# Title Page

## Title of the article.

Systematic review and evidence synthesis of non-cervical human papillomavirus-related disease health systems costs and quality of life estimates.

## Full name, postal address, e-mail and telephone number of the corresponding author.

|  |  |
| --- | --- |
| Corresponding author |  |
| Full name | Koh Jun Ong |
| Postal address | Centre for Infectious Disease Surveillance and Control  *National Infection Service*  Public Health England  61 Colindale Avenue,  London NW9 5EQ,  United Kingdom |
| E-mail | [kohjun.ong@phe.gov.uk](mailto:kohjun.ong@phe.gov.uk) |
| Telephone number | 0208 327 6739 |
| Highest academic degrees | MSc |

## Full name, department, institution, city and country of all co-authors.

|  |  |
| --- | --- |
| Co-author 1 |  |
| Full name | Marta Checchi |
| Department, institution, city and country | National Infection Service, Public Health England, London, United Kingdom |
| Highest academic degrees | MSc |
| Co-author 2 |  |
| Full name | Lorna Burns |
| Department, institution, city and country | Peninsula Schools of Medicine and Dentistry, University of Plymouth, Plymouth, Devon, United Kingdom |
| Highest academic degrees | MSc |
| Co-author 3 |  |
| Full name | Charlotte Pavitt |
| Department, institution, city and country |  |
| Highest academic degrees | MSc |
| Co-author 4 |  |
| Full name | Maarten J Postma |
| Department, institution, city and country | 1. Department of Pharmacy, University of Groningen , Groningen, Netherlands 2. Department of Health Sciences, University Medical Center Groningen, Groningen, Netherlands 3. Department of Economics, Econometrics & Finance, University of Groningen, Groningen, Netherlands |
| Highest academic degrees | PhD |
| Co-author 5 |  |
| Full name | Mark Jit |
| Department, institution, city and country | 1. National Infection Service, Public Health England, London, United Kingdom 2. Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom |
| Highest academic degrees | PhD |

## Word count, excluding title page, abstract, references, figures and tables.

|  |  |
| --- | --- |
| Abstract | 298 of 300 max. |
| Main text | 2,322 of 3,000 max. |
| Number of figures and tables | 3 Figures and 1 Table |

# KeyWORDS

Papillomaviridae

costs and cost analysis

meta-analysis

systematic review

Condylomata Acuminata

recurrent respiratory papillomatosis

anus neoplasms

head and neck neoplasms

penile neoplasms

vulvar neoplasms

vaginal neoplasms

# AUTHORS’ CONTRIBUTIONS

KJO, MJP, and MJ conceived and planned the systematic review. LB conducted the systematic literature searches. KJO, MC, and CP, carried out sifting and data extraction of the systematic literature search results. KJO conducted the meta-analysis and took the lead in writing the manuscript, with guidance from MJP and MJ. All authors provided critical feedback on the manuscript.

# cORRESPONDING AUTHOR STATEMENT

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in STI and any other BMJPGL products and sub-licences such use and exploit all subsidiary rights, as set out in our licence

http://group.bmj.com/products/journals/instructions-for-authors/licence-forms

# Abstract

## BACKGROUND

Many economic evaluations of human papillomavirus (HPV) vaccination consider multiple disease outcomes in addition to cervical cancer, including anogenital warts, recurrent respiratory papillomatosis, and anal, oropharyngeal, penile, vulvar and vaginal cancers. However, these evaluations mostly derive cost and utility parameters for these outcomes from single studies or informal rapid literature reviews.

## METHODS

We conducted a systematic review of articles up to June 2016 to identify costs and utility estimates admissible for an economic evaluation from a single-payer health care provider’s perspective. Meta-analysis was performed for studies that used same utility elicitation tools for similar diseases. Costs were adjusted to 2016/17 US dollars.

## RESULTS

Sixty one papers (35 costs; 24 utilities; 2 costs and utilities) were selected from 10,742 initial records. Cost per case ranges were US$124–US$883 (anogenital warts), US$6,912–US$52,579 (head and neck cancers), US$12,936–US$51,571 (anal cancer), US$17,524–34,258 (vaginal cancer), US$14,686–28,502 (vulvar cancer), and US$9,975–27,629 (penile cancer). Total cost for 14 adult RRP patients was US$137,601 (1 paper).

Utility per warts episode ranged from 0.651–1 (12 papers, various utility elicitation methods), with pooled mean EQ-5D and EQ-VAS of 0.86 (95% CI 0.85–0.87) and 0.74 (95% CI 0.74–0.75), respectively. Fifteen papers reported utilities in head and neck cancers, with range across studies of 0.29 to 0.94. Mean utility reported ranged from 0.5 to 0.65 (anal cancer; range across studies), 0.59 (0.54–0.64) (vaginal cancer), 0.65 (0.60–0.70) (vulvar cancer), and 0.79 (0.74–0.84) (penile cancer).

## CONCLUSIONS

Differences in values reported from each paper reflect variations in cancer site, disease stages, study population, treatment modality/setting, and utility elicitation methods used. As patient management changes over time, corresponding effects on both costs and utility need to be considered to ensure health economic assumptions are up-to-date and closely reflect the case-mix of patients.

# Key Messages

* This systematic review identified 61 papers (35 costs; 24 utilities; 2 costs and utilities) reporting economic parameters for HPV-related non-cervical diseases.
* Differences in cost and utility estimates arise from study population, disease stage, cancer type, treatment strategies and country perspective taken.
* Authors of economic evaluations need to consider economic parameter assumptions to ensure they accurately reflect the timing and perspective of the population considered.

# Introduction

Almost a hundred economic evaluations of human papillomavirus (HPV) vaccination had been published by June 2016[1–3]. Initially most of these analyses focused on the health and economic benefits of HPV vaccination in preventing cervical cancer and its precursors, since these were the only cancer outcomes listed in the initial licensure indication for the first two licensed HPV vaccines (the bivalent vaccine Cervarix and the quadrivalent vaccine Gardasil)[4,5]. More recently, evidence has emerged of other diseases that are potentially HPV vaccine-preventable, including recurrent respiratory papillomatoses (RRP) and non-cervical cancers such as vulvar, vaginal, anal, penile, and head and neck cancers[6,7]. Although attributable risk of HPV in each of these non-cervical cancers varies[7], these outcomes are important to incorporate into cost of illness studies of HPV-related diseases and economic evaluation of HPV vaccination for two reasons: (i) they give a comprehensive picture of the (direct and indirect) benefits of introducing HPV vaccination, and (ii) they are the key drivers of comparative evaluations of different strategies for vaccination, such as gender-neutral compared with female-only vaccination and the choice between nonavalent, quadrivalent and bivalent vaccination.

Economic evaluations require input parameters in terms of the costs and disutilities (measured in units such as quality adjusted life years or QALYs) for different disease outcomes. To our knowledge, most published economic evaluations to date have relied on data from the authors’ own knowledge or from informal rapid reviews of the literature. Additionally, there exist a number of systematic reviews (without quantitative evidence synthesis) conducted before 2013 covering quality of life for specific diseases such as anogenital warts[8] and head and neck cancers[8–11] but none known of in more recent years covering a wider range of non-cervical HPV-related diseases on both costs and utilities. This gap in the literature may have led to bias in published economic evaluations because they may have failed to consider the entirety of the literature in their parameter estimates.

To address this shortcoming, we have conducted a systematic review to compile and summarise costs and quality of life (utility) estimates relevant to HPV-related diseases apart from cervical cancer. We have selected studies that would be admissible for an economic evaluation from the perspective of a single-payer health care provider such as the reference case used by the National Institute for Health and Care Excellence (NICE) in the United Kingdom[12].

# Methods

## Search Methods

A search of the databases Ovid Medline, Embase, Cinahl, Scopus and NHS Economic Evaluations Database was performed in June 2016. The search strategy combined terms for HPV-related diseases with health economics terms. HPV-related disease terms included both free text and, where available, subject headings for the following (ICD-10 codes in parentheses): anogenital warts – AGW (A63.0), recurrent respiratory papillomatosis – RRP (D14), cervical cancer (C53), vulvar cancer (C51), vaginal cancer (C52), anal cancer (C21), penile cancer (C60), oropharyngeal cancer (C09 and C10), oral cavity cancer (C01 to C05) – including cancer of the tonsil, laryngeal cancer (C32), and head and neck cancer as a general term included for completeness, recognising that not all head and neck cancers are HPV-attributed. Health economics terms included terms for health utilities/disutilities, costs, quality of life, quality of life instruments (e.g. EQ-5D) and measurement methods such as time-trade off (TTO) and standard gamble (SG). Results were limited to peer-reviewed full research articles in the English language only. Inclusion criteria covered all papers on HPV-related diseases costs and/or disutilities from high-income countries as defined by the Organisation for Economic Cooperation and Development, stated in Appendix 1[13].

Details of the full search strategies used are provided in Appendix 1.

## Result Screening

Screening was undertaken from September to December 2016. The initial 10,742 articles identified were independently single screened based on titles and abstracts to identify potentially relevant papers (KJO, MC, CP). Allocation decisions at this stage were done leniently, with titles that were uncertain marked for a further round of screening. The 2,785 references selected were entered into another round of single screening (KJO, MC, CP), whereby the results were reconsidered and categorised by type (cost or disutility) and disease area.

Although the objective of this systematic review focused on non-cervical diseases, for completeness, the search strategy and first two stages of single screening included cervical precancer/cancer. Selected titles for cervical precancer/cancer can be made available to interested researchers.

## Selection criteria

Once titles from the second single screen had been identified, full-text papers were proportionately distributed to each reviewer (KJO, MC, CP) for the final round of paper selection and data extraction. For HPV-related disease management costs we included only papers that took the perspective of a health care provider from a country with universal healthcare system (either Bismarck-type or Beveridge-type). For utility estimates, any paper that reported on quality of life loss that was reported on a scale from 0 to 1 and measured using either an indirect generic utility elicitation tool such as the EuroQol EQ-5D, or one of the primary/direct methods such as time-trade off or standard gamble were included. These criteria ensured that selected studies would be admissible for economic evaluations in most single-payer health care jurisdictions (eg. the NICE reference case[12]).

## Data extraction

A standard form to collect the data was created. Relevant data extracted from the papers are described in Appendix 2.

Data extraction was done by one reviewer and checked by a second reviewer, with discrepancies resolved through discussion.

## Data synthesis

A descriptive comparison of data extracted from different papers was made. Costs were adjusted to 2016/17 US dollars using the hospital and community health services inflation indices, with foreign currencies converted to US dollars using historical Bank of England average exchange rates for a reported year[14,15]. Quality of life values were presented separately for utility score and duration of disutility, if reported in a paper.

Meta-analyses using random effect models were conducted for AGW utility estimates for papers whereby utility estimates were generated using standard utility elicitation instruments, such that outcomes measured were comparable. Meta-analyses were not conducted for utility weights of non-AGW outcomes nor were they conducted for any cost estimates, given higher heterogeneity in how costs were measured and the specific disease type and stages considered.

## Software

References were collected in EndNote and transferred to Eppi-Reviewer 4 software (Thomas J, Brunton J, Graziosi S, 2010) for screening. Final papers were captured in Mendeley Version 1.15.3. Data extraction was collated in Microsoft Excel 2010. Meta-analysis was conducted in STATA13.

# Results

The initial search strategy identified 10,742 records after deduplication. Screening based on titles and abstracts reduced these to 729 full-text papers that were reviewed. Of these, 61 papers were selected. A PRISMA flow diagram is presented in Figure 1.

## Costs

A total of 37 papers reported non-cervical HPV-related disease management costs[16–52], about half of which reported costs for AGWs[16–35]. Four papers reported costs for more than one disease[26,30,36,37]. Management costs from studies differed by country, disease stages or management settings used, and data collection method.

Figure 2 (Panel A) presents a summary of the various cost per case estimates, where presented, for AGWs. Estimated cost per case of AGW ranged from US$124 per case in a patient seen for care in Canada[25] to US$883 per case in Spain[34]. AGW management costs were derived from information collected from case note reviews (13 papers)[18–22,25,26,28,29,31–34], expert opinion (3 papers)[16,24,35], surveillance data (3 papers) [17,23,27] or the literature (1 paper) [30].

Cost per case reported for the various cancers is presented in Figure 2 (Panel B). Six papers reported management cost for anal cancers[30,36–40], but half of these were annual treatment costs[37,39,40] not cost per case. Cost per anal cancer case ranged from US$12,936 (Italy[30]) to US$51,571 (Denmark[36]). Twelve reported head and neck cancer treatment costs and differed depending on cancer site and stage[30,37,41–50], with costs ranging from US$6,912 (Laryngeal cancer, T1 carcinoma, the Netherlands[48]) to US$52,579 (weighted average costs for cancers of the oral cavity, larynx or oropharynx, the Netherlands[45]). There were four papers each that reported cost for vaginal[26,30,36,37], vulvar[26,30,36,37], and penile[30,36,37,51] cancers, with cost ranges of US$17,524–34,258, US$14,686–28,502, and US$9,975–27,629, respectively. Six papers only presented total spend and/or annual spend for the non-cervical cancers[37,39,40,42,44,52], detailed findings are reported in Appendix 2.

One paper reported on total treatment cost covering 14 adult patients seen for RRP care at a clinic in Glasgow, Scotland, between January 2013 to April 2014 was reported at US$137,601[52].

## Utilities

A total of 25 papers on health-related quality of life were identified (full reference list in Appendix 2)[19,20,53–60;W1-W15]. Two of these covered multiple diseases[53,W15]. Fifteen papers covered head and neck cancers, including oral and laryngeal cancers[53,W2–W15], whilst another 12 papers reported on quality of life for AGWs[19,20,53–60,W1,W16].

Utility per case of AGW ranged from 0.651–1, depending on the method of utility elicitation used. Utility values were generally higher when measured using EQ-5D, compared with Visual Analog Scale (VAS), TTO, or SG methods used within a single study. Full details of study background and findings are presented in Appendix 2. Meta-analyses of EQ-5D and EQ-VAS, from nine papers each, found high heterogeneity (I-squared >90%) in the utility values reported (Figure 3). Pooled mean EQ-5D and EQ-VAS were 0.86 (95% CI 0.85-0.87) and 0.74 (95% CI 0.74-0.75), respectively.

Methods used to elicit utility for HPV-related cancers included EQ-5D, EQ-VAS, HUI3 (Health Utility Index Mark 3), TTO, SG, SF-36 (Short-Form 36), SF-6D (Short-Form Six-Dimension), and 15D. Utility estimates for head and neck cancers differed depending on the utility elicitation method used to generate utility scores, cancer site, patient age, the disease stage at point of completion of the quality of life questionnaire, and treatment modality. For example, patients who had early stage oral cancers completed utility questionnaires at a later point in time in Govers et al. [W3], whilst another study by Loimu et al. [W7] was a prospective study where patients with laryngeal, pharyngeal or nasal cavity carcinoma had their utility measured at month-0, 3, 6, and 12 after treatment initiation. We present summary study details and key utility output presented in each of these 15 papers on quality of life for HPV-related cancers in Table 1 with further details in Appendix 2.

# Table

## Table 1 Summary utility measurement and value ranges for HPV-related non-cervical cancers

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | Author, year | Cancer type; notes | Country | n | Utility elicitation instrument used; mean (unless otherwise specified) values and/or ranges reported |
| 1 | Aro, 2016[W2] | Head and neck | Finland | 214 | 15D; 0.872 |
| 2 | Govers, 2016[W3] | Oral; mean years after treatment range 1.9 (SD 1.4, range 0.4-4.1) to 5.2 (SD 3.2, range 0.4-11.0) | The Netherlands | 174 | EQ5D; range 0.794 (SE 0.04) to 0.863 (SE 0.05)  EQVAS; range 69.7 (SE 3.7) to 79.6 (SE 4.8) |
| 3 | Pickard, 2016[W4] | Head and neck | US | 50 | EQ5D; 0.828  EQVAS; 60.8 |
| 4 | Rettig, 2016[W5] | Head and neck; sites include larynx, oral cavity, oropharynx, hypopharynx, nasopharynx, and nasal cavity/paranasal sinuses | US | 1653 | SF6D; range 83.7 (95% CI 82.0, 85.4) to 88.0 (95% CI 86.2, 89.7) |
| 5 | Kent, 2015[W6] | Oral cavity and pharynx | US |  | SF6D; 0.69 (95% CI 0.68, 0.70) |
| 6 | Loimu, 2015[W7] | Head and neck | Finland | 64 | 15D; range 0.829 (0.12) to 0.886 (0.10) |
| 7 | Noel, 2015[W8] | Head and neck | Canada |  | EQ5D; 0.82 (SD 0.18, range -0.07-1.0)  EQVAS; 0.76 (SD 0.19, range 0.2-1.0)  SG; 0.91 (SD 0.17, range 0.2-1.0)  TTO; 0.94 (SD 0.14, range 0.3-1.0)  HUI3; 0.75 (SD 0.25, range -0.06-1.0) |
| 8 | Pottel, 2015[W9] | Head and neck | Belgium | 81 | EQ5D; median (Q1, Q3) range 0.29 (0.0, 0.76) to 0.66 (0.55, 0.76) |
| 9 | Lango, 2014[W10] | Head and neck | US | 159 | EQ5D; median 85 (IQR: 70-90) |
| 10 | Nijdam, 2008[W11] | Head and neck | The Netherlands | 119 | EQ5D; median 75 |
| 11 | Rogers, 2006[W12] | Head and neck | UK |  | EQ5D; 0.75 (SE 0.02; range -0.18 - 1.0)  EQVAS; 74 (SE 1) |
| 12 | Ringash, 2000[W13] | Laryngeal | Canada | 84 | TTO; 0.878 (SD 0.174; range 0.25 - 1) |
| 13 | Downer, 1997[W14] | Oral | UK | 100 | SG; range 0.68 (SD 0.33) to 0.88 (SD 0.20) |
| 14 | Marcellusi, 2015[53] | Anal | Italy | 26 | EQ5D; 0.6 (SD 0.3)  TTO; range 0.5 (SD 0.26; 95% CI 0.4-0.61) to 0.52 (SD 0.25; 95% CI 0.36-0.67) |
| Head and neck; squamous cell carcinoma | Italy | 79 | EQ5D; 0.8 (SD 0.2)  TTO; range 0.69 (SD 0.3; 95% CI 0.62-0.75) to 0.59 (SD 0.3; 95% CI 0.46-0.72) |
| 15 | Conway, 2012[W15] | Anal | Australia | 95 | SG; 0.57 (95% CI 0.52 - 0.62); median 0.65 (IQR 0.45 - 0.75) |
| Oropharyngeal | Australia | 99 | SG; 0.58 (95% CI 0.53 - 0.63); median 0.65 (IQR 0.45 - 0.75) |
| Vaginal | Australia | 98 | SG; 0.59 (0.54 - 0.64); median 0.65 (IQR 0.45 - 0.75) |
| Vulvar | Australia | 98 | SG; 0.65 (0.60 - 0.70); median 0.65 (IQR 0.45 - 0.85) |
| Penile | Australia | 97 | SG; 0.79 (0.74 - 0.84); median 0.85 (IQR 0.65 - 1.0) |

# Discussion

## Statement of principal findings

This systematic review provides an updated and comprehensive summary of the cost and utility evidence for non-cervical HPV-related diseases that can be used in economic evaluations conducted from the perspective of a national health care provider. There appeared to be high heterogeneity in the papers identified, in terms of disease stages, population studied, treatment modality and setting, as well as utility elicitation methods used. The EuroQoL EQ-5D or EQ-VAS was commonly used in AGWs and in at least half of the non-cervical cancers studies.

Whilst the evidence in terms of both costs and utility values appear to be abundant for AGWs, it is less so for other cancers. This may reflect the fact that protection against AGWs is one of the main differentiating factors between the two competing HPV vaccines (quadrivalent and bivalent) on the market until licensure of the nonavalent vaccine in 2015, with several published economic evaluations focusing on the difference in cost-effectiveness between the two vaccines[W17].

## Strengths and weaknesses of the study

Many papers did not report a single overall cost or utility estimate for a disease episode. Instead, they reported cost or utility values at different stages of the disease, which means that to obtain a single overall figure over entire disease episode, further details about patient case mix and changes in utility over time are needed. This includes a combination of treatment received at different stages of disease. For example, Kim *et al.*, 2011, reported post-operative management cost for a selective group of head and neck cancer patients who had received surgical resection[43].

In addition, treatment modalities are likely to change over time, with corresponding effects on both treatment costs and quality of life (due to changes in recovery time and patient experience). This means that applying the same methodology to the same group of patients but managed differently will likely return different costs and utility estimates.

The NICE-recommended utility elicitation method is EQ-5D completed by patients and scored using population norms. This type of evidence is not always available. When alternative utility elicitation methods are used, such as direct utility elicitation methods, their score can be quite different, as demonstrated by Noel *et al.*, 2015[68]. In their study, patients with upper aerodigestive tract cancer completed five direct/indirect utility measures (EQ-5D, VAS, HUI3, standard gamble, and time trade-off). The authors found that direct utility elicitation methods (SG and TTO) returned higher utility scores, possibly due to patients being more risk-averse. When the SG method was used in another study (Conway et al., 2012[W15]) completed by general population, the utility score for oropharyngeal cancers was lower than head and neck cancers scored using SG in Noel et al., 2015[68], although this could be due to the scenario descriptions used.

## Meaning of the study: possible mechanisms and implications for clinicians or policymakers

This systematic review highlights the importance of understanding the data source used in economic evaluation, ensuring that health economic assumptions are up-to-date and closely reflect the case-mix of patients considered in the analysis.

## Unanswered questions and future research

During the paper screening and evaluation of eligibility stage, many papers on head and neck cancers were identified but they often used SF-36 generic utility measures and reported two summary scores covering physical and mental domains separately. Only four studies[56,59,W5,W6] reported a single summary score and were included. To be most applicable to economic evaluations, mapping exercises are needed to convert SF-36 values to single SF-6D scores specific to a country's population. Future analyses could consider extracting findings from relevant papers and converting to SF-6D scores, especially for diseases with insufficient utility estimates evidence.

Future research can also focus on identifying the duration of disutility to be applied to a disease, since quality of life changes over time, and is an important component of the QALY calculations.

# References

1 Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries : A systematic review. *Vaccine* 2013;**31**:3786–804. doi:10.1016/j.vaccine.2013.06.060

2 Marra F, Cloutier K, Oteng B, *et al.* Effectiveness and Cost Effectiveness of Human Papillomavirus Vaccine A Systematic Review. 2009;**27**:127–47.

3 Seto K, Marra F, Raymakers A, *et al.* The cost effectiveness of human papillomavirus vaccines: a systematic review. *Drugs* 2012;**72**:715–43. doi:10.2165/11599470-000000000-00000

4 Baylor N. October 16, 2009 Approval Letter - Cervarix. Vaccines, Blood Biol. 2009.

5 Baylor N. June 8, 2006 Approval Letter - Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant. Vaccines, Blood Biol. 2006.

6 Plummer M, de Martel C, Vignat J, *et al.* Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Heal* 2016;**4**:e609–16.http://dx.doi.org/10.1016/S2214-109X(16)30143-7

7 International Agency for Research on Cancer. A Review of Human Carcinogens. Part B: Biological agents / IARC Working Group on the Evaluation of Carginogenic Risks to Humans. Lyon, France: : International Agency for Research on Cancer 2012. http://monographs.iarc.fr/ENG/Monographs/vol100B/

8 Scarbrough Lefebvre C, Kriekinge G Van, Gonc MA, *et al.* Appraisal of the burden of genital warts from a healthcare and individual patient perspective. *Public Health* 2011;:464–75. doi:10.1016/j.puhe.2011.01.016

9 Rathod S, Livergant J, Klein J, *et al.* A systematic review of quality of life in head and neck cancer treated with surgery with or without adjuvant treatment. *Oral Oncol* 2015;**51**:888–900. doi:10.1016/j.oraloncology.2015.07.002

10 Rogers SN, Ahad S, Murphy A. A structured review and theme analysis of papers published on ‘ quality of life ’ in head and neck cancer : 2000 – 2005. *Oral Oncol* 2007;:843–68. doi:10.1016/j.oraloncology.2007.02.006

11 So WKW, Chan RJ, Chan DNS, *et al.* Quality-of-life among head and neck cancer survivors at one year after treatment – A systematic review. 2012;:2391–408. doi:10.1016/j.ejca.2012.04.005

12 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London, United Kingdom: 2013.

13 Organisation for Economic Co-operation and Development. Country Classification 2011. 2011;:14.

14 Curtis L, Burns A. *Unit Costs of Health & Social Care*. Kent, United Kingdom: : Personal Social Services Research Unit 2016. http://www.pssru.ac.uk/project-pages/unit-costs/2016/

15 Bank of England. Bank of England daily spot exchange rate against Sterling. Bank’s Publ. Scheme. 2015.http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp

16 Coles VAH, Chapman R, Lanitis T, *et al.* The costs of managing genital warts in the UK by devolved nation: England, Scotland, Wales and Northern Ireland. *Int J STD AIDS* 2016;**27**:51–7. doi:10.1177/0956462415573121

17 Lanitis T, Carroll S, O’Mahony C, *et al.* The cost of managing genital warts in the UK. *Int J STD AIDS* 2012;**23**:189–94. doi:10.1258/ijsa.2011.011218

18 Desai S, Wetten S, Woodhall SC, *et al.* Genital warts and cost of care in England. *Sex Transm Infect* 2011;**87**:464–8. doi:10.1136/sti.2010.048421

19 Woodhall SC, Jit M, Soldan K, *et al.* The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. *Sex Transm Infect* 2011;**87**:458–63. doi:10.1136/sextrans-2011-050073

20 Woodhall SC, Jit M, Cai C, *et al.* Cost of treatment and QALYs lost due to genital warts: Data for the economic evaluation of HPV vaccines in the United Kingdom. *Sex Transm Dis* 2009;**36**:515–21. doi:10.1097/OLQ.0b013e3181a74c2c

21 Brown RE, Breugelmans JG, Theodoratou D, *et al.* Costs of detection and treatment of cervical cancer, cervical dysplasia and genital warts in the UK. *Curr Med Res Opin* 2006;**22**:663–70. doi:10.1185/030079906X99972

22 Langley PC, White DJ, Drake SM. The costs of treating external genital warts in England and Wales : a treatment pattern analysis. *Int J STD AIDS* 2004;**15**:501–8.

23 Pirotta M, Stein AN, Conway EL, *et al.* Genital warts incidence and healthcare resource utilisation in Australia. *Sex Transm Infect* 2010;**86**:181–6. doi:10.1136/sti.2009.040188

24 Annemans L, Rémy V, Lamure E, *et al.* Economic burden associated with the management of cervical cancer, cervical dysplasia and genital warts in Belgium. *J Med Econ* 2008;**11**:135–50. doi:10.3111/13696990801961611

25 Marra F, Ogilvie G, Colley L, *et al.* Epidemiology and costs associated with genital warts in Canada. *Sex Transm Infect* 2009;**85**:111–5. doi:10.1136/sti.2008.030999

26 Salo H, Leino T, Kilpi T, *et al.* The burden and costs of prevention and management of genital disease caused by HPV in women: A population-based registry study in Finland. *Int J Cancer* 2013;**133**:1459–69. doi:10.1002/ijc.28145

27 Herse F, Reissell E. The annual costs associated with human papillomavirus types 6, 11, 16, and 18 infections in Finland. *Scand J Infect Dis* 2011;**43**:209–15. doi:10.3109/00365548.2010.541492

28 Hillemanns P, Breugelmans JG, Gieseking F, *et al.* Estimation of the incidence of genital warts and the cost of illness in Germany: A cross-sectional study. *BMC Infect Dis* 2008;**8**:1–10. doi:10.1186/1471-2334-8-76

29 Gianino MM, Delmonte S, Lovato E, *et al.* A retrospective analysis of the costs and management of genital warts in Italy. *BMC Infect Dis* 2013;**13**:1–9. doi:10.1186/1471-2334-13-470

30 Baio G, Capone A, Marcellusi A, *et al.* Economic Burden of Human Papillomavirus-Related Diseases in Italy. *PLoS One* 2012;**7**. doi:10.1371/journal.pone.0049699

31 Merito M, Largeron N, Cohet C, *et al.* Treatment patterns and associated costs for genital warts in Italy. *Curr Med Res Opin* 2008;**24**:3175–83. doi:10.1185/03007990802485694

32 Dee A, Howell F, O’Connor C, *et al.* Determining the cost of genital warts: A study from Ireland. *Sex Transm Infect* 2009;**85**:402–3. doi:10.1136/sti.2008.033837

33 Meijden WI Van Der, Notowicz A, Blog FB, *et al.* A Retrospective Analysis of Costs and Patterns of Treatment for External Genital Warts in the Netherlands. 2002;**24**:183–96.

34 Castellsague X, Cohet C, Puig-tintore LM, *et al.* Epidemiology and cost of treatment of genital warts in Spain. *Eur J Public Health* 2008;**19**:106–10. doi:10.1093/eurpub/ckn127

35 Östensson E, Fröberg M, Leval A, *et al.* Cost of Preventing, Managing, and Treating Human Papillomavirus (HPV)-Related Diseases in Sweden before the Introduction of Quadrivalent HPV Vaccination. *PLoS One* 2015;:1–15. doi:10.1371/journal.pone.0139062

36 Olsen J, Jørgensen TR, Kofoed K, *et al.* Incidence and cost of anal , penile , vaginal and vulvar cancer in Denmark. Published Online First: 2012. doi:10.1186/1471-2458-12-1082

37 Borget I, Abramowitz L, Mathevet P. Economic burden of HPV-related cancers in France. *Vaccine* 2011;**29**:5245–9. doi:10.1016/j.vaccine.2011.05.018

38 Keeping ST, Tempest MJ, Stephens SJ, *et al.* The cost of anal cancer in England: retrospective hospital data analysis and Markov model. *BMC Public Health* 2014;**14**:1123. doi:10.1186/1471-2458-14-1123

39 Heitland W, Schadlich PK, Chen X, *et al.* Annual cost of hospitalization, inpatient rehabilitation and sick leave of anal cancer in Germany. *J Med Econ* 2013;**16**:364–71. doi:10.3111/13696998.2012.759582

40 Abramowitz L, Remy V, Vainchtock A. Economic burden of anal cancer management in France. *Rev Epidemiol Sante Publique* 2010;**58**:331–8.

41 van der Linden N, Buter J, Pescott CP, *et al.* Treatments and costs for recurrent and/or metastatic squamous cell carcinoma of the head and neck in the Netherlands. *Head Neck* 2016;**273**:455–64. doi:10.1007/s00405-015-3495-y

42 Klussmann JP, Schädlich PK, Chen X, *et al.* Annual cost of hospitalization , inpatient rehabilitation , and sick leave for head and neck cancers in Germany. *Clin Outcomes Res* 2013;**5**:203–13.

43 Kim K, Amonkar MM, Högberg D, *et al.* Economic burden of resected squamous cell carcinoma of the head and neck in an incident cohort of patients in the UK. *Head Neck Oncol* 2011;**3**:1–10.

44 St Guily JL, Borget I, Vainchtock A, *et al.* Head and neck cancers in France : an analysis of the hospital medical information system ( PMSI ) database. *Head Neck Oncol* 2010;**2**:1–8.

45 Agthoven M Van, Ineveld BM Van, Boer MF De, *et al.* The costs of head and neck oncology : primary tumours , recurrent tumours and long-term follow-up. *Eur J Cancer* 2001;**37**:2204–11.

46 Corbridge R, Cox G. The cost of running a multidisciplinary head and neck oncology service - an audit. *Rev Laryngol Otol Rhinol* 2000;**121**:151–3.

47 Lowry J. Maxillofacial surgery: the economic aspect. *Br J Oral Maxillofac Surg* 1990;**28**:16–9.

48 van Agthoven M, Heule-Dieleman H, Knegt P, *et al.* Compliance and efficiency before and after implementation of a clinical practice guideline for laryngeal carcinomas. *Eur Arch Otorhinolaryngol* 2006;**263**:729–37. doi:10.1007/s00405-006-0062-6

49 Zavras A, Andreopoulos N, Katsikeris N, *et al.* Oral cancer treatment costs in Greece and the effect of advanced disease. *BMC Public Health* 2002;**8**:8–15.

50 Preuss S, Quante G, Semrau R, *et al.* An analysis of surgical complications, morbidity, and cost calculation in patients undergoing multimodal treatment for operable oropharyngeal carcinoma. *Laryngoscope* 2007;**117**:101–5.

51 Keeping ST, Tempest MJ, Stephens SJ, *et al.* Penile cancer treatment costs in England. *BMC Public Health* 2015;**15**:1305. doi:10.1186/s12889-015-2669-2

52 Harrison A, Montgomery J, Macgregor FB. Economic impact of recurrent respiratory papillomas in a UK adult population. *J Laryngol Otol* 2016;**130**:645–9. doi:10.1017/S0022215116001201

53 Marcellusi A, Capone A, Favato G, *et al.* Health utilities lost and risk factors associated with HPV-induced diseases in men and women: The HPV Italian collaborative study group. *Clin Ther* 2015;**37**:156–67. doi:10.1016/j.clinthera.2014.11.002

54 Vriend HJ, Nieuwkerk PT, Sande MAB Van Der. Impact of genital warts on emotional and sexual well-being differs by gender. *Int J STD AIDS* 2014;**25**:949–55. doi:10.1177/0956462414526706

55 Dominiak-Felden G, Cohet C, Atrux-Tallau S, *et al.* Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. *BMC Public Health* 2013;**13**:1065. doi:10.1186/1471-2458-13-1065

56 Drolet M, Brisson M, Maunsell E, *et al.* The Impact of Anogenital Warts on Health-Related Quality of Life : A 6-Month Prospective Study. *Sex Transm Dis* 2011;**38**:949–56. doi:10.1097/OLQ.0b013e3182215512

57 Mennini FS, Panatto D, Marcellusi A, *et al.* Time trade-off procedure for measuring health utilities loss with human papillomavirus-induced diseases: A multicenter, retrospective, observational pilot study in Italy. *Clin Ther* 2011;**33**:1084–95.e4. doi:10.1016/j.clinthera.2011.06.012

58 Senecal M, Brisson M, Maunsell E, *et al.* Loss of quality of life associated with genital warts : baseline analyses from a prospective study. *Sex Transm Infect* 2011;**87**:209–15. doi:10.1136/sti.2009.039982

59 Marra C, Ogilvie G, Gastonguay L, *et al.* Patients With Genital Warts Have a Decreased Quality of Life. *Sex Transm Dis* 2009;**36**:258–60. doi:10.1097/OLQ.0b013e318191a55e

60 Pirotta M, Ung L, Stein A, *et al.* The psychosocial burden of human papillomavirus related disease and screening interventions. *Sex Transm Infect* 2009;**85**:508–13. doi:10.1136/sti.2009.037028

W1 Woodhall S, Ramsey T, Cai C, *et al.* Estimation of the impact of genital warts on health- related quality of life. *Sex Transm Infect* 2008;**84**:161–6. doi:10.1136/sti.2007.029512

W2 Aro K, Back L, Loimu V, *et al.* Trends in the 15D health-related quality of life over the first year following diagnosis of head and neck cancer. *Eur Arch Otorhinolaryngol* 2016;**273**:2141–50. doi:10.1007/s00405-015-3732-4

W3 Govers T, Schreuder W, Klop W, *et al.* Quality of life after different procedures for regional control in oral cancer patients: cross-sectional survey. *Clin Otolaryngol* 2016;**41**:228–33.

W4 Pickard AS, Jiang R, Lin H, *et al.* Using Patient-reported Outcomes to Compare Relative Burden of Cancer : EQ-5D and Functional Assessment of Cancer Therapy-General in Eleven Types of Cancer. *Clin Ther* 2016;**38**:769–77. doi:10.1016/j.clinthera.2016.03.009

W5 Rettig E, D’Souza G, Thompson C, *et al.* Health-Related Quality of Life Before and After Head and Neck Squamous Cell Carcinoma : Analysis of the Surveillance , Epidemiology , and End Results – Medicare Health Outcomes Survey Linkage. *Cancer* 2016;**122**:1861–70. doi:10.1002/cncr.30005

W6 Kent E, Ambs A, Mitchell S, *et al.* Health-related quality of life in older adult survivors of selected cancers: data from the SEER-MHOS linked data resource. *Cancer* 2015;**121**:758–65. doi:10.1002/cncr.29119.

W7 Loimu V, Makitie A, Back L, *et al.* Health-related quality of life of head and neck cancer patients with successful oncological treatment. *Eur Arch Otorhinolaryngol* 2015;**272**:2415–23. doi:10.1007/s00405-014-3169-1

W8 Noel C, Lee D, Kong Q, *et al.* Comparison of Health State Utility Measures in Patients with Head and Neck Cancer. *JAMA Otolaryngol Head Neck Surg* 2015;**141**:696–703.

W9 Pottel L, Lycke M, Boterberg T, *et al.* G-8 indicates overall and quality-adjusted survival in older head and neck cancer patients treated with curative radiochemotherapy. *BMC Cancer* 2015;**15**:1–11. doi:10.1186/s12885-015-1800-1

W10 Lango MN, Egleston B, Fang C, *et al.* Baseline Health Perceptions , Dysphagia , and Survival in Patients With Head and Neck Cancer. *Cancer* 2014;**120**:840–7. doi:10.1002/cncr.28482

W11 Nijdam WM, Levendag PC, Noever I, *et al.* Longitudinal changes in quality of life and costs in long-term survivors of tumors of the oropharynx treated with brachytherapy or surgery. *Brachytherapy* 2008;**7**:343–50. doi:10.1016/j.brachy.2008.05.001

W12 Rogers SN, Miller RD, Ali K, *et al.* Patients’ perceived health status following primary surgery for oral and oropharyngeal cancer. *Int J Oral Maxillofac Surg* 2006;**35**:913–9. doi:10.1016/j.ijom.2006.07.017

W13 Ringash J, Redelmeier D, O’Sullivan B, *et al.* Quality of life and utility in irradiated laryngeal cancer patients. *Int J Radiat Oncol Biol Phys* 2000;**47**:875–81.

W14 Downer M, Jullien J, Speight P. An interim determination of health gain from oral cancer and precancer screening: 1. obtaining health state utilities. *Community Dent Health* 1997;**14**:139–42.

W15 Conway EL, Farmer KC, Lynch WJ, *et al.* Quality of life valuations of HPV-associated cancer health states by the general population. *Sex Transm Infect* 2012;**88**:517–21. doi:10.1136/sextrans-2011-050161

W16 Shi J, Kang D, Qi S, *et al.* Impact of genital warts on health related quality of life in men and women in mainland China : a multicenter hospital-based cross-sectional study. *BMC Public Health* 2012;**12**. doi:10.1186/1471-2458-12-153

W17 Suijkerbuijk A, Donken R, Lugnér A, *et al.* The whole story: a systematic review of economic evaluations of HPV vaccination including non-cervical HPV-associated diseases. *Expert Rev Vaccines* 2017;**16**:361–75. doi:10.1080/14760584.2017.1256778

# Figure legend

## Figure 1 PRISMA flow diagram

## Figure 2 Disease management costs reported in selected papers. Panel A outlines costs reported for anogenital warts (AGWs). Panel B contains an extraction of non-cervical cancer management costs; Panel A: Cost per case of AGWs management as reported in the relevant papers; Note that overall cost per patient is presented where this information is available, otherwise, cost per patient broken down by e.g. gender or new/recurrences presented and these are specified; Herse et al., 2011 not included as they presented minimum and maximum total cost of all patients, not per patient; Cost per patient for resistant cases reported in Hillemanns et al., 2008 not presented on this figure; Panel B: Cost per case of cancer management; Figure only presents cost per patient for their cancer management, excluding where only annual costs were reported or where total cost to the health care system was reported but not per patient cost; Note: H&N=Head and neck; Preuss, 2007, minimum and maximum costs reported for oropharyngeal carcinomas treatment with surgery and postoperative radio(chemo)therapy.

## Figure 3 Forest plots of pooled mean (95% CI) of studies reporting AGW EQ-5D (Panel A) and EQ-VAS (Panel B) utility estimates; Panel A: Pooled AGW EQ-5D utility estimates; Panel B: Pooled AGW EQ-VAS utility estimates. Note: utility estimates for different subgroups within Vriend, 2014[54] and Drolet, 2011[56] were pooled together and the combined mean and 95% CI were subsequently added to utility estimates from the other studies to generate an overall pooled mean and 95% CI.