Seropositivity to Non-vaccine Incorporated Genotypes Induced by the Bivalent and Quadrivalent HPV Vaccines: A Systematic Review and Meta-Analysis

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Submission to: *Vaccine*

Figure and Tables:

Table 1. Summary of studies

Figure 1. Flow chart

Figure 2. Pooled seropositivity estimates

Figure 3. Comparison with VE data

Figure 4. Neutralizing antibody titers

Supplementary Figure. Pooled estimates of Age, timing

Running title (40 chars):

Non-vaccine type seropositivity

Highlights

- Evaluation of HPV vaccine seroconversion rates for non-vaccine genotypes
- Pooled estimates for HPV31 and HPV45 higher for bivalent vaccine
- Similar seroconversion rates for HPV33, HPV52 and HPV58
- Estimated seroconversion rates positively associated with vaccine efficacy data

Abstract

Background: Human papillomavirus vaccines have demonstrated remarkable efficacy against persistent infection and disease associated with vaccine-incorporated genotypes and a degree of efficacy against some genetically related, non-vaccine-incorporated genotypes. The vaccines differ in the extent of cross-protection against these non-vaccine genotypes. Data supporting the role for neutralizing antibodies as a correlate or surrogate of cross-protection are lacking, as is a robust assessment of the seroconversion rates against these non-vaccine genotypes.

Methods: We performed a systematic review and meta-analysis of available data on vaccine-induced neutralizing antibody seropositivity to non-vaccine incorporated HPV genotypes.

Results: Of 304 articles screened, 9 were included in the analysis representing *ca*. 700 individuals. The pooled estimate for seropositivity against HPV31 for the bivalent vaccine (86%; 95%CI 78 – 91%) was higher than that for the quadrivalent vaccine (61%; 39 – 79%; p=0.011). The pooled estimate for seropositivity against HPV45 for the bivalent vaccine (50%; 37 – 64%) was also higher than that for the quadrivalent vaccine (16%; 6 – 36%; p=0.007). Seropositivity against HPV33, HPV52 and HPV58 were similar between the vaccines. Mean seropositivity rates across non-vaccine genotypes were positively associated with the corresponding vaccine efficacy data reported from vaccine trials.

Conclusions: These data improve our understanding of vaccine-induced functional antibody specificity against non-vaccine incorporated genotypes and may help to parameterize vaccine-impact models and improve patient management in a post-vaccine setting.

Keywords

Human Papillomavirus

Vaccine

Antibody

Systematic review

Meta-analysis

Introduction

Human papillomavirus (HPV) is associated with 5% of all human cancers worldwide and around 30% of those cancers attributed to infectious agents [1]. The bivalent (Cervarix®) and quadrivalent (Gardasil®) prophylactic HPV vaccines comprise virus-like particles (VLP) based upon the major capsid protein (L1) of HPV16 and HPV18 [2], which are the two genotypes associated with the majority (*ca*. 70%) of cervical cancers [3]. Gardasil® also contains VLP representing genotypes associated with the development of genital warts (HPV6 and HPV11). Both vaccines are highly efficacious at preventing persistent infection and cervical cancer precursors associated with HPV16 and HPV18 in vaccine trials [4-6]. These findings are starting to be reflected in post-licensure impact surveillance data following the implementation of national HPV immunization programmes [7]. Neutralizing antibodies against HPV16 and HPV18 genotypes can be detected in the serum and genital secretions of vaccinees [8], appearing to corroborate pre-clinical animal model data that support type-specific protection being mediated by neutralizing antibodies [9-11].

A degree of cross-protection has also been demonstrated in vaccine trials against persistent infection and disease associated with some non-vaccine genotypes that are genetically related to the vaccine genotypes [4, 12], a phenomenon that is also starting to be seen in vaccinated populations [7, 13]. The vaccines exhibit differential efficacy in this respect such that Cervarix® appears to be more protective against HPV31 (related to HPV16) than Gardasil® and this difference in efficacy is more marked for HPV45 (related to HPV18). These two non-vaccine genotypes alone are associated with *ca*. 10% of cervical cancers [3]. Cross-neutralizing antibodies can be detected in the serum and, in one study, the genital secretions of vaccinees [14-20]. These data are derived from relatively small immunogenicity studies, using one or both vaccines and carried out in different age groups, factors that may affect interpretation of whether the detection of such antibodies may be useful as a correlate or surrogate of vaccine-induced cross-protection. This report presents a systematic review and meta-analysis of available data on vaccine-induced neutralizing antibody

seropositivity to non-vaccine incorporated HPV genotypes in order to provide a robust estimate of seroconversion rates against non-vaccine incorporated genotypes.

Methods

Search Strategy and Selection Criteria

A systematic search was undertaken of PubMed to identify papers reporting seropositivity data in conjunction with cross-neutralizing antibody titers against HPV non-vaccine genotypes. A combination of the following free terms were used to search titles and abstracts: ("HPV" or "Human Papillomavirus") and "Vaccine" and "Antibod*" and "Neutrali*". Two of the authors (SLB and AG) independently identified papers for analysis that were returned by the search terms up until June 2016. The *a priori* exclusion criteria were (i) description of a novel antigen, not a licensed HPV vaccine; (ii) description of antibodies elicited by natural infection, not vaccination; (iii) no neutralization data were presented; (iv) no cross-neutralization data were presented in the same or linked study specific paper; (v) not the primary evaluation of study neutralization data. Papers were initially excluded based upon title only, followed by a second round of exclusion based upon abstract content. Where the abstract stated or implied the inclusion of neutralization data within the published study the full text of the paper was reviewed.

Data Extraction

Key information retrieved for analysis included: participant characteristics (sex, age group), study characteristics (study setting, vaccine(s) used, sample collection times) and assay characteristics (assay format, target antigens, seropositivity, titers). The primary outcome measure was seropositivity to the two oncogenic vaccine incorporated genotypes (HPV16 and HPV18) and five non-vaccine incorporated genotypes (HPV31, HPV33, HPV45, HPV52 and HPV58) for which both efficacy and seropositivity have been consistently evaluated. The secondary outcome measure was the antibody titer to vaccine (HPV16, HPV18) and non-vaccine genotypes (HPV31, HPV45). Two of the authors (SBL and AG) performed the data extraction into a template spreadsheet and a data integrity check was performed (SB) before use.

Statistical methods

Estimates of seropositivity to each genotype following vaccination with either Gardasil® or Cervarix® were pooled using a DerSimonian-Laird random effects model, with logit transformed outcome variables. Cochran's Q-test was used as a test of interaction to see if the type of vaccine (or other variable) had a significant impact on seropositivity by genotype.

The association between vaccine efficacy (against persistent infection and CIN2+) as reported from clinical trials [12] and the mean seropositivity generated in this study was investigated. To propagate the uncertainty in these variables to the uncertainty in the linear relationship, we used a resampling technique known as the bootstrap [21]. To do this, we randomly sampled with replacement 1000

times from the set of positive and negative individuals in the populations of the studies used to estimate efficacy and seroprevalence. Each random sample was then used to construct a related estimate of vaccine efficacy, to construct a set of 1000 bootstrap estimates of vaccine efficacy. This was associated to 1000 similarly constructed estimates of seroprevalence using linear regression.

Vaccine efficacy and seropositivity were plotted on graphs. The uncertainty in the graphs represents the 95% range of predictions across the models. Exact 95% confidence intervals for data points were calculated using the Fisher's exact method for vaccine efficacy (1-odds ratio) and Clopper-Pearson for seroprevalence. Significance was taken at the 5% level and 95% confidence intervals used. Two-sided significance tests were used. R version 3.1.2 (R Development Core Team) was used for the analyses.

Results

We identified 304 articles of which 9 (representing 7 discrete studies) were included for this analysis (**Figure 1**) [14-20, 22, 23]. Details on the individual studies can be found in **Table 1**. All studies included females (>95% of total assessed population) while one study [18, 23] also included males. Three studies [14, 16, 19] included adolescent girls at the approximate target age for vaccination (11 - 15 years old) while four studies [15, 17, 18, 20, 22, 23] included women over 18 years of age. Two studies [16, 19] collected serum from adolescent girls taking part in national vaccination programmes, while five studies [14, 15, 17, 18, 20, 22, 23] collected serum from individuals in the context of a vaccination trial. Post-vaccination seropositivity was assessed at month 7 (1 month post third vaccine dose; M7) [14, 17, 18, 20, 22, 23], month 12 (6 months post third vaccine dose; M12) [14-16, 18, 20, 23], or in one study [19], using data collected between month 7 and month 12. All studies [14-20, 22, 23] evaluated Cervarix® vaccinees while five studies [14, 17-20, 22, 23] also included Gardasil® vaccinees. All studies [14-20, 22, 23] used HPV pseudovirus targets HPV16, HPV18, HPV31 and HPV45 in neutralizing antibody tests with five studies [14-16, 18, 20, 23] including one or more additional Alpha-7 (related to HPV18) and Alpha-9 (related to HPV16) genotypes.

Seropositivity against HPV16 and HPV18 was essentially 100% following three doses of either Cervarix® or Gardasil® vaccine; a slightly lower (98%) HPV18 seropositivity was reported by one study following Gardasil® vaccination (data not shown). A higher proportion of Cervarix® vaccinees (86%; 95%CI 78 – 91%; pooled estimate using the random effects model) were seropositive against HPV31 than Gardasil® vaccinees (61%; 39 – 79%; p=0.011) (**Figure 2**). Cervarix® vaccinees (50%; 37 – 64%) also exhibited a markedly higher proportion of seropositivity against HPV45 than

Gardasil® vaccinees (16%; 6 – 36%; *p*=0.007). Pooled estimates for seropositivity against HPV33, HPV52 and HPV58 demonstrated no significant difference between the vaccines.

One of these studies [18, 23] examined bivalent and quadrivalent vaccine immunogenicity in a cohort of human immunodeficiency virus (HIV-1) infected individuals. Pooled estimates for seropositivity against HPV31 (Cervarix®: 87%; 95%CI 78 – 92%; Gardasil®: 63%; 38 – 83%; *p*=0.027) and HPV45 (Cervarix®: 47%; 33 – 62%; Gardasil®: 11%; 4 – 28%; *p*=0.002) not including these individuals were similar to the overall estimates.

There was a significant positive association between the overall seropositivity rates against non-vaccine incorporated genotypes and the vaccine efficacy data [12] against 6 month persistent infection (mean line coefficient 1.017; 95% range 0.100 – 2.241; **Figure 3a**) and positive but non-significant association with cervical intraepithelial neoplasia grade 2 or greater (CIN2+) (mean line coefficient 1.781; 95% range -0.636 – 9.212; **Figure 3a**) reported from vaccine trials.

These immunogenicity studies were carried out in adolescent girls (<18 years old) and adults (18 years or older) and included samples collected between one (M7) and six (M12) months after the third dose of vaccine. There were too few studies to allow a subset analysis, whereby the influence of vaccine, age group, and sampling time on genotype-specific seropositivity could be evaluated independently. Instead, seropositivity to HPV31 or HPV45 was evaluated using age group (irrespective of vaccine and sampling time) and sampling time (irrespective of vaccine and age group) as composite variables (**Supplementary figure**). This was a similar approach to that taken for the evaluation of seropositivity stratified by vaccine, irrespective of age group and sampling time (**Figure 2**). The pooled estimate for seropositivity against HPV31 in the adolescent age group (87%; 71 – 95%) was slightly higher than that achieved in adults (66%; 50 – 80%; p=0.045). Seropositivity against HPV45 for adolescents (31%; 15 – 52%) was similar to that in adults (38%; 19 – 61%; p=0.613). Overall, seropositivity against HPV31 (M7: 76%; 57 – 89% vs. M12: 81%; 65 – 91%; p=0.636) and HPV45 (M7: 35%; 19 – 56% vs. M12: 51%; 33 – 69%; 0.268) was similar regardless of sampling time.

The magnitude of the vaccine antibody responses were reported as the median or geometric mean titers for both vaccine (HPV16 and HPV18) and non-vaccine (HPV31 and HPV45) genotypes. Although the magnitude of the titers for both vaccine and non-vaccine genotypes varied widely between studies, the non-vaccine genotype titers appeared to track their respective vaccine-type titers with some consistency (**Figure 4**). HPV16 titers were a median 170 (inter-quartile range, IQR, 134 - 262) fold higher than HPV31 titers for Cervarix® and a median 337 (201 - 365) fold for

Gardasil®. HPV18 titers were a median 478 (296 - 1,413) fold higher than HPV45 titers for Cervarix® and a median 146 (108 - 1,377) fold for Gardasil®.

Discussion

We performed a systematic review and meta-analysis of available seropositivity data against non-vaccine genotypes representing seven studies and approximately seven hundred individuals vaccinated with three doses of either Cervarix® or Gardasil® HPV vaccine [14-20, 22, 23].

The estimated seroconversion rate for neutralizing antibodies against HPV31 was higher than that for HPV45, with Cervarix® vaccinees exhibiting higher rates of seroconversion against both of these genotypes than Gardasil® vaccinees. For HPV33, HPV52 and HPV58 the seroconversion rates were similar between the vaccines. There was a strong association between the seropositivity rates for these non-vaccine genotypes and the efficacy data reported from HPV vaccine trials [24, 25]. HPV31 seropositivity has been shown to be coincident with a reduced risk of HPV31 acquisition post-vaccination with Cervarix®, although data supporting a similar relationship for HPV45 and HPV58 were lacking [26].

This review incorporated data from adolescent girls around the target age for vaccination in national immunization programmes and from older women and included data collected between one and six months after the third vaccine dose. Of these variables, only the younger age at vaccination was shown to be associated with a higher seropositivity against HPV31. Where individual studies have compared the immune response to HPV vaccines in populations of similar ages, and using samples collected at the same time point post-vaccination, they have consistently demonstrated higher rates of seroconversion and/or higher titers against both HPV16 and HPV18 [14, 20, 22, 23] and non-vaccine genotypes [14, 17, 18, 20] following Cervarix® vaccination. Similarly, where studies compared serological responses between one and six months following the third vaccine dose, a small decline in seropositivity and/or titers was seen for both adolescents [14] and older women [17, 18, 20, 22, 23]. The issue of age is more problematic. Only one study in this review examined age-dependent immune responses against vaccine and non-vaccine genotypes by stratifying a cohort of 18 – 45 year old mid adult women into three sub-groups (18 – 26, 27 – 35 and 36 – 45 years) and demonstrated some degree of age-related influence on responses against vaccine genotypes [22], but the influence on responses against non-vaccine genotypes was less clear [17]. A stronger serological response elicited in adolescents compared to adult women has been demonstrated for both vaccines [27-30], but only against vaccine-incorporated genotypes using binding assays. The removal of data from one study [18, 23] comprising HIV-infected subjects made little difference to the pooled estimates for seropositivity against HPV31 and HPV45 suggesting, based on these

limited study data, that the HIV serostatus of vaccine recipients may have little impact on HPV vaccine immunogenicity [31].

The magnitude of the neutralizing antibody response varied between studies with responses against non-vaccine genotypes at least two orders of magnitude lower than those elicited against vaccine-incorporated genotypes. The long-term durability of cross-neutralizing antibodies is unclear; thus far, antibodies against HPV31 and HPV45 have been detected out to twenty-four months post-vaccination [17, 22]. In the same vaccine comparison study, responses against HPV16 and HPV18 remain robust out to 5 years [32].

There are several shortcomings to this study. The small number of available studies limited a robust evaluation for some non-vaccine genotypes, notably HPV33, HPV52 and HPV58. This is particularly true for estimating seroconversion rates for Gardasil® vaccinees, which were represented by a single study or pair of studies in some cases. The small number of available studies also precluded an analysis of the influence of each variable (vaccine, age group, sampling time) independently. Thus, the differences in seropositivity due to the vaccine may have been confounded by the influence of the age at vaccination and the sampling time post third dose. This confounding likely led to the high heterogeneity scores seen here and potentially obscured more subtle effects of age and sampling time on seropositivity.

This review evaluated studies incorporating a three-dose schedule. Reduced dose arms in vaccine trials have demonstrated non-inferior seropositivity to vaccine genotypes and similar vaccine efficacy [33, 34], resulting in a recommendation for a two dose schedule to be adopted worldwide [35]. However, reduced seropositivity to HPV31 has been demonstrated for less than three doses [36], which is likely to be a factor in the reduced vaccine efficacy observed against non-vaccine genotypes HPV31 and HPV45 in a *post-hoc* analysis of Cervarix® trial data [37]. Nevertheless, this report represents an analysis of the only available functional data with which to evaluate seroconversion rates against non-vaccine incorporated genotypes.

Recently, the nonavalent Gardasil®9 vaccine comprising additional genetically related genotypes HPV31, HPV33, HPV45, HPV52 and HPV58 has demonstrated efficacy in a three dose schedule [38] and non-inferiority of antibody responses for two doses [39]. A nonavalent vaccine has the potential to reduce the incidence of cervical cancer by over 90% [3, 40], is expected to be cost effective [41, 42]. Nonavalent vaccine efficacy against persistent infection or low grade disease associated with any of these additional genotypes in the per protocol population was ≥96% which is considerably higher than any beneficial cross-protective vaccine efficacy induced by either the

bivalent or quadrivalent vaccines against these genotypes [24, 25, 43]. Although national immunization programmes will likely adopt the nonavalent vaccine in time, to date tens of millions of adolescent girls have been vaccinated with the bivalent or quadrivalent vaccine [44], for which a better understanding of their immunogenic properties including the seroconversion rates, breadth, magnitude and durability of the antibody responses against vaccine and non-vaccine genotypes is warranted.

Contributions

SLB and AG performed the systematic review. MJ and SB performed the meta-analysis. SB wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

Acknowledgements

We are grateful to Emily Coates and Julie Ledgerwood (Vaccine Research Center, National Institute of Allergy and Infectious Diseases [NIAID], Bethesda, MD) for providing supplemental data for this analysis. We also thank Nicholas Andrews, PHE, for statistical advice.

Conflict of interest statement

We declare no conflicts of interest.

Funding

This study received no specific funding.

Figure 1. Flowchart of the study selection process

Figure 2. Pooled estimates for seroconversion against non-vaccine incorporated genotypes
Estimates of seropositivity to each genotype following vaccination with either Gardasil® or Cervarix® pooled using a DerSimonian-Laird random effects model, with logit transformed outcome variables. Test for subgroup differences using Cochran's Q-test.

Figure 3. Comparison of neutralizing antibody seropositivity and reported vaccine efficacy
Mean seropositivity data from this meta-analysis, derived using the random effects model are plotted against (a) efficacy against persistent infection and (b) efficacy against CIN2+ reported from trials of Cervarix® (blue points) and Gardasil® (red points) vaccinees for each non-vaccine HPV type (HPV31, HPV33, HPV45, HPV52 and HPV58). Vertical error bars represent exact 95% confidence intervals for the efficacy data, while horizontal error bars represent exact 95% confidence intervals for the neutralization seropositivity data. The best fitting linear relationship between the two variables (black line) and the 95% range of bootstrap estimates for this relationship (dotted lines) is also shown. Exact 95% confidence intervals for data points were calculated using the Fisher's exact method for vaccine efficacy (1-odds ratio) and Clopper-Pearson for seropositivity.

Figure 4. Vaccine and non-vaccine neutralizing antibody titers
Neutralizing antibody titers against (a) HPV16 (dark shade) and HPV31 (light shade) and (b) HPV18 (dark shade) and HPV45 (light shade) for Cervarix® (blue) and Gardasil® (red) vaccinees. First author name and year of publication given for each article with target age group (G, girls <18 years; W, women 18 or more years old) and sampling time (7 or 12 months post first dose; 7+ represents a range from 7-12 months for one study). Data represent the geometric mean (95%CI) neutralizing antibody titers apart from Kemp (2011) and Draper (2011) which represent the median (IQR) neutralizing antibody titers. Size of data points reflect approximate sample sizes in each study.

Supplementary Figure. Pooled estimates for age group and sampling time
Pooled estimates of seropositivity to (a, c) HPV31 and (b, d) HPV45 stratified by (a, b) age group or (c, d) sampling time following vaccination with either Cervarix® (denoted by an asterisk) or Gardasil® using a DerSimonian-Laird random effects model, with logit transformed outcome variables. Test for subgroup differences using Cochran's Q-test.

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Table 1. Study characteristics

Author	Year	Sex	Age group [a]	Medical exclusion criteria	Setting	HPV status	Vaccines assessed	Months post 1st dose	HPV targets	Reporter [b]	Assay threshold [c]	No. sera per target (Min – Max) [d]
Kemp	2011	F	18 - 25	Yes	Trial	Unselected	Cervarix®	M12	16 18 31 45 52 58	seAP	10 (50%)	46
Draper	2011	F	13 - 14	No	Programme	Unselected	Cervarix®	M12	16 18 31 33 45 52 58	Luc	20 (80%)	69
Einstein	2011	F	18 - 26	Yes	Trial	Seronegative and DNA negative	Cervarix® and Gardasil®	M7	16 18 31 45	seAP	40 (50%)	103 - 131
Draper	2013	F	12 - 15	Yes	Trial	Unselected	Cervarix® and Gardasil®	M7 & M12	16 18 31 33 45 52 58	Luc	20 (80%)	91 - 97
Toft	2014	MF	>18	Yes	Trial	Seronegative and DNA negative	Cervarix® and Gardasil®	M7 & M12	16 18 31 33 45	Luc	40 (50%)	12 - 26
Barzon	2014	F	11 - 13	Yes	Programme	Unselected	Cervarix® and Gardasil®	M7 - M12	16 18 31 45	seAP	40 (50%)	50 - 126
Herrin	2015	F	18 - 25	Yes	Trial	Unselected	Cervarix® and Gardasil®	M7 & M12	16 18 31 45 58	seAP	10 (50%)	7 - 12

[a] Age range of participants except for Toft_2014 where median ages of Cervarix® vaccinees (47.0; IQR 38.6 – 54.2) and Gardasil® (44.5; 38.2 – 51.9) were given.
[b] Assay readout makes use of Luciferase (Luc) or Secreted embryonic alkaline phosphatase (seAP) reporter gene expression
[c] Assay threshold defined by lowest antibody titer considered positive and in parentheses the percentage reduction in reporter activity required to be considered positive
[d] Number of serum used varies in some studies so numbers are presented as the minimum used (against any target type for any vaccine) to the maximum used.

Figure 1

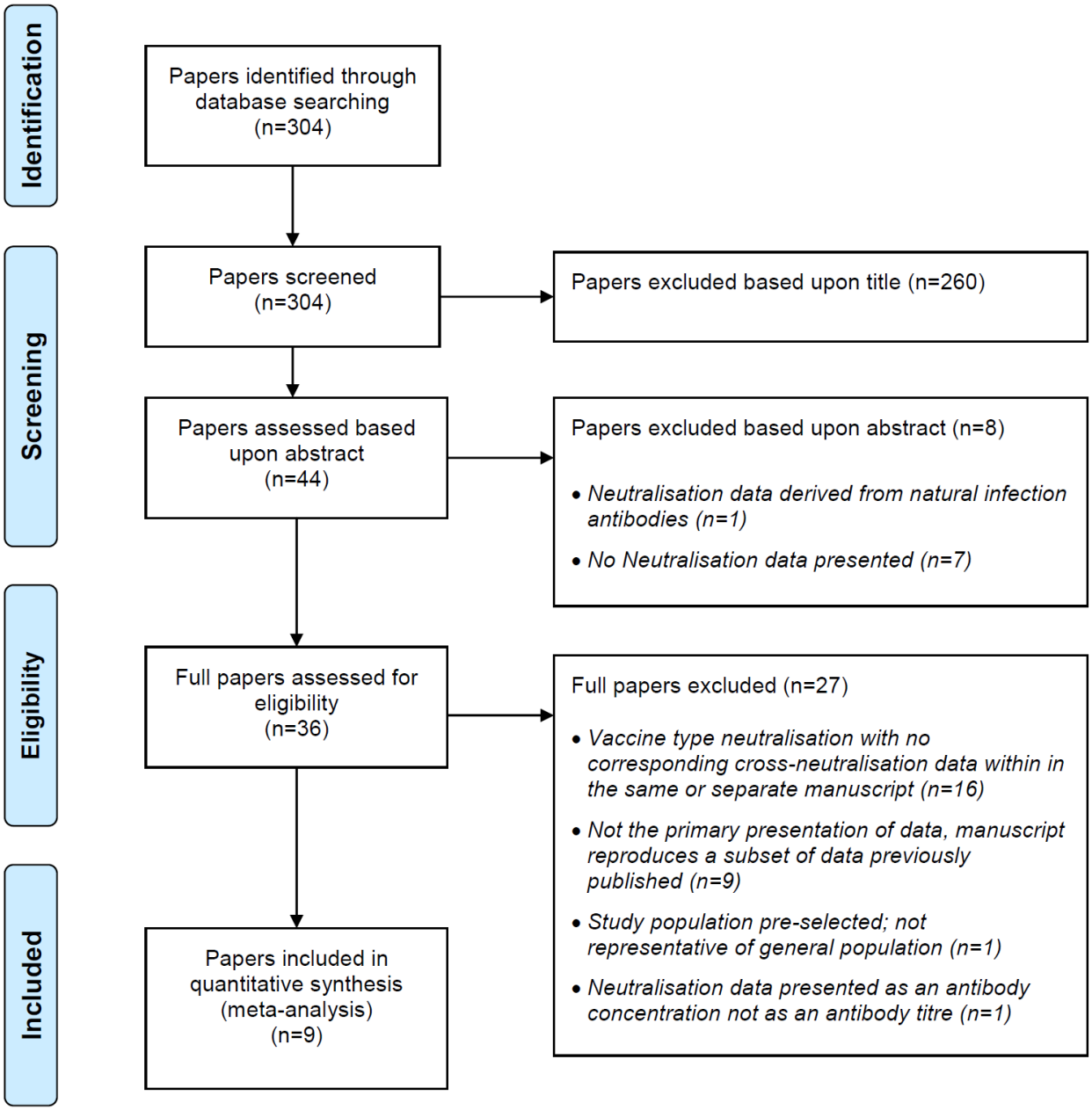

Identification
Screening
Eligibility
Included
Papers identified through database searching (n=304)
Papers screened (n=304)
Papers excluded based upon title (n=260)
Papers assessed based upon abstract (n=44)
Papers excluded based upon abstract (n=8)
• Neutralisation data derived from natural infection antibodies (n=1)
• No Neutralisation data presented (n=7)
Full papers assessed for eligibility (n=36)
Full papers excluded (n=27)
• Vaccine type neutralisation with no corresponding cross-neutralisation data within in the same or separate manuscript (n=16)
• Not the primary presentation of data, manuscript reproduces a subset of data previously published (n=9)
• Study population pre-selected; not representative of general population (n=1)
• Neutralisation data presented as an antibody concentration not as an antibody titre (n=1)
Papers included in quantitative synthesis (meta-analysis) (n=9)

Figure 2

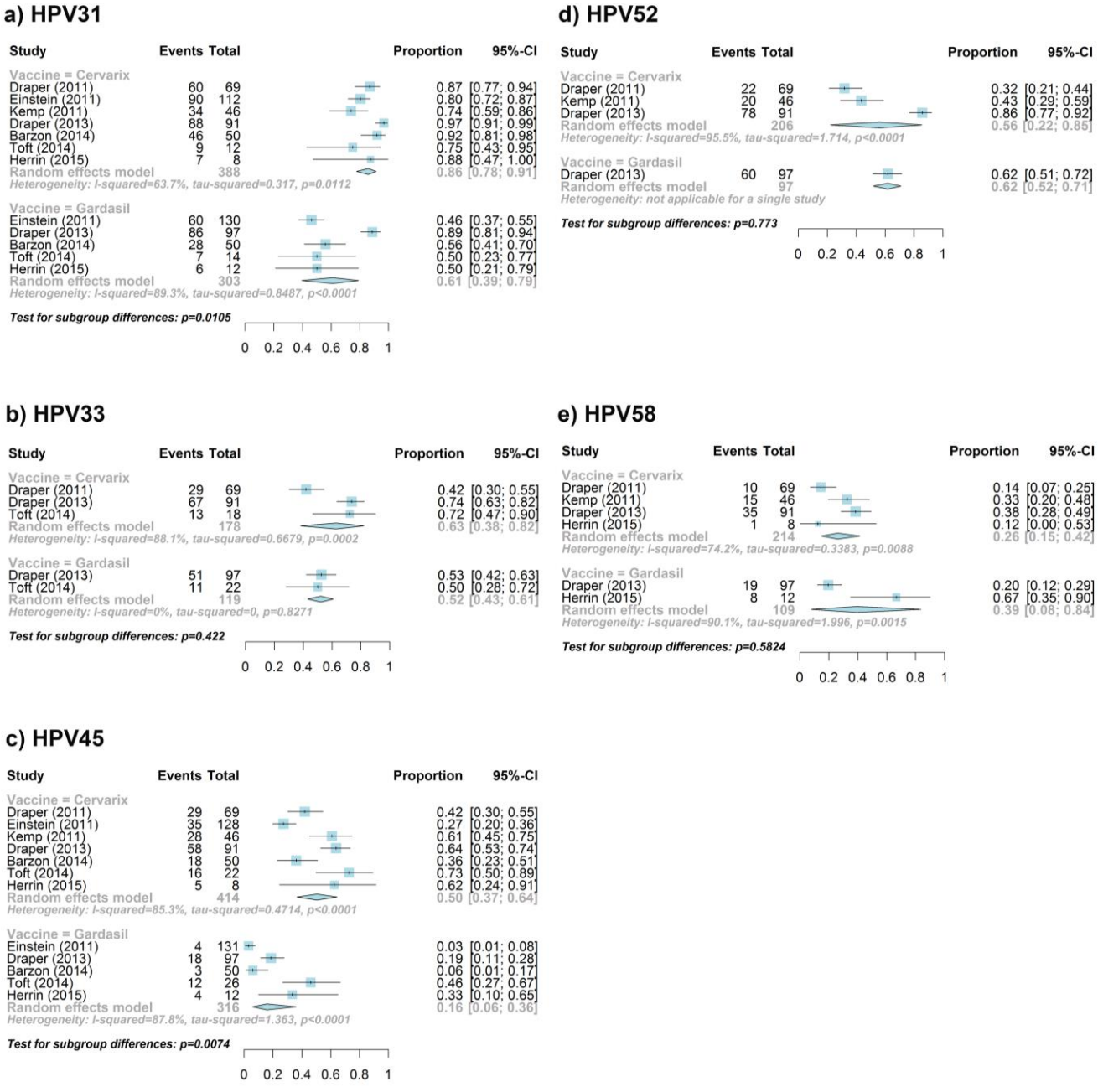

a) HPV31
Study Events Total Proportion 95%-CI
Vaccine = Cervarix
Draper (2011) 60 69 0.87 [0.77; 0.94]
Einstein (2011) 90 112 0.80 [0.72; 0.87]
Kemp (2011) 34 46 0.74 [0.59; 0.86]
Draper (2013) 88 91 0.97 [0.91; 0.99]
Barzon (2014) 46 50 0.92 [0.81; 0.98]
Toft (2014) 9 12 0.75 [0.43; 0.95]
Herrin (2015) 7 8 0.88 [0.47; 1.00]
Random effects model 388 0.86 [0.78; 0.91]
Heterogeneity: I-squared=63.7%, tau-squared=0.317, p=0.0112
Vaccine = Gardasil
Einstein (2011) 60 130 0.46 [0.37; 0.55]
Draper (2013) 86 97 0.89 [0.81; 0.94]
Barzon (2014) 28 50 0.56 [0.41; 0.70]
Toft (2014) 7 14 0.50 [0.23; 0.77]
Herrin (2015) 6 12 0.50 [0.21; 0.79]
Random effects model 303 0.61 [0.39; 0.79]
Heterogeneity: I-squared=89.3%, tau-squared=0.8487, p<0.0001
Test for subgroup differences: p=0.0105
0 0.2 0.4 0.6 0.8 1
d) HPV52
Study Events Total Proportion 95%-CI
Vaccine = Cervarix
Draper (2011) 22 69 0.32 [0.21; 0.44]
Kemp (2011) 20 46 0.43 [0.29; 0.59]
Draper (2013) 78 91 0.86 [0.77; 0.92]
Random effects model 206 0.56 [0.22; 0.85]
Heterogeneity: I-squared=95.5%, tau-squared=1.714, p<0.0001
Vaccine = Gardasil
Draper (2013) 60 97 0.62 [0.51; 0.72]
Random effects model 97 0.62 [0.52; 0.71]
Heterogeneity: not applicable for a single study
Test for subgroup differences: p=0.773
0 0.2 0.4 0.6 0.8 1
b) HPV33
Study Events Total Proportion 95%-CI
Vaccine = Cervarix
Draper (2011) 29 69 0.42 [0.30; 0.55]
Draper (2013) 67 91 0.74 [0.63; 0.82]
Toft (2014) 13 18 0.72 [0.47; 0.90]
Random effects model 178 0.63 [0.38; 0.82]
Heterogeneity: I-squared=88.1%, tau-squared=0.6679, p=0.0002
Vaccine = Gardasil
Draper (2013) 51 97 0.53 [0.42; 0.63]
Toft (2014) 11 22 0.50 [0.28; 0.72]
Random effects model 119 0.52 [0.43; 0.61]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.8271
Test for subgroup differences: p=0.422
0 0.2 0.4 0.6 0.8 1
e) HPV58
Study Events Total Proportion 95%-CI
Vaccine = Cervarix
Draper (2011) 10 69 0.14 [0.07; 0.25]
Kemp (2011) 15 46 0.33 [0.20; 0.48]
Draper (2013) 35 91 0.38 [0.28; 0.49]
Herrin (2015) 1 8 0.12 [0.00; 0.53]
Random effects model 214 0.26 [0.15; 0.42]
Heterogeneity: I-squared=74.2%, tau-squared=0.3383, p=0.0088
Vaccine = Gardasil
Draper (2013) 19 97 0.20 [0.12; 0.29]
Herrin (2015) 8 12 0.67 [0.35; 0.90]
Random effects model 109 0.39 [0.08; 0.84]
Heterogeneity: I-squared=90.1%, tau-squared=1.996, p=0.0015
Test for subgroup differences: p=0.5824
0 0.2 0.4 0.6 0.8 1
c) HPV45
Study Events Total Proportion 95%-CI
Vaccine = Cervarix
Draper (2011) 29 69 0.42 [0.30; 0.55]
Einstein (2011) 35 128 0.27 [0.20; 0.36]
Kemp (2011) 28 46 0.61 [0.45; 0.75]
Draper (2013) 58 91 0.64 [0.53; 0.74]
Barzon (2014) 18 50 0.36 [0.23; 0.51]
Toft (2014) 16 22 0.73 [0.50; 0.89]
Herrin (2015) 5 8 0.62 [0.24; 0.91]
Random effects model 414 0.50 [0.37; 0.64]
Heterogeneity: I-squared=85.3%, tau-squared=0.4714, p<0.0001
Vaccine = Gardasil
Einstein (2011) 4 131 0.03 [0.01; 0.08]
Draper (2013) 18 97 0.19 [0.11; 0.28]
Barzon (2014) 3 50 0.06 [0.01; 0.17]
Toft (2014) 12 26 0.46 [0.27; 0.67]
Herrin (2015) 4 12 0.33 [0.10; 0.65]
Random effects model 316 0.16 [0.06; 0.36]
Heterogeneity: I-squared=87.8%, tau-squared=1.363, p<0.0001
Test for subgroup differences: p=0.0074
0 0.2 0.4 0.6 0.8 1

Figure 3

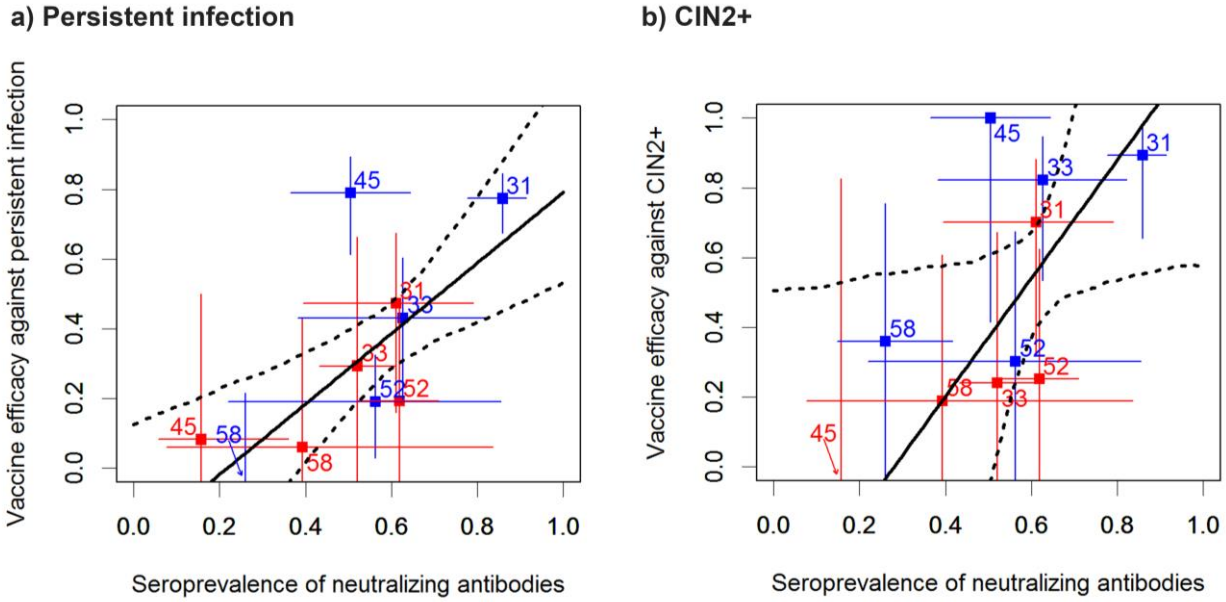
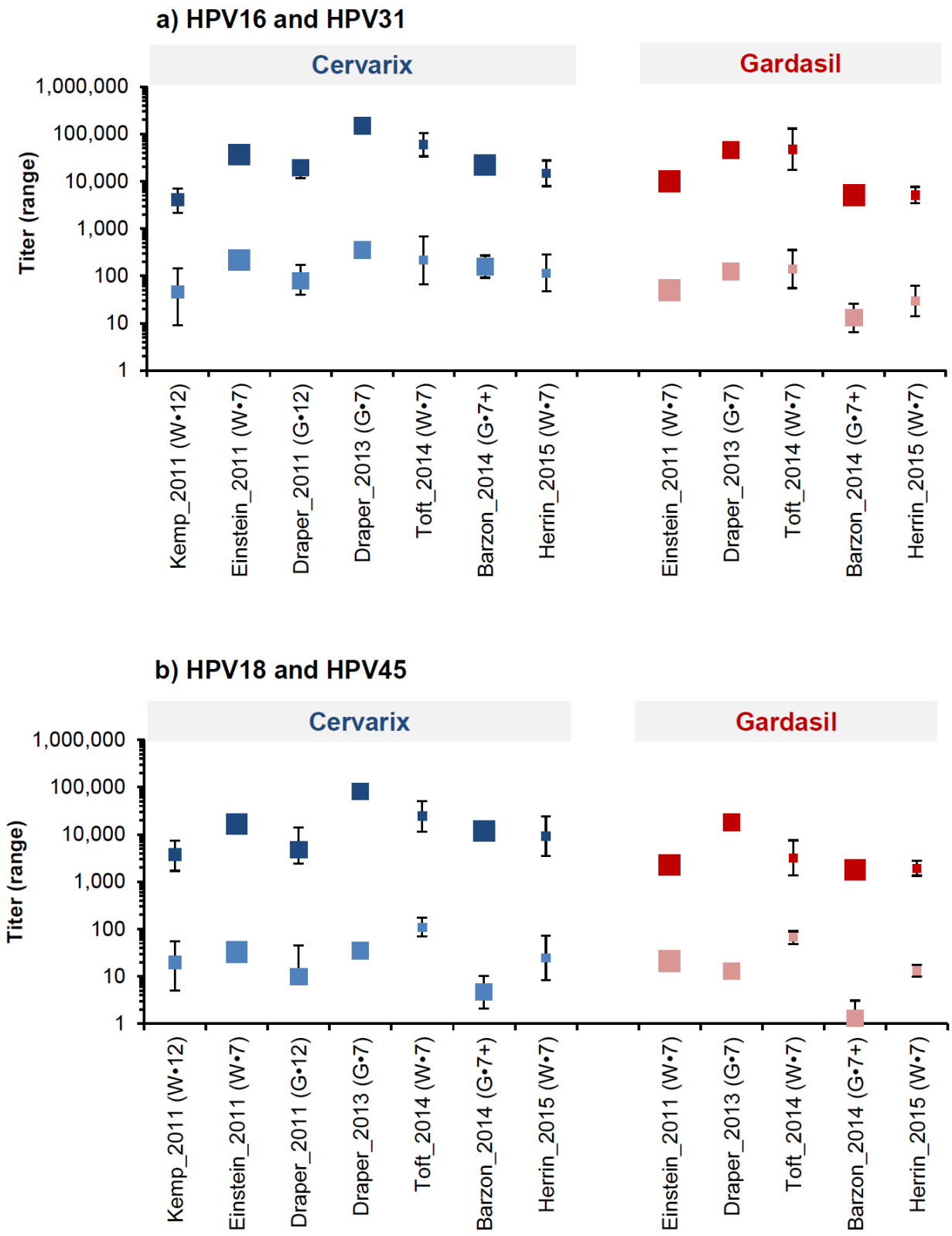
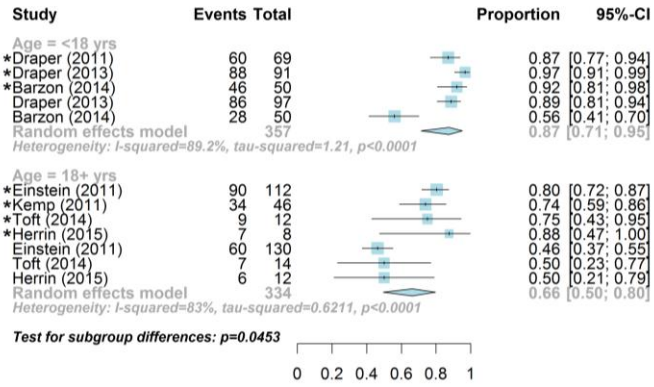

a) Persistent infection
b) CIN2+
Vaccine efficacy against persistent infection
Vaccine efficacy against CIN2+
Seroprevalence of neutralizing antibodies
Seroprevalence of neutralizing antibodies
0.0
0.2
0.4
0.6
0.8
1.0
45
31
33
51
52
58

Figure 4

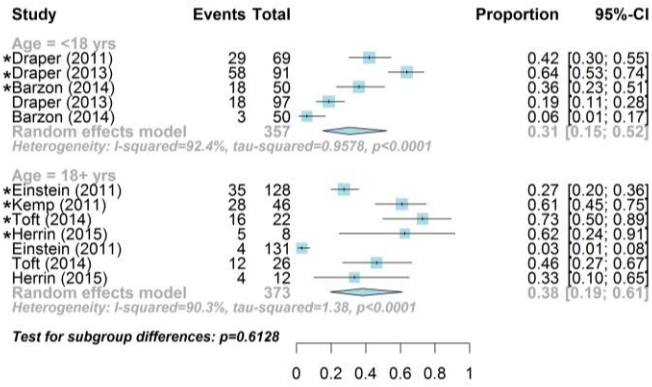

a) HPV16 and HPV31
Cervarix
Gardasil
Titer (range)
1,000,000
100,000
10,000
1,000
100
10
1
Kemp_2011 (W•12)
Einstein_2011 (W•7)
Draper_2011 (G•12)
Draper_2013 (G•7)
Toft_2014 (W•7)
Barzon_2014 (G•7+)
Herrin_2015 (W•7)
Einstein_2011 (W•7)
Draper_2013 (G•7)
Toft_2014 (W•7)
Barzon_2014 (G•7+)
Herrin_2015 (W•7)
b) HPV18 and HPV45
Cervarix
Gardasil
Titer (range)
1,000,000
100,000
10,000
1,000
100
10
1
Kemp_2011 (W•12)
Einstein_2011 (W•7)
Draper_2011 (G•12)
Draper_2013 (G•7)
Toft_2014 (W•7)
Barzon_2014 (G•7+)
Herrin_2015 (W•7)
Einstein_2011 (W•7)
Draper_2013 (G•7)
Toft_2014 (W•7)
Barzon_2014 (G•7+)
Herrin_2015 (W•7)

Supplemental Figure

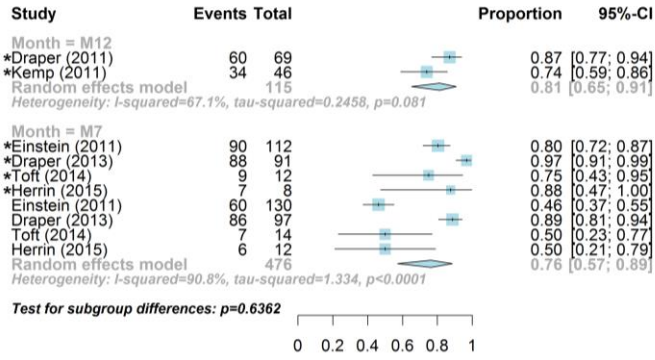
a) HPV31 Age



b) HPV45 Age



c) HPV31 Sampling time



d) HPV45 Sampling time