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ASSESSMENT

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities of the ECDC NITAG Collaboration, in close cooperation with the European Commission and the European Health and Digital Executive Agency. The commissioning and production of this review was coordinated by Kate Olsson (ECDC) and Karam Adel Ali (ECDC).

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Abbreviations

AEs	Adverse events
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Control group
CoE	Certainty of the evidence
CIN	Cervical intraepithelial neoplasia
CIN 2+	Cervical intraepithelial neoplasia grade 2+
CIN 3+	Cervical intraepithelial neoplasia grade 3+
CI	Confidence interval
CKD	Chronic kidney disease
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EU/mL	ELISA-Unit per millilitre
GMR	Geometric mean ratio
GMT	Geometric mean titre
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCT	Hematopoietic cell transplantation
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
HSCT	Haematological stem cell transplantation
IG	Intervention group
IQR	Inter-quartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
IBD	Inflammatory bowel disease
JIA	Juvenile idiopathic arthritis
LU/mL	Luminex Units per milliliter
MESH	Medical Subject Headings
mMU/mL	MilliMerck Units per milliliter
NA	Not applicable
NR	Not reported
NRSI	Non-randomised study of intervention
OR	Odds ratio
PBNA	Pseudovirion-based neutralization assay
Post allo-HCT	Allogeneic cell transplant
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
RCT	Randomised controlled trial
RD	Risk difference
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Intervention
RR	Risk ratio
RRP	Recurrent Respiratory Papillomatosis
SAEs	Serious adverse events
SD	Standard deviation
SLE	Systemic lupus erythematosus
USA	United States of America
VE	Vaccine efficacy or effectiveness
VIN	Vulvar intraepithelial neoplasia
VIN2+	Vulvar intraepithelial neoplasia grade 2+
VLP	Virus-like particles
WHO	World Health Organization
2vHPV	Bivalent HPV vaccine
4vHPV	Quadrivalent HPV vaccine
9vHPV	Nonavalent HPV vaccine

Executive summary

Background

Cervical cancer is the fourth most common cancer affecting women worldwide. It is caused by persistent infection with oncogenic types of human papillomavirus (HPV). More than 200 types of HPV have been identified and more than 40 types of them infect the genital tract. HPV 16 and 18 are the two primary oncogenic types and responsible for 77% of cervical cancers (i.e. squamous cell carcinoma), and combined with HPV 31, 33, 45, 52 and 58, account for 94.9% of cervical cancers [1-3]. While HPV infections are common and usually resolve without any consequences, persistent infections with high-risk HPV can progress to premalignant glandular or squamous intraepithelial lesions (cervical dysplasia).

HPV vaccination in adolescents is an important measure to prevent cancer [4, 5]. To date, most HPV vaccination programmes target adolescent girls and/or boys, while some countries have extended HPV vaccination catch-up programmes to adults [6]. In Europe, three HPV vaccines are currently approved: bivalent, quadrivalent and nonavalent. All three HPV vaccines include virus-like particles of the high-risk oncogenic HPV types 16 and 18, and the nonavalent HPV vaccine comprises the five additional (oncogenic) HPV types 31, 33, 45, 52 and 58.

Although HPV vaccination of adolescents showed beneficial effects in the general population, it is unclear whether and to what extent the HPV vaccine offers protection to an immunocompromised population, such as individuals with organ transplants, stem cell therapy or populations under immunomodulatory therapy. Immunocompromised individuals have a potentially higher risk for infectious diseases and certain cancers compared to the general population, and studies on HPV suggest that immunocompromised individuals are at an increased risk for HPV related diseases (e.g. cervical cancer) [7-12].

While existing evidence syntheses on HPV vaccination in immunocompromised individuals primarily focuses on populations with human immunodeficiency virus (HIV) [13-15], there is no comprehensive systematic review on other immunocompromised populations [16-18].

Objectives

The objective of this review was to investigate the efficacy, effectiveness, immunogenicity and safety of HPV vaccination in non-HIV immunocompromised individuals of any age.

Search methods

The systematic search was conducted on 6 May 2024 in three electronic databases: Ovid MEDLINE, Ovid Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). The study registry ClinicalTrials.gov was also searched to identify ongoing studies or unpublished completed studies. No date or language restrictions were used.

Selection criteria

Randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSI) were included. Studies included those investigating immunocompromised individuals, including primary or secondary immunodeficiencies and individuals under therapy, as defined in section 3.1.2. Studies on HIV and other infectious diseases (e.g. malaria or helminthiasis) were excluded of any age and sex. Studies included (i) nonavalent HPV vaccine, (ii) quadrivalent HPV vaccine and (iii) bivalent HPV vaccine.

Studies that were included compared a vaccinated immunocompromised group with any of the following groups:

- Unvaccinated immunocompromised control group with the same disease or condition (comparison 1);
- No vaccination;
- Placebo (containing no active agent, only the adjuvant of the HPV vaccine);
- A non-HPV vaccine.

In addition, the following groups were considered:

- Other vaccinated immunocompromised control group with a different disease or condition that affects the immune system (comparison 2);
- Other immunocompromised group who received the HPV vaccination;
- Vaccinated healthy control group (comparison 3);
- Healthy control participants from the general population who are not immunocompromised (as defined in section 3.3.1) who received the HPV vaccination.

For safety/adverse outcomes data, studies without an independent comparison group (i.e. single-arm studies) were also included.

The following outcomes prospectively prioritised by the experts of the HPV Working Group were included:

- Patient relevant outcomes (for HPV type 16/18): Precancer or cancer of the cervix, precancers or cancers of the vulva, vagina, penis or anus and oropharyngeal cancer;
- HPV infection (for HPV type 16/18);
- Immunogenicity (for HPV type 16/18);
- Safety/adverse outcomes: Any serious adverse event (as defined by clinical trial authors).

Data collection and analysis

The results of random-effects meta-analyses for the primary analyses was used and the Hartung-Knapp adjustment in case of three or more studies was also applied. The risk of bias was assessed (with the ROBINS-I tool) and the certainty of evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results

Key characteristics of the included studies

A total of 27 reports were included with 23 NRSI contributing data to this systematic review. Overall, two studies were identified comparing a vaccinated immunocompromised group with an unvaccinated immunocompromised control group with the same disease or condition (comparison 1). Most included studies provided indirect evidence by comparing vaccinated immunocompromised participants to other vaccinated immunocompromised groups with a different disease or condition (comparison 2) (n=2), or to vaccinated healthy control groups (comparison 3) (n=14). Additionally, six single-arm studies were identified. Studies took place in Europe (n=4), North America (n=14), Australia (n=1), South America (n=2) and Asia (n=2) and were published between 2013 and 2023. Studies comprised a wide range of immunocompromised individuals including participants with allogeneic stem cell transplant, autoimmune diseases, Fanconi anemia, inflammatory bowel disease, juvenile idiopathic arthritis, juvenile dermatomyositis, systemic lupus erythematosus, survivors of cancer, and organ transplant recipients (e.g. liver and kidney).

Summary of main results

Since variability in participant groups introduced substantial clinical heterogeneity, separate meta-analyses and certainty of evidence assessments for each participant group was conducted, thereby limiting the ability to perform further subgroup and sensitivity analyses, e.g. for sex, age, timing of the vaccination and specific immunosuppressive treatments.

Studies assessed patient relevant outcomes (as described in the methods) rarely. Only one NRSI, a case-control study, assessed precancer or cancer of the cervix (i.e. CIN 2+ and CIN 3+) comparing a vaccinated immunocompromised group to an unvaccinated immunocompromised control group. Hence, the effect of HPV vaccination on CIN 2+ and CIN 3+ was of very low certainty. As a result, most of the review's findings were based on the remaining comparisons – i.e. vaccinated immunocompromised participants compared to other vaccinated immunocompromised groups with a different disease or condition, or to vaccinated healthy control participants – reporting on immunogenicity data, predominantly measured at seven months after initial vaccination (seropositivity rates and geometric mean ratios [GMRs]), accompanied by limited safety data.

Overall, the certainty of evidence of immunogenicity and safety data was low to very low across all comparisons, primarily downgraded due to (very) serious risk of bias and (considerable) imprecision. All vaccinated immunocompromised groups (e.g. cancer survivors, juvenile idiopathic arthritis or systemic lupus erythematosus) demonstrated seroconversion rates (seropositivity) of 100 or nearly 100 percent and were similar to other vaccinated immunocompromised groups (comparison 2) or to vaccinated healthy control groups (comparison 3). Most immunocompromised groups had similar GMTs compared to healthy control groups (comparison 3) but the results were often imprecise, as the 95% confidence intervals frequently overlapped the null effect of GMR = 1, indicating effects that potentially vary.

Seropositivity rates and GMRs were comparable between different time points (i.e. 7 months and 12 months and more after first vaccination). All findings from meta-analyses remained robust under the fixed-effect model in sensitivity analyses.

SAEs (e.g. hospital admissions) were rare in the vaccinated groups and deemed unrelated to the HPV vaccine by the study authors. Common local adverse events across HPV vaccine types were pain, induration, erythema and edema, while systemic adverse events frequently included headache, fatigue and nausea.

Conclusions

Data on patient relevant outcomes (e.g. precancer or cancer of the cervix) are lacking. Most evidence relies on immunogenicity data and some safety outcomes from studies comparing vaccinated immunocompromised participants to other vaccinated immunocompromised groups with a different disease or condition, or to vaccinated healthy control participants. Overall, HPV vaccination appears to be immunogenic and generally safe across immunocompromised groups, considering that the data is of low to very low certainty of evidence. Due to the unclear correlate of protection (e.g. towards HPV-associated cancers) and lack of standardisation of assays and protocols for antibody measurement, it is important to interpret immunogenicity data with caution. Moreover, immunogenicity results may be influenced by various factors, including the underlying clinical conditions that affect the immune system, different immunosuppressive treatments, timing of the vaccine administration, prior exposure to HPV, as well as variations in age and sex. Thus, further research is needed to better differentiate between immunocompromised groups and subgroups.

Summary of findings table

Table 1. Vaccinated immunocompromised group vs. unvaccinated immunocompromised control group with the same disease or condition (comparison 1)

Outcome № of participants (studies)	Results	Certainty	Comments
Patient relevant outcomes: Precancer or cancer of the cervix (CIN 2+)			
Participants: Mixed population§			
1 NRSI (case-control study: 506 cases, 2672 controls)	The study reports an adjusted rate ratio of 0.96 (0.68 to 1.37)*	⨁◯◯◯ Very low[a,b]	The evidence from NRSI is of very low certainty about the effect of HPV vaccination on CIN 2+.
Patient relevant outcomes: Precancer or cancer of the cervix (CIN 3+)			
Participants: Mixed population§			
1 NRSI (case-control study: 215 cases, 1142 controls)	The study reports an adjusted rate ratio of 0.96 (0.54 to 1.70)*	⨁◯◯◯ Very low[a,b]	The evidence from NRSI is of very low certainty about the effect of HPV vaccination on CIN 3+.
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident 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 certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.			

[a] Risk of bias downgraded by one level: mainly due to serious concerns regarding confounding, selection of participants into the study, deviations from intended interventions and missing outcome data.
[b] Imprecision downgraded by two levels: due to the considerably wide 95%-CI of the rate ratio.
**As reported in the study and adjusted for immunosuppression history, vaccination, immunosuppression, smoking, hormone therapy or oral contraceptives, race and ethnicity, recent sexually transmitted infections, parity, and prior number of outpatient visits.*
§ Including: ever prior solid organ transplant, immunosuppressive therapy, HIV-infected.

Table 2. Vaccinated immunocompromised group vs. other vaccinated immunocompromised control group with a different disease or condition that affects the immune system (comparison 2)

Outcome № of participants (studies)	Relative effect (95%-CI)	Anticipated absolute effects (95%-CI)			Certainty	Comments
		Other vaccinated immunocompromised group (chronic kidney disease)	Vaccinated immunocompromised group (dialysis)	Difference		
Immunogenicity outcomes: Seropositivity rates						
Participants: Dialysis compared to chronic kidney disease (CKD)						
HPV 16, 7 months 2 NRSI (27 participants in intervention group, 27 in control group)	**RR 0.96** (0.87 to 1.05)	100%	**96.0%** (87 to 100)	**4.0% fewer** (13 fewer to 5 more)	⨁⨁◯◯ Low [a,b]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 16 between dialysis and CKD participants.
HPV 18, 7 months 2 NRSI (27 participants in intervention group, 27 in control group)	**RR 0.98** (0.81 to 1.17)	96.3%	**94.4%** (78 to 100)	**1.9% fewer** (18.3 fewer to 16.4 more)	⨁⨁◯◯ Low [a,b]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 18 between dialysis and CKD participants.
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident 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 certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.						

Outcome № of participants (studies)	Relative effect (95%-CI)	Anticipated absolute effects (95%-CI)			Certainty	Comments
		Other vaccinated immunocompromised group (chronic kidney disease)	Vaccinated immunocompromised group (transplant)	Difference		
Immunogenicity outcomes: Seropositivity rates						
Participants: Transplant compared to chronic kidney disease (CKD)						
HPV 16, 7 months 2 NRSI (51 participants in intervention group, 27 in control group)	**RR 0.94** (0.86 to 1.03)	100%	**94.0%** (86 to 100)	**6.0% fewer** (14 fewer to 3 more)	⨁⨁◯◯ Low[a,b]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 16 between transplant and CKD participants.
HPV 18, 7 months 2 NRSI (51 participants in intervention group, 27 in control group)	**RR 0.77** (0.63 to 0.94)	96.3%	**74.1%** (60.7 to 90.5)	**22.1% fewer** (35.6 fewer to 5.8 fewer)	⨁◯◯◯ Very low[a,c]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be a reduction in seropositivity rates in transplant compared to CKD participants.
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident 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 certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.						

[a] *Risk of bias downgraded by one level: serious concerns regarding confounding, selection of participants into the study, missing data and measurement of outcomes.*
[b] *Imprecision downgraded by one level: due to absolute differences that indicate fewer or more events and imprecision due to a small sample size.*
[c] *Imprecision downgraded by two levels: due to absolute differences that indicate considerably fewer or more events and imprecision due to a small sample size.*

Table 3. **Vaccinated immunocompromised group vs. vaccinated healthy control group (comparison 3)**

Outcome № of participants (studies)	Relative effect (95%-CI)	Anticipated absolute effects (95%-CI)			Certainty	Comments
		Vaccinated healthy control group	Vaccinated immunocompromised group	Difference		
Immunogenicity outcomes: Seropositivity rates						
Participants: Cancer survivors*						
HPV 16, 7 months 1 NRSI (358 participants in intervention group, 14923 in control group)	**RR 1.002**§ (1.000 to 1.003)	99.8%	**100%** (99.8 to 100)	**0.2% more** (0.0 fewer to 0.3 more)	⊕⊕◯◯ Low[a]	The evidence is of low certainty, but suggests that there may be no difference in seropositivity rates for HPV 16 between cancer survivors and healthy participants.
HPV 18, 7 months 1 NRSI (369 participants in intervention group, 15834 in control group)	**RR 1.001**§ (1.001 to 1.002)	99.6%	**99.7%** (99.7 to 99.8)	**0.1% more** (0.1 to 0.2 more)	⊕⊕◯◯ Low[a]	The evidence is of low certainty, but suggests that there may be no difference in seropositivity rates for HPV 18 between cancer survivors and healthy participants.
Participants: Fanconi anemia						
HPV 16, 12 months and more 1 NRSI (60 participants in intervention group, 21 in control group)	**RR 0.98** (0.83 to 1.15)	90.5%	**88.7%** (75.1 to 100)	**1.8% fewer** (15.4 fewer to 13.6 more)	⊕◯◯◯ Very low[a,c]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18.There may be little to no difference in seropositivity rates for HPV 16 between Fanconi anemia and healthy participants.
HPV 18, 12 months and more 1 NRSI (60 participants in intervention group, 21 in control group)	**RR 0.81** (0.66 to 1.00)	90.5%	**73.3%** (59.7 to 90.5)	**17.2% fewer** (30.8 fewer to 0.0 fewer)	⊕◯◯◯ Very low[a,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be reduced seropositivity rates to no differences in Fanconi anemia compared to healthy participants.
Participants: Inflammatory bowel disease (IBD)						
HPV 16, 7 months 1 NRSI (33 participants in intervention group, 4164 in control group)	**RR 1.002**§ (1.000 to 1.003)	99.8%	**100%** (99.8 to 100)	**0.2% more** (0 fewer to 0.3 more)	⊕⊕◯◯ Low[a]	The evidence is of low certainty, but suggests that there may be no difference in seropositivity rates for HPV 16 between IBD and healthy participants.
HPV 18, 7 months 1 NRSI (33 participants in intervention group, in control group 4488)	**RR 0.945**§ (0.868 to 1.029)	99.5%	**94.0%** (86.4 to 100)	**5.5% fewer** (13.1 fewer to 2.9 more)	⊕◯◯◯ Very low[a,c]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 18 between IBD and healthy participants.
Participants: Juvenile dermatomyositis (JDM)						
HPV 16, 7 months 1 NRSI (31 participants in intervention group, 15 in control group)	**RR 1.000**§ (0.904 to 1.106)	100%	**100%** (90.4 to 100)	**0.0% fewer** (9.6 fewer to 10.6 more)	⊕◯◯◯ Very low[a,c]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 16. There may be little to no difference in seropositivity between JDM and healthy participants.

HPV 18, 7 months 1 NRSI (31 participants in intervention group, 15 in control group)	**RR 0.968**§ (0.909 to 1.031)	100%	**96.8%** (90.9 to 100)	**3.2% fewer** (9.1 fewer to 3.1 more)	⊕◯◯◯ Very low[a,c]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be little to no difference in seropositivity between JDM and healthy participants.
Immunogenicity outcomes: Seropositivity rates						
Participants: Juvenile idiopathic arthritis (JIA)						
HPV 16, 7 months 2 NRSI (62 participants in intervention group, 62 in control group)	**RR 1.000**§ (0.959 to 1.043)	100%	**100%** (95.9 to 100)	**0.0% fewer** (4.1 fewer to 4.3 more)	⊕⊕◯◯ Low[b,e]	The evidence is of low certainty, but suggests that there may be no difference in seropositivity rates for HPV 16 between JIA and healthy participants.
HPV 16, 12 months and more 1 NRSI (43 participants in intervention group, 44 in control group)	**RR 0.98** (0.93 to 1.02)	100%	**98.0%** (93 to 100)	**2.0% fewer** (7.0 fewer to 2.0 more)	⊕⊕◯◯ Low[b,c]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 16 between JIA and healthy participants.
HPV 18, 7 months 2 NRSI (62 participants in intervention group, 62 in control group)	**RR 1.000**§ (0.959 to 1.043)	100%	**100.0%** (95.9 to 100)	**0.0% fewer** (4.1 fewer to 4.3 more)	⊕⊕◯◯ Low[b,e]	The evidence is of low certainty, but suggests that there may be no difference in seropositivity rates for HPV 18 between JIA and healthy participants.
HPV 18, 12 months and more 1 NRSI (43 participants in intervention group, 44 in control group)	**RR 0.98** (0.93 to 1.02)	100%	**98.0%** (93 to 100)	**2.0% fewer** (7.0 fewer to 2.0 more)	⊕⊕◯◯ Low[b,c]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 18 between JIA and healthy participants.
Participants: Allogeneic cell transplant (post allo-HCT)						
HPV 16, 7 months 1 NRSI (44 participants in intervention group, 20 in control group)	**RR 0.968**§ (0.899 to 1.042)	100%	**96.8%** (89.9 to 100)	**3.2% fewer** (10.1 fewer to 4.2 more)	⊕⊕◯◯ Low[b,c]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 16 between post allo-HCT and healthy participants.
HPV 18, 7 months 1 NRSI (44 participants in intervention group, 20 in control group)	**RR 0.948**§ (0.862 to 1.043)	100%	**94.8%** (86.2 to 100)	**5.2% fewer** (13.8 fewer to 4.3 more)	⊕⊕◯◯ Low[b,c]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 18 between post allo-HCT and healthy participants.
Immunogenicity outcomes: Seropositivity rates						
Participants: Systemic lupus erythematosus (SLE)						
HPV 16, 7 months 3 NRSI (181 participants in intervention group, 717 in control group)	**RR 0.988**§ (0.945 to 1.033)	98.2%	**97.0%** (92.8 to 100)	**1.2% fewer** (5.4 fewer to 3.2 more)	⊕◯◯◯ Very low[a,c]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 16. There may be little to no difference in seropositivity rates between SLE and healthy participants.
HPV 16, 12 months and more 1 NRSI (39 participants in intervention group, 44 in control group)	**RR 0.97** (0.89 to 1.06)	97.7%	**94.8%** (87 to 100)	**2.9% fewer** (10.7 fewer to 5.9 more)	⊕⊕◯◯ Low[b,c]	The evidence is of low certainty, but suggests that there may be little to no difference in seropositivity rates for HPV 16 between SLE and healthy participants.

HPV 18, 7 months 3 NRSI (188 participants in intervention group, 778 in control group)	**RR 0.943**§ (0.835 to 1.065)	96.3%	**90.8%** (80.4 to 100)	**5.5% fewer** (15.9 fewer to 6.3 more)	⊕◯◯◯ Very low[a,c]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be little to no difference in seropositivity rates between SLE and healthy participants.
HPV 18, 12 months and more 1 NRSI (38 participants in intervention group, 40 in control group)	**RR 0.95** (0.75 to 1.21)	80.0%	**76.0%** (60 to 96.8)	**4.0% fewer** (20.0 fewer to 16.8 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be reduced or slightly increased seropositivity rates in SLE compared to healthy participants.
Participants: Transplant recipients (kidney and liver)						
HPV 16, 7 months 1 NRSI (10 participants in intervention group, 3 in control group)	**RR 0.810**§ (0.604 to 1.086)	100%	**81.0%** (60.4 to 100)	**19.0% fewer** (39.6 fewer to 8.6 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 16. There may be reduced or slightly increased seropositivity rates in transplant compared to healthy participants.
HPV 18, 7 months 1 NRSI (10 participants in intervention group, 3 in control group)	**RR 0.905**§ (0.744 to 1.101)	100%	**90.5%** (74.4 to 100)	**9.5% fewer** (25.6 fewer to 10.1 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be reduced or slightly increased seropositivity rates in transplant compared to healthy participants.
Participants: Transplant recipients (kidney)						
HPV 16, 12 months and more 1 NRSI (6 participants in intervention group, 13 in control group)	**RR 0.69** (0.41 to 1.16)	100%	**69.0%** (41 to 100)	**31.0% fewer** (59.0 fewer to 16.0 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 16. There may be reduced or slightly increased seropositivity rates in kidney transplant compared to healthy participants.
HPV 18, 12 months and more 1 NRSI (6 participants in intervention group, 13 in control group)	**RR 0.69** (0.41 to 1.16)	100%	**69.0%** (41 to 100)	**31.0% fewer** (59.0 fewer to 16.0 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be reduced or slightly increased seropositivity rates in kidney transplant compared to healthy participants.
Participants: Transplant recipients (liver)						
HPV 16, 12 months and more 1 NRSI (6 participants in intervention group, 13 in control group)	**RR 1.00** (0.78 to 1.28)	100%	**100%** (78 to 100)	**0.0% fewer** (22.0 fewer to 28.0 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 16. There may be reduced or increased seropositivity rates in liver transplant compared to healthy participants
HPV 18, 12 months and more 1 NRSI (6 participants in intervention group, 13 in control group)	**RR 0.85** (0.61 to 1.17)	100%	**85.0%** (61 to 100)	**15.0% fewer** (39.0 fewer to 17.0 more)	⊕◯◯◯ Very low[b,d]	The evidence is of very low certainty about the effect of HPV vaccination on seropositivity rates for HPV 18. There may be reduced or slightly increased seropositivity rates in liver transplant compared to healthy participants

Outcome № of participants (studies)	GMR (based on GMTs)	Certainty	Comments
Immunogenicity outcomes: Geometric mean ratio (GMR)			
Participants: Cancer survivors*			
HPV 16, 7 months 1 NRSI (358 participants in intervention group, 14923 in control group)	GMR **2.59** (2.05 to 3.26)	⊕⊕◯◯ Low[a]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) for HPV 16 in cancer survivors compared to healthy participants.
HPV 18, 7 months 1 NRSI (369 participants in intervention group, 15834 in control group)	GMR **2.52** (1.94 to 3.27)	⊕⊕◯◯ Low[a]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) for HPV 18 in cancer survivors compared to healthy participants.
Participants: Fanconi anemia (FA)			
HPV 16, 12 months and more 1 NRSI (60 participants in intervention group, 21 in control group)	GMR **0.59** (0.13 to 2.64)	⊕◯◯◯ Very low[a,g]	The evidence is of very low certainty about the effect of HPV vaccination on GMR for HPV 16. There may be large effects in both directions.
HPV 18, 12 months and more 1 NRSI (60 participants in intervention group, 21 in control group)	GMR **0.56** (0.12 to 2.58)	⊕◯◯◯ Very low[a,g]	The evidence is of very low certainty about the effect of HPV vaccination on GMR for HPV 18. There may be large effects in both directions.
Participants: Inflammatory bowel disease (IBD)			
HPV 16, 7 months 1 NRSI (33 participants in intervention group, 4168 in control group)	GMR **1.06** (0.60 to 1.88)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be a little to no difference in antibody titres (GMTs) for HPV 16 between IBD and healthy participants.
HPV 18, 7 months 1 NRSI (33 participants in intervention group, 4493 in control group)	GMR **1.12** (0.62 to 2.02)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 18 in IBD compared to healthy participants.
Participants: Juvenile idiopathic arthritis (JIA)			
HPV 16, 7 months 1 NRSI (41 participants in intervention group, 41 in control group)	GMR **0.40** (0.20 to 0.82)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) for HPV 16 in healthy participants compared to JIA.
HPV 16, 12 months and more 1 NRSI (43 participants in intervention group, 44 in control group)	GMR **0.44** (0.22 to 0.87)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) for HPV 16 in healthy participants compared to JIA.

HPV 18, 7 months 1 NRSI (41 participants in intervention group, 41 in control group)	GMR **0.52** (0.27 to 1.01)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 18 in healthy participants compared to JIA.
HPV 18, 12 months and more 1 NRSI (43 participants in intervention group, 44 in control group)	GMR **0.63** (0.31 to 1.25)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 18 in healthy participants compared to JIA.
Immunogenicity outcomes: Geometric mean ratio (GMR)			
Participants: Allogeneic cell transplant (post allo-HCT)			
HPV 16, 7 months 1 NRSI (44 participants in intervention group, 20 in control group)	GMR **0.88** (0.40 to 1.97)	⊕◯◯◯ Very low[b,g]	The evidence is of very low certainty about the effect of HPV vaccination on GMR for HPV 16. There may be large effects in both directions.
HPV 16, 12 months and more 1 NRSI (44 participants in intervention group, 20 in control group)	GMR **0.86** (0.40 to 1.85)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 16 in healthy participants compared to post allo-HCT.
HPV 18, 7 months 1 NRSI (44 participants in intervention group, 20 in control group)	GMR **0.74** (0.37 to 1.48)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 18 in healthy participants compared to post allo-HCT.
HPV 18, 12 months and more 1 NRSI (44 participants in intervention group, 20 in control group)	GMR **0.88** (0.46 to 1.70)	⊕⊕◯◯ Low[b,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 18 in healthy participants compared to post allo-HCT.
Immunogenicity outcomes: Geometric mean ratio (GMR)			
Participants: Systemic lupus erythematosus (SLE)			
HPV 16, 7 months 1 NRSI (19 participants in intervention group, 657 in control group)	GMR **1.43** (1.02 to 2.02)	⊕◯◯◯ Very low[a,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 16 in SLE compared to healthy participants.
HPV 18, 7 months 1 NRSI (27 participants in intervention group, 722 in control group)	GMR **1.75** (1.23 to 2.48)	⊕◯◯◯ Very low[a,f]	The evidence is of low certainty, but suggests that there may be higher antibody titres (GMTs) to no difference for HPV 18 in SLE compared to healthy participants.
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident 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 certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.			

[a] *Risk of bias downgraded by two levels: due to very serious concerns regarding confounding.*
[b] *Risk of bias downgraded by one level: mainly due to serious concerns regarding confounding, selection of participants into the study, deviations from intended interventions or missing outcome data.*
[c] *Imprecision downgraded by one level: due to absolute differences that indicate fewer or more events and imprecision due to a small sample size.*
[d] *Imprecision downgraded by two levels: due to absolute differences that indicate considerably fewer or more events and imprecision due to a small sample size.*
[e] *Imprecision downgraded by one level: due to a small sample size.*
[f] *Imprecision downgraded by one level: imprecision due to a small sample size and wide 95%-CI of the GMR.*
[g] *Imprecision downgraded by two levels: due to considerably wide 95%-CI of the GMR and imprecision due to a small sample size.*
[*] *Including: leukaemia, lymphoma, solid tumour participants.*
[§] *Three decimal places displayed to avoid misinterpretation due to rounding.*

Table 4. Serious adverse events (SAEs): comparison 2 to comparison 3

Outcome № of participants (studies)	Result	Certainty	Comments
Safety outcomes: Serious adverse events (SAEs)			
Participants: All participant populations			
9 NRSI (any time point, ≈500 participants in intervention group, ≈300 control group); participants incompletely reported in studies	Overall, most studies do not report any SAEs for the immunocompromised individuals or healthy participants at all, or only a small number of SAEs that were judged to be unrelated to the HPV vaccine.	⊕◯◯◯ Very low[a,b]	The evidence is of very low certainty about the effect of HPV vaccination on SAEs.
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident 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 certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.			

[a] *Risk of bias downgraded by two levels: due to very serious concerns regarding confounding.*
[b] *Inconsistency downgraded by one level: due to slightly varying effects between the included studies.*

1. Background

Human papillomavirus (HPV) infection can cause anogenital and oropharyngeal diseases in males and females. More than 200 types of HPV have been identified with more than 40 types infecting the genital tract. While most HPV infections (70-90%) resolve without consequences (transient infections), persistent infections of oncogenic HPV types can progress to precancerous lesions which, if undetected, can lead to cancer, such as cervical or anal, vulvar, vaginal and penile cancer. HPV infection is also associated with cancers of the head and neck, especially oropharyngeal cancer [1, 2]. HPV 16 and 18 are two oncogenic types that are estimated to be responsible for 77% of all cervical cancers (i.e. squamous cell carcinoma), 85% of HPV-related head and neck cancers and 87% of all anal cancers. HPV 16, 18, 31, 33, 45, 52, and 58 together account for 94.9% of cervical cancers [1-3]. HPV 6 and 11 are non-oncogenic types, which cause 90% of anogenital warts [2].

HPV vaccination of adolescents is an important measure to prevent cancer [4, 5]. To date, most HPV vaccination programmes target adolescent girls and/or boys, while some countries have extended HPV catch-up vaccination programmes to adults [6]. In Europe, three HPV vaccines are currently approved: bivalent, quadrivalent and nonavalent. While all three HPV vaccines include virus-like particles of the high-risk oncogenic HPV types 16 and 18, the nonavalent HPV vaccine comprises five additional (oncogenic) HPV types [31, 33, 45, 52, and 58]. Furthermore, the quadrivalent and nonavalent HPV vaccines also target the non-oncogenic HPV types 6 and 11 [6]. The HPV vaccines have shown sustainable protection against infection with vaccine HPV types, as well as cross-protection by bivalent and quadrivalent HPV vaccines [19-22].

Although HPV vaccination of adolescents have shown beneficial effects in the general population, it is unclear whether and to what extent the HPV vaccine offers protection to an immunocompromised population, such as individuals with organ transplants, stem cell therapy or populations under immunomodulatory therapy. Immunocompromised individuals consist of a heterogeneous group with varying categorisations and degrees that represents, according to estimates from the United States and England, between 2.7% and 6.6% of the overall population. Prevalence in younger populations from 18–39 years ranges between 1.6% and 3.3% [23-26]. Immunocompromised individuals have a potentially higher risk for certain cancers compared to the general population. Studies on HPV suggest that compared to the general population, immunocompromised individuals are at an increased risk for HPV related diseases (e.g. cervical cancer) [7-12]. However, pivotal trials on HPV vaccines usually excluded immunocompromised individuals, which raised the need for additional data on the efficacy, effectiveness and safety for this population [27-33].

While existing evidence syntheses on HPV vaccination in immunocompromised primarily focus on populations with human immunodeficiency virus (HIV) [13-15], there is no comprehensive systematic review on other immunocompromised populations [16-18].

2. Objectives

The current systematic review and meta-analyses aims to investigate the efficacy, effectiveness, immunogenicity and safety of HPV vaccination in non-HIV immunocompromised individuals. The systematic review is registered in the international Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/, CRD42024554574).

3. Methods

This systematic review is recorded in accordance with the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [34].

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

To assess the efficacy, effectiveness and safety of HPV vaccination in immunocompromised individuals, the aim was to include randomised controlled trials (RCTs), as this study design, if performed appropriately, provides the best evidence for clinical questions.

Other study designs also included were defined as:

- Non-randomised studies of interventions (NRSI) where participants (individuals or clusters of individuals) are allocated to different groups (intervention and control group) using methods that are not random;
- Observational studies, i.e. prospective and retrospective cohort studies with a control group and case control studies. In observational studies the allocation to a group is determined by factors outside the investigator's control which can bias the selections of participants into the study;
- Single-arm studies (i.e. cohort studies that are sampled based on HPV vaccination status).

3.1.2 Types of participants

Studies investigating individuals of any age and sex with one or more of the following pre-specified conditions were included:

Conditions (with or without therapy):

- Primary immunodeficiencies;
- Autoinflammatory diseases (e.g. Familial Mediterranean Fever);
- Autoimmune diseases (e.g. Rheumatoid arthritis);
- Hematological diseases;
- Oncological diseases;
- Organ transplantation;
- Patients on dialysis;
- Chronic kidney diseases;
- Stem cell therapy;
- Any other secondary immunodeficiency (excluding HIV and other infectious diseases, such as malaria or helminthiasis).

Under therapy: immunomodulatory or immunosuppressive drugs (e.g. glucocorticoids)

Studies were also included if the population of interest (i.e. immunocompromised individuals) comprised a minimum of 80% of the entire study population or if the studies reported results of immunocompromised individuals separately.

Studies focusing on individuals with HIV and other infectious diseases were excluded.

3.1.3 Types of intervention

Types of intervention included (i) nonavalent HPV vaccine (Gardasil 9, 9vHPV), (ii) quadrivalent HPV vaccine (Gardasil, 4vHPV) and (iii) bivalent HPV vaccine (Cervarix, 2vHPV).

3.1.4 Comparison

Studies that compared a vaccinated immunocompromised group with any of the following groups were included:

- Unvaccinated immunocompromised control group with the same disease or condition (comparison 1);
- No vaccination;
- Placebo (containing no active agent, only the adjuvant of the HPV vaccine);
- A non-HPV vaccine.

In addition, the following control groups were considered in the review:

- Other vaccinated immunocompromised control group with a different disease or condition that affects the immune system (comparison 2);
- Other immunocompromised group (as defined in section 3.1.2) who received the HPV vaccination;

- Vaccinated healthy control group (comparison 3);
- Healthy control participants from the general population that are not immunocompromised (as defined in section 3.1.2) who received the HPV vaccination.

Additionally, safety/adverse outcomes data of studies without independent comparison group were also descriptively reported:

- No independent control (e.g. before and after comparisons within the same individuals);
- No control group (non-comparative, single-arm studies).

3.1.5 Types of outcome measures

3.1.5.1 Outcome measurements

1. Patient relevant outcomes:

- Precancer or cancer of the cervix (including the histopathologically confirmed cervical lesions as defined by WHO [e.g. CIN 2+]) (2)
  - By HPV type: for disease-related HPV types 16/18.
- Precancers or cancers of the vulva (e.g. vulvar intraepithelial neoplasia [VIN], vagina (e.g. vaginal intraepithelial neoplasia), penis (e.g. penile intraepithelial neoplasia) or anus (e.g. anal intraepithelial neoplasia), and oropharyngeal cancer
  - By HPV type: for disease-related HPV types 16/18.
- Anogenital warts (as reported by the study authors)
  - By HPV type: for disease-related HPV types 6/11.
- HPV infection (incident and persistent infections)
  - By HPV type: for disease-related HPV types 16/18.
- Mortality caused by HPV-related cancers.

2. Immunogenicity parameters of interest:

- Seropositivity rates (as defined by clinical trials);
- Geometric mean ratio (GMR) to measure the antibody response.

3. Safety/adverse outcomes:

- Any adverse events (as defined by clinical trials);
- Any serious adverse events (SAEs, as defined by clinical trials);
- Specific adverse effects related to the HPV vaccine: local events and systemic events (as defined by clinical trials).

3.1.5.2 Timing of outcome measurement

Information on outcomes from all-time points reported in the publications were collected.

3.2 Search methods for the identification of studies

3.2.1 Literature searches

An information specialist conducted comprehensive systematic literature searches for relevant studies. The complete electronic search strategies were peer-reviewed by a second information specialist following the recommendation of PRESS (Peer Review of Electronic Search Strategies [35]) and validated by checking whether the strategy identifies studies already known.

No date or language restrictions were used in the electronic searches. For each database, the search interface used, date of search, search strategy as well as number of search results was documented.

The search strategies for the databases mentioned below were adapted from the Medline strategy (see Annex A).

3.2.2 Searches for published studies

Searches were conducted for published studies in the following electronic data sources on 6 May 2024:

- Medline (ALL) (via Ovid);
- Embase (via Ovid);
- Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Library/Wiley).

3.2.3 Searches for unpublished or ongoing studies

Additional searches were performed for ongoing studies or unpublished completed studies on ClinicalTrials.gov [www.clinicaltrials.gov] on 6 May 2024.

3.2.4 Supplementary searches

Supplementary searches covered reference lists of relevant studies and systematic reviews. Experts in the field were also contacted to enquire about any further relevant studies or unpublished data that may not have been retrieved by the electronic searches. The websites of two regulatory agencies - European Medicines Agency and Food and Drug Administration - were also searched () on 24 April 2024.

3.3 Data collection and analysis

3.3.1 Study selection and management

Two reviewers (title and abstract screening [PK, WS, LG, AT]) independently screened titles and abstracts of the citations identified in electronic data sources. All full texts of potentially relevant articles were obtained. Two reviewers (PK, WS) independently checked full texts for eligibility, documented reasons for exclusions (full text screening) and resolved disagreements by consensus, moderated by a third reviewer, if necessary (LG, JM).

The 'title and abstract screening' was piloted using a random subset of 50 search results. The 'full text screening' was piloted on five included studies. The complete screening process was conducted in Covidence (https://www.covidence.org/home).

Full-text journal publications and preprint articles were included, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes.

Studies reported in abstract form only (due to limited information on study methods), theses, editorials, letters and comments were excluded.

3.3.2 Data extraction

Two review authors [PK, WS, LG, HS] extracted 20% of the data independently, using a customised data extraction form. One reviewer extracted the remaining studies, followed by a second reviewer that verified the data. Disagreements were resolved by discussion. The following information was extracted, if reported:

- General information: author and year of publication, study type;
- Study characteristics: start and end of study (including follow-up time), sample size (total and for each study arm), recruitment method, study funding sources, presentation of Declaration of Interests (DoI), geographical setting;
- Participants characteristics: definition of immunocompromised population, age, sex, ethnicity, other comorbidities;
- Intervention: type of HPV vaccine, number of doses, ascertainment of the vaccination status (e.g. by study team, self-reported, medical chart review, immunisation registry, vaccination card/pass);
- Control intervention: no intervention, placebo intervention (e.g. no active product, only the adjuvant of the HPV vaccine), type of non-HPV vaccine, other characteristic of comparison (as prespecified in section 3.1.4);
- Outcomes: as defined under 3.1.5.1, outcome description (including classification system used for diagnosis, e.g. histopathological confirmation of precancers or cancers, virological description [HPV type], type of immunoassay and cut-off values), time between vaccination and outcome measurement (follow-up).

3.3.3 Assessment of the risk of bias of the included studies

Two reviewers [PK, LG] assessed the risk of bias of each individual study on outcome level and resolved any disagreements by consensus, moderated by a third reviewer [WS], if necessary. Only NRSI were assessed, since there was no identification of RCTs. Risk of bias of single-arm studies were not assessed.

NRSI were evaluated according to the 'Risk of Bias in Non-randomised Studies of Interventions' tool (ROBINS-I) considering the following domains [36]: (i) bias due to confounding (e.g. age, screening history, socioeconomic differences); (ii) bias in selection of participants into the study (e.g. inception bias); (iii) bias in measurement of the intervention; (iv) bias due to deviations from intended intervention; (v) bias due to missing data; (vi) bias in measurement of outcomes; (vii) bias in selection of the reported result; and (viii) overall bias. Domains were judged as 'low' or 'moderate' or 'serious' or 'critical' risk of bias. To provide a comprehensive overview of the available data, which was expected to be limited, all studies - regardless the risk of bias judgement - were included in the meta-analyses. When possible, additional sensitivity analyses excluding studies with a critical risk of bias are presented (see section 3.3.9).

3.3.4 Dealing with missing data

If possible, data on intention-to-treat (ITT) basis or according to recently developed recommendations for systematic reviewers for addressing missing data in clinical studies (37) were analysed.

3.3.5 Assessment of reporting biases

A funnel plot and appropriate statistical tests (i.e. Egger's test) for small study effects for ≥ 10 studies addressing the same outcome [38] was planned. Furthermore, the impact of publication bias was minimised by ensuring a comprehensive search for eligible studies including searches in the trial registry.

3.3.6 Data synthesis and analysis

Effect estimates on antibody titres were expressed as the GMR with its 95%-CI. If no GMRs were available, then they were calculated based on geometric mean titres (GMTs) and the corresponding 95%-CI. Vaccine efficacy or effectiveness was expressed as percentage and pooled GMRs by applying the inverse variance method.

Dichotomous outcomes, i.e. safety/adverse outcomes, were reported descriptively and by using the risk ratio (RR) as effect estimate with the corresponding 95%-CI. Dichotomous data was pooled using the Mantel-Haenszel method.

For random-effects meta-analyses with three or more studies, the Hartung-Knapp adjustment (39, 40) was used and for ad hoc correction, the 95%-CI of the classic random-effects model or the Hartung-Knapp meta-analysis (whichever was wider) (41) was used. Meta-analyses was conducted using the random-effects as primary analysis and, as sensitivity analysis, the fixed-effect model. For the analyses, the statistical software R (version 4.3.2) using the package meta (42, 43) was used.

A narrative description synthesised the direction and size of any observed effects in the absence of a meta-analysis.

3.3.7 Assessment of heterogeneity

Different types of heterogeneity (owing to different clinical characteristics, methodological diversity or small study effects) were evaluated and statistically quantified based on I2 and the statistical test chi square [37]. The following thresholds to interpret an I^2 were used:

- 0% to 40%: might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- ≥ 75 %: considerable heterogeneity.

Additionally, 95% prediction intervals for assessing heterogeneity in meta-analyses with more than three studies was calculated indicating the 95% probability range of a future study with similar characteristics to those included in the meta-analysis [44].

3.3.8 Subgroup analysis

Subgroup analyses was planned for prioritised outcomes using the random-effects model to investigate clinical heterogeneity for the following characteristics:

Characteristics of the population

- Types of immunomodulatory or immunosuppressive therapies;
- Age;
- Sex.

Characteristics of the intervention

- Type of HPV vaccine: nonavalent HPV vaccine, quadrivalent HPV vaccine, bivalent HPV vaccine;
- Number of doses: one dose, two doses, three doses (independent of time between doses);
- Ascertainment of vaccination status (e.g. self-reported, medical record).

Characteristics of the setting

- Geographic location (e.g. low-middle income and high-income countries).

Characteristics of the study type

- Study design (prospective, retrospective studies).

3.3.9 Sensitivity analysis

Sensitivity analyses were planned for the following characteristics:

- Risk of bias assessment (exclusion of studies with critical risk of bias);
- Fixed-effect model (referred to as common-effect model in the forest plots).

3.3.10 Unit of analysis

The unit of analysis was the individual study participant.

3.4 Summary of findings and certainty of the evidence assessment

The GRADEpro GDT was used to create a summary of findings table (Version 3). According to Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions, the "most critical and/or important health outcomes, both desirable and undesirable," should be included in the summary of findings table [45, 46].

The following outcomes were included and prospectively prioritised by the experts of the HPV Working Group:

- Clinical outcomes: precancer or cancer of the cervix (e.g. CIN 2+, CIN 3+), precancers or cancers of the vulva, vagina, penis or anus and oropharyngeal cancer.
  - By HPV type: for disease-related HPV types 16/18.
- HPV infection
  - By HPV type: for disease-related HPV types 16/18.
- Immunogenicity.
- Safety/adverse outcomes: Any serious adverse event.

The GRADE approach uses five domains (risk of bias, inconsistency, imprecision, indirectness and publication bias) to assess the certainty in the body of evidence for each prioritised outcome.

The certainty of evidence was downgraded as follows:

- Serious (- 1) or very serious (- 2) risk of bias; the certainty of evidence was downgraded by one level if the body of evidence was rated as "serious" with ROBINS-I and by two levels if the body of evidence was rated as "critical" with ROBINS-I.
- Serious (- 1) or very serious (- 2) inconsistency.
- Serious (- 1) or very serious (- 2) uncertainty about directness.
- Serious (- 1) or very serious (- 2) imprecise or sparse data; the certainty of evidence for dichotomous outcomes was downgraded by one for absolute differences that indicate fewer or more events (i.e. ≈5% more or less in seropositivity rates) and/or imprecision due to a small sample size. For continuous outcomes the certainty of evidence was downgraded by one for wide 95%-CI (i.e. crossing 0.5 and/or 2.07 of the 95%-CI of the GMR) and/or imprecision due to a small sample size. The certainty of evidence was downgraded by two if differences in events were considerably large for dichotomous outcomes or 95%-CI were considerably wide for continuous outcomes.
- Serious (- 1) or very serious (- 2) probability of reporting bias.

The GRADE system used the following criteria for assigning grade of evidence:

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The current GRADE guidance was followed as recommended in the Cochrane Handbook for Systematic Reviews of Interventions, Chapter 14 [45]. The overall risk of bias judgement was used to inform the decision on downgrading for risk of bias. In accordance with the GRADE guidelines for NRSI assessed with ROBINS-I, the assessment started with a high certainty of evidence [36]. The results are presented per outcome in a Summary of Findings Table as suggested by the GRADE Working Group. The findings and certainty in the evidence is phrased as suggested in the informative statement guidance [47]. The GRADE assessments were conducted independently by two reviewers (PK, WS). Any disagreements were resolved by discussion and consensus involving a third person, if needed (JM).

4. Results

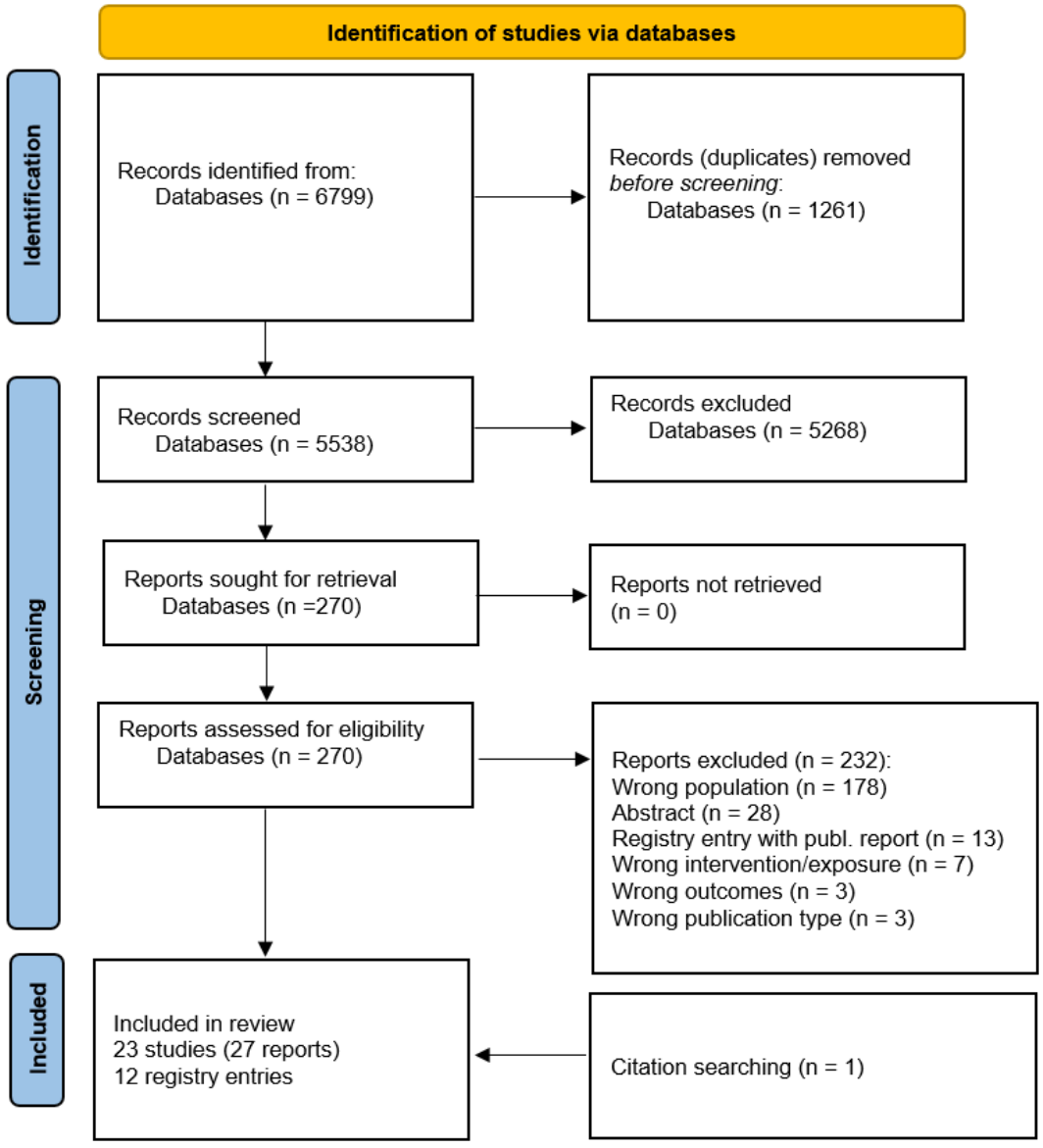
4.1 Description of studies

The literature search resulted in 6 799 records. One record was identified via additional searches of reference lists. After deduplication, 5 538 titles and abstracts were screened, which then proceeded to full-text screening with 270 records. From these 270 records, 232 records were excluded. Detailed reasons for exclusion are provided in Annex B. Finally, 27 reports of 23 NRSI (see Annex C) were included and additionally 12 registry entries (see Annex D) contributing data to this review. The flow of records including the reasons for exclusions is illustrated in Figure 1.

Overall, two studies were identified comparing a vaccinated immunocompromised group with an unvaccinated immunocompromised control group with the same disease or condition (comparison 1) [48, 49]. Most included studies provided indirect evidence by comparing vaccinated immunocompromised participants to other immunocompromised groups with a different disease or condition (comparison 2), [50, 51] or to vaccinated healthy control groups (comparison 3) [51-64]. Additionally, six single-arm studies were identified [65-71]. Across all comparisons, 14 studies provided data for meta-analysis [49-53, 55-62, 64].

4.1.1 Results of the search

Figure 1. PRISMA 2020 flow diagram



4.2 Vaccinated immunocompromised group compared to unvaccinated immunocompromised control group with the same disease or condition (comparison 1)

4.2.1 Characteristics of the included studies

Baseline study characteristics

Two NRSI were included in comparison 1 – one registry-based cohort study [48], and one case-control study [49] – as detailed in Table 5. Studies were conducted in Europe (n=1, [48]) and North America (n=1, [49]) and published between 2016 and 2020. Both studies reported public, non-profit funding [48, 49]. One study provided sufficient data for analysis of patient relevant outcomes [49].

Participant characteristics and interventions

The age of participants ranged from approximately 10 to over 30 years. Both studies included exclusively female participants [48, 49]. Participants of included studies had various underlying conditions, including autoimmune diseases, organ transplant or were under immunosuppressive therapy (see Table 5, Annex E). Both studies reported on participants that received the quadrivalent HPV vaccine [48, 49]. One study reported that participants received a minimum of one dose [49], while Grönlund et al. 2016 reported that approximately 60% received three doses of the HPV vaccine. The HPV vaccine was administered outside the study context, i.e. the vaccination status was obtained from electronic health records [49] or a national registry [48].

Table 5. Key study characteristics (comparison 1)

Study	Country	Study type	Funding	DoI	Clinical condition	N intervention	N control	Age (years)	Sex (%)	Intervention
Grönlund 2016 (48)	Sweden	NRSI (registry based)	Public, non-profit	Interests declared	Autoimmune disease	11,256	59,009	All participants: 10-14: 19 847 15-19: 14 909 20-24: 14 932 25-30: 20 577	Female (100)	Quadrivalent HPV vaccine
Silverberg 2020 (49)	USA	NRSI (case-control)	Public, non-profit	No interests declared	Ever prior solid organ transplant, immunosuppressive therapy, HIV-infected§	4357 (cases)#	21,773 (controls)#	All participants (mean): 26.3	Female (100)	Quadrivalent HPV vaccine

CKD: Chronic kidney disease; DoI: Declaration of Interests; HIV: human immunodeficiency viruses; N: number of participants
§ The study does not exclude HIV participants. However, cases with HIV were rare (intervention: 4 participants, control: 5 participants).
 # This review incorporates only a subsample of this study.

4.2.2 Risk of bias of included studies

One study provided patient relevant outcomes and was assessed for risk of bias with the ROBINS-I tool [36]. The ROBINS-I judgements for the patient relevant outcomes are displayed in Annex F. The study was judged to have an overall serious risk of bias, mainly due to confounding (i.e. study considered not all baseline confounders that are possibly relevant), selection of the participants and the selection of the reported results (e.g. no study protocol was available, which can lead to selective reporting) [49].

4.2.3 Patient relevant outcomes

Precancer or cancer of the cervix

The evidence is very uncertain about the effect of the HPV vaccine on CIN 2+ and CIN 3+ (due to serious concerns in risk of bias and considerable imprecision). Only evidence from one case-control study was available. There was no decrease of CIN 2+ and CIN 3+ associated with quadrivalent HPV vaccination (adjusted rate ratio 0.96, 95%-CI 0.68–1.37 for CIN 2+; 0.96, 95%-CI 0.54–1.7 for CIN 3+, Table 1).

4.2.4 Immunogenicity

4.2.4.1 Seropositivity

No data available for analysis on seropositivity.

4.2.4.2 Geometric mean ratios

No data available for analysis on geometric mean ratios (GMRs).

4.2.5 Safety

4.2.5.1 Serious adverse events

None of the studies identified for comparison 1 assessed serious adverse events. However, the study by Grönlund et al. 2016 reported the onset of new autoimmune events in participants with autoimmune diseases. In the unvaccinated group, 5 428 new-onsets of autoimmune diseases were observed during 245 807 person-years (rate of 22.1 95%-CI 21.5 to 22.7 new events per 1 000 person-years) compared to vaccinated women, with 124 new events during 7 848 person-years (rate of 15.8 95%-CI 13.2 to 18.8 new events per 1 000 person-years). There was no increase in incidence of new autoimmune events associated with the quadrivalent HPV vaccine during the risk period (adjusted incidence rate ratio 0.77, 95%-CI 0.65 to 0.93); in fact, a slightly reduced risk was observed.

4.2.5.2 Other adverse events

No data available on other adverse events or adverse effects related to the vaccine.

4.2.6 Subgroup analysis

There were insufficient data (only one study reported prioritised outcome data in comparison 1) for conducting meaningful subgroup analyses, such as by sex, age, immunosuppressive treatments, or characteristics of the HPV vaccination (as defined in section 3.3.8).

4.2.7 Sensitivity analysis

There were insufficient data (only one study reported prioritised outcome data in comparison 1) for conducting meaningful sensitivity analyses according to risk of bias assessment and the fixed-effect model.

4.3 Vaccinated immunocompromised group compared to other vaccinated immunocompromised control group with a different disease or condition that affects the immune system (comparison 2)

4.3.1 Characteristics of the included studies

Baseline study characteristics

Two NRSI [50, 51] were included in comparison 2, as detailed in Table 6. The study of Nelson et al. 2016 additionally provides data for comparison 3. The studies were conducted in North America and published between 2016 and 2020 [50, 51]. Both studies reported industry funding [50, 51]. Both studies provided sufficient data for analysis [50, 51].

Participant characteristics and Interventions

The age of participants ranged from 11 to 21 years [50, 51]. Both studies included exclusively female participants [50, 51]. Participants of identified studies included dialysis, transplant recipients, and chronic kidney disease (CKD) (see Table 6). In both studies, participants received immunosuppressive medications at baseline (Annex E) (50, 51). All participants received the quadrivalent HPV vaccine [50, 51]. The majority of included participants in the two studies received three doses of the HPV vaccine (range: 85–90.3%) [50, 51]. The HPV vaccine was prospectively administered within the study context in both studies [50, 51].

Table 6. Key study characteristics (comparison 2)

Study	Country	Study type	Funding	DoI	Clinical condition	Clinical condition of control group	N intervention	N control	Age (years)	Sex (%)	Intervention
Nailescu 2020 (50)	USA	NRSI (prospective)	Industry	No interests declared	Dialysis, transplant recipients (kidney, liver)	Chronic kidney disease (CKD)	47	18	All participants (mean, SD): 13.6 (2.6)	Female (100)	Quadrivalent HPV vaccine
Nelson 2016 (51)	USA	NRSI (prospective)	Industry	NR	Dialysis, transplant recipients (kidney)	CKD	38	29	CKD (mean, range): 15.2 (11-21), Dialysis (mean, range): 15.3 (12-18), Transplant (mean, range): 16.8 (11-21)	Female (100)	Quadrivalent HPV vaccine

CKD: Chronic kidney disease; DoI: Declaration of Interests; HPV: human papillomavirus; N: number of participants; SD: Standard deviations; NRSI: non-randomised studies of interventions; USA: United States of America.

4.3.2 Risk of bias of included studies

Two studies provided data for analysis and were assessed using the ROBINS-I tool [36]. The ROBINS-I judgements for each outcome are displayed in Figure 2, Figure 3 and Annex F. Both studies were judged with an overall serious risk of bias, mainly due to confounding (i.e. studies considered not all baseline confounders that are possibly relevant), selection of the participants in the study (i.e. some participants were retrospectively included into the study) and unclear information on missing outcome data [50, 51].

4.3.3 Patient relevant outcomes

No data available for analysis on patient relevant outcomes.

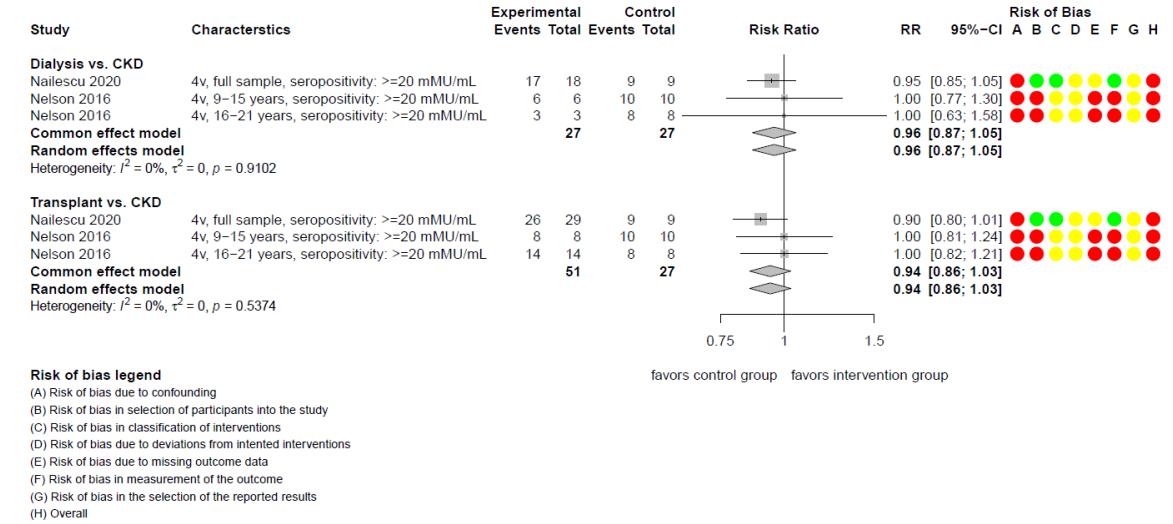
4.3.4 Immunogenicity

4.3.4.1 Seropositivity

HPV 16 at seven months

HPV vaccination is associated with very high rates of seropositivity in dialysis, transplant recipients and CKD participants for HPV 16 at seven months. The evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision). There may be little to no difference in seropositivity rates between dialysis or transplant participants compared to CKD participants (2 NRSI [50, 51], low certainty of evidence, Figure 2, Table 2, Annex G).

Figure 2. Seropositivity of HPV 16 at seven months (comparison 2)

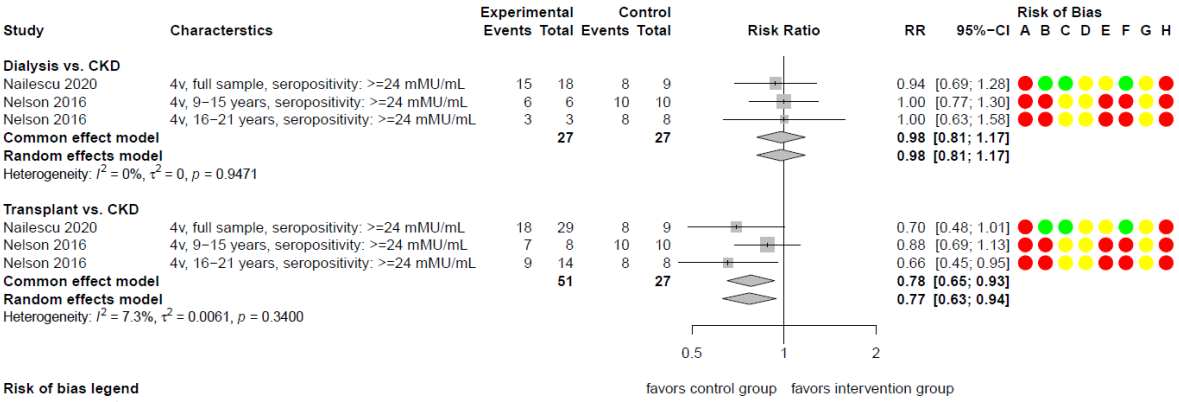


HPV 18 at seven months

HPV vaccination is associated with very high rates of seropositivity in dialysis and CKD participants for HPV 18 at seven months. The evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision). There may be little to no difference in seropositivity rates between dialysis and CKD participants (2 NRSI [50, 51], low certainty of evidence, Figure 3, Table 2, Annex G).

HPV vaccination is associated with very high rates of seropositivity in transplant recipients and CKD participants for HPV 18 at seven months. The evidence was assessed to be very uncertain (due to serious concerns in risk of bias and considerable imprecision). There may be a reduction in seropositivity rates in transplant participants compared to CKD participants (2 NRSI [50, 51], very low certainty of evidence, Figure 3, Table 2, Annex G).

Figure 3. Seropositivity of HPV 18 at seven months (comparison 2)



4.3.3.2 Geometric mean ratios

No data available for analysis on GMRs.

4.3.5 Safety

4.3.5.1 Serious adverse events

Nailescu et al. 2020 reported no serious adverse events in either of the investigated groups: CKD (n=18), dialysis (n=18), transplant (n=29). However, two participants experienced acute rejection episodes within six months following their final vaccine dose. Upon reviewing chart data, these episodes were deemed likely to be related to medication non-adherence.

In the study by Nelson et al. 2016, one transplant recipient developed acute rejection during the HPV vaccination series (between doses 2 and 3) at 10 months post-transplant. Another transplant recipient experienced rejection one month after completing the vaccination series, at four months post-transplant. The rejection rate of 8.6% (two out of 23 transplant recipients) is consistent with nationally reported data from the North American Pediatric Renal Trials and Collaborative Studies (2011), indicating no increased risk of rejection in this cohort [72].

4.3.5.2 Other adverse events

Nelson et al. 2016 additionally reported local and systemic events, including pain, bruising and headache after HPV vaccination across the CKD, dialysis and transplant recipient groups (see Annex H) [51].

4.3.6 Subgroup analysis

As all immunocompromised groups were analysed separately (i.e. separation of dialyses and transplant participants), there was insufficient data to conduct further meaningful subgroup analyses, such as by sex, age, immunosuppressive treatments, or characteristics of the HPV vaccination (as defined in section 3.3.8).

4.3.7 Sensitivity analysis

There were insufficient data for conducting meaningful sensitivity analyses according to risk of bias assessment. The sensitivity analysis using the fixed-effect model (common-effect model) was consistent with the results from the random-effects model.

4.4 Vaccinated immunocompromised group compared to vaccinated healthy control group (comparison 3)

4.4.1 Characteristics of the included studies

Baseline study characteristics

Fourteen NRSI [51-64] were included in comparison 3, as detailed in Table 7. The study of Nelson et al. 2016 additionally provide data for comparison 2. Studies were conducted across Europe (n=2, [53, 57]), North America (n=9 [51, 52, 54, 58-60, 62-64]), South America (n=2, [55, 56] and Asia (n=1, [61]) and published between 2013 and 2023. The majority of studies reported industry [51, 52, 54, 59, 61] or mixed (i.e. industry and public, non-profit) funding [56-58, 60]. Eleven studies provided sufficient data for analysis [52, 53, 55-62, 64].

Participant characteristics and interventions

The age of participants ranged from approximately nine to over 38 years [51-64]. Most studies included exclusively females [51-53, 55-59, 61, 62] (n=10), while four studies focused on both sexes [54, 60, 63, 64]. Participants of identified studies had various underlying conditions, including allogeneic cell transplant recipients (post allo-HCT), CKD, dialysis, FA, IBD, JDM, JIA, transplant recipients, survivors of cancer and SLE. Twelve studies reported that participants received immunosuppressive medications at baseline (Annex E) [51-62]. Most studies reported on participants that received the quadrivalent HPV vaccine (n=11) [51, 52, 54-56, 58, 59, 61-64], two studies on the bivalent HPV vaccine [53, 57] and one study on various vaccines (nonavalent and quadrivalent HPV vaccines) [60]. The majority of participants of the intervention group received three doses of the HPV vaccine (range: 77.3 - 100%) [51-63], while one study reported that less than 40% of the participants received three HPV vaccine doses [54]. One study did not provide information on dosing [64]. Information on dosing of the control group (i.e. healthy participants) was missing in seven studies [51, 52, 54, 58, 60, 63, 64]. Six studies compared their study data with data from previous studies/data on vaccinated healthy participants (i.e. historic controls) [51, 52, 54, 58, 60, 63]. The HPV vaccine was prospectively administered within the study context (for immunocompromised groups) in most of the studies (n=8) [51-54, 57, 60-62]. Four studies retrospectively included participants after HPV vaccination [55, 56, 58, 59] who had received the HPV vaccine prior to the study, with unclear methods for assessing vaccination status in this group. In the study of Alter et al. 2014, the HPV vaccine was administered outside the study context, and vaccination status was either self-reported by the participants or obtained from electronic health records [63].

Table 7. Key study characteristics (comparison 3)

Study	Country	Study type	Funding	DoI	Clinical condition	N Intervention group	N control group	Age (years)	Sex (%)	Intervention
Alter 2014 (63)	USA	NRSI (prospective/ retrospective, historic control)	Public, non profit	NR	Fanconi anemia (FA)	38	107*	Overall (vaccinated) FA: (median, range): 22 (12-59) DBA: 17 (16-20) DC: 18 (13-26) SDS: 22 TAR: NA	FA: female (≈50) §, male (≈50) § DBA: female (40.5), male: (59.5) DC: female (≈30) §, male (≈70) § SDS: female (57.1), male (42.9) TAR: female (50), male (50)	Quadrivalent HPV vaccine
Dhar 2017 (52, 73)	USA	NRSI (prospective, historic control)	Industry	No interests declared	Systemic lupus erythematosus (SLE)	37	NR	SLE: (mean): 38.1	Female (100)	Quadrivalent HPV vaccine
Esposito 2014 (53)	Italy	NRSI (prospective)	Public, non profit	No interests declared	Juvenile idiopathic arthritis (JIA)	21	21	JIA: (median, range):15 (12-25); healthy (median, range): 15 (12-25)	Female (100)	Bivalent HPV vaccine
Grein 2020a (55)	Brasil	NRSI (prospective)	Public, non profit	No interests declared	Childhood SLE	234	41	Childhood SLE: (median, min, max): 11.8 (1-18) Healthy: (median, min, max): 15.5 (9-19)	Female (100)	Quadrivalent HPV vaccine
Grein 2020b (56)	Brasil	NRSI (prospective)	Mixed	No interests declared	Juvenile dermatomyositis (JDM)	47	41	JDM: (range): 9-20	Female (100)	Quadrivalent HPV vaccine
Gomez-Lobo 2014 (54)	USA	NRSI (prospective, historic control)	Industry	NR	Transplant recipients	20	5	Kidney recipients: (median, range): 14 (11-19) Liver recipients recruited: (median, range): 16 (13-17)	Kidney recipients: female (30%), male (70%) Liver recipients recruited: female (100)	Quadrivalent HPV vaccine
Heijstek 2014 (57)	Nether-lands	NRSI (prospective)	Mixed	Interests declared	JIA	68	55	JIA: (mean, SD): 14.1 (1.6); Healthy: (mean, SD):14.3 (1.2)	Female (100)	Bivalent HPV vaccine
Jacobson 2013 (58)	USA	NRSI (prospective, historic control)	Mixed	Interests declared	Inflammatory bowel disease (IBD)	52	NR	IBD: (median, min, max): prospectively included 15 (9, 26) retrospectively included: 18 (14, 26) Healthy: (range): 9-15 and 15-26	Female (100)	Quadrivalent HPV vaccine
Kitano 2023 (59)	Canada	NRSI (prospective)	Industry	Interests declared	Transplant recipients	17	19	Kidney: (median,10th-90th percentile): 14 (13.6-16.4) Liver: (median,10th-90th percentile):12.5 (4.8-16.1) Healthy: (median,10th-90th percentile): 16 (14-17.5)	Female (100)	Quadrivalent HPV vaccine

Study	Country	Study type	Funding	DoI	Clinical condition	N Intervention group	N control group	Age (years)	Sex (%)	Intervention
Landier 2022 (60)	USA	NRSI (prospective, historic control)	Mixed	Interests declared	Survivors of cancer[#]	453	26486	Survivors of cancer: (mean, SD): 15.6 (4.6)	Survivors of cancer: Female (42) [§], Male (58) [§]	Intervention group: Quadrivalent HPV vaccine (58.3%) Nonavalent HPV vaccine (41.7%) Control group: Quadrivalent HPV vaccine and Nonavalent HPV vaccine (proportions vary)
Mok 2013 (61)	China	NRSI (prospective)	Industry	No interests declared	SLE	50	50	SLE: (mean, SD): 25.8 (3.9) Healthy: (mean, SD): 25.8 (3.9)	Female (100)	Quadrivalent HPV vaccine
Nelson 2016 (51)	USA	NRSI (prospective, historic control)	Industry	NR	Chronic kidney disease (CKD), Dialysis, transplant recipients (kidney)	67	917-3329	CKD: (mean, range): 15.2 (11-21), Dialysis: (mean, range): 15.3 (12-18), Transplant: (mean, range): 16.8 (11-21)	Female (100)	Quadrivalent HPV vaccine
Sauter 2021 (64)	USA	NRSI (cross-sectional study)	Public, non profit	Interests declared	FA	212	111	FA: ≤ 11: 93 12-15: 32 16-20: 25 ≥21: 62 Healthy: ≤ 11: 32 12-15: 25 16-20: 13 ≥21: 41	Female (55.1) Male (44.9)	Quadrivalent HPV vaccine (primarily)
Stratton 2020 (62)	USA	NRSI (prospective)	Public, non profit	Interests declared	Allogeneic cell transplant recipients (post allo-HCT)	44	20	Receiving immunosuppression medication (median, range): 34.3 (18.3-48.1) Not receiving immunosuppression medication (median, range): 32.2 (18.3-49.9) Healthy (median, range): 32.9 (23.0-45.8)	Female (100%)	Quadrivalent HPV vaccine

CKD: Chronic kidney disease; DBA: Diamond Blackfan anemia, DC: Dyskeratosis congenital; DoI: Declaration of Interests; FA: Fanconi anemia; HPV: Human papillomavirus; IBD: Inflammatory bowel disease; JDM: Juvenile dermatomyositis; JIA: Juvenile idiopathic arthritis; N: number of participants; NRSI: non-randomised studies of interventions; SD: Standard deviations, SDS: Shwachman Diamond syndrome; SLE: Systemic lupus erythematosus; TAR: Thrombocytopenia-absent radius; USA: United States of America

** Number of participants in the control group based on individuals with DBA, DC, SDS, and TAR. The study includes a descriptive comparison to healthy participants.*

[§] Of participants that received at least one dose.

[#] Including: leukaemia, lymphoma, solid tumour.

4.4.2 Risk of bias of included studies

Eleven studies provided data for analysis and were assessed using the ROBINS-I tool [36]. The ROBINS-I judgements accounts for each outcome separately and is displayed in Figure 4. Six studies were judged to have an overall serious risk of bias, mainly due to confounding (i.e. studies considered not all baseline confounders that are possibly relevant), selection of the participants in the study (i.e. some participants were retrospectively included into the study) and selection of the reported results (e.g. deviations from the study plan) [53, 55, 57, 59, 61, 62]. The remaining six studies were judged with critical risk of bias, due to very problematic confounding (e.g. uncontrolled differences in participant characteristics at baseline) [51, 52, 56, 58, 60, 64].

4.4.3 Patient relevant outcomes

No data available for analysis on patient relevant outcomes.

4.4.4 Immunogenicity

4.4.4.1 Seropositivity

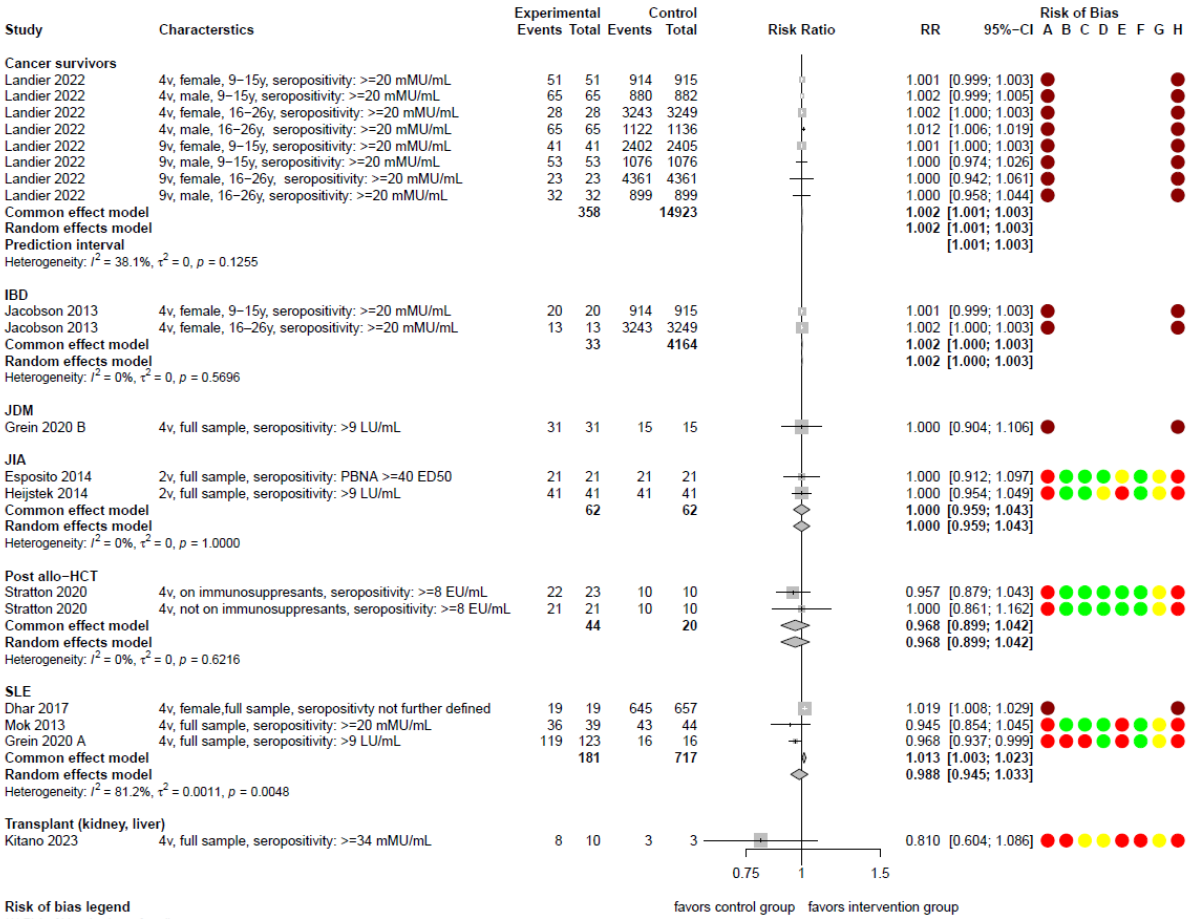
HPV 16 at seven months

HPV vaccination is associated with very high rates of seropositivity in JDM, post allo-HCT, SLE participants and healthy participants for HPV 16 at seven months. The evidence was assessed to be uncertain to very uncertain (due to serious to very serious concerns in risk of bias and imprecision). There may be little to no difference in seropositivity rates in JDM, post allo-HCT and SLE participants compared to healthy participants (5 NRSI [52, 55, 56, 61, 62], low to very low certainty of evidence, see Figure 4, Table 3).

HPV vaccination is associated with very high rates of seropositivity in cancer survivors, IBD, JIA and healthy participants for HPV 16 at seven months. The evidence was assessed to be uncertain (due to serious to very serious concerns in risk of bias and imprecision). There may be no difference in seropositivity rates in cancer survivors, IBD and JIA participants compared to healthy participants (4 NRSI [53, 57, 58, 60], low certainty of evidence, see Figure 4 Table 3).

HPV vaccination is associated with very high rates of seropositivity in transplant recipients (kidney and liver) and healthy participants for HPV 16 at seven months. The evidence was assessed to be very uncertain (due to serious concerns in risk of bias and considerable imprecision). There may be reduced or slightly increased seropositivity rates in transplant participants compared to healthy participants (1 NRSI [59], very low certainty of evidence, see Figure 4, Table 3).

Figure 4. Seropositivity of HPV 16 at seven months (comparison 3)



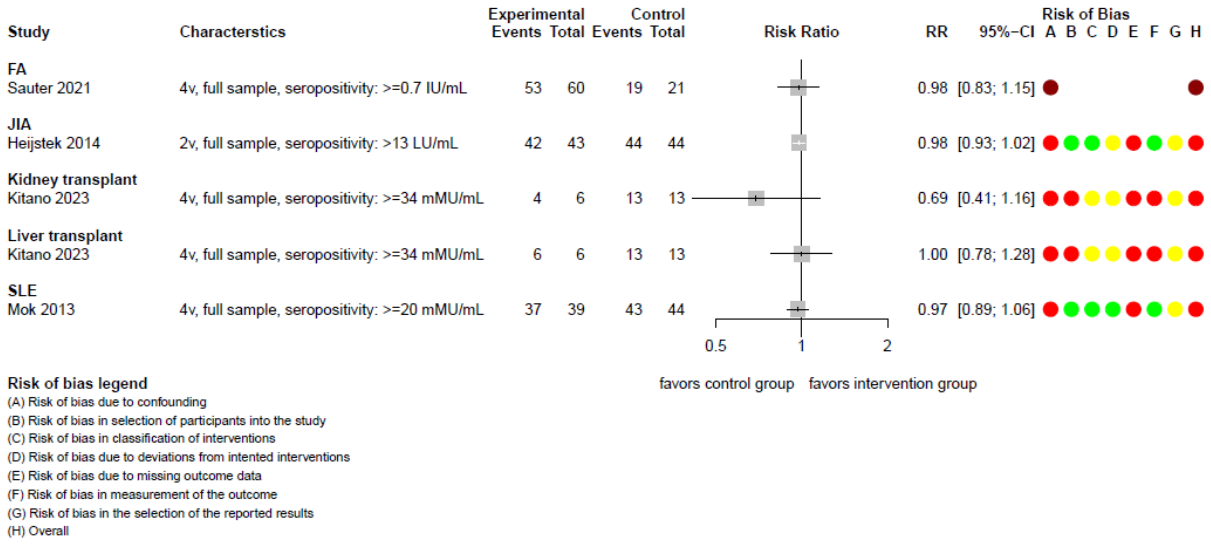
Risk of bias legend
(A) Risk of bias due to confounding
(B) Risk of bias in selection of participants into the study
(C) Risk of bias in classification of interventions
(D) Risk of bias due to deviations from intented interventions
(E) Risk of bias due to missing outcome data
(F) Risk of bias in measurement of the outcome
(G) Risk of bias in the selection of the reported results
(H) Overall

HPV 16 at 12 months and more

HPV vaccination is associated with high rates of seropositivity in FA, JIA, SLE participants and healthy participants for HPV 16 at 12 months and more. The evidence was assessed to be uncertain to very uncertain (due to serious to very serious concerns in risk of bias and imprecision). There may be little to no difference in seropositivity rates in FA, JIA and SLE participants compared to healthy participants (3 NRSI [57, 61, 64], low to very low certainty of evidence, see Figure 5, Table 3).

HPV vaccination is associated with high rates of seropositivity in kidney and liver transplant recipients and healthy participants for HPV 16 at 12 months and more. The evidence was assessed to be very uncertain (due to serious concerns in risk of bias and considerable imprecision). There may be reduced or (slightly) increased seropositivity rates in transplant participants compared to healthy participants (1 NRSI [59], very low certainty of evidence, see Figure 5, Table 3).

Figure 5. Seropositivity of HPV 16 at 12 months and more (comparison 3)



Risk of bias legend
(A) Risk of bias due to confounding
(B) Risk of bias in selection of participants into the study
(C) Risk of bias in classification of interventions
(D) Risk of bias due to deviations from intented interventions
(E) Risk of bias due to missing outcome data
(F) Risk of bias in measurement of the outcome
(G) Risk of bias in the selection of the reported results
(H) Overall

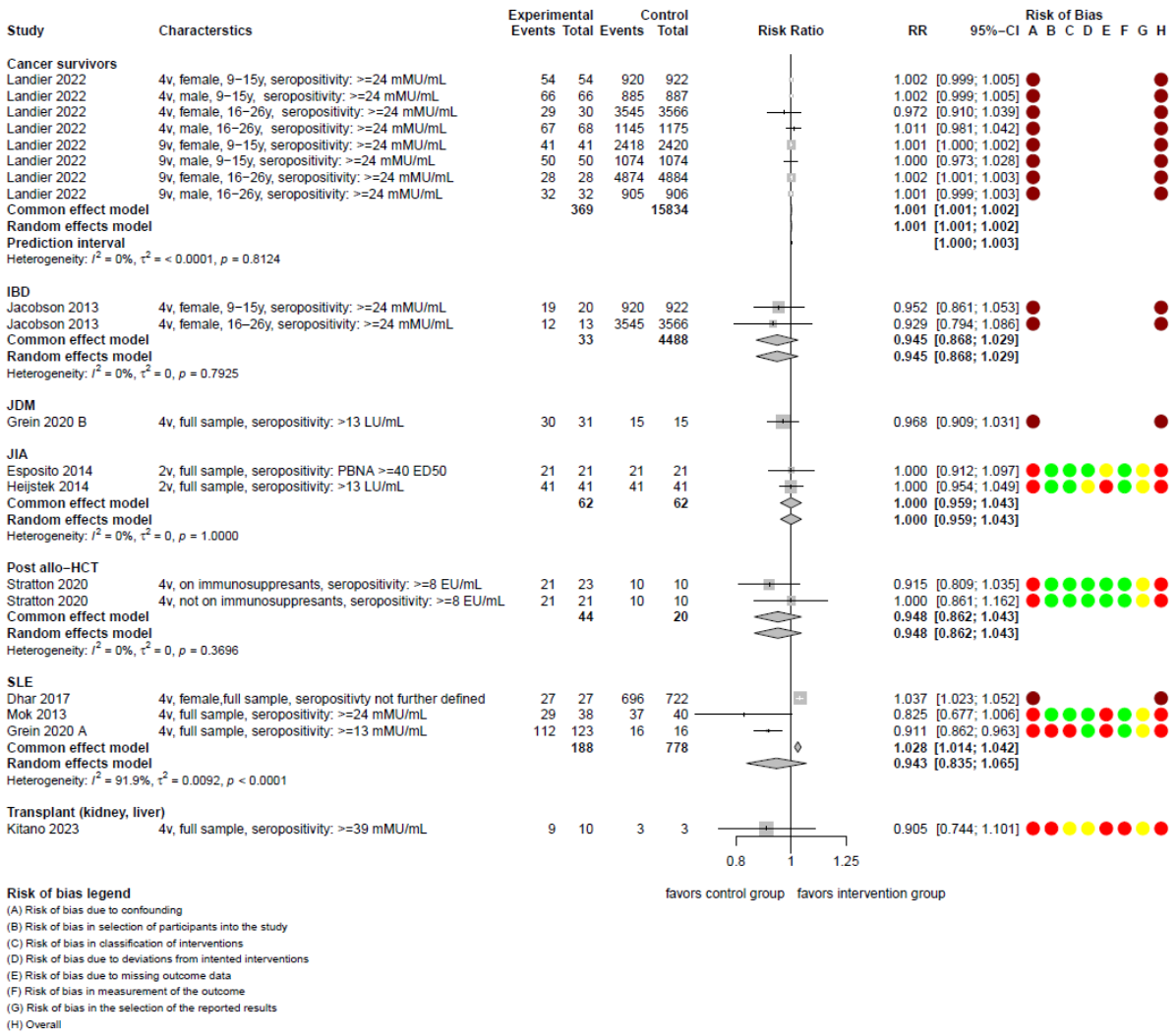
HPV 18 at seven months

HPV vaccination is associated with very high rates of seropositivity in IBD, JDM, post allo-HCT, SLE and healthy participants for HPV 18 at seven months. The evidence was assessed to be uncertain to very uncertain (due to serious to very serious concerns in risk of bias and imprecision). There may be little to no difference in seropositivity rates in IBD, JDM, post allo-HCT and SLE participants compared to healthy participants (6 NRSI [52, 55, 56, 58, 61, 62], low to very low certainty of evidence, see Figure 6, Table 3).

HPV vaccination is associated with very high rates of seropositivity in cancer survivors, JIA and healthy participants for HPV 18 at seven months. The evidence was assessed to be uncertain (due to serious to very serious concerns in risk of bias and imprecision).There may be no difference in seropositivity rates in cancer survivors and JIA participants compared to healthy participants (3 NRSI [53, 57, 60], low certainty of evidence, see Figure 6, Table 3).

HPV vaccination is associated with very high rates of seropositivity in transplant recipients (kidney and liver) and healthy participants for HPV 18 at 7 months. The evidence was assessed to be very uncertain (due to serious concerns in risk of bias and considerable imprecision). There may be reduced or slightly increased seropositivity rates in transplant recipients (kidney and liver) compared to healthy participants (1 NRSI [59], very low certainty of evidence, see Figure 6, Table 3).

Figure 6. Seropositivity of HPV 18 at seven months (comparison 3)

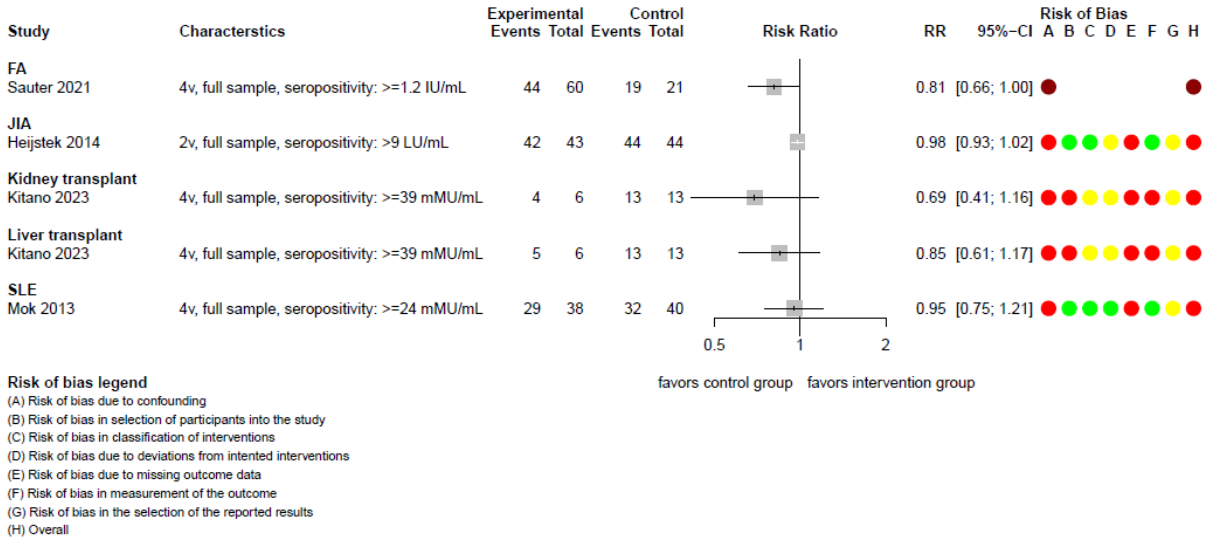


HPV 18 at 12 months and more

HPV vaccination is associated with very high rates of seropositivity in JIA participants and healthy participants for HPV 18 at 12 months and more, but the evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision). There may be little to no difference in seropositivity rates in JIA participants compared to healthy participants (1 NRSI [57], low certainty of evidence, see Figure 7, Table 3).

HPV vaccination is associated with very high rates of seropositivity in FA, SLE, kidney and liver transplant recipients and healthy participants for HPV 18 at 12 months and more, but the evidence was assessed to be very uncertain (due to serious to very serious concerns in risk of bias and considerable imprecision). There may be reduced, no differences or slightly increased seropositivity rates in SLE and kidney and liver transplant recipients compared to healthy participants (3 NRSI [59, 61, 64], very low certainty of evidence, see Figure 7, Table 3).

Figure 7. Seropositivity of HPV 18 at 12 months and more (comparison 3)



Risk of bias legend
(A) Risk of bias due to confounding
(B) Risk of bias in selection of participants into the study
(C) Risk of bias in classification of interventions
(D) Risk of bias due to deviations from intented interventions
(E) Risk of bias due to missing outcome data
(F) Risk of bias in measurement of the outcome
(G) Risk of bias in the selection of the reported results
(H) Overall

4.4.4.2 Geometric mean ratios

HPV 16 at seven months

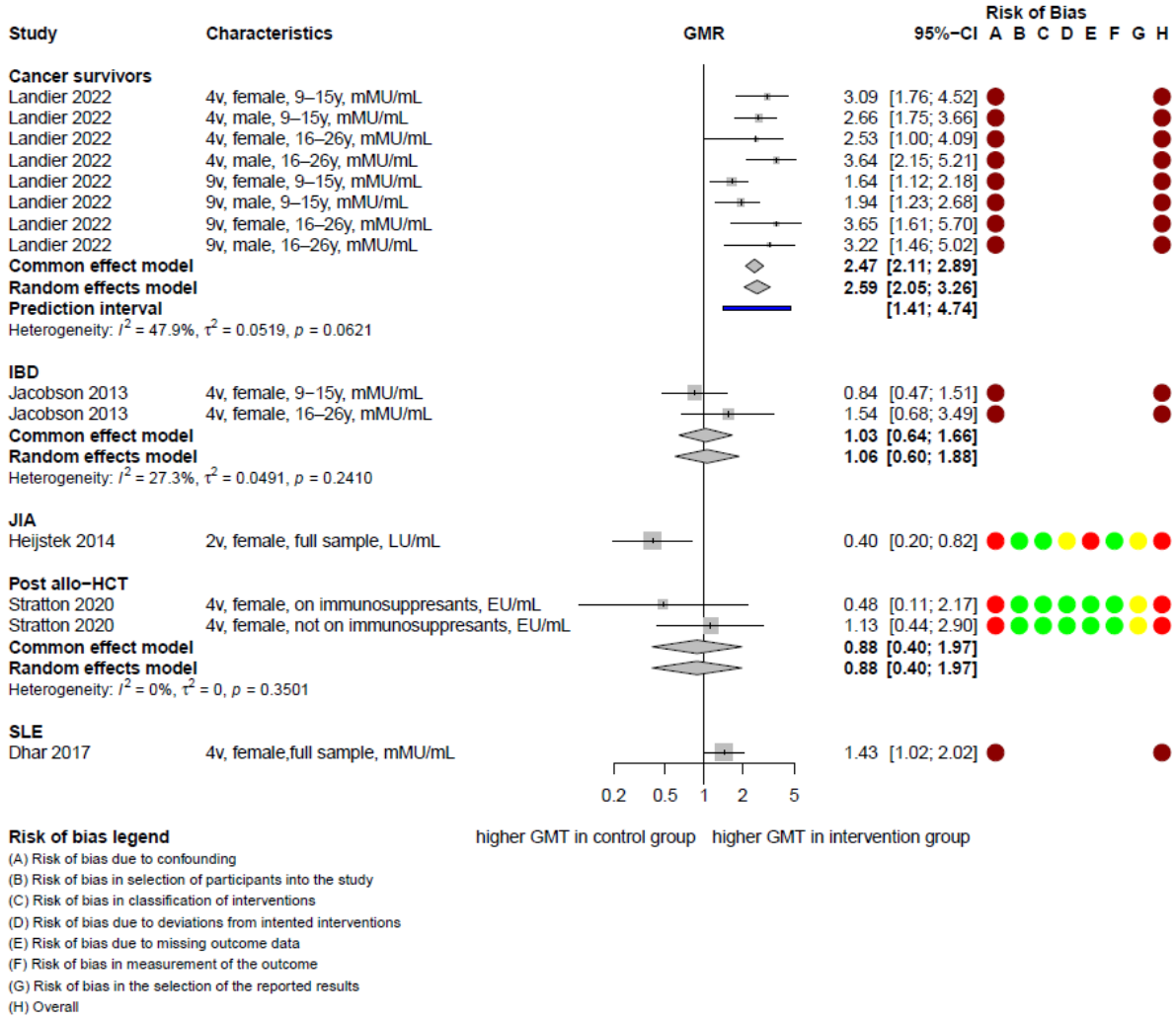
HPV vaccination may result in little to no difference in antibody titres (GMTs) for HPV 16 at seven months between IBD and healthy participants, but the evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision) (1 NRSI [58], low certainty of evidence, see Figure 8, Table 3, Annex G).

The evidence was assessed on post allo-HCT to be very uncertain about the effect of HPV vaccination on antibody titres (GMTs) compared to healthy participants (due to serious concerns in risk of bias and considerable imprecision). The effects of HPV vaccination may be large for HPV 16 in both, the immunocompromised groups (i.e. post allo-HCT participants) or healthy participants (1 NRSI [62], very low certainty of evidence, see Figure 8, Table 3, Annex G).

HPV vaccination may result in higher antibody titres (GMTs) for HPV 16 at seven months in cancer survivors compared to healthy participants, but the evidence was assessed to be uncertain (due to very serious concerns in risk of bias) (1 NRSI [60], low certainty of evidence, see Figure , Table 3, Annex G). Conversely, the evidence suggests that there may be higher antibody titres (GMTs) for HPV 16 at seven months in healthy participants compared to JIA participants, considering that the evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision) (1 NRSI [57], low certainty of evidence, see Figure 8, Table 3, Annex G).

The evidence on SLE was assessed to be very uncertain about the effect of HPV vaccination on seropositivity compared to healthy participants (due to very serious concerns in risk of bias and imprecision). HPV vaccination may result in higher antibody titres (GMTs) for HPV 16 at seven months in SLE compared to healthy participant. The confidence intervals of the effects indicate that there may also be no difference between the groups (1 NRSI [52], very low certainty of evidence see Figure 8, Table 3, Annex G).

Figure 8. GMR of HPV 16 at seven months (comparison 3)



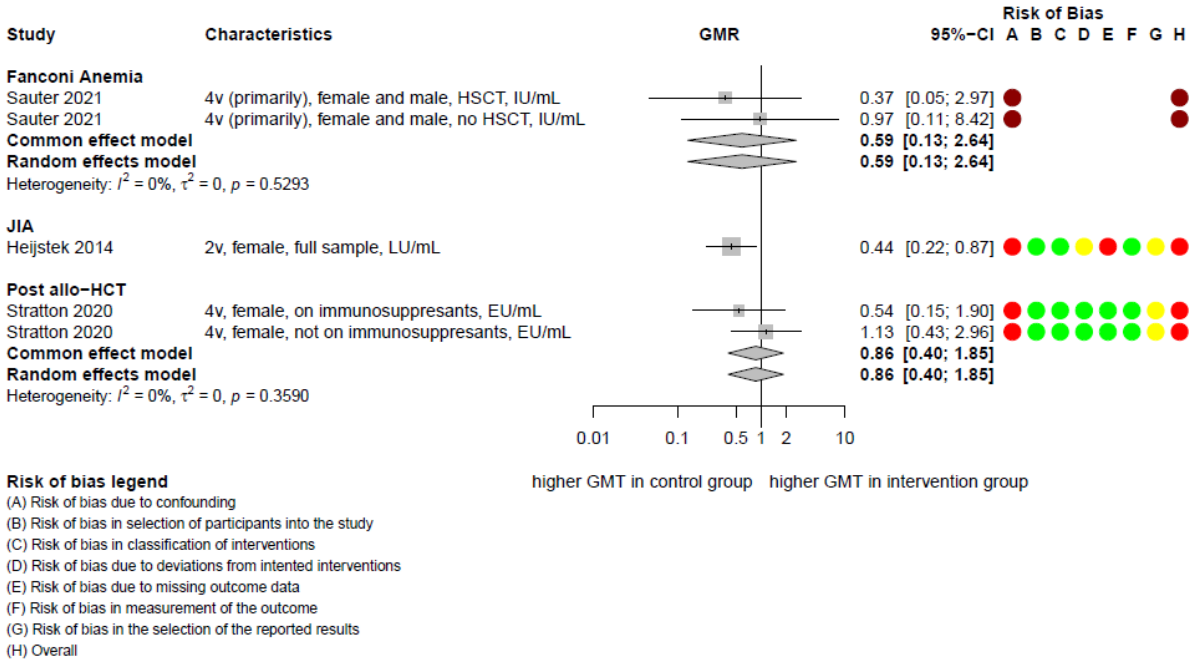
Risk of bias legend
(A) Risk of bias due to confounding
(B) Risk of bias in selection of participants into the study
(C) Risk of bias in classification of interventions
(D) Risk of bias due to deviations from intented interventions
(E) Risk of bias due to missing outcome data
(F) Risk of bias in measurement of the outcome
(G) Risk of bias in the selection of the reported results
(H) Overall

HPV 16 at 12 months and more

The evidence on FA participants was assessed to be very uncertain about the effect of HPV vaccination on antibody titres (GMTs) compared to healthy participants (due to very serious concerns in risk of bias and considerable imprecision). The effects of HPV vaccination may be large for HPV 16 at 12 months and more in both, the FA group or healthy participants group (1 NRSI [64], very low certainty of evidence, see Figure 9, Table 3, Annex G).

HPV vaccination may result in higher antibody titres (GMTs) for HPV 16 at 12 months and more in healthy participants compared to JIA and post allo-HCT participants, but the evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision) (2 NRSI [57, 62], low certainty of evidence, see Figure 9, Table 3, Annex G). Further, the confidence intervals of the effect indicate that there may also be no difference between the groups.

Figure 9. GMR of HPV 16 at 12 months and more (comparison 3)



Risk of bias legend
(A) Risk of bias due to confounding
(B) Risk of bias in selection of participants into the study
(C) Risk of bias in classification of interventions
(D) Risk of bias due to deviations from intented interventions
(E) Risk of bias due to missing outcome data
(F) Risk of bias in measurement of the outcome
(G) Risk of bias in the selection of the reported results
(H) Overall

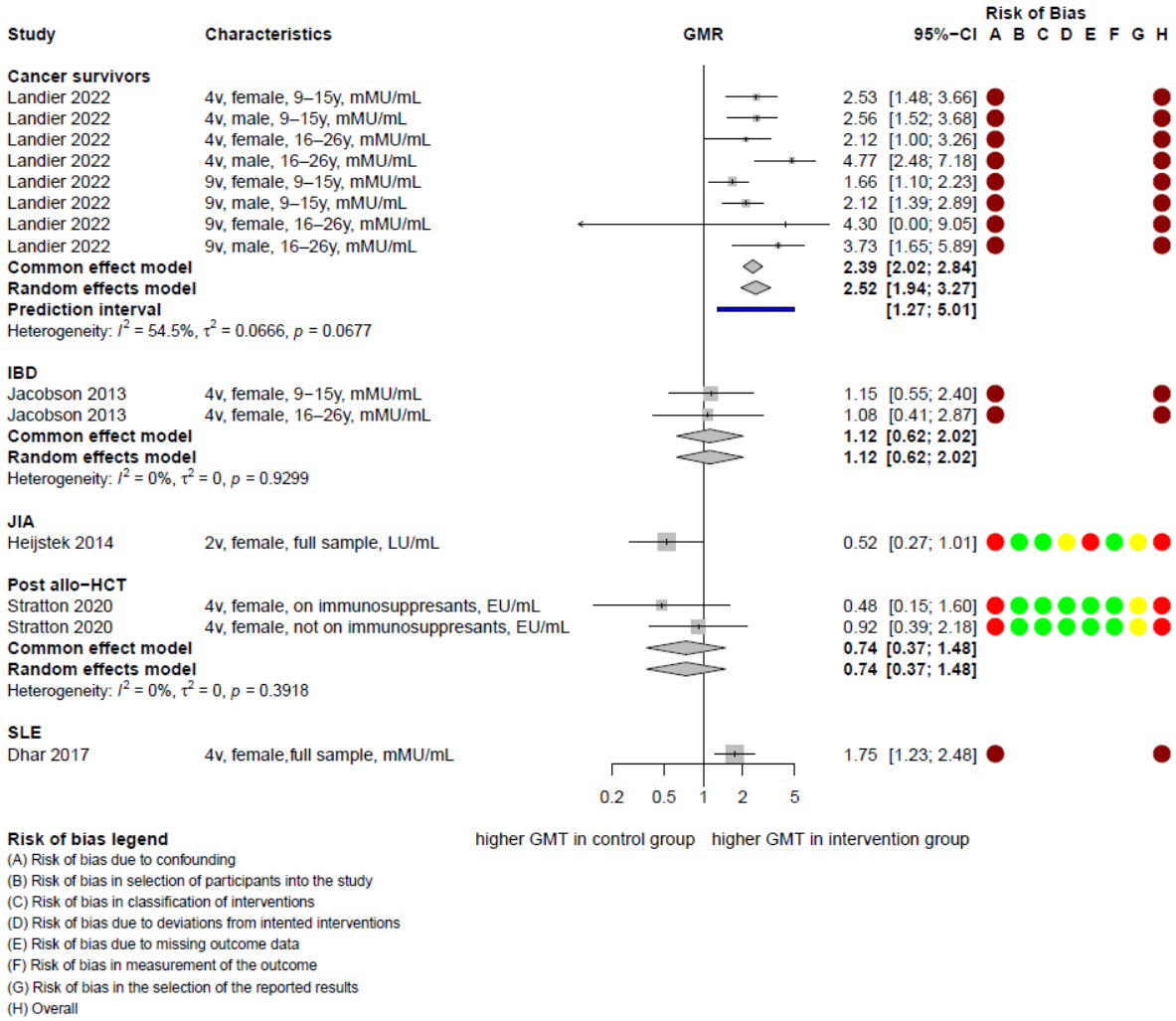
HPV 18 at seven months

HPV vaccination may result in higher antibody titres (GMTs) for HPV 18 at seven months in healthy participants compared to JIA and post allo-HCT participants, but the evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision) (2 NRSI [57, 62], low certainty of evidence, see Figure 10, Table 3, Annex G). Further, the confidence intervals of the effects indicate that there may also be no difference between the groups.

HPV vaccination may result in higher antibody titres (GMTs) for HPV 18 at seven months in cancer survivors compared to healthy participants, but the evidence was assessed to be uncertain (due to very serious concerns in risk of bias) (1 NRSI [60], low certainty of evidence, see Figure 10, Table 3, Annex G).

The evidence on IBD, SLE was assessed to be uncertain to very uncertain about the effect of HPV vaccination on seropositivity compared to healthy participants (due to very serious concerns in risk of bias and imprecision). HPV vaccination may result in higher antibody titres (GMTs) for HPV 18 at seven months in SLE compared to healthy participants. The confidence intervals of the effects indicate that there may also be no difference between the groups (2 NRSI [52, 58], low to very low certainty of evidence see Figure 10, Table 3, Annex G).

Figure 10. GMR of HPV 18 at seven months (comparison 3)

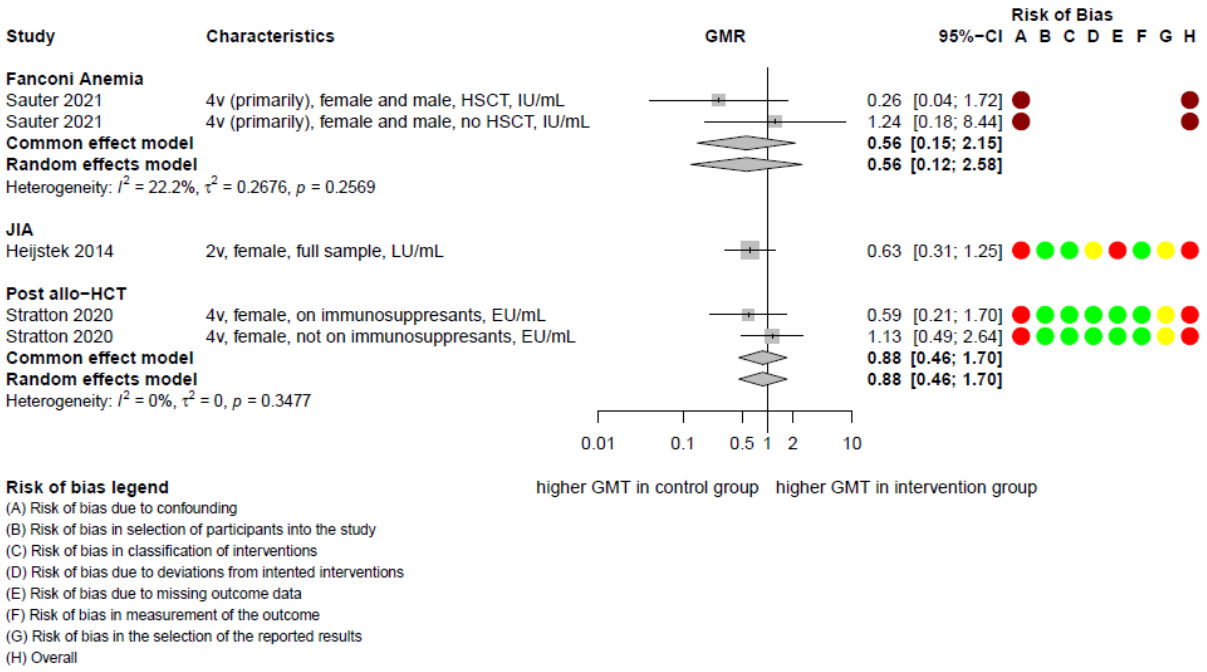


HPV 18 at 12 months and more

The evidence on FA participants was assessed to be very uncertain about the effect of HPV vaccination on antibody titres (GMTs) compared to healthy participants (due to very serious concerns in risk of bias and considerable imprecision). The effects of HPV vaccination may be large for HPV 18 at 12 months and more in both, the FA participant group or healthy participants group (1 NRSI [64], very low certainty of evidence, see Figure 11, Table 3, Annex G).

HPV vaccination may result in higher antibody titres (GMTs) for HPV 18 at 12 months and more in healthy participants compared to JIA and post allo-HCT participants, but the evidence was assessed to be uncertain (due to serious concerns in risk of bias and imprecision) (2 NRSI, low certainty of evidence, see Figure 11, Table 3, Annex G). Further, the confidence intervals of the effect indicate that there may also be no difference between the groups.

Figure 11. GMR of HPV 18 at 12 months and more (comparison 3)



Risk of bias legend
(A) Risk of bias due to confounding
(B) Risk of bias in selection of participants into the study
(C) Risk of bias in classification of interventions
(D) Risk of bias due to deviations from intented interventions
(E) Risk of bias due to missing outcome data
(F) Risk of bias in measurement of the outcome
(G) Risk of bias in the selection of the reported results
(H) Overall

4.4.5 Safety

4.4.5.1 Serious adverse events

Most studies did not report serious adverse events (SAEs) in the HPV vaccination groups (see Table 8) [53, 54, 56, 59, 61, 62]. In particular, HPV vaccination was generally not related to SAEs (e.g., Jacobson et al., 2013; Landier et al., 2022). Heijstek et al. 2014 observed SAEs in 11 out of 68 cases, though they noted that most were related to pre-planned interventions (diagnostic hospital admissions for pre-existing complaints or adverse events associated with the treatment of JIA disease). Jacobson et al. 2013 used a healthy control group based on data from the prescription information for quadrivalent HPV vaccine, which reported SAEs in 128 out of 15.706 participants (0.8%), none of which were fatal. The cohort study by Gomez-Lobo et al. 2014 described no hospitalisations following HPV vaccination among seven kidney transplant recipients and two liver transplant recipients.

4.4.5.2 Other adverse events

All studies reported on local and systemic adverse events (see Table 8). Most common local adverse events across HPV vaccines (i.e. bivalent, quadrivalent and nonavalent HPV vaccine) were pain, induration, erythema or edema [52, 53, 55-62]. Three studies reported that some local events (e.g. edema, erythema and pain) were more frequent in healthy participants compared to the immunocompromised groups [57, 60, 62]. Most common systemic adverse events across HPV vaccines were headache, fatigue and nausea [52, 53, 55-58, 60-62]. Studies did not report any major differences in systemic adverse events compared to healthy participants. Some studies reported additional adverse events, such as rectal bleeding and diarrhea, or disease related adverse events [52, 54, 58, 60, 61].

Table 8. Serious adverse events (comparison 3)

Study	Participants, HPV vaccine	SAE information	Time point, dose	IG: Number of SAE	IG: total number	CG: Number of SAE	CG: total number
Dhar 2017 (including results from Dhar 2018) (52, 73)	SLE, 4v	All SAEs not related to vaccine or SLE, and all resolved	4–6 months safety follow up after the third dose	9	34	NR	NR
Esposito 2014 (53)	JIA, 2v	SAEs, no definition	14 days after first dose	0	21	0	21
			14 days after second dose	0	21	0	21
			14 days after third dose	0	21	0	21
Grein 2020a (55)	SLE, 4v	SAEs, no definition; death; not related to vaccination	After first dose within 14 days (at baseline)	2	201	0	38
		SAEs, no definition;	After second dose within 14 days (Month 1 or 2)	2	210	0	38

Study	Participants, HPV vaccine	SAE information	Time point, dose	IG: Number of SAE	IG: total number	CG: Number of SAE	CG: total number
		death; not related to vaccination					
		SAEs, no definition	After third dose within days (Month 6)	0	180	0	35
Grein 2020b (56)	JDM, 4v	SAEs following vaccination defined as life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires intervention to prevent permanent impairment or damage	After first dose within 14 days (at baseline)	0	40	0	38
			After second dose within 14 days (Month 1 or 2)	0	41	0	38
			After third dose within days (Month 6)	0	40	0	35
Heijstek 2014 (57)	JIA, 4v	SAEs, no definition; majority were preplanned interventions, diagnostic hospital admissions for pre-existing complaints or adverse events associated with the treatment of JIA disease; therefore all SAEs judged to be unrelated to HPV vaccination	14 days after each vaccine dose	11	68	1	55
Jacobson 2013 (58)	IBD, 4v	Admitted to hospital/ went to emergency dept.: Exacerbation of inflammatory bowel disease; unlikely related to the vaccine	Timing relative to dose: Day 3 and 8	2	from 32-35	NR	NR
		Admitted to hospital/ went to emergency dept.: Pneumonia; unlikely related to the vaccine	Timing relative to dose: Week 3	1	from 32-35	NR	NR
		Admitted to hospital/ went to emergency dept.: Endometriosis with an ovarian torsion; unrelated to the vaccine	Timing relative to dose: Day 2	1	from 32-35	NR	NR
		Admitted to hospital/ went to emergency dept.: Sinus pain and ED visit; unrelated to the vaccine	Timing relative to dose: Week 3	1	from 32-35	NR	NR
Kitano 2023 (59)	Transplant, 4v	SAEs defined as adverse events of special interest in previous relevant articles (i.e., autoimmune disease, acute disseminated encephalomyelitis, complex regional pain syndrome, Guillain-Barré syndrome, multiple sclerosis, postural orthostatic tachycardia syndrome and premature ovarian insufficiency) for dose 1-3	7 days after vaccination	0	17	0	19
Landier 2022 (60)	Cancer survivors, 9v	SAEs (all) defined as death, life-threatening conditions, unplanned admission to hospital for longer than 24 h, persistent or substantial disability, second cancer, or other medical event that was deemed by the investigator to jeopardise participant health—were reported in real time until month 24.	24 months, ≥1 dose	12	182	NR	NR
		From those 12 SAEs: vaccine-related only	24 months, ≥1 dose	1	182	NR	NR

Study	Participants, HPV vaccine	SAE information	Time point, dose	IG: Number of SAE	IG: total number	CG: Number of SAE	CG: total number
		From those 12 SAE: death	24 months, ≥1 dose	2	182	NR	NR
	Cancer survivors, 4v	Serious AE (all)	24 months, ≥1 dose	20	253	NR	NR
		From those 20 SAE: vaccine-related only	24 months, ≥1 dose	0	253	NR	NR
		From those 10 SAEs: death	24 months, ≥1 dose	0	253	NR	NR
Mok 2013 (including results from Mok 2018) (61, 74)	SLE, 4v	SAEs, no definition	Within 12 months, ≥1 dose	0	50	0	50
Stratton 2020 (62)	Post allo-HCT, on immunosuppressive drugs, 4v	SAE, no definition (same control group as for subgroup below)	for 5 days after each dose vaccination	0	23	0	20
	Post allo-HCT, not on immunosuppressive drugs, 4v	SAE, no definition (same control group as for subgroup above)	for 5 days after each dose vaccination	0	23	0	20

AE: adverse events; CG: control group; HPV: Human papilloma virus; IG: intervention group; Inflammatory bowel disease; JDM: Juvenile dermatomyositis; JIA: Juvenile idiopathic arthritis; NR: not reported; SAE: serious adverse event; SLE: Systemic lupus erythematosus; 4v: quadrivalent; 9v: nonavalent.

4.4.6 Subgroup analysis

As all immunocompromised groups were analysed separately (e.g., separation of cancer survivors and IBD participants), there was insufficient data to conduct further meaningful subgroup analyses, such as by sex, age, immunosuppressive treatments, or characteristics of the HPV vaccination (as defined in section 3.3.8).

4.4.7 Sensitivity analysis

Sensitivity analyses were possible for the analyses on seropositivity of HPV 16 and 18 at 7 months based on risk of bias (excluding studies with critical risk of bias). The effect for seropositivity of HPV 16 and 18 was comparable to the primary analyses, with effect estimates and 95%-CIs indicating no relevant differences (HPV 16) or a slightly favourable effect (HPV 18) for healthy participants (Annex I). The sensitivity analysis using the fixed-effect model (common-effect model) was consistent with the results from the random-effects model.

4.5 Vaccinated immunocompromised individuals (single-arm studies)

4.5.1 Characteristics of the included studies

Baseline study characteristics

Six single-arm studies [65-71] were included, as detailed in Table 9. Studies were conducted across Europe (n=1, [66]), North America (n=3 [65, 68, 71]), Australia (n=1, [69, 70]) and Asia (n=1, [67]) and published between 2013 and 2021. All studies reported industry [65-67, 71] or mixed (i.e. industry and public, non-profit) funding [68-70].

Participant characteristics and interventions

The age of participants ranged from five to 55 years [65-71]. Two studies included exclusively females [65, 71], while four studies focused on both sexes [66-70]. Participants of identified studies had various underlying conditions, including, CKD, SLE, transplant recipients and mixed groups with various underlying diseases. Four studies reported that participants received immunosuppressive medications at baseline [66, 68-71]. One study reported on participants that received the nonavalent HPV vaccine [66], while the remaining five studies received the quadrivalent HPV vaccine [65, 67-71]. In most studies, the majority of participants of the intervention group received three doses of the HPV vaccine (range: 74.1-100%) [65-67, 69-71], while one study did not give the exact information on dosing [68]. The HPV vaccine was prospectively administered within the study context in most of the studies (n=5) [66-71]. One study obtained the vaccination status from a registry [65].

Table 9. Key study characteristics (single-arm studies)

Study	Country	Clinical condition	Funding	DoI	N Intervention group	Age (years)	Sex (%)	Intervention
Boey 2021 (66)	Belgium	Transplant recipients	Industry	Interests declared	171	Median, range: 46 (19–55)	Female (31) Male (69)	Nonavalent HPV vaccine
Kumar 2013 (68)	Canada	Transplant recipients	Mixed	Interests declared	47	Median, range: 25.9 (18-35)	Female (66) Male (34)	Quadrivalent HPV vaccine
Liu 2018 (65)	Canada	History of immune mediated diseases*	Industry	Interests declared	NA	Range: 12-17	Female (100)	Quadrivalent HPV vaccine
MacIntyre 2016 and 2019 (69, 70)	Australia	Immunocompromised children§	Mixed	Interests declared	59	Mean, range: 12.3 (5–18)	Female (44) Male (56)	Quadrivalent HPV vaccine
Praditpornsilpa 2016 (67)	Thailand	CKD (Stage4-5)	Industry	Interests declared	60	Mean, SD 21.5 6 (4.6)	Female (47) Male (53)	Quadrivalent HPV vaccine
Soybilgic 2013 (71)	USA	SLE	Industry	Interests declared	27	Mean: 20.5	Female (100)	Quadrivalent HPV vaccine

CKD: Chronic kidney desease; DoI: Declaration of Interests; HPV: Human papillomavirus; N: number of participants; SD: standard deviation; SLE: Systemic lupus erythematosus; USA: United States of America
** Including: asthma, anaphylaxis and other atopic manifestations*
§ Including: haematological stem cell transplantation (HSCT), liver transplantation, kidney transplantation, juvenile idiopathic arthritis, inflammatory bowel disease.

4.5.2 Safety

4.5.2.1 Serious adverse events

Boey et al. 2021 reported that eight participants had at least one SAE (e.g. infections and infestations or respiratory, thoracic, and mediastinal disorders) 1-15 days after any vaccine and 28 participants any time within seven months after the first dose. However, none of the SAEs were considered HPV vaccine related and described to be similar to healthy participants [66]. None of the remaining studies reported any SAEs [65, 67-71]. Kumar et al. 2013 did not report any SAEs in 27 cases. MacIntyre et al. 2016 observed no SAEs among 59 participants followed until month 24, and MacIntyre et al. 2019 reported none in 37 participants followed until month 60. Praditpornsilpa et al. 2016 reported no SAEsin 60 participants until month seven. Soybilgic et al. 2013 noted that out of 12 participants with SLE, two experienced worsening renal function during or after the study and progressed to renal failure within 18 months. Liu et al. 2018 did not report on SAEs, but highlighted that 41 out of 681 participants with a history of immune-mediated diseases developed a new autoimmune disorder.

4.5.2.2 Other adverse events

Three studies reported on local and systemic adverse events [66, 68, 70]. Most common local adverse events across HPV vaccines (i.e. bivalent, quadrivalent and nonavalent HPV vaccine) were pain and tenderness at infection side [66, 68]. Most comon systemic adverse events across HPV vaccines were headache and fatigue ([66, 68].

5. Discussion

5.1 Summary of the main results

A total of 27 reports were included with 23 NRSI contributing data to this systematic review. Among these, 14 NRSI provided data for meta-analyses. The risk of bias for most outcomes was rated as serious or critical, primarily due to serious to very serious concerns about confounding, a common methodological issue in NRSI.

Identified studies comprised a wide range of immunocompromised individuals including participants with post allo-HCT, autoimmune diseases, FA, IBD, JIA, SLE, JDM, survivors of cancer, and organ transplant recipients (e.g. liver and kidney). The consideration of all these variable participant groups introduced substantial clinical heterogeneity. This led to the decision by the HPV expert working group to conduct separate meta-analyses and certainty of evidence assessments for each participant group, thereby limiting the ability to perform subgroup and sensitivity analyses (as defined in section 3.3.8), e.g. for sex, age, timing of the vaccination and specific immunosuppressive treatments.

Most of the available evidence was based on the quadrivalent HPV vaccine (20 out of 23 studies, 87%), with the majority of studies comparing vaccinated immunocompromised individuals to vaccinated healthy control participants (comparison 3, 14 out of 23 studies, 61%).

Patient relevant outcomes outlined in the protocol (and described in the methods) – such as precancer or cancer of the cervix, vulva, vagina, penis or anus and oropharyngeal cancer, anogenital warts, HPV infection or mortality caused by HPV-related cancers – were very rarely assessed in the identified NRSI. Only one NRSI, a case-control study by Silverberg et al. 2020, assessed precancer or cancer of the cervix (i.e. CIN 2+ and CIN 3+) comparing a vaccinated immunocompromised group to an unvaccinated immunocompromised control group. Hence, the effect of HPV vaccination on CIN 2+ and CIN 3+ was of very low certainty. As a result, most of the review's findings across all comparisons were based on immunogenicity data (seropositivity and GMR) accompanied by limited safety data.

Overall, the certainty of evidence was very low or low across all comparisons, primarily downgraded due to (very) serious risk of bias and (considerable) imprecision. Interestingly, all vaccinated immunocompromised groups demonstrated similarly high (100 or nearly 100 percent) seroconversion rates (seropositivity) when compared to other vaccinated immunocompromised groups (comparison 2) or to vaccinated healthy control groups (comparison 3), suggesting a ceiling effect for seroconversion. Most immunocompromised groups had similar GMTs compared to healthy control groups (comparison 3) but the results were often imprecise, as the 95% confidence intervals frequently overlapped the null effect of GMR = 1, indicating effects that potentially vary (comparison 3). Seropositivity rates and GMRs were comparable between different time points (i.e. seven months and 12 months and more after first vaccination). All findings from meta-analyses remained robust under the fixed-effect model in sensitivity analyses.

Serious adverse events (e.g. hospital admissions) were rare in the vaccinated groups and were generally deemed unrelated to the HPV vaccine by the study authors. Common local adverse events across HPV vaccine types were pain, induration, erythema and edema, while systemic adverse events frequently included headache, fatigue and nausea.

5.2 Overall completeness and applicability of the evidence

Available evidence per comparison

This systematic review reflects the most recent evidence on the efficacy, effectiveness, immunogenicity and safety of HPV vaccines across a range of immunocompromised individuals. However, data directly comparing vaccinated immunocompromised groups to unvaccinated immunocompromised control groups with the same disease or condition (comparison 1) was rare and derived from NRSI (n=2). Most included studies provided indirect evidence by comparing vaccinated immunocompromised participants to other vaccinated immunocompromised groups with a different disease or condition (comparison 2) (n=2), or to vaccinated healthy control participants (comparison 3) (n=14)[i]. Six studies provided single-arm data on safety.

[i] One study reports data for both, comparison 2 and 3.

Questioning the value of immunogenicity data

Only one case-control study presented data on precancer and cancer of the cervix (i.e. CIN 2+ and CIN 3+). The majority of studies assessed only immunogenicity outcomes (i.e. seropositivity rates and GMRs). However, it is important to interpret immunogenicity data with caution, as no antibody titre thresholds have been established that correlate with protection against HPV-associated cancers [75]. This is particularly true for immunocompromised individuals. Thus, higher GMTs or seropositivity rates do not necessarily indicate better protection. Despite the efforts of WHO to standardise assays and protocols for antibody measurement [76], the methodologies used in different studies remained inconsistent in some cases. Overall, the clinical relevance of immunogenicity outcomes remains uncertain, as there are no validation studies confirming immunogenicity as a reliable surrogate endpoint for patient relevant outcomes. Furthermore, immunogenicity markers are impacted by various factors, including the underlying clinical conditions that affect the immune system, different immunosuppressive medications, timing of the vaccine administration, and prior exposure to HPV [75]. This review encompasses a wide range of immunocompromised participants, each affected by unique factors. As a result, the presented data should not be generalised across different populations.

Generalisability

The studies included in this review predominantly reported immunogenicity data within seven months after the initial vaccination. Some studies, however, also reported extended follow-ups (i.e. 12 months or longer after initial vaccination), showing comparable immunogenicity outcomes. In addition, Mok et al. 2018 reported immunogenicity data at five-years in SLE participants, suggesting sustained immunogenicity in most participants. The single-arm study of MacIntyre et al. 2019 supports these findings, observing similar five-year immunogenicity results in a mixed immunocompromised population[ii]. However, long-term follow-up data is rare and should be interpreted with caution, given the limitations of the study design and inherent risk of bias.

The generalisability of our findings to various subgroups – such as different immunocompromised groups, types of immunosuppressive medications, age, sex, and HPV vaccine types – remains uncertain. However, some studies on transplant recipients suggest that immunogenicity may be suboptimal compared to other populations, though results were often imprecise; 95% confidence intervals frequently overlapped the null effect (RR=1, GMR=1) [50, 51, 59]. Data from single-arm studies support the observation that immunogenicity in transplant recipients may be suboptimal [66, 68].

Most studies reported that participants were under immunosuppressive medications at the study start. As subgroup analyses were not feasible, the impact of specific immunosuppressive medications on immunogenicity could not be further explored.

Studies predominantly enrolled younger and female participants. Only three studies with healthy control groups included male participants [60, 63, 64], but failed to provide robust results. Two studies involved adults over 25 years with SLE, reporting seropositivity rates comparable to those of healthy control participants and other immunocompromised groups [52, 61]. Also, studies reporting participants in the age groups 9-15 and 16-26 years showed comparable results [51, 60]. However, the certainty of the data was assessed to be low to very low and generally deemed insufficient for groups outside the scope of current HPV vaccine programmes. Few studies reported on the bivalent and nonavalent HPV vaccine, thus most data is based on the quadrivalent HPV vaccine. However, the included studies generally reached to similar conclusions on immunogenicity and SAEs across HPV vaccine types.

5.3 Potential limitations of the evidence base and the review process

To avoid potential bias in the review process, this systematic review was conducted close to published guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions [77]. While the possibility of missing unpublished or unregistered studies cannot be entirely ruled out, this is unlikely, since the reference lists of included studies and systematic reviews were thoroughly reviewed. Data on HIV participants and other infectious diseases (e.g. studies on malaria) were not included, as this would have resulted in a much wider and potentially too broad research question. Furthermore, the possibility of baseline differences, such as prior HPV vaccination or pre-existing infections cannot be excluded and may have influenced the results.

It is important to note that risk of bias assessment inherently involves some degree of subjectivity and other reviewers might have come to different conclusions. Subjectivity was minimised by having pairs of reviewers conduct independent assessments and allowing for an in-depth team discussion of the risk of bias judgements. Finally, evidence on patient relevant outcomes (e.g. precancer or cancer of the cervix) is lacking. Evidence is

[ii] Including: haematological stem cell transplantation (HSCT), liver transplantation, kidney transplantation, juvenile idiopathic arthritis, inflammatory bowel disease

mainly based on immunogenicity markers reported by NRSI that were assessed with serious to critical risk of bias. Due to the lacking data, subgroup-analyses was not able to be conducted as had been pre-planned.

5.4 Agreement and disagreement with other studies or reviews

In contrast to previous reviews, this is the first systematic review summarising evidence on the efficacy, effectiveness, immunogenicity and safety of HPV vaccination across various immunocompromised individuals. The narrative review of Garland et al. 2017 concludes that HPV vaccination is highly immunogenic and safe for immunocompromised participants. However, the review authors drew their conclusions primarily based on HIV participants. Concerns in terms of generalisability and study quality were insufficiently assessed or discussed in the review [8].

The review of Vinkenes et al. 2019 presents three studies on transplant recipients, summarising that the findings were inconclusive due to small sample sizes and imprecise results [78]. This current review includes one additional NRSI with control group on transplant recipients published in 2023 [59], but does not alter the mentioned limitations in the data. To date, most evidence on the effect of HPV vaccination in immunocompromised individuals is based on participants with HIV. The systematic review of Staadegard et al. 2022 identified 18 studies, including seven RCTs, showing a robust immune response in HIV participants, but no data on patient relevant outcomes. However, the study found only a few SAEs and the HPV vaccine was deemed safe. Overall, these findings are in alignment with our review findings [13].

6. Conclusions

This systematic review summarises the current evidence on the efficacy, effectiveness, immunogenicity, and safety of HPV vaccines across a broad spectrum of immunocompromised groups. However, data directly comparing vaccinated immunocompromised groups to unvaccinated immunocompromised control groups with the same disease or condition (comparison 1) were rare and only derived from NRSI. Most included studies provided indirect evidence by comparing vaccinated immunocompromised participants to other vaccinated immunocompromised groups with a different disease or condition (comparison 2), or to vaccinated healthy control participants (comparison 3).

Data on patient relevant outcomes (e.g. precancer or cancer of the cervix) are lacking. Most evidence relies on immunogenicity data and some safety outcomes. Overall, the certainty of evidence was low to very low across groups and outcomes, primarily downgraded due to (very) serious risk of bias and (considerable) imprecision. However, seropositivity rates were high across all immunocompromised groups and time points. Most immunocompromised groups had similar GMTs compared to healthy control groups (comparison 3), but the results were often imprecise. Nevertheless, due to the unclear correlate of protection (e.g. towards HPV-associated cancers) and lack of standardisation of assays and protocols for antibody measurement, it is important to interpret data with caution. Furthermore, the immunogenicity results may be influenced by various factors, including the underlying clinical conditions that affect the immune system, different immunosuppressive treatments, timing of the vaccine administration, and prior exposure to HPV. Generalisability is therefore limited. Serious adverse events were rare in the vaccinated immunocompromised groups and generally deemed unrelated to the HPV vaccine by the study authors. Common local adverse events across HPV vaccine types were pain, induration, erythema and edema, while systemic adverse events frequently included headache, fatigue and nausea.

In summary, HPV vaccination appears to be immunogenic and generally safe for immunocompromised individuals, considering that the data is of low to very low certainty of evidence. To date, there is a lack of data on patient-relevant outcomes, such as HPV-associated precancers and cancers. Additionally, more data are needed to differentiate between the variety of immunocompromised groups and subgroups, including differences in sex, age, and specific immunosuppressive treatments.

7. References

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Annex A. Search strategies

Ovid MEDLINE(R) ALL 1946 to May 03, 2024 (searched May 06, 2024)

#	Search	Results
1	exp Papillomavirus Vaccines/	10 620
2	((hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*) and (vaccin* or immuni*)).ti,kf.	11 010
3	((hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*) adj3 (vaccin* or immuni*)).ab.	12 871
4	(cecolin* or cervarix* or gardasil*).mp.	767
5	1 or 2 or 3 or 4	17 081
6	exp Papillomavirus Infections/	44 282
7	exp Papillomaviridae/	39 329
8	(hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*).ti,ab,kf.	67 675
9	Vaccination/ or exp Immunization/	215 696
10	(6 or 7 or 8) and 9	6 455
11	5 or 10	17 658
12	Cancer survivors/	9 845
13	Cancer Care Facilities/	5 950
14	((cancer* or tumor* or tumour* or neoplas* or malignan* or oncolog* or carcinoma* or adenocarcinoma* or choriocarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma* or hodgkin* or nonhodgkin* or lymphoma* or melanoma* or myeloma* or palliative) adj2 (survivor* or survival or treatment* or care)).ti,ab,kf.	363 261
15	exp Transplantation/	580 548
16	((organ or tissue or heart or kidney or liver or lung or pancreas) adj transplant*).ti,ab,kf.	205 065
17	exp Primary Immunodeficiency Diseases/	15 478
18	exp Phagocyte Bactericidal Dysfunction/ or exp Lymphopenia/ or exp Dysgammaglobulinemia/ or Agammaglobulinemia/ or Common Variable Immunodeficiency/	24 076
19	exp Autoimmune Diseases/ or exp Immunocompromised Host/ or exp Hereditary Autoinflammatory Diseases/	601 334
20	(immunocompromis* or autoinflammat* or autoimmune* or asplenia or behcet or cryopyrin* or familial mediterranean fever or mevalonate kinase deficien* or ataxia telangiectasia or bloom syndrome or Chediak Higashi or Leukocyte-Adhesion or Wiskott-Aldrich or rheumatoid arthritis or systemic lupus erythematosus or sle or myasthenia gravis or multiple sclerosis).ti,ab,kf.	516 435
21	exp Immunosuppressive Agents/	349 800
22	exp Immunosuppression Therapy/	67 342
23	Plasmapheresis/	9 284
24	Intravenous Immunoglobulins/ or Immunoglobulins/	60 554
25	Lymphatic Irradiation/	1 322
26	Celecoxib/ or Glatiramer Acetate/ or Minocycline/ or Thalidomide/ or Interleukin 1 Receptor Antagonist Protein/ or Pentoxifylline/ or Glucocorticoid/	105 244
27	Immunogenicity/	3 500
28	(immunologic or immunosuppress* or immunomodulat* or plasmapheresis or immunoglobulin* or (lymph* adj irradiation) or celecoxib or glatiramer or minocycline or thalidomide or anakinra or NP001 or pentoxiphylline or pentoxifylline).ti,ab,kf.	529 174
29	exp Hematologic Diseases/	821 072
30	hematolog*.ti,ab,kf.	137 446
31	exp Hematopoietic Stem Cell Mobilization/	4 543
32	exp Allograft/ or exp Allotransplantation/ or exp Myeloablative Agent/ or exp Bone Marrow Rescue/	12 201
33	exp Graft Versus Host Reaction/	0
34	((allogen* or bone or cell or blood or marrow) adj2 transplant*).ti,ab,kf.	133 883
35	(myeloablative therapy or myeloablative agonist? or allograft? or haematopo?etic or hematopo?etic or haemopo?etic or hemopo?etic or haematocytopo?etic or hematocytopo?etic or HSCT or cotransplant* or coinfus* or co transplant* or co infus* or HLA matched or HLA identical or haploidentical).ti,ab,kf.	228 379
36	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	3 231 342
37	11 and 36	1 391
38	(animals not (humans and animals)).sh.	5 184 144
39	37 not 38	1 310

OVID Embase 1974 to May 03 2024 (searched May 06, 2024)

#	Search	Results
1	exp Papillomavirus Vaccines/	3 297
2	((hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*) and (vaccin* or immuni*)).ti,kf.	14 348
3	((hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*) adj3 (vaccin* or immuni*)).ab.	16 928
4	(cecolin* or cervarix* or gardasil*).mp.	3 465
5	1 or 2 or 3 or 4	22 664
6	exp Papillomavirus Infections/	39 845
7	exp Papillomaviridae/	63 121
8	(hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*).ti,ab,kf.	91 207
9	Vaccination/ or exp Immunization/	392 955
10	(6 or 7 or 8) and 9	17 330
11	5 or 10	26 167
12	Cancer survivors/	31 950
13	Cancer Care Facilities/	48 865
14	((cancer* or tumor* or tumour* or neoplas* or malignan* or oncolog* or carcinoma* or adenocarcinoma* or choriocarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma* or hodgkin* or nonhodgkin* or lymphoma* or melanoma* or myeloma* or palliative) adj2 (survivor* or survival or treatment* or care)).ti,ab,kf.	54 3831
15	exp Transplantation/	1 276 600
16	((organ or tissue or heart or kidney or liver or lung or pancreas) adj transplant*).ti,ab,kf.	346 746
17	exp Primary Immunodeficiency Diseases/	658 599
18	exp Phagocyte Bactericidal Dysfunction/ or exp Lymphopenia/ or exp Dysgammaglobulinemia/ or Agammaglobulinemia/ or Common Variable Immunodeficiency/	62 349
19	exp Autoimmune Diseases/ or exp Immunocompromised Host/ or exp Hereditary Autoinflammatory Diseases/	832 489
20	(immunocompromis* or autoinflammat* or autoimmune* or asplenia or behcet or cryopyrin* or familial mediterranean fever or mevalonate kinase deficien* or ataxia telangiectasia or bloom syndrome or Chediak Higashi or Leukocyte-Adhesion or Wiskott-Aldrich or rheumatoid arthritis or systemic lupus erythematosus or sle or myasthenia gravis or multiple sclerosis).ti,ab,kf.	772 724
21	exp Immunosuppressive Agents/	137 1521
22	exp Immunosuppression Therapy/	264 689
23	Plasmapheresis/	42 717
24	Intravenous Immunoglobulins/ or Immunoglobulins/	142 533
25	Lymphatic Irradiation/	180 079
26	Celecoxib/ or Glatiramer Acetate/ or Minocycline/ or Thalidomide/ or Interleukin 1 Receptor Antagonist Protein/ or Pentoxifylline/ or Glucocorticoid/	235 382
27	Immunogenicity/	81 318
28	(immunologic or immunosuppress* or immunomodulat* or plasmapheresis or immunoglobulin* or (lymph* adj irradiation) or celecoxib or glatiramer or minocycline or thalidomide or anakinra or NP001 or pentoxiphylline or pentoxifylline).ti,ab,kf.	75 1667
29	exp Hematologic Diseases/	286 1881
30	hematolog*.ti,ab,kf.	255 035
31	exp Hematopoietic Stem Cell Mobilization/	8 629
32	exp Allograft/ or exp Allotransplantation/ or exp Myeloablative Agent/ or exp Bone Marrow Rescue/	72 366
33	exp Graft Versus Host Reaction/	82 788
34	((allogen* or bone or cell or blood or marrow) adj2 transplant*).ti,ab,kf.	228 240
35	(myeloablative therapy or myeloablative agonist? or allograft? or haematopo?etic or hematopo?etic or haemopo?etic or hemopo?etic or haematocytopo?etic or hematocytopo?etic or HSCT or cotransplant* or coinfus* or co transplant* or co infus* or HLA matched or HLA identical or haploidentical).ti,ab,kf.	351 508
36	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	6 987 805
37	11 and 36	5 606
38	(exp animal/ or exp invertebrate/ or nonhuman/ or animal experiment/ or animal tissue/ or animal model/ or exp plant/ or exp fungus/) not (exp human/ or human tissue/)	7 910 896
39	37 not 38	5 066

Cochrane CENTRAL (via the Cochrane Register of Studies Online) (searched May 06, 2024)

#	Search	Results
1	MESH DESCRIPTOR Papillomavirus Vaccines EXPLODE ALL AND CENTRAL:TARGET	676
2	((hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*) and (vaccin* or immuni*)):TI,KY AND CENTRAL:TARGET	1 356
3	((hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*) adj3 (vaccin* or immuni*)):AB AND CENTRAL:TARGET	1 430
4	(cecolin* or cervarix* or gardasil*):TI,AB,KY AND CENTRAL:TARGET	264
5	#1 OR #2 OR #3 OR #4	1 749
6	MESH DESCRIPTOR Papillomavirus Infections EXPLODE ALL AND CENTRAL:TARGET	1 095
7	MESH DESCRIPTOR Papillomaviridae EXPLODE ALL AND CENTRAL:TARGET	1 097
8	(hpv* or human papilloma virus* or human papiloma virus* or human papillomavirus* or human papilomavirus*):TI,AB,KY AND CENTRAL:TARGET	4 469
9	MESH DESCRIPTOR Vaccination AND CENTRAL:TARGET	4 771
10	MESH DESCRIPTOR Immunization EXPLODE ALL AND CENTRAL:TARGET	8 067
11	(#6 OR #7 OR #8) AND (#9 OR #10)	460
12	#5 OR #11	1 759
13	MESH DESCRIPTOR Cancer survivors AND CENTRAL:TARGET	977
14	MESH DESCRIPTOR Cancer Care Facilities AND CENTRAL:TARGET	119
15	((cancer* or tumor* or tumour* or neoplas* or malignan* or oncolog* or carcinoma* or adenocarcinoma* or choriocarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma* or hodgkin* or nonhodgkin* or lymphoma* or melanoma* or myeloma* or palliative) adj2 (survivor* or survival or treatment* or care)):TI,AB,KY AND CENTRAL:TARGET	45 687
16	MESH DESCRIPTOR Transplantation EXPLODE ALL AND CENTRAL:TARGET	18 343
17	((organ or tissue or heart or kidney or liver or lung or pancreas) adj transplant*):TI,AB,KY AND CENTRAL:TARGET	15 624
18	MESH DESCRIPTOR Primary Immunodeficiency Diseases EXPLODE ALL AND CENTRAL:TARGET	241
19	MESH DESCRIPTOR Phagocyte Bactericidal Dysfunction EXPLODE ALL AND CENTRAL:TARGET	38
20	MESH DESCRIPTOR Lymphopenia EXPLODE ALL AND CENTRAL:TARGET	128
21	MESH DESCRIPTOR Dysgammaglobulinemia EXPLODE ALL AND CENTRAL:TARGET	17
22	MESH DESCRIPTOR Agammaglobulinemia EXPLODE ALL AND CENTRAL:TARGET	63
23	MESH DESCRIPTOR Common Variable Immunodeficiency EXPLODE ALL AND CENTRAL:TARGET	40
24	MESH DESCRIPTOR Autoimmune Diseases EXPLODE ALL AND CENTRAL:TARGET	26 815
25	MESH DESCRIPTOR Immunocompromised Host EXPLODE ALL AND CENTRAL:TARGET	338
26	MESH DESCRIPTOR Hereditary Autoinflammatory Diseases EXPLODE ALL AND CENTRAL:TARGET	272
27	(immunocompromis* or autoinflammat* or autoimmune* or asplenia or behcet or cryopyrin* or familial mediterranean fever or mevalonate kinase deficien* or ataxia telangiectasia or bloom syndrome or Chediak Higashi or Leukocyte-Adhesion or Wiskott-Aldrich or rheumatoid arthritis or systemic lupus erythematosus or sle or myasthenia gravis or multiple sclerosis):TI,AB,KY AND CENTRAL:TARGET	38 758
28	MESH DESCRIPTOR Immunosuppressive Agents EXPLODE ALL AND CENTRAL:TARGET	26 502
29	MESH DESCRIPTOR Immunosuppression Therapy EXPLODE ALL AND CENTRAL:TARGET	2 972
30	MESH DESCRIPTOR Plasmapheresis AND CENTRAL:TARGET	332
31	MESH DESCRIPTOR Immunoglobulins, Intravenous AND CENTRAL:TARGET	1 107
32	MESH DESCRIPTOR Immunoglobulins AND CENTRAL:TARGET	1 512
33	MESH DESCRIPTOR Lymphatic Irradiation AND CENTRAL:TARGET	90
34	MESH DESCRIPTOR Celecoxib AND CENTRAL:TARGET	1 202
35	MESH DESCRIPTOR Glatiramer Acetate AND CENTRAL:TARGET	471
36	MESH DESCRIPTOR Minocycline AND CENTRAL:TARGET	665
37	MESH DESCRIPTOR Thalidomide AND CENTRAL:TARGET	1111
38	MESH DESCRIPTOR Interleukin 1 Receptor Antagonist Protein AND CENTRAL:TARGET	452
39	MESH DESCRIPTOR Pentoxifylline AND CENTRAL:TARGET	3 125
40	(immunologic or immunosuppress* or immunomodulat* or plasmapheresis or immunoglobulin* or (lymph* adj irradiation) or celecoxib or glatiramer or minocycline or thalidomide or anakinra or NP001 or pentoxiphylline or pentoxifylline):TI,AB,KY AND CENTRAL:TARGET	39 851
41	MESH DESCRIPTOR Hematologic Diseases EXPLODE ALL AND CENTRAL:TARGET	20 431
42	hematolog*:TI,AB,KY AND CENTRAL:TARGET	21 283
43	MESH DESCRIPTOR Hematopoietic Stem Cell Mobilization EXPLODE ALL AND CENTRAL:TARGET	360
44	MESH DESCRIPTOR Allografts EXPLODE ALL AND CENTRAL:TARGET	369
45	MESH DESCRIPTOR Vascularized Composite Allotransplantation EXPLODE ALL AND CENTRAL:TARGET	7
46	((allogen* or bone or cell or blood or marrow) adj2 transplant*):TI,AB,KY AND CENTRAL:TARGET	13 326
47	(myeloablative therapy or myeloablative agonist? or allograft? or haematopo?etic or hematopo?etic or haemopo?etic or hemopo?etic or haematocytopo?etic or hematocytopo?etic or HSCT or cotransplant* or coinfus* or co transplant* or co infus* or HLA matched or HLA identical or haploidentical):TI,AB,KY AND CENTRAL:TARGET	12 869

#	Search	Results
48	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	206 423
49	#12 AND #48	161

ClinicalTrials.gov (searched May 06, 2024)

Conditions: immunocompromised OR autoimmune OR sle OR hematology OR transplant OR ((cancer OR tumor OR carcinoma OR adenocarcinoma OR metastatic OR melanoma) AND (survivor OR survival OR treatment OR care)
Intervention/treatment: (hpv OR human papilloma virus OR human papiloma virus OR human papillomavirus OR human papilomavirus) AND (vaccine OR vaccination OR immune OR immunization)

Annex B. Publications excluded by full text

Abstract (n = 28)

1. Dhar JP, Essenmacher L, Dhar R, Magee A, Ager J, Sokol R: Safety and immunogenicity of quadrivalent human papilloma virus (qHPV) vaccine (gardasil) in systemic lupus erythematous (SLE), phase I trial completion. Arthritis and Rheumatology 2015; 67.
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8. Nailescu C, Slaven J, Saha C, Shew M: The response to human papillomavirus vaccination in pediatric patients before and after kidney transplantation. Pediatric Transplantation 2015; 19: 80.
9. Nelson D, Neu A, Abraham A, Amaral S, Batisky D, Fadrowski J: Immunogenicity of human papillomavirus recombinant vaccine in children with CKD. Pediatric Nephrology 2016; 31: 1747-8.
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Registry entry with corresponding publication report (n = 13)

1. Alberta Uo: Safety and Immunogenicity of Human Papillomavirus (HPV) Vaccine in Solid Organ Transplant Recipients. https://classic.clinicaltrials.gov/show/NCT00677677 2008.
2. Chicago Uo, Sharp M, Llc D: Immunogenicity and Safety of HPV Vaccine Gardasil in Young Women. https://classic.clinicaltrials.gov/show/NCT00786409 2008.
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5. Hospital TM: Long-term Immunogenicity of a HPV Vaccine in SLE. https://classic.clinicaltrials.gov/show/NCT02477254 2015.
6. Institute MHR, Sharp M, Llc D: Does the HPV Vaccine Cause the Same Response in Adolescent Kidney and Liver Transplant Patients as in Healthy Controls? : https://classic.clinicaltrials.gov/show/NCT01101750 2010.
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8. Nct: Long-term Immunogenicity of a HPV Vaccine in SLE. https://clinicaltrialsgov/show/NCT02477254 2015.
9. University JH, Sharp M, Llc D: Antibody Response to Human Papillomavirus Recombinant Vaccine (Gardasil®) in Girls and Young Women With Chronic Kidney Disease. https://classic.clinicaltrials.gov/show/NCT00806676 2008.
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Wrong intervention/exposure (n = 7)

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Wrong outcomes (n = 3)

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Wrong population (n= 178)

1. Arana JE, Harrington T, Cano M, et al.: Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009-2015. Vaccine 2018; 36: 1781-8.
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177. Garland SM, Anagani M, Bhatla N, et al.: Immunogenicity and safety of quadrivalent and 9-valent human papillomavirus vaccines in Indian clinical trial participants. Human Vaccines and Immunotherapeutics 2022; 18: 2105067.
178. Ferris D, Samakoses R, Block SL, et al.: Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics 2014; 134: e657-e65.

Wrong publication type (n = 3)

1. Ogilvie G, Sauvageau C, M DI, et al.: Immunogenicity of 2 vs 3 doses of the quadrivalent human papillomavirus vaccine in girls aged 9 to 13 years after 60 months. JAMA - Journal of the American Medical Association 2017; 317: 1687-8.
2. Keam SJ, Harper DM: Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted, adsorbed) [CervarixTM]. Drugs 2008; 68: 359-72.
3. Borja-Hart NL, Benavides S, Christensen C: Human papillomavirus vaccine safety in pediatric patients: an evaluation of the Vaccine Adverse Event Reporting System. The Annals of pharmacotherapy 2009; 43: 356-9.

Annex C. Included studies

Vaccinated immunocompromised group vs. unvaccinated immunocompromised control group with the same disease or condition (comparison 1)

1. Grönlund O, Herweijer E, Sundström K, Arnheim-Dahlström L. Incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease after quadrivalent human papillomavirus vaccination: a cohort study. Journal of internal medicine. 2016;280(6):618-26.
2. Silverberg MJ, Leyden WA, Lam JO, Chao CR, Gregorich SE, Huchko MJ, et al. Effectiveness of 'catch-up' human papillomavirus vaccination to prevent cervical neoplasia in immunosuppressed and non-immunosuppressed women. Vaccine. 2020;38(29):4520-3.

Vaccinated immunocompromised group vs. other vaccinated immunocompromised control group with a different disease or condition that affects the immune system (comparison 2)

1. Nailescu C, Nelson RD, Verghese PS, Twombley KE, Chishti AS, Mills M, et al. Human Papillomavirus Vaccination in Male and Female Adolescents Before and After Kidney Transplantation: A Pediatric Nephrology Research Consortium Study. Frontiers in pediatrics. 2020;8:46.
2. Nelson DR, Neu AM, Abraham A, Amaral S, Batisky D, Fadrowski JJ. Immunogenicity of Human Papillomavirus Recombinant Vaccine in Children with CKD. Clinical journal of the American Society of Nephrology: CJASN. 2016;11(5):776-84.

Vaccinated immunocompromised group vs. vaccinated healthy control group (comparison 3)

1. Alter BP, Giri N, Pan Y, Savage SA, Pinto LA. Antibody response to human papillomavirus vaccine in subjects with inherited bone marrow failure syndromes. Vaccine. 2014;32(10):1169-73.
2. Dhar JP, Essenmacher L, Dhar R, Magee A, Ager J, Sokol RJ. The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus. Vaccine. 2017;35(20):2642-6.

Secondary publication:
Dhar JP, Essenmacher L, Dhar R, Magee A, Ager J, Sokol RJ. The effect of history of abnormal pap smear or preceding HPV infection on the humoral immune response to Quadrivalent Human Papilloma virus (qHPV) vaccine in women with systemic lupus erythematosus. Human vaccines & immunotherapeutics. 2018;14(9):2318-22.

1. Esposito S, Corona F, Barzon L, Cuoco F, Squarzon L, Marcati G, et al. Immunogenicity, safety and tolerability of a bivalent human papillomavirus vaccine in adolescents with juvenile idiopathic arthritis. Expert review of vaccines. 2014;13(11):1387-93.
2. Grein IHR, Pinto NF, Lobo A, Groot N, Sztajnbok F, da Silva CAA, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in patients with childhood systemic lupus erythematosus: a real-world interventional multi-centre study. Lupus. 2020a;29(8):934-42.
3. Grein IHR, Pinto NBF, Groot N, Martins CB, Lobo A, Aikawa NE, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in patients with juvenile dermatomyositis: a real-world multicentre study. Pediatric rheumatology online journal. 2020b;18(1):87.
4. Gomez-Lobo V, Whyte T, Kaufman S, Torres C, Moudgil A. Immunogenicity of a prophylactic quadrivalent human papillomavirus L1 virus-like particle vaccine in male and female adolescent transplant recipients. Pediatric transplantation. 2014;18(3):310-5.
5. Heijstek MW, Scherpenisse M, Groot N, Tacke C, Schepp RM, Buisman AM, et al. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: A prospective controlled observational cohort study. Annals of the Rheumatic Diseases. 2014;73(8):1500-7.
6. Jacobson DL, Bousvaros A, Ashworth L, Carey R, Shrier LA, Burchett SK, et al. Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. Inflammatory bowel diseases. 2013;19(7):1441-9.
7. Kitano T, Schwartz KL, Abdulnoor M, Garfield H, Booran NK, Avitzur Y, et al. Immunogenicity of a quadrivalent human papillomavirus vaccine in pediatric kidney and liver transplant recipients. Pediatric transplantation. 2023;27(3):e14476.
8. Landier W, Bhatia S, Wong FL, York JM, Flynn JS, Henneberg HM, et al. Immunogenicity and safety of the human papillomavirus vaccine in young survivors of cancer in the USA: a single-arm, open-label, phase 2, non-inferiority trial. The Lancet Child & adolescent health. 2022;6(1):38-48.
9. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Annals of the rheumatic diseases. 2013;72(5):659-64.

Secondary publication:
Mok CC, Ho LY, To CH. Long-term immunogenicity of a quadrivalent human papillomavirus vaccine in systemic lupus erythematosus. Vaccine. 2018;36(23):3301-7.

1. Nelson DR, Neu AM, Abraham A, Amaral S, Batisky D, Fadrowski JJ. Immunogenicity of Human Papillomavirus Recombinant Vaccine in Children with CKD. Clinical journal of the American Society of Nephrology: CJASN. 2016;11(5):776-84.
2. Sauter SL, Zhang X, Romick-Rosendale L, Wells SI, Myers KC, Brusadelli MG, et al. Human papillomavirus oral-and sero-positivity in fanconi anemia. Cancers. 2021;13(6):1-18.

Secondary publication:
Katzenellenbogen RA, Carter JJ, Stern JE, Butsch Kovacic MS, Mehta PA, Sauter SL, et al. Skin and mucosal human papillomavirus seroprevalence in persons with Fanconi Anemia. Clinical and vaccine immunology : CVI. 2015;22(4):413-20.

1. Stratton P, Battiwalla M, Tian X, Abdelazim S, Baird K, Barrett AJ, et al. Immune Response Following Quadrivalent Human Papillomavirus Vaccination in Women After Hematopoietic Allogeneic Stem Cell Transplant: A Nonrandomized Clinical Trial. JAMA oncology. 2020;6(5):696-705.

Single-arm studies

1. Boey L, Curinckx A, Roelants M, Derdelinckx I, Van Wijngaerden E, De Munter P, Vos R, Kuypers D, Van Cleemput J, Vandermeulen C. Immunogenicity and Safety of the 9-Valent Human Papillomavirus Vaccine in Solid Organ Transplant Recipients and Adults Infected With Human Immunodeficiency Virus (HIV). Clin Infect Dis. 2021 Aug 2;73(3):e661-e671.
2. Liu EY, Smith LM, Ellis AK, Whitaker H, Law B, Kwong JC, et al. Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Vaccine Cohort Study. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne. 2018;190(21):E648-E55.
3. Kumar D, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A. Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(9):2411-7.
4. MacIntyre CR, Shaw P, Mackie FE, Boros C, Marshall H, Barnes M, et al. Immunogenicity and persistence of immunity of a quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children. Vaccine. 2016;34(36):4343-50.

Secondary publication:
MacIntyre CR, Shaw PJ, Mackie FE, Boros C, Marshall H, Seale H, et al. Long term follow up of persistence of immunity following quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children. Vaccine. 2019;37(37):5630-6.

1. Praditpornsilpa K, Kingwatanakul P, Deekajorndej T, Rianthavorn P, Susantitaphong P, Katavetin P, et al. Immunogenicity and safety of quadrivalent human papillomavirus types 6/11/16/18 recombinant vaccine in chronic kidney disease stage IV, V and VD. Nephrol Dial Transplant. 2017;32(1):132-6.
2. Soybilgic A, Onel KB, Utset T, Alexander K, Wagner-Weiner L. Safety and immunogenicity of the quadrivalent HPV vaccine in female Systemic Lupus Erythematosus patients aged 12 to 26 years. Pediatric rheumatology online journal. 2013;11:29.

Annex D. Registered studies

Table 10. Registered studies without corresponding publication

Study ID/country	Register link	Type of study/Actual or planed sample size	Status
NCT01687192 / (PRIMAVERA) France	https://clinicaltrials.gov/study/NCT01687192	NRSI / 37	completed - no results posted actual study completion date: 10/2016
NCT00505063/ United States of America	https://clinicaltrials.gov/study/NCT00505063	NRSI / 75	active - not recruiting estimated study completion date: 07/2025
NCT03180359 / (COVAGREF) France	https://clinicaltrials.gov/study/NCT03180359	NRSI / 55	completed - no results posted estimated study completion date: 10/2019
NCT03023631 / United States of America	https://clinicaltrials.gov/study/NCT03023631	NRSI / 48	active - not recruiting estimated study completion date: 05/2025
NCT01896986 / Australia	https://clinicaltrials.gov/study/NCT01896986	NRSI / 37	completed - results posted actual study completion date: 03/2012
NCT03519464 / United States of America	https://clinicaltrials.gov/study/NCT03519464	NRSI / 100	active - recruiting estimated study completion date: 12/2025
NCT05557370 / United States of America	https://clinicaltrials.gov/study/NCT05557370	NRSI / 100	active - recruiting estimated study completion date: 12/2035
NCT00964210 / Australia	https://clinicaltrials.gov/study/NCT00964210	NRSI / 240	completed - no results posted actual study completion date: 04/2011
NCT03036930 / United States of America	https://clinicaltrials.gov/study/NCT03036930	NRSI / 52	active - not recruiting estimated study completion date: 03/2025
NCT05439083 / Spain	https://clinicaltrials.gov/study/NCT05439083	NRSI / 120	active - recruiting estimated study completion date: 03/2025
NCT03100682 / (HPVaxResponse Study) Germany	https://clinicaltrials.gov/study/NCT03100682	NRSI / 140	unknown estimated study completion date: 12/2022
NCT00573651 / (CHASE) United States of America	https://clinicaltrials.gov/study/NCT00573651	NRSI / 43	completed - results posted actual study completion date: 10/2014

Annex E. Additional study characteristics

Table 11. Comparison 1-3, single-arm studies: Additional study characteristics

Study	Immunosuppressive medication at baseline	HPV vaccination status at baseline
C1		
Grönlund 2016 (48)	NR	Study excluded participants with a history of HPV vaccination.
Silverberg 2020 (49)	**Cases:** • One recent (<18 months) immunosuppressive medication: 470 • Two or more medications: 30 **Controls:** • One immunosuppressive medication: 2565 • Two or more immunosuppressive medication: 100	Study only included women eligible for catch-up HPV vaccine since its availability in 2006.
C2		
Nailescu 2020 (50)	• Prednisone, Tacrolimus, Mycophenolate mofetil or Aazathioprine: 38 (61.3%)	Study excluded participants with a history of HPV vaccination.
Nelson 2016 (51)	**Immunocompromised group (CKD)** • Prednisone: 1 (4%) • Tacrolimus: 1 (4%) • Rapamycin: 0 (0%) • Cyclosporin: 2 (8%) • Mycophenolate mofetil: 2 (8%) • Abatacept: 0 (0%) • Leflunomide: 0 (0%) **Immunocompromised group (dialysis):** • Prednisone: 4 (44%) • Tacrolimus: 2 (22%) • Rapamycin: 1 (11%) • Cyclosporin: 0 (0%) • Mycophenolate mofetil: 1 (11%) • Abatacept: 0 (0%) • Leflunomide: 0 (0%) **Immunocompromised group (post kidney transplantation):** • Prednisone: 19 (83%) • Tacrolimus: 17 (74%) • Rapamycin: 3 (13%) • Cyclosporin: 1 (4%) • Mycophenolate mofetil: 15 (65%) • Abatacept: 1 (4%) • Leflunomide: 1 (4%)	Study included those who had been previously vaccinated or started the vaccination series with their primary care physician within 2 years before the enrolment period were eligible for inclusion.
C3		
Alter 2014 (63)	NR	NR
Dhar 2017 (52)	**Information from inclusion criteria:** • Prednisone dose <15 mg/day, and hydroxychloroquine dose <400 mg/day	Study excluded participants with a history of HPV vaccination.
Esposito 2014 (53)	**Immunocompromised group:** • Non-steroidal anti-inflammatory drugs: 10 (47.6%) • Methotrexate: 5 (23.8%) • Etanercept: 6 (28.6)	NR
Grein 2020a (55)	**Immunocompromised group:** • Prednisone: 133 (60.7%) • Azathioprine: 196 (89.5%) • Mycophenolate: 73 (33.3%) • Methotrexate: 16 (7.3%) • Cyclosporine: 13 (5.9%) • Cyclophosphamide: 10 (4.5%) • No medication: 8 (3.6%)	**Immunocompromised group:** • 5 participants received the first dose of the HPV vaccine before the study (remaining doses within study). • Control group: 2 participants received the first and second dose of the HPV vaccine before the study (remaining doses within study).
Grein 2020b (56)	**Immunocompromised group:** • 35 (74.5%) of the participants used at least one immunosuppressive medication	**Immunocompromised group:** • 33 participants received the first dose of the HPV vaccine before the study (remaining doses within study). • 18 participants received the first and second dose of the HPV vaccine before the study (remaining doses within study). **Control group:**

Study	Immunosuppressive medication at baseline	HPV vaccination status at baseline
		• 2 participants received the first and second dose of the HPV vaccine before the study (remaining doses within study).
Gomez-Lobo 2014 (54)	**Immunocompromised group (kidney recipients recruited):** • Tacrolimus: 12 (60%) • Cyclosporine: 1 (5%) • Sirolimus: 1 (5%) • Mycophenolate mofetil: 14 (70%) • Prednisone: 9 (45%) **Immunocompromised group (liver recipients recruited):** • Tacrolimus: 3 (60%) • Sirolimus: 1 (20%) • Mycophenolate mofetil: 1 (20%)	NR
Heijstek 2014 (57)	**Intervention group:** • Methotrexate: 24 (36%) • Non-steroidal anti-inflammatory drugs: 37 (54%) • Other disease modifying antirheumatic drugs: 6 (9%) • Anti-TNFα treatment: 9 (13%) • Anti-IL1 treatment: 1 (1%) • Oral steroids: 0 (0%)	Study excluded participants with a history of HPV vaccination.
Jacobson 2013 (58)	**Immunocompromised group (prospective intervention group):** • TNF-alpha inhibitor: 19 (51%) • Immunomodulator: 18 (49%)	The prospective cohort had not previously received HPV immunization. The previously immunized cohort consisted of patients who had already received the 3-dose Gardasil HPV vaccine series.
Kitano 2023 (59)	**Immunocompromised group (kidney transplant):** • One agent: 0 (0%) • Two agents: 1 (14%) • Three agents: 6 (86%) • Sirolimus: 1 (14%) • Tacrolimus: 6 (86%) • Mycophenolate mofetil: 7 (100%) • Steroid: 6 (86%) **Immunocompromised group (liver transplant):** • One agent: 9 (90%) • Two agents: 1 (10%) • Three agents: 0 (0%) • Sirolimus: 0 (0%) • Tacrolimus: 10 (100%) • Mycophenolate mofetil: 1 (10%) • Steroid: 0 (0%)	Study excluded participants with incomplete vaccination at baseline.
Landier 2022 (60)	**Immunocompromised group:** • Chemotherapy: 414 (95%) • Radiation: 157 (36%) **Other:** • Haematopoietic stem cell transplant: 62 (14%)	Study excluded participants with a history of HPV vaccination.
Mok 2013 (61)	**Immunocompromised group:** • Prednisolone: 35 (70%) • Hydroxychloroquine: 33 (66%) • Azathioprine: 24 (48%) • Mycophenolate mofetil: 9 (18%) • Ciclosporin A: 2 (4%) • Tacrolimus: 5 (10%) Methotrexate: 3 (6%)	Study excluded participants with a history of HPV vaccination.
Nelson 2016 (51)	**Immunocompromised group (CKD):** • Prednisone: 1 (4%) • Tacrolimus: 1 (4%) • Rapamycin: 0 (0%) • Cyclosporin: 2 (8%) • Mycophenolate mofetil: 2 (8%) • Abatacept: 0 (0%) • Leflunomide: 0 (0%) **Immunocompromised group (dialysis):** • Prednisone: 4 (44%) • Tacrolimus: 2 (22%) • Rapamycin: 1 (11%) • Cyclosporin: 0 (0%) • Mycophenolate mofetil: 1 (11%) • Abatacept: 0 (0%)	Study included those who had been vaccinated previously or started the vaccination series with their primary care physician within 2 years before the enrolment period.

Study	Immunosuppressive medication at baseline	HPV vaccination status at baseline
	• Leflunomide: 0 (0%) **Immunocompromised group (post kidney transplantation):** • Prednisone: 19 (83%) • Tacrolimus: 17 (74%) • Rapamycin: 3 (13%) • Cyclosporin: 1 (4%) • Mycophenolate mofetil: 15 (65%) • Abatacept: 1 (4%) • Leflunomide: 1 (4%)	
Sauter 2021 (64)	NR	NR
Stratton 2020 (62)	**Immunocompromised group:** • Receiving immunosuppression: 23 (52.3%) • Rituximab: 8 (18.2%), 2 (5%) during the study	Study excluded women post-transplant with a history of prior HPV vaccination.
Single-arm studies		
Boey 2021 (66)	**Kidney transplant recipients:** • One immunosuppressive agent: 0 (0%) • Two immunosuppressive agents: 38 (67.9%) • Three immunosuppressive agents: 18 (32.1%) • Methylprednisolone: 24 (42.9%) • Azathioprine: 6 (10.7%) • Cyclosporine: 4 (7.1%) • Tacrolimus: 44 (78.6%) • Mycophenolate mofetil: 51 (91.1%) • Sirolimus or Everolimus: 0 (0%) **Heart transplant recipients:** • One immunosuppressive agent: 2 (3.5%) • Two immunosuppressive agents: 55 (96.5%) • Three immunosuppressive agents: 0 (0%) • Methylprednisolone: 3 (5.3%) • Azathioprine: 3 (5.3%) • Cyclosporine: 5 (8.8%) • Tacrolimus: 45 (79.0%) • Mycophenolate mofetil: 50 (87.7%) • Sirolimus or Everolimus: 6 (10.5%) **Lung transplant recipients:** • One immunosuppressive agent: 0 (0%) • Two immunosuppressive agents: 7 (12.1%) • Three immunosuppressive agents: 51 (87.9%) • Methylprednisolone: 56 (96.6%) • Azathioprine: 17 (29.3%) • Cyclosporine: 4 (6.9%) • Tacrolimus: 36 (62.1%) • Mycophenolate mofetil: 53 (91.4%) • Sirolimus or Everolimus: 1 (1.7%) **All transplant recipients:** • One immunosuppressive agent: 2 (1.2%) • Two immunosuppressive agents: 100 (58.5%) • Three immunosuppressive agents: 69 (40.4%) • Methylprednisolone: 83 (48.5%) • Azathioprine: 26 (15.2%) • Cyclosporine: 13 (7.6%) • Tacrolimus: 125 (73.1%) • Mycophenolate mofetil: 154 (90.1%) • Sirolimus or Everolimus: 7 (4.1%)	Study excluded participants with a history of HPV vaccination.
Liu 2018 (65)	NR	Study excluded girls who received HPV vaccination before programme eligibility and those whose vaccination records were either unavailable or inactive.
Kumar 2013 (68)	• Prednisone: 36 (76.6%) • Calcineurin-inhibitor: 43 (91.5%) • Mycophenolate mofetil: 42 (87.5%) • Sirolimus: 3 (6.4%)	NR
MacIntyre 2016 and 2019 (69, 70)	• One immunosuppressive agent: 13 (22.0%) • More than one immunosuppressive agent: 24 (40.7%)	Study excluded participants with a history of HPV vaccination.

Study	Immunosuppressive medication at baseline	HPV vaccination status at baseline
Praditpornsilpa 2016 (67)	Study excluded people receiving immunosuppressive agents.	Study excluded participants with a history of HPV vaccination.
Soybilgic 2013 (71)	• Hydroxychloroquine: 27 (100%) • Prednisone: 16 (59.2%) • Mycophenolate mofetil: 9 (33.3%) • Azathioprine: 9 (33.3%) • Methotrexate: 6 (22.2%) In the past, 14.8% and 18.5% had received cyclophosphamide and rituximab, respectively.	Study excluded participants with a history of HPV vaccination.

CKD: chronic kidney disease; HPV: Human papillomavirus; NR: not reported

Annex F. Detailed risk of bias assessments (ROBINS-I)

Table 12. **Risk of bias for C1 (ROBINS-I)**

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Silverberg 2020 (49)	CIN2+/CIN3+	Serious (Insufficient information on confounding variables for sub-sample of interest; analysis to control differences described; probably not all relevant confounders considered)	Serious (Selection of participants retrospective; selection of participants into the study was probably related to intervention or outcome (due to case-control design)	Moderate (Vaccination status prospectively retrieved from electronic health records; unclear time points of vaccinations; participants received probably the same vaccine type and number of doses)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Moderate (Insufficient information reported on missing data)	Moderate (Retrospective study; assessment probably appropriate and comparable between groups; unclear if follow-up differed between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious

Table 13. **Risk of bias for C2 (ROBINS-I)**

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Nelson 2016 (51)	Immunogenicity outcomes	Serious (Confounding variables measured; probably not all relevant confounders considered)	Serious (Selection of some participants retrospective; selection of participants into the study was probably related to intervention or outcome; not all participants followed from the start of the intervention (i.e. sometimes pre-vaccinated)	Moderate (Vaccination status for retrospective group probably from medical records (verified by physician); unclear if time points of vaccination differ between participants; vaccine types do not differ between participants; doses do not differ between participants)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with incomplete vaccination were excluded from analyses)	Serious (Considerable amount of data missing; reasons for missing participant data insufficiently described; proportion of participants between groups different)	Serious (Assessment appropriate and comparable between groups; follow-up time different between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious
Nailescu 2020 (50)	Immunogenicity outcomes	Serious (Confounding variables measured; differences in sex and race; analysis to control differences described; probably not all relevant confounders considered)	Low Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Intervention groups clearly defined; vaccination status prospectively retrieved and probably recorded by study team)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with incomplete vaccination were excluded from analyses)	Moderate (Insufficient information reported on missing data)	Low (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Nailescu 2020 (50)	Serious adverse events	Serious (Confounding variables measured; differences in sex and race; analysis to control differences described; probably not all relevant confounders considered)	Low Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Intervention groups clearly defined; vaccination status prospectively retrieved and probably recorded by study team)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with incomplete vaccination were excluded from analyses)	Moderate (Insufficient information reported on missing data)	Serious (Unclear blinding of outcome assessments; subjective outcome; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious

Table 14. Risk of Bias for C3 (ROBINS-I)

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Dhar 2017 (52)	Immunogenicity outcomes	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Dhar 2017; Dhar 2018 (52, 73)	Serious adverse events	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Esposito 2014 (53)	Immunogenicity outcomes	Serious (Confounding variables measured; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Intervention groups clearly defined; vaccination status prospectively retrieved and probably recorded by study team)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Moderate (Insufficient information reported on missing data)	Low (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious
Esposito 2014 (53)	Serious adverse events	Serious (Confounding variables measured; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Intervention groups clearly defined; vaccination status prospectively retrieved and probably recorded by study team)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Moderate (Insufficient information reported on missing data)	Serious (Unclear blinding of outcome assessments; subjective measurement; follow-up time probably similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious
Grein 2020a (55)	Immunogenicity outcomes	Serious (Confounding variables measured; some participants in the intervention group were seropositive at baseline, while we had no information for the control group; not all relevant confounders considered)	Serious (Selection of some participants retrospective; selection of participants into the study was probably related to intervention or outcome; not all participants followed from the start of the intervention (i.e. sometimes pre-vaccinated)	Serious (Vaccination status for retrospective group probably self-reported; unclear if time points of vaccination differ between participants; vaccine types do not differ between participants; doses differ between participants)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Serious Data missing; reasons for missing participant data insufficiently described; analysis to address missing data probably insufficient)	Low (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Grein 2020a (55)	Serious adverse events	Serious (Confounding variables measured; some participants in the intervention group were seropositive at baseline, while we had no information for the control group; not all relevant confounders considered)	Serious (Selection of some participants retrospective; selection of participants into the study was probably related to intervention or outcome; not all participants followed from the start of the intervention (i.e. sometimes pre-vaccinated))	Serious (Vaccination status for retrospective group probably self-reported; unclear if time points of vaccination differ between participants; vaccine types do not differ between participants; doses differ between participants)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Serious Data missing; reasons for missing participant data insufficiently described; analysis to address missing data probably insufficient)	Serious (Unclear blinding of outcome assessments; subjective measurement; follow-up time probably similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious
Grein 2020b (56)	Immunogenicity outcomes	Critical (Confounding variables measured; differences in age and seropositivity at baseline between groups; no analysis to control differences described; probably not all relevant confounders considered)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Grein 2020b (56)	SAE	Critical (Confounding variables measured; differences in age and seropositivity at baseline between groups; no analysis to control differences described; probably not all relevant confounders considered)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Heijstek 2014 (57)	Immunogenicity outcomes	Serious (Confounding variables measured; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study was probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Intervention groups clearly defined; vaccination status prospectively retrieved and probably recorded by study team)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with postponed vaccination were excluded from analyses)	Serious (Data missing; reasons for missing participant data insufficiently described)	Low (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (Registry entry (prospective) available; study reports measurement of immunogenecity differently to study registry; however, selection of reported results is unlikely)	Serious

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Heijstek 2014 (57)	Serious adverse events	Serious (Confounding variables measured; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study was probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Intervention groups clearly defined; vaccination status prospectively retrieved and probably recorded by study team)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with postponed vaccination were excluded from analyses)	Serious (Data missing; reasons for missing participant data insufficiently described)	Serious (Unclear blinding of outcome assessments; subjective measurement; follow-up time probably similar between groups)	Moderate (Registry entry (prospective) available; study reports AEs but does not give further information; however, selection of reported results is unlikely)	Serious
Jacobson 2013 (58)	Immunogenicity outcomes	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Jacobson 2013 (58)	Serious adverse events	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Kitano 2023 (59)	Immunogenicity outcomes	Serious (Confounding variables measured; some participants in the intervention group were seropositive at baseline, while we had no information for the control group; probably not all relevant confounders considered)	Serious (Selection of some participants retrospective; selection of participants into the study was probably related to intervention or outcome; not all participants followed from the start of the intervention (i.e. sometimes pre-vaccinated)	Moderate (Vaccination status for retrospective group probably from medical records; unclear if time points of vaccination differ between participants; vaccine types do not differ between participants; doses do not differ between participants)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with incomplete vaccination were excluded from analyses)	Serious (Data missing; reasons for missing participant data insufficiently described; analysis to address missing data probably insufficient)	Serious (assessment appropriate and comparable between groups; follow-up time different between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Kitano 2023 (59)	Serious adverse events	Serious (Confounding variables measured; some participants in the intervention group were seropositive at baseline, while we had no information for the control group; probably not all relevant confounders considered)	Serious (Selection of some participants retrospective; selection of participants into the study was probably related to intervention or outcome; not all participants followed from the start of the intervention (i.e. sometimes pre-vaccinated)	Moderate (Vaccination status for retrospective group probably from medical records; unclear if time points of vaccination differ between participants; vaccine types do not differ between participants; doses do not differ between participants)	Moderate (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study; participants with incomplete vaccination were excluded from analyses)	Moderate (Insufficient information reported on missing data)	Serious (Unclear blinding of outcome assessments; subjective measurement; follow-up time probably similar between groups)	Moderate (No protocol; selection of the reported result unlikely, since the outcome is commonly reported)	Serious
Landier 2022 (60)	Immunogenicity outcomes	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Landier 2022 (60)	Serious adverse events	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Mok 2013 (61)	Immunogenicity outcomes	Serious (Confounding variables measured; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Vaccination status prospectively retrieved and probably recorded from study team; time points of vaccination alike between participants; participants received probably the same vaccine type and number of doses)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Serious (Data missing; reasons for missing participant data insufficiently described; no analysis to address missing data probably insufficient)	Low (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (Registry entry (prospective) available; reporting of registry entry insufficient; selection of the reported result unlikely, since the outcome is commonly reported)	Serious
Mok 2013 (61)	Serious adverse events	Serious (Confounding variables measured; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Vaccination status prospectively retrieved and probably recorded from study team; time points of vaccination alike between participants; participants received probably the same vaccine type and number of doses)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Moderate (Insufficient information reported on missing data)	Serious (Unclear blinding of outcome assessments; subjective measurement; follow-up time probably similar between groups)	Moderate (Registry entry (prospective) available; reporting of registry entry insufficient; selection of the reported result unlikely, since the outcome is commonly reported)	Serious

Study	Outcomes	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended intervention	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Nelson 2016 (51)	Serious adverse events	Critical (Study compares participants to historic control group; considerable confounding expected)	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Sauter 2021 (64)	Immunogenicity outcomes	Critical Insufficient information on confounding variables for sub-sample of interest; study reporting and design indicates risk of considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	No further assessment due to considerable confounding	Critical
Stratton 2020 (62)	Immunogenicity outcomes	Serious (Confounding variables measured; differences in sexually activity, education and ethnicity at baseline between groups, but deemed not related to immunogenicity parameters; probably not all relevant confounders considered)	Low (Selection of participants prospective; selection of participants into the study probably not related to intervention or outcome; participants probably followed from the start of the intervention)	Low (Vaccination status prospectively retrieved and probably recorded from study team; time points of vaccination alike between participants; participants received probably the same vaccine type and number of doses)	Low (We cannot exclude deviations from intended intervention. However, no major deviations are expected in the context of this study)	Low (Data reasonable complete; number of participants with missing outcome data small)	Low (Unclear blinding of outcome assessments; assessment appropriate and comparable between groups; follow-up time similar between groups)	Moderate (Protocol (retrospective) and registry entry (prospective) available; study report measurement of immunogenicity differs to study registry; however, selection of reported results is unlikely)	Serious

Annex G. Outcome data extracted from the included studies

Table 15. Comparison 2: GMT and GMR of HPV 16 at seven months

Study	Clinical condition, intervention, measurement unit	IG: N	IG: GMT	IG: dispersion measure GMT	CG: N	CG: GMT	CG: dispersion measure GMT	GMR (95%-CI)
Nailescu 2020 (50)	Chronic kidney disease (CKD): CKD vs. dialysis patients; mMU/mL	18	Median 5639.5; Mean: 4390.79	IQR: 934-9189	29	Median 1581.5; Mean: 1709.62	IQR: 436-3404	GMR_{Median}: 3.57 GMR_{Mean}: 2.57
Nailescu 2020 (50)	Chronic kidney disease (CKD): CKD vs. transplant patients; mMU/mL	18	Median 5639.5; Mean: 4390.79	IQR: 934-9189	29	Median 436; Mean: 508.43	IQR: 74-4316	GMR_{Median}: 12.94 GMR_{Mean}: 8.64

CG: control group; CI: confidence interval; CKD: chronic kidney disease; GMR: geometric mean ratio; GMT: geometric mean titre; IG: intervention group; IQR: inter-quartile range; mMU/mL: milli-Merck Units per millilitre

Table 16. Comparison 2: GMT and GMR of HPV 18 at seven months

Study	Clinical condition, intervention, measurement unit	IG: N	IG: GMT	IG: dispersion measure GMT	CG: N	CG: GMT	CG: dispersion measure GMT	GMR (95%-CI)
Nailescu 2020 (50)	Chronic kidney disease (CKD): CKD vs. dialysis patients; mMU/mL	18	Median 1406.5; Mean: 1039.62	IQR: 150-5121	29	Median 331.5; Mean: 266.45	IQR: 436-3404	Median GMR_{Median}: 4.24 GMR_{Mean}: 3.90
Nailescu 2020 (50)	Chronic kidney disease (CKD): CKD vs. transplant patients; mMU/mL	18	Median 1406.5; Mean: 1039.62	IQR: 150-5121	29	Median 52; Mean: 91.30	IQR: 74-4316	GMR_{Median}: 27.05 GMR_{Mean}: 11.39

CG: control group; CI: confidence interval; CKD: chronic kidney disease; GMR: geometric mean ratio; GMT: geometric mean titre; IG: intervention group; IQR: inter-quartile range; mMU/mL: milli-Merck Units per millilitre

Table 17. Comparison 3: GMT and GMR of HPV 16 at seven months

Study	Clinical condition, intervention, measurement unit	IG: N	IG: GMT	IG: dispersion measure GMT	CG: N	CG: GMT	CG: dispersion measure GMT	GMR (95%-CI)
Alter 2014 (63)	Fanconi anemia (FA) and other inherited bone marrow failure syndromes (IBMFS); quadrivalent HPV vaccine (probably, just Gardasil mentioned): 11 (92%); Bivalent HPV vaccine: 1 (8%)	Results were reported without summarizing GMTs across patients. Titres were compared to the general population. Authors' conclusion: "Both FA and other IBMFS patients developed antibody levels following vaccination that were similar to those previously described in healthy women, and those levels appeared to be sustained out to 5 years after immunization. Thus, antibody responses to the HPV L1 VLP vaccine in patients with FA and other IBMFS appeared to be similar to the responses reported in the general population, implying potential efficacy against future infections with the HPV types contained in the vaccine."						
Dhar 2017 (52, 73)	SLE, quadrivalent HPV vaccine, mMU/mL	19	3052.1	Lower, upper CI: 2186.8, 4259.9	657	2129.5	Lower, upper CI: 1962.7, 2310.5	1.43 (1.02; 2.02)
Esposito 2014 (53)	Juvenile idiopathic arthritis (JIA), bivalent HPV vaccine, pseudovirion-based neutralization assay (PBNA); SEAP Reporter Gene Assay	21	6834.38	Range: 160-40960	21	12,177.48	Range: 2560-40960	0.56 (NA)
Gomez-Lobo 2014 (54)	Transplant recipients (Kidney), quadrivalent HPV vaccine, mMU/mL	7	6872	NR	850	5168	NR	1.33 (NA)
	Transplant recipients (Liver), quadrivalent HPV vaccine, mMU/mL	1	824	NR	850	5168	NR	0.16 (NA)
Heijstek 2014 (57)	JIA, bivalent HPV vaccine, LU/mL	41	5498.72	Upper CI 9590.79	41	13618.93	Lower, upper CI: 8631.71, 20684.14	0.40 (0.20; 0.82)

Study	Clinical condition, intervention, measurement unit	IG: N	IG: GMT	IG: dispersion measure GMT	CG: N	CG: GMT	CG: dispersion measure GMT	GMR (95%-CI)
Jacobson 2013 (58)	Inflammatory bowel disease (IBD), 9-15 years, quadrivalent HPV vaccine, mMU/mL	20	4155.1	Lower, upper CI: 2339.5, 7379.7	915	4918.5	Lower, upper CI: 4556.6, 5309.1	0.85 (0.47; 1.51)
	IBD, 16-26 years, quadrivalent HPV vaccine, mMU/mL	13	3713.1	Lower, upper CI: 1638.3, 8416.7	3253	2411.3	Lower, upper CI: 2311.1, 2515.9	1.54 (0.68, 3.49)
Kitano 2023 (59)	Transplant recipients (Kidney), quadrivalent HPV vaccine, mMU/mL	4	35.7	NR	3	4391.6	NR	0.01 (NA)
	Transplant recipients (Liver), quadrivalent HPV vaccine, mMU/mL	6	3097.3	NR	3	4391.6	NR	0.71 (NA)
Landier 2022 (60)	Survivors of cancer, female, 9-15, quadrivalent HPV vaccine, mMU/mL	51	15209.7	Lower, upper CI: 10152.4, 20267.1	915	4918.5	Lower, upper CI: 4556.6, 5309.1	3.09 (1.76; 4.52)
	Survivors of cancer, male, 9-15, quadrivalent HPV vaccine, mMU/mL	65	16134.6	Lower, upper CI: 11944.7, 20324.5	882	6056.5	Lower, upper CI: 5601.3, 6548.7	2.66 (1.75; 3.66)
	Survivors of cancer, female, 16-26, quadrivalent HPV vaccine, mMU/mL	28	6107.3	Lower, upper CI: 3149.1, 9065.5	3249	2409.2	Lower, upper CI: 2309, 2513.8	2.53 (1.00; 4.09)
	Survivors of cancer, male, 16-26, quadrivalent HPV vaccine, mMU/mL	65	8740	Lower, upper CI: 6000.6, 11479.5	1136	2403.3	Lower, upper CI: 2243.4, 2574.6	3.64 (2.15; 5.21)
	Survivors of cancer, female, 9-15, nonavalent HPV vaccine, mMU/mL	41	11763.6	Lower, upper CI: 8826.8, 14700.4	2405	7159.9	Lower, upper CI: 6919.7, 7408.5	1.64 (1.12; 2.18)
	Survivors of cancer, male, 9-15, nonavalent HPV vaccine, mMU/mL	53	16419.6	Lower, upper CI: 11743.7, 21095.5	1076	8444.9	Lower, upper CI: 8054.2, 8854.5	1.94 (1.23; 2.68)
	Survivors of cancer, female, 16-26, nonavalent HPV vaccine, mMU/mL	23	11522.9	Lower, upper CI: 6301.3, 16744.5	4361	3159	Lower, upper CI: 3088.6, 3231.1	3.65 (1.61; 5.70)
	Survivors of cancer, male, 16-26, nonavalent HPV vaccine, mMU/mL	32	10770.4	Lower, upper CI: 6127.8, 15412.9	899	3346	Lower, upper CI: 3158.9, 3544.1	3.22 (1.46; 5.02)
Mok 2013 (61)	SLE, quadrivalent HPV vaccine, mMU/mL	39	2791.1	Upper limit: 5567.78	44	3266.37	Upper limit: 7238.7	0.86 (0.30; 2.45)
Nelson 2016 (51)	Chornic kidney disease (CKD), 9-15 years, quadrivalent HPV vaccine, mMU/mL	10	2093	NR	915	4918	NR	0.43 (NA)
	Dialysis, 9-15 years, quadrivalent HPV vaccine, mMU/mL	6	5916	NR	915	4918	NR	1.20 (NA)
	Transplant, 9-15 years, quadrivalent HPV vaccine, mMU/mL	8	409	NR	915	4918	NR	0.08 (NA)
	CKD, 16-26 years, quadrivalent HPV vaccine, mMU/mL	8	2871	NR	3249	2409	NR	1.19 (NA)
	Dialysis, 16-26 years, quadrivalent HPV vaccine, mMU/mL	3	1340	NR	3249	2409	NR	0.56 (NA)
	Transplant, 16-26 years, quadrivalent HPV vaccine, mMU/mL	13	137	NR	3249	2409	NR	0.06 (NA)
Stratton 2020 (62)	Allogeneic cell transplant, quadrivalent HPV vaccine, on immunosuppresants, EU/mL	23	1144.9	Lower, upper CI: 303.3, 4322.3	20	2368.8	Lower, upper CI: 1447.3, 3876.9	0.48 (0.11; 2.17)
	Allogeneic cell transplant, quadrivalent HPV vaccine, not on immunosuppresants, EU/mL	21	2667.2	Lower, upper CI: 1404.5, 5064.9	20	2368.8	Lower, upper CI: 1447.3, 3876.9	1.13 (0.44; 2.90)

CG: control group; CI: confidence interval; CKD: Chronic kidney disease; EU/mL: ELISA-Unit per millilitre; FA: Fanconi anemia; GMR: geometric mean ratio; GMT: geometric mean titre; HPV: Human papillomavirus; IBD: Inflammatory bowel disease; IBMFS: inherited bone marrow failure syndromes; IG: intervention group; JIA: Juvenile idiopathic arthritis; mMU/mL: milli-Merck Units per millilitre; NA: not applicable; NR: not reported; PBNA: pseudoviron-based neutralization assay; SEAP: secreted embryonic alkaline phosphatase; SLE: Systemic lupus erythematosus; VLP: virus-like particles

Table 18. Comparison 3: GMT and GMR of HPV 18 at seven months

Study	Clinical condition, intervention, measurement unit	IG: N	IG: GMT	IG: dispersion measure GMT	CG: N	CG: GMT	CG: dispersion measure GMT	GMR (95%-CI)
Alter 2014 (63)	Fanconi anemia (FA) and other inherited bone marrow failure syndromes (IBMFS); Quadrivalent HPV vaccine (probably, just Gardasil mentioned): 11 (92%); Bivalent HPV vaccine: 1 (8%)	Results were reported as case series without summarizing GMTs across patients. Titres were compared to the general population. Authors' conclusion: "Both FA and other IBMFS patients developed antibody levels following vaccination that were similar to those previously described in healthy women, and those levels appeared to be sustained out to 5 years after immunization. Thus, antibody responses to the HPV L1 VLP vaccine in patients with FA and other IBMFS appeared to be similar to the responses reported in the general population, implying potential efficacy against future infections with the HPV types contained in the vaccine."						
Dhar 2017 (52, 73)	SLE, quadrivalent HPV vaccine, mMU/mL	27	567.7	Lower, upper CI: 404.2, 797.4	722	324.6	Lower, upper CI: 297.6, 354	1.75 (1.23;2.48)
Esposito 2014 (53)	Juvenile idiopathic arthritis (JIA), bivalent HPV vaccine, pseudovirion-based neutralization assay (PBNA); SEAP Reporter Gene Assay	21	5120	Range: 640-20480	21	6347.86	Range: 640-40960	0.81 (NA)
Gomez-Lobo 2014 (54)	Transplant recipients (Kidney), quadrivalent HPV vaccine, mMU/mL	7	1619	NR	850	1064	NR	1.52 (NA)
	Transplant recipients (Liver), quadrivalent HPV vaccine, mMU/mL	1	1616	NR	850	1064	NR	1.52 (NA)
Heijstek 2014 (57)	JIA, bivalent HPV vaccine, LU/mL	41	2926.83	Upper CI 4745.42	41	5589.43	Lower, upper CI: 3584.52, 8778	0.52 (0.27; 0.01)
Jacobson 2013 (58)	Inflammatory bowel disease (IBD), 9-15 years, quadrivalent HPV vaccine, mMU/mL	20	1193.8	Lower, upper CI: 571.1, 2495.5	922	1042.6	Lower, upper CI: 967.6, 1123.3	1.15. (0.55; 2.40)
	IBD, 16-26 years, quadrivalent HPV vaccine, mMU/mL	13	515.5	Lower, upper CI: 195, 1362.8	3571	475.6	Lower, upper CI: 459.2, 492.6	1.08 (0.41, 2.87)
Kitano 2023 (59)	Transplant recipients (Kidney), quadrivalent HPV vaccine, mMU/mL	4	42.4	NR	3	902.6	NR	0.05 (NA)
	Transplant recipients (Liver), quadrivalent HPV vaccine, mMU/mL	6	835.7	NR	3	902.6	NR	0.93 (NA)
Landier 2022 (60)	Survivors of cancer, female, 9-15, quadrivalent HPV vaccine, mMU/mL	54	2638.3	Lower, upper CI: 1792.5, 3484.1	922	1042.6	Lower, upper CI: 967.6, 1123.3	2.53 (1.48; 3.66)
	Survivors of cancer, male, 9-15, quadrivalent HPV vaccine, mMU/mL	66	3472.2	Lower, upper CI: 2407.9, 4536.5	887	1357.4	Lower, upper CI: 1249.4, 1474.7	2.56 (1.52; 3.68)
	Survivors of cancer, female, 16-26, quadrivalent HPV vaccine, mMU/mL	30	1009.6	Lower, upper CI: 582.9, 1436.3	3566	475.2	Lower, upper CI: 458.8, 492.1	2.12 [1.00; 3.26)
	Survivors of cancer, male, 16-26, quadrivalent HPV vaccine, mMU/mL	68	1920	Lower, upper CI: 1210.2, 2629.9	1175	402.6	Lower, upper CI: 374.6, 432.7	4.77 (2.48; 7.18)
	Survivors of cancer, female, 9-15, nonavalent HPV vaccine, mMU/mL	41	3457.2	Lower, upper CI: 2545, 4369.4	2420	2085.5	Lower, upper CI: 2002.2, 2172.3	1.66 (1.10; 2.23)
	Survivors of cancer, male, 9-15, nonavalent HPV vaccine, mMU/mL	50	5559.8	Lower, upper CI: 4081.9, 7037.7	1074	2620.4	Lower, upper CI: 2474.3, 2775.2	2.12 (1.39; 2.89)
	Survivors of cancer, female, 16-26, nonavalent HPV vaccine, mMU/mL	28	3483.3	Lower, upper CI: 408.6, 6557.9	4884	809.9	Lower, upper CI: 789.2, 831.1	4.30 (0.00; 9.05)

Study	Clinical condition, intervention, measurement unit	IG: N	IG: GMT	IG: dispersion measure GMT	CG: N	CG: GMT	CG: dispersion measure GMT	GMR (95%-CI)
	Survivors of cancer, male, 16-26, nonavalent HPV vaccine, mMU/mL	32	3013.4	Lower, upper CI: 1685.1, 4341.6	906	808.2	Lower, upper CI: 754.9, 865.4	3.73 (1.65; 5.89)
Mok 2013 (61)	SLE, quadrivalent HPV vaccine, mMU/mL	38	562.4	Upper limit: 1474.4	40	847.7	Upper limit: 2120.4	0.66 (0.18; 2.51)
Nelson 2016 (51)	Chronic kidney disease (CKD), 9-15 years, quadrivalent HPV vaccine, mMU/mL	10	317	NR	917	1043	NR	0.30 (NA)
	Dialysis, 9-15 years, quadrivalent HPV vaccine, mMU/mL	6	1032	NR	917	1043	NR	0.99 (NA)
	Transplant, 9-15 years, quadrivalent HPV vaccine, mMU/mL	8	61	NR	917	1043	NR	0.06 (NA)
	CKD, 16-26 years, quadrivalent HPV vaccine, mMU/mL	8	429	NR	3329	475	NR	0.90 (NA)
	Dialysis, 16-26 years, quadrivalent HPV vaccine, mMU/mL	3	199	NR	3329	475	NR	0.42 (NA)
	Transplant, 16-26 years, quadrivalent HPV vaccine, mMU/mL	13	36	NR	3329	475	NR	0.08 (NA)
Stratton 2020 (62)	Allogeneic cell transplant, quadrivalent HPV vaccine, on immunosuppresants, EU/mL	23	366.6	Lower, upper CI: 120.6, 1115.1	20	759.5	Lower, upper CI: 555.6, 1038.2	0.48 (0.15; 1.60)
	Allogeneic cell transplant, quadrivalent HPV vaccine, not on immunosuppresants, EU/mL	21	698.3	Lower, upper CI: 333.3, 1463.3	20	759.5	Lower, upper CI: 555.6, 1038.2	0.92 (0.389; 2.18)

CG: control group; CI: confidence interval; CKD: Chronic kidney disease; EU/mL: ELISA-Unit per millilitre; FA: Fanconi anemia; GMR: geometric mean ratio; GMT: geometric mean titre; HPV: Human papillomavirus; IBD: Inflammatory bowel disease; IBMFS: inherited bone marrow failure syndromes; IG: intervention group; JIA: Juvenile idiopathic arthritis; mMU/mL: milli-Merck Units per millilitre; NA: not applicable; NR: not reported; PBNA: pseudoviron-based neutralization assay; SEAP: secreted embryonic alkaline phosphatase; SLE: Systemic lupus erythematosus; VLP: virus-like particles

Annex H. Other adverse events

Table 19. Bivalent vaccine: local adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Juvenile idiopathic arthritis, Esposito 2014 (53); Heijstek 2014 (57)	Any local event, first dose, 14 days after first dose	9	21	42.9	10	21	47.6
	Any local event, second dose, 14 days after second dose	9	21	42.9	9	21	42.9
	Any local event, third dose, 14 days after third dose	6	21	28.6	8	21	38.1
	Bruise, any dose, 14 days after each vaccine dose	14	54	25.9	39	44	88.6
	Edema, any dose, 14 days after each vaccine dose	25	54	46.3	18	44	40.9
	Edema, first dose, 14 days after first dose	5	21	23.8	8	21	38.1
	Edema, second dose, 14 days after second dose	6	21	28.6	7	21	33.3
	Edema, third dose, 14 days after third dose	5	21	23.8	6	21	28.6
	Erythema, any dose, 14 days after each vaccine dose	20	54	37.0	43	44	97.7
	Erythema, first dose, 14 days after first dose	2	21	9.5	4	21	19.0
	Erythema, second dose, 14 days after second dose	3	21	14.3	5	21	23.8
	Erythema, third dose, 14 days after third dose	2	21	9.5	3	21	14.3
	induration, any dose, 14 days after each vaccine dose	26	54	48.1	21	44	47.7
	Pain, any dose, 14 days after each vaccine dose	52	54	96.3	44	44	100.0
	Pain, first dose, 14 days after first dose	9	21	42.9	7	21	33.3
	Pain, second dose, 14 days after second dose	9	21	42.9	6	21	28.6
	Pain, third dose, 14 days after third dose	4	21	19.0	4	21	19.0

AE: adverse event; CG: control group; IG: intervention group; N: number

Table 20. Quadrivalent vaccine: local adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Chronic kidney disease, dialysis and kidney transplant, Nelson 2016 (51)	Bruising, probably any dose, time point NR	1	57	1.8	NA	NA	NA
	Pain, probably any dose, time point NR	8	57	14.0	NA	NA	NA
Fanconi Anemia not on immunosuppression, Stratton 2020 (62)	Edema: Swelling (1 inch) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	4	20	20.0
	Edema: Swelling (2 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Edema: Swelling (3 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Edema: Swelling (>3 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Erythema (mild: 0-1 inch) at injection site, any dose, 5 days after each vaccination (last dose month 6)	2	21	9.5	5	20	25.0
	Erythema (moderate: 2 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Erythema (severe: ≥3 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Pruritus (mild) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Pruritus (moderate or severe) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
	Other local event (bruise, reaction to bandage adhesive, rash) at injection site, any dose, 5 days after each vaccination (last dose month 6)	3	21	14.3	2	20	10.0

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
	Pain (mild) at injection site, any dose, 5 days after each vaccination (last dose month 6)	12	21	57.1	14	20	70.0
	Pain (moderate) at injection site, any dose, 5 days after each vaccination (last dose month 6)	2	21	9.5	6	20	30.0
	Pain (severe) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
Fanconi Anemia on immunosuppression, Stratton 2020 (62)	Edema: Swelling (1 inch) at injection site, any dose, 5 days after each vaccination (last dose month 6)	4	23	17.4	4	20	20.0
	Edema: Swelling (2 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	1	23	4.3	0	20	0.0
	Edema: Swelling (3 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	1	23	4.3	0	20	0.0
	Edema: Swelling (>3 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	23	0.0	0	20	0.0
	Erythema (mild: 0-1 inch) at injection site, any dose, 5 days after each vaccination (last dose month 6)	4	23	17.4	5	20	25.0
	Erythema (moderate: 2 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	23	0.0	0	20	0.0
	Erythema (severe: ≥3 inches) at injection site, any dose, 5 days after each vaccination (last dose month 6)	2	23	8.7	0	20	0.0
	Pruritus (mild) at injection site, any dose, 5 days after each vaccination (last dose month 6)	3	23	13.0	0	20	0.0
	Pruritus (moderate or severe) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	23	0.0	0	20	0.0
	Other local event (bruise, reaction to bandage adhesive, rash) at injection site, any dose, 5 days after each vaccination (last dose month 6)	1	23	4.3	2	20	10.0
	Pain (mild) at injection site, any dose, 5 days after each vaccination (last dose month 6)	11	23	47.8	14	20	70.0
	Pain (moderate) at injection site, any dose, 5 days after each vaccination (last dose month 6)	5	23	21.7	6	20	30.0
	Pain (severe) at injection site, any dose, 5 days after each vaccination (last dose month 6)	0	23	0.0	0	20	0.0
Inflammatory bowel disease, Jacobson 2013 (58)	Edema, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Edema, after dose 2 (month 2)	3	32	9.4	NA	NA	NA
	Edema, after dose 3 (month 6)	2	33	6.1	NA	NA	NA
	Erythema, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Erythema, after dose 2 (month 2)	3	32	9.4	NA	NA	NA
	Erythema, after dose 3 (month 6)	6	33	18.2	NA	NA	NA
	Itching, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Itching, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Itching, after dose 3 (month 6)	2	33	6.1	NA	NA	NA
	Pain, after dose 1 (day 1)	17	35	48.6	NA	NA	NA
	Pain, after dose 2 (month 2)	15	32	46.9	NA	NA	NA
	Pain, after dose 3 (month 6)	17	33	51.5	NA	NA	NA
	Swelling and severe pain in arm (minor adverse event), day 3 relative to dose	1	NR	NA	NA	NA	NA
Juvenile dermatomyositis, Grein 2020b (56)	Bruise, after first dose within 14 days (at baseline)	0	40	0.0	0	38	0.0
	Bruise, after second dose within 14 days (month 1 or 2)	1	41	2.4	1	38	2.6
	Bruise, after third dose within 14 days(month 6)	0	40	0.0	5	35	14.3

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
	Edema, after first dose within 14 days (at baseline)	5	40	12.5	5	38	13.2
	Edema, after second dose within 14 days (month 1 or 2)	4	41	9.8	8	38	21.1
	Edema, after third dose within 14 days(month 6)	1	40	2.5	8	35	22.9
	Redness, after first dose within 14 days (at baseline)	5	40	12.5	4	38	10.5
	Redness, after second dose within 14 days (month 1 or 2)	2	41	4.9	3	38	7.9
	Redness, after third dose within 14 days (month 6)	0	40	0.0	2	35	5.7
	Induration, after first dose within 14 days (at baseline)	6	40	15.0	9	38	23.7
	Induration, after second dose within 14 days (month 1 or 2)	4	41	9.8	4	38	10.5
	Induration, after third dose within 14 days (month 6)	4	40	10.0	5	35	14.3
	Pain, after first dose within 14 days (at baseline)	22	40	55.0	23	38	60.5
	Pain, after second dose within 14 days (month 1 or 2)	19	41	46.3	23	38	60.5
	Pain, after third dose within 14 days (month 6)	16	40	40.0	19	35	54.3
Survivors of cancer, Landier 2022 (60)	Edema, days 1-5 post any dose (with available safety data)	15	253	5.9	1722	8181	21.0
	Erythema, days 1-5 post any dose (with available safety data)	15	253	5.9	1774	8181	21.7
	Pain, days 1-5 post any dose (with available safety data)	90	253	35.6	6168	8181	75.4
Systemic lupus erythematosus, Dhar 2017 (52); Mok 2013 (61)	Any AE: Vaccine site reaction, mostly pain, across all time points	NA	NA	62.0	NA	NA	83.90
	Gastrointestinal (events; none related to vaccine or SLE), across all time points	49 (events)	34	NA	NA	NA	NA
	Erythema and pain at injection site, probably after the vaccine, time point unclear	3	50	6.0	2	50	4.0
	Dermatologic (events; none related to vaccine or SLE)	45 (events)	34	NA	NA	NA	NA
	Rash, probably after the vaccine, time point unclear	1	50	2.0	0	50	0.0
	Rash, during study period	4	27	14.8	NA	NA	NA
Systemic lupus erythematosus (children) Grein 2020a (55)	Bruise, after first dose within 14 days (at baseline)	11	179	6.1	0	38	0.0
	Bruise, after second dose within 14 days (month 1 or 2)	8	182	4.4	1	38	2.6
	Bruise, after third dose within 14 days (month 6)	4	194	2.1	5	35	14.3
	Edema, after first dose within 14 days (at baseline)	21	179	11.7	5	38	13.2
	Edema, after second dose within 14 days (month 1 or 2)	30	182	16.5	8	38	21.1
	Edema, after third dose within 14 days (month 6)	25	194	12.9	8	35	22.9
	Redness, after first dose within 14 days (at baseline)	9	179	5.0	4	38	10.5
	Redness, after second dose within 14 days (month 1 or 2)	14	182	7.7	3	38	7.9
	Redness, after third dose within 14 days (month 6)	9	194	4.6	2	35	5.7
	Induration, after first dose within 14 days (at baseline)	27	179	15.1	9	38	23.7
	Induration, after second dose within 14 days (month 1 or 2)	36	182	19.8	4	38	10.5
	Induration, after third dose within 14 days (month 6)	29	194	14.9	5	35	14.3
	Pain, after first dose within 14 days (at baseline)	109	179	60.9	23	38	60.5

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
	Pain, after second dose within 14 days (month 1 or 2)	87	182	47.8	23	38	60.5
	Pain, after third dose within 14 days (month 6)	71	194	36.6	19	35	54.3
Transplant recipients, Gomez-Lobo 2014 (54); Kitano 2023 (59); Kumar 2013 (68); MacIntyre 2016 (70)	Acute rejection, 1 year after enrolment	2	45	4.4	NA	NA	NA
	Pain at injection site for dose 1-3, 7 days after vaccination	2 (events)	23 (doses)	8.7	0 (events)	57 (doses)	0.0
	Swelling and pain at the injection site, any dose, time point: NR	3	NR	NA	NA	NA	NA
	Tenderness at the injection site, 48h and 7 days after 1 dose	10	45	22.2	NA	NA	NA
	Tenderness at the injection site, 48h and 7 days after 2 dose	1	45	2.2	NA	NA	NA
	Local adverse events within 2 weeks from baseline vaccination	16	57	28.1	NA	NA	NA
	Local adverse events within 2 weeks from dose 2 vaccination at month 2	10	55	18.2	NA	NA	NA
	Local adverse events within 2 weeks from dose 2 vaccination at month 6	8	52	15.4	NA	NA	NA

AE: adverse event; CG: control group; IG: intervention group; N: number; NA: not applicable; NR: not reported; SLE: Systemic lupus erythematosus

Table 21. Nonavalent vaccine: local adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Survivors of cancer, Landier 2022 (60)	Edema, any dose, days 1-5 post any dose (with available safety data)	15	182	8.2	5698	15776	36.1
	Erythema, any dose, days 1-5 post any dose (with available safety data)	17	182	9.3	4859	15776	30.8
	Pain, any dose, days 1-5 post any dose (with available safety data)	84	182	46.2	13118	15776	83.2
Transplant recipients, Boey 2021 (66)	Bruise, any dose, days 1–5 following any vaccination visit	0	170	0.0	NA	NA	NA
	Edema, any dose, days 1–5 following any vaccination visit	14	170	8.2	NA	NA	NA
	Edema: swelling, mild (0 to ≤2.5 cm), any dose, days 1–5 following any vaccination visit	13	170	7.6	NA	NA	NA
	Edema: swelling, moderate (>2.5 to ≤5.0 cm), any dose, days 1–5 following any vaccination visit	2	170	1.2	NA	NA	NA
	Edema: swelling, severe (<5.0 cm), any dose, days 1–5 following any vaccination visit	1	170	0.6	NA	NA	NA
	Erythema, any dose, days 1–5 following any vaccination visit	10	170	5.9	NA	NA	NA
	Erythema, mild (0 to ≤2.5 cm) any dose, days 1–5 following any vaccination visit	9	170	5.3	NA	NA	NA
	Erythema, moderate (>2.5 to ≤5.0 cm), any dose, days 1–5 following any vaccination visit	10	170	5.9	NA	NA	NA
	Erythema, severe (<5.0 cm), any dose, days 1–5 following any vaccination visit	0	170	0.0	NA	NA	NA
	Induration, any dose, days 1–5 following any vaccination visit	0	170	0.0	NA	NA	NA
	Pruritus, any dose, days 1–5 following any vaccination visit	3	170	1.8	NA	NA	NA
	Other, any dose, days 1–5 following any vaccination visit	98	170	57.6	NA	NA	NA
	Other, any dose, days 1–5 following any vaccination visit	14	170	8.2	NA	NA	NA
	Pain, any dose, days 1–5 following any vaccination visit	93	170	54.7	NA	NA	NA
	Pain, mild, any dose, days 1–5 following any vaccination visit	93	170	54.7	NA	NA	NA
	Pain, moderate, any dose, days 1–5 following any vaccination visit	15	170	8.8	NA	NA	NA
	Pain, severe, any dose, days 1–5 following any vaccination visit	0	170	0.0	NA	NA	NA

AE: adverse event; CG: control group; IG: intervention group; N: number; NA: not applicable; NR: not reported

Table 22. Bivalent vaccine: systemic adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Juvenile idiopathic arthritis, Esposito 2014 (53); Heijstek 2014 (57)	At least one systemic event, 14 days after first dose	3	21	14.3	2	21	9.5
	At least one systemic event, 14 days after second dose	1	21	4.8	1	21	4.8
	At least one systemic event, 14 days after third dose	1	21	4.8	1	21	4.8
	Arthralgia (newly onset symptoms or worsening of pre to existing symptoms), 14 days after each vaccine dose	11	54	20.4	6	44	13.6
	Fatigue (newly onset symptoms or worsening of pre to existing symptoms), 14 days after each vaccine dose	30	54	55.6	22	44	50.0
	Fever (>38.5ºC), 14 days after each vaccine dose	6	54	11.1	3	44	6.8
	Fever (≥38°C), 14 days after first dose	0	21	0.0	0	21	0.0
	Fever (≥38°C), 14 days after second dose	0	21	0.0	0	21	0.0
	Fever (≥38°C), 14 days after third dose	0	21	0.0	0	21	0.0
	Headache, 14 days after first dose	1	21	4.8	0	21	0.0
	Headache, 14 days after second dose	0	21	0.0	0	21	0.0
	Headache, 14 days after third dose	0	21	0.0	0	21	0.0
	Headache (newly onset symptoms or worsening of pre to existing symptoms), 14 days after each vaccine dose	22	54	40.7	22	44	50.0
	Malaise, 14 days after first dose	2	21	9.5	1	21	4.8
	Malaise, 14 days after second dose	1	21	4.8	1	21	4.8
	Malaise, 14 days after third dose	1	21	4.8	1	21	4.8
	Myalgia (newly onset symptoms or worsening of pre to existing symptoms), 14 days after each vaccine dose	29	54	53.7	19	44	43.2
	Rash, 14 days after first dose	0	21	0.0	0	21	0.0
	Rash, 14 days after second dose	0	21	0.0	0	21	0.0
	Rash, 14 days after third dose	0	21	0.0	0	21	0.0
	Rash (newly onset symptoms or worsening of pre to existing symptoms), 14 days after each vaccine dose	11	54	20.4	6	44	13.6
	Syncope after vaccination (newly onset symptoms or worsening of pre to existing symptoms), 14 days after each vaccine dose	1	54	1.9	0	44	0.0
	Vomiting/diarrhea, 14 days after first dose	1	21	4.8	1	21	4.8
	Vomiting/diarrhea, 14 days after second dose	0	21	0.0	0	21	0.0
	Vomiting/diarrhea, 14 days after third dose	0	21	0.0	0	21	0.0

AE: adverse event; CG: control group; IG: intervention group; N: number

Table 23. Quadrivalent HPV vaccine: systemic adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Chronic kidney disease, dialysis and kidney transplant, Nailescu 2020 (50); Nelson 2016 (51)	Acute rejection, probably any dose, time point NR	2	23	8.6	NA	NA	NA
	Acute rejection period, 6 months (following last dose)	2	29	6.9	NA	NA	NA
	Headache, probably any dose, time point NR	2	57	3.5	NA	NA	NA
Fanconi anemia not on immunosuppression, Stratton 2020 (62)	Fatigue or Flu-like symptom (includes any reported fatigue, dizziness, systemic weakness, aches, malaise, lethargy or nausea), 5 days after each vaccination (last dose month 6)	4	21	19.0	4	20	20.0
	Headache, 5 days after each vaccination (last dose month 6)	5	21	23.8	1	20	5.0
	Other event (bladder pain, back pain, edema, difficulty sleeping), 5 days after each vaccination (last dose month 6)	2	21	9.5	0	20	0.0
	5 days after each vaccination (last dose month 6)	0	21	0.0	0	20	0.0
Fanconi anemia on immunosuppression, Stratton 2020 (62)	Fatigue or flu-like symptom (includes any reported fatigue, dizziness, systemic weakness, aches, malaise, lethargy or nausea), 5 days after each vaccination (last dose month 6)	7	23	30.4	4	20	20.0
	Headache, 5 days after each vaccination (last dose month 6)	1	23	4.3	1	20	5.0
	Other event (bladder pain, back pain, edema, difficulty sleeping), 5 days after each vaccination (last dose month 6)	2	23	8.7	0	20	0.0
	5 days after each vaccination (last dose month 6)	2	23	8.7	0	20	0.0
Inflammatory bowel disease, Jacobson 2013 (58)	Abdominal pain (minor adverse event), week 2, (relative to dose)	3	NR	NA	NA	NA	NA
	Allergic asthma wheezing, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Allergic asthma wheezing, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Allergic asthma wheezing, after dose 3 (month 6)	0	33	0.0	NA	NA	NA
	Dizziness, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Dizziness, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Dizziness, after dose 3 (month 6)	0	33	0.0	NA	NA	NA
	Fatigue, after dose 1 (day 1)	1	35	2.9	NA	NA	NA
	Fatigue, after dose 2 (month 2)	3	32	9.4	NA	NA	NA
	Fatigue, after dose 3 (month 6)	1	33	3.0	NA	NA	NA
	Headache, after dose 1 (day 1)	3	35	8.6	NA	NA	NA
	Headache, after dose 2 (month 2)	3	32	9.4	NA	NA	NA
	Headache, after dose 3 (month 6)	2	33	6.1	NA	NA	NA
	Hives, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Hives, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Hives, after dose 3 (month 6)	0	33	0.0	NA	NA	NA
	Low grade fever, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Low grade fever, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Low grade fever, after dose 3 (month 6)	0	33	0.0	NA	NA	NA
	Migraine (minor adverse event), month 3	1	NR	NA	NA	NA	NA
	Nausea, after dose 1 (day 1)	1	35	2.9	NA	NA	NA
	Nausea, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Nausea, after dose 3 (month 6)	3	33	9.1	NA	NA	NA
	Rash on their chin (minor adverse event), day 2 (relative to dose)	1	NR	NA	NA	NA	NA
	Respiratory distress, after dose 1 (day 1)	0	35	0.0	NA	NA	NA
	Respiratory distress, after dose 2 (month 2)	0	32	0.0	NA	NA	NA
	Respiratory distress, after dose 3 (month 6)	0	33	0.0	NA	NA	NA
Juvenile dermatomyositis, Grein 2020b (56)	Fainting, after first dose within 14 days (at baseline)	0	40	0.0	0	38	0.0
	Fainting, after second dose within 14 days (month 1 or 2)	0	41	0.0	0	38	0.0
	Fainting, after third dose within 14 days (month 6)	0	40	0.0	0	35	0.0
	Fatigue, after first dose within 14 days (at baseline)	6	40	15.0	7	38	18.4
	Fatigue, after second dose within 14 days (month 1 or 2)	4	41	9.8	7	38	18.4
	Fatigue, after third dose within 14 days (month 6)	4	40	10.0	5	35	14.3
	Fever, after first dose within 14 days (at baseline)	1	40	2.5	0	38	0.0
	Fever, after second dose within 14 days (month 1 or 2)	1	41	2.4	0	38	0.0
	Fever, after third dose within 14 days (month 6)	0	40	0.0	1	35	2.9

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
	Headache, after first dose within 14 days (at baseline)	9	40	22.5	10	38	26.3
	Headache, after second dose within 14 days (month 1 or 2)	10	41	24.4	10	38	26.3
	Headache, after third dose within 14 days (month 6)	6	40	15.0	7	35	20.0
	Initial or worsened articular pain, after first dose within 14 days (at baseline)	1	40	2.5	0	38	0.0
	Initial or worsened articular pain, after second dose within 14 days (month 1 or 2)	1	41	2.4	0	38	0.0
	Initial or worsened articular pain, after third dose within 14 days (month 6)	0	40	0.0	0	35	0.0
	Initial or worsened muscular pain, after first dose within 14 days (at baseline)	2	40	5.0	2	38	5.3
	Initial or worsened muscular pain, after second dose within 14 days (month 1 or 2)	2	41	4.9	1	38	2.6
	Initial or worsened muscular pain, after third dose within 14 days (month 6)	0	40	0.0	0	35	0.0
	Itchiness, after first dose within 14 days (at baseline)	1	40	2.5	1	38	2.6
	Itchiness, after second dose within 14 days (month 1 or 2)	3	41	7.3	1	38	2.6
	Itchiness, after third dose within 14 days (month 6)	7	40	17.5	0	35	0.0
	Nausea, after first dose within 14 days (at baseline)	9	40	22.5	1	38	2.6
	Nausea, after second dose within 14 days (month 1 or 2)	1	41	2.4	2	38	5.3
	Nausea, after third dose within 14 days (month 6)	2	40	5.0	4	35	11.4
	New cutaneous abnormalities (patients described new rash on face or on body, that subsided in a maximum of 4 days), after first dose within 14 days (at baseline)	2	40	5.0	0	38	0.0
	New cutaneous abnormalities (patients described new rash on face or on body, that subsided in a maximum of 4 days), after second dose within 14 days (month 1 or 2)	1	41	2.4	0	38	0.0
	New cutaneous abnormalities (patients described new rash on face or on body, that subsided in a maximum of 4 days), after third dose within 14 days (month 6)	1	40	2.5	0	35	0.0
	Vomiting, after first dose within 14 days (at baseline)	2	40	5.0	0	38	0.0
	Vomiting, after second dose within 14 days (month 1 or 2)	0	41	0.0	0	38	0.0
	Vomiting, after third dose within 14 days (month 6)	0	40	0.0	0	35	0.0
Survivors of cancer, Landier 2022 (60)	Dizziness, 15 days post any dose	47	253	18.6	NR	8181	NA
	Fatigue, 15 days post any dose	10	253	4.0	670	10115	6.6
	Fever ≥37·8°C, 1-5 days post any dose	53	253	20.9	NR	8181	NA
	Headache, 15 days post any dose	29	253	11.5	403	8181	4.9
	Nausea, 15 days post any dose	47	253	18.6	NR	8181	NA
Systemic lupus erythematosus Mok 2013 (61)	Headache, any dose, within 12 months	1	50	2.0	1	50	2.0
	Nausea, any dose, within 12 months	1	50	2.0	0	50	0.0
Systemic lupus erythematosus (children), Grein 2020a (55)	Articular pain, after first dose within 14 days (at baseline)	21	179	11.7	3	38	7.9
	Articular pain, after second dose within 14 days (month 1 or 2)	28	182	15.4	3	38	7.9
	Articular pain, after third dose within 14 days (month 6)	16	194	8.2	2	35	5.7
	Fainting, after first dose within 14 days (at baseline)	0	179	0.0	0	38	0.0
	Fainting, after second dose within 14 days (month 1 or 2)	0	182	0.0	0	38	0.0
	Fainting, after third dose within 14 days (month 6)	0	194	0.0	0	35	0.0
	Fatigue, after first dose within 14 days (at baseline)	48	179	26.8	7	38	18.4
	Fatigue, after second dose within 14 days (month 1 or 2)	37	182	20.3	7	38	18.4
	Fatigue, after third dose within 14 days (month 6)	26	194	13.4	5	35	14.3
	Fever, after first dose within 14 days (at baseline)	3	179	1.7	0	38	0.0
	Fever, after second dose within 14 days (month 1 or 2)	2	182	1.1	0	38	0.0
	Fever, after third dose within 14 days (month 6)	2	194	1.0	1	35	2.9
	Headache, after first dose within 14 days (at baseline)	60	179	33.5	10	38	26.3
	Headache, after second dose within 14 days (month 1 or 2)	42	182	23.1	10	38	26.3
	Headache, after third dose within 14 days (month 6)	30	194	15.5	7	35	20.0
	Itchiness, after first dose within 14 days (at baseline)	9	179	5.0	1	38	2.6

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
	Itchiness, after second dose within 14 days (month 1 or 2)	3	182	1.6	1	38	2.6
	Itchiness, after third dose within 14 days (month 6)	1	194	0.5	0	35	0.0
	Muscular pain, after first dose within 14 days (at baseline)	26	179	14.5	4	38	10.5
	Muscular pain, after second dose within 14 days (month 1 or 2)	19	182	10.4	4	38	10.5
	Muscular pain, after third dose within 14 days (month 6)	18	194	9.3	2	35	5.7
	Nausea, after first dose within 14 days (at baseline)	28	179	15.6	1	38	2.6
	Nausea, after second dose within 14 days (month 1 or 2)	26	182	14.3	2	38	5.3
	Nausea, after third dose within 14 days (month 6)	14	194	7.2	4	35	11.4
	Skin abnormalities, after first dose within 14 days (at baseline)	9	179	5.0	0	38	0.0
	Skin abnormalities, after second dose within 14 days (month 1 or 2)	3	182	1.6	0	38	0.0
	Skin abnormalities, after third dose within 14 days (month 6)	0	194	0.0	0	35	0.0
	Vomiting, after first dose within 14 days (at baseline)	6	179	3.4	0	38	0.0
	Vomiting, after second dose within 14 days (month 1 or 2)	5	182	2.7	0	38	0.0
	Vomiting, after third dose within 14 days (month 6)	1	194	0.5	0	35	0.0
Transplant recipients, Gomez-Lobo 2014 (54); Kumar 2013 (68); MacIntyre 2016 (70)	Dizziness, 48h and 7 days after 1 dose	1	45	2.2	NA	NA	NA
	Fatigue, 48h and 7 days after 1 dose	4	45	8.9	NA	NA	NA
	Fever, 48h and 7 days after 1 dose	1	45	2.2	NA	NA	NA
	Fever, 48h and 7 days after 2 dose	1	45	2.2	NA	NA	NA
	Fever, any dose, time point NR	4	NR	NA	NA	NA	NA
	Diarrhea, any dose, time point NR	1	NR	NA	NA	NA	NA
	Headache, any dose, time point NR	1	NR	NA	NA	NA	NA
	Headache, 48h and 7 days after 1 dose	1	45	2.2	NA	NA	NA
	Systemic adverse events, within 2 weeks from baseline vaccination	9	57	15.8	NA	NA	NA
	Systemic adverse events, within 2 weeks from dose 2 vaccination at month 2	7	55	12.7	NA	NA	NA
	Systemic adverse events, within 2 weeks from dose 2 vaccination at month 6	3	52	5.8	NA	NA	NA

AE: adverse event; CG: control group; IG: intervention group; N: number; NA: not applicable; NR: not reported

Table 24. Nonavalent HPV vaccine: systematic adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Survivors of cancer, Landier 2022 (60)	Dizziness, 15 days post any dose	2	182	1.1	355	15776	2.3
	Fatigue, 15 days post any dose	24	182	13.2	294	15776	1.9
	Fever (≥37.8°C), 1-5 days post any dose	12	182	6.6	661	9354	7.1
	Headache, 15 days post any dose	33	182	18.1	2090	15776	13.2
	Nausea, 15 days post any dose	21	182	11.5	503	15776	3.2
Transplant recipients, Boey 2021 (66)	All systemic events, days 1–15 following any vaccination visit	74	170	43.5	NA	NA	NA
	Vaccine-related systemic events, days 1–15 following any vaccination visit	35	170	20.6	NA	NA	NA
	Dizziness, vaccine-related, days 1–15 following any vaccination visit	0	170	0.0	NA	NA	NA
	Fatigue, vaccine-related, days 1–15 following any vaccination visit	5	170	2.9	NA	NA	NA
	Headache, vaccine-related, days 1–15 following any vaccination visit	14	170	8.2	NA	NA	NA
	Nausea, vaccine-related, days 1–15 following any vaccination visit	4	170	2.4	NA	NA	NA
	Pyrexia (≥37.8°C), days 1–15 following any vaccination visit	2	170	1.2	NA	NA	NA
	Other vaccine-related systemic events, days 1–15 following any vaccination visit	23	170	13.5	23	170	13.5

AE: adverse event; CG: control group; IG: intervention group; N: number; NA: not applicable

Table 25. Quadrivalent vaccine: additional adverse events

Population, study	AE, dose, time point	N IG	Total IG	% IG	N CG	Total CG	% CG
Inflammatory bowel disease, Jacobson 2013 (58)	Asthma-related (minor AE), day 5 (relative to dose)	1	NR	NA	NA	NA	NA
	Axillary abscess, day 9 (relative to vaccine)	1	NR	NA	NA	NA	NA
	Leg pain, day 1 (relative to dose)	1	NR	NA	NA	NA	NA
	Rectal bleeding and diarrhea, days 2 and 23 (relative to dose)	2	NR	NA	NA	NA	NA
Survivors of cancer, Landier 2022 (60)	>1 AE (any type), across all time points	129	253	51,0	NR	NR	NR
Systemic lupus erythematosus, Dhar 2017 (52); Mok 2013 (61)	Irregular menses, any dose, within 12 months	1	50	2.0	1	50	2.0
	General disorders (events; none related to vaccine or SLE), any dose, across all time points	45 (events)	34	NA	NA	NA	NA
	Musculoskeletal (events; none related to vaccine or SLE), any dose, across all time points	106 (events)	34	NA	NA	NA	NA
	Nervous system (mostly headaches) (events; none related to vaccine or SLE), any dose, across all time points	98 (events)	34	NA	NA	NA	NA
	Total (events; none related to vaccine or SLE), any dose, across all time points	493 (events)	33	NA	NA	NA	NA
	Upper respiratory tract infection, any dose, within 12 months	1	50	2.0	1	50	2.0
Transplant recipients, Gomez-Lobo 2014 (54)	Acne, probably any dose, time point NR	1	NR	NA	NA	NA	NA
	Cough, probably any dose, time point NR	1	NR	NA	NA	NA	NA
	Pneumonia, probably any dose, time point NR	1	NR	NA	NA	NA	NA

AE: adverse event; CG: control group; IG: intervention group; N: number; NA: not applicable; NR: not reported; SLE: Systemic lupus erythematosus

Annex I. Sensitivity analyses

Table 26. Sensitivity analyses

Outcome/characteristics for sensitivity analyses	Estimate	Heterogeneity (I^2)	Studies	Participants
Seropositivity of HPV 16 at 7 months (comparison 3), SLE				
NRSI: Random-effect model (primary analysis)	**RR 0.988** (0.945 to 1.033)	81%	3	898
NRSI: Random-effect model, exclusion of critical risk of bias*	**RR 0.965** (0.936 to 0.996)	0%	2	222
Seropositivity of HPV 18 at 7 months (comparison 3), SLE				
NRSI: Random-effect model (primary analysis)	**RR 0.943** (0.835 to 1.065)	92%	3	966
NRSI: Random-effect model, exclusion of critical risk of bias*	**RR 0.904** (0.858 to 0.954)	0%	2	217

** Exclusion of the study of Dhar 2017*

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