BMC Public Health

RESEARCH

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Vaccination and rheumatoid arthritis: an updated systematic review and meta-analysis of data from 25,949,597 participants

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Abstract

Objectives This systematic review and meta-analysis aimed to investigate the association between vaccinations and the risk of rheumatoid arthritis (RA), specifically addressing concerns about a potential increased risk among vaccinated individuals.

Methods A systematic search for cohort studies and case-control studies examining the association between vaccinations and RA was conducted using Medical Subject Headings and relevant keywords across PubMed, EMBASE, and Cochrane Library databases from inception to September 2024. The risk of bias of included studies was assessed using the Newcastle-Ottawa Scale. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was employed to evaluate the overall certainty of evidence. Statistical analyses, i.e., pooling of relative risk (RR) and corresponding 95% confidence intervals (CI), were performed using a random-effects model on STATA software (version 14.0). Due to the I^2 value exceeding 50%, we did not perform an asymmetry test to assess publication bias.

Results This meta-analysis included 16 observational studies conducted between 2008 and 2024 and involving a total of 25,949,597 participants. The follow-up duration ranged from 0.03 to 9 years, while the data collection period varied from 2.75 to 9.5 years. The analysis found no significant association between vaccination exposure and RA [RR = 1.03, 95% CI (0.95–1.11), I^2=93.4%, P = 0.456, low level of evidence]. Sensitivity analyses confirmed the robustness of this result. Subgroup analyses revealed no significant risk of RA associated with HPV vaccination [RR = 1.27 95% CI (0.78–2.08), I^2=81.4%, P = 0.339], influenza vaccination [RR = 1.10, 95% CI (0.98–1.23), I^2=52.4%, P = 0.112], Anthrax vaccination [RR = 2.21, 95% CI (0.75–6.52)], Herpes Zoster vaccination [RR = 2.70, 95% CI (1.70–4.29)], or COVID-19 vaccination [RR = 0.94, 95% CI (0.82–1.07), I^2=97.4%, P = 0.340]. However, the subgroup with a follow-up duration varying between 0.5 and 1.8 years showed that (HPV & COVID-19) vaccination had a significant protective effect on RA [RR = 0.92, 95% CI (0.87–0.98), I^2=95.3%, P = 0.005].

Conclusion The evidence for the association between vaccination and RA risk is insufficient, and vaccination may serve as a protective factor for RA over a less than one year follow-up duration.

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Keywords Vaccinations, Rheumatoid arthritis, Meta-analysis, Observational study

Introduction

Vaccination is essential for disease prevention, offering effective and cost-efficient means to protect against infectious diseases [1]. Notably, the widespread use of childhood vaccines has improved global child survival rates and health outcomes [2]. Seasonal influenza vaccines effectively reduce virus transmission and are recommended for individuals aged six months and older by the Centers for Disease Control and Prevention (CDC) [3]. The Hepatitis B vaccine (HBV) provides a long-lasting protection for over two decades, reducing both HBV infection- and cancer-related deaths [4, 5]. During the coronavirus disease 19 (COVID-19) pandemic, promoting COVID-19 vaccinations has been vital in controlling the virus spread [6]. However, concerns about vaccine safety persist, underscoring the need for a thorough evaluation of their risks and benefits within national healthcare initiatives [7].

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disorder that causes pain, swelling, and stiffness in synovial joints, affecting about 1% of adults [8, 9]. Recent years have seen an increase in its incidence [10], with a 2023 United Kingdom study showing a rise from 58 cases per 100,000 person-years between 2000 and 2002 to 94 cases per 100,000 person-years between 2017 and 2019 [11]. RA poses significant economic challenges, decreases quality of life, and increases mortality risk [12, 13]. Therefore, early identification of risk factors is essential for understanding its pathogenesis, preventing its onset, and enabling timely interventions to reduce the burden on affected individuals.

While some documented cases associate vaccination to RA onset [14–18], epidemiological studies have shown conflicting results: some suggest a potential causal association of vaccination on RA [19–24], others indicate a protective effect [25, 26], and several others report no significant association [27–34]. A 2017 meta-analysis suggested an increased risk of RA following vaccination [35], However, recent studies, including those on a novel vaccine—the COVID-19 vaccine—as well as two large-scale studies with larger sample sizes and new regions such as Korea [24, 25], have not yet been included in the analysis. We conducted an updated systematic review and meta-analysis to thoroughly assess the association between vaccinations and RA incidence and relapse.

Methods

Review reporting and registration

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36] and followed a preregistered protocol available on the PROSPERO platform (CRD42023445857).

Search strategy

A comprehensive search strategy was implemented to identify relevant publications from the PubMed, EMBASE, and Cochrane Library databases. The search covered articles from the inception of each database through September 22, 2024. Medical Subject Headings terms for PubMed and Emtree terms for EMBASE were utilized alongside appropriate keywords to enhance both the sensitivity and specificity of the search. Key search terms included "vaccination," "vaccines," "immunization," "arthritis, rheumatoid," "risk," and their synonyms. A detailed account of the search strategy can be found in Supplementary Tables 1–3. Additionally, the reference lists of pertinent systematic reviews were manually screened to ensure comprehensive identification of relevant studies [35].

Inclusion criteria

The inclusion criteria for studies in this meta-analysis were as follows: (1) Population: Patients with RA and those without RA, irrespective of age or nationality; (2) Exposure: Any type of vaccination, including influenza, Human Papilloma Virus (HPV) and COVID-19 vaccinations; (3) Comparator: Individuals with or without RA who did not receive vaccinations; (4) Outcomes: Effect magnitude estimates (relative risks (RRs), odds ratios (ORs) and hazard ratios (HRs)) and corresponding 95% confidence intervals (CIs) for the association between vaccination exposure and RA (incidence or relapse); (5) Study design: observational case-control and cohort studies.

Exclusion criteria

The exclusion criteria for this systematic review and meta-analysis included: (1) Duplicate articles with incomplete information for our analysis; (2) Articles published in the form of reviews, conference abstracts, comments, or letters; (3) Articles published in languages other than English.

Study selection

The literature selection process was carried out independently by two authors (HJ Pan and Y Yu) to ensure a comprehensive and unbiased selection. We imported the retrieved references into EndNote (version 21), used the software's automatic deduplication feature to identify duplicate studies, and then manually checked and

excluded irrelevant or duplicate articles based on titles and abstracts. We subsequently retrieved the full texts of studies that seemed to meet the inclusion criteria for assessing their eligibility. Any disagreements between the two authors were resolved through discussion, with XL Li acting as a mediator to reach a consensus.

Data extraction

Data was extracted independently by two authors (HJ Pan and Y Yu) and cross-checked. A pre-designed data extraction form was used. The extracted information included the first author's name, publication year, study design, country or region, participant characteristics, sample size, control selection, vaccine type, follow-up time, adjusted confounders, and effect magnitude estimates with 95% confidence intervals (CIs). In the meta-analysis, only the adjusted effect magnitude estimates from studies that provided both adjusted and unadjusted estimates were included. Any discrepancies during the data extraction process were resolved through discussion among all authors after reviewing the literature to ensure accuracy and consistency in the data extraction process.

Risk of bias assessment in primary studies

Two authors (XL Li and MJ Wang) independently evaluated and cross-checked the methodological quality of included cohort and case-control studies using the Newcastle-Ottawa Scale (NOS) tool (available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) [37]. Any discrepancies were discussed and analyzed during group meetings until a consensus was reached, thus ensuring the reliability of results. The NOS focuses mainly on three domain areas: participant selection (four stars), comparability (two stars), and outcomes (three stars). For case-control studies specifically, the focus is on the selection of cases and controls, matching adequacy, reliability of exposure measurement, and whether a blinding was done. For cohort studies, the NOS puts an emphasis on participant selection criteria, follow-up duration, and outcome assessment. This means that a NOS-based assessment of the methodological quality of a cohort study should mainly consider whether three important facts have been observed: sufficient follow-up time, bias attributable to loss to follow-up, and objective assessment of outcomes. Accordingly, studies are classified as being of low (0–3 stars), moderate (4–6 stars), or high (7–9 stars) quality.

Statistical analysis

Data analysis was conducted using the Stata software (version 14). Considering the potential for clinical and methodological heterogeneity in any meta-analysis, we applied the random-effects model of DerSimonian and Laird to pool the RRs and corresponding 95% CIs for the association between Vaccination and RA. A two-sided P-value of "less than 0.05" was considered statistically significant for any pooled RR. If the RR was not provided in studies, we calculated the RR for that study based on the adjusted OR [38, 39]. When I^2 exceeded 50%, we conducted a meta-regression to identify potential sources of heterogeneity. Variables assessed through meta-regression included the study design (case-control or cohort), duration of follow-up (with one year being the cut-off), methodological study quality, and vaccine type. We first used data from studies with a follow-up duration ≥ one year, then performed a sensitivity analysis using data from studies with a follow-up duration < one year. Subgroup analyses were then conducted based on study design (case-control or cohort) and vaccine type (HPV, influenza, anthrax, HBV, tetanus, herpes zoster, or COVID-19). Although we included more than 10 studies, the I^2 value was above 50%, which impeded the realization of an asymmetry test [40]. As a result, we were unable to assess the risk of publication bias. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations were used to ascertain the level of evidence presented in this meta-analysis [41]. According to GRADE recommendations, the level of evidence from observational studies is considered to be low. However, the quality of evidence from cohort studies can be improved when large effect sizes (RR ≥ 2 or ≤ 0.5) and, or by effectively addressing possible confounding factors that could reduce the quality of evidence. In the end, the level of evidence for outcomes can be rated as high, moderate, low, or very low.

Results

Characteristics of included studies

A total of 3,784 records were retrieved. Finally, 16 observational studies published between 2008 and 2024 [19–34] were included in the meta-analysis. The study selection process is shown in Fig. 1.

These included 12 cohort studies [20, 22–30, 33, 34] and four case-control studies [19, 21, 31, 32]. Among the included studies, six were conducted in Europe [22, 27, 28, 31, 33, 34], Five in North America [19, 21, 23, 30, 32], five in Asia [20, 24–26, 29]. The sample sizes ranged from 202 to 9,258,803 participants, with follow-up periods varying from 0.03 to 9 years. Data extraction periods ranged from 2.75 to 9.5 years, and participant ages varied from 9 years to over 80. This meta-analysis included studies on seven types of vaccines: six studies focused on the HPV vaccine [19, 23, 26, 27, 30, 33, 34], five on the influenza vaccine [22, 23, 28, 29, 31], three on the COVID-19 vaccine [20, 24, 25], and one HBV, anthrax, tetanus, and herpes zoster vaccines. A summary of the characteristics of the included studies is presented in Table 1.

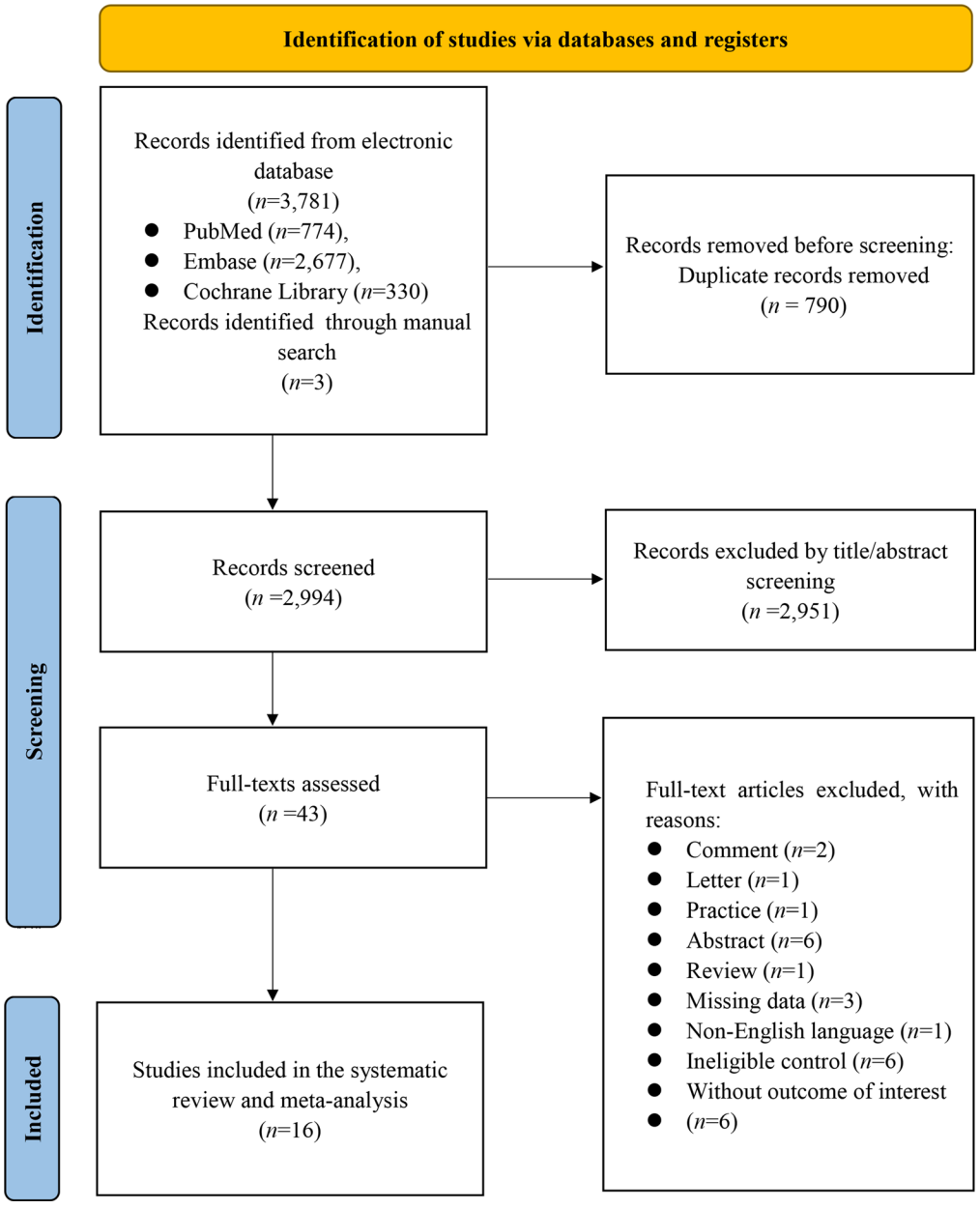

Fig. 1 PRISMA flow chart of study selection

Nine studies [20, 22–25, 29, 31–33] received a ≥ 7, classifying them as high quality with a low risk of bias. Five studies [19, 26, 27, 30, 34] scored 6, indicating moderate, while two studies [21, 28] scored 5, indicating low (Table 2).

Overall estimation of the association between vaccinations and RA risk

The meta-analysis, which included the 16 selected studies, revealed no significant association between vaccinations and an increased risk for new-onset or relapsing rheumatoid arthritis (RA) [RR = 1.03, 95% CI (0.95–1.11), I^2=93.4%, P = 0.456, Fig. 2]. Sensitivity analyses indicated that no individual study significantly influenced the overall effect estimate, potentially enhancing the reliability of our results (Supplementary Figure A).

Subgroup analysis

By duration of follow-up

Results from the subgroup with < 1 years of follow-up demonstrated that vaccination had a significant protective effect on RA [RR = 0.92, 95% CI (0.87–0.98), I^2=95.3%, P = 0.005, Table 3]. Conversely, studies with ≥ 1 years of follow-up yielded a pooled RR for RA association with vaccinations at 0.99 [95% CI (0.91–1.09), I^2=0.0%, P = 0.908, Table 3]. Even after excluding studies

Table 1 Characteristics of the 16 studies included in the systematic review and meta-analysis

Author	Country	Study design	Types of vaccines adminisstered	Participants	Effect size	Duration of follow-up/ Data collection period*	Age	Factors independently adjusted in the statistical analysis
Verstraeten T 2008 [27]	Belgium	Cohort	HPV vaccine	68,512 participants involved in adjuvanted vaccines of AS04	RR	1.78 years (mean)	adolescents and young adults	/
Bengtsson C 2010 [31]	Sweden	Case-control	Influenza vaccine	1,998 incident cases of RA and 2,252 randomly selected controls matched for age, sex, and residency.	OR	5 years	18–70	Age, sex, and residency zone
Ray P 2011 [23]	USA	Cohort	Tetanus vaccine; Influenza vaccine; HBV vaccine	2,587,199 participants aged 15–59 years from 1997 through 1999	RR	2 years	15–19	Race, sex, and exact number of utilization visits.
Chao C 2012 [30]	USA	Cohort	HPV vaccine	189,629 women who received at least one dose of HPV vaccine between 2006 and 2008	RR	0.49 years	9–26	Age.
Ho TY 2012 [29]	Taiwan	Cohort	Influenza vaccine	41,986 vaccinated elderly persons and 50,973 unvaccinated elderly persons	OR	1 years	65–80+	Gender, age, comorbidity, geographic region and urbanization of residence, and individual socioeconomic status.
Arnheim-Dahlstrom L2013 [33]	Sweden	Cohort	HPV vaccine	997,585 girls and 296,826 of them received HPV vaccines	RR	4.17 years	10–18	Country, age, calendar year, parental educational level, parental country of birth, and paternal socioeconomic status.
Angelo MG 2014 [34]	Belgium	Cohort	HPV vaccine	31,173 adolescent girls and adult women receiving HPV vaccine and 24,241 controls	RR	3.25 years	9–26+	/
Persson I 2014 [22]	Sweden	Cohort	Influenza Vaccine vaccination with Pandemrix	3,347,467 were vaccinated with Pandemrix between 2009 and 2010 and 2,497,572 non-vaccinated individuals.	HR	2.25 years	0–80+	County of residence, age, gender, education, income, birthplace, number of hospitalizations, and number of ambulatory care visits.
Vaughn DW 2014 [28]	Belgium	Cohort	Influenza vaccine	22,521 participants	RR	3 years for vaccine recipients; 0.5 years for control recipients.	44.0 ± 18 0.1	age, gender, race
Lai YC 2015 [21]	USA	Case-control	Herpes Zoster vaccine	140 RA patients and 448 controls	RR	9.5 years	/	/
Bardenheier BH 2016 [32]	USA	Case-control	Anthrax Vaccine	77 RA patients and 229 controls	OR	2.75 years	18–45+	Sex, age, service branch, calendar time of beginning under medical surveillance, and deployment status.
Geier DA 2016 [19]	USA	Case-control	HPV vaccine	43 RA patients and 48,809 controls	OR	9 years	6–39	/

Table 1 (continued)

Author	Country	Study design	Types of vaccines adminisstered	Participants	Effect size	Duration of follow-up/ Data collection period*	Age	Factors independently adjusted in the statistical analysis
Geng Y 2023 [20]	China	Cohort	COVID-19 vaccine [Sinovac (70, 67.3%) Sinopharm (27, 26.0%) followed by recombinant subunit vaccine from Zhifei Longcom (7, 6.7%)]	98 patients received no vaccine shot and 104 patients received two doses of vaccine	OR	1.08 years	vaccination group: 51.6 ± 14.0 non-vaccination group: 55.5 ± 13.0	Female, Age (years), Disease duration (years), Body mass index (kg/m2), Smoking history, Comorbidities
Ju H J 2023 [25]	Korea	Cohort	COVID-19 vaccine (BNT162b2 mRNA-1273)	Individuals who received vaccination:3,838,120. Historical prepandemic controls were matched for age and sex in a 1:1 ratio: of 3,834,804.	HR	Vaccination cohort:0.28 ± 0.25 years; historical cohort:0.28 ± 0.24 years.	Vaccination:45.7 ± 18.7; Historical control:44.8 ± 18.7	Age, Sex, Insurance type, Income level, Location of residence, Underlying disease
Yang G 2023 [26]	China	Cohort	HPV vaccine	After the propensity score matching, the vaccinated group was 497; and the unvaccinated group was 497.	RR	9 years	Vaccinated:28.21 ± 8.56 Unvaccinated:28.27 ± 8.12	age, sex, race, education level, marital status, smoking, diabetes, hypertension, hyperlipidemia, and Body mass index (BMI)
Jung SW 2024 [24]	Korea	Cohort	COVID-19 vaccine (BNT162b2, Pfizer–BioNTech vs. mRNA-1273, Moderna)	In total, 4,445,333 and 4,444,932 patients were included in the vaccination and historical control cohorts, respectively.	HR	Vaccination cohort:1.29 ± 0.18 years; historical control cohor: 1.29 ± 0.18 years.	Vaccination:53.42 ± 14.19; Historical control: 51.42 ± 14.19	Age, Sex, Insurance type, Area of residence, Underlying disease, Income level quartile

HBV, hepatitis B virus; HPV, human papillomavirus; COVID-19, coronavirus disease 2019

*Follow-up refers to the duration of follow-up time in cohort studies. Data collection period refers to the time range for data or case collection and recruitment in case-control studies

Table 2 Risk of bias assessment in the 16 observational studies assessing the association between vaccinations and RA

Author	Selection[a]	Comparability[b]	Outcome ascertainment[c]	Quality score (Total)
Verstraeten T 2008 [27]	★★★	★	★★	Medium (6)
Bengtsson C 2010 [31]	★★	★★	★★★	High (7)
Ray P 2011 [23]	★★★★	★★	★★★	High (9)
Chao C 2012 [30]	★★★	★	★★	Medium (6)
Ho TY 2012 [29]	★★★★	★★	★★	High (8)
Arnheim-Dahlstrom L 2013 [33]	★★★★	★★	★★	High (8)
Angelo MG 2014 [34]	★★★	★	★★	Medium (6)
Persson I 2014 [22]	★★★★	★★	★★★	High (9)
Vaughn DW 2014 [28]	★★	★	★★	Low (5)
Lai YC 2015 [21]	★★★	0	★★	Low (5)
Bardenheier BH 2016 [32]	★★	★★	★★★	High (7)
Geier DA 2016 [19]	★★★	0	★★★	Medium (6)
Geng Y 2023 [20]	★★★★	★★	★★★	High (9)
Ju H J 2023 [25]	★★★	★★	★★	High (7)
Yang G 2023 [26]	★★★	★★	★	Medium (6)
Jung SW 2024 [24]	★★★	★★	★★★	High (8)

We assessed the included case-control studies and cohort studies using the relevant items from the NOS scale (Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

[a] Selection refers to how participants are chosen for the study and whether the selection process is free from bias. [b] Comparability refers to the extent to which the groups being compared are similar at the baseline, controlling for potential confounding factors. [c] Outcome ascertainment refers to how the outcomes of interest are measured and whether the measurement process is consistent and reliable

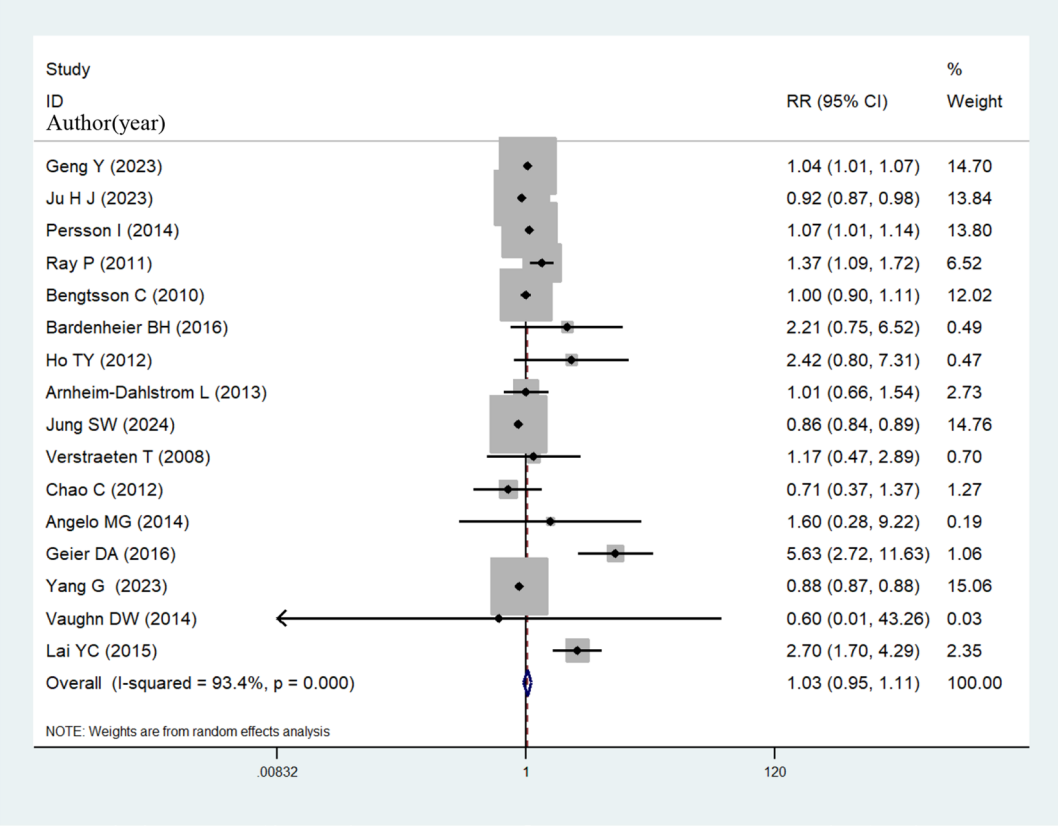

Fig. 2 Forest plot for the association between vaccinations and RA risk

Table 3 Results of subgroup analysis

Subgroups	Included studies	RR		Heterogeneity	
		95% CI	*P*-values	I^2 (%)	*P*-values
Follow-up duration					
<1year	3	0.92(0.87–0.98)	0.005	95.3	0.000
≥ 1year	9	0.99(0.91–1.09)	0.908	0.0	0.647
Vaccine type					
HPV	6	1.27(0.78–2.08)	0.339	81.4	0.000
Influenza	5	1.10(0.98–1.23)	0.112	52.4	0.078
COVID-19	3	0.94(0.82–1.07)	0.340	97.4	0.000
Anthrax	1	2.21(0.75,6.52)	0.151	/	/
Herpes Zoster	1	2.70(1.70,4.29)	0.000	/	/
Study quality					
High	9	1.02(0.93–1.12)	0.701	92.7	0.000
Moderate or Low	7	1.56(0.81–3.01)	0.186	87.8	0.000
Study design					
Cohort	12	0.98(0.91–1.05)	0.545	93.6	0.000
Case-control	4	2.32(0.98–5.50)	0.005	92.3	0.000

RR, Relative Risk; 95%CI, 95% confidence interval; HPV, human papillomavirus; COVID-19 Coronavirus disease 19

of moderate or lower quality, no significant association was found between vaccinations and an increased risk for RA [RR = 1.02, 95% CI (0.93–1.12), I^2=92.7%, *P* = 0.701, Table 3].

By study design

Data from the 12 cohort studies showed no association between RA risk and vaccination [RR = 0.98, 95% CI (0.91–1.05), I^2=93.6%, *P* = 0.791, Table 3], a finding consistent with data from the four included case-control studies [RR = 2.32, 95% CI (0.98–5.50), I^2=92.3%, *P* = 0.055, Table 3].

Results of heterogeneity assessment

In the 16 studies examining the association between vaccination and the risk of RA, significant heterogeneity was observed (I^2=93.4%). Meta-regression analysis indicated that the duration of follow-up for outcome assessment (*P* = 0.45), the quality of the studies (*P* = 0.27), and the type of vaccine (*P* = 0.54) were not sources of heterogeneity. However, the study design (*P* = 0.02) was potentially a source of heterogeneity.

Certainty of evidence

The level of evidence for RA risk associated with any type of vaccine was very low according to GRADE recommendations. Specifically, the GRADE level of evidence was very low for RA risk with HPV, Anthrax, Herpes Zoster and COVID-19 vaccines, while it was low for the influenza vaccine. Furthermore, the GRADE level of evidence was very low for the risk of RA in both case-control and cohort studies. This evidence was consistently rated as very low across high-quality, moderate-quality, and low-quality studies. Additionally, the GRADE level of evidence remains very low regardless of the duration of follow-up (above or below one year). The certainty of evidence for these outcomes is presented in Table 4.

Discussion

Main findings

The overall results of the meta-analysis, which included 16 studies, show no statistically significant increase in RA risk associated with vaccination. Notably, subgroup analysis with follow-up times less than one year indicated a protective effect of vaccination against RA, highlighting the importance of short-term follow-up in exploring the association between the.

Interpretation of findings

A previous systematic review [35], which included 13 observational studies, suggested that vaccinations are associated with an increased risk of RA [RR = 1.32; 95%CI 1.09–1.60]. However, in contrast, our review found no significant association between vaccination and RA [RR = 1.03, 95% CI (0.95–1.11), I^2 = 93.4%, *P* = 0.456]. The earlier review [35] also highlighted several subgroup analyses, including those of high-quality studies [RR = 1.24; 95%CI 1.03–1.49, *P* = 0.025] funded by non-pharmaceutical companies [RR = 1.40; 95%CI 1.14–1.72, *P* = 0.002], case-control studies [RR = 2.51; 95%CI 1.13–5.57, *P* = 0.024], cohort studies [RR = 1.17; 95%CI 1.09–1.26, *P* < 0.001], short-term vaccination periods [RR = 1.48; 95%CI 1.08–2.03, *P* = 0.015], and studies focused on influenza vaccines [RR = 1.17; 95%CI 1.09–1.25, *P* < 0.001]. These analyses supported the findings of the review. In line with our review [RR = 1.27, 95% CI (0.78–2.08), I^2 = 81.4%, *P* = 0.339], the subgroup analysis of the HPV vaccine in the previous review [RR = 1.44, 95% CI (0.65–3.21), I^2 = 80.5%, *P* = 0.370] also found no significant association with RA. Our review, however, introduced a new vaccine—the COVID-19 vaccine [RR = 0.94, 95% CI (0.82–1.07), I^2=97.4%, *P* = 0.340]—and provided a more comprehensive assessment of the association between vaccination and RA. Additionally, we included two large-scale studies [24, 25], which increased both the sample size and population diversity. This also added data from Korea, further enhancing geographical diversity.

However, short-term follow-up data show that vaccination is a protective factor for RA. This difference may be due to the fact that vaccines activate the immune system and provide protection against certain infections or immune responses. However, over time, the immune response may weaken, or long-term effects may

Table 4 Results of ascertainment of the level of evidence using GRADE recommendations

Outcome	Exposure	Study numbers	GRADE					Evidence quality
			Risk of bias	Inconsistency*	Indirectness**	Imprecision***	Publication bias	
RA	Any type of vaccine	16	0	-1[a]	0	0	0	Very Low
RA	HPV	7	0	-1[a]	0	0	0	Very Low
RA	Influenza	5	0	0	0	0	0	Low
RA	COVID-19	3	0	-1[a]	0	0	0	Very Low
RA	Anthrax	1	0	0	0	0	0	Very Low
RA	Herpes Zoster	1	0	0	0	0	0	Very Low
RA	Duration of follow-up<1year	3	0	-1[a]	0	0	0	Very Low
RA	Duration of follow-up ≥ 1 year	9	0	-1[a]	0	0	0	Very Low
RA	Cohort study	12	0	-1[a]	0	0	0	Very Low
RA	Cace-control study	4	0	-1[a]	0	0	0	Very Low
RA	High quality study	9	0	-1[a]	0	0	0	Very Low
RA	Moderate or Low quality study	7	0	-1[a]	0	0	0	Very Low

RA: Rheumatoid Arthritis; Explanations: a. high heterogeneity; The relevant information on GRADE certainty of evidence can be found at https://gradepro.org/

* Inconsistency refers to the variability in the results across studies, often characterized by non-overlapping confidence intervals or high heterogeneity, suggesting that the studies are not measuring the same underlying effect. This could be due to differences in study populations, interventions, or methods. ** Indirectness occurs when the population, intervention, or outcomes in the studies do not directly answer the review question, or the results are not directly applicable to the population or intervention of interest in the review. *** Imprecision refers to the lack of sufficient data to draw reliable conclusions, often due to wide confidence intervals or a small sample size in the studies, which prevent precise estimates of the effect

be influenced by other factors, such as environmental or genetic factors, which may explain why the overall analysis did not show a significant association. The number of studies with comprehensive short-term follow-up is limited, and there is considerable heterogeneity. Differences in study types may have obscured the true association between vaccination and RA, highlighting the need for larger and higher-quality studies to confirm our findings. To reinforce the reliability of our findings, we have consulted existing research. Multiple studies support the idea that the COVID-19 vaccine does not significantly impact RA [42, 43]. Peng et al. reported that while COVID-19 is associated with an increased risk of various autoimmune diseases, vaccination may help mitigate this risk [44]. HBV immunization is widely recognized as a safe routine practice [45]. Extensive research on HPV vaccinations in specific vaccine-type subgroups demonstrates their safety, tolerability, and efficacy in preventing persistent infections and cervical diseases in young women [46]. Herpes viruses, including HPV, are generally not associated with the occurrence of autoimmune diseases [47, 48]. Both previous studies and our own outcomes indicate that HPV vaccines do not elevate the risk of RA, aligning with existing literature. Given the disparities in estrogen levels and immune responses, females are at a higher risk of developing RA than males, making our findings particularly reassuring [49].

In this study, we explored the underlying mechanisms and found that, due to the autoimmune nature of RA itself and treatment strategies aimed at improving the condition, particularly the use of biologic DMARDs, the incidence of infectious diseases has increased [50–52]. Previous studies suggest that infections may exert a potential protective effect on autoimmune diseases through mechanisms such as antigen competition, immune regulation, and innate immune stimulation. As an immune intervention that can induce immune responses without causing disease, vaccination may reduce the occurrence or alleviate clinical symptoms of RA in the short term through similar immune regulatory mechanisms [53, 54]. Therefore, the protective effect observed in the short-term follow-up subgroup (less than one year) is most likely explained by the vaccine effectively preventing RA-related infections, thereby reducing the risk of RA occurrence or relapse. However, in the long-term follow-up period (over one year), no significant association between vaccination and RA was observed. The disappearance of this protective effect may be related to the vaccine's inability to continuously and effectively prevent infections in the long term. Additionally, it is possible that vaccination did not induce side effects related to RA occurrence or relapse. Relevant studies indicate that vaccination is generally safe and immunogenic in patients with mild or resolved autoimmune diseases. For example, the immunogenicity of the influenza and pneumococcal vaccines has been confirmed in patients with systemic lupus erythematosus (SLE) and RA [55].

Strengths and limitations

Our review's strengths include its large sample size and the incorporation of various study designs, such as cohort and case-control studies, which contribute to robust assessments of vaccine and RA risks. Additionally, the results of our sensitivity analysis further support the epidemiological evidence suggesting no association between vaccines and RA risk. Nonetheless, there are several limitations to our review. First, significant heterogeneity was observed in the meta-analysis, which may be due to differences in study design, participant characteristics, and vaccine types, all of which could affect the reliability of the results. The meta-regression analysis suggested that study design is a potential source of heterogeneity in the association between vaccination and RA risk ($P = 0.02$), but no other major sources of heterogeneity were identified. Given the limited number of relevant studies, this may reduce the statistical power of the meta-regression analysis. Furthermore, since retrospective cohort and case-control studies may be influenced by recall bias, future research should include more prospective cohort studies to further confirm the association between vaccination and RA risk.

Second, many of the original studies did not clearly distinguish between RA patients and non-RA patients. Since these two groups are not independent, we combined them in our analysis, which may introduce clinical heterogeneity. Another limitation is that there are few studies focusing specifically on vaccines such as HBV, anthrax, and shingles, which hinder subgroup analyses for more precise conclusions. Moreover, the estimated risks of RA onset and recurrence in our review were based on the combined effects of vaccines that vary greatly in nature and mechanisms of action. Some vaccines, such as herpes vaccines, target microorganisms (like herpes viruses) that are known not to be related to RA pathogenesis, which is a major limitation of this systematic review and meta-analysis.

Third, our research primarily includes studies from European, American, and Asian populations, revealing a gap in studies on African populations, likely due to economic limitations and lower vaccine coverage [1]. Since the populations in our review differ from those in countries with heavier infectious disease burdens, such as South Africa, caution is needed when applying these results to different countries and regions. Additionally, because the I^2 exceeded 50% and did not meet the criteria for an asymmetric test [40], we were unable to assess publication bias. This difference highlights the need for more research on African populations to provide conclusive evidence.

Finally, despite our comprehensive literature search, some relevant studies may have been overlooked, which remains an ongoing challenge.

Implication for clinical practice

The GRADE assessment indicates that there is currently no clear evidence supporting the correlation between RA and vaccination. Based on the existing research findings, future studies could be improved in the following areas: First, studies should distinguish between different populations, particularly by separating high-risk RA populations from the general population. Factors such as smoking and family history significantly increase the risk of developing RA. Therefore, future research should assess the impact of vaccination on RA relapse in different populations, particularly in RA patients in states of incomplete and complete remission. Second, both quantitative, qualitative, and mixed methods should be employed to thoroughly evaluate the effects of different types of vaccines on these populations. Based on the findings from these improved studies, healthcare providers can offer personalized education on the safety and necessity of vaccination for different risk groups. This information will also assist public health policymakers in making more scientifically informed decisions when allocating resources and formulating effective vaccination strategies.

Conclusion

This updated meta-analysis suggests that there is no clear evidence supporting an association between vaccination and the RA risk. However, it is important to consider factors such as the type of vaccine, the population studied, and the duration of follow-up when interpreting these findings.

Abbreviations

RA	Rheumatoid arthritis
CI	Confidence interval
HBV	Hepatitis B virus
HPV	Human papillomavirus
HR	Hazard ratio
OR	Odds ratio
RR	Relative Risk
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative risk
COVID-19	Coronavirus Disease 2019
NOS	Newcastle-Ottawa Scale
GRADE	Grading of Recommendations Assessment Development and Evaluation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22093-9.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions
QD D and L H: conceived the study. HJ P and Y Y: collected the data and drafted the manuscript. XL L and MJ W revised the manuscript and language. CP W conducted the subgroup analysis and edited the manuscript. All authors have read and approved the manuscript.

Funding
This work was supported by the National Administration of Traditional Chinese Medicine– Joint Project with Zhejiang Provincial Administration of Traditional Chinese Medicine [No.GZY-ZJ-KJ-23009]; and the Basic public welfare research program of Zhejiang Province [No.LY24H270004].

Data availability
This study is a systematic review and meta-synthesis that utilizes data extracted from previously published research. All data supporting the findings of this study can be found in the original articles, which are cited in the manuscript. No new data were generated or analyzed during this study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 14 May 2024 / Accepted: 25 February 2025
Published online: 10 March 2025

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