Institution: King's College London		
Unit of Assessment: UoA1		
Title of case study: Influencing and informing the introduction of human papillomavirus testing into England's cervical screening programme through evidence-based research		
Period when the underpinning research was undertaken: 2018 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Dr Matejka Rebolj Mr Christopher Mathews	Role(s) (e.g. job title): Senior Epidemiologist (MR), Senior Data Manager (CM)	**Period(s) employed by submitting HEI:** Both Jan 2018 – present
Period when the claimed impact occurred: February 2018 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

The NHS Cervical Screening Programme in England tests 3,500,000 women per year, to prevent cervical cancer. When the UK National Screening Committee decided to implement HPV primary screening – to replace the cytological 'smear test' – for women aged 25-64, they first recommended a pilot to confirm the benefits of a national rollout. King's researchers were commissioned to monitor and evaluate the epidemiological data from this pilot. The findings of their work heavily influenced and informed the implementation of this new approach to screening. King's work helped the UK National Screening Committee, Public Health England and the NHS choose which labs were the most appropriate to carry out the screening tests and gave expert advice to commissioners and providers of cervical screening services. They informed major service redesign of the operational delivery of the screening programme, specifically leading to the change in the screening interval from 3 to 5 years and the decision that screening labs would not be required to carry out genotyping tests in HPV-positive women. Their work was also used by European professional organisations to inform the internationally preferred approaches to cervical screening and subsequent diagnostic testing of women.

2. Underpinning research

Around 3200 women in the UK are diagnosed with cervical cancer each year, of whom 850 will die. Cervical screening helps prevent cervical cancer from developing and saves thousands of lives every year in the UK. The primary goal of screening is to identify precancerous lesions caused by human papillomavirus so they can be removed to prevent invasive cancers from developing. A secondary goal is to find cervical cancers at an early stage, when they can usually be treated successfully. Cervical screening needs to be repeated throughout most of a woman's adult life, as protection from a single test wanes over time. The UK has used cytology for cervical screening since the 1960's, and around 3,500,000 women aged 25-64 are tested per year; of these, more than 100,000 are referred for diagnostic procedures. For many years, cytology-based screening (known as the smear test) was the only method of screening.

Human papillomavirus (HPV) testing is a cervical cancer screening test that performs better than cytology. Virtually all cases of cervical cancer are caused by infection with sexually transmitted oncogenic, or high-risk, types of HPV. Numerous epidemiological studies, including several randomised controlled trials, have shown that HPV testing finds more preinvasive lesions than cytology. Like cytology, HPV testing is based on the material sampled from cervical mucus, but once it arrives in a laboratory, it is analysed by a machine rather than by visual inspection of a slide. The HPV test checks whether a woman has an HPV infection which may lead to cervical cancer. Cytology checks for whether cells in the cervix are abnormal (precancerous). For England, it was estimated that this alternative method of testing could prevent more than 500 additional cases of cervical cancer per year.

However, before it was possible to implement a national roll-out of HPV testing, the UK National Screening Committee (UKNSC), Public Health England (PHE), and NHS England (NHSE) required contemporary data on the practicability of HPV testing from the screening laboratories, general practitioners and colposcopy clinics in England. Between 2013 and 2016, PHE

commissioned an HPV testing pilot in six routine NHS screening laboratories, which included ~1,300,000 women screened by either HPV testing or cytology. To date, the pilot represents the largest and most comprehensive observational evidence of HPV testing from a routine national screening programme. It was designed and has been overseen by a multidisciplinary steering committee comprised of representatives of PHE and NHS, the participating laboratories, clinicians, and academic institutions. The initial epidemiological evaluation and data monitoring of the pilot was led by Professor Sue Moss and colleagues at Queen Mary University of London until her retirement. From 2018, this work has been led and further developed by King's researchers Dr Matejka Rebolj (principal investigator) and Mr Christopher Mathews (senior data manager).

King's epidemiological evaluation addressed two priority issues for the implementation of England's national roll-out of HPV testing. Based on the encouraging preliminary results from the pilot, in 2016 the UKNSC made an initial recommendation that HPV testing should replace cytology, however, it was not possible to implement this change without further research on the safety, effectiveness and essential components of such a programme. King's researchers undertook a substantial epidemiological evaluation of the pilot data, from 2018 onwards, and provided crucial answers to the questions necessary to inform the nature and implementation of the national roll-out of HPV testing as recommended by the UKNSC.

1. King's research confirmed the safety profile of human papillomavirus testing (1). Before implementing HPV testing, the encouraging findings from the randomised trials carried out in other countries needed to be replicated within the routine setting of the English screening programme. All previous randomised trials utilised two types of HPV tests which were no longer in use, and the challenge for the English screening programme was to demonstrate that it could achieve the same impressive results by using alternative tests that were becoming commercially available. King's researchers' analysis of pilot data collected using such alternative tests confirmed a substantially increased detection of high-grade preinvasive lesions at any age (>50%) compared to smear tests. Furthermore, data from ~33,000 women aged <50 years with negative HPV tests, who were rescreened after 3 years in line with the national guidelines at the time, showed no new cases of cervical cancer and very few new preinvasive lesions. By contrast, data from ~77,000 women with negative cytology at first testing showed 15 new cervical cancer cases at the subsequent screen 3 years later, and a substantially higher number of new preinvasive lesions. Collection of data for women aged ≥50, who were recommended to have a 5-year screening interval, is still on-going.

2. King's research demonstrated negligible clinical benefit of using human papillomavirus typing to prioritise cytology-negative women with (persistent) infections for colposcopy (2). Owing to the very high prevalence of HPV infections, most of which are harmless, screening based on HPV testing requires triage testing, which involves several stages of testing to identify specific sub-groups of women with a higher risk of lesions. Virtually all HPV screening programmes globally are using cytology for triage, however, for fear of missing progressive preinvasive lesions in women with negative triage cytology, some programmes additionally use HPV genotyping to identify whether the highest risk type infections (16 and 18) are present. Some commercial HPV tests offer a genotyping function automatically but others do not, and so some English screening labs were set up to run HPV testing with genotyping, while others were not. Consequently, a decision on whether or not this extra test was a necessary component of the English screening programme would determine how the HPV testing was implemented (or 'which tests or labs were suitable'). This HPV-16/18 typing was used in three pilot laboratories for women with persistent infections and negative cytology results at the 12-month re-test (representing about 4% of the screened population). King's researchers showed that the benefit of typing to the programme is minimal at most, and could safely be replaced by a re-test at 24 months for HPV-16/18 positive women, which was already proposed to be in place for women with non-16/18 HPV infections anyway (as piloted in the remaining three laboratories). In other words, this provided categorical evidence that a further, more specialised round of triage testing to identify the HPV infection type after initial cytological triage had no meaningful impact on the detection of preinvasive lesions. Importantly, this also gave clear evidence that the capacity to run HPV testing with 16/18 genotyping should not be a criterion for laboratories to carry out the screening since it had no effect on the number of cancers that could be prevented.

3. References to the research

1. Rebolj M, Rimmer J, Denton K, Tidy J, **Mathews C**, Ellis K, Smith J, Evans C, Giles T, Frew V, Tyler X, Sargent A, Parker J, Holbrook M, Hunt K, Tidbury P, Levine L, Smith D, Patnick J, Stubbs R, Moss S, Kitchener H. Primary Cervical Screening With High Risk Human Papillomavirus Testing: Observational Study. *BMJ* 2019;364:l240. doi: 10.1136/bmj.l240.

2. Rebolj M, Brentnall AR, **Mathews C**, Denton K, Holbrook M, Levine T, Sargent S, Smith J, Tidy J, Tyler X, Kitchener H. 16/18 Genotyping in Triage of Persistent Human Papillomavirus Infections With Negative Cytology in the English Cervical Screening Pilot. *Br J Cancer* 2019;121:455-463. doi: 10.1038/s41416-019-0547-x.

4. Details of the impact

Given the nature of this work, the research and impact described for this case study happened largely in parallel from 2018 onwards, with the evaluation of pilot data **(1,2)** happening hand in glove with the decision-making process around the implementation of HPV testing in England, the rollout itself, and the dissemination of results to healthcare professionals. Once King's academics had completed the analysis and evaluation of the HPV testing pilot data **(1, 2)**, they presented the findings of this PHE-commissioned project to UKNSC, PHE and NHSE in early 2018 (before publication of the academic papers describing the results). These heavily influenced and informed the English NHS Cervical Screening Programme, and in 2019, the national roll-out of HPV primary screening for women aged 25-64 was completed. King's research was showcased by PHE as one of its flagship studies and King's academics were invited to present the findings to hundreds of healthcare professionals at various scientific and educational events **(A)**. King's researchers were also invited to present the findings from the pilot to those involved in changing the cervical screening programme in Ireland **(A.3)**. On behalf of the pilot group, King's has communicated the benefits of these changes to the screening programme through various mass media outlets including BBC Radio 4, The Sun, and The Daily Mail to raise public awareness **(B)**.

King's researchers provided evidence that allowed the national roll-out of human papillomavirus (HPV) primary screening to go ahead (C). King's analyses of the English pilot data (commissioned by PHE) contributed to the evidence which reassured decision makers of the effectiveness of HPV testing in preventing cervical cancer. On the back of this King's-led research, the English Cervical Screening Programme proceeded with the planned national roll-out of HPV primary screening. The National Programme Manager for the National Cervical Screening Programme for England has said: "*The evaluation [led by King's] has proved to be pivotal in providing the data and evidence to inform the decision from the UKNSC to recommend to Ministers the implementation of HPV Primary screening in the wider screening programme (…) A subsequent Independent Cancer Taskforce Report, 'Achieving world class outcomes' stated that full national coverage for HPV primary testing would be achieved by 2020. This target was achieved, and HPV Primary screening was fully implemented across the nation in December 2019* **(D)**."

Kings helped NHSE choose which labs were the most appropriate to carry out the screening tests (and which tests were required) for the English programme. After King's demonstrated 16/18 genotyping wasn't sufficiently beneficial **(2)**, the 2018 national tender to select the laboratories to provide HPV testing for the screening programme did not require them to be able to carry out genotyping tests. King's work **(2)** was one of the crucial pieces of evidence that led UKNSC to recommend only cytology-based triage of women with HPV infections regardless of the infecting type **(E)**, thus shaping the criteria of the tender process. This was confirmed by the Manager of the Screening Programme: "*King's analysis informed the UKNSC decision and showed that women with positive screening test results can be managed just as effectively without information on viral genotyping. This simplified the national guidelines on triage of human papillomavirus positive women. The simplification of the pathway provides a uniform approach that is clear for providers to adhere to and reduces risk in the programme (…) Every aspect of the planning and delivery of HPV primary screening has been informed by the evidence from Dr Rebolj and Mr Mathews* **(D)**."

Furthermore, the decision not to require HPV typing as part of the triage testing of HPV-positive women, has beneficially impacted the potential cost savings for the NHS. Had typing been recommended for triage, all screening laboratories would have had to procure one of the HPV tests with typing; however, one of the few clinically validated HPV tests, associated with fewer false-positive tests and unnecessary colposcopy referrals, does not incorporate genotyping. As this was not required, several laboratories – processing more than half of all screening tests in the English programme collectively – have proceeded with procurement of this HPV test. A recent study estimated that, if all screening in the English Cervical Screening Programme were done with this HPV test, there is an additional cost saving to the NHS of several million GBP per year **(F)**. These savings would not be achievable had typing tests been made a requirement in the tender for screening laboratories.

King's researchers gave expert advice to commissioners and providers of cervical screening services that shaped operational delivery. Compared to a screening programme that is based on cytology, a programme based on HPV testing needs far fewer cytology workforce (lab professionals) but substantially more colposcopy capacity (specialised obstetrician-gynaecologists). King's analyses estimated a reduction of cytology readers of about 85% and an increase of more than 50% in the colposcopy capacity in the first few years of the roll-out **(1)**. These findings were presented to various professional groups within PHE, the UKNSC, and NHSE. These groups used King's research as input for advance planning of the screening capacities needed across the NHS. As the Manager of the Screening programme explained: "*The evidence from the epidemiological evaluation [provided by King's] informed major service redesign of the operational delivery of the screening programme. An options appraisal to determine the best option for a reduced laboratory provision taking account of the wider footprint of the programme and quality aspects was informed by the data. These findings lead to rationalisation of the 49 cytology laboratories. The final outcome was that NHS England (NHSE) commissioned services for 9 laboratory lots, and 8 laboratories were successful in winning the contracts* **(D)**."

King's research led to the change in the screening interval from 3 to 5 years. After the first results of King's research were communicated in February 2018 **(G)**, UKNSC opened a public consultation which reported no objections to extending the screening interval **(E)**. The improved safety of HPV testing – reassured by King's research **(1,2)** – requires fewer screens during a woman's lifetime while maintaining the same level of protection from cervical cancer. In the UK, the extension of the screening interval from 3 to 5 years for women younger than 50 will reduce the lifetime number of screening invitations from 12 to 8. In the coming years, this will have a substantial effect on both the women and the NHS. Some women report feelings associated with cervical screening tests of embarrassment, inconvenience, pain, or discomfort during the screening procedure, which may last a few days; this is also known to prevent or delay some women from going for screening. With millions of women undergoing screening every year, tens of thousands will be able to avoid these short-term consequences of screening participation. Furthermore, a longer screening interval is expected to decrease NHSE healthcare costs and free up valuable time for primary care services. The Manager of the Screening Programme stated that "*the implementation of the change to the screening intervals is currently in progress, so we cannot provide the exact extent of these savings but a 2019 study* **(H)** *predicted that £23 million per year would be saved under the new interval compared to keeping the 3-year interval* **(D)**."

King's research was used by European professional organisations to inform the internationally preferred approaches to screening and subsequent diagnostics of women (I). A joint position paper on the future of cervical screening was published by The European Society of Gynaecologic Oncology, Europe's leading society for guidelines for treatment of gynaecological cancers with more than 3400 professional members, and the European Federation of Colposcopy, which includes 34 national colposcopy societies. Their aim is to set minimum standards for colposcopy and treatment of preinvasive cervical lesions in Europe. In this position paper, pilot data published by King's researchers **(2)** was used to discuss the role of HPV typing and highlighted that, in contrast to what was previously thought, the use of typing should be dependent on the setting. These are two major international organisations in the field using King's research to shed light on the use of genotyping and screening.

Public Health England invited King's researchers to design a new national study and participate in advisory groups (D). Building on the evidence PHE has gained from the pilot and the data acquired, the UK screening programmes are now considering further opportunities that HPV primary screening provides, for example, self-sampling, where instead of going in for an appointment, the woman can take the sample herself, in the privacy of her own home and have it sent to the lab. In February 2020, they invited Dr Rebolj to help them design a new national clinical study to evaluate the impact self-sampling will have on the national screening programme in England. She has been a member of the Project Board, the highest level of governance for the study, and is also an active member of the Operational Steering Group. Dr Rebolj has also been asked to be one of only three authors to draft the first ever English guidelines on how to validate HPV self-sampling tests for future use in the English Cervical Screening Programme. The protocol and the ultimate list of approved technologies will be published by PHE and on the UK Government website – the first clinical validation study using these guidelines received ethics approval in Winter 2020 and is expected to be launched before end of April 2021.

5. Sources to corroborate the impact

(A) Sources that corroborate dissemination by King's researchers at various scientific and educational events (PDF): A.1 Public Health England Research and Science Conference (20 March 2018, Coventry); **A.2** NHS Cervical Screening Programme Celebrating Successes: Past, Present, Future (16 March 2020, London); **A.3** CERVIVA National Human Papillomavirus Awareness Symposium (22 November 2019, Dublin, Ireland)

(B) Sources that corroborate dissemination of screening programme changes by King's researchers to the general public: B.1 BBC Radio 4 Woman's Hour, 8 February 2019; **B.2** New Scientist, 6 February 2019; **B.3** The Sun, 6 February 2019; **B.4** The Daily Mail, 6 February 2019

(C) Sources that corroborate national roll-out of primary HPV screening in England: C.1 Public Health England Screening blog, 23 January 2020 - Significant landmark as primary HPV screening is offered across England; **C.2** Public Health England Screening blog, 12 January 2019 - HPV primary cervical screening pilot report published in BMJ

(D) Testimonial: National Programme Manager for the National Cervical Screening Programme for England, Public Health England (PDF)

(E) Cervical Screening Programme modifications looking at; interval/ surveillance, women over 64 and self-sampling: UK National Screening Committee (UKNSC), 27 February 2019

(F) Study estimating NHS cost savings if all screening were done with the non-typing HPV test chosen at the laboratory tender: Weston G, et al. Use of the Aptima mRNA high-risk human papillomavirus (HR-HPV) assay compared to a DNA HR-HPV assay in the English cervical screening programme: a decision tree model based economic evaluation. BMJ Open 2020;10(3):e031303. doi: 10.1136/bmjopen-2019-031303

(G) Meeting Minutes: UK National Screening Committee meeting, 28 February 2018

(H) Study predicting £23 million per year cost saving to NHS with new 5-year interval: Bains I, Choi YH, Soldan K, Jit M. Clinical impact and cost-effectiveness of primary cytology versus human papillomavirus testing for cervical cancer screening in England. Int J Gynecol Cancer 2019;29:669–675. doi:10.1136/ijgc-2018-000161

(I) Joint position paper on the future of cervical screening: Kyrgiou M, et al. Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). British Journal of Cancer (2020) 123:510–517; [page 516, item 30]