Institution: University of Liverpool

Unit of Assessment: UoA1- Clinical Medicine

Title of case study: Human papillomavirus (HPV)-positive Head & Neck Cancer – Driving Change in UK Vaccination Policy & Clinical Practice

Period when the underpinning research was undertaken: 2009-2018

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:
Andrew Schache	NIHR Academic Clinical Lecturer, Clinical Senior Lecturer and now Reader	2013-present
Terry Jones	Professor	2006-present
Richard Shaw	Professor	2007-present

Period when the claimed impact occurred: 2015-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Human papillomavirus (HPV) is linked to 5% of all cancers worldwide. Since 2008 girls in the UK have received HPV vaccination to reduce the incidence of cervical cancer. UoL provided evidence that HPV was also linked to a high incidence of Head and Neck cancer. This was pivotal to the UK government's decision to also offer HPV vaccination to all 12-13-year-old boys from September 2019, with up to 350,000 additional annual vaccinations delivered. The at-risk population has thus already been reduced, with Public Health England estimating almost 29,000 male cancer cases to be avoided by 2058. This equates to an additional 763 cancers avoided each year. Reduced cancer incidence alone will effect an NHS treatment cost savings of GBP494,000,000 by 2058. Through understanding of HPV disease pathology, UoL has informed NICE protocols, changed clinical practice in diagnosis, and informed clinical trials through accurate stratification and recruitment.

2. Underpinning research (indicative maximum 500 words)

In 2010 Schache/Shaw/Jones, published evidence of a significant rise (greater than 3-fold) in cancers caused by HPV arising in the oropharynx between 1988 and 2009 [3.1]. Following receipt of a research grant from GlaxoSmithKline between 2013-16, UoL (Jones/Schache) led the UK HPV Prevalence consortium, producing robust multicentre cross-sectional data that demonstrated a doubling of Oropharynx Squamous Cell Carcinoma (OPSCC) incidence between 2002-2011 in the UK population. It was also shown that over half of those tumours were HPV-positive, and it was asserted that instigation of gender-neutral prophylactic HPV vaccination now, could prevent the anticipated heavy burden of HPV-positive Head & Neck (H&N) cancer in the future [3.2]. Further, Shaw/Jones evidenced the considerable UK health economic impact of the growing disease burden stratified by male and female patients (2018) and the critical patient-centred, quality of life outcomes. The research demonstrated that head & neck cancers disproportionately impacted the male population, accounting for almost 75% of the total economic burden [3.3]. In combination with rising disease incidence, it was evident that a dramatic climb in related healthcare spending was apparent for OPSCC in particular: a 76% rise in real costs in 4 years. These research findings reinforced the case for prevention strategies to help contain both the epidemiological and economic burden of HPV-related H&N cancer.

Between 2011-13 Schache/Shaw defined the capabilities of the various clinically available diagnostic tests against the recognised research laboratory (non-clinical) gold standard test. Despite numerous tests existing in clinical use worldwide, benchmarking against the gold standard

had not previously been performed[3.1]. This research provided the evidence necessary to underpin UK clinical guidance; NICE guidance and national H&N multidisciplinary guidelines (NICE Guidance [NG36], 2015, updated 2018) making specific recommendations for diagnostic tests to be applied within clinical scenarios; HPV status has profound influence on clinical outcomes in OPSCC, meaning this research has influenced practice in all routine H&N pathology services, underpinning the management of approximately 2,500 UK OPSCC patients per year [3.3]. This has additional significant global influence through cancer network guidance and best practice protocols. Additional research assessing the capabilities of a novel HPV diagnostic platform against these newly defined standards [3.4] led to NICE guidance recommending such platforms to be a "priority for further research".

Translation of best practice HPV diagnostics into clinical care has facilitated investigation of de-intensified cancer treatments [3.5] such that they are being assessed in the context of a Liverpool-led, late phase international clinical trial [3.6].

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

3.1 **Schache AG**, Liloglou T, Risk JM, Filia A, **Jones TM**, Sheard J, Woolgar JA, Helliwell TR, Triantafyllou A, Robinson M, Sloan P, Harvey-Woodworth C, Sisson D, Shaw RJ. Evaluation of Human Papilloma Virus Diagnostic Testing in Oropharyngeal Squamous Cell Carcinoma: Sensitivity, Specificity, and Prognostic Discrimination. (2011) Clinical Cancer Research 17(19);6262-71 doi: 10.1158/1078-0432.CCR-11-0388

3.2 **Schache AG**, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, Rapozo D, Long A, Cubie H, Junor E, Monaghan H, Harrington KJ, Nutting CM, Schick U, Lau AS, Upile N, Sheard J, Brougham K, West CM, Oguejiofor K, Thomas S, Ness AR, Pring M, Thomas GJ, King EV, McCance DJ, James JA, Moran M, Sloan P, Shaw RJ, Evans M, **Jones TM**. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. (2016) Cancer Research 15;76(22):6598-6606 doi: 10.1158/0008-5472.CAN-16-0633

3.3 Keeping ST, Tempest MJ, Stephens SJ, Carroll SM, Simcock R**, Jones TM, Shaw R.** The cost of oropharyngeal cancer in England: A retrospective hospital data analysis. (2018) Clinical Otolaryngology 43(1):223-229 doi: 10.1111/coa.12944

3.4 **Schache AG,** Liloglou T, Risk JM, Jones TM, Ma XJ, Wang H, Bui S, Luo Y, Sloan P, Shaw RJ, Robinson M. Validation of a novel diagnostic standard in HPV-positive oropharyngeal squamous cell carcinoma. (2013) Br J Cancer Apr 2;108(6):1332-9. doi: 10.1038/bjc.2013.63

3.5 Wilkie MD, Upile NS, Lau AS, Williams SP, Sheard J, Helliwell TR, Robinson M, Rodrigues J, Beemireddy K, Lewis-Jones H, Hanlon R, Husband D, Shenoy A, Roland NJ, Jackson SR, Bekiroglu F, Tandon S, Lancaster J, **Jones TM.** Transoral laser microsurgery for oropharyngeal squamous cell carcinoma: A paradigm shift in therapeutic approach. (2016) Head Neck Aug;38(8):1263-70. doi: 10.1002/hed.24432

3.6 Owadally W, Hurt C, Timmins H, Parsons E, Townsend S, Patterson J, Hutcheson K, Powell N, Beasley M, Palaniappan N, Robinson M, **Jones TM**, Evans M. PATHOS: a phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human papillomavirus (HPV) positive oropharyngeal cancer. (2015) BMC Cancer. Aug 27;15:602. doi: 10.1186/s12885-015-1598-x.

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

Context

Human papillomavirus (HPV) is the causative agent for various cancers, including Head and Neck cancer in the form of oropharyngeal squamous cell carcinoma (oropharyngeal cancer or OPSCC). Since the 1990s there has been a continued rise in oropharyngeal cancer numbers with UK registry data showing that the disease incidence was rising faster than any other solid tumour type. Despite a recognised link between HPV infection and oropharyngeal cancer there was a lack of robust data evidencing the UK burden of HPV positive disease or the health economic impact. As a direct consequence of this paucity of evidence, when the UK instigated a nationwide HPV vaccination programme in 2008 it was offered only to females for potential cervical cancer reduction alone [5.1]

Vaccination programme to eradicate HPV-positive oropharyngeal cancer

UoL led multicentre studies to address this shortfall in understanding and evidence. Schache/Jones produced research demonstrating that greater than 50% of all UK oropharyngeal cancers are HPV positive, a finding in contrast to previous best evidence considered by the Joint Committee on Vaccination and Immunisation (JCVI) of at most 28% HPV positive disease fraction. In addition, the disease incidence doubled in the single decade between 2002 and 2011 to over 2,200 cases per year [3.2] while the cost of oropharyngeal cancer treatment rose by 75% from GBP17,000,000 to GBP30,000,000 from 2006 to 2010 [3.3].

This specific evidence was provided to the JCVI through proactive direct communication from Jones (as lead for the UK HPV Prevalence consortia) [5.2] and indirectly via patient advocacy groups resulting in a recommendation to government to reverse prior advice, and therefore recommend UK-wide gender-neutral vaccination referencing UoL's work [5.3] as the sole evidence of disease burden. As a consequence of this decision, from September 2019, more than 350,000 year 8 schoolboys were offered HPV vaccination [5.4], removing them from the potential population at risk of HPV positive oropharyngeal cancer. Despite a government-advised pause in school-aged vaccinations due to the COVID-19 pandemic, a first dose of HPV vaccine had already been delivered to 54.4% of these boys in 2019/20. This is a comparable level to that seen in girls (59.2%; 2019/20) allowing an expectation of parity in a COVID-unaffected year such as 2018/19 where 88.0% of girls received their first dose [5.5]. There will be a further economic net benefit to the commercial provider of vaccine through increased NHS provisioning to account for the additional 700,000 doses of vaccine per annum, under a 2-dose regime.

By 2058, with OPSCC incidence otherwise expected to continue to rise unabated, over 14,000,000 boys will have been offered the HPV vaccine. Conservative estimates from Public Health England (PHE) have concluded that almost 29,000 male cancers will be prevented as a result of this change to UK vaccination policy [5.6]. As HPV vaccination also conveys protection against other (low risk) HPV disease types, all vaccinated individuals will receive additional protection from diseases such as of genital warts, the debilitating sexually transmitted disease.

In addition to an immeasurable reduction in the personal impact of cancer with its considerable treatment-related morbidity, and the additional mitigation of lost earnings/tax revenue, a GBP494,000,000 saving in NHS treatment costs will be realised by 2058 (based on extrapolation of known NHS treatment costs in 2010/11 [3.3] and oropharyngeal cancer incidence).

Driving Change in UK Clinical Practice;

The expanded vaccination programme will address HPV-mediated disease in the long term. The lag time to maximal cancer reduction from today's vaccination of pre-sexual males is anticipated to be evident only when they are in their 5th decade of life. To address the increasing disease burden in the short to medium term, UoL have also directed best practice clinical guidelines providing a consistent, evidence-based regime for HPV diagnostics and intervention in oropharyngeal cancer in UK clinical practice.

The NICE guidelines are derived from the first evidence from UoL evidencing the diagnostic accuracy of the currently-applied (global) clinical diagnostic testing regimes against the gold standard laboratory analyses. In clinical practice, the precise identification of HPV positive patients has enabled provision of accurate prognostic information (primarily improved survival) for over 1,500 individuals each year. Standardised HPV diagnostic regimes have facilitated access to late phase clinical trials for each of these individuals [3.6]. These tests have been applied in this setting to ensure only truly HPV positive patients enter the much-anticipated trials of de-escalation of treatment intensity (thereby optimising patient benefit, reducing participation of unsuitable patients and ensuring the most accurate outcomes from the trials). For example, as of January 2021, the PATHOS phase III trial has recruited 492 patients from 38 trial centres across the UK, Europe, USA and Australasia.

Our research demonstrated that a specific combination test (p16 immunohistochemistry and HPV in situ hybridisation) has the best clinical capability to report HPV positive disease status. It similarly retained the necessary prognostic capability to inform survival for patients. This output was extensively evidenced and applied in NICE guidance [NG36] [5.7], [5.8], now forming the sole basis of UK HPV diagnostic practice across all cancer networks. All individuals diagnosed with oropharyngeal cancer in routine clinical care can now receive prognostic information which is accurate to their disease. This is of critical importance given the large disparity in survival between individuals with HPV positive cancer and those with HPV negative cancer. Additionally, this research provided the international standard for HPV diagnostics in HNSCC, against which evolution in testing in practice is measured (over 300 citations). Given its impact on clinical practice, this work attracted considerable press attention. [5.9]

In numerical terms, each of the 2,850 new oropharyngeal cancers presenting in the UK annually [3.3], [5.10] are tested in accordance with this guidance. The diagnostic algorithm is also central to clinical trial recruitment protocols, defining the disease and therefore trial recruitment opportunities (in both HPV positive and HPV negative trials; for inclusion and exclusion) where trials seek alternative therapeutic intensity.

Summation of Impact
Vital evidence from UoL research has been pivotal to national policy decision making. This has been translated to a significant reduction in the population at risk of cancer in the long term, with consequent profound individual, healthcare provider and societal benefit. Meanwhile, by informing diagnostic practice via national guidelines, more accurate prognostics have been adopted enabling approaches seeking the most appropriate interventions for oropharyngeal cancer.

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

5.1 JCVI interim statement on HPV vaccination 2016 (subsequently revised)
https://www.gov.uk/government/publications/jcvi-statement-extending-the-hpv-vaccination-programme

5.2 UK HPV Prevalence Consortium direct submission of evidence to JCVI public consultation
Letter to JCVI Secretariat and CMOs on HPV vaccination 07 February 2018.pdf

5.3 JCVI statement on HPV vaccination 2018
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on_HPV_vaccination_2018.pdf

5.4 UK Government; Department for Education (2017) Education and Training Statistics for the United Kingdom 2017: Table 1.2
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/657907/SFR64_2017_Tables.xlsx

5.5 Human papillomavirus (HPV) vaccination coverage in adolescent females and males in England: academic year 2019 to 2020. Health Protection Report, Volume 14, Number 19 20 October 2020 PHE publications gateway number: GW-1663.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/927694/hpr1920_HPV-vc.pdf

5.6 Public Health England (PHE) Statement 9 July 2019
https://www.gov.uk/government/news/hpv-vaccine-could-prevent-over-100-000-cancers
(publication associated with considerable media impact; BBC, Sky, CRUK etc)

5.7 NICE Guidance 2015 [NG36]
https://www.nice.org.uk/guidance/ng36/update/NG36/documents/upper-aerodigestive-tract-cancer-full-guideline2

5.8 NICE Guidance Updated 2018 [NG36]
https://www.nice.org.uk/guidance/ng36

5.9 AACR Press Release (wrt Schache et al. 2011 CCR)
i.Science Daily October 3rd 2011
https://www.sciencedaily.com/releases/2011/10/111003080413.htm
ii.RNAscope HPV Diagnostics
https://acdbio.com/science/applications/disease-areas/hpv-related-cancer
iii.Associated NCRI Press Release (NCRI Research output RNAscope
https://www.ncri.org.uk/hpv-test-for-oral-cancers-may-improve-patient-outcomes-and-treatments/?highlight=hpv

5.10 Office for National Statistics Cancer registration statistics, England: 2017 showing cancer registrations for tonsil (1,632) and other tongue (1,233) giving a total of 2,865 for 2017.
https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017