

Institution: Queen Mary University of London		
Unit of Assessment: 1		
Title of case study: More Effective Primary HPV Screening for Cervical Cancer Replaces Cytology Internationally		
Period when the underpinning research was undertaken: 2003-2014		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
1) Jack Cuzick	1) Director, Wolfson Institute of Preventive Medicine	1) 12/2002 – present
2) Peter Sasieni	2) Professor of Biostatistics and Cancer Epidemiology	2) 01/12/2002 – 31/10/2017
3) Sue Moss	3) Professor of Cancer Epidemiology	3) 25/10/2011 – 31/10/2016
4) David Mesher	4) Statistician	4) 19/09/2005 – 30/09/2011
5) Anne Szarewski	5) Senior Clinical Lecturer	5) 31/03/2011 – 24/08/2013
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact (indicative maximum 100 words) Queen Mary research has contributed to the decision to replace cytological screening for the human papillomavirus (HPV), which causes cervical cancer, with more effective primary screening for the presence of the virus. As a result, programmes to convert to primary HPV cervical screening are being introduced around the world. European guidelines published in 2015 recommend primary HPV screening for over 100,000,000 eligible women. Primary HPV testing was introduced in 2014 in Turkey, in 2017 in the Netherlands and Australia, and was fully rolled out in Wales in 2018, England in 2019, and Scotland in 2020. In 2020, the American Cancer Society changed its cervical cancer screening guidelines to recommend primary HPV screening. This will affect approximately 86,000,000 women in the US. It is estimated that HPV primary screening in the NHS will prevent around 600 new cases of cervical cancer each year.		
2. Underpinning research (indicative maximum 500 words) Cervical cancer is the fourth most common female cancer worldwide, with 570,000 estimated new cases in 2018. The commonest cause of cervical cancer is the human papillomavirus (HPV). Cytological screening for HPV was introduced in the UK in 1988. However, its sensitivity for high-grade lesions is lower than assumed and the rate of false positives is relatively high, resulting in unnecessary treatments, interventions and anxiety. Thus, research efforts worldwide have focused on finding alternatives with fewer side effects and greater accuracy, such as primary HPV screening. <i>Evaluation of primary HPV screening</i> In a series of publications since 2003, Prof. Cuzick and his team, with international collaborators, reported the results of the HART, Hammersmith, New Technologies for Cervical Cancer Screening (NTCC), and POBASCAM studies, and conducted meta-analyses comparing conventional cytology with primary HPV cervical screening. Long-term follow up of over 11,000 women in UK general practices in the HART study showed that, after five years, women HPV positive at baseline were more likely to develop high grade cervical neoplasia than women with negative HPV screening results [3.1]. In the Hammersmith study, follow up of nearly 3,000 women showed that HPV testing offered excellent protection from high grade cervical neoplasia for at least six years after a negative test [3.2]. The NTCC randomised controlled trial, conducted in nine Italian centres, compared several HPV based screening strategies in women in two different age groups over two recruitment phases [3.3]. A meta-analysis in 2008 pooled relative sensitivity and specificity estimates from a number of randomised and nonrandomised studies from the past decade and demonstrated a 14% higher sensitivity of HPV DNA testing compared with cytology. In the POBASCAM trial published in 2012 [3.4], Cuzick and colleagues showed that implementation of HPV DNA testing in cervical screening leads to earlier detection of clinically relevant high grade neoplasia which, if adequately treated, improves protection against more severe grade neoplasia and cervical cancer. The report		

concluded that HPV testing should be implemented for all women aged ≥ 29 . A long term follow up of four European studies (including POBASCAM and NTCC) published in 2014 showed that HPV based screening provides 60-70% greater protection against cervical carcinomas than cytology, and supported the initiation of HPV based screening from age 30 [3.5].

Evaluation of cost-effectiveness

In a 2012 paper published in the BMJ [3.6], Prof. Sasieni and colleagues assessed the cost effectiveness of primary HPV screening compared with cytology screening in European settings. The work, based on a Dutch microsimulation model, showed that primary HPV screening was the preferred test for women over age 30 in multiple scenarios, and concluded that most European countries should consider switching to primary HPV screening.

Thus, Queen Mary's research validated the use of primary HPV screening to replace cytology testing in screening programmes.

3. References to the research (indicative maximum of six references)

- [3.1] Mesher, D., Szarewski, A., Cadman, L., Cubie, H., Kitchener, H., Luesley, D., Menon, U., Hulman, G., Desai, M., Ho, L., Terry, G., Williams, A., Sasieni, P. & Cuzick, J. (2010). Long-term follow-up of cervical disease in women screened by cytology and HPV testing: results from the HART study. *British Journal of Cancer*, 102 (9), 1405-1410. <https://doi.org/10.1038/sj.bjc.6605619>
- [3.2] Cuzick, J., Szarewski, A., Mesher, D., Cadman, L., Austin, J., Perryman, K., Ho, L., Terry, G., Sasieni, P., Dina, R. & Soutter, W. P. (2008). Long-term follow-up of cervical abnormalities among women screened by HPV testing and cytology-Results from the Hammersmith study. *International Journal of Cancer*, 122 (10), 2294-2300. <https://doi.org/10.1002/ijc.23339>
- [3.3] Ronco, G., Giorgi-Rossi, P., Carozzi, F., Confortini, M., Dalla Palma, P., Del Mistro, A., Ghiringhello, B., Girlando, S., Gillio-Tos, A., De Marco, L., Naldoni, C., Pierotti, P., Rizzolo, R., Schincaglia, P., Zorzi, M., Zappa, M., Segnan, N., Cuzick, J. & The New Technologies for Cervical Cancer screening (NTCC) Working Group. (2010). Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *The Lancet Oncology*, 11 (3), 249-257. [https://doi.org/10.1016/S1470-2045\(09\)70360-2](https://doi.org/10.1016/S1470-2045(09)70360-2)
- [3.4] Rijkaart, D. C., Berkhof, J., Rozendaal, L., van Kemenade, F. J., Bulkmand, N. W., Heideman, D. A., Kenter, G. G., Cuzick, J., Snijders, P. J. & Meijer, C. J. (2012). Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *The Lancet Oncology*, 13 (1), 78-88. [https://doi.org/10.1016/S1470-2045\(11\)70296-0](https://doi.org/10.1016/S1470-2045(11)70296-0)
- [3.5] Ronco, G., Dillner, J., Elfström, K. M. & The international HPV screening working group. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *The Lancet*, 383 (9916), 524-532. [https://doi.org/10.1016/S0140-6736\(13\)62218-7](https://doi.org/10.1016/S0140-6736(13)62218-7)
- [3.6] de Kok, I. M., van Rosmalen, J., Dillner, J., Arbyn, M., Sasieni, P., Iftner, T. & van Ballegooijen, M. (2012). Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model. *The BMJ*, 344, e670. <https://doi.org/10.1136/bmj.e670>

Evidence of the quality of the research

- [EQR.1] Cuzick, J. (1 April 2004-31 March 2009). Epidemiology, Maths and Statistics Unit [C569/A5030]. *Cancer Research UK*. Programme Grant. GBP3,387,222.
- [EQR.2] Sasieni, P. (1 April 2009-31 March 2014). Cervical Screening and HPV Control [C8162/A10406]. *Cancer Research UK*. Programme Grant. GBP2,349,731.
- [EQR.3] Cuzick, J. (1 April 2009-31 March 2014). Prevention of Hormone Related Cancers [C569/A10404]. *Cancer Research UK*. Programme Grant. GBP5,309,642.
- [EQR.4] Moss, S. (1 May 2013-31 December 2017). HPV Primary Screening Pilot [EMSH1C4R]. *Public Health England*. Service Agreement. GBP299,191.

4. Details of the impact (indicative maximum 750 words)

Queen Mary's research has been instrumental in effecting the decision to replace cytological screening with primary HPV screening. This fundamental innovation is now being implemented or

planned in national screening programmes around the world.

Informing international clinical guidelines

In Europe

The European Commission's 2015 'European guidelines for quality assurance in cervical cancer screening. Second Edition - Supplements', co-authored by Prof. Cuzick, recommend primary HPV screening [5.1]. In the UK, the Advisory Committee for Cervical Screening concluded that "there is grade A evidence to support a switch from primary cytology to primary HPV testing in cervical screening. This should save life years and cost less" [5.2]. Its recommendation [5.2] was that HPV testing should replace cytological testing, based on "studies showing the effectiveness of HPV testing for cervical cancer screening" [3.4, 3.6], as reported by the BMJ in [2012](#). The algorithm, produced by Queen Mary's Prof. Moss, remains the national screening service protocol [5.3].

In the US

The United States Preventive Services Task Force 2018 cervical cancer screening guidelines also recommend HPV testing alone as a first-line screening test to detect cervical cancer and pre-cancer [5.4], citing Queen Mary's work [3.3-3.5]. In 2020 the American Cancer Society published new guidelines, citing references [3.3] and [3.5], recommending primary HPV testing every 5 years for the 86,000,000 American women aged 25-64 [5.5].

Reshaping cervical cancer screening programmes worldwide

In Europe

Cuzick was a member of the international advisory board for the primary HPV screening programme set up in Turkey between 2014 and 2016, from which 4,000,000 women had benefitted by 2019 [5.6]. In the Netherlands, following the European Commission's 2015 guidelines, HPV primary screening commenced in 2017. 500,000 women participate in cervical screening each year [5.7]. In other parts of Europe (where the eligible population numbers are approximately 106,500,000 women of screening age), as of 2016, HPV is the primary screening test offered by some programmes in areas of Denmark, Finland, Italy, and Sweden, Romania and Malta (co-testing with cytology) and in Portugal (both as a stand-alone and in co-testing) [5.8].

Following a successful pilot study using a protocol written by Moss, primary HPV screening was put in place across Wales in September 2018 [5.9], England in December 2019 [5.10], and Scotland in March 2020 [5.11]. The decision was based on the "grade A" research evidence [3.4, 3.6] provided to the UK Advisory Committee for Cervical Screening in 2015 [5.2]. It is estimated that HPV primary screening in the NHS will prevent around 600 new cases of cervical cancer each year.

In Australia

Cuzick's work [3.3-3.5] led to the decision to commence HPV primary screening in Australia, in December 2017 for women aged 25-74 every 5 years. An estimated additional 4,000 high and more severe grade cervical neoplasia cases and 129 cases of invasive cervical cancer are detected each year [5.12].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] European Commission. (2015). *European guidelines for quality assurance in cervical cancer screening. Second Edition - Supplements*.

https://www.gisci.it/documenti/news/EW0115451ENN_002.pdf

[5.2] Advisory Committee for Cervical Screening. (2015). *Report to the National Screening Committee*. https://legacy.screening.phe.org.uk/policydb_download.php?doc=555

[5.3] Public Health England. (2016). *HPV Primary Screening Pilot Protocol Algorithm (V3.0)*.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/529496/HPVPSFlowchart-Version3_Jan16.CURRENTppt.pdf

[5.4] US Preventive Services Task Force. (2018). *Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement*. *JAMA: The Journal of the American Medical*

Association, 320 (7), 674-686. <https://doi.org/10.1001/jama.2018.10897>

[5.5] Fontham, E. T. H., Wolf, A. M. D., Church, T. R., Etzioni, R., Flowers, C. R., Herzig, A., Guerra, C. E., Oeffinger, K. C., Tina Shih, Y., Walter, L. C., Kim, J. J., Andrews, K. S., DeSantis, C. E., Fedewa, S. A., Manassaram-Baptiste, D., Saslow, D., Wender, R. C. & Smith, R. A. (2020). Cervical Cancer Screening for Individuals at Average Risk: 2020 Guideline Update from the American Cancer Society. *CA: A Cancer Journal for Clinicians*, 70 (5).

<https://doi.org/10.3322/caac.21628>

[5.6] Gultekin, M., Karaca, M. Z., Kucukyildiz, I., Dundar, S., Keskinilic, B. & Turkyilmaz, M. (2019). Mega Hpv laboratories for cervical cancer control: Challenges and recommendations from a case study of Turkey. *Papillomavirus Research*, 7, 118-122.

<https://doi.org/10.1016/j.pvr.2019.03.002>

[5.7] Aitken, C. A., van Agt, H. M. E., Siebers, A. G., van Kemenade, F. J., Niesters, H. G. M., Melchers, W. J. G., Vedder, J. E. M., Schuurman, R., van den Brule, A. J. C., van der Linden, H. C., Hinrichs, J. W. J., Molijn, A., Hoogduin, K. J., van Hemel, B. M. & de Kok, I. M. C. M. (2019). Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. *BMC Medicine*, 17, 228.

<https://doi.org/10.1186/s12916-019-1460-0>

[5.8] European Commission. (2017). *Cancer Screening in the European Union: Report on the implementation of the Council Recommendation on cancer screening*.

https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf

[5.9] Gething, V. (2018, 18 September). Written Statement - Implementation of HPV testing by Cervical Screening Wales. *Welsh Government*. <https://gov.wales/written-statement-implementation-hpv-testing-cervical-screening-wales>

[5.10] Stubbs, R. (2020, 23 January). Significant landmark as primary HPV screening is offered across England. *PHE Screening*.

<https://phescreening.blog.gov.uk/2020/01/23/significant-landmark-as-primary-hpv-screening-is-offered-across-england/>

[5.11] Scottish Government (2020, 15 March). *Smear test to screen for HPV*.

<https://www.gov.scot/news/smear-test-to-screen-for-hpv/>

[5.12] Hall, M. T., Simms, K. T., Lew, J.-B., Smith, M. A., Saville, M. & Canfell, K. (2018). Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017–2035: Example from Australia. *PLoS ONE*, 3 (2), e0185332.

<https://doi.org/10.1371/journal.pone.0185332>