

Estimating incidence rates of grouped HPV types: A systematic review and comparison of the impact of different epidemiological assumptions

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ABSTRACT

Background: Some studies on human papillomavirus (HPV) provide not only type-specific incidence rates (IR), but also IRs of HPV groupings (e.g. the nonavalent grouping). We made an inventory of the different approaches used to calculate such IRs and assessed their impact on the estimated IRs of HPV groupings.

Methods: We performed a systematic review assessing all approaches used in literature to estimate IRs. Subsequently we applied these approaches to data of a Dutch cohort study on HPV in men who have sex with men (H2M). IRs were estimated for six different HPV groupings.

Results: The systematic review yielded six different approaches (A-F) for estimating the IRs, varying in exclusion criteria at baseline, and the definitions of an incident event and person-time. Applying these approaches to the H2M dataset (n = 749), we found differences in the number of participants at risk, number of incident events, person-time, and IR. For example, for the nonavalent grouping, depending on the approach chosen, the IR varied between 3.09 and 6.54 per 100 person-months.

Conclusion: In published studies different epidemiological assumptions are used to estimate IRs of grouped HPV types, leading to widely differing estimates of IRs. IRs between different studies may therefore not be comparable.

1. Introduction

Human papillomavirus (HPV) is a highly prevalent sexually transmitted infection (STI) and is the cause of several types of cancer, including cervical, penile and anal cancer [1,2]. HPV types can be classified into oncogenic (or high-risk), which can cause cancer; and non-oncogenic (or low-risk) [1].

The incidence rate (IR), expressed as the number of incident events per person-time, is an important metric for the occurrence of new cases in a certain population at risk, and has been used in numerous studies, including randomized controlled trials (RCT) of vaccines [3–5]. The measure of efficacy of a vaccine in such studies is based on the comparison of IRs in the vaccine arm versus the control group ($VE = 1 - [IR_{\text{vaccine}}/IR_{\text{control}}]$) [6].

There is heterogeneity between studies in the definition of incident events and person-time, which affects the estimates of the IR. Most investigators define an infection as a positive sample following a

negative sample, but some investigators use a definition requiring two subsequent positive samples for an infection event. Some investigators assume that the infection has occurred on the date of the first positive sample, while others use a midpoint assumption, whereby the infection is assumed to have occurred halfway in the interval between the last negative and the first positive sample.

An important case of discrepancy occurs in the calculation of IRs of grouped HPV types, e.g. of high-risk HPV types as a group, or of low-risk HPV types as a group, or of nonavalent-vaccine types as a group. When using grouped HPV types as outcome, investigators take different approaches regarding the participants to be included in estimations of the IR, the definition of an incident event, and the calculation of person-time.

All these factors may lead to lack of comparability of reported IRs of HPV across studies. In this study, we examined the phenomenon of grouped HPV incidence rates in more detail. We did this by (1) performing a systematic review of the recent literature, leading to an

Abbreviations: CI, confidence interval; HPV, human papillomavirus; IR, incidence rate; MSM, men who have sex with men; STI, sexually transmitted infections

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inventory of the various approaches employed by different studies to obtain a grouped HPV IR; and by (2) applying these various approaches to a dataset of a well-characterised cohort study of anal HPV incidence among men who have sex with men (MSM) in Amsterdam, the Netherlands (H2M study).

2. Methods

This systematic review was reported according to the PRISMA guidelines [7].

2.1. Search strategy

We screened the PubMed database for relevant studies, using pre-defined search terms (Title or Title/Abstract), indexing terms (MeSH Terms) and keywords (All fields). Keywords, MeSH terms and their combinations used in the searches included “papillomaviridae”, “human papillomavirus”, “human papillomavirus infection”, “HPV infection”, “incidence rate”, “incidence” and “acquisition”. The full search strategy is provided in [Supplementary Appendix A](#). The last search was run on 19 September 2018. Studies were screened by title or abstract to determine eligibility by one researcher (VJ). Eligible studies were thereafter read in full by two researchers (VJ and MSVDL). Additionally, full-text papers were searched for references to other relevant papers.

2.2. Inclusion criteria systematic review

We included all articles that were published in English from 1 January 2010 onwards. This date was arbitrary, but based on the fact that after 2010 most research groups used modern and sensitive methods to detect and genotype HPV. All articles that detected DNA of HPV and reported incidence rates of grouped HPV types in the cervix, genitals, anus, penis or oropharyngeal cavity using person-time were included. Studies only reporting on type-specific incidence, or only on sero-incidence, prevalence, or cumulative incidence were excluded, as were commentaries and reviews.

2.3. Data extraction systematic review

A data extraction sheet (in Microsoft Excel) was designed to capture relevant details of each report. Data were extracted by two reviewers separately (VJ and MSVDL). In case of disagreement, differences were discussed until a consensus was reached. The following general characteristics were extracted from all selected studies: first author, full title, year of publication, journal and impact factor, and the country/countries where the study was conducted. Additionally, data were extracted on (i) the type of test used for HPV typing, (ii) anatomical site(s) involved, (iii) whether any participants were excluded from IR calculation, (iv) the definition of an incident event, (v) the definition of person-time, and (vi) the assumed timing of the infection (midpoint or endpoint). The Methods section of each paper was searched for information on iii, iv, v and vi. If the Methods did not provide this information, the Results section and the Tables were examined, and information on i, ii, iii, and iv was deduced from there when possible. Based on i, ii and iii six approaches to estimate the IR were identified (see Results section).

2.4. H2M: study participants and data collection

Study design and data collection methods of the H2M cohort study have been described in detail elsewhere [8,9]. In short, HIV-infected and HIV-uninfected MSM aged 18 years or older were recruited in 2010–2011 to take part in a prospective cohort study in Amsterdam, the Netherlands. Data were collected at enrollment and at 6-month intervals during a 24-month follow-up period. Anal self-swabs, collected at

each visit, were tested for HPV DNA, and if positive genotyping was done (SPF₁₀-PCR DEIA/LiPA₂₅ system (version 1) [10]). LiPA₂₅ allows the differentiation of 25 specific mucosal HPV genotypes (6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68/73, 70 and 74).

2.5. HPV grouping

The incidence rate of HPV in the H2M cohort study was calculated using six commonly used HPV groupings:

1. Any HPV: including all 25 HPV genotypes included in LiPA₂₅.
2. High-risk (HR) HPV including 12 genotypes: 16,18,31,33,35,39,45,51,52,56,58 and 59 [1].
3. Low-risk (LR) HPV including 13 genotypes: 6,11,34,40,42,43,44,53,54,66,68/73,70 and 74.
4. Bivalent vaccine related HPV (2vHPV): HPV types 16 and 18.
5. Quadrivalent vaccine related HPV (4vHPV): HPV types 6,11,16 and 18.
6. Nonavalent vaccine related HPV (9vHPV): HPV types 6,11,16,18,31,33,45,52 and 58.

2.6. Statistical analysis

The aim of the analyses was to assess and compare anal incidence rates of grouped HPV types obtained from calculations following six different approaches. In all analyses incidence was defined as one positive test result for a specific HPV type preceded by one negative test result for that same HPV type. We used the midpoint assumption in all analyses, meaning that we assumed the incident event happened at the midpoint between the last negative and first positive HPV test result. Reinfection with the same HPV-type, after clearance of a first infection, was ignored in this analysis.

Incidence rates with 95% confidence intervals (CIs) were calculated for the six HPV groupings.

Statistical analyses were performed using Stata (version 13.1; StataCorp, College Station, Texas, USA).

3. Results

3.1. Systematic review

A total of 2387 articles were identified from PubMed database searches. All articles published before 2010 ($n = 828$) were excluded. In total 1449 titles were excluded after screening of title or abstract, and the remaining 110 articles were assessed in full. After full-text assessment, a further 54 articles were excluded because they did not match the inclusion criteria. Of note, of these 54, nine articles provided incidence rates of HPV, but only type-specific incidence rates [9,11–18]. By screening reference lists of the included papers 1 additional article was identified. A total of 57 studies were included in this systematic review ([Fig. 1](#)).

Of the 57 included studies, seven were randomized controlled trials (RCT), while the other 50 were cohort studies. The studies used different methods for HPV DNA typing. The study populations of the included articles varied: women from the general population, men from the general population, MSM, heterosexual couples, HIV-positive participants, uncircumcised men and others. Mean/median follow-up (FU) time ranged from 3.6 months to almost 6 years, the sample size from 94 to 14,204 participants, and the median age of the participants ranged from 18 to 48 years. Key characteristics of the eligible articles are presented in [Table 1](#).

Of the 57 articles reporting on grouped HPV IRs, 28 articles excluded all participants that had an HPV infection within an HPV grouping at baseline (e.g. when a participant was infected with HPV-16 at baseline, this participant was excluded from the any, high-risk, 2-

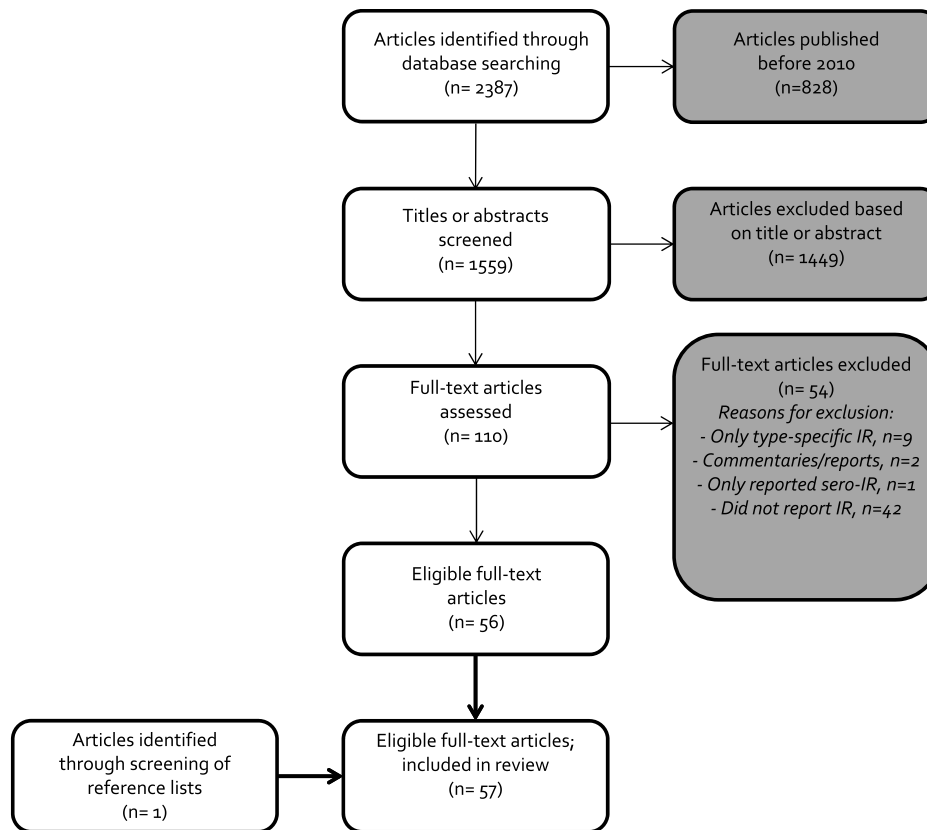


Fig. 1. Flow chart of inclusion and exclusion of articles on incidence rate of HPV for the systematic review.

valent, 4-valent and 9-valent HPV groupings), 14 articles only excluded participants when they were infected with all HPV types within a grouping at baseline, and three studies used both exclusion methods [4,19,20]. For 12 studies it was unclear whether or how participants were excluded.

The majority of articles ($n = 37$) defined an incident event as the first detection of a genotype within a group of HPV types. Fourteen articles also included subsequent incident events with other HPV types that were found during follow-up; three of these studies considered multiple incident infections at the same visit as one incident event [19,21,22], ten articles considered all incident infections, regardless whether infections occurred at the same point in time or not [4,20,23–30] and one article did not specify how they dealt with the timing of an incident event [31]. Six articles gave no clear definition of an incident event.

Most articles ($n = 30$) calculated person-time as the time from enrollment until the date of the first incident event. Twelve articles estimated the person-time as the time between baseline until the last possible event in a person had occurred; this mostly meant participants contributed their total follow-up time. One article estimated person-time in two ways: as the time between baseline and the last possible event, and as the sum of the person-time per individual HPV type [26]. This meant that one person could contribute 14 years of observation-time (1 year for each high-risk HPV type) during one year of study participation. This method was not taken into account in the current analysis; we focused here on commonly used methods of IR estimation. Person-time was not defined in 15 articles. Seventeen articles used the midpoint assumption for the calculation of person-time, 12 articles used date of detection, and 28 did not specify their assumption for the timing of an incident event.

In total, six approaches were defined based on the information mentioned above, varying in the exclusion criteria of participants at baseline, and the definitions of an incident event and person-time. The

approaches are visualized in Fig. 2 and Table 2; a detailed description can be found in Appendix B.

Table 3 shows the approach the authors used to estimate IR in their study. Of the 57 articles, 22 [32–53], one [22], and two [23,25] used approaches A, B and C respectively, and six [54–59], one [21], and five [24,26,28–30] articles used approaches D, E and F respectively. One study used both approaches B and E [19] and two studies used both C and F [4,20]. For 17 articles the approach could not be identified.

3.2. H2M cohort study

Anal samples were available for 777 of the 795 recruited MSM in the H2M study. Of these, 27 were lost to follow-up after the baseline visit and excluded from the analyses. One participant was excluded because of a missing sample. Baseline characteristics of the 749 included MSM are shown in Supplementary Table 1. The median age of the participants was 40.2 years (IQR: 34.8–47.4) and the median follow-up time was 24.2 months (IQR: 23.4–25.1). At baseline 301 (40.2%) participants were HIV infected, of whom most were on combination antiretroviral therapy (cART) (74.1%) and had an undetectable viral load (65.4%); the median CD4 count was 540 cells/mm³ (IQR 410–694). Five hundred and five (67.4%) participants were infected with any HPV type at baseline; 393 (52.5%) were infected with a high-risk HPV type (Supplementary Table 2).

3.2.1. Exclusion criteria

Excluding all participants from the H2M dataset with any HPV infection belonging to the relevant HPV grouping at baseline (approaches A, B, and C), resulted in a population at risk of 578 for the bivalent grouping, 461 for the quadrivalent grouping, 367 for the nonavalent grouping, 339 for the LR grouping, 356 for the HR grouping and 244 for the any HPV grouping. When participants were only excluded when they were infected with all HPV types within a grouping (approach D,

Table 1
Characteristics of included studies ordered by year of publication.

Author and year of publication	Country	Study design	Study population	Age in years	Sample size ^a	Mean FU time	Median FU time	HPV assay	Anatomical location
Banura et al. (2010) [32]	Uganda	Cohort	Women	Range 12 - 24	380		18.5 m (IQR 9.7–26.6)	LIPA25	Cx
Lu et al. (2010) [63]	USA	Cohort	Men	Mean 29.8 (SD 8.1)	285		15.5 m	RLA	MG
Chao et al. (2010) [23]	Taiwan	Cohort	Women	Median 45 (IQR 30–73)	413		34.7 m	HPV Blot	Cx
Serwadda et al. (2010) [54]	Uganda	RCT	HIV-positive men	Range 15 - 49	174	NS	NS	RLA	P
Tam et al. (2010) [24]	Hong Kong	Cohort	Women with SLE	Mean 41 (SD 9)	144		30.8 m	RLA	Cx
Nyiray et al. (2011) [33]	Brazil, Mexico, USA	Cohort	MSM & MSW	MSM median 32.5; MSW median 33.0	1110		6.7 m	RLA	A
Giuliano et al. (2011) [34]	Brazil, Mexico, USA	Cohort	Men	Mean 32.1 (SD 10.8)	1159	23.6 m	27.5 m (IQR 18.0–31.2)	RLA	P
González et al. (2011) [35]	Spain	Cohort	Women	FSW median 29 (IQR 24–35); Wgenpop median 34 (IQR 27–41)	736		16.8 m	HC2 HPV DNA Test	Cx
Grey et al. (2011) [55]	Uganda	RCT	HIV-negative men	Range 15 - 49	840	0.93 y		RLA	P
Sánchez-Alemán et al. (2011) [64]	Mexico	Cohort	Female college students	Mean 21.2	237	1.67 y		Hybrid capture	V
Wawer et al. (2011) [56]	Uganda	RCT	HIV-negative female partners of HIV-negative men	Range 15 - 49	1032	1.64 y		RLA	V
Palefsky et al. (2011) [59]	Australia, Brazil, Canada, Croatia, Germany, Spain and USA	RCT	MSM	R 16-26	602	2.2 y		Multiplex PCR assay (Taddeo/Merck)	A
Louvanto et al. (2011) [25]	Finland	Cohort	Women	Mean 25.5	203	58.6 m (SD 25.2)	64.3 m	Multiplex-HPV-genotyping kit (Multiplex)	Cx
Datta et al. (2012) [65]	India	Cohort	Young women	Range 16 - 24	1300	NS	NS	RLA	Cx
Pickard et al. (2012) [31]	USA	Cohort	Young men and women	Median 21 (IQR 19–23)	985	3.6 m	3.7 m (IQR 3.3–3.8)	RLA	O
Tobian et al. (2012) [26]	Uganda	Cohort	Uncircumcised men	Range 15 - 49	999	1.2 y		RLA	P
Mbulawa et al. (2012) [66]	South Africa	Cohort	HIV-positive and HIV-negative men and women	Women mean 35; Men mean 38	972	NS	NS	RLA	Cx, P
Morales et al. (2012) [36]	Mexico	Cohort	Heterosexual men	Median 36 (IQR 30–44)	351		19.8 m (IQR 13.1–25.8)	PCR products (reverse hybridization), with nylon strips	Cx, P
Backes et al. (2013) [37]	Kenya	Cohort	HIV-negative, uncircumcised men	Median 20	966		12.1 m	RLB	P
Konopnicki et al. (2013) [38]	Belgium	Cohort	HIV-positive, African women living in Europe	Median 40	165	NS	NS	Hybrid capture	Cx
Kreimer et al. (2013) [39]	USA, Brazil, Mexico	Cohort	Men	Median 32 (IQR 24–41)	1626		12.7 m (IQR 12.1–14.7)	RLA	O
Louvanto et al. (2013) [27]	Finland	Cohort	Women	Mean 25.5	299 or 308	28.7 m or 27.9 m		Multimetrix kit	O
Mullins et al. (2013) [40]	USA	Cohort	Adolescents	Mean 16.8 (SD 1.2)	261	22.4 m (SD 10.8)	22.4 m (SD 10.8)	Dot-blot analysis	A
Phanuphak et al. (2013) [67]	Thailand	Cohort	MSM	HIV-positive mean 28.8 (SD 6.9); HIV-negative 28.9 (SD 7.4)	246	8 m		RLA	A
	The Netherlands	Cohort	Women	Mean 23.5 yr	2065		12.3 m	LIPA25	FG

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Table 1 (continued)

Author and year of publication	Country	Study design	Study population	Age in years	Sample size ^a	Mean FU time	Median FU time	HPV assay	Anatomical location
Schmeink et al. (2013) [41]	Spain	Cohort	HIV-infected men	Median 41 (IQR 36–47)	Anal 153; Penile 405; Oral 451		24 m (IQR 12–36)	IVD-CE F-HPV	A, P, O
Videla et al. (2013) [42]									
Watson-Jones et al. (2013) [43]	Tanzania	RCT	Women	Median 18 (IQR 13–19)	308	NS	NS	RLB, based on SPF-10	Cx
Glick et al. (2014) [44]	USA	Cohort	Young MSM	Median 21 (IQR 19–23)	94	NS	NS	LBMA	A
Moreira et al. (2014) [45]	18 countries in Africa, Asia, Europa, Latin- & North America	Cohort	MSW	Mean 20 (SD 1.8)	1721	NS	NS	Multiplex PCR assay (Taddeo/Merck)	P
Albero et al. (2014) [46]	USA, Mexico, Brazil	Cohort	Men	Un-circumcised mean 33.3 (SD 10.3); circumcised mean 31.0 (SD 12.2)	4033		17.5 m (IQR 6.9–31.0)	RLA	P
Hernandez et al. (2014) [21]	USA	Cohort	HIV-positive MSM	Mean 45 (SD 8)	369	1.55 y		PCR with LI consensus primers	A
Liu, M. et al. (2014) [68]	China	Cohort	Men	Median 44 (IQR 37–55)	1059	27.0 m (SD11.8)	31.8 m (IQR 15.4–37.9)	Sanger sequencing-based genotyping procedure	P
Nyitray et al. (2014) [47]	USA	Cohort	Heterosexual couples	Mean 33	198		25 m	RLA	Cx, V, A, P
Ong et al. (2014) [69]	Australia	Cohort	HIV-positive MSM	Mean 52 (SD 14)	173	NS	NS	RLA	O
Castellsagué et al. (2014) [19]	Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK, and USA	Cohort	Women with sexual debut < 6 m prior to enrollment	Mean 17.4	982	1.87 y		LIPA25	Cx
Ingles et al. (2015) [48]	USA, Brazil, Mexico	Cohort	HIV-negative men	Range 18 - 70	4032		48.6 m	RLA	P
Bennett et al. (2015) [57]	Canada	Cohort	Inuit women	Mean 32 (SD 11.2)	416	37.5 m	36.3 m	RLA	Cx
Zou et al. (2015) [28]	Australia	Cohort	MSM	Median 19 (IQR 18–20)	200	NS	NS	RLA	A, P, O
Borghetti et al. (2015) [71]	Italy	Cohort	HIV-positive men and women	Median 44 (IQR 39–48)	233		13 m (IQR 10–15)	Multiplex PCR: papillomachek	A
Nyitray et al. (2015) [72]	Brazil, Mexico, USA	Cohort	Men	MSM & MSWM: median 32; MSW: median 31	3593		40.4 m	RLA	MG
Joura et al. (2015) [4]	Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, South Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand & USA	RCT	Women	Mean 21.9 (SD 2.5)	14,204	NS	NS	In-house Merck Taddeo assay	FG
Ceccato Junior et al. (2016) [73]	Brazil	Cohort	HIV-positive and HIV-negative women	≥18	163	NS	NS	ABI Prism 3100-Avant genetic analyzer & nested PCR	Cx
Donà et al. (2016) [22]	Italy	Cohort	HIV-negative MSM	Median 33 (IQR 26.8–40.7)	155		12.2 m (IQR 7.0–18.1)	RLA	A
Houlihan et al. (2016) [74]	Tanzania	Cohort	HPV-unvaccinated girls	Range 15 - 16	105		17.8 m (IQR 17.4–17.9)	RLA	V
Ramanakumar et al. (2016) [58]	North America & Brazil	Cohort	Women	Range 15 - 25	553	51.8 m	68.2 m	LIPA25	Cx
Zou et al. (2016) [75]	China	Cohort	Women	≥15	1993	205 d	159 d (IQR 85–302)	A gene-chip by HbryMax	Cx
Houlihan et al. (2016) [29]	Tanzania	Cohort	Not sexually active girls	Range 15 - 16	119	NS	NS	RLA	V
	India	Cohort	HIV-positive women	Median 31 (IQR 29–36)	215		11 m (IQR 8–18.3)	RLA	Cx

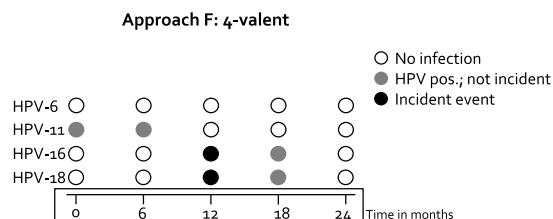
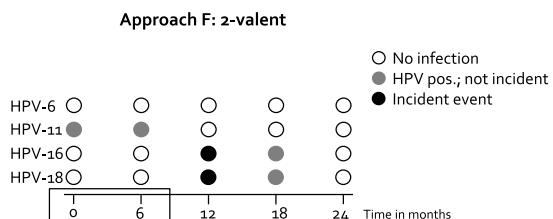
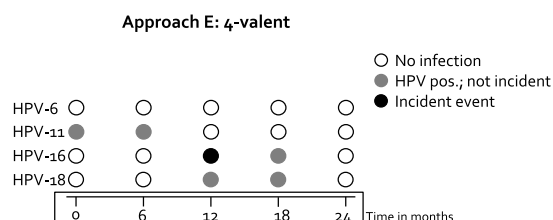
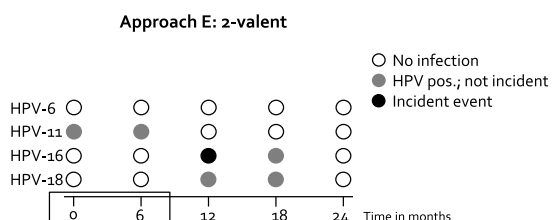
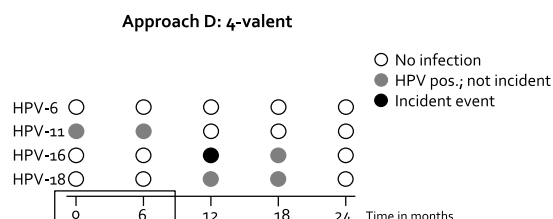
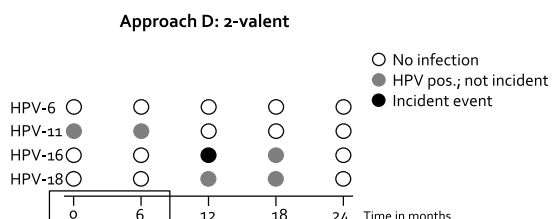
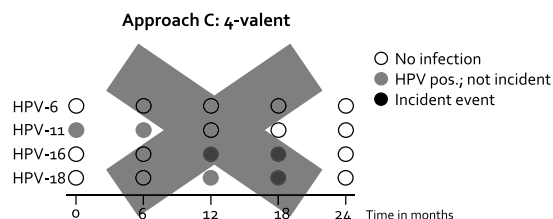
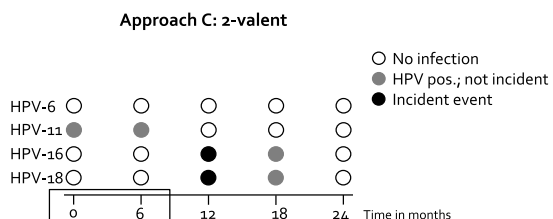
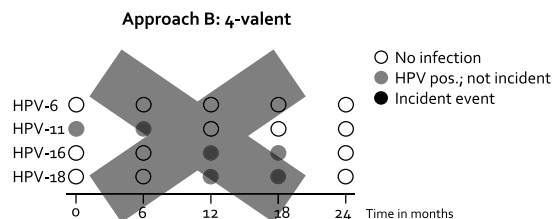
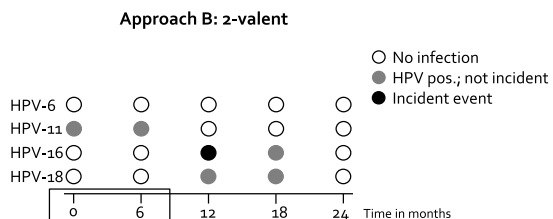
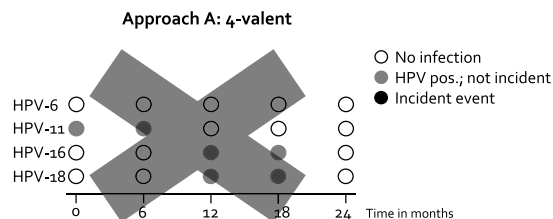
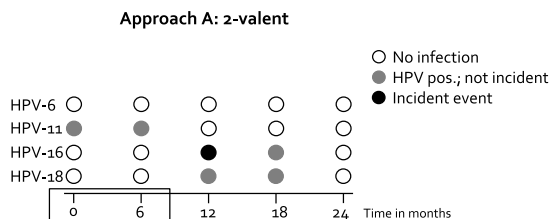
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Table 1 (continued)

Author and year of publication	Country	Study design	Study population	Age in years	Sample size ^a	Mean FU time	Median FU time	HPV assay	Anatomical location
Mane et al. (2017) [49]									
Mendoza-Pinto et al. (2017) [30]	Mexico	Cohort	Women diagnosed with SLE	Mean 45 (SD 11)	127		34 m	RLA	Cx
Camacho-Gonzalez et al. (2017) [50]	USA	Cohort	HIV-positive children and adolescents	Mean 18.3 (SD 3.8)	1042	No STI 3.58 y (SD 1.36); STI 3.74 y (SD 1.27)		NS	NS
Ma et al. (2017) [77]	USA	Cohort	Women	Mean 22 (SD 1.7)	164	12.6 m (SD 3.4)		RLA	V
Sudenga et al. (2017) [52]	Brazil, Mexico, USA	Cohort	Men	Range 18 - 70	4085		Brazil 49.9 m (IQR 47.7–52.9); Mexico 47.6 m (IQR 29.4–55.0); USA 43.2 m (IQR 12.8–50.4)	RLA	P
Sudenga et al. (2017) [51]	Brazil, Mexico, USA	Cohort	Men	Range 18 - 70	2030		7.1 m (IQR 6.5–18.8)	RLA	A
Zhang et al. (2017) [78]	China	Cohort	Men and women	Median 48 (IQR 42–59)	3289		18.3 m (IQR 12.2–36.5)	Sequencing	O
Huh et al. (2017) [20]	Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, South Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand & USA	RCT	Women	Mean 21.9 (SD 2.5)	14,204	4 y		In-House Merck-Taddeo assay	FG
Liu, Z. et al. (2018) [53]	USA, Brazil, Mexico	Cohort	Men	Range 18 - 17	1887			Nonvirgins 38.2 m; virgins initiating sex 44.3 m; virgins 27.6 m	P
Kojic et al. (2018) [79]	USA	Cohort	HIV-infected Women	Median 38 (IQR 31–44)	126		59.4 m	RLA	A, Cx

Abbreviations: A, anus; Anatom, anatomical; Cx, cervix; d, days; FG, female genital; FSW, female sex workers; FU, follow-up; HAART, highly active antiretroviral therapy; HC2, hybrid capture; HIV, human immunodeficiency virus; HPV, human papillomavirus; IQR, interquartile range; m, months; LBMA, liquid bead microarray assay; LiPA25, line probe assay; MG, male genital; MSM, men who have sex with men; MSW, men who have sex with women; NS, not stated; O, oral; P, penis; PCR, polymerase chain reaction; RCT, randomized controlled trial; RLA, Roche Linear Array; RLB, reverse-line blot hybridization; SD, standard deviation; SLE, systemic lupus erythematosus; STI, sexually transmitted infection; USA, United States of America; V, vagina; Wgenpop, women of general population; y, years.

^a Sample size used for the IR calculation.



(caption on next page)

Fig. 2. Hypothetical example of one participant for the six approaches used for the calculation of incidence rate for two groupings of HPV types (bivalent types and quadrivalent types).

On the left the six approaches are depicted using the bivalent vaccine related HPV types as outcome, and on the right the six approaches are depicted using the quadrivalent vaccine related HPV types as outcome. For approaches A, B and C, if an individual is positive at baseline ($t = 0$) for any of the HPV types belonging to an HPV grouping, he is excluded from analyses (depicted by a big grey cross). The box indicates the number of person-months the participant contributed when estimating the IR. All black and grey solid circles represent infections with the specific HPV-type indicated on the left. The black solid circles indicate HPV infections that are counted as incident events for the IR calculation, while grey solid circles are not counted as incident events for the IR calculation, either because they are prevalent infections (e.g. HPV-11 infection at 0 months in approaches D, E, and F 4-valent), or because they occurred at the same moment in time as another infection (e.g. HPV-18 infection at 12 months in approach C 2-valent), or because they were persistent infections instead of a new infection (e.g. HPV-16 infection at month 18 in approaches D, E, and F 4-valent).

Note that the choice for HPV-16 as the incident event instead of HPV-18 in approaches A, B, D and E for both groupings, was arbitrary.

E, and F), all participants ($n = 749$) were considered to be at risk for all HPV groupings except for the bivalent grouping; in this grouping, 15 participants were excluded because they were infected with both HPV-16 and HPV-18 at baseline (Supplementary Table 3).

3.2.2. Events included

The number of incident events, per approach, for the six HPV groupings is shown in Fig. 3a and Supplementary Table 3. The number of incident events was higher in approaches B and C, which allowed multiple events, compared to A, and higher in approaches E and F compared to D. The more HPV types were included into an HPV grouping, the more prominent these differences were.

3.2.3. Observation time

Substantial differences were found in the amount of person-time calculated. Approaches E and F, including follow-up time until all possible events had been observed, had the largest amount of person-time for all HPV groupings; approach A had the least amount of person-time. Approaches B and C had equal amounts of person-time, as did E and F. Again, the more HPV types were included into an HPV grouping, the more substantial these differences were (Fig. 3b, Supplementary Table 3).

3.2.4. Incidence rate

The variation in the incidence rate between the HPV groupings for the different approaches is shown in Fig. 3c and Supplementary Table 3. IRs between approaches differed most for larger HPV groupings, notably the Any HPV grouping (range from 5.39 to 11.30 per 100 person-months). The less HPV types were included into a grouping, the smaller the differences between the IRs became, with the smallest differences for the bivalent HPV grouping. The highest IR calculated was estimated when using approaches C and F, except for the nonavalent HPV grouping where approach D led to the highest IR (IR = 6.54 per 100 person-months; 95% CI 6.01–7.12).

4. Discussion

In this systematic review we identified six different approaches for the calculation of IRs for grouped HPV among studies published since 2010. These approaches differed in the number of participants at risk, and the definitions of an incident event and person-time. Applying these six approaches to a dataset of an existing cohort study resulted in substantial differences in the sample size, the number of incident events, the person-time, and ultimately the IR. These differences were more prominent when more HPV types were included in a grouping.

Based on our findings, there are several considerations that should be taken into account when estimating a grouped HPV IR. Excluding participants from the risk set with any HPV infection belonging to the relevant HPV grouping at baseline (approaches A, B, and C) is necessary if the aim of the research study is to estimate the IR in a completely susceptible population (e.g. for vaccine efficacy studies). On the other hand, excluding participants infected with HPV at baseline may lead to selection bias, because in reality, participants can be infected with more than one HPV type (e.g. a participant can be infected with one high-risk

type, and still acquire another high-risk HPV type).

When the number of events and the amount of follow-up are to be defined, one should consider whether to include only the first or also subsequent events. Only including the first incident event and stopping the time at risk for that person at the time point that an event occurs (approaches A and D), leads to a lower number of incident events and person-time compared to the other approaches. This does not always lead to reduced incidence rates (Fig. 2C). These approaches may be useful if the research interest is in the occurrence of the first incident event (e.g. for conservative estimates of vaccine efficacy). Allowing several incident HPV infection events (approaches B, C, E and F) in the IR estimation is needed if the study intends to provide an estimate of HPV incidence in the studied population. It should be noted that, when the aim of a research is to identify risk factors for HPV infection, and HPV infections of various types are included in such analysis, multi-variable analyses methods accommodating for multiple events per participant can and should be used (e.g. generalized estimating equations, multilevel models).

Moreover, it is important to consider that the number of observed events (and thus the incidence rate) in approaches B and E is influenced by the frequency of testing (possibly more so than the other approaches), as two incident infections may be counted as one event in less-frequent testing scenarios, and as two events in more frequent testing scenarios. Therefore, approaches B and E seem less suited to provide population estimates of HPV incidence.

Considering the above, approaches A, C, D and F could all be used to estimate the IR of grouped HPV types. However, when defining the study protocol researchers should keep in mind that these approaches answer slightly different research questions and may be useful in different scenarios.

4.1. Strength and limitations

To the best of our knowledge this is the first systematic review examining the different epidemiological assumptions used for estimating grouped HPV IRs. Furthermore, this is also the first study to demonstrate the effect of these different assumptions on an existing cohort dataset.

This study is not without limitations. First, despite an elaborate search strategy, it is possible that not all eligible studies were identified, because the search strategy might not have been sensitive enough to capture the various terminologies used among papers, and because we limited our search to PubMed and English-language papers only. Second, we did not take possible reinfections with the same HPV type into account, meaning that, in our calculations, a participant could not be infected with the same HPV type more than once. This could have led to an underestimation of the total number of incident events. Since this applied to all approaches, this did not influence the differences between the six approaches described in this study. Furthermore, the incidence rate can be influenced by a wide range of other factors not examined in this study, amongst others: the way the specimen was taken, transported and stored; the way the sample was processed and DNA extracted; the test that was used to detect DNA of HPV; the test that was used to differentiate between HPV types; and the frequency of

Table 2
Overview of the six approaches to calculate incidence rates of grouped HPV types, and on which epidemiological assumptions they are based.

Approach	1. HPV status at baseline of participants in risk set	2. Maximum no. of incident events per person over whole f-u	3. Maximum no. of incident events per person at one visit	4. Observation time per person
A	Neg for all relevant HPV	1	1	From baseline till timing of first event
B	Neg for all relevant HPV	> 1	1	From baseline till infection of all relevant HPV types has occurred
C	Neg for all relevant HPV	> 1	> 1	From baseline till infection of all relevant HPV types has occurred
D	Neg for at least one of the relevant HPV types	1	1	From baseline till timing of first event
E	Neg for at least one of the relevant HPV types	> 1	1	From baseline till infection of all relevant HPV types has occurred
F	Neg for at least one of the relevant HPV types	> 1	> 1	From baseline till infection of all relevant HPV types has occurred

Abbreviations: HPV, human papillomavirus; Neg, negative; no., number; f-u, follow-up.

sampling. Last, in this study we did not do a comparison between the two assumptions used for the occurrence of incidence events in time (i.e. midpoint or date of detection) and instead only used the midpoint assumption. Although both the 'midpoint' and the 'date of detection' assumption assume that the date of HPV infection is known with certainty, it is more likely that an HPV infection happened sometime between the last negative and the first positive visit rather than at the date the infection was detected. Moreover, the midpoint assumption is the convention in many fields of research, e.g. HIV research (see e.g. Refs. [60–62]). Using the midpoint assumption (or any other point assumption) means that the precision in the data is overestimated, and the confidence intervals around estimates do not fully represent the uncertainty around the estimates.

4.2. Recommendations

As the quality of reporting on the IR calculation varied widely between studies, some approaches had to be deduced from the result section or the tables, or could not be derived at all. Therefore we advocate for clearer description of the approach taken in HPV studies, as the approach taken influences the estimated IR and therefore the comparability of these estimates.

The IR of HPV groupings can be interpreted as the occurrence of any of the types within an HPV grouping in a population at risk, which is less straightforward than the occurrence of a type-specific HPV type, and ignores biological differences between the specific HPV types. As the type-specific IR is biologically more relevant and the interpretation is more straightforward than that of grouped HPV types, we would recommend to primarily report type-specific IRs. Finally, if IRs of HPV groupings are necessary to answer a research question, researchers should focus on selecting the most appropriate approach to answer their research question.

4.3. Conclusion

In current literature different epidemiological assumptions are used to estimate IRs of grouped HPV types, leading to six different approaches. These approaches lead to widely differing estimates of IRs, which were more prominent when more HPV types were included in a grouping. This means that the interpretation of grouped HPV IRs is not straightforward and that the IRs between studies may not be comparable.

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Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Declaration of competing interest

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Table 3
Definitions used for calculating incidence rate for HPV in the 57 studies.

Author names	Outcome reported for which HPV groupings?	Participants excluded from grouped IR calculation	Definition incident event within a group	Assumption timing of incident event	Definition of person-time	Conclusion
Banura et al. [32]	Any, HR, LR, single, multiple, 16-related, 18-related	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Lu et al. [63]	16-related, 18-related, other types	Participants infected with 1 or more HPV types within a group at baseline	NS	NS	NS	A/B/C
Chao et al. [23]	HR, LR, multiple types	Participants infected with 1 or more HPV types within a group at baseline	Any incident infection within a grouping; also > 1 per interval/visit	NS	Until timing of last possible event in person has happened	C
Serwadda et al. [54]	HR, multiple types	Participants infected with all HPV types within a group at baseline	First detection of a genotype within a group	NS	NS	D
Tam et al. [24]	Any, HR, LR, 16/52, 18/58	Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping; also > 1 per interval/visit	NS	Until timing of last possible event in person has happened	F
Nyitray et al. [33]	Any, HR, LR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Giuliano et al. [34]	Any, HR, LR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
González et al. [35]	HR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	NS	A
Grey et al. [55]	HR, LR	Participants infected with all HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	D
Sánchez-Alemán et al. [64]	HR	Participants infected with 1 or more HPV types within a group at baseline	NS	NS	NS	A/B/C
Wawer et al. [56]	HR, LR	Participants infected with all HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	D
Palefsky et al. [59]	2v, 4v	ITT: Participants infected with all HPV types within a group at baseline	First detection of a genotype within a group (ITT)	NS	Time from enrollment to date of first incident event (ITT)	D (ITT)
Louvanto et al. [25]	Multiple types, HPV a-5, a-6, a-7, a-9, a-10, a-11	Participants infected with 1 or more HPV types within a group at baseline	Any incident infection within a grouping; also > 1 per interval/visit	NS	Until timing of last possible event in person has happened	C
Datta et al. [65]	Any	NS	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	A/D
Pickard et al. [31]	Any	Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping	Midpoint	Until timing of last possible event in person has happened	E/F
Tobian et al. [26]	HR	Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping; also > 1 per interval/visit	Midpoint	Until timing of last possible event in person has happened	F
Mbulawa et al. [66]	Any, HR, LR, a-1, a-3, a-5, a-6, a-7, a-8, a-9, a-10, a-11, a-13, a-15	NS	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A/D
Morales et al. [36]	Any, HR, LR, 2v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A
Backes et al. [37]	Any, HR, LR, multiple	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A
Konopnicki et al. [38]	HR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	NS	A
Kreimer et al. [39]	Any, HR, LR, 4v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A

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Table 3 (continued)

Author names	Outcome reported for which HPV groupings?	Participants excluded from grouped IR calculation	Definition incident event within a group	Assumption timing of incident event	Definition of person-time	Conclusion
Louvanto et al. [27]	Multiple, a-5, a-6, a-7, a-9, a-10, a-11	NS	Any incident infection within a grouping; also > 1 per interval/visit	NS	Until timing of last possible event in person has happened	C/F
Mullins et al. [40]	Any, HR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Phanuphak et al. [67]	HR	NS	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A/D
Schmeink et al. [41]	HR, LR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	A
Videla et al. [42]	Any, single infection, multiple infections	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	NS	A
Watson-Jones et al. [43]	Any, HR, LR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A
Glick et al. [44]	Any, HR, LR, 2v, 4v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	A
Moreira et al. [45]	4v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A
Albero et al. [46]	Any, HR, LR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Hernandez et al. [21]	Any, HR, LR	Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping; but only max 1 per interval/visit	Midpoint	Until timing of last possible event in person has happened	E
Liu, M. et al. [68]	Any, HR, LR	NS	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A/D
Nyitray et al. [47]	Any, HR, LR	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Ong et al. [69]	Any, HR	NS	First detection of a genotype within a group	NS	NS	A/D
Castellsagué et al. [19]	Any, HR, LR	Virgins: Participants infected with 1 or more HPV types within a group at baseline Non-virgins: Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping; but only max 1 per interval/visit	NS	Until timing of last possible event in person has happened	B (virgins) & E (non-virgins)
Ingles et al. [48]	Any, HR, LR, 9v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	A
Bennett et al. [57]	HR, LR, a-3, a-7, a-9	Participants infected with all HPV types within a group at baseline	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	D
Zou et al. [28]	Any, HR, LR, 2v, 4v, 9v	Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping; also > 1 per interval/visit	Date of detection	Until timing of last possible event in person has happened	F
Borghetti et al. [71]	HR	NS	NS	NS	NS	A/B/C/D/E/F
Nyitray et al. [72]	Any, HR, LR, 4v	NS	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A/D
Joura et al. [4]	4v, 5 types related to 9v but not in 4v	PP: Participants infected with 1 or more HPV types within a group at baseline ITT: Participants infected with all HPV types within a group at baseline	Any incident infection within a grouping; also > 1 per interval/visit	NS	Until timing of last possible event in person has happened	C (PP) & F (ITT)
Ceccato Junior et al. [73]	Any	Participants infected with 1 or more HPV types within a group at baseline	NS	NS	NS	A/B/C
Donà et al. [22]	Any, HR, LR 2v, type 6/11	Participants infected with 1 or more HPV types within a group at baseline	Any incident infection within a grouping; but only max 1 per interval/visit	Midpoint	NS	B

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Table 3 (continued)

Author names	Outcome reported for which HPV groupings?	Participants excluded from grouped IR calculation	Definition incident event within a group	Assumption timing of incident event	Definition of person-time	Conclusion
Houlihan et al. [74]	Any, HR, LR	NS	NS	Midpoint	NS	A/B/C/D/E/F
Ramanakumar et al. [58]	Any, HR, LR, a-6, a-7, a-8, a-9, a-10	Participants infected with all HPV types within a group at baseline	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	D
Zou et al. [75]	Any, HR, LR, 2v, 4v, 9v	NS	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	A/D
Houlihan et al. [29]	Any, HR, LR	Participants infected with all HPV types within a group at baseline	Any incident infection within a group; also > 1 per interval/visit	Midpoint	Until timing of last possible event in person has happened	F
Mane et al. [49]	Any, HR, possible/non-carcinogenic, 2v, 9v, a-9, a-7	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	NS	A
Mendoza-Pinto et al. [30]	Any, HR, LR	Participants infected with all HPV types within a group at baseline	Any incident infection within a group; also > 1 per interval/visit	NS	NS	F
Camacho-Gonzalez et al. [50]	Any	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	NS	A
Ma et al. [77]	Any clinically relevant HPV, HR, 2v, 4v, 6/11	NS	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A/D
Sudenga et al. [52]	Any, HR, LR, 4v, 9v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Sudenga et al. [51]	Any, HR, LR, 4v, 9v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	Date of detection	Time from enrollment to date of first incident event	A
Zhang et al. [78]	Any, mucosal, HR, LR, cutaneous, 4v	NS	First detection of a genotype within a group	Midpoint	Time from enrollment to date of first incident event	A/D
Huh et al. [20]	4v, 5 types related to 9v but not in 4v	PP: Participants infected with 1 or more HPV types within a group at baseline ITT: Participants infected with all HPV types within a group at baseline	Any incident infection within a group; also > 1 per interval/visit	NS	Until timing of last possible event in person has happened	C (PP) & F (ITT)
Liu, Z. et al. [53]	Any, HR, LR, 4v, 9v	Participants infected with 1 or more HPV types within a group at baseline	First detection of a genotype within a group	NS	Time from enrollment to date of first incident event	A
Kojic et al. [79]	HR, 2v, 9v, any non-9v HR	Participants infected with all HPV types within a group at baseline	NS	NS	NS	D/E/F

Abbreviations: a-, alpha genus; HPV, human papillomavirus; IR, incidence rate; HR, high risk; LR, low risk; 2v, HPV types in quadrivalent vaccine; 9v, HPV types in nonavalent vaccine; PP, per protocol; ITT, intention to treat; NS, not stated.

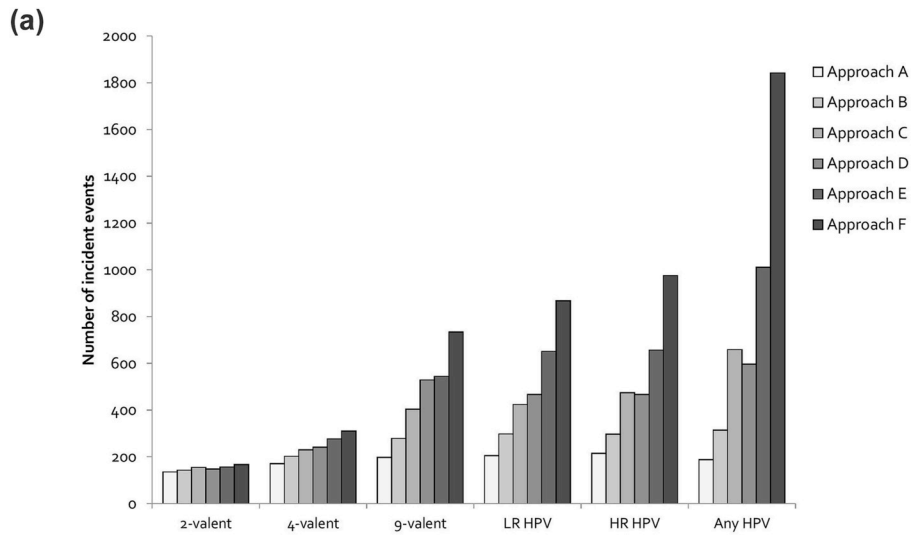


Fig. 3A. Total number of incident events, amount of person-time and the incidence rates of the six approaches, shown for six HPV groupings. Incident events.

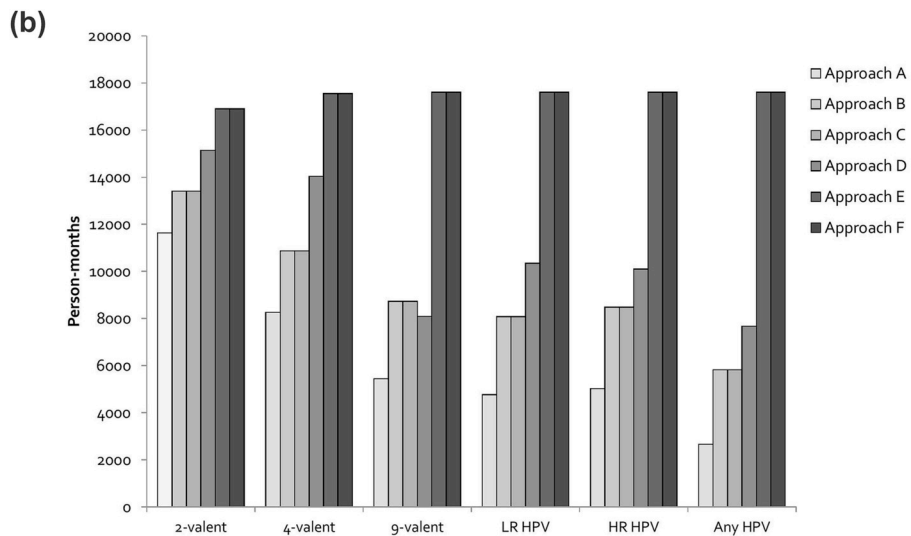


Fig. 3B. Total number of incident events, amount of person-time and the incidence rates of the six approaches, shown for six HPV groupings. Person-months.

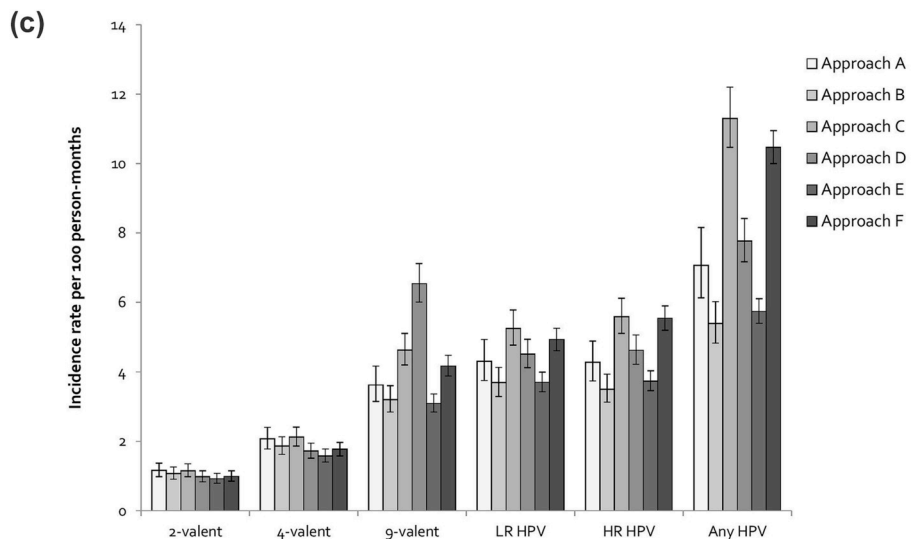


Fig. 3C. Total number of incident events, amount of person-time and the incidence rates of the six approaches, shown for six HPV groupings. Incidence rates per 100 person-months.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pvr.2019.100187>.

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