SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Literature search and Search strategy

No language or geographic restrictions were set. Grey literature and reference lists of relevant reviews and articles selected for inclusion were manually searched for publications possibly missed during the initial search. Discrepancies in the screening process were discussed and resolved by IK and MK.

The mesh terms used for the 5 different electronic databases during the literature search process are provided in following table.

Electronic database	Search terms*	Number of results
PubMed	(papillomavirus vaccine OR papillomavirus vaccination OR HPV vaccine OR HPV vaccination OR HPV vaccination status) AND (treatment OR therapy OR prevention OR large loop excision procedure OR LEEP OR NETZ OR conization OR ablation) AND (cervical intraepithelial neoplasia OR cervical dysplasia OR HPV related disease OR recurrence OR warts OR AIN OR anal neoplasia)	3804
Scopus**	HPV vaccination AND (treatment OR therapy OR conization) AND (recurrence OR warts OR CIN OR VIN)	8060
Web of Science	HPV vaccination AND (treatment OR therapy OR conization OR recurrence OR warts OR CIN)	2177
Cochrane	HPV vaccination AND (treatment OR therapy OR conization) AND (recurrence OR warts OR CIN OR VIN)	17
ClinicalTrials.gov	HPV vaccine and recurrence	19

*The literature search was conducted on the 31st of March 2021.

** In Scopus, search was limited to “articles”, “reviews”, “conference papers” and “short surveys” using filters.

Although published dissertations were excluded from the literature search, since they usually contain preliminary or incomplete data, abstracts submitted in conferences were considered eligible. Authors of published abstracts were contacted via email to provide additional data if available. Google scholar screening, customised Google searches and consultation with experts were also used to identify articles in the grey literature.

Inclusion and exclusion criteria

The systematic review included all studies irrespective of the presence of a comparison group. Additionally, although studies that included women found to have invasive disease at the time of treatment were presented in the systematic review, women that were diagnosed with cancer were excluded from the meta-analysis. The specific criteria for the inclusion and exclusion of studies in the meta-analysis can be found in the following table.

Studies were eligible irrespective of study design (observational studies, controlled non-randomised and randomised clinical trials, post-hoc analyses of randomised controlled trials (RCTs), case series, case reports). Studies were included irrespective of vaccine type if at least one dose had been administered and irrespective of the timing of the vaccination in relation to local surgical excision. We included all surgical treatment techniques (excisional or ablative) for cervical and other-HPV related disease.

We excluded studies exploring the vaccine efficacy after treatment for invasive disease and extragenital HPV-related diseases, such as respiratory papillomatosis and cutaneous skin warts. Studies on immunodeficient or paediatric patients and experimental animal models were excluded. Studies were also excluded if the intervention included experimental vaccines or immunotherapy and studies that used non-surgical treatment (i.e. salicylic acid or imiquimod cream).

	Inclusion criteria	**Exclusion criteria**
Publication type	• Original Articles • Conference abstracts	• Reviews • Protocols • Dissertations
Study design	• Observational studies • RCTs • Post-hoc analyses of RCTs	• Case series • Case reports
Population	• Women receiving excisional treatment for HPV-related lesions	• Studies on experimental animal models and paediatric populations
Treatment	Cervical lesions • LLETZ/LEEP • NETZ/SWETZ • Cold Knife Conisation (e.g. CKC) • Laser conisation • Laser ablation • Cryotherapy • Cold coagulation Other HPV-related lesions non-cervical lesions • Surgical excision • Laser ablation • Cryotherapy	• Salicylic acid • Imiquimod cream
Intervention	• Prophylactic HPV vaccine (irrespective of number of doses and timing related to treatment	• Experimental vaccines • Immunotherapy
Outcomes	Recurrence of HPV-related lesions after treatment including: • CIN2+	Recurrence of extragenital HPV-related diseases: • Respiratory papillomatosis

	• CIN1+ • CIN3 • CIN2 • CIN1 • CIN2+ (HPV 16-18 related) • CIN1+ (HPV 16-18 related) • VIN/VaIN2+ • VIN/VaIN1+ • Abnormal cytology • High grade AIN • Persistent HPV infection • Incident HPV infection.	• Cutaneous warts

AIN: anal intraepithelial neoplasia, CIN: cervical intraepithelial neoplasia, LEEP: Loop Electrosurgical Excision Procedure, LLETZ: large loop excision of the transformation zone, NETZ: needle excision of the transformation zone, RCT: randomised controlled trial, SWETZ: straight wire excision of the transformation zone, VIN/VaIN: vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia

Data extraction and risk of bias

Data regarding authors, year of publication, country of origin and design, setting (hospital, outpatient clinic), scope of the study (e.g. studies examining risk factors for recurrence or assessing the effectiveness of HPV vaccine as adjuvant to local surgical excision), patient characteristics (age, smoking, multiparity, previous excisional treatment for HPV-related lesions), possible confounding factors according to the authors, treatment type, HPV vaccination type and timing, and recurrence rates for HPV-related diseases (number of recurrent and non-recurrent cases for both vaccinated and unvaccinated patients) were abstracted. Additional data for specific HPV infection types before and after treatment, positive margins after excisional treatment and follow-up times were also collected if available. Data for recurrence either unadjusted or adjusted based on specific variables (e.g. age, smoking, positive margins) were collected. A 0.5 correction was added in all cells of a 2×2 table if any cell had zero events.

Risk of bias was assessed by two authors independently (KSK and SB) using ROBINS-I tool for observational studies and RoB-2 tool for RCTs. Using ROBINS-I, we assessed pre-intervention (e.g. bias due to confounding), intervention (e.g. bias in intervention classification) and post-intervention (e.g. bias from missing data or differences in the measurement of outcome) sources of bias and labelled studies as having low, moderate, serious or critical risk of bias. Similarly, using RoB2 tool we assessed domains such as randomisation process, assignment and adhering to intervention, missing data and measurement of outcome and finally categorised RCTs to low, moderate, or high risk of bias.

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool for the assessment of the quality of evidence. The analysis was performed using GRADEpro GDT online software as per Cochrane recommendation. The quality of evidence of two clinically notable outcomes, namely cervical intraepithelial neoplasia grade 2 or worse (CIN2+), and HPV16- or HPV18-

related CIN2+, was assessed in two groups based on study design (randomised controlled trials and observational studies). According to the GRADE approach the quality of evidence in RCTs without important limitations is high. On the other hand, the quality of evidence in observational studies without special strengths is considered low. Hence, in RCTs we started with a high certainty of evidence judgment and downgraded appropriately in case of serious concerns, whereas in observational studies we started at low certainty and upgraded according to their strengths. Decisions to downgrade (or upgrade) certainty were provided in the footnotes of each table.

Definitions of outcome

Although histopathological classification was used in preference, cytology was used to define recurrence in the absence of histological confirmation (HSIL cytology was classified as CIN2+ and LSIL as CIN1). Persistent HPV infection was defined in included studies as the detection of an HPV genotype at baseline and 6 months after treatment and the incident as the detection of a new HPV genotype 6 months after treatment or later.

Statistical analysis

If only one study was available for one of the explored outcomes, its results were described narratively.

Follow-up duration: For the calculation of median follow-up durations, we assumed that mean=median if a study reported the mean but not the median follow-up duration. Additionally, if a study reported the minimum but not the median follow-up duration, we assumed that median=minimum. As a result, our calculations for the median of the median follow up duration might have been slightly underestimated.

In the random-effects model and the Hartung-Knapp-Sidik-Jonkman (HKSJ) approach we used a 0.5 correction where needed.

Prediction Intervals: The prediction intervals provide a range of values for the effect size in the event of new study that would have similar characteristics to the included studies. Prediction intervals were calculated for all outcomes.

Publication Bias: We made moderate assumptions about the probability of publication bias of the smaller and larger (in terms of standard error) studies, where we assumed that the smallest study has a probability of publication equal to 40-50% and the largest study has a probability of 80-90%.

Generalized linear mixed model (GLMM): Because our meta-analysis examined rare events and publication bias was possible we performed a GLMM allowing for the binomial likelihood within studies.

SUPPLEMENTARY RESULTS

We identified 10662 articles through the literature search; 949 bibliographic references were removed as duplicates and 9499 articles were excluded through title and abstract screening. Two authors reviewed 53 full text articles for eligibility and 4 eligible articles were also retrieved from reference lists of relevant narrative reviews. Six clinical trials were also identified on ClinicaTrials.gov with 4 of them examining the effect of HPV vaccination as an adjuvant agent to reduce the recurrence of CIN after local surgical treatment and 2 focusing on the effect of HPV vaccination on the recurrence of genital warts after excisional treatment. While all the trials are active, only 3 of them are currently recruiting patients.

From the 22 articles included in the systematic review, 3 were case series and 1 was a case report. These 4 studies were excluded from the meta-analysis. The first case series described the management of two patients with cervical lesions that received treatment and HPV vaccination at the same visit. Both patients experienced recurrence of cervical lesions at 6 months. Similarly, a case report by Moscato et al. reported the recurrence of cervical lesions in a patient who received excisional treatment and HPV vaccination at the time of the treatment. Another case series conducted in Germany reported 6 cases of genital warts recurrence in men who received the HPV vaccine at the time of ablation. On the other hand, lower rates of genital warts recurrence were reported from a case series conducted in Turkey which described 33 cases. All the patients received the quadrivalent vaccine and were followed up for 48 months.

From the 18 studies included in the meta-analysis, only the 4 post-hoc analyses of RCTs used placebo for the non-vaccinated participants; this included the hepatitis A vaccine in 2 studies, aluminum hydroxyphosphate sulfate in 1 study and aluminum hydroxide in 1 study. Ten studies were conducted in Europe, 4 in Asia, 2 in America and 2 were multinational. Seven studies used the quadrivalent vaccine, 5 studies used the bivalent vaccine, 5 studies used either the bivalent or the quadrivalent vaccines and 1 study did not provide data on vaccine type. Vaccination timing of the first dose in relation to excisional treatment varied widely amongst RCTs and observational studies. In 2 studies the vaccine was administered 3 to 1 month before treatment, in 2 studies was given at the time of treatment and in 7 studies was administered after treatment (range 1 to 12 months), ranging from 1 to 12 months after treatment. In the 4 post-hoc analyses of RCTs vaccination took place 27 to 50 months before treatment. The treatment for cervical lesions included Large Loop Excision of the Transformation Zone (LLETZ) in 8 studies, LLETZ or cold knife conisation (CKC) in 3 studies and LLETZ or CKC or ablation in 2 studies. Similarly, treatment for non-cervical HPV-related lesions (VIN/VaIN, high-grade AIN, warts) included local excision in 3 studies and cryotherapy in 2 studies

while the exact treatment type was not determined in 3 studies. Only 5 studies provided adjusted data for the recurrence of HPV-related lesions (Table S1).

Risk of Bias

Using ROBINS-I, 37% (6/16) of the studies were found to have critical and 12% (2/16) serious biases due to confounding factors. Another 44% (7/16) had serious risk of bias as a result of the selection of participants and 12% (2/16) due to the measurement of outcome (Table S3).

CIN Recurrence and HPV infection rates after local surgical treatment for CIN

The rate of CIN1+ recurrence was lower in vaccinated vs non-vaccinated women (5 studies; 1,045 participants; RR 0.55, 95%CI 0.31-0.96; I^2=63%, τ^2=0.15) (Figure S2a). The risk of CIN3 recurrence was also reduced among vaccinated patients. However, this was only reported in 3 studies and had large uncertainty (3 studies; 17,757 participants; RR 0.28, 95%CI 0.01-6.37; I^2=71%, τ^2=1.23).

The rate of incident and persistent HPV infection was reported in two studies (1 post-hoc analysis of an RCT and 1 observational study). [1] [2] Both outcomes did not differ between patients receiving the HPV vaccine after local surgical treatment and unvaccinated cohorts.

Recurrence of other non-cervical HPV-related diseases after local surgical treatment of non-cervical disease

Only one study assessed VIN/VaIN1+ recurrence and showed no difference between vaccinated and non-vaccinated patients (Table 1). Only one study also examined the effect of HPV vaccination on high-grade AIN recurrence in men that have sex with men undergoing surgical treatment and reported reduction (Table 1).

The second meta-analysis of post-hoc analyses of RCTs, showed no benefit of HPV vaccination compared to the non-vaccinated women treated for VIN/VAIN for the recurrence of VIN/VaIN 1+ (3 studies, 1,670 participants; RR 1.3, 95% CI 0.23-7.43, I^2=29%, τ^2=0.29) (Figure S5i) and VIN/VaIN 2+ lesions (3 studies, 1,666 participants; RR 1.01, 95% CI 0.24-4.15, I^2=0%, τ^2=0) (Table 2, Figure S5j).

Only one small observational study of male participants and one post-hoc analysis of an RCT in females explored anogenital warts recurrence after surgical wart treatment and found no significant difference [3] [4].

SUPPLEMENTARY DISCUSSION

Additional and Secondary Analyses

The analysis of the post-hoc studies from RCT data with historic vaccination at randomisation before the development of the disease reported inconsistent results. Although there was strong evidence of benefit for CIN1+, this did not reach nominal significance for CIN2+. The reasons for this are unclear and may be partially explained by type II error as these studies were not powered for this outcome.

The effect size on secondary outcomes in our study showed possible beneficial effect from vaccination, although the evidence remains unclear. The number of studies and participants included in these meta-analyses was low and as such the power of detecting a vaccine effect was low. Larger appropriately powered studies are required to assess these outcomes. The data was consistent in the effect irrespective of the type of vaccine; there were no studies exploring the efficacy of the new Gardasil9® vaccine that covers 90% of oncogenic infections. The effect was stronger when the treated lesion contained HPV16/18, which are the HPV types that the first-generation vaccines targeted. Whether vaccination with broader, nonavalent vaccine may have better effect for prevention recurrence also of lesions with non-16/18 related lesions would be an interesting area for further research.

Mechanism of Action

Whilst local surgical treatment for cervical high-grade pre-invasive lesions is highly efficacious, the recurrence rate for high-grade pre-invasive disease can be as high as 5-10%[5 6] and women post-conisation remain at high-risk of cervical and other HPV-related cancers than the general population [7-12]. Women who develop high grade CIN in the first place constitute a subgroup of infected individuals who are particularly sensitive to the HPV infection for reasons incompletely understood. These could be genetic, epigenetic, immunological or microbiome factors, but also lifestyle and environmental, such as smoking[13-19]. As a result, these women can rapidly acquire re-infections post-treatment[20]. It is plausible that the high frequency of infections places these women after treatment at higher risk of pre-invasive or invasive recurrent disease that can be more difficult to detect and prevent[5]. Repeat conisations have been associated with adverse reproductive outcomes[21-25]. These women constitute therefore a particularly high-risk population that requires risk-reducing interventions to protect against HPV re-infections by the same or difference subtype[20].

There is ample prior data that HPV vaccines are much more immunogenic than the infection. Originally shown by Harro et al.[26] and confirmed in numerous studies, the response to the vaccine is 10-100 times higher than the response to the infection. There is strong evidence that supports the fact

that a systemic administration of HPV VLPs can elicit an immune response even on those that have not been able to raise antibodies following natural HPV infection[27]. This evidence comes both from the original pilot studies from the HPV positive but sero-negative women that were vaccinated but also from the 'booster' effect seen in adult women vaccination. The most widely accepted explanation is that the infection is local and lacks a viraemic phase, whereas the vaccine is given intramuscularly and directly enters the bloodstream.

It has been previously reported that the vaccines are effective in women and men with a previous cleared infection. In a post-hoc analysis of 2,617 women of HPV seropositive but DNA negative subjects from 3 trials, no subject receiving the HPV 6/11/16/18 vaccine developed disease related to the vaccine type, whilst there were 7 cases cervical disease and 8 cases of external genital disease related to a vaccine HPV type in the placebo arm. This study demonstrates that the vaccine confers protection from re-infection or re-activation, and that natural immunity from induced antibodies does not protect overtime[28]. As such, it is plausible that the vaccine has a substantial benefit against new infections not present at time of treatment and re-infections from the same HPV subtype soon after treatment, although it less is likely that this promotes clearance of an existing infection in isolation. It remains an open question whether the vaccine has the potential to work in conjunction with local surgical treatment (that removes the CIN and most of the infection) to boost the effect of treatment and viral clearance or whether the vaccine could help following clinical clearance of the infection after treatment to ensure that there is no latent infection or re-occurrence of the infection by the same subtypes.

Limitations

The high diversity between the diagnostic methods and follow-up used in the studies, the inclusion of different HPV vaccines and the differences in the vaccination timing could potentially influence the accuracy of the effect estimate. For example, although histology was used in preference to cytology for the definition of outcome, studies did not consistently report histology that may affect effect estimates due to the comparatively reduced accuracy of cytology. Furthermore, the use of random-effect model with HKSJ in preference to fixed effects model using the Der Simonian and Laird method and the Wald type approach led to wide intervals. This is an intrinsic limitation of the HKSJ method that leads to overconservative effect estimates when less than three studies are analysed[29-31]. Additionally, although the Egger's test has suboptimal performance for odds ratios, there is no better alternative.

The effect estimate was consistent when the vaccine was given at the time or up to 12 months after treatment. The effect estimate was similar for those receiving the vaccine up to 3 months before treatment but did not reach nominal significance. This may be related to small number of studies and

participants, existing bias or may also be explained by the local immune response when the vaccine is given at the time of treatment that may boost clearance of the infection. Results remained consistent in all sensitivity analyses and heterogeneity was reduced after excluding studies with high and serious overall risk of bias. The exclusion of studies that used cytology to define outcome showed consistent results and did not reduce the heterogeneity.

The data was consistent in the effect irrespective of the type of vaccine; there were no studies exploring the efficacy of the new Gardasil9® vaccine that covers 90% of oncogenic infections. The effect was stronger when the treated lesion contained HPV16/18, which are the HPV types that the first-generation vaccines targeted. Whether vaccination with broader, nonavalent vaccine may have better effect for prevention recurrence also of lesions with non-16/18 related lesions would be an interesting area for further research.

To conclude, the credibility of our findings is overall low for a number of reasons. The individual study results included in the meta-analysis were predominantly obtained from observational studies (only 2 RCTs were included in the meta-analysis), increasing the probability of confounding. The presence of rare events in the evidence database, and the random-effects meta-analysis based on the normal distribution model is difficult to justify. Even if applying the Mantel-Haenszel method under the fixed-effect model that does not require continuity corrections, it does not overcome the normal distributional assumptions, which is not appropriate for discrete data and small samples. Despite using more advanced models allowing for the binomial likelihood within studies (GLMM model) and for random effects on the intervention effect, this does not minimize biases due to different study designs and populations. Estimation of heterogeneity can be challenging, particularly in the presence of rare events. In our dataset, we expect heterogeneity because the effect likely varies across populations, and due to the different study designs and characteristics. The funnel plot asymmetry and the disagreement between the random-effects and fixed-effect estimates indicate the possibility of the presence of small-study effects pointing to one direction of effect.

Future Impact

National HPV vaccination programs involving adolescents will, in the foreseeable future, significantly reduce exposure to the oncogenic HPV types in countries with high coverage 79-81. The numbers of high-grade CIN lesions, that require screening and treatment, will, however, remain high among the unvaccinated birth cohorts for several decades. The coverage worldwide continues to be low, not just in low resource settings but in many European countries (and Japan) (e.g., 19% coverage in France 82), while population exchange is the norm. The impact of a post-treatment vaccination policy could be a substantial contribution to an effective cervical cancer elimination program for many decades to come. Being able to prevent even half of the recurrent HPV infections, referrals to colposcopy, the

occurrence of recurrent high-grade disease requiring repeat local surgical treatment resulting in increased reproductive morbidity in women of childbearing age and other HPV-related diseases will also be hugely beneficial to women and to the health care systems.

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SUPPLEMENTARY TABLES

Table S1. Characteristics of the included studies.

	Author Year	Country	Study design◊	Population	Treatment	Comparison	Vaccination timing	Follow up duration	Outcomes†
Studies in women treated for HPV-related lesions	**Randomised controlled trials**								
	Pieralli 2018	Italy	RCT	178 women treated for CIN with negative HPV test, cytology, and colposcopy 3 months after treatment [Vaccine Group 89 – Non-vaccine Group 89] Age: 32 (mean) [Vaccine Group 32.1 - Non-vaccine Group 31.8] CIN grade: 30 LSIL, 148 HSIL	N/A	Quadrivalent vaccine [3 doses] vs No HPV vaccination	3 months after treatment	36 months (minimum)	CIN1+ CIN2+ CIN1+ HPV 16-18 CIN2+ HPV 16-18 CIN1 Abnormal cytology VIN/VaIN 1+ VIN/VaIN 2+
	Karimi-Zarchi 2020	Iran	RCT	242 women treated for CIN1 or high grade CIN (CIN2-3) [Vaccine group 138 – Non-vaccine Group 104] Age: 32.59 (mean) [Vaccine Group 31.7 – Non-Vaccine Group 33.04] CIN grade: 80 CIN1, 85 CIN2, 77 CIN3 [Vaccine group: 45 CIN1, 50 CIN2, 43 CIN3 – Non-Vaccine Group 35 CIN1, 35 CIN2, 34 CIN3]	LLETZ, CKC, Ablation	Quadrivalent vaccine [35/138 2 doses, 103/138 3 doses] Vs No HPV vaccination	At the time of treatment	24 months (minimum)	CIN1+ CIN2+ CIN1 ICC
	Observational studies								
	Grzes 2011	Poland	Prospective Cohort (abstract)	75 women treated for CIN (+persistent HPV infection) [Vaccine group 25 – Non-vaccine Group 50] Age: N/A	LLETZ, CKC	Quadrivalent vaccine [doses N/A] vs No HPV vaccination	After the treatment	N/A	CIN2+ *** CIN1+ ***
	Kang 2013 ‡	Korea	Retrospecti ve cohort	737 women treated for CIN2-3 [Vaccine group 360 – Non-vaccine Group 377] Age: 36.7 (mean) CIN grade: 125 CIN2, 612 [Vaccine Group 54 CIN2, 306 CIN3 – Non-vaccine Group 71 CIN2, 306 CIN3] Positive margin: 136/737 [Vaccine group 63/360 – Non-vaccine Group 73/377]	LLETZ	Quadrivalent vaccine [3 doses] vs No HPV vaccination	One week after treatment	42 months (median)	CIN2+ ** CIN2+ HPV 16-18 **
	Ortega-Quinonero 2018 ‡	Spain	Retrospecti ve cohort	264 women treated for CIN2-3 [Vaccine group 103 – Non-vaccine Group 139] Age: 36 (median)	LLETZ	Bivalent (70/103) or Quadrivalent vaccine (33/103) [3 doses]	1 month before (46/103) or	24 months (minimum)	CIN2+ CIN2+ HPV16-18

				[Vaccine group 33 – Non-vaccine Group 39] CIN grade: 106 CIN2, 242 CIN3 [Vaccine group 51 CIN2, 52 CIN3 – Non-vaccinate group 55 CIN2, 84 CIN3] Positive margin: 62/242 [Vaccine group 26/103 – Non-vaccine Group 36/139]		vs No HPV vaccination	1 month after treatment (57/103)		
	Ghelardi 2018	Italy	Prospective cohort	344 women treated for CIN2-3/stage IA1 cervical cancer [Vaccine group 172 – Non-vaccine Group 172] Age: N/A CIN grade: 9 CIN2, 330 CIN3, [Vaccine group 6 CIN2, 163 CIN3, IA1 3 – Non-vaccine group 3 CIN2, 167 CIN3, IA1 2] Positive margin: 52/350 [Vaccine group 18/174 – Non-vaccine Group 24/176]	LLETZ	Quadrivalent vaccine [3 doses] vs No HPV vaccination	1 month after treatment	36 months (median)	CIN2+ CIN2+ HPV 16-18 CIN2 CIN3 Persistent HPV infection
	Vinnytska 2019	Ukraine	Prospective Cohort (non-peer reviewed)	106 women treated for HSIL [Vaccine group 76 – Non-vaccine Group 37] Age: N/A	LLETZ	Bivalent or Quadrivalent vaccine [3 doses] vs No HPV vaccination	2 months before treatment	N/A	HSIL *** HSIL HPV16-18
Studies in women treated for HPV-related lesions	Sand 2019 ‡	Denmark	Retrospective cohort	17128 women diagnosed with CIN3 or CIS on the cone [Vaccine group 2074 – Non-vaccine Group 15054] Age: N/A CIN grade: 12403 CIN3, 4724 CIS [Vaccine group 1508 CIN3, 565 CIS – Non-vaccinated 10895 CIN3, 4159 CIS]	Conisation	N/A	3 months before (399/2074) or until 1 year after treatment (1675/2074)	48 months (minimum)	CIN2+ CIN2 CIN3
	Petrillo 2020 ‡	Italy	Prospective cohort	285 women treated for cervical dysplasia [Vaccine group 182 – Non-vaccine Group 103] Age: 39 (median) [Vaccine group 37.5 – Non-vaccine Group 41] CIN grade: 2 normal, 5 CIN1, 153 CIN2, 117 CIN3, 16 CIS [Vaccine group 1 normal, 3 CIN1, 96 CIN2, 72 CIN3, 9 CIS – Non-vaccine 1 normal, 2 CIN1, 57 CIN2, 45 CIN3, 7 CIS] Positive margin: 28/286 [Vaccine group 13/183 – Non-vaccine Group 15/103]	LLETZ	Quadrivalent (179/182) or bivalent (3/182) vaccine [3 doses] vs No HPV vaccination	1 month after treatment	24 months (minimum)	CIN1+ CIN2+ CIN1 CIN2 CIN3 ICC

	Del Pino 2020 ‡	Spain	Prospective cohort	265 women treated for cervical dysplasia [Vaccine group 153 – Non-vaccine Group 112] Age: 39.8 (mean) CIN grade: 25 CIN1, 240 CIN2-3 [Vaccine group 12 CIN1, 141 CIN2-3 Non-vaccine group:13 CIN1, 99 CIN2-3] Positive margin: 91/265 [Vaccine group 59/153 – Non-vaccine Group 32/112]	LLETZ	Bivalent (30/153) or Quadrivalent (7/153) or Nonavalent (98/153) or unknown (18/153) vaccine [118/153 3 doses, 16/153 2 doses, 7/153 1 dose, 12/153 unknown doses] vs No HPV vaccination	At the time of treatment	21.7 months (median)	CIN1+ ** CIN2+ ** CIN2+ HPV 16-18 ** CIN1 **
	Bogani 2021	Italy	Retrospecti ve cohort	1914 women treated for HSIL [Vaccine group 116 – Non-vaccine group 1798] Age: 41 (median) [Vaccine group 35 – Non-vaccine group 39] CIN grade: 160 CIN2, 140 CIN3 [Vaccine group 54 CIN2, 46 CIN3 – Non-vaccine group 106 CIN2, 94 CIN3] Positive margin: 73/300 [Vaccine group 24/100 – Non-vaccine group 49/200]	LLETZ	Bivalent (7%) or Quadrivalent (93%) vaccine [68/100 3 doses, 18/100 2 doses, 14/100 unknown doses] Vs No HPV vaccination	Within 1 month (70/100), 1-3 months (12/100) or 3-6 months (4/100) after the treatment, unknown timing (14/100)	60 months (minimum)	HSIL
	Ghelardi 2021	Italy	Prospective case control study	149 women treated for high grade VIN [Vaccine group 76 – Non-vaccine group 42] Age: 46 (median) [Vaccine group 41.2 – Non-vaccine group 40.6]	LLETZ, Laser ablation	Quadrivalent vaccine vs No HPV vaccination	Within 30 days after the treatment	24 months (minimum)	VIN/VaIN 2+ Incident HPV infection
	Post-hoc analyses of randomised controlled trials								
	Joura 2012	Multi-national (13 countries)	Post-hoc analysis of RCT	1350 women treated for cervical disease [Vaccine group 587 – Non-vaccine Group 763] Age: 19.8 (mean) [Vaccine group 19.9 – Non-vaccine Group 19.8] CIN grade: 113 ASCUS, 23 ASCH, 232 LSIL, 65 HSIL [Vaccine group 47 ASCUS, ASCH 13, 112 LSIL, 36 HSIL Non vaccine group 65 ASCUS, 10 ASCH, 120 LSIL, 29 HSIL]	LLETZ (84.7%), Conization (13%), Cryotherapy (0.7%), other (2.1%)	Quadrivalent vaccine [585/587 3 doses, 2/587 2 doses] vs 225 g aluminum hydroxyphosphate sulfate	Before the treatment	44 months (maximum)•	CIN1+ CIN2+ CIN1+ HPV 16-18 CIN2+ HPV 16-18 CIN1 CIN2 CIN3 VIN/VaIN 1+ VIN/VaIN 2+ Genital warts

	Hildesheim 2016	Costa Rica	Post-hoc analysis of RCT	311 women treated for high grade cervical disease [Vaccine group 142 – Non-vaccine Group 169] Age: N/A CIN Grade: 154 normal, 67 LSIL, 87 HSIL [Vaccine group 1 Inadequate, 57 normal, 36 LSIL, 47 HSIL – Non-vaccine group 1 inadequate, 97 normal, 31 LSIL, 40 HSIL]	LLETZ	Bivalent vaccine [3 doses 80%, 2 doses 12.4%, 1 dose 7.4%] vs Hepatitis A vaccine	28.2 months (median) before treatment	27.3 months (median)	CIN2+ ** CIN2+ HPV 16-18 ** Abnormal cytology Persistent HPV infection Incident HPV infection
	Garland 2016	Multi-national (14 countries)	Post-hoc analysis of RCT	454 women treated for cervical lesions [Vaccine group 190 – Non-vaccine Group 264] Age: N/A	LLETZ, Conization	Bivalent vaccine [doses N/A] vs Hepatitis A vaccine	19.1 (1.5-46.5) and 26.5 (0.8-48.3) months before the treatment	47.3 (median)•	CIN1+ CIN2+ CIN1+ HPV 16-18 CIN2+ HPV 16-18 CIN1 CIN2 Abnormal cytology VIN/VaIN 1+ VIN/VaIN 2+
	Zhao 2020	China	Post-hoc analysis of RCT	166 women treated for cervical lesions [Vaccine group 86 – Non-vaccine Group 80] Age: 18-25	LLETZ, Conisation	Bivalent vaccine vs Aluminum hydroxide	17 months (median) before the treatment	50 months (median)	CIN1+ CIN2+ CIN2+ HPV 16-18 CIN1 CIN2 CIN3 VIN/VaIN 1+ VIN/VaIN 2+
	Case series and case reports								
	Gianella 2015 ⁂	Italy	Case series	2 women treated for cervical disease and received HPV vaccine Age: 33 and 35 CIN grade: CIN1 and CIN3	LLETZ	Quadrivalent vaccine [3 doses]	After the treatment	18 months (maximum)	CIN2+ Persistent HPV infection Incident HPV infection
	Moscato 2015 ⁂	Italy	Case report	1 woman treated for cervical disease and received HPV vaccine Age: 24	LLETZ	Quadrivalent vaccine [3 doses]	After the treatment	N/A	CIN1+ CIN2+
	Senol 2016 ⁂	Turkey	Case series (non-peer reviewed)	33 women treated for anogenital warts [Vaccine group 33 – Non-vaccine Group 0] Age: N/A	Ablation	Quadrivalent vaccine [3 doses]	After the treatment	48 months (maximum)	Genital warts

Studies in men treated for HPV-related lesions	**Observational studies**								
	Coskuner 2014	Turkey	Prospective Cohort	171 men treated for genital warts [Vaccine group 91 – Non-vaccine Group 80] Age: 34.5 (mean) [Vaccine group 32.1– Non-vaccine Group 36.4]	Local excision	Quadrivalent vaccine vs No HPV vaccination	At the day of the treatment	46.1 months (mean)	Genital warts
	Swedish 2012	USA	Prospective Cohort	202 men (MSM) treated for HGAIN [Vaccine group 88 – Non-vaccine Group 114] Age: 40.4 (mean) [Vaccine group 37.5– Non-vaccine Group 42.6]	Local excision, Ablation	Quadrivalent vaccine vs No HPV vaccination	One month before treatment	N/A	High grade AIN
	Case series and case reports								
	Kreuter 2013 ⁂	Germany	Case series	6 men treated for genital warts [Vaccine group 6 – Non-vaccine Group 0] Age: 26.1 (mean)	Ablation	Quadrivalent vaccine	At the day of the treatment	N/A	Genital warts

AIN: anal intraepithelial neoplasia, CIN: cervical intraepithelial neoplasia, CKC: cold knife conisation, HPV: human papilloma virus, HSIL: high-grade squamous intraepithelial neoplasia, ICC: invasive cervical cancer, LLETZ: large loop excision of the transformation zone, LSIL: low-grade squamous intraepithelial neoplasia, MSM: men who have sex with men, N/A: not applicable, RCTs: randomised controlled trials, VIN/VaIN: vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia

◊ Study design as defined by the authors of the study.

† The outcome was confirmed by histology in most of the studies.

‡ Studies that provided adjusted data.

* Describes studies were outcome was determined by cytology alone.

** Describes studies were outcome was determined by either histology or cytology.

*** Describes studies which did not determine a specific method of outcome diagnosis.

⁂ Studies that didn't provide data for a control (no vaccination) group and therefore they were excluded from the data synthesis.

• Follow up after HPV vaccination in the original randomised controlled trial.

Table S2. Follow-up duration of the studies which reported on the primary outcome (CIN2+ recurrence after local surgical treatment).

Author year	Study design	Follow-up duration as reported by the authors of the study (months)				Calculation of medians*
		Minimum	Maximum	Mean	Median	
Pieralli 2018	RCT	36	N/A	NA	NA	>24m
Karimi-Zarchi 2020	RCT	24	24	N/A	N/A	≤24m
Grzes 2011**	Observational	N/A	N/A	N/A	N/A	N/A
Kang 2013	Observational	N/A	N/A	N/A	42	>24m
Ortega-Quinonero 2018	Observational	24	N/A	N/A	N/A	>24m
Ghelardi 2018	Observational	6	48	N/A	36	36
Vinnytska 2019**	Observational	N/A	N/A	N/A	N/A	N/A
Sand*** 2019	Observational	48	N/A	N/A	N/A	>24m
Petrillo 2020	Observational	24	N/A	N/A	N/A	>24m
Del Pino 2020	Observational	8	N/A	22.4	21.7	21.7
Bogani 2021	Observational	60	N/A	N/A	N/A	>24m
Joura‡ 2012	Post-hoc analysis of RCT	N/A	44	N/A	N/A	N/A
Hildesheim 2016	Post-hoc analysis of RCT	N/A	N/A	N/A	27.3	27.3
Garland‡ 2016	Post-hoc analysis of RCT	N/A	48	N/A	47.3	N/A
Zhao 2020	Post-hoc analysis of RCT	N/A	N/A	N/A	50	50

N/A: not available, RCT: randomised controlled trial

* When minimum or maximum follow-up duration was available, we assumed that median>minimum and median<maximum (due to attrition rate).

**Authors reported follow-up intervals only.

*** Follow-up started 1 year after treatment. Recurrences within this year were missed.
‡ The authors reported the follow-up duration after vaccination and not after treatment.

Table S3. Risk of bias assessment for a. randomized (RoB-2 tool) and b. observational (ROBINS-I tool) studies.

a.

Author Year	Randomization process	Assignment to intervention	Adhering to intervention	Missing outcome data	Measurement of outcome	Selection of the reported result	RoB-2 overall score
Karimi-Zachri 2020	Low	Low	Low	Low	Low	Some concern	Low
Pieralli 2018	Low	Low	Low	Low	Low	Some concern	Low

b.

Author Year	Domain 1: Confounding factors	Domain 2: Selection of participants	Domain 3: Intervention classification	Domain 4: Deviation from intervention	Domain 5: Missing data	Domain 6: Measurement of outcome	Domain 7: Selection of reported result	ROBINS-I overall score
Bogani 2021	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Ghelardi 2021	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Zhao 2020	Critical	Serious	Low	Low	Low	Moderate	Moderate	Serious
Del Pino 2020	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Petrillo 2020	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Sand 2019	Serious	Low	Low	Low	Moderate	Moderate	Moderate	Serious
Vinnytska 2019	Critical	Serious	Serious	Serious	Serious	Moderate	Moderate	Critical
Ghelardi 2018	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate

Ortega-Quinonnero 2018	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Garland 2016	Critical	Serious	Low	Serious	Low	Moderate	Serious	Serious
Hildesheim 2016	Critical	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Coskuner 2014	Serious	Low	Serious	Low	Moderate	Moderate	Moderate	Serious
Kang 2013	Moderate	Serious	Low	Low	N/A	Serious	N/A	Serious
Swedish 2012	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Joura 2012	Critical	Serious	Low	Low	Low	Moderate	Moderate	Serious
Grzes 2011	Critical	Serious	Serious	Serious	Serious	Critical	Serious	Critical

RoB-2: risk of bias-2 tool, ROBINS-I: Risk of Bias In Non-randomised Studies of Interventions tool

*ROBINS-I is a tool which assesses the risk of bias in non-randomised studies of interventions by looking into pre-intervention, intervention and post-intervention domains. Studies with low risk of bias (no or one moderate concern in the included domains) are comparable to randomised controlled trials. Studies with moderate risk of bias (up to four moderate concerns in the included domains) can be characterised as credible but cannot considered comparable to a well performed randomised trial. Studies with serious risk of bias (at least one serious concern or multiple moderate concerns in the included domains) have important problems in the design. Studies with critical risk of bias (critical concerns or multiple serious concerns in the included domains) are too problematic to provide useful evidence on the intervention effect.

Table S4. Quality rating for the analyses of two clinically notable outcomes (CIN2+ recurrence and CIN2+ HPV16-18 related recurrence after local surgical treatment) based on GRADE.

Certainty assessment							Summary of findings				
Studies (participants)	**Risk of bias**	**Inconsistency ***	**Indirectness ****	**Imprecision *****	**Publication bias**	**Overall certainty of evidence †**	**Study event rates (%)**		**RR (95% CI)**	**Anticipated absolute effects**	
							Placebo or Control	**HPV vaccination**		**Risk with placebo**	**Risk difference with HPV vaccination**
CIN2+ recurrence											
2 RCTs (420)	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	⊕⊕⊕◯ MODERATE	45/193 (23.3%)	23/227 (10.1%)	RR 0.41 (0.03 to 5.13)	233 per 1,000	138 fewer per 1,000 (from 226 fewer to 963 more)
CIN2+ recurrence											
9 observational studies (19497)	serious [b]	not serious	not serious	not serious	publication bias strongly suspected [a]	⊕◯◯◯ Very low	881/16248 (5.4%)	118/3249 (3.6%)	RR 0.43 (0.29 to 0.64)	54 per 1,000	34 fewer per 1,000 (from 38 fewer to 20 fewer)
CIN2+ recurrence (HPV16-18 related)											
1 RCT (178)	not serious	serious [c]	not serious	not serious	publication bias strongly suspected [a]	⊕⊕◯◯ LOW	4/89 (4.5%)	0/89 (0.0%)	RR 0.11 (0.01 to 2.03)	45 per 1,000	40 fewer per 1,000 (from 44 fewer to 46 more)
CIN2+ recurrence (HPV16-18 related)											
5 observational studies (1885)	serious [d]	not serious	not serious	not serious	publication bias strongly suspected [a]	⊕◯◯◯ Very low	49/837 (5.9%)	13/864 (1.5%)	RR 0.27 (0.16 to 0.47)	59 per 1,000	43 fewer per 1,000 (from 49 fewer to 31 fewer)

CI: Confidence interval, CIN: cervical intraepithelial neoplasia, GRADE: Grading of Recommendations, Assessment, Development and Evaluations, RCT: randomised controlled trial, ROBINS-I: Risk Of Bias In Non-randomised Studies of Interventions, RR: Risk ratio

* Inconsistency: similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2
** Indirectness: differences in population, intervention and outcome and indirect comparisons
*** Imprecision: examination of 95% CIs and optimal information size
† For the aforementioned outcomes plausible residual confounding (e.g. inadequate follow-up period, demographic characteristics of the included populations including age, distribution of high risk HPV subtypes) would potentially suggest spurious effect.

a. Asymmetry was observed in the funnel plot reflecting the possibility of publication bias. Although asymmetry was not discernible using adjusted data the possibility of publication bias among the included studies cannot be excluded.
b. From the 9 included studies, 2 were found having critical and 3 serious risk of bias based on ROBINS-I tool.
c. Only one RCT provided data for this outcome.
d. From the 5 included studies, 1 was found having critical and 1 serious risk of bias based on ROBINS-I tool.

GRADE Working Group grades of evidence definitions
High quality: Confidence that the true effect lies close to that of the estimate of the effect
Moderate quality: Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low quality: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table S5. Sensitivity analysis for the primary outcome (CIN2+ recurrence after local surgical treatment).

	No of studies (references)	Total number of participants	Intervention Group Events per total n/N (%)	Comparison group Events per total n/N (%)	RR (95% CI) [Random effect model - Inverse variance method]*	I^2	τ^2
Excluding studies retrieved from grey literature	10 (18, 19, 21, 22, 42, 44, 45, 47-49)	19796	134/3396 (3.9%)	920/16400 (5.6%)	0.41 (0.28-0.59)	63%	0.16
Excluding studies with serious or critical RoB	7 (18, 21, 22, 45, 47-49)	1856	43/937 (4.5%)	115/919 (12.5%)	0.36 (0.27-0.48)	0%	0
Excluding studies with high attrition bias (>10%)	8 (19, 21, 22, 42, 44, 45, 46, 48)	16280	131/3018 (4.3%)	890/15962 (5.6%)	0.45 (0.29-0.70)	64%	0.17
Excluding studies that did not use histopathological confirmation for the diagnosis of the outcome	7 (18, 19, 21, 22, 45, 48, 49)	18699	119/2829 (4.2%)	878/15870 (5.5%)	0.39 (0.22-0.70)	71%	0.26
Excluding studies with high percentage (>75%) of CIN3 cases before treatment	10 (18, 21, 22, 42, 44-49)	2781	59/1398 (3.7%)	149/1383 (10.7%)	0.37 (0.30-0.46)	0%	0
Using fixed effect meta-analysis model	11 (18, 19, 21, 22, 42, 44-49)	19909	141/3472 (4%)	926/16437 (5.6%)	0.40 (0.36-0.44) **	90%	0.24
Using unadjusted data only	11 (18, 19, 21, 22, 42, 44-49)	19909	141/3472 (4%)	926/16437 (5.6%)	0.41 (0.30-0.56)	51%	0.12
Using GLMM model (approximate likelihood)	11 (18, 19, 21, 22, 42, 44-49)	19909	141/3472 (4%)	926/16437 (5.6%)	0.39 (0.27-0.58) ***	41%	0.12

CIN: cervical intraepithelial neoplasia, GLMM: Generalized linear mixed models, OR: odds ratio RoB: risk of bias, RR: risk ratio, 95% CI: 95% confidence interval, MH: Mantel-Haenszel

*Adjusted data were used when available. **Fixed effect model with MH method. ***GLMM calculates only OR

Table S6. Subgroup analysis for the primary outcome (CIN2+ recurrence after local surgical treatment).

	Subgroups	**No of studies (references)**	**Total number of participants**	**Intervention Group Events per total n/N (%)**	**Comparison group Events per total n/N (%)**	**RR (95% CI) [Random effect model - Inverse variance method]***	**I^2**	**τ^2**
Vaccination timing	Before the treatment	2 (19, 46)	4183	21/475 (4.4%)	195/3708 (5.2%)	0.37 (0.02-6.43)	0%	0
	At the time of or after the treatment	10 (18, 19, 21, 22, 42, 44, 45, 47-49)	15546	120/2997 (4%)	731/12549 (5.8%)	0.41 (0.30-0.56)	62%	0.17
Vaccine type	Gardasil	4 (18, 21, 22, 42)	1501	34/759 (4.4%)	83/742 (11.1%)	0.38 (0.23-0.60)	0%	0
	Gardasil or Cervarix	5 (45-49)	1205	25/614 (4%)	65/591 (10.1%)	0.36 (0.23-0.57)	0%	0
	Unknown type	2 (19, 44)	17128	82/2099 (3.9%)	778/15104 (5.1%)	0.86 (0.66-1.12)	0%	0
Continent	Europe	8 (18, 19, 21, 45-49)	18930	109/2974 (3.6%)	858/15956 (5.3%)	0.42 (0.25-0.69)	62%	0.22
	Asia	2 (22, 42)	979	32/498 (6.4%)	68/481 (14.1%)	0.40 (0.15-1.11)	0%	0
Continent 2	Asia	2 (22, 42)	979	32/498 (6.4%)	68/481 (14.1%)	0.40 (0.15-1.11)	0%	0
	Italy	4 (18, 21, 47, 49)	1107	10/543 (1.8%)	40/564 (7%)	0.34 (0.18-0.64)	0%	0
	Rest of Europe	4 (19, 45, 46, 48)	17748	99/2406 (4.1%)	817/15342 (5.3%)	0.48 (0.17-1.35)	71%	0.30
Age	Mean age >35	4 (42, 47-49)	1587	22/795 (2.7%)	64/792 (8%)	0.33 (0.21-0.53)	0%	0
	Mean age ≤35	2 (21, 22)	420	23/227 (10.1%)	45/198 (22.7%)	0.41 (0.03-5.13)	0%	0

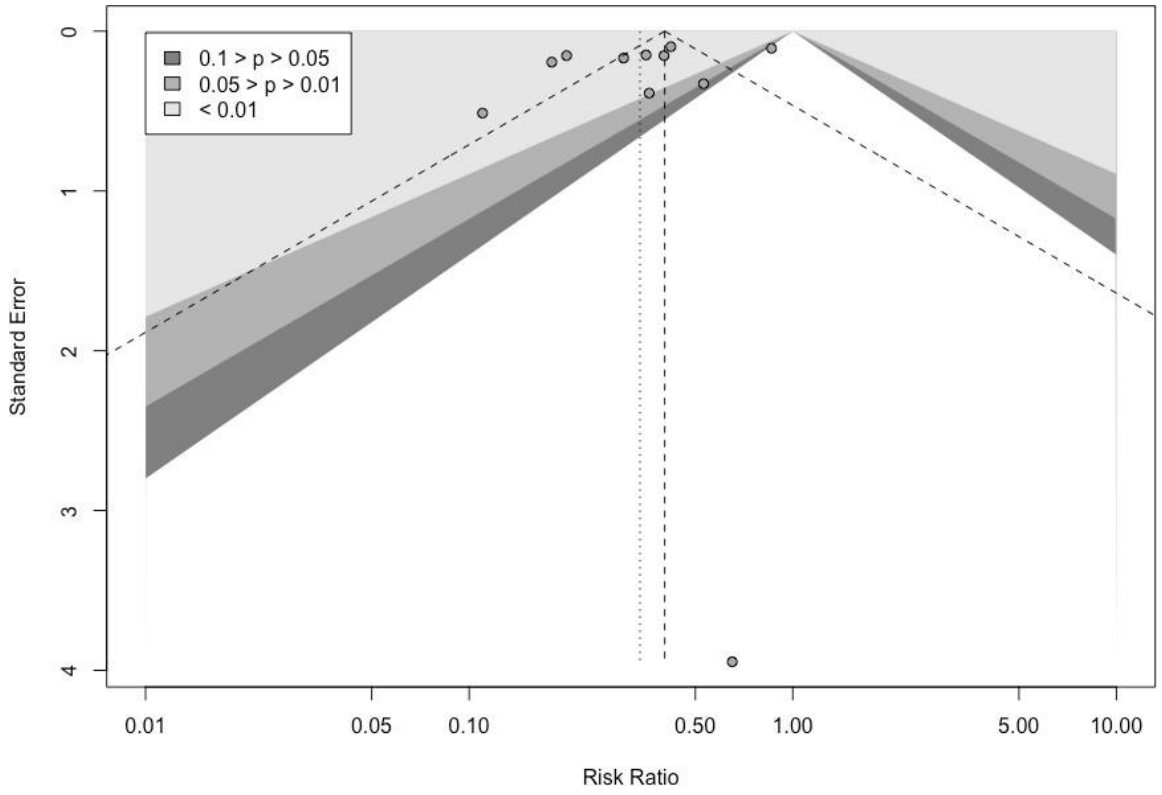
	Unknown mean age	5 (18, 19, 44-46)	17902	96/2450 (3.9%)	817/15452 (5.2%)	0.55 (0.27-1.14)	41%	0.19
Follow-up duration	Median ≤24 months	2 (22, 48)	507	28/291 (9.6%)	53/216 (24.5%)	0.33 (0-28.56)	47%	0.13
	Median >24 months	7 (18, 19, 21, 42, 45, 47, 49)	19214	106/3080 (3.4%)	866/16134 (5.4%)	0.44 (0.26-0.73)	61%	0.19
Study design	RCT	2 (21, 22)	420	23/227 (9.2%)	45/193 (23.3%)	0.41 (0.03-5.13)	0%	0
	Observational	9 (18, 19, 42, 44-49)	19489	118/3245 (3.6%)	881/16244 (5.4%)	0.43 (0.29-0.64)	60%	0.18

CIN: cervical intraepithelial neoplasia, RR: risk ratio, 95% CI: 95% confidence interval, MH: Mantel-Haenszel, RCT: randomised controlled trial
*Adjusted data were used when available

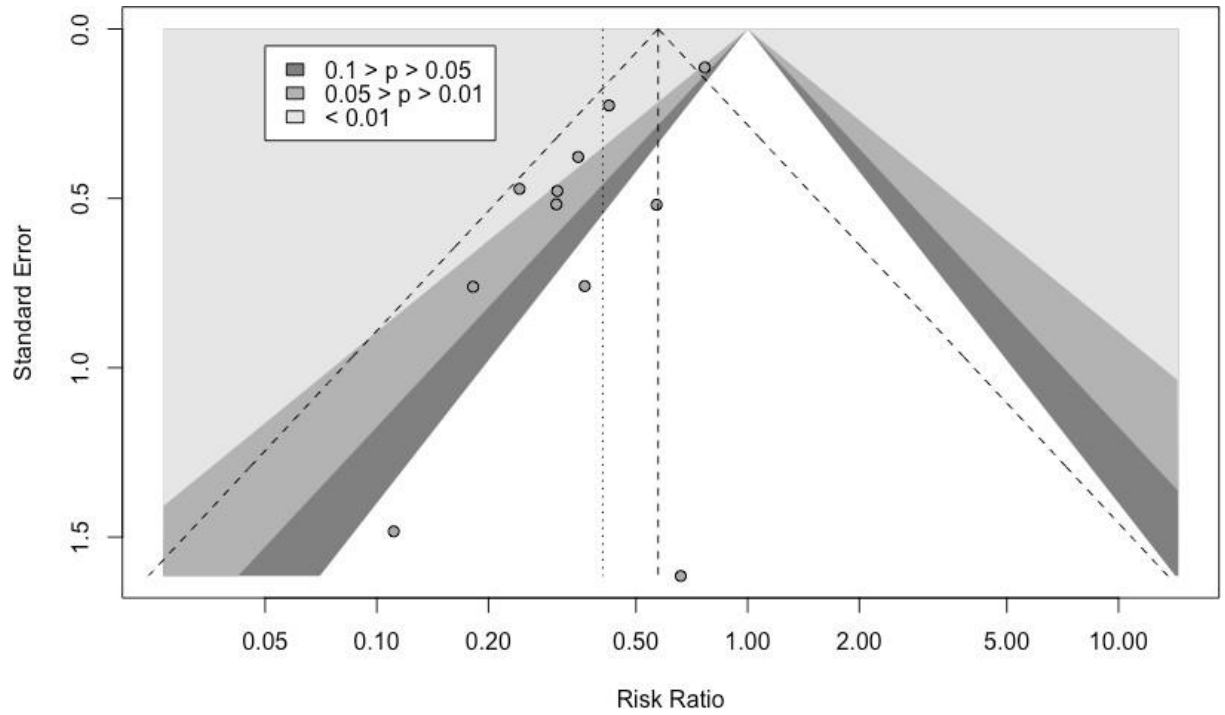
SUPPLEMENTARY FIGURES

Figure S1. Contour enhanced funnel plot of studies examining CIN2+ recurrence for the assessment of publication bias (RCTs and observational studies) using a. adjusted data and b. unadjusted data. The study-specific risk ratios are plotted against their corresponding standard errors. The dashed vertical line represents the summary effect obtained by the fixed effect meta-analysis model, whereas the dotted vertical line corresponds to the summary effect estimated in a random effects model. The pseudo 95% confidence limits illustrate the expected 95% confidence interval about the summary fixed-effect estimate. Contours of statistical significance are overlaid on the funnel plot to facilitate whether the areas where studies exist are areas of statistical significance, and hence detect publication bias due to suppression of non-significant results. Different grey levels are used to distinguish the contours. The unshaded white region in the middle corresponds to p-values greater than 0.10, the dark grey-shaded region corresponds to p-values between 0.10 and 0.05, the medium grey-shaded region corresponds to p-values between 0.05 and 0.01, and the region outside of the funnel corresponds to p-values below 0.01.

a.



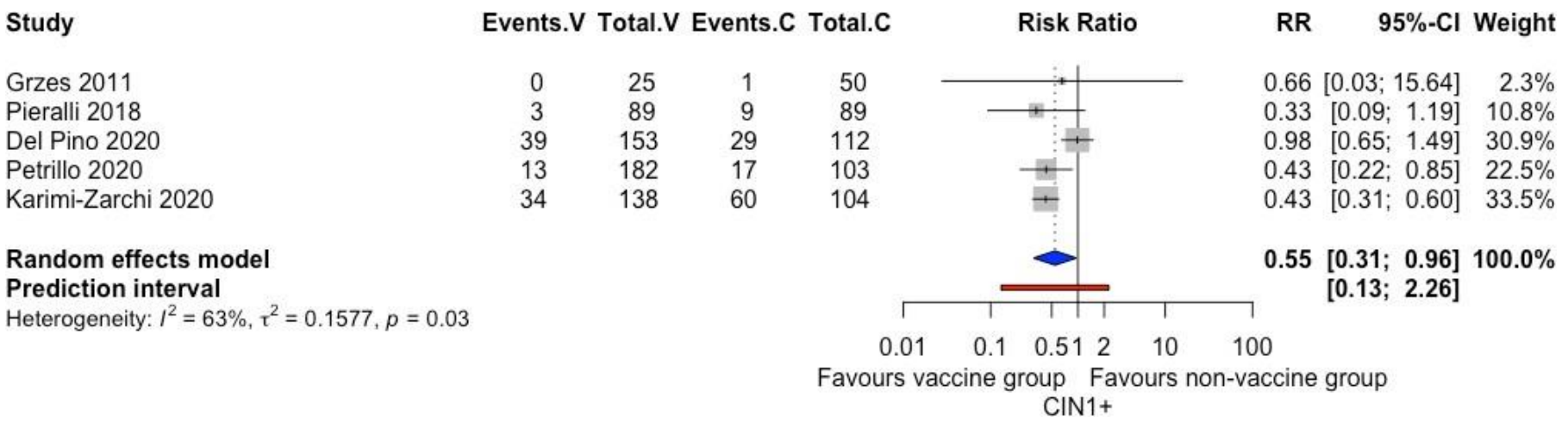
b.



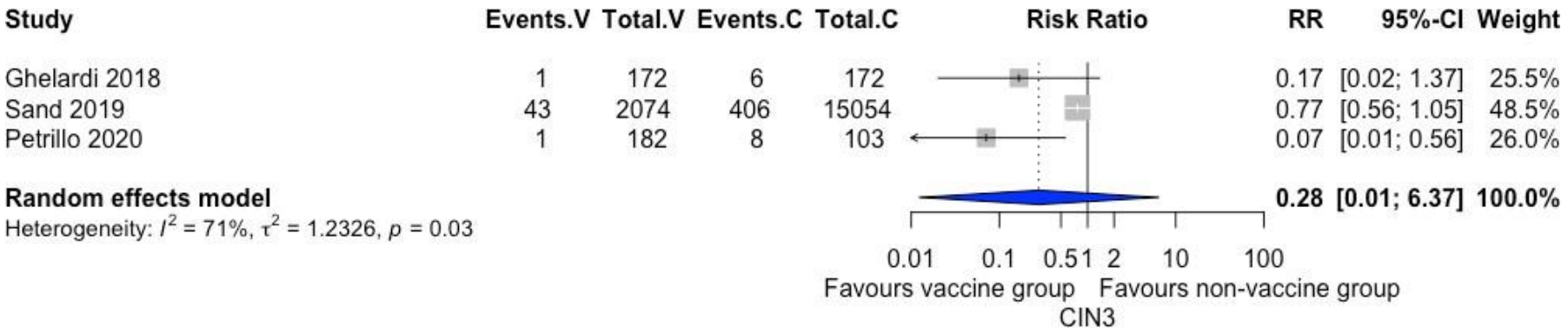
Although asymmetry was not present in the funnel plot when using adjusted data (Figure S1a), it was noticed with the unadjusted data reflecting the possibility of publication bias (Figure S1b). Additionally, evidence of small-study effects was observed when using only unadjusted data based on Egger's statistic (p= 0.004). The selection model for this analysis showed a correlation coefficient = -0.69 (-0.86, -0.41) reflecting the belief that the propensity for publication was associated with the observed effect size.

Figure S2. Forest plots demonstrating the effect of HPV vaccination on the recurrence rates of a) CIN1+ b) CIN3 c) CIN2 d) CIN1 e) VIN/VaIN2+ after local surgical treatment for genital HPV-related disease (RCTs and observational studies).

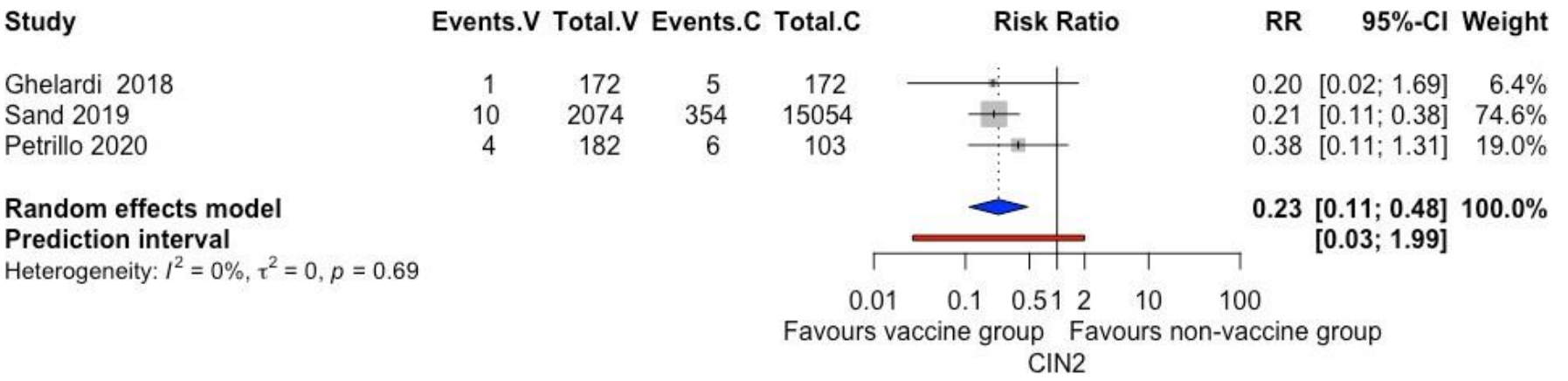
a. CIN1+ recurrence



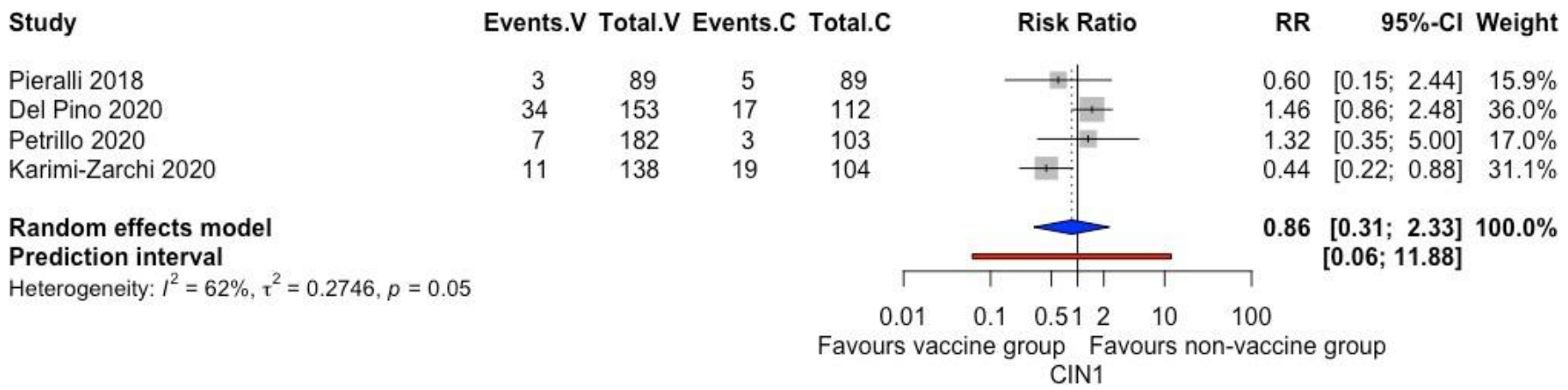
b. CIN3 recurrence



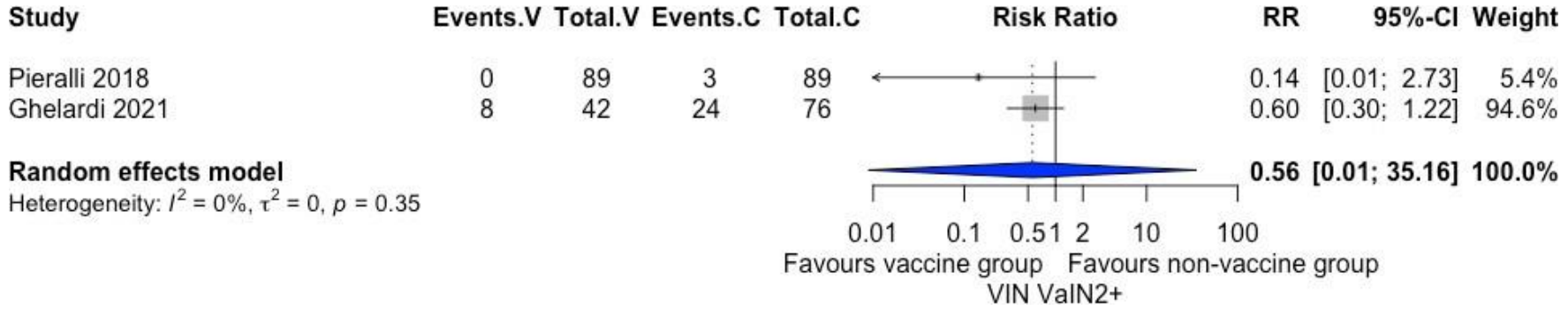
c. CIN2 recurrence



d. CIN1 recurrence



e. VIN/VaIN2+ recurrence



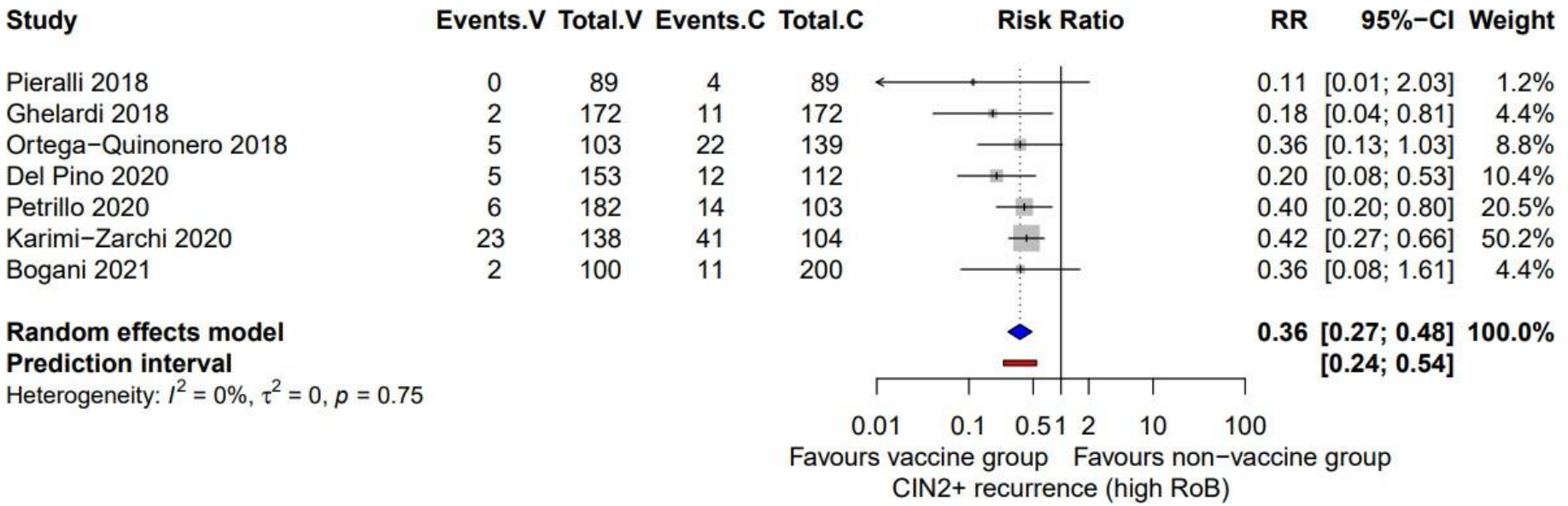
CI: confidence interval, CIN: cervical intraepithelial neoplasia, RCTs: randomised controlled trials, RR: risk ratio, VIN/VaIN: vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia

*All studies included an intervention (vaccination) and a control (no vaccination) group.

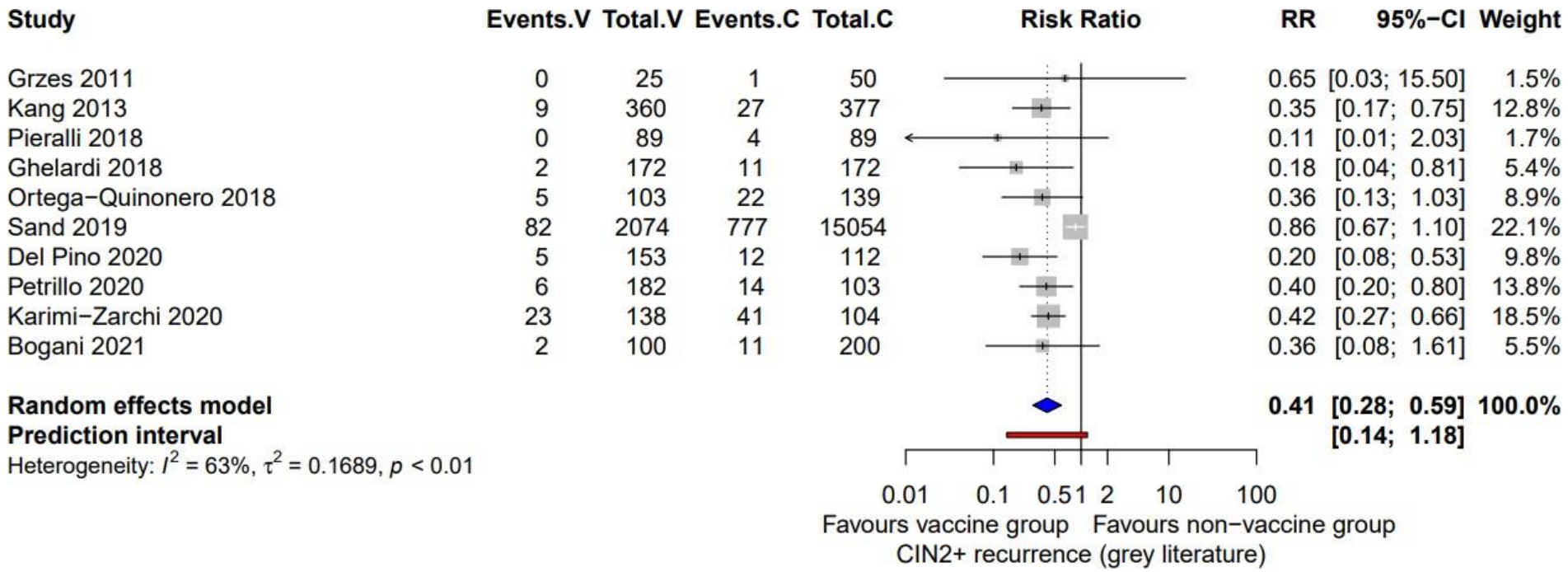
**Adjusted data were used when available

Figure S3. Forest plots demonstrating the sensitivity analyses for the primary outcome (CIN2+ recurrence after local surgical treatment) excluding a) studies with high risk of bias b) studies retrieved from grey literature c) studies with high attrition rate (>10%) d) studies that did not use histopathological confirmation for the diagnosis of the outcome e) studies with high percentage (>75%) of CIN3 cases before treatment f) using the random effect meta-analysis model, g) using only unadjusted data and h) using the GLMM model (approximate likelihood) (RCTs and observational studies).

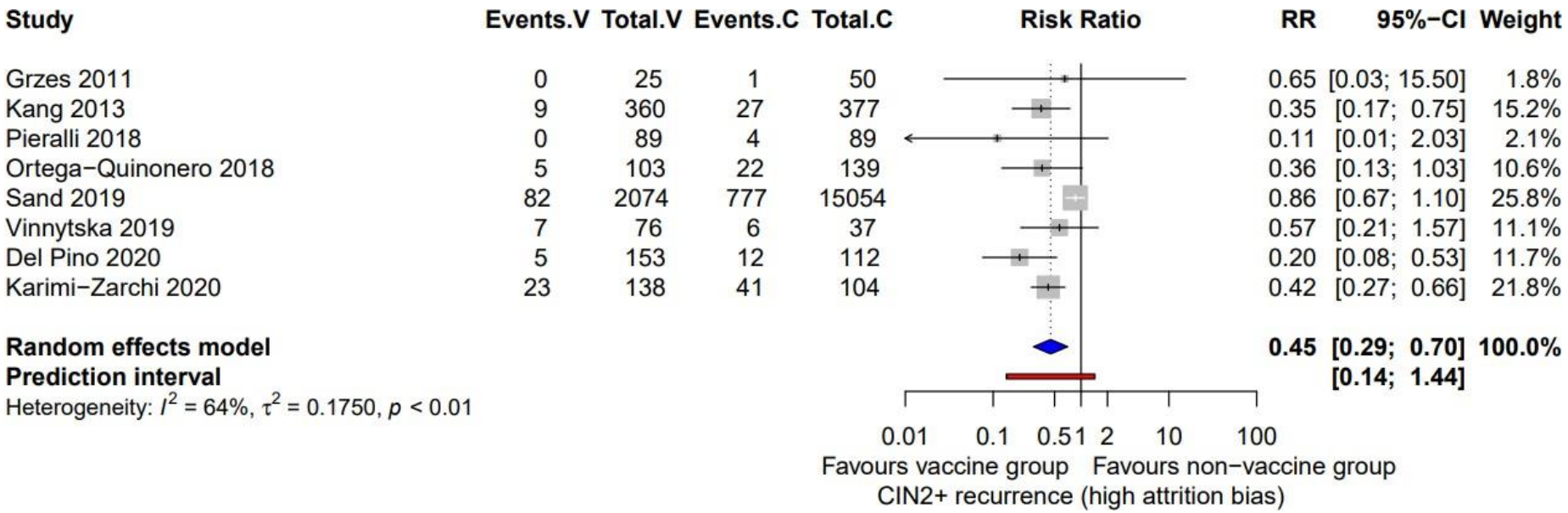
a. CIN2+ recurrence excluding studies with high risk of bias



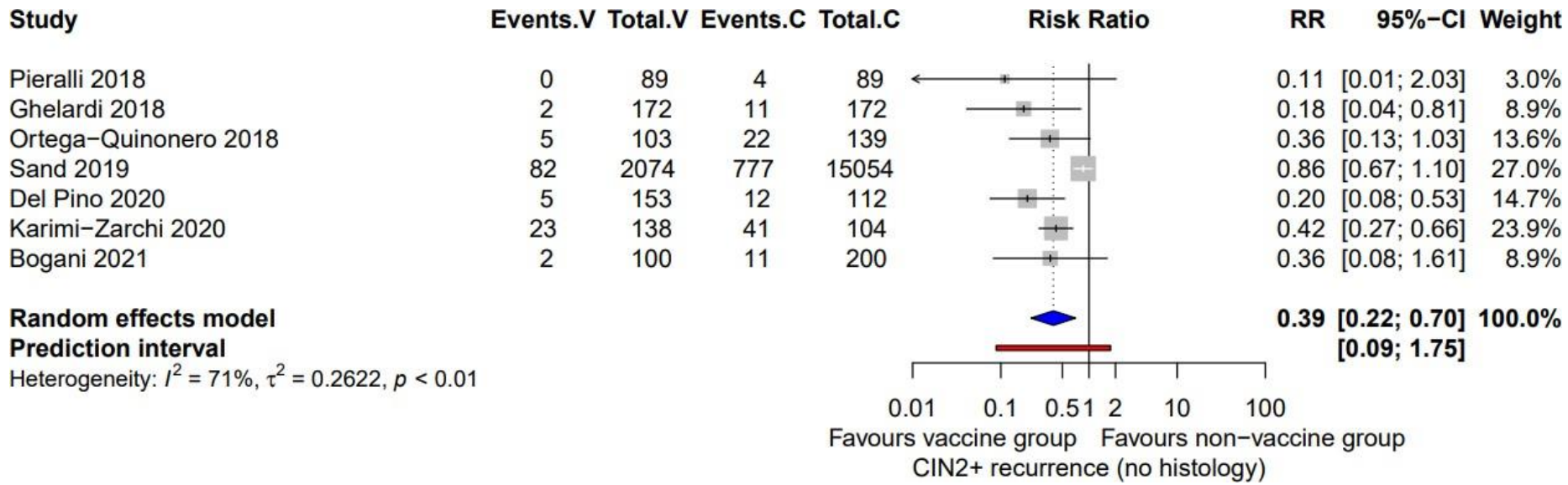
b. CIN2+ recurrence excluding studies retrieved from grey literature



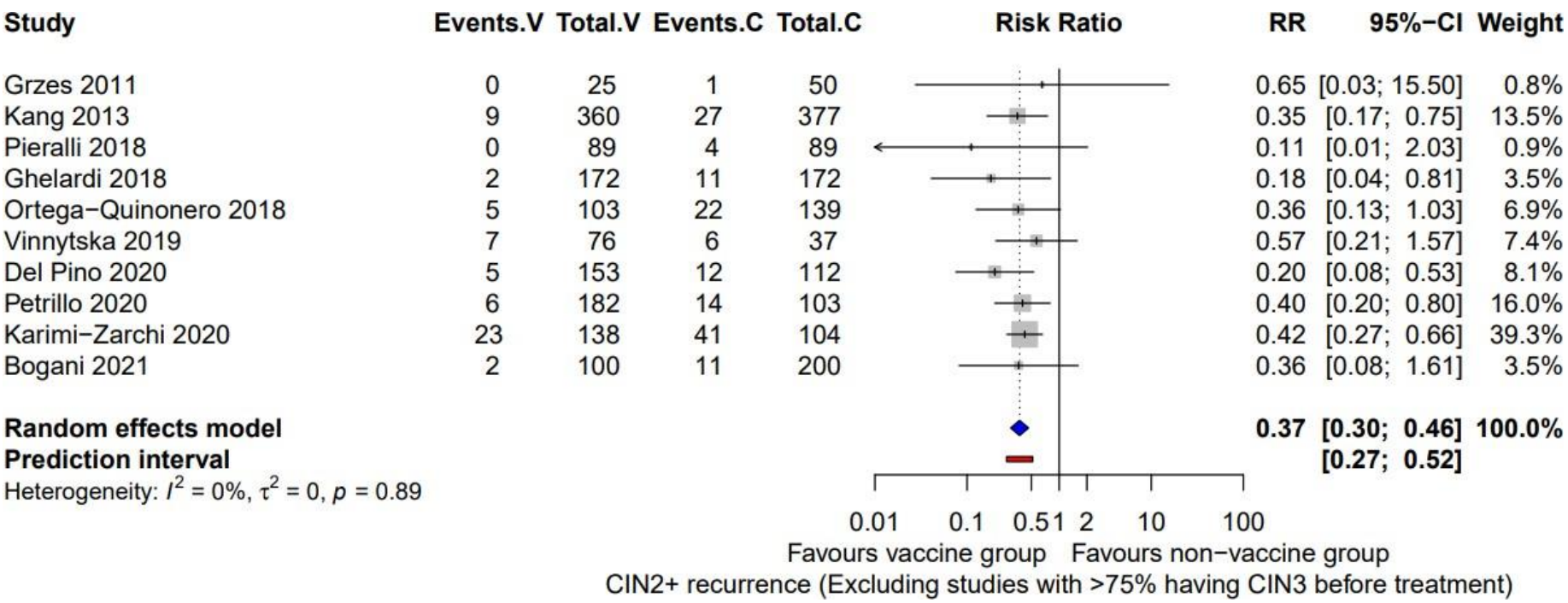
c. CIN2+ recurrence excluding studies with high attrition rate (>10%)



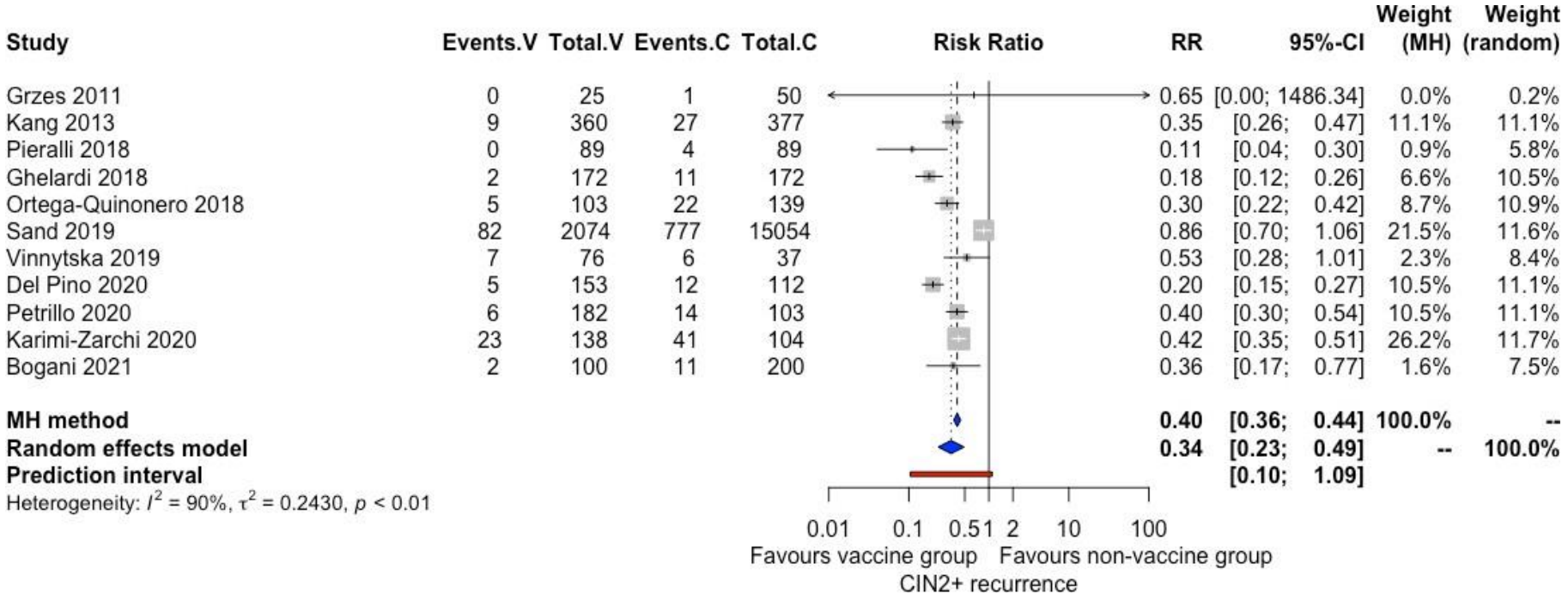
d. CIN2+ recurrence excluding studies that did not use histopathology for the confirmation of diagnosis



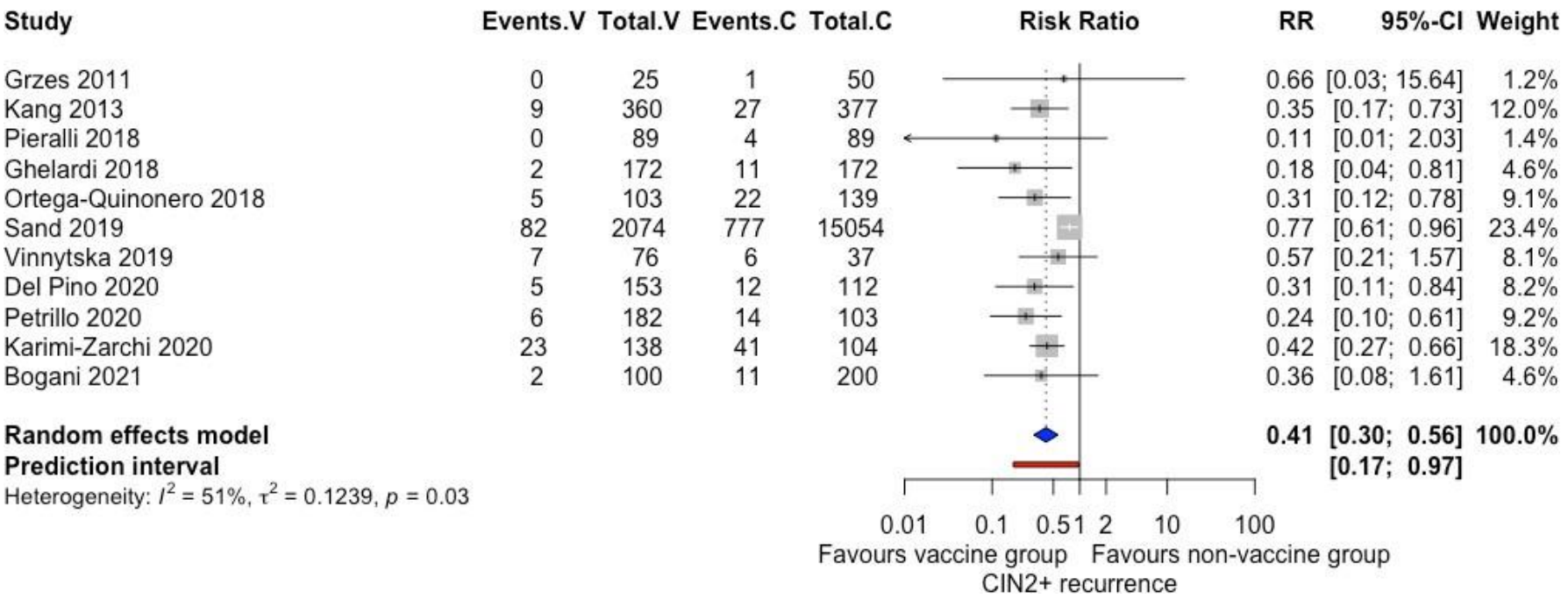
e. CIN2+ recurrence excluding studies with high percentage (>75%) of CIN3 cases before treatment



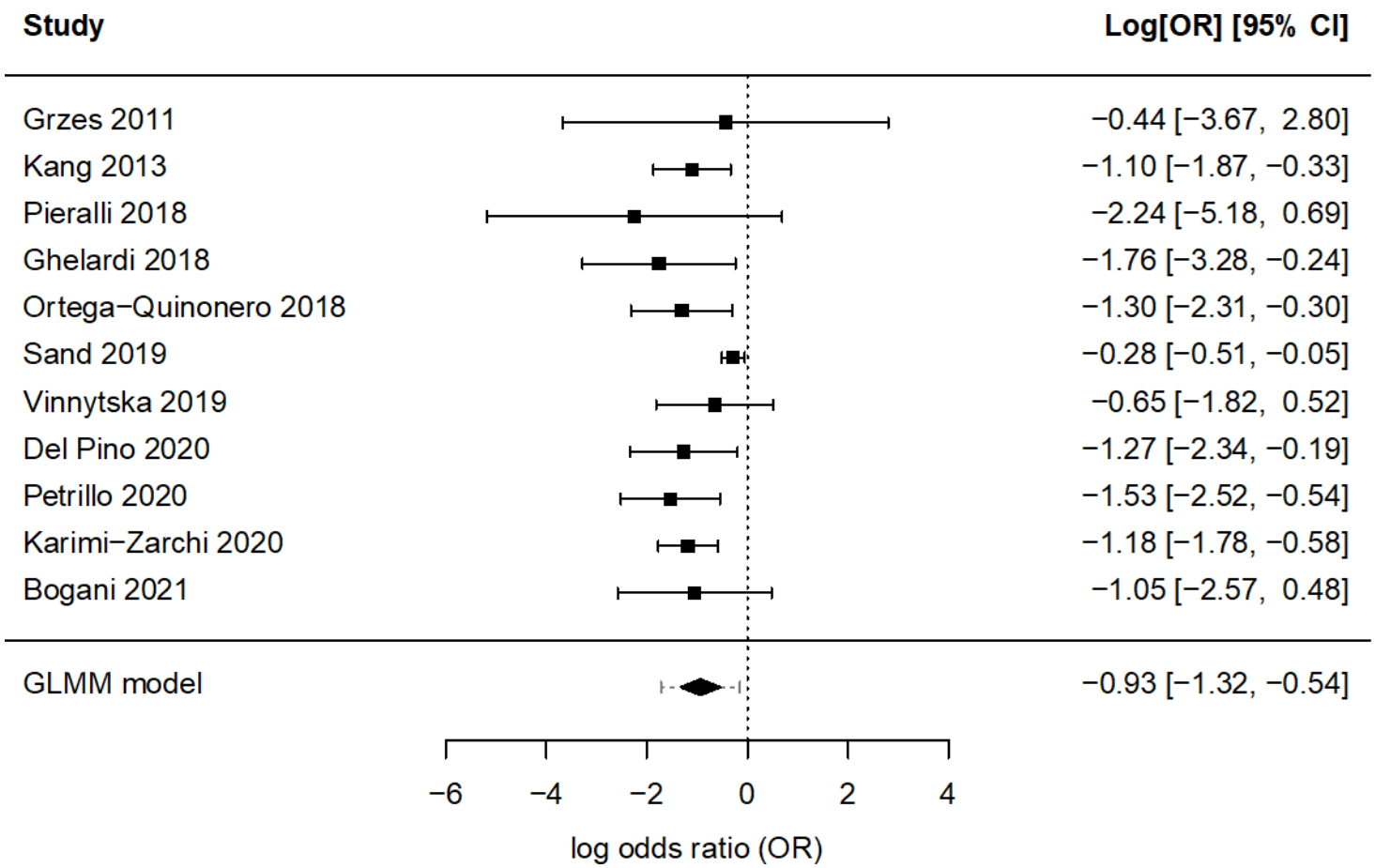
f. CIN2+ recurrence using fixed effect meta-analysis model



g. CIN2+ recurrence using only unadjusted data



h. CIN2+ recurrence using the GLMM model (approximate likelihood)



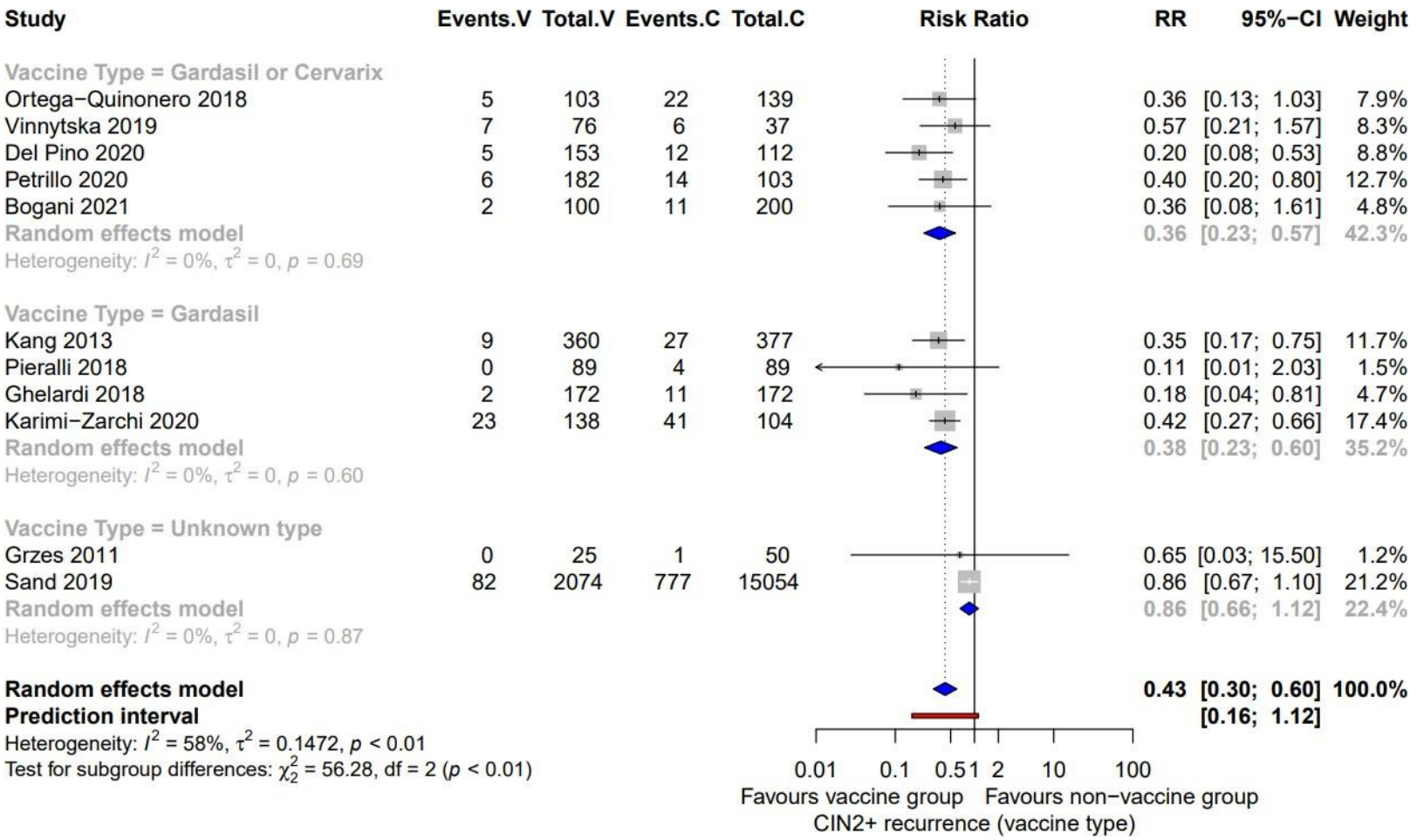
CI: confidence interval, CIN: cervical intraepithelial neoplasia, GLMM: Generalized linear mixed models, RCTs: randomised controlled trials, RR: risk ratio

*All studies included an intervention (vaccination) and a control (no vaccination) group.

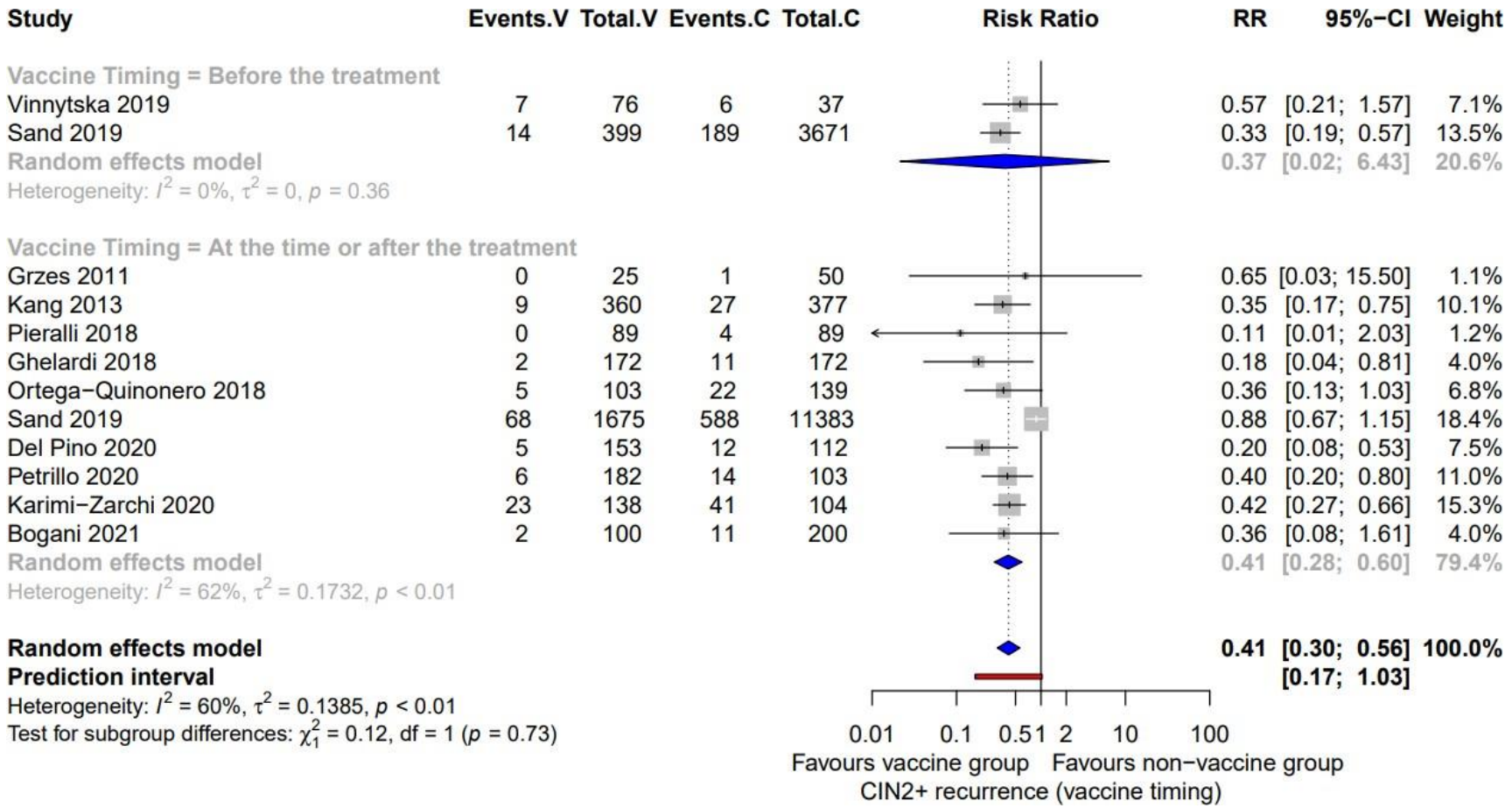
**Adjusted data were used when available apart from S4h.

Figure S4. Forest plots demonstrating the subgroup analyses for the primary outcome (CIN2+ recurrence after local surgical treatment) based on a) vaccine type b) vaccination timing and c) continent (Asia vs Europe) d) continent (Asia vs Italy vs Rest of Europe) e) mean age of the included population f) median follow-up duration after surgical treatment (RCTs and observational studies).

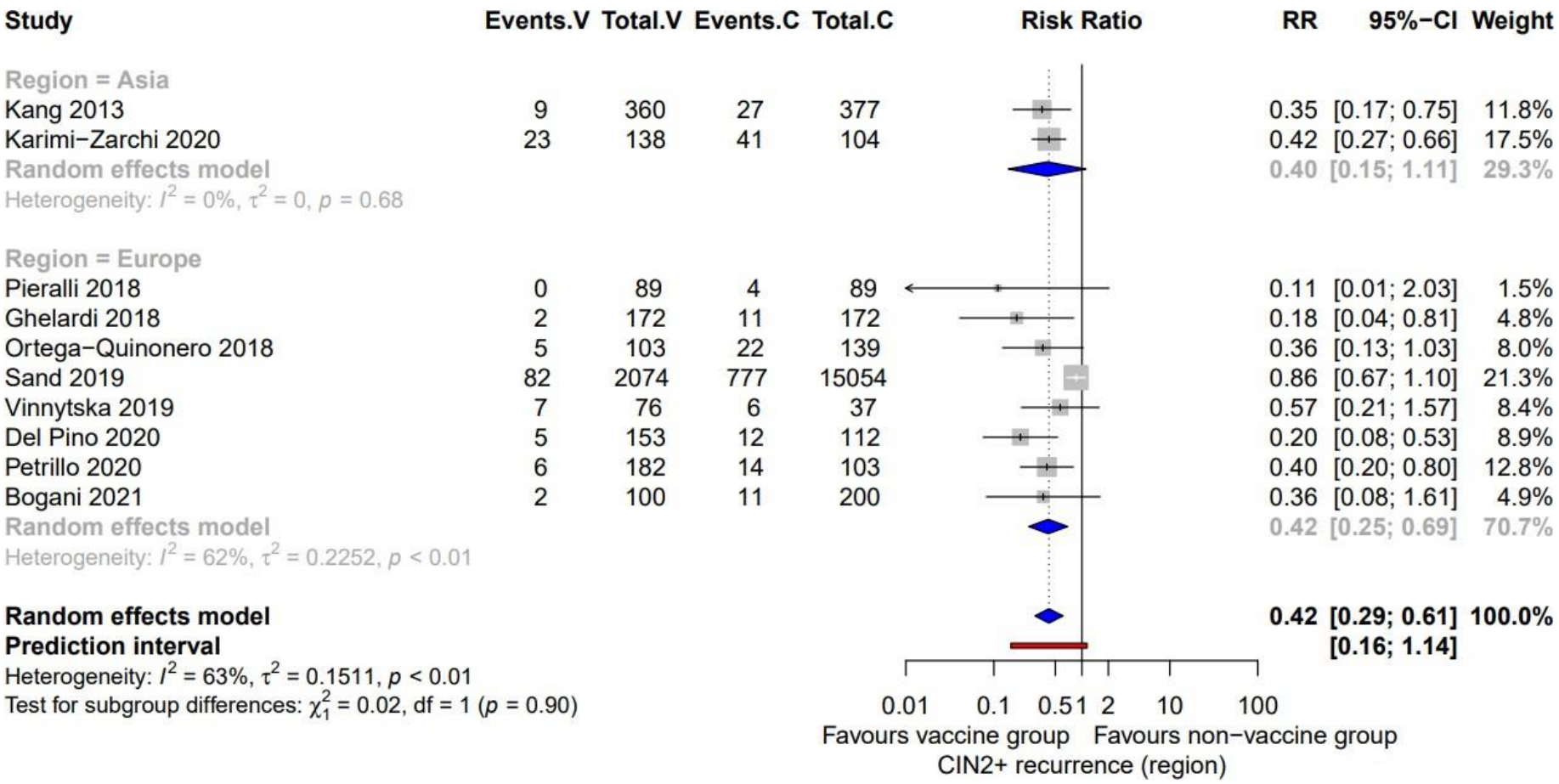
a. CIN2+ recurrence based on vaccine type



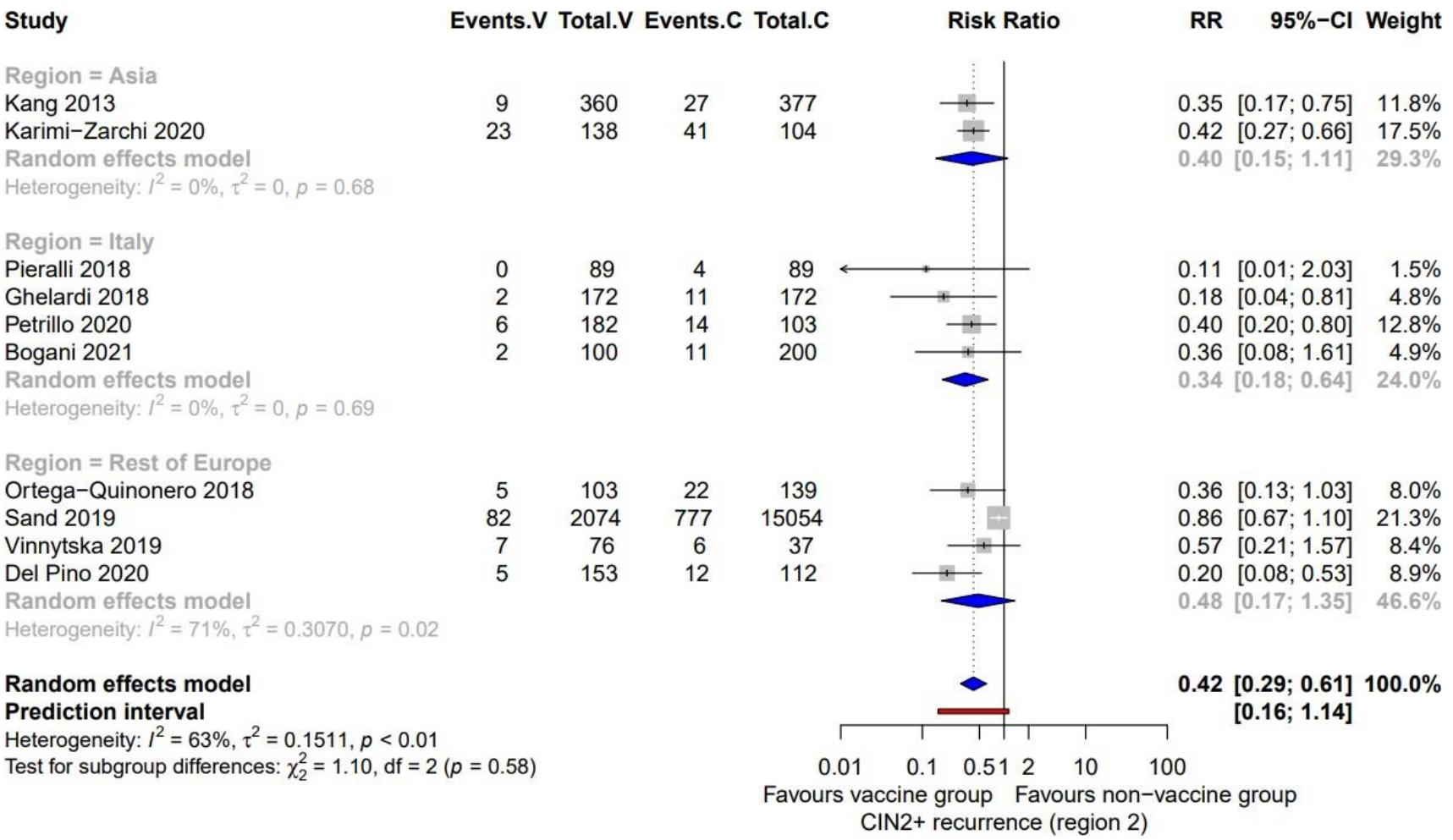
b. CIN2+ recurrence based on vaccination timing



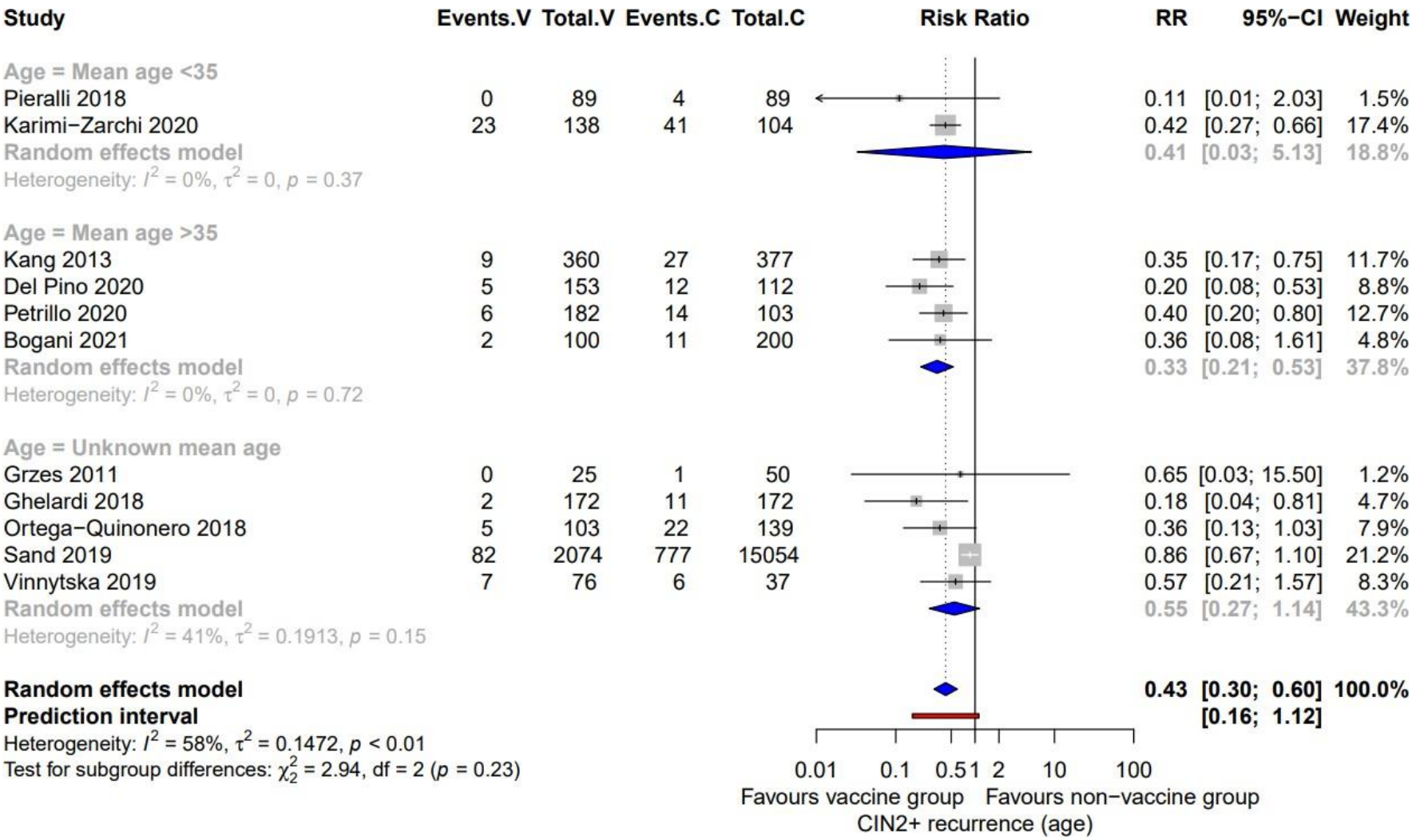
c. CIN2+ recurrence based on continent



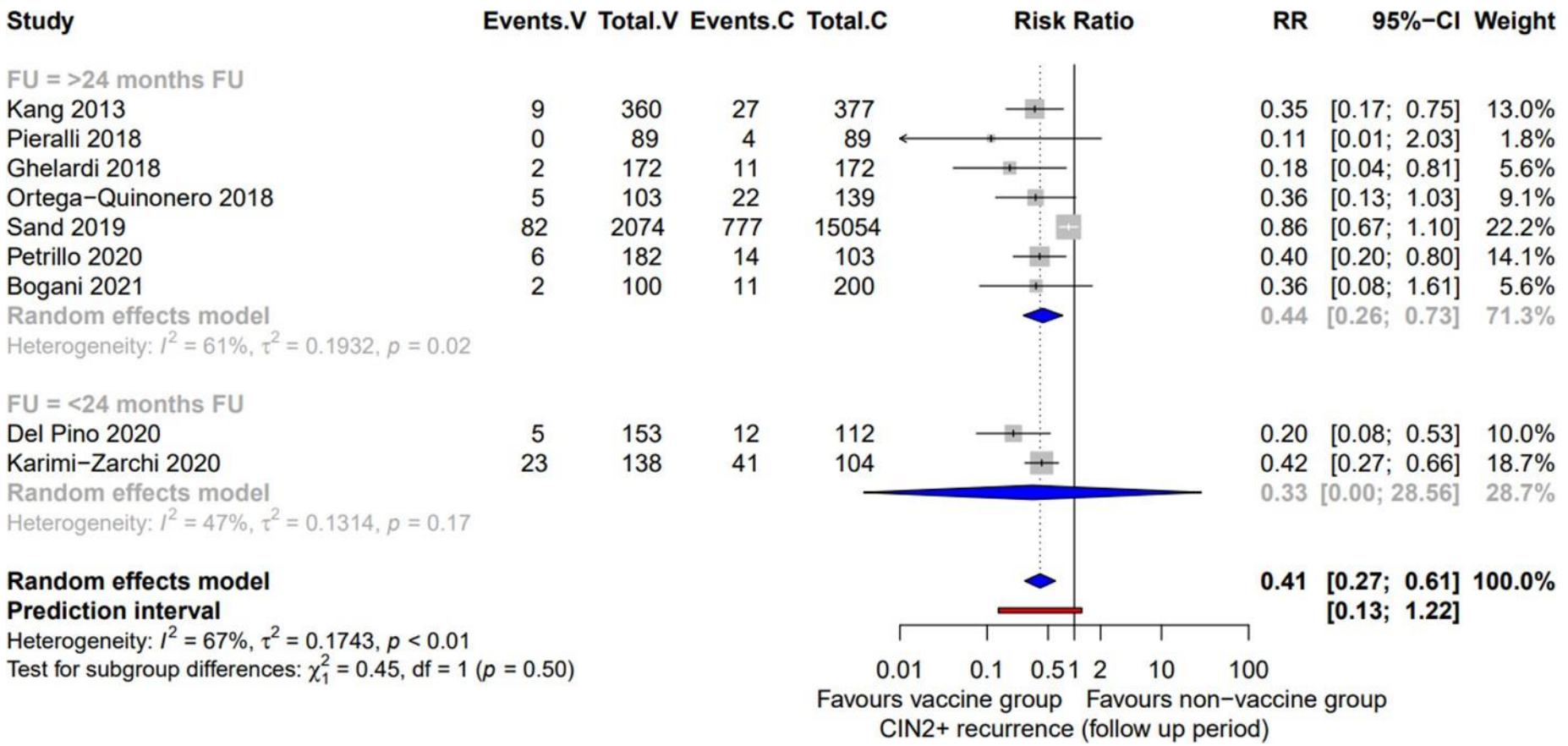
d. CIN2+ recurrence based on continent



e. CIN2+ recurrence based on mean age of the included population



f. CIN2+ recurrence based on the median follow-up duration



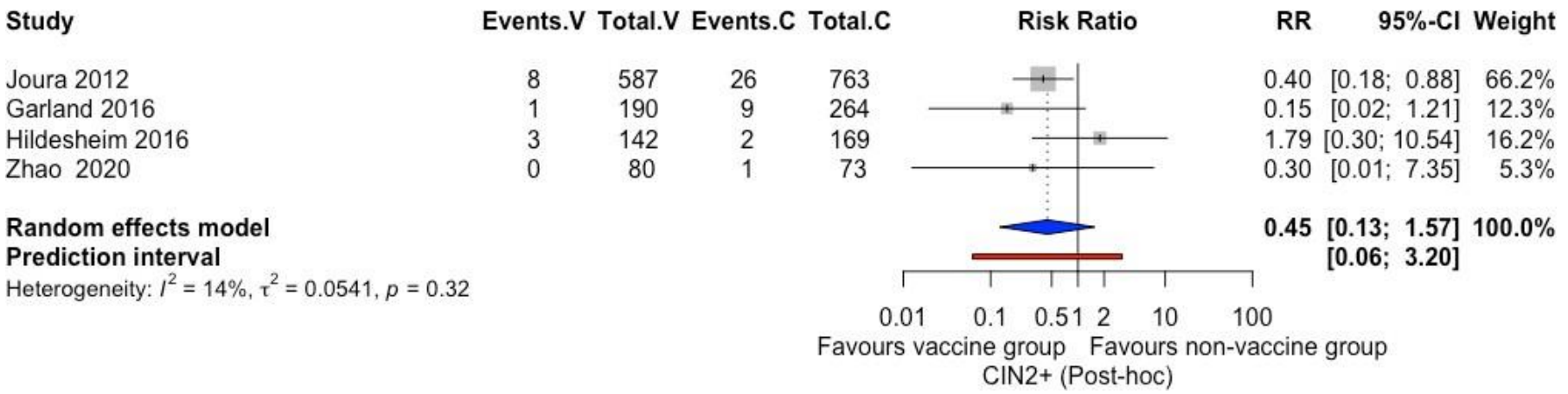
CI: confidence interval, CIN: cervical intraepithelial neoplasia, FU: follow-up period, RCTs: randomised controlled trials, RR: risk ratio

*All studies included an intervention (vaccination) and a control (no vaccination) group.

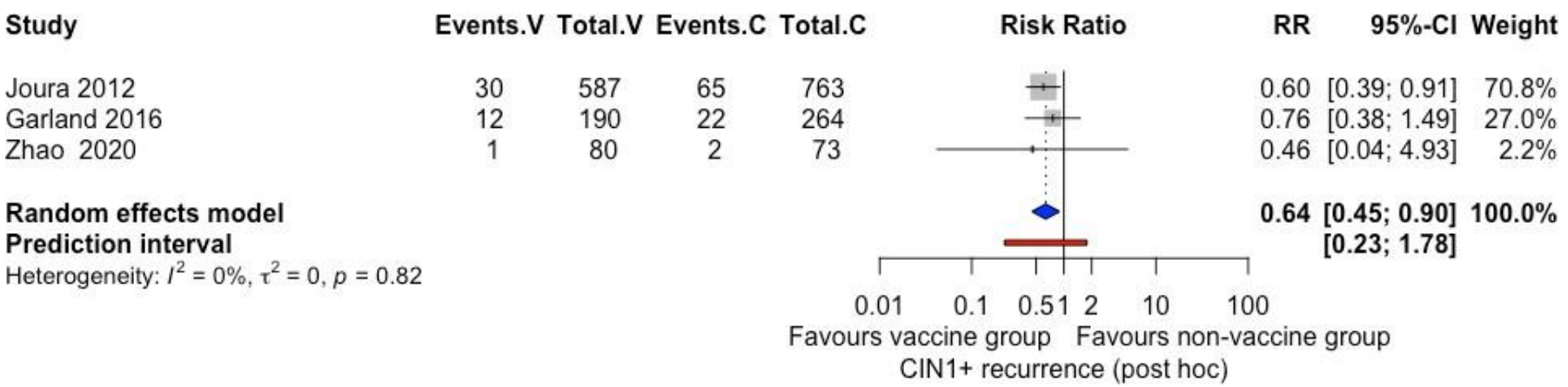
**Adjusted data were used when available.

Figure S5. Forest plots demonstrating the effect of HPV vaccination on the recurrence rates of a) CIN2+ b) CIN1+ c) CIN3 d) CIN2 e) CIN1 f) CIN2+ HPV 16-18 related g) CIN1+ HPV 16-18 related h) Abnormal cytology i) VIN/VaIN1+ j) VIN/VaIN2+ after local surgical treatment for genital HPV-related disease (post-hoc analyses of RCTs).

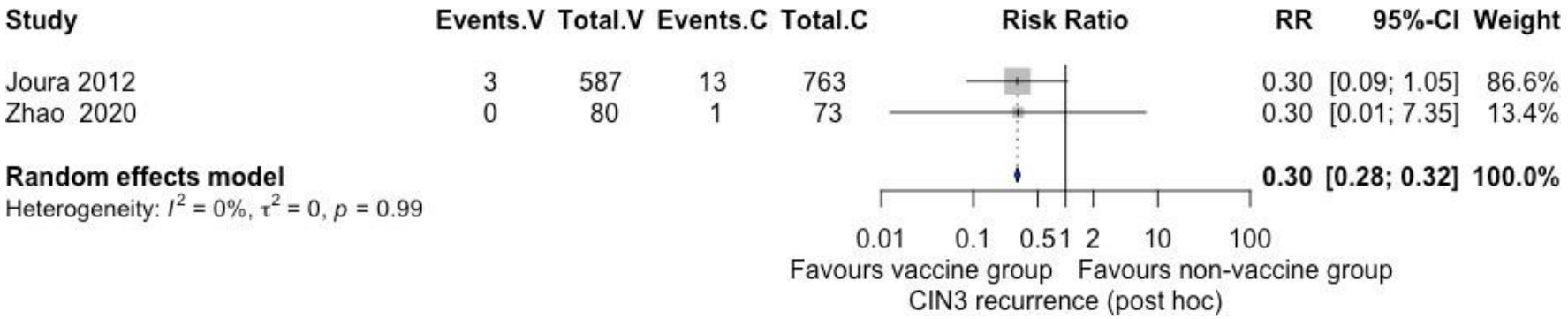
a. CIN2+ recurrence



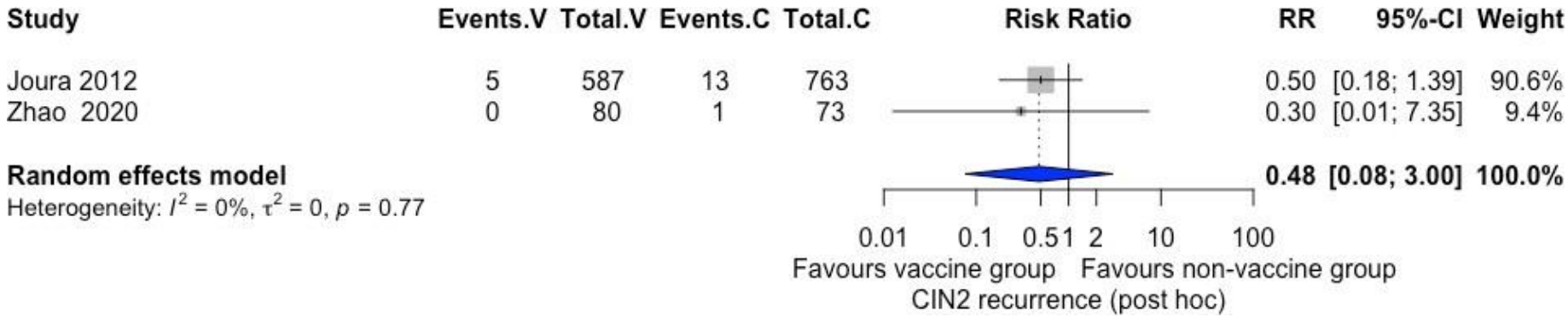
b. CIN1+ recurrence



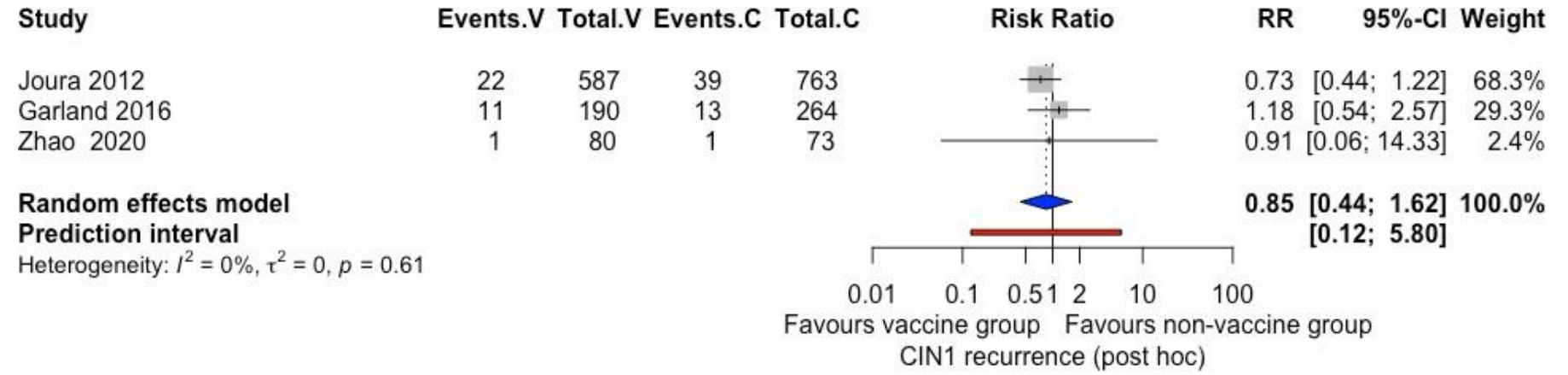
c. CIN3 recurrence



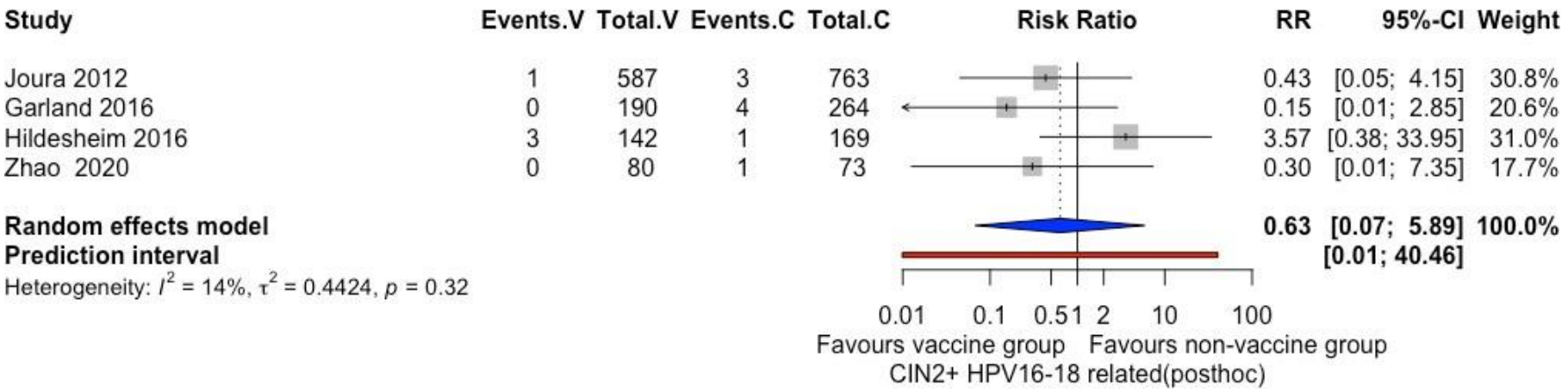
d. CIN2 recurrence



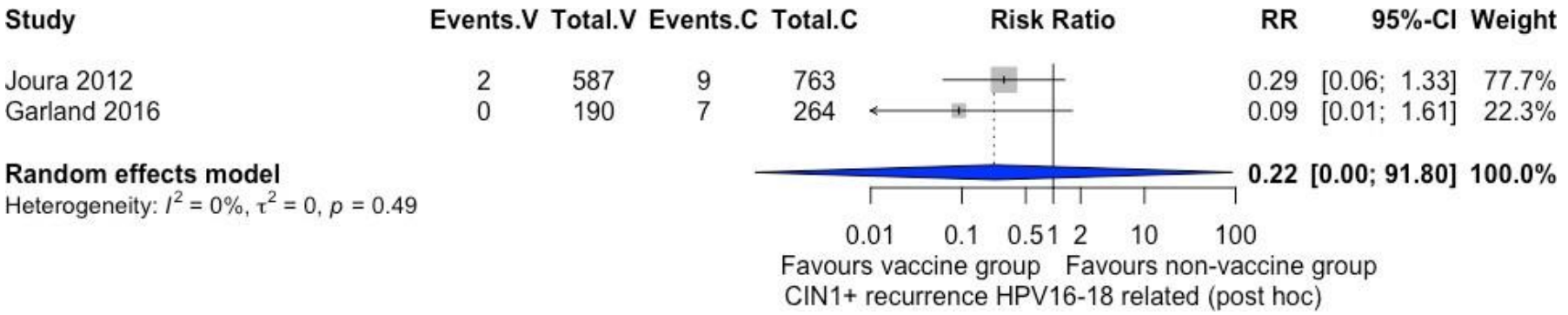
e. CIN1 recurrence



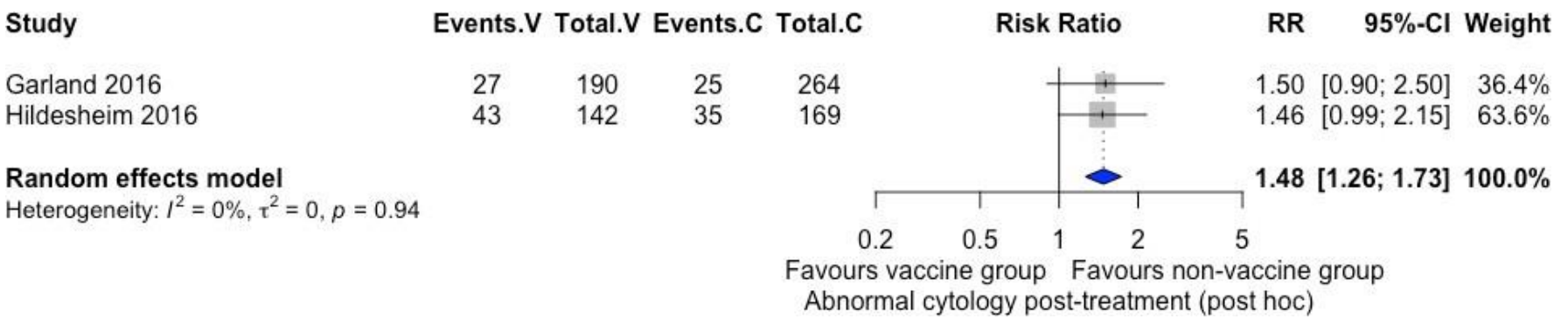
f. CIN2+ HPV 16-18 related recurrence



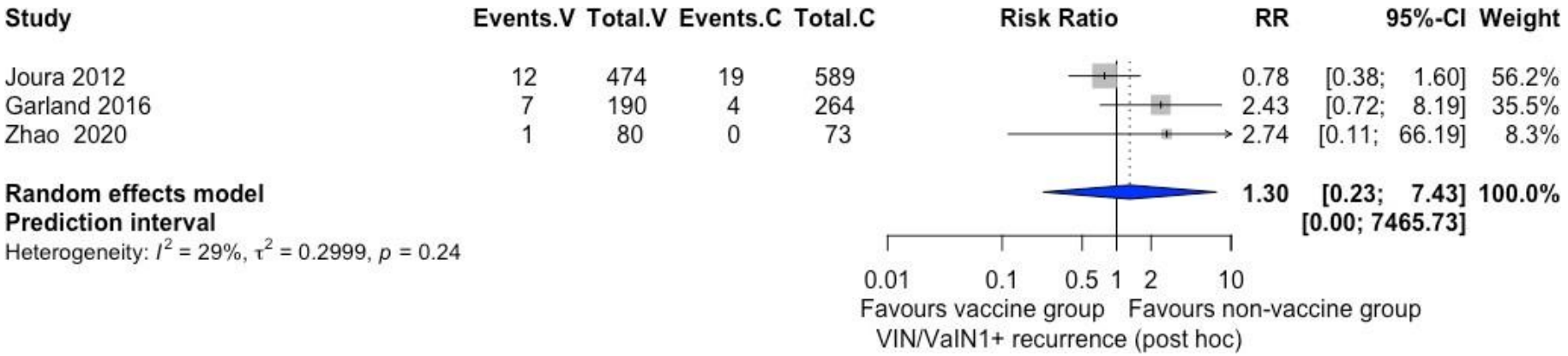
g. CIN1+ HPV 16-18 related recurrence



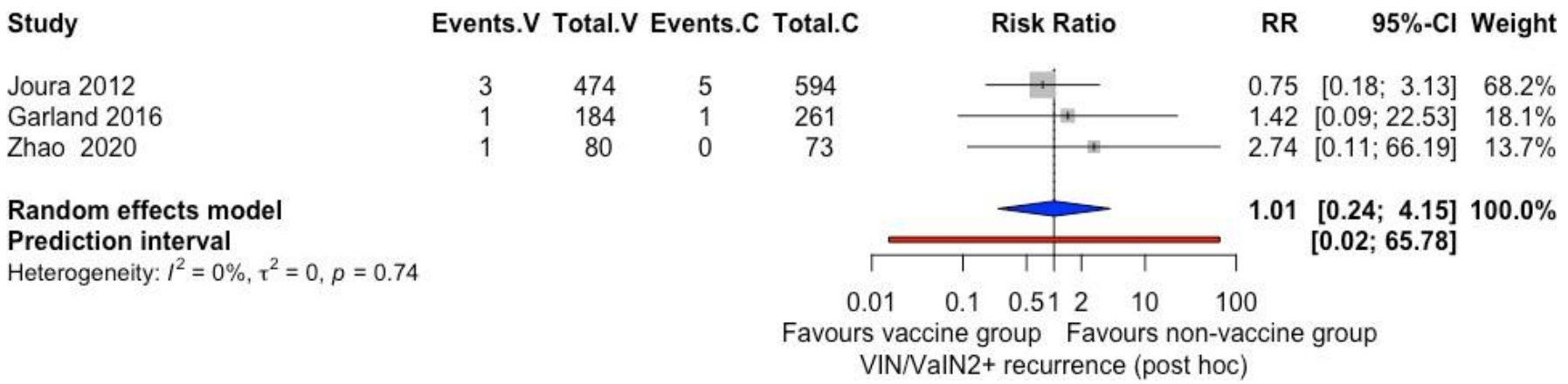
h. Abnormal cytology post treatment



i. VIN/VaIN1+ recurrence



j. VIN/VaIN2+ recurrence

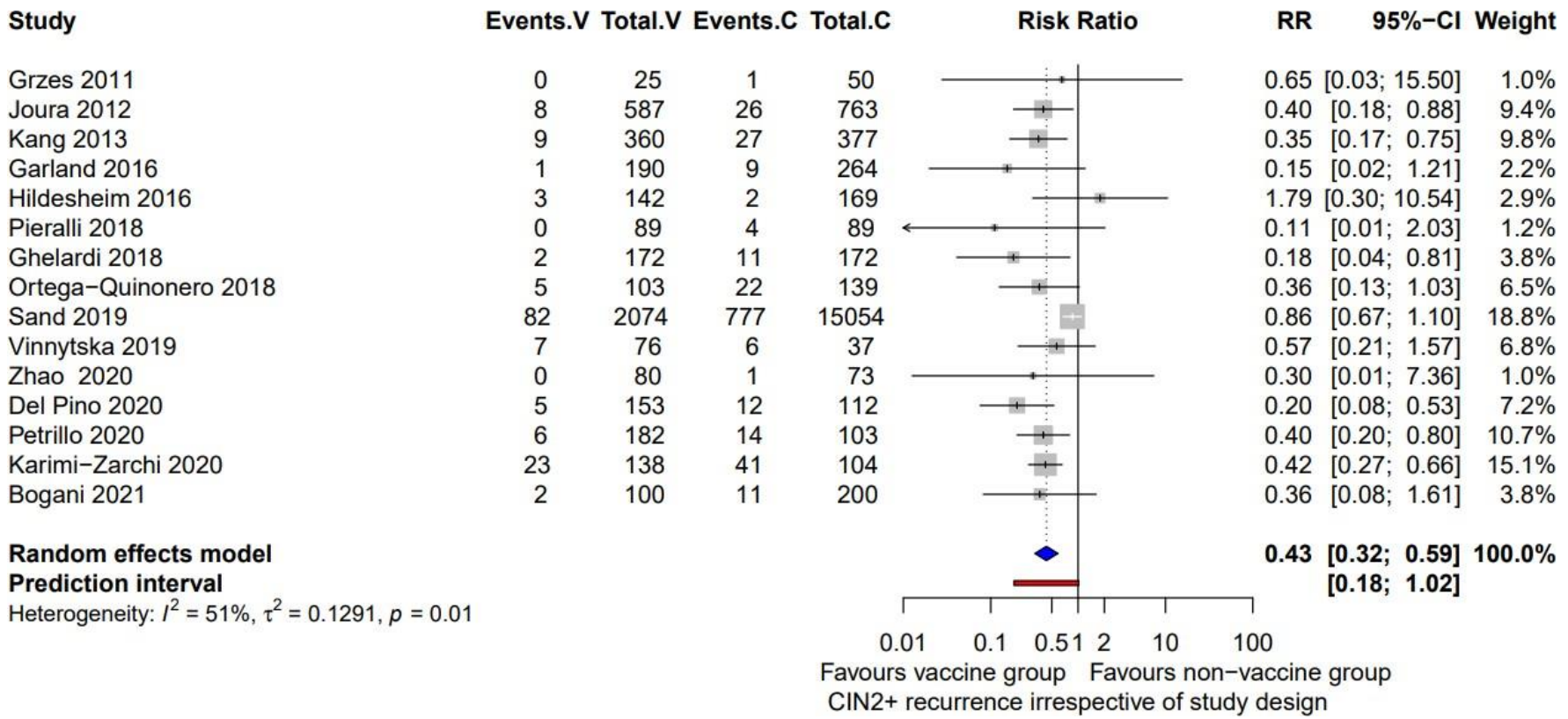


CI: confidence interval, CIN: cervical intraepithelial neoplasia, HPV: human papilloma virus, RCTs: randomised controlled trials, RR: risk ratio, VIN/VaIN: vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia

*All studies included an intervention (vaccination) and a control (placebo) group.

Figure S6. Forest plots assessing CIN2+ recurrence rates between HPV vaccinated and non-vaccinated group after local surgical treatment for CIN irrespective of study design (RCTs, observational studies and post-hoc analyses of RCTs).

a. CIN2+ recurrence irrespective of study design

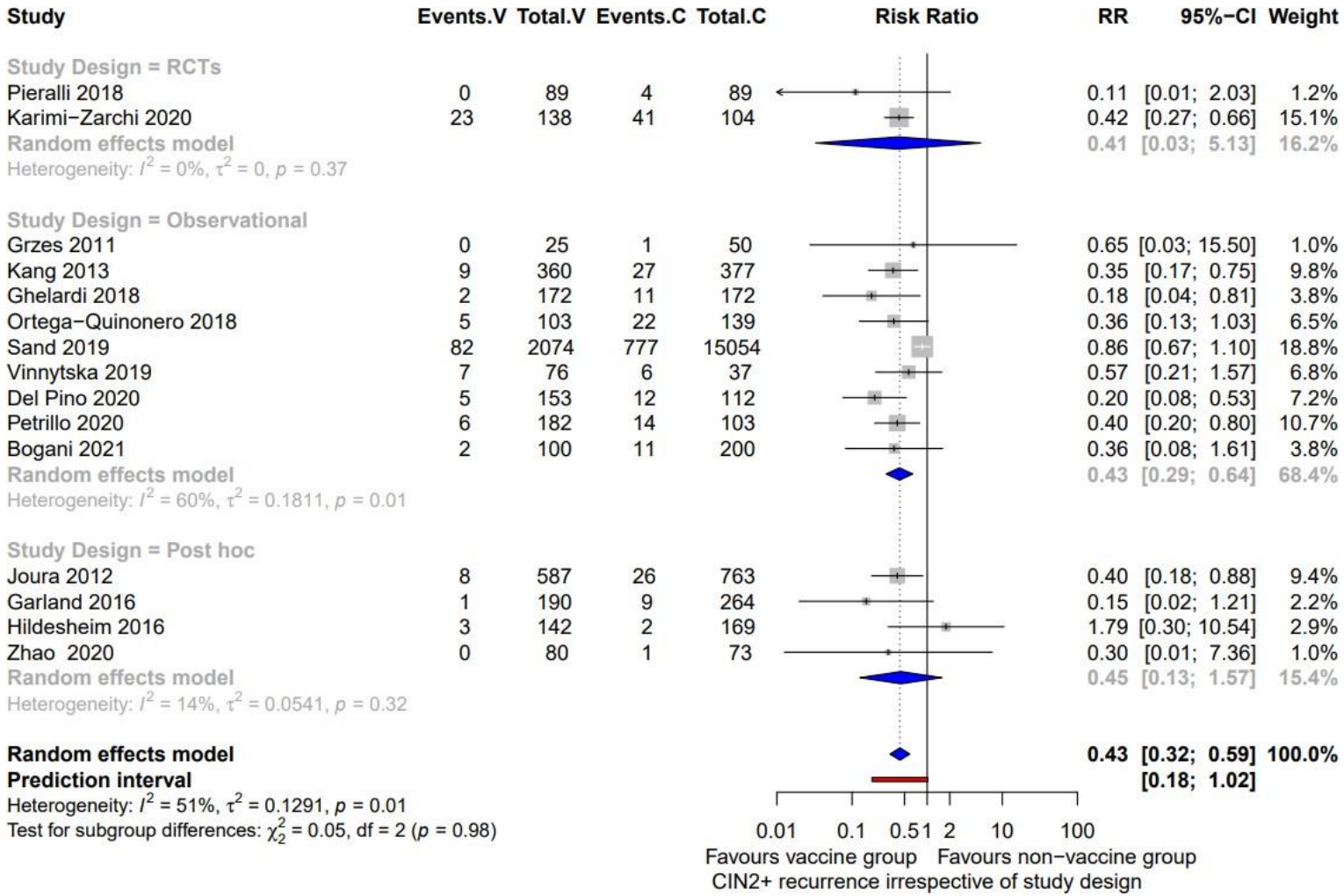


CI: confidence interval, CIN: cervical intraepithelial neoplasia, HPV: human papilloma virus, RCTs: randomised controlled trials, RR: risk ratio, VIN/VaIN: vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia

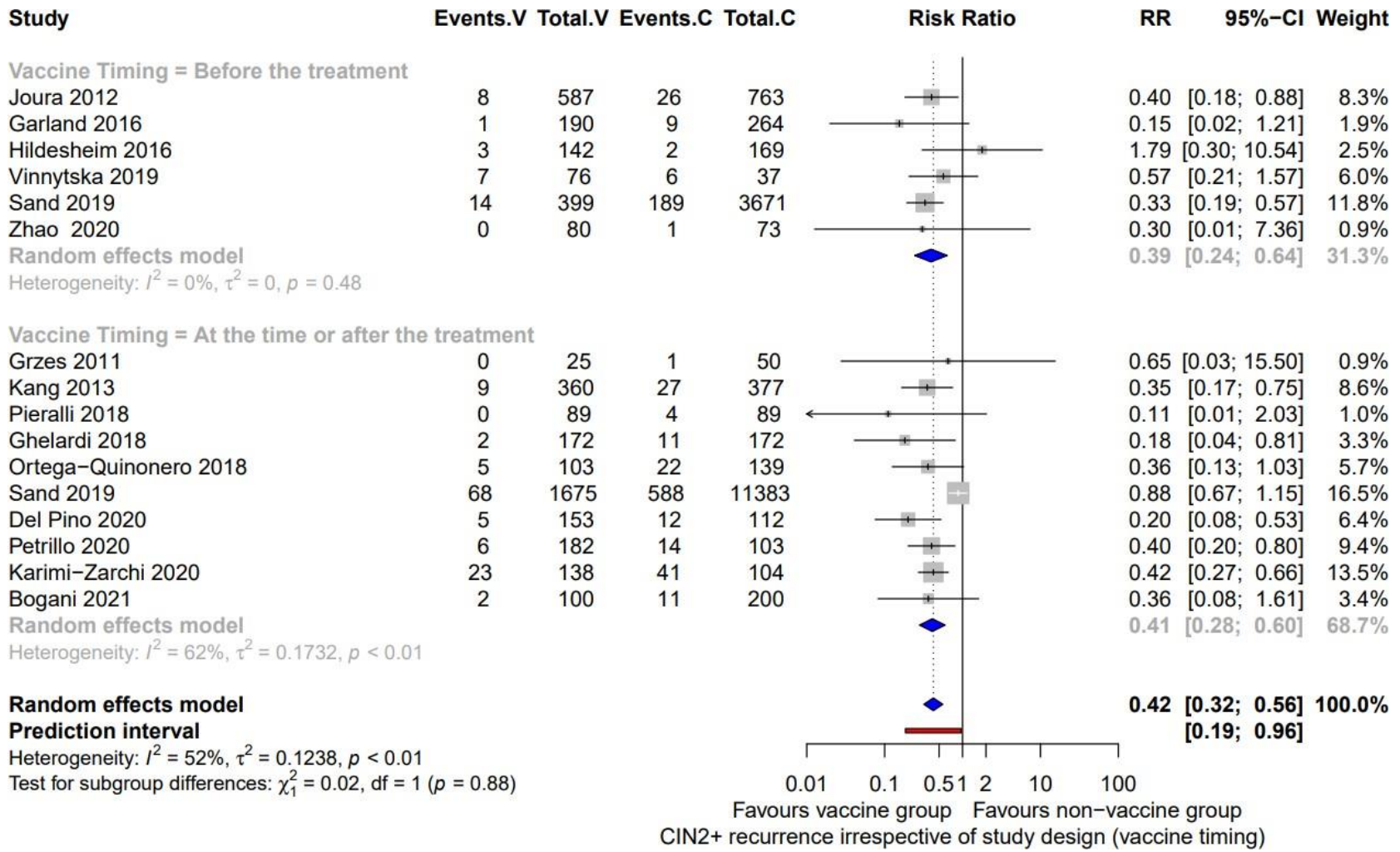
*All studies included an intervention (vaccination) and a control (placebo) group.

Figure S7. Forest plots demonstrating the subgroup analysis for the main outcome (CIN2+ recurrence after local surgical treatment) including all study designs based on a) study design and b) vaccination timing (RCTs, observational studies and post-hoc analyses of RCTs).

a. CIN2+ recurrence based on study design



b. CIN2+ recurrence based on vaccination timing



CI: confidence interval, CIN: cervical intraepithelial neoplasia, HPV: human papilloma virus, RCTs: randomised controlled trials, RR: risk ratio
*All studies included an intervention (vaccination) and a control (placebo) group