly expensive to opportunistic HPV triage (strategy 2, with liquid-based cytology sampling and examination cost of €15.00 and €27.40, respectively), despite being the strategy requiring the most testing.

The incremental cost-effectiveness results (Table 5-7) show primary HPV screening every 5 years (strategy 5) to be cost-effective at a willingness-to-pay of €17,701 per life-years saved,

compared to no screening. Organised repeat conventional cytology and 3-yearly primary HPV screening (strategies 7 and 4) would follow as cost-effective at €36,822 and €91,979 per life-years saved, respectively.

Opportunistic HPV triage (strategy 2) was dominated by organised repeat cytology (strategy 7). Organised HPV triage according to either English or Portuguese guidelines (strategies 3 and 6) was dominated by strategy 4. Opportunistic repeat conventional cytology (strategies 1) was extendedly dominated (more costly per life-year saved than the next more efficient strategy) by strategy 5, leaving no screening, 5-yearly primary HPV testing, organised repeat cytology, and 3-yearly primary HPV screening on the efficiency frontier of the cost-effectiveness plane (Figure 5-1A).

The results of the probabilistic analysis are presented on Figure 5-1C, where each cost-effectiveness acceptability curve (CEAC) represents the probability of each protocol or no screening being cost-effective over a range of values of willingness-to-pay. The cost-effectiveness acceptability frontier is also shown on top of the CEACs identifying the optimal option (in terms of having the highest expected net benefit) at a given willingness-to-pay. Despite not having the highest probability of being cost-effective at €18,000 to €36,000 per life-year saved, primary HPV testing every 5 years was the optimal strategy within that range of willingness-to-pay with 21% probability of being the most cost-effective option. For thresholds between €36,000 and €91,000 per life-year saved, organised repeat cytology becomes optimal and over €44,000 per life-year saved it is also the option with highest probability of being cost-effective (21-22%).

HRQoL scenarios

Under HRQoL scenario 1, assuming disutility only from cervical cancer, strategy 3 (organised HPV triage as per Portuguese guidelines) joins the efficiency frontier as the most efficient and most costly protocol compared to those in our base case analysis, with organised HPV screening every 5 years and repeat cytology being cost-effective at a slightly lower willingness-to-pay of €17,081 and €24,123 per QALY saved, respectively, compared to no screening (Figure 5-2A)**.** The cost-effectiveness acceptability curves for this scenario **(**Figure 5-2C**)** show a similar pattern to that of our base case analysis, with 5-yearly primary HPV screening being optimal at thresholds between €18,000 and €24,000 per QALY saved and 21% probability of being cost-effective, while organised screening with repeat cytology for triage of ASCUS lesions (strategy 7) became optimal at a lower threshold (€25,000 per QALY saved) having the highest probability of being cost-effective (23-25%) from €39,000 to €92,000 per QALY saved.

In a scenario where substantial disutility from screening was assumed, as with the study by Kitchener and colleagues[33] (HRQoL scenario 2), the most effective and least expensive strategy was no screening (Figure 5-3A), dominating all screening strategies which would yield greater QALY loss. Among protocols under organised screening, 5-yearly primary HPV testing had the least QALY loss, as it yielded fewer testing. Table 5-8 provides the detailed incremental cost-utility analysis for both scenarios.

2018 Contract cost scenario

Under the scenario of a fixed uniform unit cost per screening test (including subsequent triage) analysed by laboratories in public hospitals, opportunistic screening with repeat conventional cytology (Strategy 1) becomes part of the cost-effectiveness frontier with the lowest ICER of €30,052 per life-year saved compared to no screening (Figure 5-4A), given the absence of an alternative cheaper organised screening strategy, for instance entailing less frequent screening. The ICER of primary HPV screening every 5 or 3 years increased to €44,989 and €134,211 per life-year saved compared to strategy 1 and strategy 5, respectively (Table 5-9). Figure 5-4C shows that 5-yearly HPV screening would be optimal over a willingness-to-pay of €45,000 per life-year saved with 15% probability of being cost-effective.

5.2.5. Discussion

Our findings suggest that primary HPV screening every 5 years may be cost-effective compared to no screening with similar cost as opportunistic screening, provided that the unit cost of HPV DNA test is sufficiently lower than liquid-based cytology, for instance half as much as is reported in England (in our base case analysis). The transition to a countrywide HPV- or cytology-based organised cervical screening programme is likely more effective in cancer prevention than opportunistic screening, and the total annual cost of 5-yearly primary HPV screening is comparable to that of opportunistic repeat cytology screening. Organised programmes with primary liquid-based cytology and HPV triage of ASCUS and LSIL were on average more costly and less effective preventing cancers than primary HPV testing every 3 years.

These results are compatible with those from both modelling studies and trial-based economic evaluations in unvaccinated women in other European settings. Primary HPV screening has proven more effective than cytology-based screening in cervical cancer prevention in 4 large European randomised controlled trials, independently of the diverse protocols used[15]. Other model-based economic evaluations of primary HPV testing have also found it cost-effective (in the Netherlands using Population-Based SCreening study Amsterdam (POBASCAM) trial data[36]), or dominant (cost-saving and more effective, as in our base case analysis based on

average discounted cost per life-year saved) compared to HPV triage in countries such as England (using data from the A Randomised Trial In Screening To Improve Cytology (ARTISTIC) trial[33]), France [37], Italy[38], and Norway[39]. The cost-effectiveness of repeat cytology strategies in a low cytology cost European scenario was also reported in the model-based study by de Kok and colleagues[40], who also pointed out the importance of organising primary HPV screening so that the examination costs of HPV testing are minimised, such as having most tests concentrated in a few large laboratories.

Our probabilistic sensitivity analysis indicated substantial joint parameter uncertainty with primary HPV screening every 5 years being the optimal option between €18,000 and €36,000 per life-year saved with a probability of being cost-effective of only 21-22% at that range of willingness-to-pay. This is likely driven by the similar effectiveness predicted for protocols under organised screening and the relative cost of the technologies involved. For instance, the unit cost of sampling for primary HPV testing (assumed the same as for liquid-based cytology in our base case) is twice as much as that for conventional cytology in the Portuguese NHS, which is predicted similarly effective as primary HPV testing every 3 years (on average prevented slightly more cancers). Our assumption that the performance of conventional cytology in Portugal is the same as that of automated liquid-based cytology in England is likely overestimating the effectiveness of organised repeat cytology screening.

Our scenario of a uniform unit cost per examination of screening test (regardless of technology used and associated triage) in public hospitals for organised programmes suggests that primary HPV screening every 5 years would be cost-effective at a willingness-to-pay of €45,000 per life-years saved compared to opportunistic repeat conventional cytology, albeit with a high uncertainty around this decision, mainly due to the examination cost of conventional cytology in opportunistic screening being about 1/8 of its cost in an organised programme. It is of note that cheaper alternative organised screening strategies that could dominate opportunistic repeat conventional cytology in this scenario, e.g. every 8 years, have not been analysed.

We used Bains and colleagues' distributions for disease progression and test performance (given the lack of data on cytology and colposcopy outcomes in Portuguese women), assuming the quality of these subjective tests to be the same under opportunistic and organised screening in Portugal as in organised screening in England; however, Ronco and colleagues[41] found evidence of the variation in cytology performance between countries (generally better where cytology-based screening has been organised for longer). Hence, we are likely overestimating the performance of opportunistic cytology in Portugal and have not accounted for costs associated with quality assurance that are essential to well organised programmes

nor eventual economies of scale due to centralisation of testing in major hospital laboratories for instance.

Given the uncertainty on the impact of cervical screening on women's HRQoL and this being a strong determinant of the cost-effectiveness of screening strategies[31,33], our base case analysis was founded on life-years saved as primary effectiveness outcome. Primary HPV screening every 5 and 3 years became slightly more cost-effective in the HRQoL scenario 1 (as de Kok and colleagues[31] found no disutility from screening, only from cervical cancer). In HRQoL scenario 2 (derived from Kitchener and colleagues[33]), disutility from a screening-positive result is just slightly less detrimental than that from colposcopy and treatment for CIN2+. Hence, greater disutility was yield from screening intensive strategies and no screening ended up dominating all screening protocols. While screening was found to impose significant disutility by Simonella and colleagues[32] who elicited preferences in women in the general population targeted for screening but not actually experiencing it, de Kok and colleagues[31] found no significant evidence of screening disutility in women attending screening and actually experiencing the screening-related health states. This difference can be explained by the disability paradox as patients tend to report better quality-of-life than healthy people asked to imagine those health states[42].Also, INFARMED's guidelines[20] recommend patients' valuations for the measurement of HRQoL and the general public as source of preference data for weighting changes in health-related quality of life, as done by de Kok and colleagues[31]. Hence, we think HRQoL scenario 1 is likely to better reflect national guidelines on capturing the impact of screening and cervical cancer on patients' quality of life than scenario 2 where the negative impact of screening was assumed to outweigh its benefit. However, we also find important to note that the impact of screening might not be appropriately captured by generic measures of HRQoL as the EQ-5D, given that it has been found significant in studies measuring condition-specific effects like anxiety and worry[43].

Despite having adopted a partial societal perspective for cost-effectiveness analyses, including productivity loss due to cervical cancer deaths in women participating in the labour market aged 20-64 years, it is important to note that direct social care costs and direct patients costs such as user charges were not included in our analysis. Also not included were indirect costs, such as patients' paid productivity loss due to attending screening, patients' unpaid productivity loss, or carers' productivity loss, nor were costs related to the implementation of a fully-organised nationwide programme.

The use of a stochastic model facilitates capturing the joint uncertainty of the parameter values used. However, we used a fixed value for some parameters in our model and the uncertainty in those estimates was not accounted for. Using other distributions for these

parameters or and performing univariate sensitivity analysis on these to investigate the impact of changes to these values on our model results may help to fully capture the parametric uncertainty in these values.

Necessary further work, particularly pertinent to support the transition to a successful well-organised countrywide programme, includes evaluating the cost-effectiveness of primary HPV screening with HPV 16/18 genotyping, currently being piloted in the North region,[7]as per the latest recommendation of the Portuguese Ministry of Health[12]. With the increasing number of vaccinated women, HPV genotyping is likely a useful tool to monitor HPV 16/18 prevalence among unvaccinated women and mathematical models can be used to help identify safe and cost-effective screening protocols[44].

5.2.6. Acknowledgements

We are grateful to Fernando Tavares at the Regional Health Administration of the North region, Portugal for the helpful advice on cervical screening programmes. DM was funded by the Foundation for Science and Technology (individual PhD studentship SFRH/BD/84974/2012) on behalf of the Portuguese Ministry of Education and Science and the Human Potential Operational Programme of the National Strategic Reference Framework, within the European Social Fund of the European Commission's 7th Framework Programme.

5.2.7. References

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5.2.8. Tables

Table 5-1. Summary of characteristics of cervical screening strategies modelled

	No screening	Strategy 1	Strategy 2	Strategy 7	Strategy 3	Strategy 6	Strategy 4	Strategy 5
Organisation of screening	n.a.	Opportunistic	Opportunistic	Organised	Organised	Organised	Organised	Organised
Primary test	n.a.	Cytology	Cytology	Cytology	Cytology	Cytology	HPV DNA	HPV DNA
Triage test	n.a.	Repeat cytology	HPV DNA	Repeat cytology	HPV DNA	HPV DNA	Cytology	Cytology
Screening frequency $^{\theta}$, median, mean (IQR) years	n.a.	2, 5.2 (1, 6)$^{\alpha}$	2, 5.2 (1, 6)$^{\alpha}$	2.1, 3 (1, 3.4)$^{\beta}$	2.1, 3 (1, 3.4)$^{\beta}$	2.1, 3 (1, 3.4)$^{\beta}$	2.1, 3 (1, 3.4)$^{\beta}$	4, 4.7 (2.3, 6.3)
Age at first screen, median, mean (IQR) years	n.a.	33.00, 32.37 (28.88, 36.67)$^{\alpha}$	33.00, 32.37 (28.88, 36.67)$^{\alpha}$	26.12, 28.09 (25.18, 28.29)$^{\beta}$	26.12, 28.09 (25.18, 28.29)$^{\beta}$	26.12, 28.09 (25.18, 28.29)$^{\beta}$	26.12, 28.09 (25.18, 28.29)$^{\beta}$	26.12, 28.09 (25.18, 28.29)$^{\beta}$
Probability of loss to follow-up of cytological abnormality or treatment	n.a.	0.5		0.2				
Probability of complying with colposcopy/ treatment referral	n.a.	0.75/ 0.97		0.88/ 0.97				

Note: Recommended screening ages and interval by the Portuguese Society of Gynaecologists: 20-64 every 3 years (opportunistic cytology-based strategies), 25-64 every 3 years (organised cytology-based strategies), 30-64 every 5 years (organised HPV-based strategies alongside cytology every 3 years for women aged 25-29)[27]; n.a., not applicable; $^{\alpha}$ derived from PTNHS2005/6; $^{\beta}$ derived from the English cervical cancer screening programme (assuming same frequency for all strategies under organised screening); $^{\theta}$ Screening frequency in England was based on cross-sectional data on time since last screen, rather than actual screen interval data. Consequently, the organised screening strategies modelled have a shorter median interval than that expected (for 3-yearly strategies, 2.1 years versus 3 years, respectively), being effectively simulations of 2-yearly and 4-yearly organised screening strategies. This error – to be corrected in subsequent publication - has affected the costs and health outcomes predicted for each strategy and the results of the cost-effectiveness analysis.

Table 5-2. Summary of the methods used

Element of economic evaluation	Description
Perspective on outcomes	All direct health effects on patients were included
Perspective on costs	As per INFARMED's recommendation, we adopted a partial societal perspective on costs, including the direct costs of providing health care for the National Health Service and the indirect costs of productivity loss by women due to cervical cancer
Type of economic evaluation	Cost-effectiveness and cost-utility analyses with fully incremental analysis
Time horizon	Lifetime
Comparator(s)	We compared alternative screening strategies, including that in place in Portugal before the introduction of regional organised programmes, with no screening.
Synthesis of evidence on health effects	We used the best evidence available on the clinical effectiveness or utility found for each alternative strategy and respective technologies
Measuring and valuing health effects	We estimated health outcomes in life-years (LY) saved and quality-adjusted life years (QALY) saved. The estimates used in both health-related quality of life scenarios were obtained with a validated and standardised HRQoL instrument - the EQ-5D.
Source of data for measurement of health-related quality of life (HRQoL)	We used estimates derived from data reported directly by women undergoing cervical screening and cervical cancer patients in the Netherlands[32], as well as data reported directly by women from the general population (a sample of women targeted for screening living in Sydney, Australia[33])
Source of preference data for valuation of changes in health-related quality of life	Estimates derived from preference data elicited by a representative sample of the Portuguese population were not available; the estimates used in the HRQoL scenarios 1 and 2 were derived from data elicited by a sample of the UK and Australian population, respectively.
Evidence on resource use and costs	Unit costs for the Portuguese National Health Service (NHS) were used
Discounting	The same annual rate of 5% was applied to both future costs and health effects as recommended for base case analysis by INFARMED
Currency	Euros (€)
Economic analysis outcomes	An incremental analysis was conducted to compare mutually exclusive strategies and assess their relative cost-effectiveness in terms of incremental cost-effectiveness ratios (ICER).
Characterisation of uncertainty	Scenario and probabilistic sensitivity analysis were conducted to assess the most relevant types of uncertainty.

Table 5-3. Health–state utility scores

Health state	Utility score, mean (SE)	Source
Scenario 1		
General population	0.86 (0.02)	De Kok 2018[31]
Cancer Stage 1	0.79 (0.06)	
Cancer Stage 2+	0.72 (0.17)	
Post-treatment cancer (any stage)	0.82 (0.03)	
Scenario 2		
Cytology normal / HPV-	0.9967 (0.0026)	Simonella 2014* [32]
LG cytology	0.9735 (0.0231)	
HPV+ with cytology normal	0.9733 (0.0233)	
LG/HG cytology/ HPV+ with colposcopy normal or CIN1	0.9724 (0.0226)	
LG/HG cytology/ HPV+ with CIN2 or 3	0.9704 (0.0233)	
Pre-treatment cervical cancer**	0.8178 (0.0531)	
Cancer (<5 years after diagnosis) Stage 1	0.76 (nr)	Elbasha 2007*[45]
Stage 2	0.67 (nr)	
Stage 3	0.56 (nr)	Goldie 2004*[46]
Stage 4	0.48 (nr)	
Cancer survivor (≥5years after diagnosis)	1 (nr)	De Kok 2012*[47]

*as used by Kitchener et al[33]; **for all stages assumed the same as early stage cervical cancer reported by Simonella et al; nr, not reported -standard error assumed to be 10% of the mean

Table 5-4. Cervical cancer cases distribution by stage and age group [IPO Porto][34]

FIGO stage	<30	30-49	50-69	70+
I	8	95	71	16
II	1	75	93	35
III	3	40	48	47
IV	0	15	25	29

FIGO, International Federation of Gynecology and Obstetrics

Table 5-5. Selected model inputs

Epidemiological parameter	**Mean**	**Sources**
General population life expectancy, years	83.3	Statistics Portugal (2014-2016)
Unit costs (€) and resource use	**Base case value***	**Sources**
Screening		
Sampling for conventional cytology (onto glass slide)	7.50	DRG 48910 Portaria 207/2017[10]
Sampling for liquid-based cytology (for "thin-prep")	15.00	DRG 48900 Portaria 207/2017[10]
Examination of conventional cytology sample by private provider	5.42	DRG 30510[11]
Patient co-payment for examination of conventional cytology sample by private provider	3.00	DRG 30510[11]
Examination of conventional cytology sample	15.20	DRG 30510 Portaria 207/2017[10]
Automated examination of liquid-based cytology sample	27.40	DRG 30650 Portaria 207/2017[10]
Automated examination of high-risk HPV DNA testing	13.70	not listed; base case assumed half of LBC cost
Examination of any cervical screening sample including triage test when applicable	67.5	NHS Contractualisation Reference terms (2018)[13]
Diagnosis		
Colposcopy	14.50	DRG 48180 Portaria 207/2017[10]
Colposcopy with biopsy	34.40	DRG 48190 Portaria 207/2017[10]
Treatment		
Conisation$^{\alpha}$	2,285	DRG 532 Portaria 207/2017[10]
Invasive cervical cancer (first year)	12,023.00	NHS Contractualisation Reference terms (2018)[13]
Invasive cervical cancer (second year)	3,551.00	NHS Contractualisation Reference terms (2018)[13]
Consultation costs		
Medical visit	34.1	Portaria 207/2017[10]
Activity rate, women 20-64 years	0.758	Statistics Portugal (2016)[25]
Net monthly average wage, women	805	Statistics Portugal (2018)[25]
Discount rate, %	5	INFARMED[20]

* unit costs were assumed lognormally distributed with a scale=0.1; No inflation-related adjustment was necessary as all the above costs are 2018 prices.

$^{\alpha}$ The cost used for conisation corresponds to that listed for the average Portuguese NHS patient treated for diagnosis-related group 532 - Disturbances of the female reproductive system, which includes cervical conisation[10]. List prices are assumed a reasonable approximation but may not entirely capture the underlying opportunity cost of resources.

Table 5-6. Predicted annual number of cervical cancer cases, cancer-related deaths and life-years lost, and total number of tests and cost with and without cancer treatment by screening strategy

Strategy	Total annual cancer cases	Total annual cancer deaths	Total life-years lost	Total annual tests, thousands	Total annual screening cost (euros, million)	Total annual treatment cost (euros, million)	Total annual productivity cost (euros, million)	Total annual cost (euros, million)
No Screening	634 (309; 999)	167 (72; 278)	4400 (2200; 7000)	-	0 (0; 0)	9.9 (4.5; 16.2)	32.7 (15.5; 53.5)	42.6 (20.4; 69.7)
S1 (OPP Repeat Cytology)	425 (328; 566)	101 (72; 141)	3100 (2400; 4300)	676 (664; 689)	16.7 (14.4; 19.6)	6.6 (4.6; 9.3)	22.9 (15.9; 32.9)	46.3 (37.3; 58.5)
S2 (OPP HPV triage)	413 (322; 553)	98 (69; 132)	3000 (2300; 4100)	700 (685; 715)	34.8 (29.6; 40.5)	6.5 (4.6; 9.2)	22.4 (15.9; 32.1)	63.6 (53.5; 77.1)
S5 (ORG HPV primary 5y)	234 (167; 337)	52 (33; 79)	1800 (1200; 2700)	637 (631; 642)	29.8 (26.0; 34.4)	3.7 (2.4; 5.4)	13.0 (8.5; 20.3)	46.5 (39.4; 56.3)
S6 (ORG HPV triage ENG algorithm)	213 (153; 308)	47 (28; 72)	1600 (1100; 2400)	965 (955; 976)	50.6 (43.4; 58.9)	3.4 (2.2; 5.0)	11.7 (7.6; 18.4)	65.7 (56.3; 76.8)
S7 (ORG Repeat Cytology)	210 (144; 308)	47 (27; 71)	1600 (1100; 2400)	1043 (1024; 1062)	36.5 (30.7; 43.2)	3.3 (2.1; 5.1)	11.7 (7.3; 18.4)	51.5 (43.4; 61.8)
S3 (ORG HPV triage PT algorithm)	199 (141; 297)	44 (26; 68)	1500 (1000; 2400)	1019 (1002; 1040)	54.2 (46.3; 62.7)	3.1 (2.1; 4.8)	11.1 (7.1; 17.9)	68.4 (59.0; 79.1)
S4 (ORG HPV primary 3y)	197 (139; 287)	43 (26; 66)	1500 (1000; 2300)	965 (957; 974)	41.5 (36.0; 47.1)	3.1 (2.0; 4.7)	11.0 (7.1; 17.2)	55.5 (47.9; 65.1)

Note: The predicted annual number of screening tests, treatments, and cervical cancer cases was calculated using the age distribution for the 2016 Portuguese female population aged 15-89[25]

Table 5-7. Incremental cost-effectiveness results

Strategy	Discounted lifetime LY lost per woman	Discounted lifetime cost per woman (euros)	Incremental LYs saved	Incremental Cost, €	ICER (€/LY gained)
No Screening	0.010107	95.083659	-	-	-
S1 (OPP Repeat Cytology)	0.008669	138.082697	0.001438	42.999038	Dominated
S5 (ORG HPV primary 5y)	0.005626	174.405110	0.003044	36.322413	17,701
S7 (ORG Repeat Cytology)	0.005170	191.202782	0.000456	16.797671	36,822
S2 (OPP HPV triage)	0.008510	192.025791	-0.003340	0.823009	Dominated
S4 (ORG HPV primary 3y)	0.004979	208.765954	0.003531	16.740163	91,979
S6 (ORG HPV triage ENG algorithm)	0.005215	234.270417	-0.000236	25.504464	Dominated
S3 (ORG HPV triage PT algorithm)	0.005031	249.173233	0.000184	14.902816	Dominated

LY, life years; ICER, incremental cost-effectiveness ratio; incremental cost and LY saved calculated relative to the immediately less expensive strategy; OPP, opportunistic screening; ORG, organised screening

Table 5-8. Incremental cost-utility results

Strategy	Discounted lifetime QALY lost per woman	Discounted lifetime cost per woman (euros)	Incremental QALYs saved	Incremental Cost, €	ICER (€/QALY gained)
HRQoL scenario 1					
No Screening	0.011014	94.754033	-	-	-
S1 (OPP Repeat Cytology)	0.009758	137.87197	0.001256	43.117937	Dominated
S5 (ORG HPV primary 5y)	0.006349	174.429877	0.003409	36.557907	17,081
S7 (ORG Repeat Cytology)	0.005672	190.778158	0.000677	16.348281	24,123
S2 (OPP HPV triage)	0.009658	191.826097	-0.003986	1.047939	Dominated
S4 (ORG HPV primary 3y)	0.005545	208.764662	0.004113	16.938565	141,692
S6 (ORG HPV triage ENG algorithm)	0.005669	234.906234	-0.000124	26.141572	Dominated
S3 (ORG HPV triage PT algorithm)	0.005474	248.487972	0.000195	13.581738	565,806
HRQoL scenario 2					
No Screening	0.01278	95.083659	-	-	-
S1 (OPP Repeat Cytology)	0.021024	138.082697	-0.008245	42.999038	Dominated
S5 (ORG HPV primary 5y)	0.01805	174.40511	0.002974	36.322413	Dominated
S7 (ORG Repeat Cytology)	0.025331	191.202782	-0.007281	16.797671	Dominated
S2 (OPP HPV triage)	0.021819	192.025791	0.003512	0.823009	Dominated
S4 (ORG HPV primary 3y)	0.021701	208.765954	0.000118	16.740163	Dominated
S6 (ORG HPV triage ENG algorithm)	0.022221	234.270417	-0.00052	25.504464	Dominated
S3 (ORG HPV triage PT algorithm)	0.026315	249.173233	-0.004095	14.902816	Dominated

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; incremental cost and LY saved calculated relative to the immediately less expensive strategy; OPP, opportunistic screening; ORG, organised screening

Table 5-9. Incremental cost-effectiveness results for 2018 fixed uniform unit cost scenario

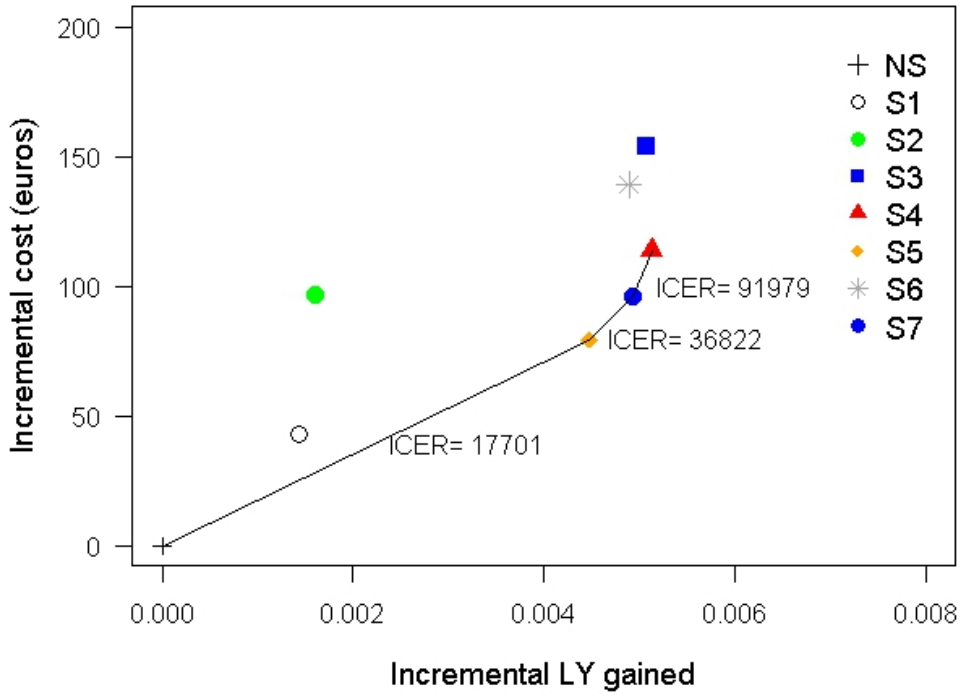
Strategy	Discounted lifetime LY lost per woman	Discounted lifetime cost per woman (euros)	Incremental LYs saved	Incremental Cost, €	ICER (€/LY gained)
No Screening	0.010107	95.031387	-	-	-
S1 (OPP Repeat Cytology)	0.008669	138.235300	0.001438	43.203913	30,052
S2 (OPP HPV triage)	0.008510	265.761499	0.000160	127.526198	Dominated
S5 (ORG HPV primary 5y)	0.005626	275.164990	0.002884	9.403491	44,989
S6 (ORG HPV triage ENG algorithm)	0.005215	347.435703	0.000411	72.270713	Dominated
S7 (ORG Repeat Cytology)	0.005170	359.198447	0.000045	11.762744	Dominated
S3 (ORG HPV triage PT algorithm)	0.005031	361.229121	0.000139	2.030674	Dominated
S4 (ORG HPV primary 3y)	0.004979	362.017520	0.000052	0.788399	134,211

LY, life years; ICER, incremental cost-effectiveness ratio; incremental cost and LY saved calculated relative to the immediately less expensive strategy; OPP, opportunistic screening; ORG, organised screening

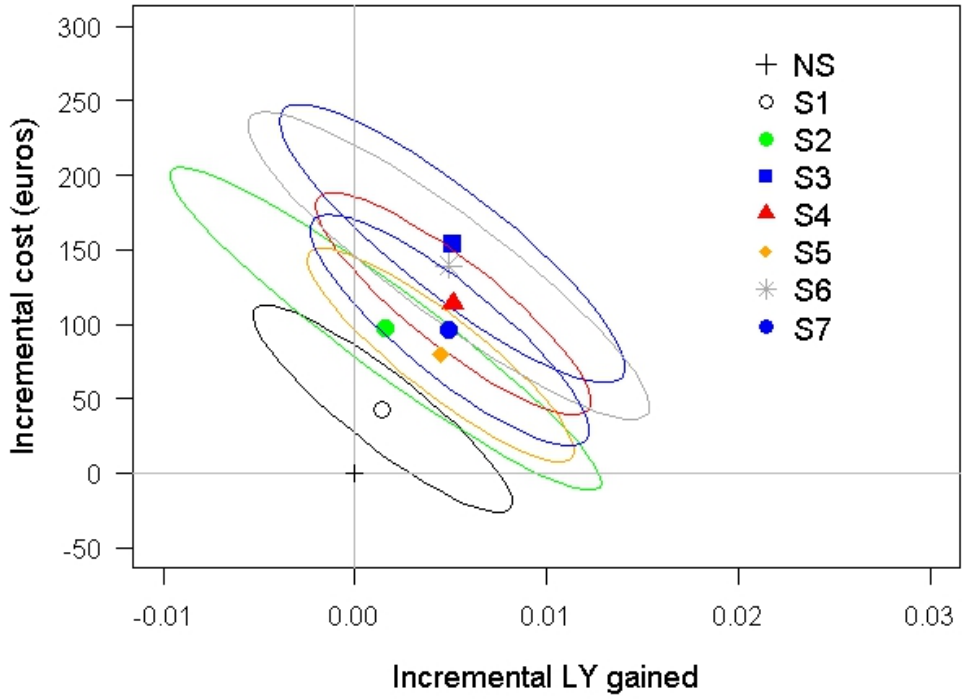
5.2.9. Figures

Figure 5-1. Cost-effectiveness plane (A) and 95%confidence ellipses (B), cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier (C) – base case analysis

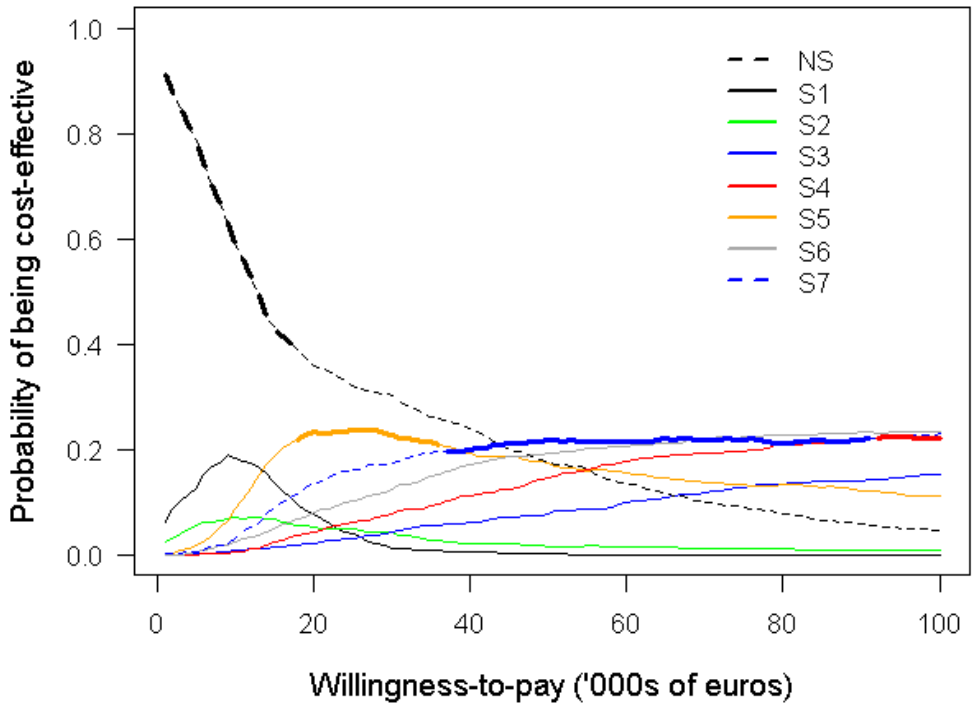
A


Incremental cost (euros)
200
150
100
50
0
0.000
0.002
0.004
0.006
0.008
Incremental LY gained
NS
S1
S2
S3
S4
S5
S6
S7
ICER= 91979
ICER= 36822
ICER= 17701

B


Incremental cost (euros)
300
250
200
150
100
50
0
-50
-0.01
0.00
0.01
0.02
0.03
Incremental LY gained
NS
S1
S2
S3
S4
S5
S6
S7

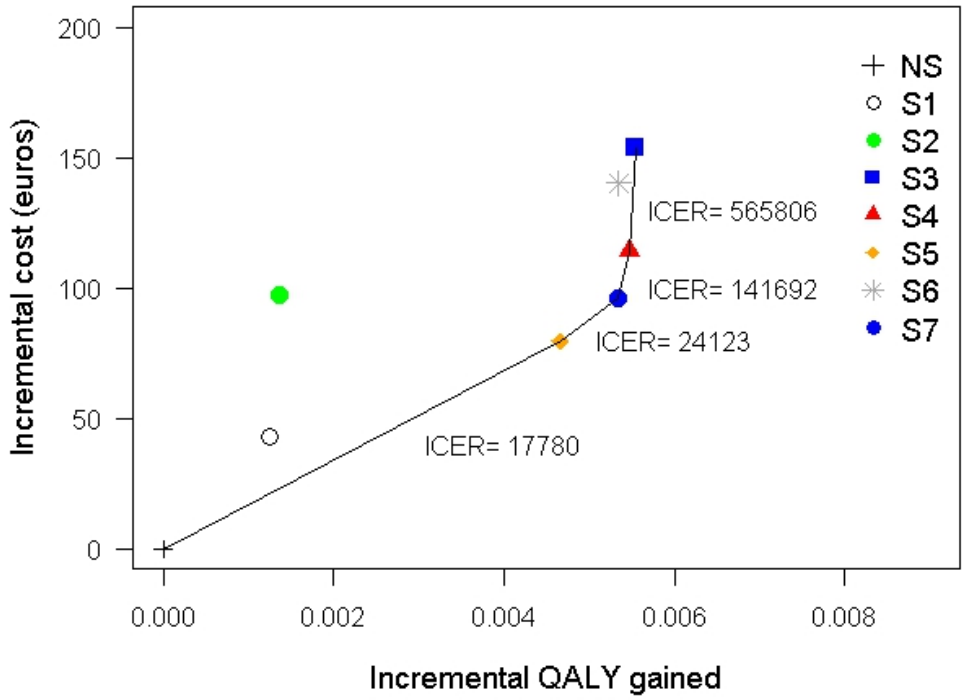
c



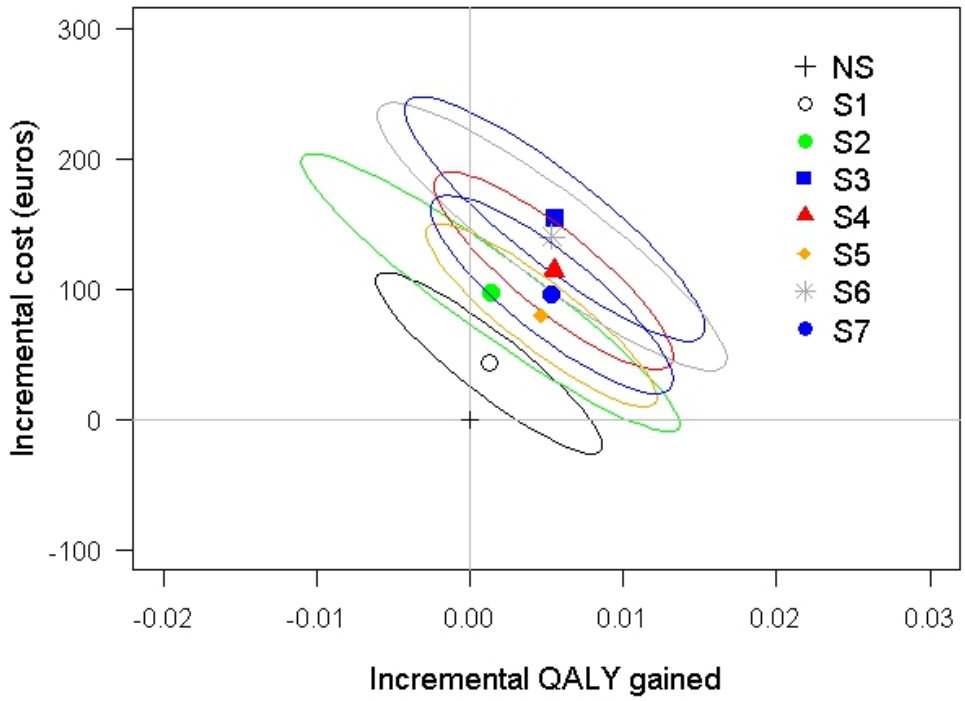
LY, life years; ICER, incremental cost-effectiveness ratio; Cost-effectiveness acceptability curves (CEACs) are shown in thin lines for no screening (NS) and the distinct screening protocols modelled; The cost-effectiveness acceptability frontier (CEAF) is presented in thicker line segments on top of the corresponding CEAC.

Figure 5-2. Cost-effectiveness plane (A) and 95% confidence ellipses (B), cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier (C) – HRQoL scenario 1

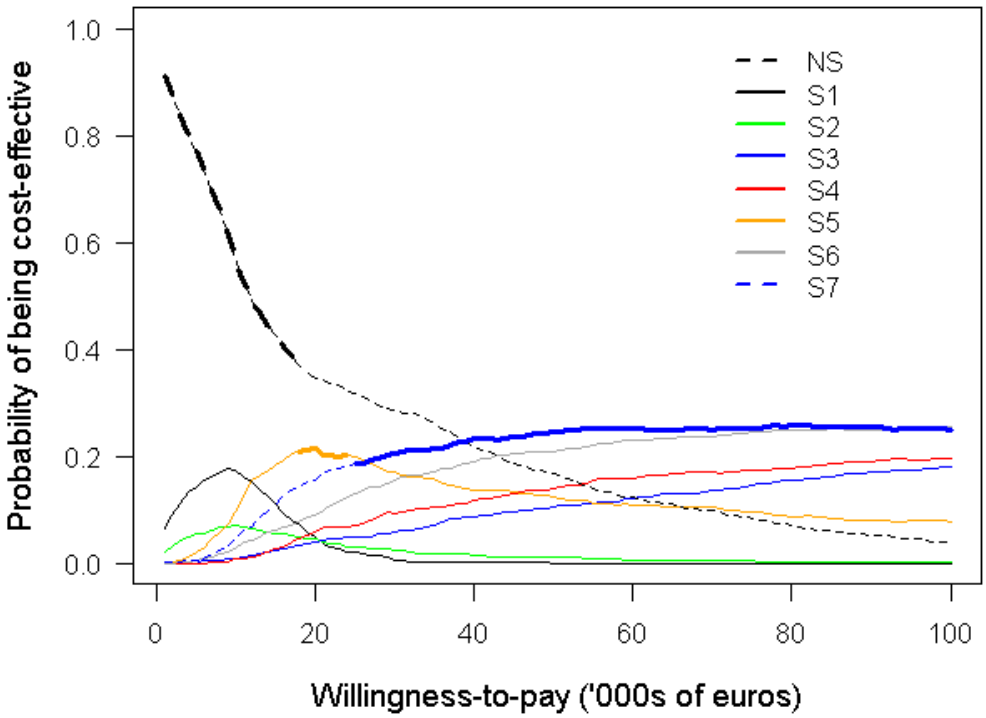
A


Incremental cost (euros)
200
150
100
50
0
0.000
0.002
0.004
0.006
0.008
Incremental QALY gained
NS
S1
S2
S3
S4
S5
S6
S7
ICER= 565806
ICER= 141692
ICER= 24123
ICER= 17780

B


Incremental cost (euros)
300
200
100
0
-100
-0.02
-0.01
0.00
0.01
0.02
0.03
Incremental QALY gained
NS
S1
S2
S3
S4
S5
S6
S7

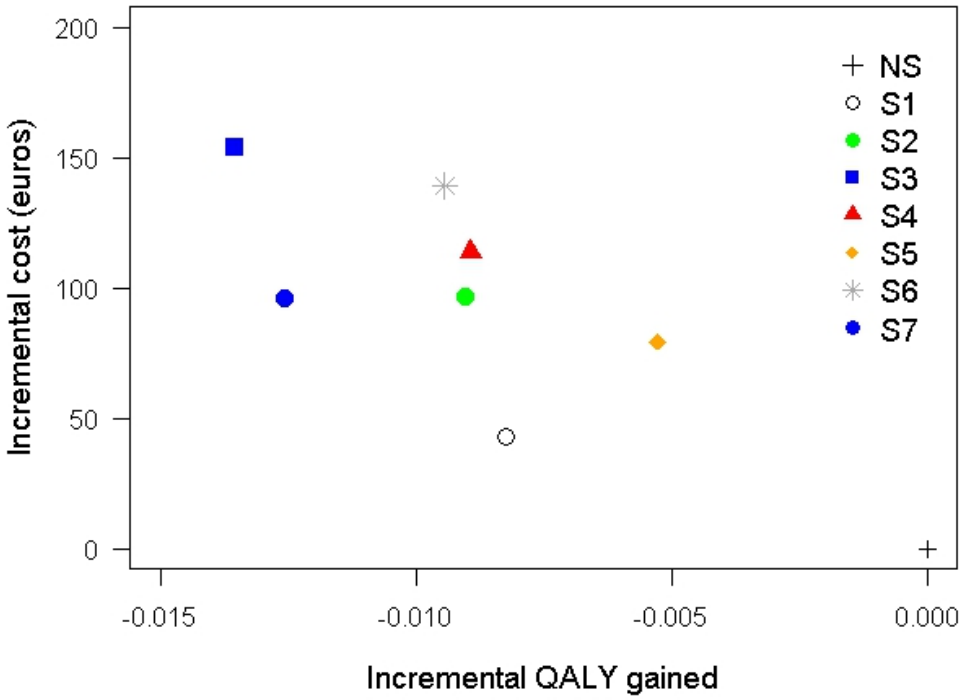
c



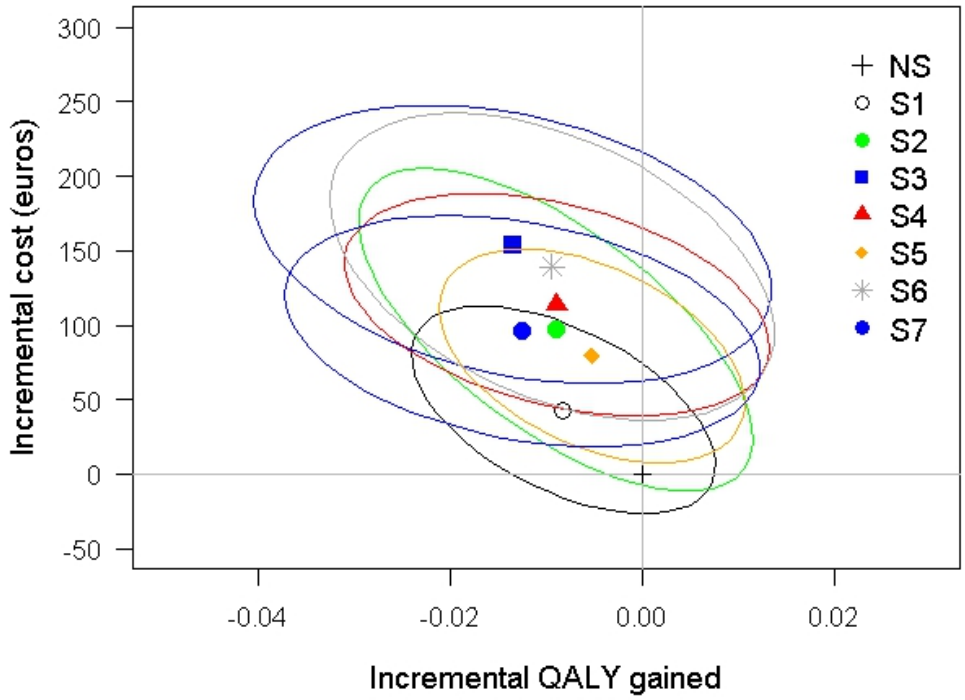
QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; Cost-effectiveness acceptability curves (CEACs) are shown in thin lines for no screening (NS) and the distinct screening protocols modelled; The cost-effectiveness acceptability frontier (CEAF) is presented in thicker line segments on top of the corresponding CEAC.

Figure 5-3. Cost-effectiveness plane (A) and 95% confidence ellipses (B), cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier (C) – HRQoL scenario 2

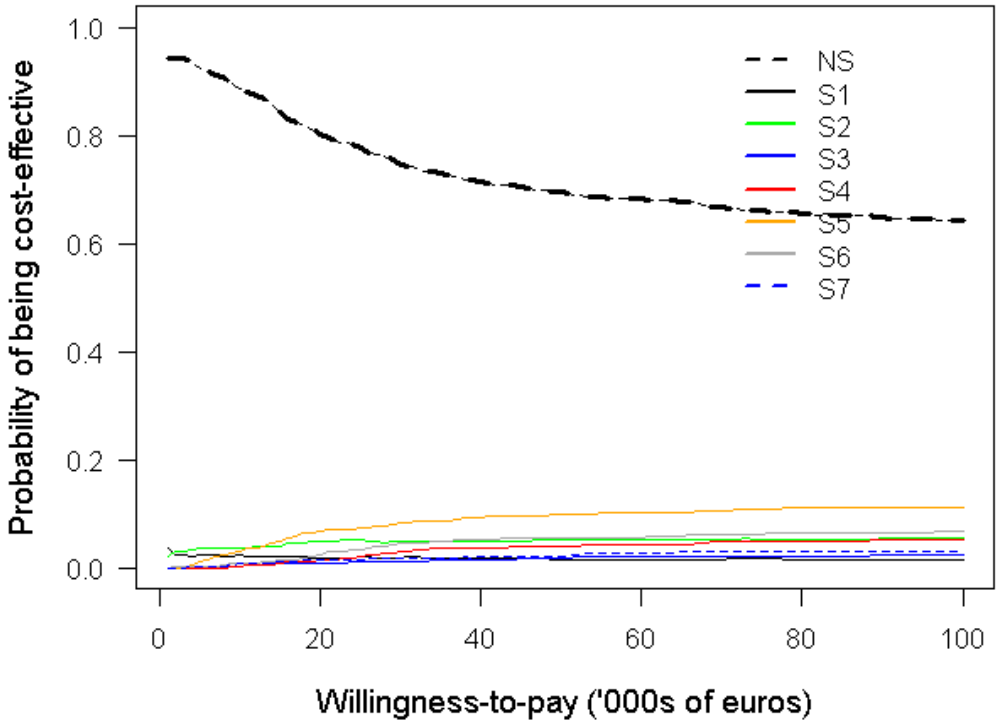
A


200
150
100
50
0
Incremental cost (euros)
-0.015
-0.010
-0.005
0.000
Incremental QALY gained
NS
S1
S2
S3
S4
S5
S6
S7

B



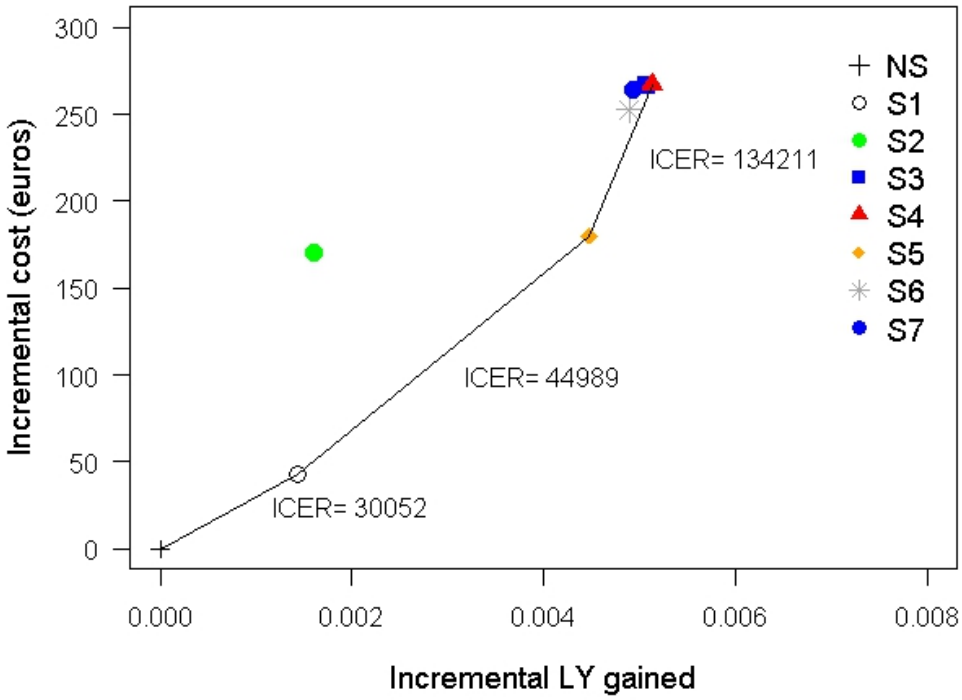
C



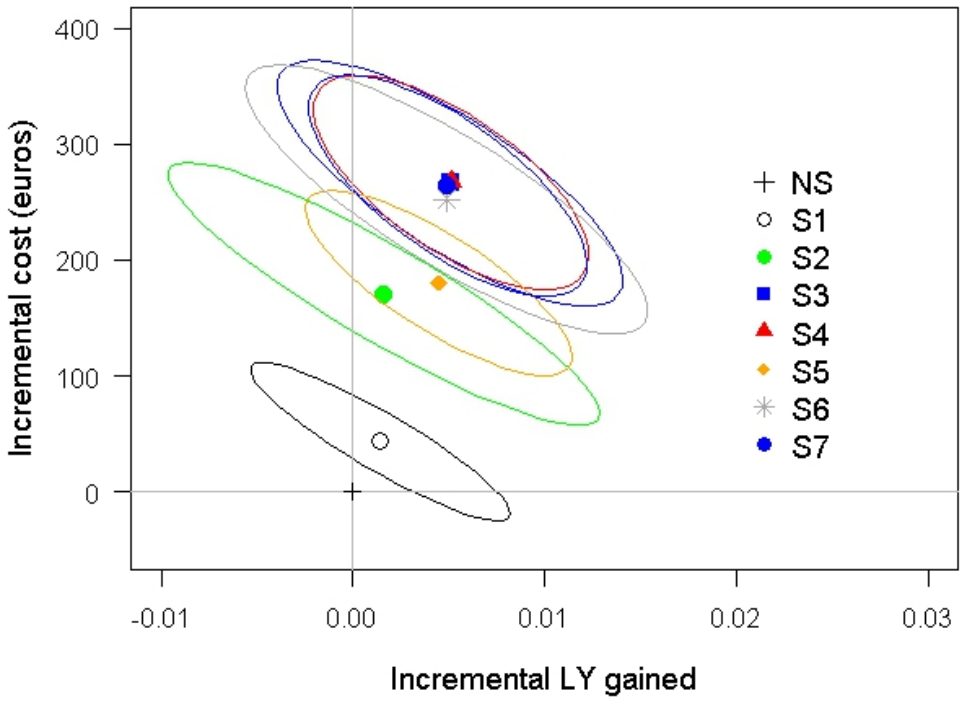
QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; Cost-effectiveness acceptability curves (CEACs) are shown in thin lines for no screening (NS) and the distinct screening protocols modelled; The cost-effectiveness acceptability frontier (CEAF) is presented in thicker line segments on top of the corresponding CEAC.

Figure 5-4. Cost-effectiveness plane (A) and 95% confidence ellipses (B), cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier (C) – 2018 contract cost scenario

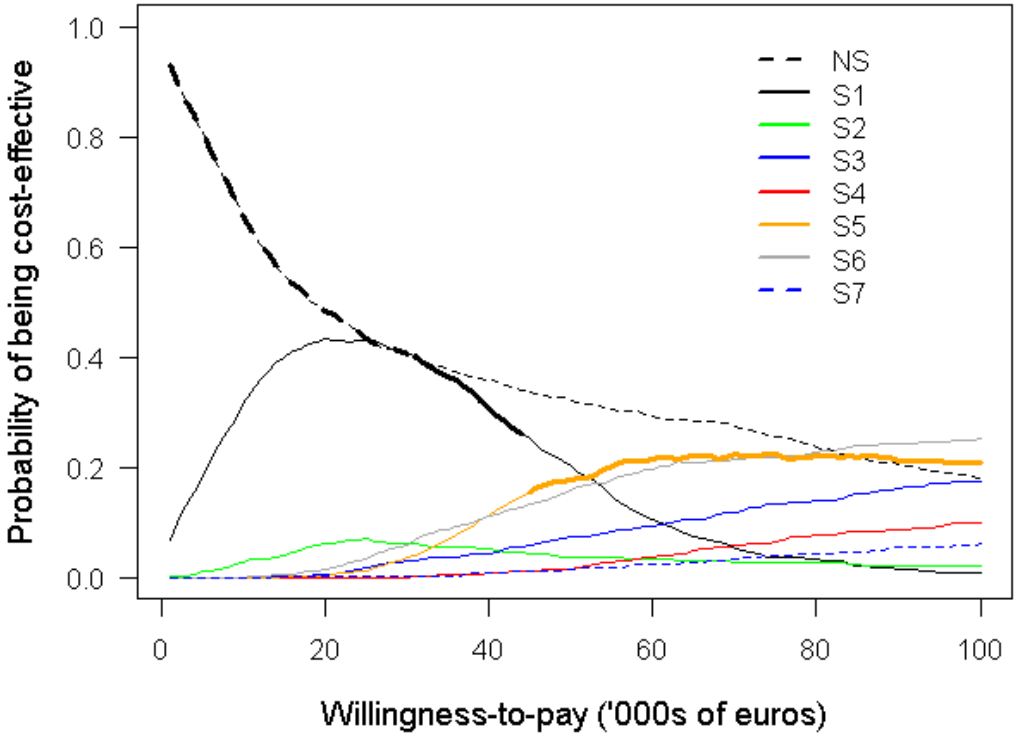
A


Incremental cost (euros)
300
250
200
150
100
50
0
0.000
0.002
0.004
0.006
0.008
Incremental LY gained
NS
S1
S2
S3
S4
S5
S6
S7
ICER= 134211
ICER= 44989
ICER= 30052

B



C



LY, life years; ICER, incremental cost-effectiveness ratio; Cost-effectiveness acceptability curves (CEACs) are shown in thin lines for no screening (NS) and the distinct screening protocols modelled; The cost-effectiveness acceptability frontier (CEAF) is presented in thicker line segments on top of the corresponding CEAC.

6. Chapter 6. Discussion

The main objective of this thesis was to evaluate the effectiveness and cost-effectiveness of cervical screening strategies in Portugal. This overall aim was achieved by conducting a comprehensive analysis of the epidemiology of HPV infection and cervical cancer in Portugal, adapting an existing mathematical model of HPV acquisition and progression of cervical cancer to the Portuguese context, and carrying out a model-based analysis of the clinical and economic impact of cervical screening protocols.

In this chapter, we summarise (i) the main findings of the work conducted for this thesis, (ii) its main contributions for cervical cancer prevention, (iii) its strengths and limitations beyond those discussed in previous chapters, and (iv) areas of future work.

6.1.Summary of main findings

Our analysis of the burden and risk factors for cervical cancer in Portugal in research paper 1[1] (Chapter 2) suggests that improvements in quality and coverage of cervical screening have the scope to achieve large reductions in incidence of cervical cancer. We found that despite the significant decline in mortality, incidence of cervical cancer in Portugal has been stable in the last decade. This contrasts with the decline that several European countries have been experiencing in incidence of cervical cancer, particularly where organised cervical screening has been introduced, such as in England[2].

We also found that HPV prevalence and non-screening risk factors for HPV infection and cervical cancer (such as lifetime number of sexual partners and smoking) were lower in Portugal than in England. Hence, these differences cannot explain the higher incidence in Portugal compared to England, but the markedly distinct screening policies that have been in place can. We found that cervical screening in Portugal remains mainly opportunistic with lower coverage than in England. Fully-organised cervical screening programmes were introduced in some Portuguese regions 20 years after the centralisation of organised screening in England and covered at most 40% of the resident population in 2014.

Despite recent developments towards a national HPV-based organised cervical screening programme[3,4], to our knowledge , the impact and cost-effectiveness of adoption of HPV DNA testing for primary screening has not been studied yet. It is pertinent to compare HPV-based screening strategies with those currently established on technologies available in the Portuguese National Health Service, namely conventional cytology (the most prevalent technology for cervical screening used opportunistically throughout the country and as part of

the programme in the Centre region) and liquid-based cytology with HPV DNA triage currently used in several regional protocols.

The systematic review (research paper 2[5]) in Chapter 3 showed that 65% of the included model-based evaluations of cervical screening protocols were published in the last decade (2003-2012), and that they were conducted in order to understand the effectiveness (12%) and cost-effectiveness (88%) of screening interventions alone (64%) or alongside vaccination (35%), particularly with new screening options as new technologies become available and vaccinated women reach screening age. The main issues addressed relate to the introduction of new technologies to an existing cytology-based programme (particularly the introduction of HPV DNA for primary screening or triage of cytological abnormalities), or changes to an existing programme (comparing alternative primary cytology protocols). LBC was recommended in most studies comparing it with conventional cytology, and HPV DNA primary testing with cytology triage was optimal in most comparisons with cytology.

Most studies found were based on static, deterministic models of groups of women at risk of cervical cancer over a lifetime (71%). The number of individual-based models has risen by 64% in the last decade. Individual-based models simulate the variability in a population, capturing the heterogeneity across individuals (such as different risk factors and previous screening history), while modelling policy decisions for the whole population[6]. Also, model calibration to observed setting-specific data has become more common as well but only reported in 46% of the studies included in our review.

Only two studies analysed the Portuguese setting - Van Ballegooijen and colleagues (2000)[7] and Novoa-Vazquez (2004)[8], in a multiple- and single-country analysis, respectively. Van Ballegooijen and colleagues' static, deterministic, individual-based model predicted up to 77% reduction of life-years lost if coverage of the current repeat conventional cytology programme of the Centre region in Portugal increased to 80%[7]. Novoa-Vazquez's[8] cost-effectiveness analysis of cervical screening in the Algarve region using a static, deterministic, aggregate model, found repeat conventional cytology under organised screening more cost-effective than opportunistic or organised screening using liquid-based cytology. Since the publication of these studies, HPV DNA testing has been integrated in screening programmes worldwide, including as primary screening test in countries such as the Netherlands and Sweden[9]. In Portugal, HPV triage of cytological minor lesions has been used in regional organised programmes and the Ministry of Health is now recommending the adoption of HPV 16/18 genotyping for primary screening[3,4]. Hence there is a need for new model-based economic evaluations considering options with this technology.

In our analysis of the effectiveness of alternative screening protocols (research paper 3 in Chapter 4), using a static, stochastic, individual-based model, we compared the introduction of HPV DNA as primary screening test in an organised programme with the currently predominant opportunistic repeat conventional cytology approach and liquid-based cytology with HPV DNA triage of minor abnormalities protocol adopted in some regional organised programmes. The impact of the current practices was modelled under organised and opportunistic screening, as well as a no screening strategy. We found that organised primary HPV screening every 3 years was more effective in preventing cervical cancer than cytology-based protocols. Extending the interval to 5 years would achieve comparable reduction in cancer incidence as organised protocols based on 3-yearly screening and require fewer tests.

Our economic evaluation of these strategies in research paper 4 (Chapter 5) estimated the health outcomes, in terms of cancer-related life-years lost and quality-adjusted life-years lost due to cancer and screening procedures, as well as the costs and resource use of the strategies described above, from a partial societal perspective. Our results suggest that organised primary HPV screening would be cost-effective at an interval of 5 years at a willingness-to-pay of just under €18,000 per life-year gained compared to no screening, if the cost of HPV DNA testing was half of that for liquid-based cytology. Organised repeat cytology would also be on the cost-effectiveness frontier at a willingness-to-pay of nearly €37,000 per life-year saved compared to 5-yearly primary HPV screening, given the relative lower cost of conventional cytology and the assumed similar effectiveness to liquid-based cytology in England. Primary HPV screening every 5 years would be the optimal option at a range of willingness-to-pay between €18,000 and €36,000 per life-years saved and our probabilistic sensitivity analysis indicates a 21% probability of this strategy being cost-effective, reflecting the joint parameter uncertainty in our model (based on the identification of the strategy with highest net benefit at a given threshold in each model iteration) further illustrated by the small differences in the probability of being cost-effective of several protocols.

6.2.Main contributions of the thesis

To our knowledge, research paper 1[1] (Chapter 2) is the first original integrated analysis of the burden of cervical cancer and the associated risk factors in Portugal, including prevention policies in place. While there has been primary research reporting cervical cancer mortality trends in Portugal[10,11] and secondary research on the epidemiology of cervical cancer in Portugal[12], we have analysed time trends of incidence and mortality together with the developments in cervical screening over the past two decades.

By comparing the burden of cervical cancer, risk factors, and preventive measures in Portugal and England, we identified screening as the main factor limiting the speed of decline in incidence of cervical cancer in Portugal. Research paper 1[1] also provides the first time trend analysis of national incidence of cervical cancer in Portugal, the most recent time trend of cervical cancer mortality in Portugal, and the first overview of the historical variation of cervical screening coverage in Portugal.

Research paper 2[5] (Chapter 3) is the first systematic review of epidemiological and economic model-based evaluations of cervical screening strategies, including the whole range of settings and technologies, for a comprehensive overview of the findings and methods employed. Previous reviews have restricted their analyses to particular technologies[12–16], outcomes[12–14,17], settings[17,18].

The two model-based studies on cervical screening in Portugal found in this review of the literature were conducted in the early 2000s, when the relevant questions for high-income countries concerned the impact of organised programmes and alternative cytology-only protocols, e.g. conventional versus liquid-based cytology. Research papers 3 and 4 (Chapter 4 and 5) consist of the first model-based evaluation of the effectiveness and cost-effectiveness, respectively, of primary HPV DNA screening, as well as of HPV DNA testing for triage of minor cytological lesions, in Portugal.

Although liquid-based cytology with HPV DNA triage has been implemented from 2008 and is currently used to a variable extent in 3 regions of Portugal, its effectiveness and cost-effectiveness as part of an opportunistic regime (with similar coverage to that currently widespread with repeat conventional cytology) or of an extended coverage and improved follow-up organised programme have not been investigated either.

Also for the first time for Portugal, we used a model calibrated to Portuguese HPV prevalence and cancer incidence, quantified health outcomes of cervical screening protocols in quality-adjusted life years, and performed probabilistic sensitivity analysis to capture the joint parameter uncertainty in our cost-effectiveness estimates.

Our analyses of alternative primary HPV- and cytology-based protocols are particularly pertinent now as (i) primary HPV testing has been recently endorsed for the Portuguese National Health System by the Portuguese Ministry of Health[3] and is being piloted in the North region[4], (ii) the implementation of organised HPV-based screening is being prepared in Lisbon and Tagus Valley, and (iii) vaccinated women have reached screening ages prompting the revision of the screening protocols in place, which will be required as well over time by the gradual decline in HPV prevalence subsequent to the increasing proportion of vaccinated

women among the screening-eligible population[19]. Although the impact of vaccination has not been investigated in our studies, a clinic-based primary HPV programme can potentially facilitate monitoring HPV prevalence, its performance is less likely to be diminished by the fall in prevalence, and its coverage can be extended by self-collected HPV testing which has shown effective in improving the adherence of typical non-attendees[20] (whose cost-effectiveness we have not studied either).

We quantified the benefits and costs associated to each algorithm and their relative cost-effectiveness, and our findings can support evidence-based decision making and help refining screening protocols. Research paper 4 (Chapter 5) also includes scenarios on the impact of alternative sets of HRQoL assumptions on the relative cost-effectiveness of the different strategies, making it the first cost-utility analysis of cervical screening programmes in Portugal. Additionally, our analyses highlight the relevance of the length of the screening interval and the unit cost of HPV testing relative to that of cytology to the affordability of primary HPV programmes.

6.3.Strengths and limitations

In research paper 1[1], we identified inadequate screening quality and coverage as the most likely factor that has prevented a further decline in incidence of cervical cancer in Portugal over the last 20 years, as seen in countries such as England. This was based on the comparison of risk factors and changes in burden and screening policies over time between Portugal and England. However, this was an ecological analysis (inherently prone to biases due to differences in ascertainment of disease and exposure between countries and within countries over time), even though we investigated the role of both (i) non-screening risk factors, such as HPV prevalence and sexual behaviour (we assumed a constant ratio between countries over time as we lacked historical data), and (ii) cervical screening coverage over time, particularly for Portugal.

This work also provided the first time trend analysis of cervical cancer incidence in Portugal and our estimates of national age-standardised incidence in Portugal were based on individual case data provided for 1998-2010 by all four Portuguese population-based regional registries (Azores, North, Centre, and South]), covering 100% of the population. However, we were not able to make any correction for registration inaccuracies that may be present. Coverage estimates and quality indicators of the Portuguese regional cancer registry data made available for our analysis (covering 1998-2010) were not provided; however, Allemani and colleagues (2015)[21] also used individual patient-data from the four Portuguese population-based

regional registries (1998-2009) and reported full population coverage and generally higher quality for Portuguese registry data compared to the European average.

In research paper 2[5], we reviewed, summarised findings, and identified trends and gaps in the voluminous literature about models used to evaluate the epidemiological and economic impact of cervical screening strategies, alone or alongside vaccination against HPV. This improved our knowledge of the features of existing models and the recent methodological developments emerging alongside new technologies. However, conclusions regarding findings on the impact of technologies must be drawn cautiously from our summary of the findings as we did not critically appraised the model-based studies included in our review nor listed the data sources and assumptions made on particular protocols and settings. Also, our systematic review included studies up to May 2013; it is possible that an update of the searches could find studies recently conducted for the Portuguese context, that were not captured in our more recent search in PubMed for research paper 4 (Chapter 5).

In research paper 3 and 4 (Chapters 4 and 5), we predicted the effectiveness and cost-effectiveness of several cervical screening protocols in Portugal by adapting a model previously developed by Bains and colleagues for England (detailed in the Appendix to this thesis).

We used Portuguese age- and type-specific HPV prevalence data to calibrate the model, making the modelled cohorts more likely to represent the Portuguese female population at risk of HPV infection. However, it is debatable whether the participants of CLEOPATRE Portugal study are a representative sample of the Portuguese population. Although this is the only population-based epidemiological study conducted in the 5 regions of mainland Portugal to determine age- and type-specific HPV cervical prevalence in the general population aged 18-64 years, the participants (n=2326) consisted of women attending gynaecology/ obstetrics or sexually transmitted disease clinics of the National Health Service. These women can potentially be at lower or higher risk than the general population, as they might be attending NHS appointments for compliance with cervical screening or routine medical checks for other clinical reason or for having or being at high-risk of a sexually transmitted infection. We compared the behaviour risk indicators reported by the participants of the CLEOPATRE Portugal study and by those of the 2007 survey on sexual behaviour and HIV/AIDS in mainland Portugal (n=1860 sexually active women aged 16-65 years) and found similar distributions for the lifetime number of sexual partners and age of sexual debut.

Our predictions for organised screening are based on the (potentially optimistic) assumption that a national cervical screening programme in Portugal would achieve similar adherence to screening as that in England, in terms of age at start of screen, screening frequency, and proportion never screened. Elfstrom and colleagues showed how widely programmes

implemented in the European Union varied in coverage in 2012/2014 (from less than 10% in Hungary to 78% in Sweden)[22]. In 2016 mainland Portugal, coverage of organised cervical screening varied from 0% in Lisbon and Tagus Valley to 97% in the Centre region, and compliance to screening invitation by letter in the existing organised programmes ranged from 73% to 96% in Alentejo and Algarve, respectively[4]. Also, the effectiveness of primary HPV screening is dependent on a well-organised programme to safely allow for the extension of the screening interval[23].

6.4.Areas of further research

An obvious future step in our work would be to consider strategies involving other tests and biomarkers besides HPV positivity and cytology. For instance, this could include a strategy with primary HPV 16/18 genotyping of women aged 25-60 years every 5 years, with cytology triage of women positive to other HPV types, as recommended by the Portuguese Ministry of Health.[3] Another potentially useful analysis would be that of the adoption of self-sampled HPV DNA testing as complement of a countrywide clinic-based programme.[20]

Also, future incidence and mortality from cervical cancer in Portugal will be determined by HPV vaccination. Vaccination against HPV 16, 18, 11, and 6 has been part of the Portuguese National Immunisation Plan since 2008 with high uptake[24] and the first cohorts of vaccinated Portuguese women reached the screening age of 25 in 2015. We would have to include transmission dynamics in our model to capture the full impact of vaccination on HPV prevalence and subsequently on the effectiveness of screening strategies[25]. A transmission dynamic, stochastic, individual-based model would be useful to model the lower prevalence of cervical cancer and the heterogeneity in sexual behaviour and screening attendance of the population at risk for future analyses of the health and economic combined impact of screening and vaccination policies.

A transmission dynamic model could also be used to address relevant questions concerning vaccination strategies, such as the effectiveness and cost-effectiveness of vaccinating boys and older women in Portugal, as well as estimating the impact of the adoption of the 9-valent vaccine (for which the impact on several other HPV-related cancers should be considered as well).

We adapted the screening component of Bains and colleagues' model to the Portuguese context, using country-specific screening algorithms and data on screening frequency and attendance. However, several data constraints limited our characterisation of opportunistic screening in Portugal, particularly regarding screening frequency, and modelling screening and

colposcopy outcomes in Portuguese women, as well as the clinical performance of screening tests in Portugal, as discussed in detail in Chapter 4.

The establishment of a national organised cervical screening programme in the near future is likely to enable the collection of data on screening outcomes and adherence, including individual women's history of attendance, which would allow capturing the heterogeneity in attendance patterns (as per Bains and colleagues, detailed in the Appendix of this thesis).

Further research is also needed on the effectiveness and cost of interventions and policy measures to improve adherence to and compliance with screening programmes, respectively. Organised screening is also likely to improve inter-laboratory concordance, the quality of lesions follow-up, and equality of access; however, it will also bring challenges such as changing existing screening patterns where opportunistic screening is frequently used.[23] Inequalities in access and frequency of screening have been reported in Portugal. For instance in the urban area of Porto, under opportunistic screening (2005-2008), over 85% of women aged 30-49 reported being screened more often than every 3 years and only 7% of women reported having cervical cytology in 3- to 5-year intervals.[26]

The linkage of screening and diagnosis databases is also fundamental to obtain data on the distribution of histological outcomes according to cytological ones and study the impact of alternative screening protocols (with distinct age groups and screening intervals) on the severity of lesions and cancers detected.

As found by De Kok and colleagues[27] and demonstrated in our research paper 4 (Chapter 5), findings on the cost-effectiveness of cervical screening strategies are highly sensitive to estimates and assumptions used for HRQoL. Further research is needed on the measurement and valuation of the impact of cervical screening and cervical cancer on HRQoL. According to INFARMED's guidance[28], this should be measured in Portuguese women undergoing cervical screening and cervical cancer patients using a validated and standardised preference-based instrument, like the EQ-5D, with the valuation of the health states elicited by a representative sample of Portuguese population. Although the latter is available[29], to our knowledge, HRQoL in Portuguese women screened for or suffering from cervical cancer has not been measured yet. It is important to note that, as a general measure, the EQ-5D may not fully capture condition-specific changes in the HRQoL of these women, such as anxiety and worry.[27] Also, HRQoL instruments based on one-time questionnaire may not capture changes in quality of life over time, e.g. the period of time women's quality of life might be compromised for by undertaking screening tests.

Finally, having a specific willingness-to-pay threshold for health interventions as an indicator of the preferences of the Portuguese population would be helpful for decision making and future economic evaluations.

6.5.References

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7. Appendix

The clinical impact and cost-effectiveness of primary cytology compared to primary human papillomavirus testing for cervical cancer screening: a model-based analysis

Iren Bains[1], Yoon Hong Choi[1], Kate Soldan[1], Mark Jit[1,2]
[1]National Infections Service, Public Health England, London, UK; [2]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

Abstract
Background: Using human papillomavirus (HPV) testing as a primary cervical screen has been shown in trials to offer better cancer protection compared to cytology. In England, HPV testing is planned to replace cytological screening by 2019. Model-based economic evaluations offer the possibility of projecting the long term clinical impact and cost-effectiveness of such screening strategies.

Methods: A stochastic, individual-based model of HPV acquisition, natural history and cervical cancer screening was used to compare primary cytological screening and primary HPV testing with cytology triage (with either 3 or 5 year screening intervals for women under 50 years). The model was fitted to data from England's Cervical Screening Programme.

Results: Primary HPV testing is likely to decrease primary screen frequency, cervical cancer incidence and health system costs. It may increase the number of colposcopies, although this can be reduced without leading to more cancers compared to primary cytology, by increasing the interval between screens to 5 years. The impact in terms of quality adjusted life years (QALYs) depends on the quality of life weight given to colposcopies vs cancer.

Conclusion: England's move from primary cytology to primary HPV screening will likely be life-saving and cost-effective. Cost-effectiveness can be improved further by extending the interval between screens or using alternative triage methods (like partial or full genotyping).

Introduction
Persistent infection with a high-risk type of human papillomavirus (HPV) is a necessary condition for cervical cancer. Cervical cancer prevention has traditionally focused on detecting and removing cervical neoplasms with abnormal cytology before they progress to cancer. The development of rapid and sensitive tests for HPV now offer an alternative means of screening for risk of developing cervical cancer. Clinical trials of HPV testing as a primary cervical screen suggest that it provides 60-70% greater protection against cervical cancer compared to cytology (Ronco Lancet 2014). However, trial results need to be extrapolated to project likely impact of different screening algorithms across varied settings, as well as to investigate the cost-effectiveness of each option. A model-based assessment of the potential costs and

benefits of different screening algorithms can synthesise available knowledge on HPV acquisition risk, cervical disease progression, cancer incidence and screening effectiveness.

In England, secondary prevention of cervical cancer has been based on cytological testing to detect cervical abnormalities since the introduction of the National Health Service Cervical Screening Programme (NHSCSP) in 1988. Testing for high risk human papillomavirus (HR-HPV) to determine management of women with borderline or low-grade abnormalities, and as a test-of-cure for recently treated women, has been used since 2011. In 2013, a pilot study of implementing screening in which the primary assessment is a test for HR-HPV was initiated at several sites across England. The National Screening Committee has agreed to replace cytological testing with HPV testing as the primary England-wide by 2019, following a review of evidence including cost-effectiveness.

However, additional considerations surround the introduction of primary HPV testing. HPV testing has higher sensitivity for high-grade lesion detection (Kelly et al., 2011) and provides stronger negative predictive power than cytology (K. et al., 2010), leading the health care community to discuss the extension of the screening interval following a negative primary HPV testing. Additionally, concern that primary HPV screening may lead to over-testing in young women, in whom there is a high prevalence of HPV infection, and increased burden on colposcopists, has led to discussions surrounding the introduction of additional triage tests prior to colposcopy.

Here we present a model-based evaluation of the potential clinical impact and cost-effectiveness of switching from primary cytology to primary HPV testing across the NHSCSP, as well as increasing the standard screening interval associated with primary HPV testing from 3 to 5 years for women under 50. This work was conducted by Public Health England in order to inform decision making by the NHSCSP.

Methods

Model overview

A stochastic, individual-based simulation model was developed to evaluate primary HPV testing and the current primary cytology protocol. The key model components are: (a) acquisition of HPV infection as a necessary pre-condition for cervical pathogenesis; (b) natural progression of HPV infection, cervical intraepithelial neoplasia (CIN) and cervical cancer; and (c) detection and treatment of women with cervical abnormalities through cervical screening. The model generates a cohort of women and simulates their history of partner acquisition, HPV infection, disease progression, and screening attendance and outcomes over their lifetime. Women can acquire multiple HPV infections, possibly simultaneously with different strains, and each infection follows its own timeline to clearance or emergence of a pre-invasive

cancer lesion, adenocarcinoma or squamous cell carcinoma. Women are categorised according to HPV infection status, as illustrated in Figure 1. Following this, women undergo screening and the life history is changed according to any treatment undertaken (screening algorithms illustrated in Figures 2-3).

Screening Interventions
Three alternative strategies were considered:

(a) primary cytological screening with HPV testing to determine further management of cytology abnormals ("primary cytology protocol"), with a 3 year (or 5 year for women over 50 years old) recall interval following a negative primary screen, which is current screening practices in England;

(b) primary HPV testing ("primary HPV protocol"), with cytology testing to determine further management of HR HPV positives, with a 3 year (or 5 year for women over 50 years old) recall interval following a negative primary screen;

(c) primary HPV testing ("5 year primary HPV protocol") with an extended 5 year recall interval following a negative primary HPV screen, for all women regardless of age.

Economic parameters
The cost and utility implications of cervical screening and cancer outcomes were estimated from the literature, and are summarised in Tables 1 and 2.

Table1: Model inputs: economic parameters and sources.

Parameter	**Costs**	**95 % range**	**Source**
Screening			
Sample collection	15.31	(12.5, 18.63)	Karnon (2003), Moss (04), Kitchner (2011), LeGood (2012); Kitchner (2014)
HPV test per sample (includes consumables, equip,ment, staff time & other overheads)	9.75	(7.23, 13.03)	LeGood (2012); Kitchner (2014); NHS supplier chain (2014); Primary HPV pilot site (2014)
Cytology test per slide (includes consumables, equip,ment, staff time, other overheads)	18.15	(14.95, 22.02)	Karnon (2003), Moss (2004), Kitchner (2011), LeGood (2012); Kitchner (2014)
Treatment of pre cancer and cancers			
Colposcopy	151.18	(124.18, 184.08)	Martin-Hirsch (2007)
Biopsy	79.84	(65.35, 97.71)	Sherlaw-Johnson (2004)
Excision	382.6	(313.89, 468.41)	Martin-Hirsch (2007)
Hysterectomy	2583.5	(2222.28, 3039.77)	Martin-Hirsch (2007)

Chemotherapy	5089	(4203.03, 6188.00)	Salter (2014)
Trachalectomy	5485.67	(4500.32, 6646.50)	Salter (2014)
Radiography	19078	(15709.73, 23126.39)	Salter(2014)
Stage 1	4,619	(4105.25, 5156.03)	Salter (2014); Cervical Cancer Audit (2010)
Stage2	20,704	(17927.10, 23509.72)	Salter (2014); Cervical Cancer Audit (2010)
Stage 3	20,387	(17638.43, 23509.18)	Salter (2014); Cervical Cancer Audit (2010)
Stage 4	17,320	(14953.77, 20008.25)	Salter (2014); Cervical Cancer Audit (2010)

Table 2: Model inputs: utility loss due to screening

	Utility loss per episode	**95 % range**	**Sources**
Screening outcomes			Simonella (2014);
Routine screen	0.0001	(0.00002, 0.00023)	Simonella (2014); Gold (1998) as used by Mandelblatt (2002) and de Kok (2014); Myers (2007) as used in Elbasha (2007) and Kitchner (2014); Insigna (2007); TOMBOLA (2007)
Negative cytology; Negative HPV			
Abnormal result with routine recall	0.0011	(0.00023, 0.002)	
Low grade cytology & negative HPV;			
Abnormal result with 12 month follow up	0.004	(0.00023, 0.0089)	
Positive HPV & normal cytology			
Normal outcome at colposcopy	0.0147	(0.0015, 0.04)	
Low grade cytology, positive HPV & normal colposcopy;			
High grade cytology & normal colp;			
Positive HPV, abnormal cytology & normal colposcopy			
CIN1 outcome at colposcopy	0.0618	(0.005, 0.11)	
Low grade cytology, positive HPV & CIN1;			
High grade cytology & CIN1;			
Positive HPV, abnormal cytology & CIN1			
CIN2 outcome at colposcopy	0.0783	(0.003, 0.13)	
Low grade cytology, positive HPV & CIN2 or worse;			
High grade cytology & CIN2 or worse;			
Positive HPV, abnormal cytology & CIN2 or worse			
Cancer			Gold (1998), Stratton(2000) and Wolfson(1996) as used in Goldie (2004), Kahn(2008), deKok (2014) and Kitchener (14); Myers (2004) as used by Elbasha (2007) and Jit (2011); Klee (2000) and Korfage (2009)
stage 1	0.295	(0.19, 0.51)	
stage 2	0.385	(0.33, 0.58)	
stage 3	0.44	(0.44, 0.58)	
stage 4	0.52	(0.4, 0.64)	
Post treatment			
stage 1	0.03	(0.01, 0.27)	
stage 2	0.065	(0.02, 0.32)	
stage 3	0.065	(0.02, 0.32)	
stage 4	0.205	(0.031, 0.53)	

Results

Primary HPV testing

The model and best fitting disease progression parameters are used to evaluate a change to the national cervical screening programme in England from primary cytology, the current protocol, to primary HPV testing, under the algorithm which is currently being rolled out nationally.

Increased number of tests carried out under primary HPV testing. A summary of clinical outcomes under the primary HPV and cytology protocols is shown in Table 4. The annual number of primary screening tests carried out is expected to increase by 5% under the standard primary HPV protocol from 3.14 million to 3.31 million per annum (Table 4); the largest increase is expected in women aged 25 to 35 and represents additional 73,000 tests carried on women that are followed up following a HPV positive result (Figure 5). Inevitably, a switch to the primary HPV protocol resulted in a large reduction in the number of women undergoing cytological testing, from 3.14 to 0.38 million tests annually. While the proportion of women with non-negative cytology outcomes increased from 8.8% under primary cytology protocol to 35% under primary HPV protocol (Figure 6). A more detailed breakdown of number of tests and outcomes is shown for each screening strategy in Tables 5 and 6.

Improved efficiency of screening under primary HPV testing. The model predicts a 25% increase in the number of women referred to colposcopy through the screening programme. The model does not consider women referred to colposcopy following a clinical indication. The number of cases of CIN 2 or worse identified annually is expected to increase by 44%; reflecting ~22,000 additional cases detected per year through the screening programme (Tables 6 and 7; Figure 7). The referral value, that is the number of women referred to colposcopy, by way of the screening programme, per detection of one CIN 2 or worse lesion, is projected to decrease from 2.6 to 2.3. In addition to the increased 'efficiency' of colposcopy, the total number of primary screens required to identify a single case of CIN2 or worse is also predicted to drop from 158 using the primary cytology protocol, to 104 under the primary HPV protocol.

Reduced cancer incidence and cancer-related-deaths under primary HPV testing. Best fitting model simulations cover a wide range of scenarios for cancer incidence when we combine cases of squamous cell carcinoma and adenocarcinoma for HPV types 16,18, 31, 33, 51, 52 and 58 . The model predicts that a switch to primary HPV testing will result in a statistically significant decrease in the mean annual incidence of cervical cancer of 14.5%; equivalent to a reduction in 290 cases per year in individuals aged 10 to 79 years (95% CI=(195, 370)) (Table 4).

The number of cases detected in women aged 35 years and over is expected to experience the largest drop, while the number of cases in women below the age of 30 was not found to be significantly different between the two protocols (Figure 2). This corresponds to a mean reduction in cervical cancer-related deaths of 15.5%; 56 fewer deaths (95% CI=(38, 75)) are predicted under primary HPV testing protocol. In terms of the 'efficiency of primary screening', we find that primary HPV protocol requires an additional 587 primary screens per cancer case avoided.

Cost savings. A switch from primary cytology to the primary HPV protocol, would lead to a total health-care cost saving of £13 million (2.9m, 22.8m). The annual screening costs are expected to be £120.5 million. The discounted lifetime cost saving per women is estimated to be £14 (1,27).

QALY changes. We do not identify a significant change in QALY outcome associated with a switch from primary cytology to a primary HPV protocol. The modelling predicts a median discounted per-woman lifetime QALY gain of (i) -0.0026 (95%CI=(-0.0064, 0.013)) under a mixed, (ii) 0.0005 (95%CI=(-0.0013, 0.0026)) under the Simonella, and (iii) -0.0033 (95%CI=(-0.0004, 0.0064)) under the Insigna basis.

Extended screening interval

We consider the impact of increasing the recall interval, following a negative primary HPV screen, to 5 years for all women regardless of age (5 year primary HPV protocol). This fixed interval compares to current practise whereby women under 50 years are recalled at 3 year intervals, and women over 50 are recalled at 5 year intervals.

As we might expect, the model predicts, a switch from primary cytology to primary HPV testing with a 5 year interval for all women, will lead to a 17% decrease in the number of primary tests carried out (from 3.1 to 2.6 million tests per year) (Table 4). The model does not predict a significant difference in the number of colposcopies with a move from primary cytology to primary HPV with 5 year recall; however, the model predicts that ~7000 additional cases of CIN2 or worse cases will be detected per year. The increased 'rate' of detection per colposcopy under a 5 year protocol arises from the increased proportion of women attending colposcopy following a moderate or severe cytological referral. Overall, the increased detection and subsequent treatment of precancerous lesions results in a drop in cancer incidence of 145 (95%CI=(82, 246)) cases per year under the 5 year primary HPV protocol, saves 47 (95%CI=(27, 67)) lives per year, and leads to a discounted per-woman lifeyear saving of 0.0008 compared to primary cytology protocol (Table 4).

Moving from primary cytology to primary HPV testing, in combination with a regular 5 year screening interval, would lead to a substantial total health-care cost saving of £33 million (23.7m, 44.1m). The annual screening costs are expected to be £97.7 million. The discounted lifetime cost saving per women is estimated to be £38 (25,49).

Using 3 alternative basis for screening-associated QALYs, our mixed weighting, the Simonella and the Insinga bases, we do not identify a significant change in QALY outcome associated with a switch to a 5 year primary HPV protocol. The modelling predicts a median discounted per-woman lifetime QALY gain of (i) -0.001 (95%CI=(-0.0047, 0.0028)) under a mixed, (ii) 0.0004 (95%CI=(-0.0018, 0.0025)) under the Simonella, and (iii) -0.0009 (95%CI=(-0.004, 0.002)) under the Insigna basis.

Discussion

The modelling work presented here predicts that a move from the current primary cytology to a primary HPV screening protocol will be both life-saving and cost-saving, while no significant difference was predicted in terms of QALY gains.

In terms of clinical outcomes, moving from the current cervical screening protocol to one employing primary HPV testing is expected to: (i) increase the number of primary screening tests carried out; (ii) increase the number of women referred to colposcopy; and (iii) increase the number of lesions of grade 2 or worse identified and treated through colposcopy. The model projects a positive impact on cervical cancer incidence and cancer-related mortality.

The impact of increasing the standard recall interval, following a negative primary HPV screen, to 5 years for all women, regardless of age, is also considered within the primary HPV protocol. The switch from a primary cytology to 5 year primary HPV protocol is expected to: (i) reduce cancer incidence; (ii) reduce cancer-related deaths; and (iii) reduce costs. As above, the model does not predict a significant change in QALYs.

The model predicts a sizable total health-care cost saving of £35 million (22.4m, 47.2m) with a switch from the current practise primary cytology protocol to the 5 year primary HPV protocol, compared to a saving of £15.8 million (2.7m, 27m) associated with a switch to the standard primary HPV protocol. The median reduction in cervical-cancer related deaths is predicted to be 56 and 47, respectively, following a switch to the 5 year- and standard-, primary HPV protocols. Despite the smaller life-years saving, the trade-off between screening- and cancer-related QALY losses means that a switch to a 5 year primary HPV protocol is more favourable in terms of net quality-adjusted life years than a switch to standard primary HPV testing. The median QALY loss predicted, using an averaged QALY weighting basis, for a switch from

current practise to a 5 year recall primary HPV protocol is 0.0010, compared to a QALY loss of 0.0026 associated with a switch from current practise to the standard HPV protocol.

Model Limitations

The model explicitly considers HPV strains 16, 18, 31, 33, 45, 51, 52 and 58, representing the most prevalent strains that are associated with cervical cancer in England. However, commercially available test, such as the commonly used HC2 assay, will also detect cases of hpv-35, 39, 56, 59 and 68. There are also reports that HPV testing may react to non HR-HPV test, however, the validation of model outcomes against preliminary data from the HPV primary pilot give us confidence that we do not underestimate HR-HPV positivity.

The model is unable to capture a second peak in cancer incidence from 70 onwards; one explanation is that cancers in older women are more likely to arise from non-model types. Joste et al. [Human Papillomavirus Genotype-Specific Prevalence across the Continuum of Cervical Neoplasia and Cancer; Cancer Epi Biomarkers Prev Jan 2015] showed that 100% of cancers in under 30s were attributable to strains considered in the model however, this dropped to 75% in women over 40. In addition, the age-incidence data represents a combined effect of cohort differences in addition to age related changes. The model calibration assumes that all women undergo screening according the current protocol from age 25 to 65; however, the national screening programme began in 1988 meaning that the cohort of women, aged 70 and over, in the 2012 dataset would only have benefited from screening from the age of 45 onwards, rather than the full 40 years. Additionally, for simplicity and viability of parameterisation, the model assumes a rate of progression to cancer that is related to time since infection, however, there may be age-related factors that result in a more rapid rate of progression to cancer in old age, ie. diminished DNA repair. As part of the Kaiser study, 10 year follow up of women aged 30 years and over was found to be associated with a higher risk of CIN3 and cervical cancer, than in those under 30 (Khan et al. JNCI 05).

Model projections give a large uncertainty range around cancer incidence. This uncertainty is in part explained by the additive uncertainty arising from combining 16 distinct cancer-causing processes– eight hpv strains leading to either squamous cell carcinoma or adenocarcinomas. The rare nature of non hpv 16/18-related cancers means that the underlying parameters can be difficult to constrain for hpv strains other than 16 and 18. Conservatively, the model simulations cover a broad range of scenarios for each HPV type.

In this work, we use the economic costs taken from historical economic analyses of screening in England, and inflate to 2014 values. The limitations of inflating historical costs are that we do not necessarily capture the reduction in technology costs over time. Economies of scale

also suggest that a switch to primary screening is likely to result in a reduction in the per sample cost of an HPV test. Overall, this is expected to lead to a further cost saving associated with a switch to primary HPV testing. A more detailed study of work flow and costs in the context of primary HPV testing is planned by the primary HPV pilot screening committee that will provide further insight into the expected changes.

The utility detriment associated with cervical screening is not well defined, reflected in the diverse estimates for QALY loss weights reported in the literature. This is particularly true for primary HPV related screening. In this work, we use a sensitivity approach that captures the extreme values reported in the literature to show that the choice of published screening-associated QALY loss values can determine whether an intervention is beneficial or detrimental. The work highlights a need for further study of QALY loss associated with screening, in order to appropriately judge the increase in colposcopy and treatment of precancerous CIN2 lesions we are willing to accept in order to reduce the incidence and death related to cervical cancer.

The current analysis is based on a static model of infection, this means that we are unable to incorporate changes in male prevalence that might arise following vaccination due to herd immunity; and limits the projections that we can make about the suitability of HPV testing to an unvaccinated female population. The introduction of a national HPV vaccination programme, in 2008, means that it is relevant to consider the implications of vaccination on HPV prevalence and disease incidence as vaccinated cohorts approach screening age.

Acknowledgments

We thank Peter Sasieni, Alex Castenon, Rebecca Landy, Julietta Patnick, Henry Kitchener, Sue Moss, David Mesher and Koh Jun Ong for many helpful discussions, feedback on previous iterations of this work and sharing insights from their own studies. This work was funded by the NHS Cervical Screening Programme.

Figures and Tables

Table 3: Summary of clinical outcomes and resource usage (mean and 95%CI). Number of tests calculated assuming an age distribution as observed by ONS in 2013.

	Primary cytology protocol	**Primary HPV protocol** with 3 year recall for women under 50, and 5 year recall otherwise	**Primary HPV protocol** with 5 year recall for all women
Number of cytology tests	**3,145,825**	**396,427**	**325,066**
	(3092564, 3195711)	(371807, 397559)	(286693, 324171)
Normal cytology	2,863,609	257,145	**206,282**
	(2806087, 2930539)	(226971, 276908)	(175124, 205872)
Borderline changes	182,912	107,725	**90,947**
	(138567, 218231)	(73542, 128330)	(66713, 90347)
Mild dyskariosis	71,910	24,634	**21,445**
	(48355, 96806)	(15695, 34081)	(13485, 20964)
Moderate dyskariosis	16,576	5,707	**5,245**
	(6500, 27929)	(3218, 8324)	(2730, 5113)
Severe dyskariosis	10,819	1,216	**1,146**
	(2418, 21514)	(571, 2117)	(478, 1053)
Number of HPV tests	**272,228**	**3,315,913**	**2,608,628**
	(220774, 313783)	(3260003, 3359351)	(2551687, 2608256)
HPV negative	157,739	2,868,372	**2,242,651**
	(115711, 196221)	(2830218, 2919485)	(2192448, 2242518)
HPV positive	114,489	447,541	**365,977**
	(89616, 134687)	(419017, 450246)	(322009, 365021)
Number of colposcopies	**106,931**	**147,386**	**123,691**
	(83824, 125307)	(127789, 154795)	(104117, 123118)
Normal	63,490	77,693	**64,918**
	(47456, 76680)	(66514, 82732)	(54067, 64602)
CIN 1	23,627	37,985	**31,774**
	(17987, 28133)	(32204, 40955)	(26133, 31628)
CIN 2 or worse	19,813	31,708	**26,999**
	(15456, 23309)	(26483, 34545)	(21884, 26856)

Table 4: Summary of costs and QALYs (mean and 95%CI)

	Primary cytology protocol	**Primary HPV protocol** with 3 year recall for women under 50, and 5 year recall otherwise	**Saving under primary HPV**	**Primary HPV protocol** with 5 year recall for all women	**Saving under primary HPV with 5 year recall**
Annual screening-associated costs (£000)	**134,173** (122855, 145382)	**120,479** (112413, 130635)	**13,078** (2924, 22814)	**97,726** (91366, 106906)	**33,958** (23749, 44166)
Annual total health costs (£000) (including cost of cervical cancers)	**153,391** (139306, 164510)	**136,707** (126156, 147393)	**15,756** (2716, 27990)	**114,196** (104471, 126831)	**35,711** (22381, 47182)
Discounted lifetime cost per women (£) (including cost of cervical cancers)	**160** (146, 172)	**145** (134, 157)	**14** (1, 27)	**121** (108, 131)	**38** (25, 49)
Annual incidence of cervical cancer	**2123** (1475, 2869)	**1828** (1016, 2738)	**290** (195, 370)	**1999** (1356, 3022)	**145** (82, 256)
Deaths related to cervical cancer (/year)	**520** (364, 704)	**461** (325, 752)	**56** (38, 75)	**475** (337, 777)	**47** (27, 67)
Discounted life years lost to cervical cancer per women	**0.0157** (0.0092, 0.0239)	**0.0146** (0.0079, 0.0212)	**0.0018** (-0.0043, 0.0082)	**0.0153** (0.0085, 0.0224)	**0.0008** (-0.0063, 0.0076)
Discounted quality-adjusted life years lost due to cancer and screening	**0.0136** (0.0105, 0.0165)	**0.0160** (0.0128, 0.0198)	**-0.0026** (-0.0064, 0.0013)	**0.0144** (0.0113, 0.0179)	**-0.0010** (-0.0047, 0.0028)
Discounted quality-adjusted life years lost due to cancer and screening, using Simonella basis for screening-related QALY detriment	**0.0060** (0.0037, 0.0080)	**0.0055** (0.0033, 0.0073)	**0.0005** (-0.0013, 0.0026)	**0.0052** (0.0032, 0.0076)	**0.0004** (-0.0018, 0.0025)

Discounted quality-adjusted life years lost due to cancer and screening, using Insigna basis for screening-related QALY detriment	**0.0195** (0.0151, 0.0225)	**0.0225** (0.0184, 0.0262)	**-0.0033** (-0.0004, 0.0064)	**0.0199** (0.0.0162, 0.0237)	**-0.0009** (-0.0040, 0.0020)

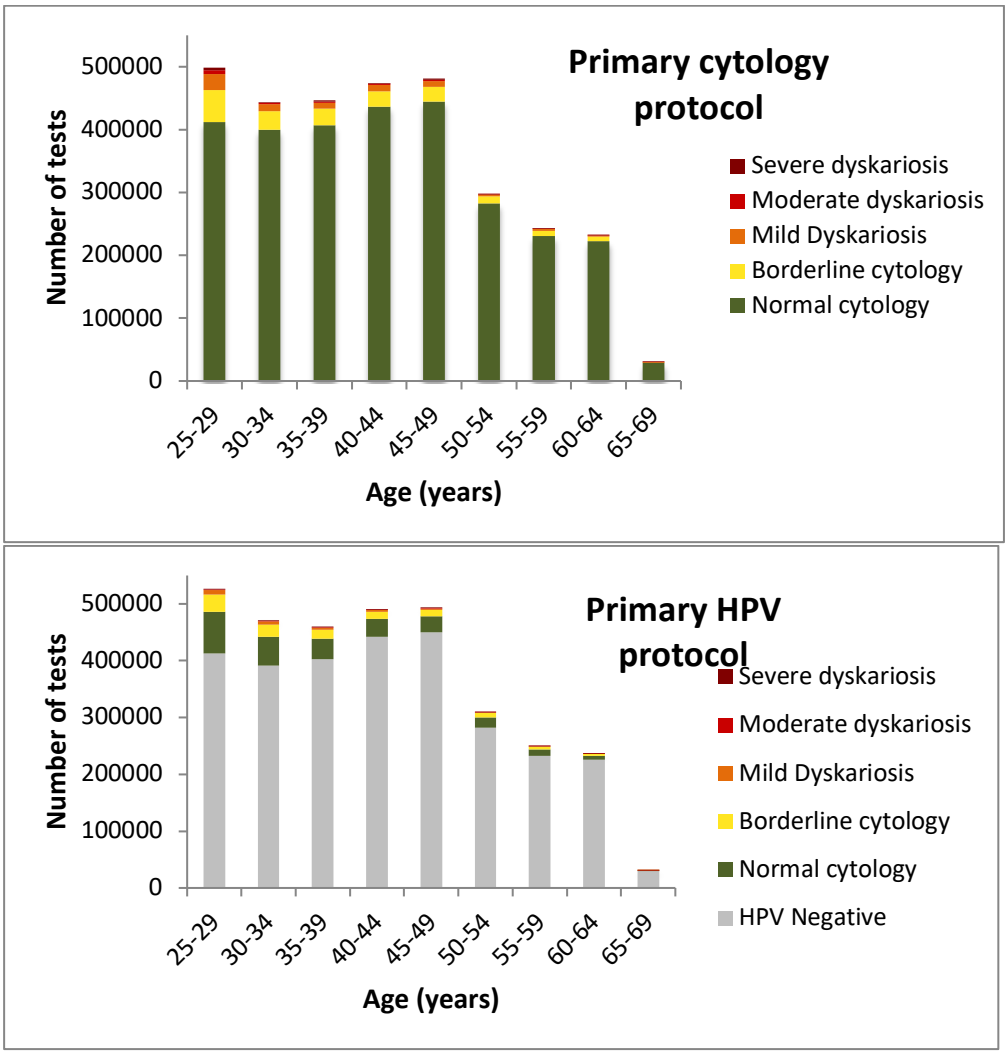

Figure 1: Number of women tested and predicted outcome under primary HPV protocol and primary cytology protocol, assuming age distribution in England as in 2013.

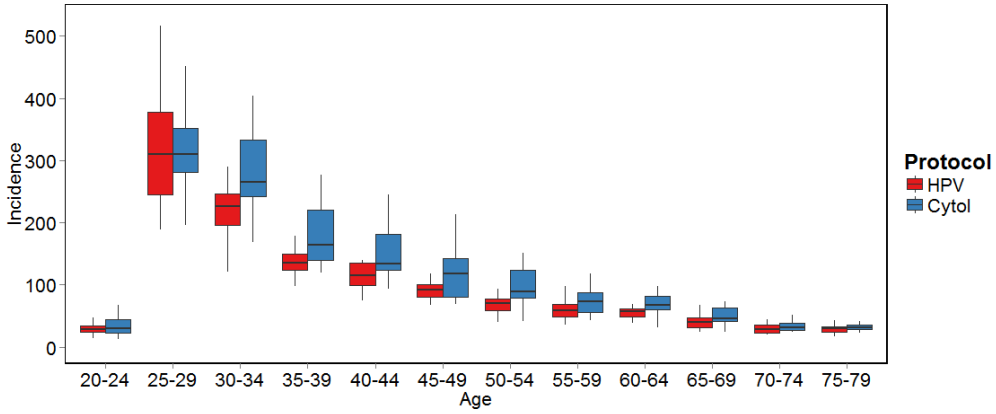

Figure 2: Cervical cancer incidence as predicted by model outcomes under primary cytology and primary HPV protocols. Boxes represent the interquartile prediction interval (primary cytology =blue; primary HPV= red).

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Appendix: The clinical impact and cost-effectiveness of primary cytology compared to primary human papillomavirus testing for cervical cancer screening: a model-based analysis

A1 Model and Parameterisation of Sexual Behaviour

The sexual behaviour characteristics described below are used to generate the age of sexual debut and formation and dissolution of subsequent sexual partnerships for a population of 100,000 women from birth to age sixty five years. Figure A1 illustrates broad model framework from sexual debut to HPV transmission, lesion development, and cervical screening and treatment.

Sexual debut

Entry into the HPV-susceptible population is determined by age of sexual debut as reported in the National Survey of Sexual attitudes and Lifestyles 2010 (NATSAL-3). The data allow us to directly determine the fraction women that are sexually active from age 16 to 75 years. For individuals aged 16 years and under, we use the distribution of reported age at first sex, S_d, (for those that report sexual activity before the age of 16 years), and scale this to the known fraction of individuals that are active by age 16 years, to determine the probability of sexual debut from age 10 onwards ($P[S_d=d] = P[S_d=d \mid S_d<=16]P[S_d <=16]$). A smooth hill function is used to fit the empirical cumulative distribution of sexual debut age before and after the age of 16 years (shown in Figure A2(A).)

Partnership acquisition

The number of new partners acquired in the last year, as reported in NATSAL-3, reveals a trend towards decreasing partner acquisition with age with significant variation between individuals at the population level. We divide the population into five-year age bands (16-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-55, 56 an over). A Poisson distribution is used to describe the number of partners, L_N, acquired over the last 12 months. A Nelder-Mead optimisation to identify the rate of partner acquisition, μ, and the size of each sexual behavioural categories, S_i, where increasing *i* reflects increasing sexual activity. The Aikake information criterion identified a model that divided the population into 4 behavioural categories to be optimal; where, S_0 represents 17%, S_1 represents 51%, S_2 represents 26%, and S_3 represents 5% of the population, repsectively. An individual within the model remains associated with a given behavioural category throughout their lifetime, however, the rate of partner acquisition associated with each behavioural category decreases with age. (Rates of partner acquisition shown in Table A1)

Partnership duration

A survival model is used, in combination with the NATSAL-3 dataset, to parameterise the cumulative probability of relationship 'survival' as a function of time and age of women at the start of relationship. In the natsal survey, individuals reported on the three most recent partners with sexual activity within the past 5 years. To counter the bias towards observing longer-relationships in a fixed-window sampling scenario, the survival of relationships is calculated using a modified Kaplan-Meier estimator that explicitly accounts for truncation (as described by Burington and colleagues[1])

$$S(x) = \prod_{y_i<x} 1 - d(y_i)/R(y_i)$$

where $d(y_i)$ represents the number of uncensored events (relationships) of length exactly y_i ;and the denominator R counts the total number of relationship events lasting more than or equal to y_i months, but excluding events that began more than y_i months before the start of the sampling window.

$$R(y_i) = \sum_j I(t_j < y_i) - \sum_j I(y_j < y_i)$$

where t_j is the time between the start of the relationship and the start of the sampling window, measured as 5 years before the date of interview according to the natsal questionnaire design, (t_j is 0 for partnerships that began after the start of the sampling period), and $I(x)$ is the indicator function, value 1 if x is true, 0 otherwise.

A partnership is defined as complete when there has been no sexual activity for 3 months. Data from the first, second and third most recent heterosexual partner is combined.

Missing partnerships: The sampling of detailed partnership information from the three most recent partnerships in the past 5 years can lead to a bias towards longer relationships and those with a large gap between relationships as they are most likely to be 'most recent' at time of interview. We compare the total number of partners in the past 5 years to the number of partners for whom we have detailed information for individual, to determine the number of missing partnerships in our data sample. It is assumed that missing partnerships are complete and therefore will be most similar to completed partnerships that have been reported in detail by the same individual.

The detailed information on complete partnerships for individual *i* can be weighted by W, $W = 1 + (\mathrm{H}_{5,\mathrm{i}} - \mathrm{T}_{\mathrm{i}})/\mathrm{C}_{\mathrm{i}})$, where $\mathrm{H}_{5,\mathrm{i}}$ is the number of partnerships reported in the last five years; T_{i} is the number of partners for whom detailed partnership data is available; C_{i} is the number of complete partnerships for whom data is available for subject i.

Relationship survival curves exhibit a biphasic decay; with a large number of short term relationships and a smaller number of very long partnerships. The data reveals that the fraction of relationships falling into the short-term category increases as a function of age at start of relationship; the five year survival for a relationship is 19%, 7% and 3,5% for women aged 16 to 20 years, 31 to 35 years, and 51 to 55 years, respectively, at the start of relationship (Figure A2(B)).

Age mixing

An age-mixing matrix is generated by directly sampling from the age of most recent partners reported by female participants in NATSAL-3. We stratify the data according to the age of female respondent at the start of relationship to reveal an increasing variance in partner age for older women. This approach is preferred to a more traditional approach to partner-matching that assumes a constant age difference distribution or an approximation of +/- 3 years, as it better captures the complexities of HPV transmission; in particular, the role of novel HPV infections in older women versus long term persistent infection. The shift in age difference is illustrated in Figure A2C).

Frequency of sex acts

We use data from NATSAL-3 to quantify the number of sex acts per month for individuals in an active relationship (defined as those participants who reported a sexual encounter in the last 3 months with the most recent partner). As above, a weighting is added to response data that scales with total 5 year partner count to remove the bias towards reporting of characteristics from long term relationships. A small fraction of new relationships are assumed to result in a single sexual contact, defined by age according to data reported in NATSAL-3. Relationships in the model are generated by randomly sampling from the weighted distribution of sex acts per month (Figure A2(D)) and according to the reported probability of a single contact (Figure A2(E)).

A2 Model and Paramterisation of HPV infection

A static model of **transmission** was applied in which male prevalence was assumed to be constant throughout the duration of model simulation; i.e. the introduction of primary HPV testing in cervical screening is assumed to have no effect on the prevalence of HPV in males. The probability of transmission of HPV is described as a function of (i) HPV prevalence among male partners according to age; and (ii) the probability of transmission per contact with an infected individual.

The HPV status of a new male partner is randomly generated using the distribution of age of new partners, reported in NATSAL-3, according to the age of the woman at start of partnership, and the prevalence of HPV among men of the preferred partner age.

HPV infection is modelled by introducing a per-sex-act probability of transmission of HPV. The probability of infection by each strain is assumed to be independent. In this work we consider HPV-16, 18, 31, 33, 45, 51, 52 and 58. Rates of clearance and transmission of HPV were parameterised using HPV prevalence data in women and sero-prevalence data in males.

In the interest of parameterisation and model simplicity, we assume that natural immunity post-infection is negligible. Approximately half of women seroconvert within 18 months of infection (Carter et al., 2000). However, the risk of subsequent infection in women who were seropositive, compared to seronegative, has been shown to be (i) reduced between 25-85% for HPV 16(Ho et al., 2002; Safaeian et al., 2010); (ii) reduced between 14-75% for HPV 18; and (iii) not statistically significantly different(Viscidi, 2004; Viscidi et al., 2005). Epidemiological evidence suggests that reinfection is observed in 10-17% of women within 5 years of clearing an infection [1,4]. There is some evidence to support the hypothesis that the majority of infections are rapidly cleared, and these transient infections are cleared by the innate immune system which does not result in the creation of a memory response[5,6].

HPV-strain specific prevalence was determined using surveillance data collected by Public Health England from residual samples taken from the NHSCSP pre-immunisation for women aged 25-65 years[2]. For women between the ages of 16 and 24 years, HPV prevalence was measured in residual samples taken from the national chlamydia screening programme (NCSP), pre-HPV-immunisation[3]. Data from these younger women is important for characterising the peak of HPV infection, however, the selective nature of women attending the NCSP means that the sample reflects a higher sexual risk group than the general population; NCSP data is accompanied by data with number of partners reported in the past 12 months which is higher than that predicted by NATSAL-3 for women aged 16-24 years. We introduce a weighting to resample the NCSP data such that the number of partners reported in the past 12 months matches that observed in natsal-3 for women aged 16-24 years, and introduce a sub-population of sexually-inactive women in the same age range (as predicted in NATSAL-3 but not present in the NCSP dataset) who are expected to be HPV-naïve. HPV prevalence is recalculated in this re-weighted population and this new comparable prevalence is merged with the NHSCSP predicted prevalence.

HPV prevalence data was not available for a sufficiently large male population in England. Instead, national surveillance data describing male sero-prevalence of HPV-16 and HPV-18 in England, collected by PHE[4], was used to estimate prevalence of HPV among males. A study of

sero-prevalence in the Netherlands revealed that sero-prevalence levels were similar in HPV-,33, 45 and 52, but approximately two-fold higher in HPV-31[5] ; a similar result was found in the German population[6]. In the parameterisation that follows, sero-prevalence of hpv 33, 45 and 52 among males was constrained by observed sero-prevalence of hpv-18, in accord with levels of hpv prevalence of these strains observed in women in England. Sero-prevelance of HPV strains 31 and 51 was estimates by scaling the observed hpv-18 sero-prevalence according to the ratio of hpv prevalence of hpv-31: hpv-18 and hpv-51: hpv-18 observed in women.

HPV infection in males

A simple three compartment differential equation model is used to analyse the sero-prevalence data and extract HPV prevalence for each HPV type. We consider individuals that are (i) infected but sero-negative (I); (ii) sero-positive, that is they have detectable HPV antibodies (S), and (iii) infected and HPV-DNA positive (H).

$$\dot{I} = f(t) - (c + k)I(t)$$

$$\dot{S} = k\, I(t) - wS(t)$$

$$\dot{H} = f(t) - cH(t)$$

Where, *f(t)* is the number of new infections at time *t*; *c* is the rate of clearance of male infection; *k* is the rate of sero-conversion; and *w* is the rate of HPV antibody waning.

The size of the infected population, H, can be estimated using numerical methods to solve the following equation:

$$\dot{H} = \frac{\ddot{S}}{k} + (w + c + k)\frac{\dot{S}}{k} + w(c + k)\frac{S}{k} - cH(t)$$

where, the observed sero-prevalence, S[t], can be described by a polynomial, and it is assumed that the half life of antibodies is at least 20 years, that is the rate of waning (w) is constrained to be less than 0.05 (/year).

The rates of sero-conversion and clearance for each male HPV strain are identified, together with the rates of female clearance and transmission, using the observed HPV sero-prevalence in males and prevalence in females. Described in detail below.Clearance of HPV infection

The rate of HPV-**clearance** is allowed to vary with time post-infection, using a weibull distribution, selected due to its generality to allow a constant, increasing or decreasing rate of clearance with time. The clearance rate is proportional to a power of time (t^{K-1}), where *t* is time post-infection and *K* is the shape parameter; *K*=1 leads to a constant rate of clearance, while *K*<1 leads to a decreasing clearance rate with time.

HPV transmission probability (per-sex act)

We find that the transmission probability per contact is not well defined. One explanation for this is that, according to the sexual behaviour data, the majority of partnerships result in multiple contacts; where the probability of contracting HPV from an infected partner, 1-(1-*Transmission.Probability*)^*'Sex.Acts'*, becomes decreasingly sensitive to the *Transmission.Probability* as the number of Sex.Acts increases. We accept the broad range of values suggested for transmission probabilities as they are able to reproduce the observed HPV prevalence within the context of known sexual behaviour.

Parameterisation

The disease transmission was parameterised independently for each HPV-subtype. In this parameterisation we assume that HPV prevalence is not sensitive to screening strategy. The reasoning is that (i) the number of women treated for cervical lesions is small relative to the number of women that are infected with HR-HPV, ~10% of population at large; and (ii) not all treatment of lesions leads to clearance of HPV-infection. As a result, we can identify the rate of disease transmission and clearance using a simplified individual-based model without screening, in a computationally tractable parameterisation. Best fitting parameters in Table A2 and model predictions and observed HPV prevalence data in Figure A3.

A Markov Chain Monte Carlo simulation, using an adaptive Metropolis algorithm, was implemented using the FME package in R to simultaneously identify the (i) HPV clearance parameters in females and males (c_1, c_2, c_m); (ii) per contact probability of transmission from males to females; and (iii) rate of sero-coversion in males. Each chain was run for a length of 20,000 and 100 parallel chains were generated using randomly generated starting values, for each strain of HPV.

A thinning interval of 50 was used to remove auto-correlation within each chain. Convergence was identified using the Geweke test statistic, a test of equality of the means of the first 10% and last 50% of the markov chain. A Gelman convergence diagnostic was then used to confirm convergence of the MCMC output in the parallel chains; a comparison of the empirical variance of each parameter within each chain should be comparable to the variance from all chains combined. The final parameter distribution reflects the joint distribution of the parallel chains.

A3 Model and Parameterisation of Disease Progression

A nested conditional probability structure is used to generate a model in which the probability of a given cytological outcomes varies as a continuous function of time post-infection for each

strain of HPV, as opposed to introducing distinct disease states. The five cytology outcomes, normal, borderline, mild, moderate and severe, are characterised by 5 parameters (p_norm1, p_norm2, p_bord, p_mild, p-mod),

$$P[Normal, T = t] = p_{norm2} + (1 - p_{norm2})e^{-t*p_{norm1}}$$

$$P[Borderline, T = t] = e^{-tp_{bord}}(1 - P[Norm, T = t])$$

$$P[Mild, T = t] = (1 - P[Normal, T = t])(1 - e^{-t*p_{bord}})e^{-t*p_{mild}}$$

$$P[Moderate, T = t] = (1 - P[Normal, T = t])(1 - e^{-t*p_{bord}})(1 - e^{-t*p_{mild}})e^{-t*p_{mod}}$$

$$P[Severe, T = t] = 1 - P[Mod|\ Mild|Bord|\ Norm, T = t])$$

where, the probability of a normal outcome decreases, while the probability of a severe outcome increase, with time since infection, and, p_{norm2} reflects the maximum probability of a normal cytology outcome at time of cancer, constrained to lie between 0 and 0.1. An accelerated hazard component is introduced by normalising the time post-infection to an individual's personal timeline to squamous cell carcinoma; T is the cancer-normalised time post-infection (= time post-infection/ Time from infection to SCC). Cytology outcomes are linked to the progression of squamous cell carcinomas, rather than adenocarcinomas because screening is thought to be poor at detecting adenocarcinoma. The introduction of the cervical screening programme in 1989 was associated with a ~35% reduction in squamous cell carcinoma cases over a 10 year period, while the number of adenocarcinomas remained stable over the same period[26].

Cytology outcome parameters were calibrated using surveillance data collected by PHE, prior to the introduction of vaccination in 2008, mapping observed cytological outcomes to HPV type, as a function of age, using residual samples (n=2370) collected by the NHSCSP [11]. Cytology screening outcomes for women who were not infected with HPV were parameterised using observed cytology outcomes from samples that tested negative for HPV [11]. The model was calibrated simultaneously for each HPV-strain, in a simulation that incorporated screening and treatment under the existing primary cytology protocol.

Cancer progression

The hazard of squamous cell carcinoma and adenocarcinoma incidence are modelled independently; the hazard of cancer is assumed to increase as a function of time post-infection and modelled by a gamma distribution.

Cancer incidence within the model was calibrated using cancer registrations in England reported by the Office for National Statistics in 2012. A breakdown of squamous cell carcinoma and adenocarcinoma cases by age was assumed to be as reported by the NHSCSP audit of

cervical cancers [15]. Screen-detected cancers are defined as those that are diagnosed through colposcopy, where the referral to colposcopy was due to an abnormal cytology outcome. The number of cases detected by the screening programme was obtained using data from Health and Social Care Information Centre (HSCIC) and NHSCSP on cervical cancer outcomes at registered at laboratories, according to cytology referral, in 2012[7]. The distribution of cases among HPV types was estimated using the distribution of HPV types measured in residual tissue sections from routinely obtained diagnostic biopsies of cervical cancers archived in NHS pathology laboratories [n=555] by Howell-Jones and colleagues at PHE[11].

Co-infection of cancer–causing strains, as defined in our model, was observed in ~7.1%, and 10%, of tissue samples taken from cervical cancers, and adenocarcinomas, respectively; ~3%, and 6%, of samples were positive for both hpv-16 and hpv-18 in cervical cancers, and adenocarcinomas, respectively. We generate cancer incidence for each model HPV-type alone plus co infection of hpv 16 and hpv 18 by scaling the incidence values with the observed distribution of types. There are not sufficient data to accurately project the co-infection with other strains; instead, we distribute the remaining joint infection cases according to the number of observed cancers associated with a single infection of each type involved.

Parameterisation

An MCMC simulation, using an adaptive Metropolis algorithm, was implemented using the FME package in R to simultaneously the parameters defining the natural progression of cytological abnormalities and incidence of cervical cancer for each HPV strain, in a population that is undergoing screening according to the current national algorithm. Each chain was run for a length of 20,000. Clearance and transmission parameters were sampled from the posterior distributions derived previously for each HPV type; 200 distinct combinations were used in total. 50 parallel chains were generated for each clearance-transmission parameter-combination using randomly generated starting values.

As before, a thinning interval of 50 was used to remove auto-correlation within each chain. Convergence was identified using the Geweke test statistic, a test of equality of the means of the first 10% and last 50% of the markov chain. A Gelman convergence diagnostic was then used to confirm convergence of the MCMC output in the parallel chains; a comparison of the empirical variance of each parameter within each chain should be comparable to the variance from all chains combined. The final parameter distributions reflect the joint distribution of the parallel chains generated using all 200 clearance parameter-combinations. Parameter values that best describe the observed cytological outcomes (Table A3) and observed squamous cell carcinoma and adeno carcinoma incidence (Table A4). Model predictions and observed

squamous cell cancer (Figure A4) and adenocarcinoma (Figure A5) incidence, according HPV type.

A4 Parameterisation of Screening Attendance & Treatment

Screening Algorithms

Three alternative strategies are considered: (i) primary cytological screening with HPV testing to determine further management of cytology abnormals ("primary cytology protocol"), which is current screening practices in England; (ii) primary HPV testing ("primary HPV protocol"), with cytology testing to determine further management of HR HPV positives; and (iii) primary HPV testing, as above, with an extended 5 year recall for all women ("5 year primary HPV protocol").

Under the primary cytology protocol, a negative test leads to recall in 3 years (or 5 years for women over 50 years old); a high grade cytological outcome leads directly to a colposcopy referral; and identification of a borderline or mild cytological abnormality is followed by HPV triage where a negative HPV outcome leads to a standard recall, while a positive result leads to an immediate colposcopy referral (Figure A6).

Under the primary HPV protocol, a negative HR HPV test leads to recall to screening in 3 years (or 5 years for women over 50 years old), while a positive HR HPV test results lead to cytological assessment of the same sample; all non-negative cytological results (including borderline) are referred to colposcopy; a negative cytology leads to a 12-month follow up. In the follow up arm, 3 successive positive HR HPV results lead to referral for colposcopy (Figure A7).

Under primary HPV 5 year protocol, a negative HR HPV test leads to recall to screening in 5 years, for all women. A positive HR HPV test results lead to cytological assessment and follow up as defined for the primary HPV protocol.

Age at First Screen

A nelder-mead optimization was used to identify the distribution of age at first cervical screening that is best able to describe the observed fraction of women that have never attended screening with age [source: Cervical Screening Programme 2011-2012]. A lognormally distribution is used to characterise the age at which a women attends her first cervical screen (for age 24.5 years and above) (Figure A8(A)). Model predictions and data reported by the cervical screening programme in Figure A8(B).

Screening adherence

We use the time between two successive screens to identify long-term behavioural screening pattern. The data is restricted to women on routine recall with no history of abnormalities. The interval between the last and penultimate screen is studied in women under 50 year with a prescribed interval of 3 years and data are stratified according to the previous inter-screening time (between screen (*n-2*) and *(n-1)*) – under 2.75, 2.75-3.5, 3.5-4.75, 4.75-5.5, 5.5-7.5, 7.5-10, 10-15 and 15 plus years and never screened). The AIC, in addition to exploration of kurtosis and skew, revealed a log cauchy distribution best describes the observed data (Figure A8(C)); a non linear regression was used to identify best-fitting log-cauchy scale and location parameters as a function of previous inter-screen wait. We interpolate between the predicted mean and 90% interval to give a smooth distribution of inter-screening waiting that is then used to predict the time to next screen given an individual's screening history (Figure A8(D)).

Screening Outcomes

The actions following colposcopy are the same in both protocols. A negative outcome at colposcopy is assumed to lead to discharge to standard recall; CIN1 is untreated but leads to a 12 month follow up; while identification of precancerous lesions of grade CIN2 or worse leads to treatment followed by 'Test of Cure' triage at 6 months.

The sensitivity of cytological testing is explicitly built into the model; cytology outcome is defined probabilistically and varies as a function of time since infection (described above). The sensitivity of the HPV test was assumed to lie between 90-95% for high risk HPV.

Attendance and outcome at colposcopy under a primary cytology protocol are determined by cytology result at referral, as reported by the cervical screening programme 2012-2013 (Table A5). The probability of attending colposcopy, and the likely outcomes, are assumed to be identical for women referred following low-grade cytology followed by HPV positivity under a primary cytology protocol, as for women referred for a positive HPV test followed by low-grade cytology result under a primary HPV protocol(Kelly et al., 2011). Colposcopy outcomes for women referred following a positive HPV test and high-grade cytology, under primary HPV protocol, are not significantly different from those reported following a high grade referral under the current primary cytology protocol. This has been evidenced in preliminary data from the pilot primary HPV programme.

We assume that of all cases of CIN2 or worse that should all be recommended for treatment, 83.1% return for treatment and 66.0% attend follow up appointments (source: cervical screening programme 2012-2013). The split between diagnostic biopsy and excision for those women that undergo treatment was assumed to be 63.2:2.6 in those originally referred due to

low grade abnormalities, and 37.6:49.1 in those attending colposcopy following a high grade referral (source: cervical screening programme 2012-2013). In the absence of recent data to inform this model parameter, the type of procedure recommended is assumed to be unchanged in the context of the HPV primary screening, however, this decision may be sensitive to knowledge that an individual is HR-HPV positive. In accord with previous cost-effectiveness studies of screening in England, the success rate of treatment is assumed to be 95% for clearance of lesions, however, 16% of treated women are assumed to remain HPV positive(Legood et al., 2012).

Age-dependent cancer survival rates

The FIGO stage of cancer is taken to be as reported by the cervical cancer audit according to age at diagnosis (Table A6). Treatment following diagnosis of cervical cancer according to FIGO stage is determined by values reported by the Cervical Cancer Audit, 2010 (Table A7).

Cancer mortality rates are calculated using 1 and 5 years survival rates published by ONS. We describe the survival using an exponential decay function following diagnosis of cancer and estimate an age-dependent mortality hazard. Rates are identified using a nelder-mead optimisation in R (Table A8).

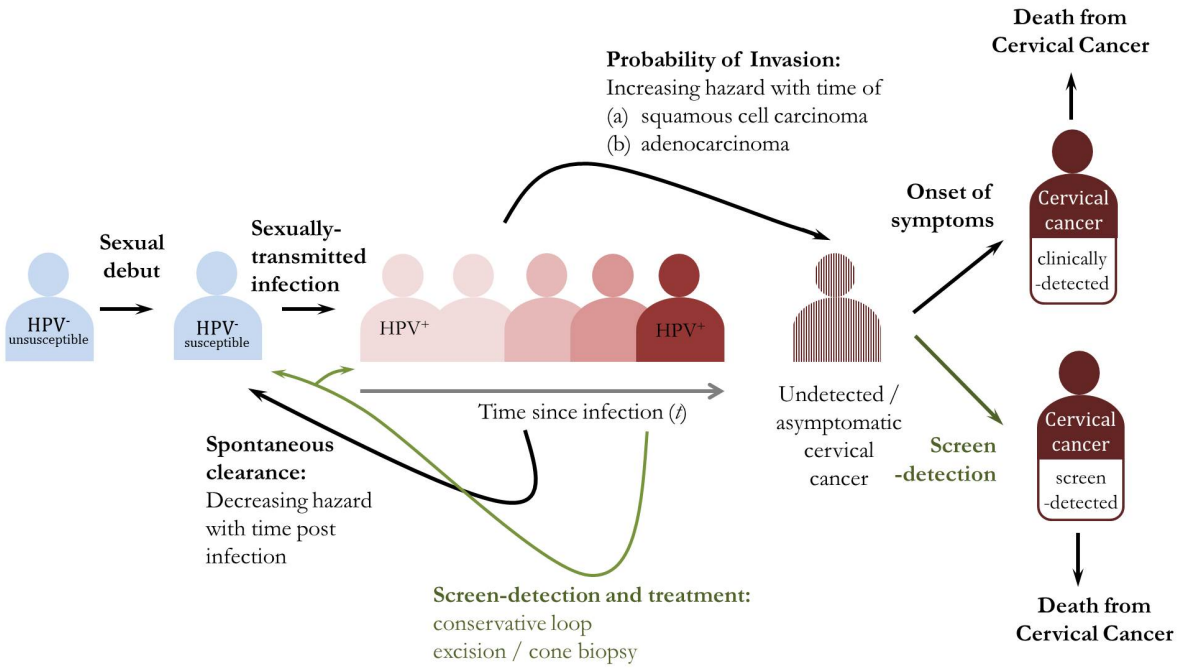


Figure A8. Model outline of HPV transmission and progression to cancer. The model simultaneously considers transmission of HPV-16, 18, 31, 33, 45, 51, 52 and 58

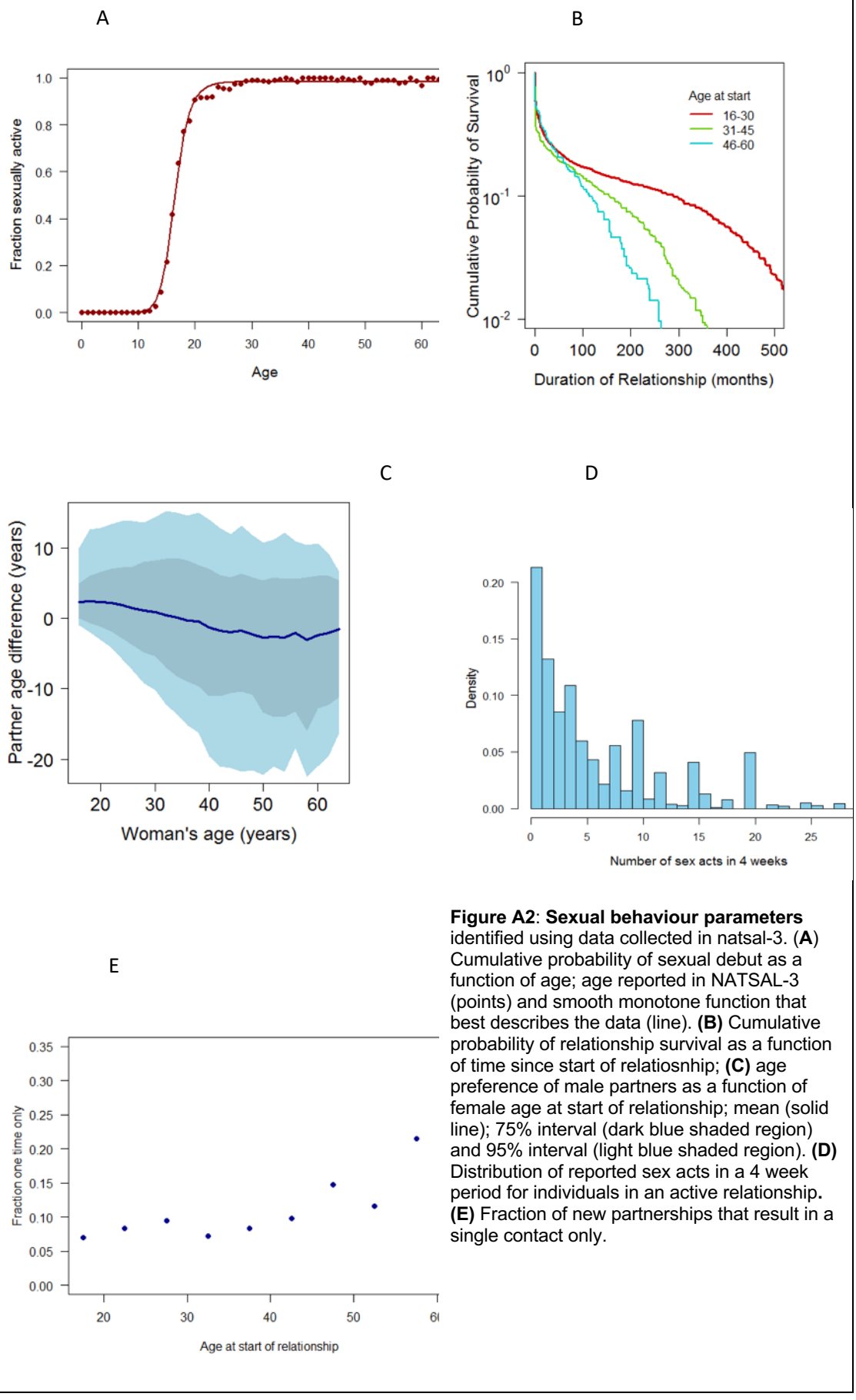


Figure A2: **Sexual behaviour parameters** identified using data collected in natsal-3. (**A**) Cumulative probability of sexual debut as a function of age; age reported in NATSAL-3 (points) and smooth monotone function that best describes the data (line). **(B)** Cumulative probability of relationship survival as a function of time since start of relatiosnhip; **(C)** age preference of male partners as a function of female age at start of relationship; mean (solid line); 75% interval (dark blue shaded region) and 95% interval (light blue shaded region). **(D)** Distribution of reported sex acts in a 4 week period for individuals in an active relationship**.** **(E)** Fraction of new partnerships that result in a single contact only.

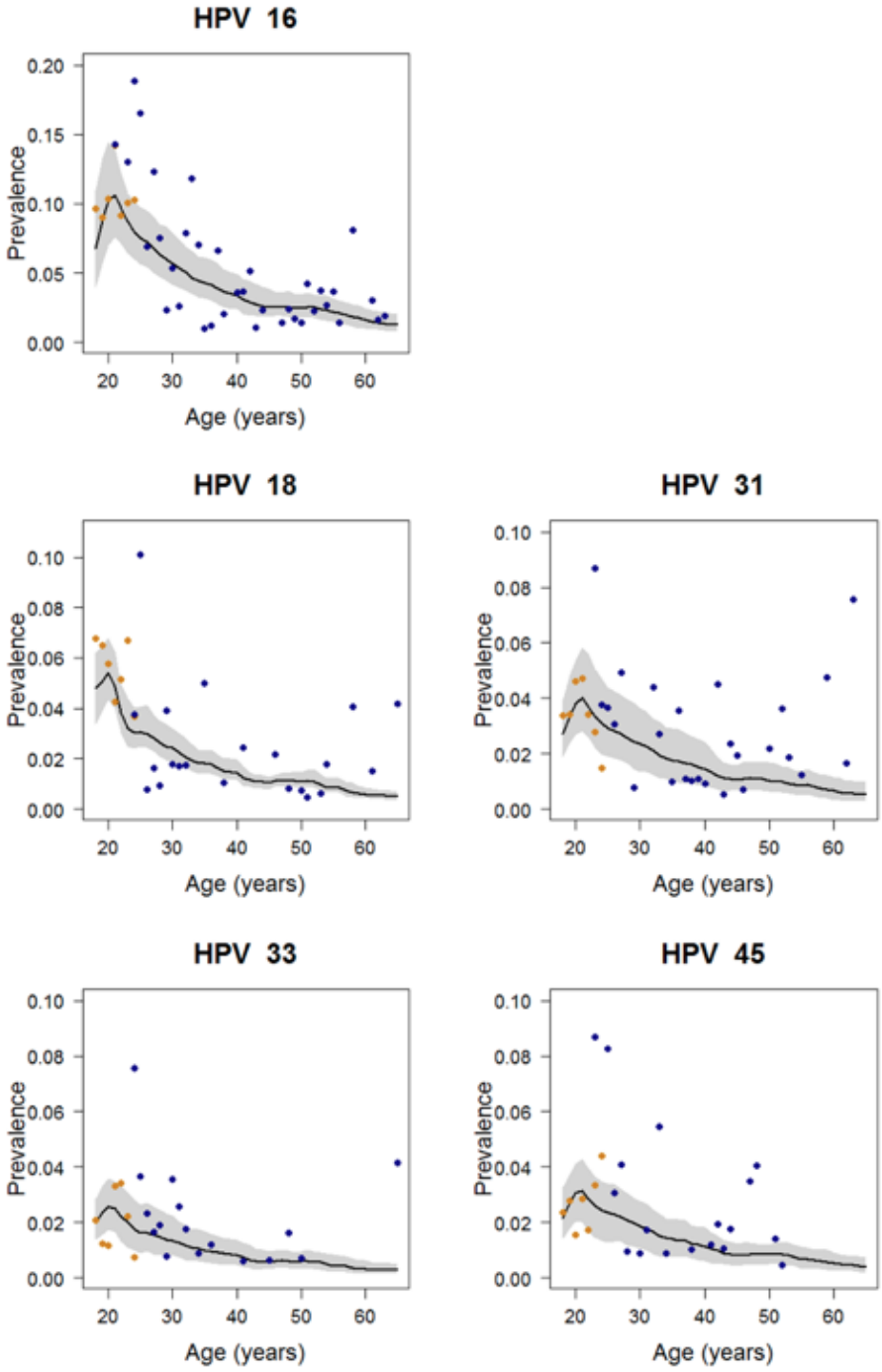


Figure A3: Observed type-specific HPV prevalence measured in residual samples from the NCSP (age 16-24 years – orange points) and NHSCSP (age 24-65 years – blue points) and best-fitting model predictions – mean (solid black line), upper and lower 95% interval (grey shaded region).

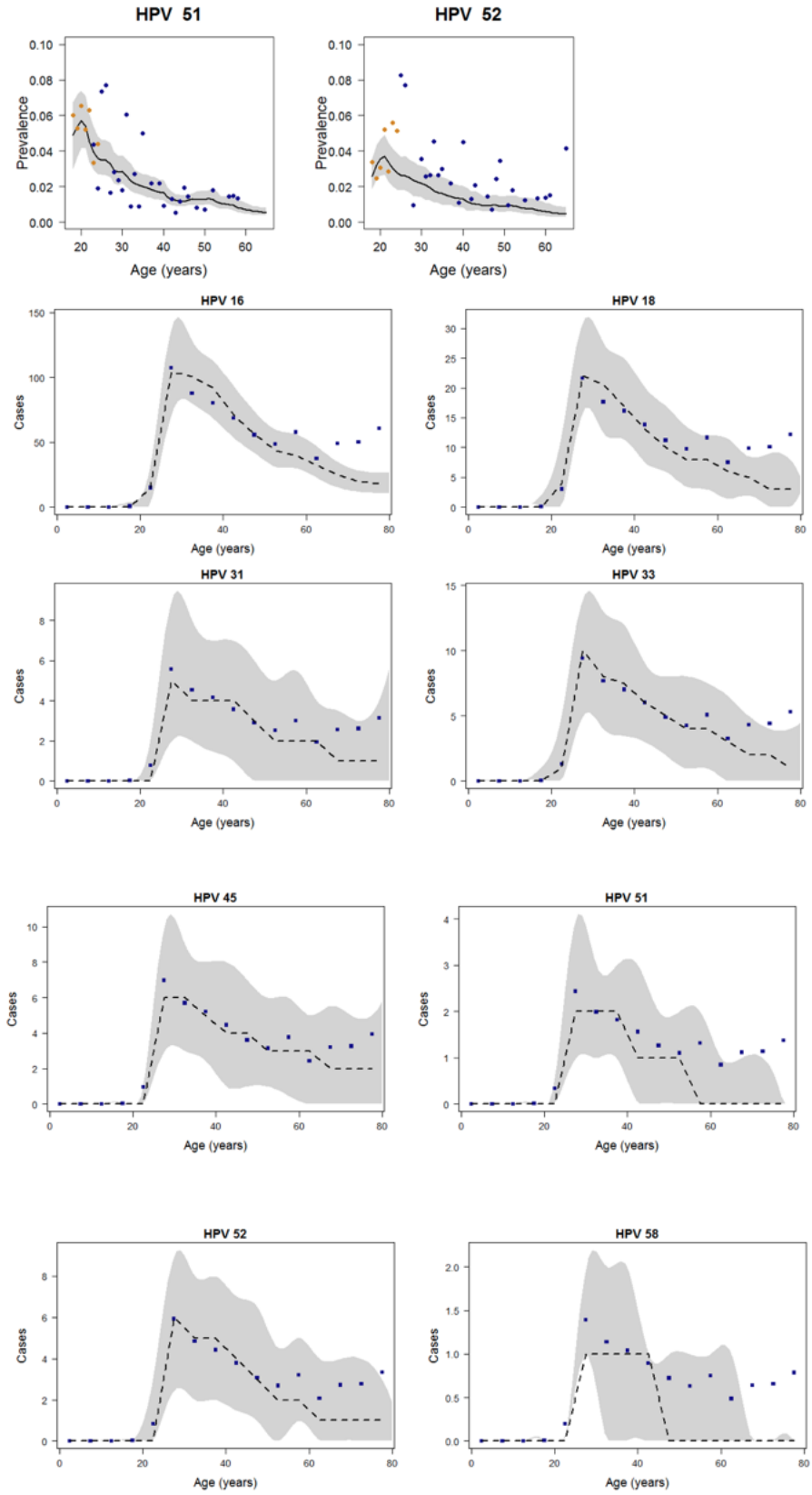


Figure A4: Incidence of squamous cell carcinoma cases attributed to type-specific HPV infections; observed data based on incidence in England in 2012 and HPV-type prevalence detected in SCC tissue samples (filled points) and best-fit model predictions (dashed lines shows median and shaded region represents 95% prediction interval).

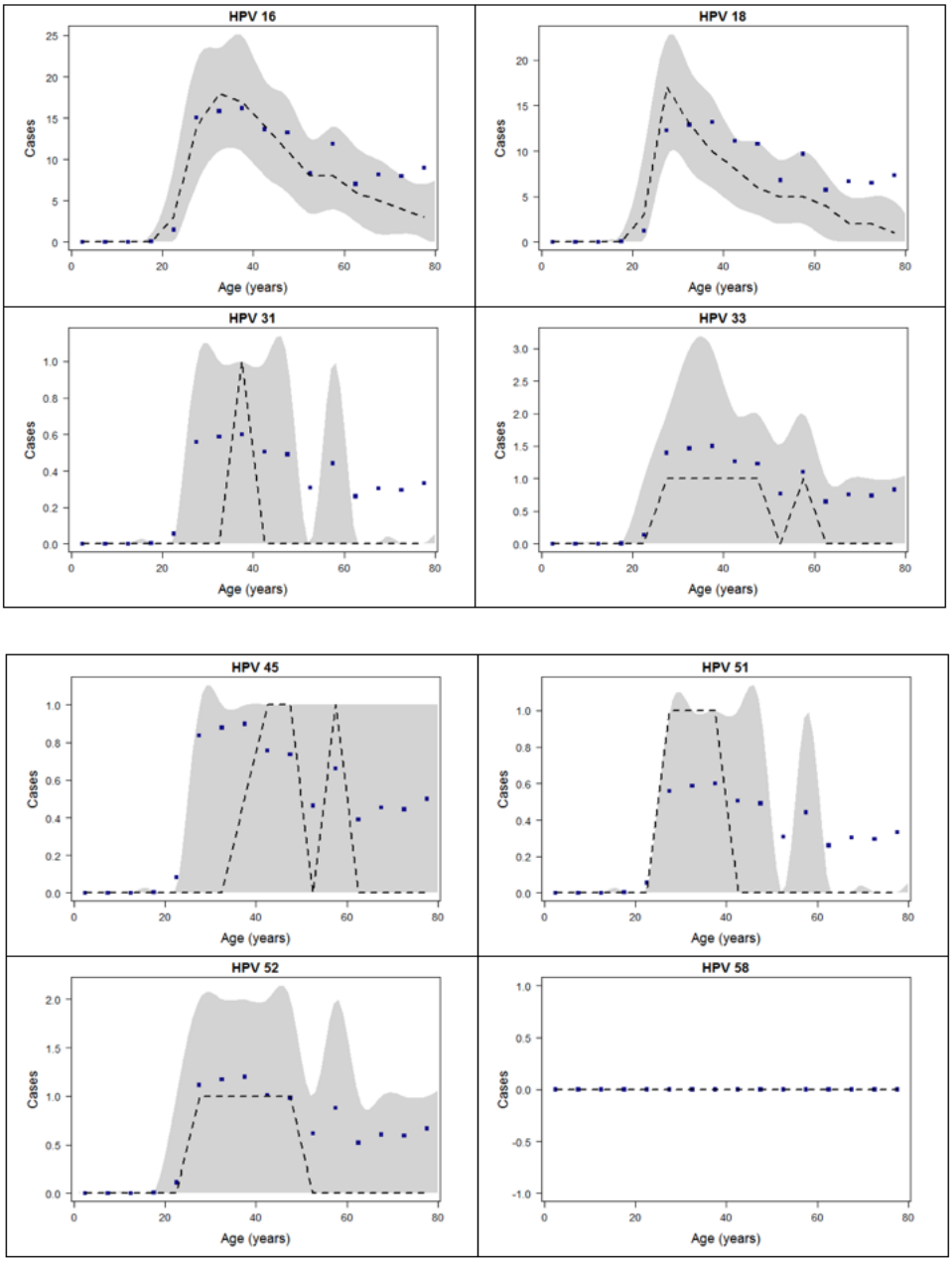


Figure A5: Incidence of adenocarcinoma cases attributed to type-specific HPV infections; observed data based on incidence in England in 2012 and HPV-type prevalence detected in adenocarcinoma tissue samples (filled points) and best-fit model predictions (dashed lines shows median and shaded region represents 95% prediction interval).

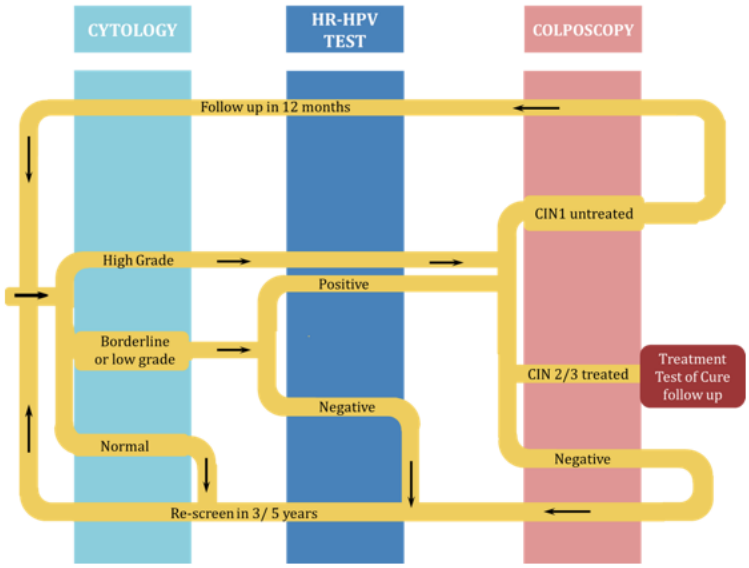


Figure A6: Primary cytology protocol – current screening practise.

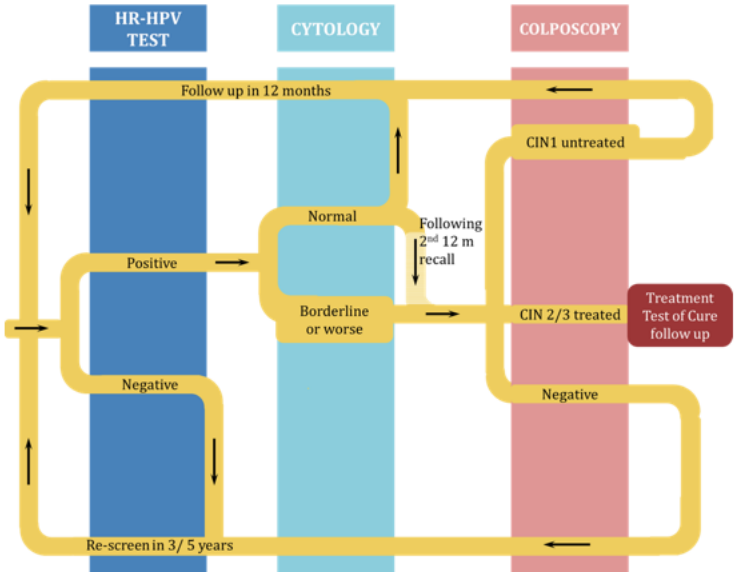
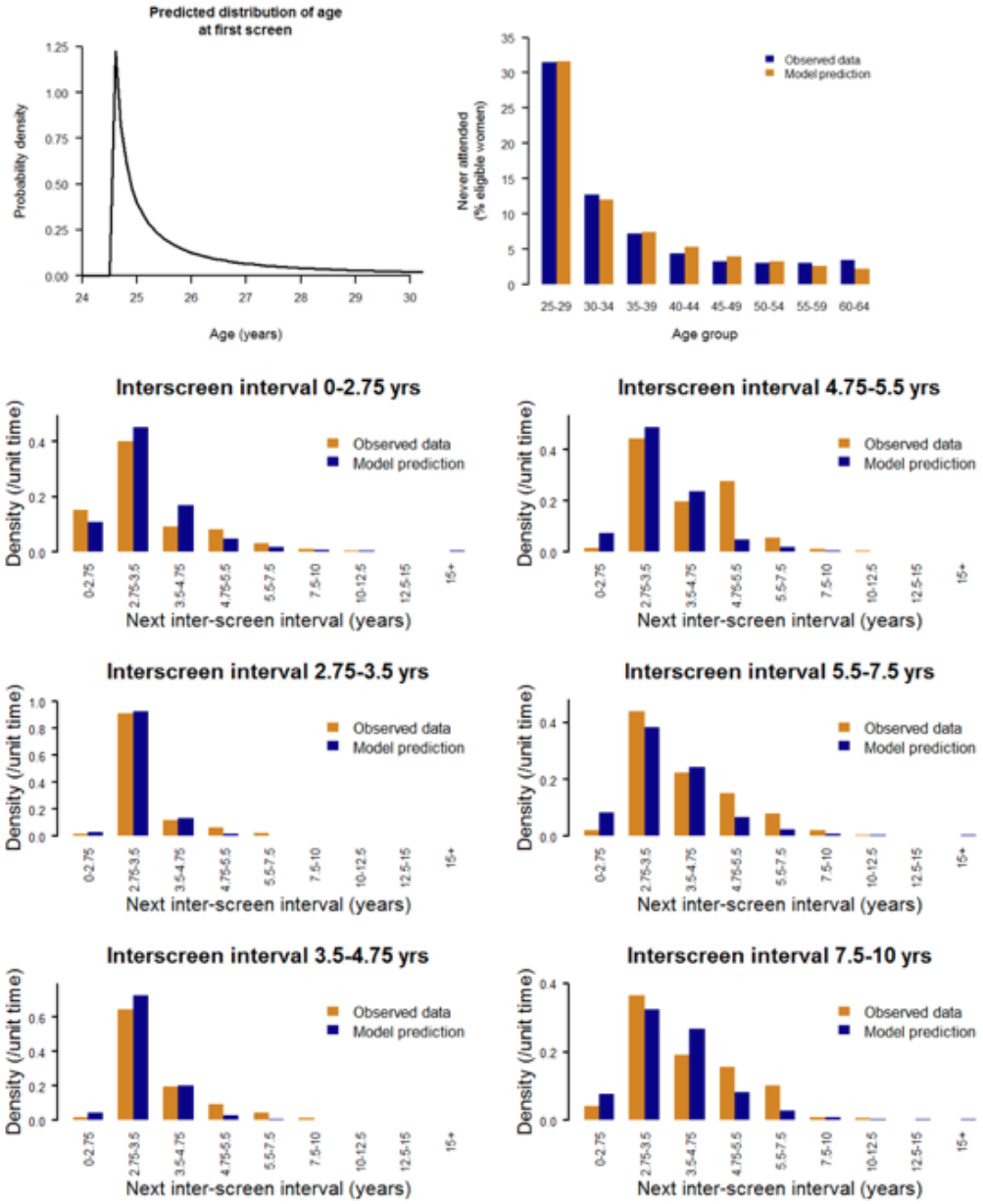


Figure A7: Primary HPV protocol



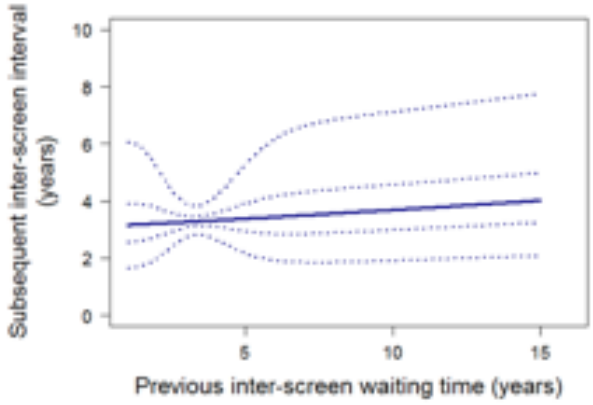


Figure A8: Age at first cervical screen. (A) Best-fit probability density (likelihood) of first attending screening at given age. (B) Model predictions and observed values for percentage of women that have never attended for screening, as a function of age.

Distribution of waiting time to next screen. (C): Observed and predicted distribution of 'next' inter-screen intervals when the previous interval was known to lie in the range 0-2.27, 2.75-3.5, 3.5-4.75, 4.75-5.5, 5.5-7.5 or 7.5-10 years. (D) Best-fitting waiting time percentiles (10th, 25th, 50th, 75th, 90th) as a function of previous inter-screen interval.

Table A1. Rate of partner acquisition predicted for each behavioural category according to age

Age range	Partner acquisition rate (/year)	Sexual Activity Group
16-20	0.419	0
16-20	0.769	1
16-20	1.768	2
16-20	3.872	3
21-25	0.096	0
21-25	0.339	1
21-25	1.312	2
21-25	3.649	3
26-30	0.053	0
26-30	0.103	1
26-30	0.717	2
26-30	2.649	3
31-35	0.026	0
31-35	0.037	1
31-35	0.423	2
31-35	2.519	3
36-40	0.015	0
36-40	0.016	1
36-40	0.216	2
36-40	1.297	3
41-45	0.047	0
41-45	0.039	1
41-45	0.32	2
41-45	1.29	3
46-50	0.048	0
46-50	0.02	1
46-50	0.214	2
46-50	0.968	3
51-55	0.046	0
51-55	0.027	1
51-55	0.124	2
51-55	1.276	3
56-60	0	0
56-60	0.045	1
56-60	0.055	2
56-60	0.161	3
61-65	0	0
61-65	0.027	1
61-65	0.022	2
61-65	0.636	3

Table A2: Best fitting infection clearance and transmission parameters for HPV-16, 18, 31, 33, 45, 51, 52, and 58 (best fitting values and 95% confidence interval.)

Strain	**Weibull shape paramter**	**Weibull scale paramter**	**Cumulative probability of clearance at 24 months in females**	**Per-contact probability of transmission**	**Male sero-conversion (/year)**	**Male rate of clearace (/year)**
HPV 16	0.833	20.8	0.679	0.536	0.042	51.001
	(0.711, 0.92)	(12.7, 30.1)	(0.561, 0.793)	(0.045, 0.98)	(0.002, 0.09)	(1.975, 97.415)
HPV 18	0.818	6.1	0.949	0.58	0.01	49.922
	(0.687, 0.916)	(2.8, 9.4)	(0.93, 0.999)	(0.051, 0.985)	(0.003, 0.03)	(2.61, 96.616)
HPV 31	0.755	18.2	0.713	0.452	0.035	50.609
	(0.618, 0.867)	(11.4, 24.3)	(0.628, 0.808)	(0.023, 0.95)	(0.014, 0.049)	(2.538, 97.065)
HPV 33	0.738	9.5	0.845	0.422	0.037	51.348
	(0.587, 0.867)	(5.3, 13.9)	(0.782, 0.913)	(0.012,0.966)	(0.014, 0.0049)	(2.776, 96.175)
HPV 45	0.748	13.7	0.774	0.418	0.036	49.239
	(0.598, 0.867)	(8.2, 19.5)	(0.69, 0.861)	(0.019, 0.974)	(0.01, 0.05)	(3.561, 97.703)

HPV 51	0.813	5.7	0.907	0.518	0.012	50.723
	(0.686, 0.908)	(2.6, 10.4)	(0.86, 0.993)	(0.042, 0.975)	(0.002, 0.032)	(2.848, 98.391)
HPV 52	0.786	17.9	0.721	0.454	0.037	48.677
	(0.658, 0.892)	(11.9, 23)	(0.644, 0.801)	(0.024, 0.97)	(0.016, 0.049)	(2.464, 97.512)
HPV 58	0.799	11.4	0.803	0.486	0.02	49.638
	(0.655, 0.894)	(5.8, 19.6)	(0.695, 0.925)	(0.037, 0.965)	(0.004, 0.044)	(3.281, 96.428)

Table A3. Model parameters that best describe the occurance of cytological abnormalities with time since infection.

	pnorm1	**pnorm2**	**pbord**	**pmild**	**pmod**	**Expected wait to abnormality (years)**
HPV 16	0.334	0.001	0.723	0.658	0.737	3
	(0.08, 1.574)	(0, 0.004)	(0.09,1.907)	(0.046, 1.912)	(0.048, 1.906)	
HPV 18	1.381	0.005	1.098	0.848	0.954	0.7
	(0.233, 1.982)	(0, 0.038)	(0.13, 1.944)	(0.045, 1.939)	(0.057, 1.939)	
HPV 31	0.187	0	0.575	0.606	0.845	5.3
	(0.018, 0.938)	(0, 0.001)	(0.03, 1.911)	(0.023, 1.893)	(0.037, 1.948)	
HPV 33	0.421	0	0.451	0.123	0.838	2.4
	(0.121, 1.671)	(0, 0.003)	(0.103, 1.685)	(0.021, 0.491)	(0.065, 1.945)	
HPV 45	0.15	0.001	0.91	0.86	0.937	6.6
	(0.006, 0.203)	(0, 0.007)	(0.039, 1.928)	(0.031, 1.945)	(0.047, 1.939)	
HPV 51	0.998	0.004	0.827	0.723	0.933	1
	(0.126, 1.965)	(0, 0.039)	(0.062, 1.87)	(0.026, 1.887)	(0.046, 1.953)	
HPV 52	0.144	0.001	0.678	0.677	0.841	6.9
	(0.028, 0.43)	(0, 0.005)	(0.039, 1.901)	(0.021, 1.916)	(0.036, 1.942)	

Table A4. Squamous cell carcinoma and adenocarcinoma. Parameters that best fit the observed incidence data (man and 95%confidence interval).

	Squamous cell carcinoma			**Adenocarcinoma**		**Time delay (years)**	
Strain	Gamma shape parameter	Gamma rate parameter	Rate of clinical diagnosis	Gamma shape parameter	Gamma rate parameter	Infection to detecting SCC	Infection to detecting ADC
	Median (95% interval)						
HPV 16	5.643	0.024	0.01	4.995	0.01	15.3	2.083
	(3.05, 8.175)	(0.007, 0.041)	(0.008, 0.015)	(1.516, 12.708)	(0.004, 0.022)	(4.9, 40.6)	(0.083, 11.833)
HPV 18	15.006	0.121	0.013	37.931	0.129	10.1	1.667

	(2.419, 71.206)	(0.004, 0.704)	(0.009, 0.23)	(2.461, 116.636)	(0.01, 1.154)	(3.6, 34.1)	(0.5, 4.913)
HPV 31	5.987	0.019	0.014	6.221	0.005	16.5	5.792
	(2.87, 39.785)	(0.004, 0.184)	(0.01, 0.035)	(2.584, 82.779)	(0.003, 0.016)	(6.6, 37.1)	(1.167, 17.944)
HPV 33	5.529	0.017	0.011	6.212	0.01	15	2
	(2.709, 10.238)	(0.004, 0.044)	(0.008, 0.016)	(1.174, 39.1)	(0.004, 0.125)	(4.2, 39.8)	(0.167, 8.492)
HPV 45	3.823	0.005	0.02	7.096	0.004	24	21.333
	(3.266, 5.261)	(0.003, 0.009)	(0.01, 0.314)	(2.998, 33.578)	(0.003, 0.01)	(5.9, 69.3)	(3.635, 61.406)
HPV 51	5.184	0.011	0.054	6.925	0.009	12.7	>100
	(3.859, 9.658)	(0.005, 0.036)	(0.011, 0.287)	(2.269, 118.528)	(0.003, 0.384)	(5.5, 25.5)	>100
HPV 52	5.922	0.019	0.011	5.572	0.011	16	3.417
	(3.709, 17.508)	(0.006, 0.076)	(0.008, 0.033)	(1.395, 44.809)	(0.003, 0.118)	(6.8, 41.8)	(0.25, 10.465)
HPV 58	75.067	0.004	0.015	79.617	0.003	20.8	>100
	(4.989, 179.38)	(0.003, 0.025)	(0.009, 1.212)	(7.121, 187.572)	(0.003, 0.021)	(18.6, 23)	>100

Table A5: Colposcopy outcomes under primary cytology algorithm (annual screening report 2012-2013), and preliminary outcomes form primary HPV pilot sites (October 2014).

	Percentage attendance	**Probability of normal outcome**	**Probability CIN1 detected**	**Probability CIN2 or worse detected**
Current screening practise				
Borderline or Mild referral (n=21,977)	75.2%	55.4%	26.9%	17.7%
Moderate or worse referral (n=38,570)	78.0%	7.4%	8.1%	84.5%
Preliminary Primary HPV pilot outcomes				
Borderline or Mild referral (n=1473)	79.6%	66.1%	17.6%	16.4%
Moderate or worse referral (n=853)	88.0%	10.9%	6.1%	83.0%

Table A6: Observed state of cancer progression, according to age at diagnosis (source: Cervical Cancer Audit, 2010)

Age at diagnosis (years)	**Cancer stage at diagnosis**					
	1A	1B	1B+	2	3	4
25	47.8%	35.4%	5.3%	6.2%	1.8%	5.3%
25 - 49	48.9%	35.7%	3.8%	7.7%	2.6%	3.0%
50 - 64	21.3%	33.9%	8.3%	17.9%	11.3%	8.3%
65 and over	6.6%	27.7%	8.4%	26.6%	17.9%	8.4%

Table A7: Treatment of cancers according to stage at diagnosis (source: Cervical Cancer Audit, 2010)

Treatment	**Cancer stage at diagnosis**					
	1A	1B	1B+	2	3	4
None	4.6%	5.4%	19.8%	8.6%	12.3%	19.6%
Cone	69.6%	18.1%	15.8%	0.7%	1.0%	15.8%
Trachelectomy	1.0%	5.6%	1.0%	0.2%	0.0%	1.0%
Hysterectomy only	20.4%	46.0%	19.8%	7.6%	1.5%	19.8%
Radiotherapy (+/- hysterectomy)	1.5%	6.9%	8.9%	20.7%	24.1%	8.9%
Chemotherapy (+/- hysterectomy)	40.0%	2.0%	4.0%	3.8%	6.9%	4.0%
Chemo-radio therapy (+/- hysterectomy)	2.6%	16.1%	30.7%	58.4%	54.2%	30.7%

Table A8: Age dependent mortality rate following diagnosis of cervical cancer

Age at diagnosis (years)	**Rate of mortality**
15 - 39	0.03
40 - 49	0.05
50 - 59	0.10
60 - 69	0.14
70 - 79	0.28
80 - 99	0.50

	Age									
	25 - 29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	All
Number of cytology tests	113,506	78,541	56,889	48,383	42,112	27,393	17,042	11,200	1,362	396,427
	(105389, 114472)	(74504, 78933)	(53111, 55944)	(46243, 48825)	(39612, 42050)	(25933, 27757)	(16009, 17381)	(9858, 10867)	(1148, 1330)	(371807, 397559)
Normal cytology	73,074	50,432	36,920	31,457	28,136	18,188	11,007	7,096	836	257,145
	(64168, 78791)	(45013, 54626)	(32069, 38938)	(28284, 34286)	(25077, 30190)	(16254, 19760)	(9638, 12098)	(5814, 7359)	(655, 860)	(226971, 276908)
Borderline changes	30,994	21,683	15,517	13,164	10,922	7,214	4,671	3,159	401	107,725
	(21793, 36741)	(14651, 25864)	(10289, 18471)	(8886, 15767)	(7442, 12888)	(4945, 8855)	(3193, 5661)	(2090, 3623)	(253, 460)	(73542, 128330)
Mild dyskariosis	7,257	4,969	3,497	2,972	2,440	1,602	1,073	731	94	24,634
	(4723, 9877)	(3185, 6839)	(2255, 4882)	(1879, 4219)	(1519, 3328)	(976, 2270)	(697, 1551)	(414, 982)	(49, 133)	(15695, 34081)
Moderate dyskariosis	1,845	1,194	776	640	499	319	238	172	25	5,707
	(1083, 2685)	(707, 1685)	(438, 1121)	(356, 939)	(270, 741)	(166, 496)	(115, 365)	(75, 254)	(9, 37)	(3218, 8324)
Severe dyskariosis	336	264	178	150	116	70	54	42	7	1,216
	(180, 617)	(140, 438)	(86, 298)	(70, 251)	(45, 193)	(24, 126)	(14, 101)	(10, 77)	(0, 15)	(571, 2117)
Number of HPV tests	534,958	482,996	467,561	497,392	498,222	314,147	251,361	237,779	31,497	3,315,913
	(518021, 546789)	(474732, 489592)	(461472, 471726)	(491570, 502147)	(492793, 503145)	(309440, 317970)	(247543, 254962)	(233619, 241097)	(30814, 31922)	(3260003, 3359351)
HPV negative	412,632	391,942	402,178	441,725	450,358	282,194	232,278	225,190	29,875	2,868,372
	(401386, 426502)	(386528, 399381)	(399189, 408371)	(437474, 446959)	(446632, 456481)	(278643, 286118)	(228997, 236072)	(222024, 229184)	(29343, 30415)	(2830218, 2919485)
HPV positive	122,326	91,054	65,383	55,667	47,865	31,953	19,082	12,589	1,623	447,541
	(113558, 123359)	(86234, 91814)	(60973, 64874)	(52903, 56426)	(44998, 47996)	(30054, 32422)	(17890, 19516)	(11037, 12250)	(1370, 1588)	(419017, 450246)
Number of	38,065	31,536	22,076	18,743	15,257	10,638	6,231	4,233	607	147,386

colposcopies										
	(32166, 40496)	(27849, 32794)	(19316, 22897)	(16463, 19682)	(13234, 15979)	(9342, 11255)	(5438, 6724)	(3487, 4337)	(495, 631)	(127789, 154795)
Normal	19,937	16,615	11,667	9,913	8,085	5,653	3,284	2,221	317	77,693
	(16752, 21421)	(14534, 17413)	(10094, 12311)	(8562, 10581)	(6890, 8630)	(4848, 6068)	(2798, 3620)	(1793, 2346)	(243, 341)	(66514, 82732)
CIN 1	9,755	8,123	5,701	4,845	3,950	2,763	1,606	1,087	155	37,985
	(8203, 10585)	(7098, 8627)	(4844, 6061)	(4116, 5193)	(3314, 4272)	(2339, 3029)	(1340, 1827)	(836, 1192)	(116, 170)	(32204, 40955)
CIN 2 or worse	8,373	6,798	4,709	3,985	3,221	2,221	1,341	925	135	31,708
	(6910, 9209)	(5808, 7293)	(3987, 5048)	(3356, 4343)	(2672, 3505)	(1859, 2461)	(1099, 1520)	(696, 1014)	(95, 150)	(26483, 34545)

Table A9: Model-generated number and outcome of HPV, cytology and colposcopy tests, per annum, under a primary HPV protocol; mean (lower & upper bound). Resident female population size and age demographic as observed in England in 2013 (source: ONS).

Table A10: Model-generated number and outcome of cytology and HPV tests, per annum, under a primary cytology protocol; mean (lower & upper bound). Resident female population size and age demographic as observed in England in 2013 (source: ONS).

	Age									
	25 - 29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	All
Number of cytology tests	498,982	443,941	446,286	474,101	480,892	297,605	242,291	231,932	29,793	3,145,825
	(483878, 512076)	(435589, 451841)	(440521, 451989)	(468438, 479485)	(475125, 486310)	(293318, 302020)	(238576, 245884)	(227991, 235779)	(29127, 30326)	(3092564, 3195711)
Normal cytology	412,036	399,523	407,046	436,011	445,027	282,333	230,835	222,199	28,598	2,863,609
	(398179, 428036)	(391129, 409680)	(399963, 415734)	(428581, 444739)	(437575, 454053)	(277634, 287429)	(226887, 234950)	(218173, 226704)	(27966, 29213)	(2806087, 2930539)
Borderline changes	50,691	30,266	26,259	25,065	23,365	11,157	8,290	6,968	852	182,912
	(39466, 59278)	(23093, 35795)	(20093, 30876)	(18903, 29785)	(17509, 27851)	(8105, 14092)	(5981, 10573)	(4851, 8870)	(566, 1111)	(138567, 218231)
Mild dyskariosis	25,302	10,390	9,543	9,565	9,193	3,157	2,409	2,092	258	71,910

	(19830, 31901)	(6872, 13693)	(6072, 13036)	(5861, 13303)	(5424, 12862)	(1845, 4708)	(1337, 3672)	(1002, 3218)	(113, 414)	(48355, 96806)
Moderate dyskariosis	6,462	2,423	2,122	2,076	1,948	609	476	409	50	16,576
	(3383, 9588)	(990, 3853)	(710, 3629)	(568, 3707)	(447, 3656)	(177, 1316)	(127, 1052)	(89, 1002)	(9, 127)	(6500, 27929)
Severe dyskariosis	4,490	1,339	1,317	1,384	1,359	349	281	264	34	10,819
	(1726, 6872)	(226, 2743)	(162, 2846)	(125, 3004)	(102, 3077)	(35, 1075)	(24, 912)	(18, 877)	(1, 109)	(2418, 21514)
Number of HPV tests	79,762	44,502	38,644	37,023	34,456	15,538	11,486	9,641	1,177	272,228
	(69200, 89395)	(36019, 50922)	(30880, 44450)	(29001, 43007)	(26609, 40011)	(12144, 18541)	(8913, 14207)	(7156, 11796)	(852, 1455)	(220774, 313783)
HPV negative	47,335	21,399	21,356	22,679	22,642	8,369	6,735	6,404	820	157,739
	(39064, 55019)	(15231, 26365)	(15017, 26678)	(15726, 28588)	(15640, 28593)	(5710, 11358)	(4568, 9517)	(4223, 8939)	(534, 1163)	(115711, 196221)
HPV positive	32,427	23,103	17,288	14,344	11,814	7,169	4,750	3,237	357	114,489
	(25567, 38220)	(18142, 27066)	(13498, 20284)	(11314, 16924)	(9158, 13639)	(5518, 8728)	(3736, 5718)	(2429, 3694)	(255, 414)	(89616, 134687)
Number of colposcopies	32,687	20,252	15,622	13,419	11,395	6,125	4,151	2,948	333	106,931
	(25702, 37379)	(16269, 23738)	(12428, 18423)	(10517, 15983)	(8738, 13506)	(4682, 7340)	(3159, 5058)	(2118, 3480)	(211, 400)	(83824, 125307)
Normal	20,405	11,423	9,054	7,978	6,943	3,438	2,349	1,705	195	63,490
	(15428, 23532)	(8924, 13732)	(6964, 10953)	(5874, 9918)	(4926, 8739)	(2470, 4296)	(1656, 3058)	(1098, 2193)	(117, 260)	(47456, 76680)
CIN 1	6,690	4,773	3,568	2,961	2,436	1,476	980	669	74	23,627
	(5158, 7987)	(3715, 5633)	(2749, 4201)	(2239, 3532)	(1815, 2858)	(1087, 1823)	(713, 1213)	(469, 797)	(43, 90)	(17987, 28133)
CIN 2 or worse	5,591	4,056	3,000	2,480	2,016	1,211	822	574	64	19,813
	(4386, 6599)	(3213, 4718)	(2390, 3478)	(1941, 2921)	(1541, 2347)	(919, 1467)	(628, 1017)	(400, 684)	(40, 78)	(15456, 23309)

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