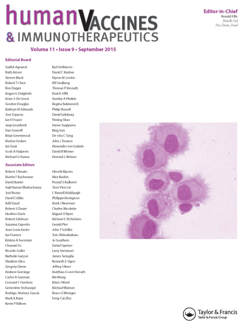

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Should human papillomavirus vaccination target women over age 26, heterosexual men and men who have sex with men? A targeted literature review of cost-effectiveness

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Abstract

Background

Human papillomavirus (HPV) vaccination for young women up to age 26 is highly cost-effective and has been implemented in 65 countries globally. We investigate the cost-effectiveness for HPV vaccination program in older women (age >26 years), heterosexual men and men who have sex with men (MSM).

Method

A targeted literature review was conducted on PubMed for publications between January 2000 and January 2017 according to the PRISMA guidelines. We included English-language articles that reported the incremental cost-effectiveness ratio (ICER) of HPV vaccination programs for women over age 26, heterosexual men, and MSM and identified the underlying factors for its cost-effectiveness.

Results

We included 36 relevant articles (six, 26 and four in older women, heterosexual men and MSM, respectively) from 17 countries (12 high-income (HICs) and five low- and middle-income (LMICs) countries). Most (4/6) studies in women over age 26 did not show cost-effectiveness ($65,000-192,000/QALY gained). Two showed cost-effectiveness, but only when the vaccine cost was largely subsidised and protection to non-naïve women was also considered. Sixteen of 26 studies in heterosexual men were cost-effective (ICER=$19,600-52,800/QALY gained in HICs; $49-5,860/QALY gained in LMICs). Nonavalent vaccines, a low vaccine price, fewer required doses, and a long vaccine protection period were key drivers for cost-effectiveness. In contrast, all four studies on MSM consistently reported cost-effectiveness (ICER=$15,000-$43,000/QALY gained), particularly in MSM age <40 years and those who were HIV-positive. Countries' vaccination coverage did not significantly correlate with its per-capita Gross National Income.

Conclusion

Targeted HPV vaccination for MSM should be next priority in HPV prevention after having established a solid girls vaccination programme. Vaccination for heterosexual men should be considered when 2-dose 4vHPV/9vHPV vaccines become available with a reduced price, whereas targeted vaccination for women over age 26 is unlikely to be cost-effective.

Key words: Human Papillomavirus, vaccine, cost-effectiveness, men who have sex with men

Introduction

Human Papillomavirus (HPV) infection is a common sexually transmitted infection (STI) and a necessary cause for cervical cancer in women [1]. It is also responsible for anal, vaginal, vulvar, oropharyngeal and penile cancers [2]. Cervical cancer was the fourth most common cancer among women globally, and second (only after breast cancer) in women in low- and middle-income countries (LMICs) [3]. According to the World Health Organization (WHO), an estimated 530,000 cervical cancers were diagnosed in 2012, and approximately 270,000 women per year died from cervical cancer worldwide. More than 90% of deaths occur in low- and middle- income countries (LMICs) due to poor access to screening and treatment services [4]. However, HPV infection is vaccine-preventable, and currently approved vaccines have achieved an excellent safety and efficacy profile [5].

National HPV vaccination programs have been initiated over a decade ago, but there are large disparities in coverage and targeted populations of vaccination strategies between countries where the program has been introduced. By mid-2016, national HPV vaccination programs have been established in 65 countries globally, most of which are high-income countries (HICs). Strong momentum has been observed to expand HPV vaccination programs to LMICs, where the majority of HPV-related cancers occur [6].

The type of HPV vaccination program that countries choose to implement depends on the countries' economic status, disease priorities, and the cost-effectiveness of the programs. Most

HPV vaccination programs target 9-14 year old schoolgirls before sexual debut and it is cost-effective if more than 70% of young women are vaccinated [7]. There remain lots of debate around whether it is cost-effective to expand the existing vaccination programs to also include women older than 26 years, heterosexual men, and men who have sex with men (MSM). Unlike HPV vaccination for adolescent girls and women up to 26 years which has been shown to be highly cost-effective in many studies [8-13], relatively fewer cost-effectiveness analyses (CEA) on HPV vaccination have been conducted in other population groups. This study aims to investigate the cost-effectiveness of HPV vaccination program for women older than 26 years, heterosexual men and MSM and the factors that drive its cost-effectiveness through a literature review.

Results

Study Selection and Characteristics

A total of 407 published articles were identified through PubMed (Figure 1). Initial screening eliminated 14 duplicated articles and a further 253 articles were excluded because they were not cost-effectiveness analyses of HPV vaccination. The remaining 140 articles were reviewed in full-text for eligibility according to our inclusion and exclusion criteria. Another 104 articles were excluded and 36 papers were eventually selected for our literature review. Among these 36 studies, six reported on women over age 26, 26 on heterosexual men, four on MSM and one reported on both women over age 26 and heterosexual men. These studies were conducted in 17 countries (12 high-income countries (HICs) and five low- and middle- income countries (LMICs), Table 1). Most (64%, n=23) selected studies were published in 2011 or later.

Cost-effectiveness of HPV vaccination for >26-year-old women

Six studies [14-19] evaluated the cost-effectiveness of 2vHPV vaccine in women >26 years. Four studies [14, 15, 17, 19] found the costs for targeted vaccination for women >26 years (ICER= US$65,000-192,000/QALY gained, Table S1) were beyond their respective cost-effectiveness thresholds (~$50,000/QALY gained) (Figure 2a). Four studies assumed vaccination cost US$283-400/3-dose vaccination schedule and concluded the program as not cost-effective. However, one study from the UK [14] showed marginal cost-effectiveness when vaccine price was below £20/dose and life-time vaccine protection for women when no loss of immunity over time was considered. Another study from Lao PDR [18] showed the program to be cost-effective with a catch-up vaccination for women up to age 75 years and the existing schoolgirls vaccination program was strongly subsidised by GAVI, the Vaccine Alliance (US$8.5/dose). Only one Belgium study [16] demonstrated their program to be very cost-effective with the 2vHPV for women age up to 33 years (Table S1). Both the Lao PDR and Belgium studies assumed high vaccination coverage (≥70%). All studies assumed 3-dose vaccination strategies and none compare it with a 2-dose vaccination strategy.

Cost-effectiveness of HPV Vaccination for Heterosexual men

Of 26 selected studies [12, 20-43] on gender-neutral vaccination (three in LMICs and 23 in HICs), two studies examined 2vHPV vaccine, 20 on 4vHPV, and four on 9vHPV vaccines.

Sixteen studies [21-24, 26, 35-45] demonstrated that HPV vaccination for heterosexual men with an existing female program was cost-effective (ICER = \$19,600-52,800/QALY gained in HICs and \$49-5,860/QALY gained in LMICs, Table S1) with respect to their respective cost-effectiveness thresholds (Figure 2a).

All four studies that assessed 9vHPV [35, 37, 39, 41] vaccine concluded that the vaccine for both girls and boys was cost-effective (ICER=\$8600-49800/QALY gained, Table S1) in comparison with 2vHPV or 4vHPV vaccination for both women and/or men. The majority (2/3) of studies with 2vHPV vaccination [23, 29] was not cost-effective, while 11/20 studies with 4vHPV vaccination were cost-effective. Interestingly, when stratified by five-year time periods (<2010, 2010-2014 and ≥2015, Figure 2b), increasing proportion of studies demonstrated cost-effectiveness of HPV vaccination for heterosexual men in recent years (p-value=0.035).

The assumed price of HPV vaccines varied substantially across studies (US \$10-130/dose), and our analysis did not show any correlation between vaccine price and program cost-effectiveness in heterosexual men. While 3-dose vaccination strategy showed mixed results (14 cost-effective and 11 not), both studies with a 2-dose vaccination strategy showed cost-effectiveness [44, 45]. Longer duration of vaccine protection (life time protection) and program evaluation (100 years horizon) led to lower ICERs in these studies.

Age was an important factor for vaccine cost-effectiveness. Eight studies showed it was cost-effective to expand existing schoolgirl program to cover schoolboys at the same age (<15 years). However, a UK study [27] and a Danish study [30] demonstrated that in the presence of a schoolgirl program, catch-up vaccination for young women up to 26 was a more cost-effective option than expanding schoolgirl program to cover the same age schoolboys. Eight studies showed that vaccination program for schoolboys and heterosexual men was no longer cost-effective if the vaccination coverage in women was beyond 70-75%. There was no evidence that the countries' economic development status and vaccine efficacy had any impact on the cost-effectiveness of vaccination program for heterosexual men.

Cost-effectiveness of HPV Vaccination for MSM

Four studies [46-49] evaluated the cost-effectiveness of 4vHPV vaccine for MSM. All four studies demonstrated that the 4vHPV vaccine for MSM compared with no vaccination was cost-effective ($15,000-43,000/QALY gained) (Figure 2 a, Table S1), and it showed lower ICERs, hence better cost-effectiveness, for vaccination against MSM at a young age (<40 years) or against those who were HIV-positive. A good cost-effectiveness of HPV vaccination for MSM was also associated with a high vaccination coverage (at least 55-80%), a potent vaccine efficacy (50-90%), a low vaccine price of 4vHPV (US$180-360/3-doses), a long duration of evaluation (life-time/100 years' time horizon) (Table 2). In all MSM studies, there was no evidence that the socio-economic development status of the countries and vaccine dosage influenced the cost-effectiveness of MSM vaccination.

Vaccination and cervical cancer screening in included countries

The HPV vaccination and cervical cancer screening programs from the selected studies were described in Table 1. The annual cervical cancer incidence was generally higher (9.4-23.7 versus 5.5-12.9 per 100,000) in women from LMIC than HIC, as was the age standardized mortality rate for cervical cancer (3.4-8.0 versus 1.4-2.1 per 100,000). Cervical cancer mortality rates were significantly and negatively correlated with Gross National Income (GNI) (Spearman, $r=-0.75$, $p<0.001$). Cervical cancer screening coverage among targeted women in HIC was more than 50-70%. In contrast, among LMIC, only Brazil reached a similar screening coverage as in HIC, while other countries were consistently below 40%. All National HPV vaccination programs for schoolgirls (up to age 14) were introduced before 2011 in HIC, and some programs included a catch-up program for young women up to age 26. To date, Austria, Australia, Canada, and the US, have expanded the vaccination program to schoolboys (age 9-14 years). In contrast, HPV vaccination began much later in LMICs, typically between 2013 and 2015 and China and Vietnam did not implement any vaccination programs until 2017. Vaccination coverage for women ranged from 40-80% in developed countries, where Germany had the lowest (40%) and the United Kingdom the highest (80%) coverage. We found no significant correlation between GNI per capita and vaccination coverage ($R=-0.0049$, $p=0.9877$).

Discussion

Our targeted literature review indicated that HPV vaccine for women >26 years would not be cost-effective, and this is consistent with current policy and practice. In contrast, HPV vaccination for heterosexual men demonstrated mixed results: programs proposing 9vHPV (compared with 4vHPV and 2vHPV), those assuming a long duration of vaccine effectiveness and those vaccinating young heterosexual men (<26) demonstrated cost-effectiveness. Further, it suggested that targeted HPV vaccination for MSM is cost-effective in all four included studies. A previous systematic review on the cost-effectiveness of HPV vaccination among adolescent girls in LMICs has shown that vaccine price is one of the key determinant of vaccination cost-effectiveness [50]. Our review further confirms this is also true in heterosexual men and MSM. In addition, we also identified a broad genotype coverage (9vHPV), less required doses and longer vaccine protection are important determinants for cost-effectiveness.

Our findings suggests that targeted HPV vaccination for MSM should be a priority worldwide. Unlike heterosexual men, MSM may benefit to a lesser extent from the herd immunity that heterosexual men may receive from the female vaccination programs [51]. On the other hand, MSM are much more at-risk than heterosexual men to HPV infection in particular anogenital warts and anal cancer. In contrast to vaccination program in women where the vaccination coverage required (~70%) is well established, the vaccination coverage required in MSM to achieve the same level of herd immunity that heterosexual men may experience is not known. Since the reproductive rate of HPV infection in MSM is much greater than heterosexual men, it is likely that a higher level of vaccination coverage will be required [52].

Despite only 16 of 26 studies in heterosexual men demonstrating cost effectiveness, our data suggest that a gender neutral vaccination strategy may become increasingly cost-effective for a number of reasons. First, recent literatures reported that 1- or 2-doses vaccination is as effective as 3-doses vaccination for people age 9-14 years, which means a potential 30% cost reduction per head if this is implemented in any school age vaccination programs [53-55]. Second, it is anticipated that the mean price of HPV vaccine for LMICs will continue to decline over time, especially with significant subsidies and influence from major international health organizations such as GAVI, UNICEF and Pan American Health Organization (PAHO) [56, 57].

Our analysis shows no correlation between individual country's socio-economic status and vaccination coverage. However, we argue that the rollout of a universal HPV vaccination program in LMICs may face more challenges. Given limited resources, LMICs generally have a lower willingness-to-pay threshold for a vaccination program. Therefore, vaccine cost needs to be substantially lowered in LMICs, not only for the consideration of cost-effectiveness, but also the upfront investment cost must not become an excessive financial burden to the country budget. The initial rollout of the program often require a one-time investment for health facilities, establishment of an efficient implementation system and training for healthcare staff. Further, in resource-poor settings, an efficient healthcare provision system is often absent to provide the scheduled vaccination program, which is an essential infrastructure for additional HPV vaccination programs. For these settings, resources from the international community should be directed to provide point-of-care vaccination where primary healthcare is absent, and 2-dose HPV vaccine should be promoted to improve vaccination coverage in the population.

A number of limitations need to be considered when interpreting our results. As a targeted literature review, we excluded studies not published in English and therefore, our study may be subject to publication bias. Second, we could not conduct a meta-analysis due to limited data available from targeted reviews. Similarly, we could not prove the robustness of outcomes because of the variations in models applied in the included studies where different assumptions and parameters were used. For instance, population impact was not reported in a consistent form across the studies, however, we emphasized that all cost-effectiveness studies included a baseline scenario and the analysis was conducted by comparing the scenarios in the presence and absence scenario. Therefore, we summarized the absolute number of studies and the factors influencing the cost-effectiveness instead. Despite these limitations, we believe our findings would be a springboard for further studies of the cost-effectiveness of HPV vaccination for these currently untargeted populations.

Conclusion

Targeted HPV vaccination for MSM should be next priority in HPV prevention after having established a solid girls vaccination programme. Vaccination for heterosexual men should be considered when 2-dose 4vHPV/9vHPV vaccines become available with a reduced price. Vaccination for women over age 26 may not be cost-effective until the vaccine price is further reduced.

Method

Search

The full electronic search was conducted in PubMed for related articles and reviews on February 15th 2017, which were published in the English language from January 1, 2000 to December 31, 2016. The search strategy was conducted using the following key words: "Human Papillomavirus" AND "Cost-effectiveness" AND "Vacc*" in MeSH terms AND "HPV" OR "Human Papillomavirus" AND "Cost-effective*" AND "Vacc*" in titles and abstracts AND "English" in language.

Eligibility Criteria

This review included English-language articles (published between 2000-2016) that assessed the incremental cost-effectiveness ratio (ICER) of HPV vaccination to the female population older than 26 years, heterosexual men and MSM, in comparison with the cost-effectiveness of existing cervical cancer screening or vaccination in young adolescent girls with a catch-up program for women age up to 26 years. In this review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) statement [58] was followed (Figure 1). Articles were excluded if they (1) were in a language other than English; (2) did not report ICER of the HPV vaccination program; and (3) only focused on young female vaccination program.

Data collection

We collected demographic data, HPV epidemiological data, impact and cost-effectiveness data from aforementioned literature review. In addition, based on the countries identified from the selected studies, we further collected data on country-specific HPV-related programs and country incomes that were not available in the literature research.

First, demographic data included age and sex of the targeted population, period of analysis (retrospective or prospective study) and country of the study population. Second, epidemiological data included status quo HPV disease burden, subtypes and vaccination coverage. Third, population impact data included the type of model used, reduction in HPV infections, number of genital warts, pre-cancerous lesions CIN-1, -2, and -3 cases, cervical cancer cases and mortality. Fourth, cost-effectiveness data included incremental cost associated with HPV vaccination programs; incremental cost-effectiveness ratios (ICERs); incremental life-years gained (LYGs) or Quality-adjusted life-years (QALYs) gained from a vaccination program. Fifth, we identified 17 countries from the selected 36 publications. For these 17 countries, we collected other HPV-related program and income data from these well-known online HPV databases: HPV Information Centre [59]; National Cancer Institute [60]; and International Agency for Research on Cancer [61]. Specific country data included: gross National Income per capita (GNI); age-standardized incidence rate of cervical cancer; age-standardized mortality rate of cervical cancer; existence of national cervical cancer screening and HPV vaccination programs; years of introduction of the national HPV vaccination program; targeted age and gender of current HPV vaccination program; vaccination coverage; and cervical cancer screening coverage. Double-entry was performed to extract these data by two independent investigators (NNS, FC). Microsoft excel 2013 was used to store and analyse these data.

Quality Assessment

The quality assessment of each included study was conducted by two independent investigators (NNS, FC). Any conflicting opinions were resolved by a third reviewer (LZ). The quality check for each included study was assessed by three domains: study design, data collection, and analysis and interpretation of the results (Cost-effectiveness study quality checklist [62], Table S2).

Data Analysis

Descriptive statistics were conducted for each study population group (older women, heterosexual men and MSM) to inform HPV program, impact and cost-effectiveness indicators. First, for each population, we categorized the selected studies that showed proposed strategy was cost-effective according to their stated willingness-to-pay threshold, and those showed it was not cost-effective. Second, the major contributing factors influencing the cost-effectiveness, including vaccination age and coverage, vaccine efficacy, price and dosage, duration of vaccine protection, and the time horizon of evaluation, were identified in both cost-effective and non-cost-effective studies. A Spearman's correlation test was used to analyse the correlation between the GNI and HPV-burden of the included countries. In addition, chi-square tests were conducted to investigate the time trend of cost-effectiveness of HPV vaccination for heterosexual males.

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Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions
Older general women (>26)									
Jane J. Kim, et al. [15]	2009	USA	No vaccination for older women	35-45yr GF, with 2vHPV (+ annual CC screenin	US$360/3-dose/person; 3% DR; 100% VE; lifetime protectio	2009-lifetime	$197,793-384,837	--	Not cost-effective (WTP: US$100,000)

				g),	n; 75% coverage.				
Tjalke A. Westra, et al. [17]	2011	Netherlands	No vaccination for older women	(+biennial CC screening)	€315/3-dose/person; 4% DR; 95% VE; lifetime protection; 100% coverage.	2011-lifetime	$115,739-272,325	Without vaccination, 565 CC cases and 205 CC-related death annually	Not cost-effective
				(+triennial CC screening)		/2011-2030	$125,336-265,095		Not cost-effective
				12-50yr GF, with 2vHPV,			12yr: €19,900 [19,200-21,600], 12-18yr: €23,500, 12-25yr: €26,900,		Cost-effective (WTP: €20,000-50,000)
							30yr: €52,100 [50,400-		Not cost-effective

							57,100]		
Nadia Demarteaua, et al. [16]	2013	Belgium	No vaccination for older women	12-40yr GF, (before and after sexual debut) with 2vHPV,	€324-€539/3-dose/person; 4% DR; 95% VE; lifetime protection; 100% coverage.	2012-lifetime	12-33yr: €8,777-27,770	Vaccination at age 12,26,40 prevent 646, 340 and 146 CC cases, respectively	Highly cost-effective (WTP: €32,200)
							34-40yr: €32,086-44,460		Cost-effective
Hugo C. Turner, et al. [14]	2013	UK	12-34yr women with 2vHPV	12-29yr GF with 2vHPV	£20/dose; 3.5% DR; 100% VE; protectio	2013-2113	20yr protection: £51,816, Lifetime protection: £33,897	--	Marginally cost-effective (WTP: £30,000/QALY)

				12-34yr GF with 2vHPV	n to non-naïve GF		20yr protection: £103,156, Lifetime protection: £50,125			Not cost-effective
				12-29yr GF with 2vHPV	£40/dose, 3.5% DR; 100% VE; protection to non-naïve GF		20yr protection: £90,320, Lifetime protection: £60,394			Not cost-effective
				12-34yr GF with 2vHPV			20yr protection: £162,040, Lifetime protection: £80,278			Not cost-effective

Yi-Jun Liu, et al. [19]	2016	China	No vaccination for general women	12-55yr GF with 2vHPV	CNY1,950/3-dose/person; 3% DR; 93% VE; lifetime protection; 70% coverage	2016-lifetime	>23yr in rural & >25yr in urban: >CNY125,723	Reduced 33-585 CC in rural and 32-691 CC in urban	Not cost-effective (WTP: CNY125,723)
Phetsavanh Chanthavilay, et al. [18]*	2016	Lao	10yr GF + 11-25yr CU with 2vHPV	10yr GF + 11-75yr CU with 2vHPV Additional 10yr heterosexual	US$8.5/dose (GAVI price); 3% DR; 100% VE; lifetime protection; 70%	2016-2115	I$5,840/DALY averted	CC reduced by 91.4% CC reduced by 81.3%	Cost-effective (WTP: 3 times Lao GDP)

				men with 2vHPV	coverage				
							Dominated		Not cost-effective

Supplementary Materials

Table 1. Summary table of key cost-effectiveness indicators from 36 included publications in this targeted review.

Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions
Heterosexual men									
Al V. Taira, et al. [20]	2004	USA	12yr GF with 2vHPV, n=U.S GF population	FM with 2vHPV vaccination	US$300/3-dose/person; 3.5% DR; 90% VE; at least	2001-lifetime	US$442,039	12GF-only vaccination reduced CC by 61.8%, FM vaccination further reduced CC	Not cost-effective (WTP: US$100,000)

					10yr protection; 70% coverage,			by 2.2%	
Jane J. Kim, et al. [23]	2007	Brazil	No vaccination for FM	FM, with 2vHPV	I$50/3-dose/person; 3% DR; 100% VE; lifetime protection; 0-90% coverage	Not reported	25% coverage: I$810/LYG	GF-only vaccination reduced CC risk by 63%, FM vaccination further reduced CC risk by 4%	Cost-effective (WTP: I$8,600/LYG)
							50% coverage: I$1,740/LYG		Cost-effective
							75% coverage: I$2,180/LYG		Cost-effective
							90% coverage: I$1,8650/LYG		Not cost-effective
Anna R.	200	USA	12yr	12yr	Not	--	US$45,056	GW, CIN	Cost-

Giuliano [21]	7		FM + 12-24yr CU with 4vHPV	FM + 12-24yr CU-FM) with 4vHPV, n=536 (F: 299, M: 237)	reported			and CC reduced by 97%, 91% and 91% respectively	effective
Shalini Kulasingam, et al. [24]	2007	Australia	No vaccination for FM	12yr FM with 2vHPV + 14-26yr with 2vHPV,	US$345/ 3-dose/person; 3% DR; 100% [93-100%] VE; lifetime protection; 80%	2005-2078	US$33,644 [24,988-68,158]	--	Cost-effective

					coverage				
Elamin H. Elbasha, et al. [22]	2007	USA	12yr GF with current vaccination	12yr FM with 4vHPV n=100,000 (F:50%, M:50%)	US$360/3-dose/person; 3% DR; 90-100% VE; lifetime protection; 70% coverage	2005-2105	Dominated		Not cost-effective (WTP: US$100,000)
			12yr GF + 12-24yr CU	12yr FM + 12-24yr CU			$4,666		Cost-effective
			12yr FM + 12-24yr	12yr FM + 12-24yr			$45,056	GW, CIN, and CC reduced by	Cost-effective

			CU	CU-FM				97%, 91%, and 91%, respectively	
Ralph P. Insinga, et al. [12]	2007	Mexico	12yr GF with 4vHPV	12yr FM with 4vHPV, n=100000	US$240/ 3-dose/person; 3% DR; 90% VE; lifetime protection; 70 [20-85]% coverage	2007-2066	US$2,719	FM vaccination reduced CC, CIN and GW by 84-98%	Not cost-effective (WTP: US$30,000)
			12yr GF + 12-24yr CU	12yr FM + 12-24yr CU			US$16,663		Cost-effective

			12yr FM + 12-24yr CU-FM	12yr FM + 12-24yr CU-FM			US$16,702		Cost-effective

Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions

Mark Jit, et al. [31]	2008	UK	12yr GF + 12-25yr CU with 4vHPV	12yr FM with 4vHPV vaccination	£210 [180-240]/3-dose/person; 3.5% DR; 100% VE; lifetime protection; 80% coverage	2007-2107	Lifetime protection: £520,255 [304,798-986,917]	--	Not cost-effective (WTP: £30,000)
							20yr protection: £172,892 [112,230-289,698]		Not cost-effective
							10yr protection: £113,846 [71,099-176,749]		Not cost-effective

Ingrid Zechmeister, et al. [28]	2009	Austria	12yr GF, with 2vHPV	12yr FM, with 4vHPV	€330/3-dose/person; 5% DR; 90% VE; 10-year to lifelong protection; 65% coverage	2008-2060	€299,000-311,000/LYG	--	Not cost-effective
Jane J. Kim and Sue Goldie [29]	2009	USA	12yr GF, with 2vHPV	12yr FM, with 2vHPV and current screening for triage	US$360/3-dose/person; 3% DR; 100% VE in GF & 90% in	2006-2106	US$114,510	Cases attributable to vaccine targeted types reduced by 50%	Not cost-effective (WTP: US$100,000)

				12yr FM with 2vHPV and current screening for triage until 30yr, & cytology and HPV DNA testing after age 30	GM; lifetime protection; 75% coverage		US$120,300		Not cost-effective

Elamin H. Elbasha, et al. [26]	2010	USA	9-26yr GF with vaccination	9-26yr FM with 4vHPV	US$400/3-dose/person; 3% DR; 90% VE; lifetime protection; 50-90% vaccine coverage	2008-2108	CD considered: $195,322 [87,426-570,330], All outcomes considered: $25,664 [13,605-48,816]	Prevented 30,750 CC, 707,489 CIN-2/3, 1,849,170 GW (F); 3297418 GW (M).	Cost-effective (WTP: US$20,000 – 50,000)
Jens Olsen, et al. [30]	2010	Denmark	12yr GF + 12-26yr CU with 4vHPV	12yr FM with 4vHPV, n=25000	£415/3-dose/person; 3% DR; 100% VE; 70% coverage	2007-2068	£18,677	--	Not cost-effective

Harrell W. Chesson, et al. [27]	2011	USA	12-26yr GF with 4vHPV	12yr FM + 12-26yr CU-GF with 4vHPV, n=191	US$500 [360-600]/3-dose/person; 3% DR; 90-95% VE; lifetime protection; varied coverage	2008-2108	20% coverage: $23,600 [11,400-39,500]	CC to HPV16/18 reduced by 81.3%, 67.4%, and 97.4%, with 30%, 20%, and 75% coverage, respectively.	Cost-effective (WTP: US$100,000)
							30% coverage: $41,400 [23,400-64,300]		Cost-effective
							75% coverage: $184,300 [115,000-276,300]		Not cost-effective

			12yr GF with 4vHPV 30% coverage	12yr FM with 4vHPV 30% coverage			$25,000		Cost-effective
			12yr GF with 4vHPV 45% coverage	12yr FM with 4vHPV 30% coverage			$103,500		Not cost-effective

Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/ QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions

MSM=Men-who-have-sex-with-men; GM=Heterosexual men; GF=Women; FM=Males and women; CU=Catch-up; DR=Discounted rate; VE=Vaccine efficacy; yr=years; NoVac=No vaccination; HR=Hazard ratio; 2vHPV=Bi-valent vaccine; 4vHPV=Quadri-valent vaccine; 9vHPV=Nona-valent vaccine; ANA=Anal cancer; GW=Genital warts; CC=Cervical Cancer; CIN=Cervical intraepithelial neoplasia; QALY=Quality-adjusted life year; LYG=Life years gained; WTP=Willingness-to-pay thresholds; Dominated=the intervention is less effective and more costly; CD=Cervical diseases

Amber L Pearson, et al. [25]	2014	New Zealand	12yr GF, with 4vHPV n=total population	12yr FM, with 4vHPV	US$400/3-dose/person; 3% DR; 99% VE; 20yr protection; Intervention 1G: 56 [54-58] % coverage; Intervention 2G: 73 [68-78] % coverage,	--	$118,000 [57,100-215,000]	--	Not cost-effective (WTP: US$29,600)
			12yr GF, with 4vHPV (Intensive 2G GF-only program)	12yr FM, with 4vHPV			$247,000 [119,000-474,000]		Not cost-effective

Jean-Francois Laprise, et al. [32]	2014	Canada	GF with 2-doses 4vHPV	FM with 2-doses 4vHPV, n= 170000	Cost: CA$85/dose; 3% DR; 90-95% VE; 2-dose: 10-30yr protection; 3-dose: 20yr-lifelong protection; 80% coverage,	2014-2083	2-dose: CA$87,042 [70,141-133,239]	Prevented an extra 3% HPV-related cancer and 9% GW cases to F-only Vac (12-13% reduction of cancers & GW)	Not cost-effective (WTP: CA$40,000)
			GF with 3-doses 4vHPV (or) FM with 2-doses 4vHPV	FM with 3-doses 4vHPV			3-dose: >CA$100,000		Not cost-effective
Wanrudee Isaranuwatchai, et al. [33]	2014	USA	12yr GF with 4vHPV	12yr FM, with 4vHPV	US$500/3-dose/person	--	US$115,000	--	Not cost-effective (WTP: $40,000)

			12yr GF with 4vHPV	9-26yr FM with 4vHPV			US$70,000		Not cost-effective

Emily A. Burger., et al. [44]	2014	Norway	12yr GF with 4vHPV	12yr FM with 4vHPV	Market price: US$150/dose; Nationally negotiated tender price: US$75/dose; 4% DR; 90 - 100% VE; lifetime protection; 71-79% coverage	2013-lifetime	US$81,700 considering only cancer for FM, US$60,100 considering all HPV-related conditions,	CC reduction varies, reduced GF GW 85%, GM GW 84%.	Marginally cost-effective (WTP: US$83,000)

Xavier Bresse, et al. [43]	2014	Austria	9yr FM without vaccination	9yr FM with 4vHPV	€360/3-dose/person; 3% DR; GF:76-100%, GM:41-96% VE; lifetime protection; 65% coverage	2014-2114	€10,033-26,701	Prevented 9,500 GW annually and 431 HPV 16/18-related cancers in FM	Cost-effective

MSM=Men-who-have-sex-with-men; GM=Heterosexual men; GF=Women; FM=Males and women; CU=Catch-up; DR=Discounted rate; VE=Vaccine efficacy; yr=years; NoVac=No vaccination; HR=Hazard ratio; 2vHPV=Bi-valent vaccine; 4vHPV=Quadri-valent vaccine; 9vHPV=Nona-valent vaccine; ANA=Anal cancer; GW=Genital warts; CC=Cervical Cancer; CIN=Cervical intraepithelial neoplasia; QALY=Quality-adjusted life year; LYG=Life years gained; WTP=Willingness-to-pay thresholds; Dominated=the intervention is less effective and more costly;

Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions
Donna M. Graham, et al. [36]	2015	Canada	No vaccination for heterosexual men	Up to 12yr male, with 4vHPV,	CA$400/3-dose/person; 5% DR; 84 [50-99]% VE. 50-70% coverage	2014-lifetime	99% VE & 70% uptake: saved $145/individual (0.05 more QALY)	--	Cost-effective
							50% VE & 50% uptake: saved $42/individual (0.023 more		Cost-effective

							QALYs)		
Jens Olsen, et al. [45]	2015	Denmark	12yr GF, with 4vHPV	12yr FM, with 4vHPV	US€369/3-dose/person; 3% DR; 100% VE; lifetime protection; 85% coverage,	2014-2075	3-dose: €41,636 and €40,615/LYG 2-dose: €28,031	5 CC, 34 ANA, 98 H&N cases avoided per year	Cost-effective (WTP: € 50,000)
Nikolaos Kotsopoulos, et al. [42]	2015	Germany	No vaccination for FM	12yr FM, with 4vHPV, n = 400,000	€244/2-dose/person; 2.4% DR; 78-100% VE;	2015-lifetime	Investing €1 in universal HPV vaccination could yield €1.7 in gross tax revenue	Prevented 857 cancer deaths, 1,527 CC, 286 ANA, 228 VAG, 116 VUL,	Cost-effective

					55% coverage		over the lifetime of the cohorts.	45,809 GW, and 127,464 CIN I-III	
Katrin Haeussler, et al. [38]	2015	Italy	GF without vaccination (screening)	12yr FM with 4vHPV, n=149,736,770	€40-140/dose; 3% DR; 50% VE; lifetime protection; 90 [66-100]% coverage,	2015-2070	€1,500	--	Highly cost-effective (WTP: €25,000-€40,000)
			GF with 4vHPV	12yr FM with 4vHPV			€11,600[10,173-13,227]		Cost-effective
M Sharma, et al.	2016	Southern Vietnam	≥9yr GF, with	≥ 9yr FM, with	I$10-200/3-dose/per	2015-longti	≤$25/dose: I$49-1,751	F-only Vac: CC risk	Cost-effective

[40]			4vHPV	4vHPV	son; 3% DR; 100% VE for GF; 85% for GM; lifetime protection; 25-90% coverage	me		reduced by 20%-56.9%. FM Vac: <=3.6% higher absolute CC risk reduction.	(WTP: I$2,800)
							≥$25-75/dose: I$1,445-5,860		Marginally cost-effective
							>$75/dose: I$3,190-16,131		Not cost-effective
Nathalie Largeron, et al. [41]	2016	Germany	9-17yr GF with 4vHPV vaccination	9-17yr FM, with 9vHPV vaccination	€336/3-dose/person for 4vHPV; €372/3-dose/person for	2015-2115	€22,987 /QALY	• Prevented 46,454 CC, 398,993 CIN1,	Cost-effective (WTP: €40,000)

					9vHPV; 3% DR; varied VE; lifetime protection; varied coverage,			571013 CIN2+, 315 VAG, 429 VUL, 364,313 F GW, 3,036 GF ANA, 1,084,422 GM GW & 5,420 GM ANA.	
David P. Durham a, et al. [35]	2016	USA	FM with 2vHPV/4vHPV	FM, with 9vHPV, n=10000	US$148/dose for 9vHPV; US$135/dose for 4vHPV; US$129/dose for 2vHPV;	2015-2050	When considering Costs: US$32,809-49,363, When considering total societal cost: US$21,398-	• Reduced CC incidence by 73% and mortality by 49% compared to NoVac	Cost-effective (WTP: US$53,000)

					3% DR		49,796	(15,947 CC, 4,912 mortality).	

MSM=Men-who-have-sex-with-men; GM=Heterosexual men; GF=Women; FM=Males and women; CU=Catch-up; DR=Discounted rate; VE=Vaccine efficacy; yr=years; NoVac=N vaccine; 9vHPV=Nona-valent vaccine; ANA=Anal cancer; GW=Genital warts; CC=Cervical Cancer; CIN=Cervical intraepithelial neoplasia; QALY=Quality-adjusted life year; LYG=L intervention is less effective and more costly;

Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions

Harrell W. Chesson, et al. [37]	2016	USA	FM with 4vHPV	FM with 9vHPV, n=191	$435/3-dose/person for 4vHPV; $474[453-513]/3-dose/person for 9vHPV; 3% DR; 95[85-100]% VE; lifetime protection; GF:70%, GM:50% coverage	2015-2115	No cross-protection for 4vHPV: <$0, Cross-protection for 4vHPV: US$8,600	With 4vHPV, CIN reduced by 43-53%, With 9vHPV, CIN reduced by 63-65%	Cost-saving

L. Boiron, et al. [39]	2016	Austria	9yr FM with 4vHPV	9yr FM with 9vHPV	€297/2-dose/person for 9vHPV; 3% DR; Varied VE; lifetime protection, GF: 60%, GM: 40% coverage	2016-2116	€16,441	Prevented an additional 14,893 CIN2/3 and 2,544 CC	Cost-effective (WTP: €30,000)

Table 2. Cost-effectiveness study quality checklist

Item	MSM				Older genereal females					
	Jane J. Kim[49]	et al.[47]	et al.[46]	Allen Lin[48]	Jane J. Kim, et al.[15]	al.[17]	al.[16]	al.[14]	Yi-Jun Liu, et al.[19]	al.[18]
Study design										
The research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The economic importance of the research	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

question is stated										
The viewpoint(s) of the analysis are clearly stated and justified	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The rationale for choosing alternative programmes or	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

interventions compared is stated										
The alternatives being compared are clearly described	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The form of economic evaluation used	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

is stated										
The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Data collection										

The source(s) of effectiveness estimates used are stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details of the design and results of effectiveness study are given (if	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓

based on a single study)										
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of	NA	NA	NA	NA	NA	NA	NA	NA	✓	✓

effectiveness studies)										
The primary outcome measure (s) for the economic evaluation are clearly stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methods to value benefits are	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

stated										
Details of the subjects from whom valuations were obtained were given	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Productivity changes (if included) are reported separatel	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

y										
The relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quantities of resource use are reported separately from	NA	NA	NA	NA	NA	NA	NA	NA	NA	✗

their unit costs										
Methods for the estimation of quantities and unit costs are described	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Currency and price data are recorded	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

of currency of price adjustments for inflation or currency conversion are given										
Details of any model used are given	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The choice of model used and	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

the key parameters on which it is based are justified										
Analysis and interpretation of results										
Time horizon of costs and benefits is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

discount rate(s) is stated										
The choice of discount rate(s) is justified	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
An explanation is given if costs and benefits are not discounted	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Details of statistical tests and CIs are given for stochastic data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The approach to sensitivity analysis is given	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The choice	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

of variables for sensitivity analysis is justified										
The ranges over which the variables are varied are justified	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Relevant alternati	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ves are compared										
Incremental analysis is reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Major outcomes are presented in a disaggregated as well as aggregated form	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

answer to the study question is given										
Conclusions follow from the data reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusions are accompanied by the appropriate caveats	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✗, no; ✓, yes; NA, not applicable.										

Study	Study year	Country	Baseline strategy	Proposed strategy (targeted population size if applicable)	Key study parameters	Duration of evaluation	Cost-effectiveness (ICER=cost/ QALY gained)	Epidemiological impacts over evaluation period	Authors' conclusions

MSM									
Jane J. Kim [49]	2010	USA	No vaccination for MSM	Vaccinate MSM up to 12, 20 and 26yr with 4vHPV	US$500/3-dose/person; 3% DR; 90% VE; lifetime protection; 50% coverage.	2006-lifetime	12yr: $15,207 [$10,100-28,824]	--	Cost-effective (WTP: US$50,000)
							20yr: $17,850-35.740		Cost-effective
							26yr: $19,160-37,830		Cost-effective
Ashish A. Deshmukh, et al. [47]	2014	USA	No targeted vaccination for HIV-	Targeted vaccination for HIV-	US$500/3-dose/person; 3% DR; 50% VE; >20yr	2013-2113	VE (HR = 0.25) $27,436-30,867	ANA reduced by 86-92%	Cost-effective (WTP: US$50,000)

			and ⩾ 27yr MSM after treatment for HGAIN	and ⩾ 27yr MSM after treatment for HGAIN with 4vHPV	protection.		VE (HR = 0.50): \$87,240-169,035	ANA reduced by 61-69%	Marginally cost-effective
							VE (HR = 0.75): \$170,975-524,079	ANA reduced by 30-34%	Not cost-effective
Ashish A. Deshmukh, et al. [46]	2015	USA	⩾ 27yr MSM (HIV+), without vaccination after treatment for HGAIN,	⩾ 27yr MSM (HIV+), with 4vHPV after treatment for HGAIN,	US\$500/3-dose/person; 3% DR; >6-8yr protection.	2014-2114	Dominance (reduction in treatment cost and gain in QALYs)	ANA reduced by 63%	Cost-saving (WTP: US\$50,000)

Allen Lin [48]	2016	England	No targeted vaccination for MSM	Target 16-40yr MSM (HIV +/-), with 4vHPV,	£48-96.5/dose/person; 3.5% DR; 64-78% VE; lifetime protection; 80% coverage.	2015-2115	£96.5/dose: £32,800	• GW incidence reduced by 15-35% within 5yr ANA reduced by 40-55% reduction over 100yr.	Cost-effective for HIV+ MSM
							£48/dose: £14,000		Cost-effective for all MSM (WTP: £20,000)

Item	Heterosexual men												
								et al.[28]					
Study design													
The research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The economic importance of the research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The viewpoint(s) of the analysis are clearl	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

y stated and justified													
The rationale for choosing alternative programmes or interventions compared	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

is stated													
The alternatives being compared are clearly described	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The form of economic evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

used is stated													
The choice of form of economic evaluation is justified in relation to the questions addre	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ssed													
Data collection													
The source(s) of effectiveness estimates used are stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details of the	✓	NA	✓	✓	✓	✓	✓	NA	NA	NA	NA	NA	✓

design and results of effectiveness study are given (if based on a single study)													
Details of the methods of synth	NA	✓	NA	NA	NA	✓	✓	✓	✓	✓	✓	✓	NA

esis or meta-analy sis of estim ates are given (if based on a synth esis of a numb er of effect ivene ss studie													

s)													
The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methods to	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

value benefits are stated													
Details of the subjects from whom valuations were obtained were given	✗	✗	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✓
Productivit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

y changes (if included) are reported separately													
The relevance of productivity changes to the study questi	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

on is discussed													
Quantities of resource use are reported separately from their unit costs	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Methods for	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

the estimation of quantities and unit costs are described													
Currency and price data are recorded	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Details of currency of price adjustments for inflation or currency conversion are given	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details of any	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

model used are given													
The choice of model used and the key parameters on which it is based are justifi	✓	✓	NA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ed													
Analysis and interpretation of results													
Time horizon of costs and benefits is stated	✓	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
The	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

discount rate(s) is stated													
The choice of discount rate(s) is justified	✗	✗	NA	✗	✗	✗	✓	✗	✓	✗	✗	✗	✗
An explanation is given if	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

costs and benefits are not discounted													
Details of statistical tests and CIs are given for stochastic data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The approach to sensitivity analysis is given	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The choice of variables for sensitivity analysis is justified	✓	NA	NA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The ranges over which the variables are varied are justified	✓	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Relevant alternatives are compared	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Incremental analysis is reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Major outcomes are presented in a disaggregated as well as aggre	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

gated form													
The answer to the study question is given	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusions follow from the data report	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ed													
Conclusions are accompanied by the appropriate caveats	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
✗, no; ✓, yes; NA, not applic													

able.													

Item	Heterosexual men												
Study design													
The research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The economic importance of the research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The viewpoint(s) of the analysis are clearly	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

stated and justified													
The rationale for choosing alternative programmes or interventions compared is	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

stated													
The alternatives being compared are clearly described	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The form of economic evaluation used	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

is stated													
The choice of form of economic evaluation is justified in relation to the questions addre	✓	NA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ssed													
Data collection													
The source(s) of effectiveness estimates used are stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details of the desig	✓	✗	✓	NA	NA	✓	✓	✓	NA	NA	✓	✓	✓

n and results of effectiveness study are given (if based on a single study)													
Details of the methods of synthesis or	NA	NA	NA	✓	✓	NA	NA	NA	✓	✓	NA	NA	NA

meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)													

The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methods to value	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

benefits are stated													
Details of the subjects from whom valuations were obtained were given	✓	✗	✓	✓	✓	✓	✓	✓	✗	✓	✗	✓	✓
Productivity chang	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

es (if included) are reported separately													
The relevance of productivity changes to the study question is discus	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

sed													
Quantities of resource use are reported separately from their unit costs	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Methods for the estim	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ation of quantities and unit costs are described													
Currency and price data are recorded	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details of	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

currency of price adjustments for inflation or currency conversion are given													
Details of any model used are	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

given													
The choice of model used and the key parameters on which it is based are justified	✓	NA	✓	✓	✓	✓	NA	✓	✓	✓	NA	✓	✓
Analysis													

and interpretation of results													
Time horizon of costs and benefits is stated	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The discount rate(s) is	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

stated													
The choice of discount rate(s) is justified	✗	NA	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
An explanation is given if costs and benefits are	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

not discounted													
Details of statistical tests and CIs are given for stochastic data	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The approach to sensiti	✓	NA	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓

vity analysis is given													
The choice of variables for sensitivity analysis is justified	✓	NA	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓
The ranges over which the	✓	NA	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓

variables are varied are justified													
Relevant alternatives are compared	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Incremental analysis is report	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ed													
Major outcomes are presented in a disaggregated as well as aggregated form	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The answer to the	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

study question is given													
Conclusions follow from the data reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusions are accompanied by the	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

appropriate caveats													
✗, no; ✓, yes; NA, not applicable.													