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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,

= 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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Introduction

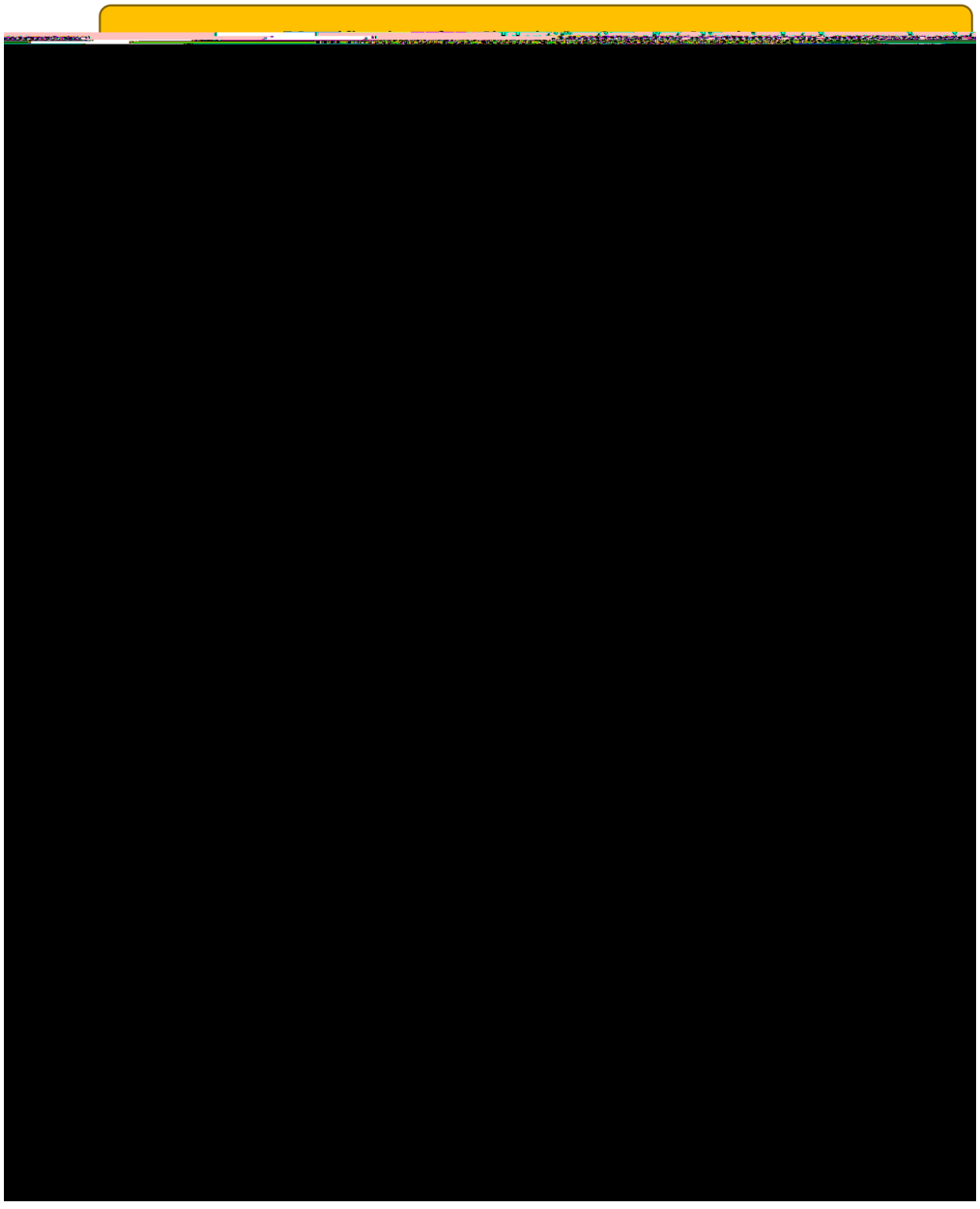

Fig. 1 PRISMA ow chart of study selection

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

e meta-analysis, which included the 16 selected studies, revealed no signi cant 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 signi cantly in uenced the overall e ect 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 signi cant protective e ect 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 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

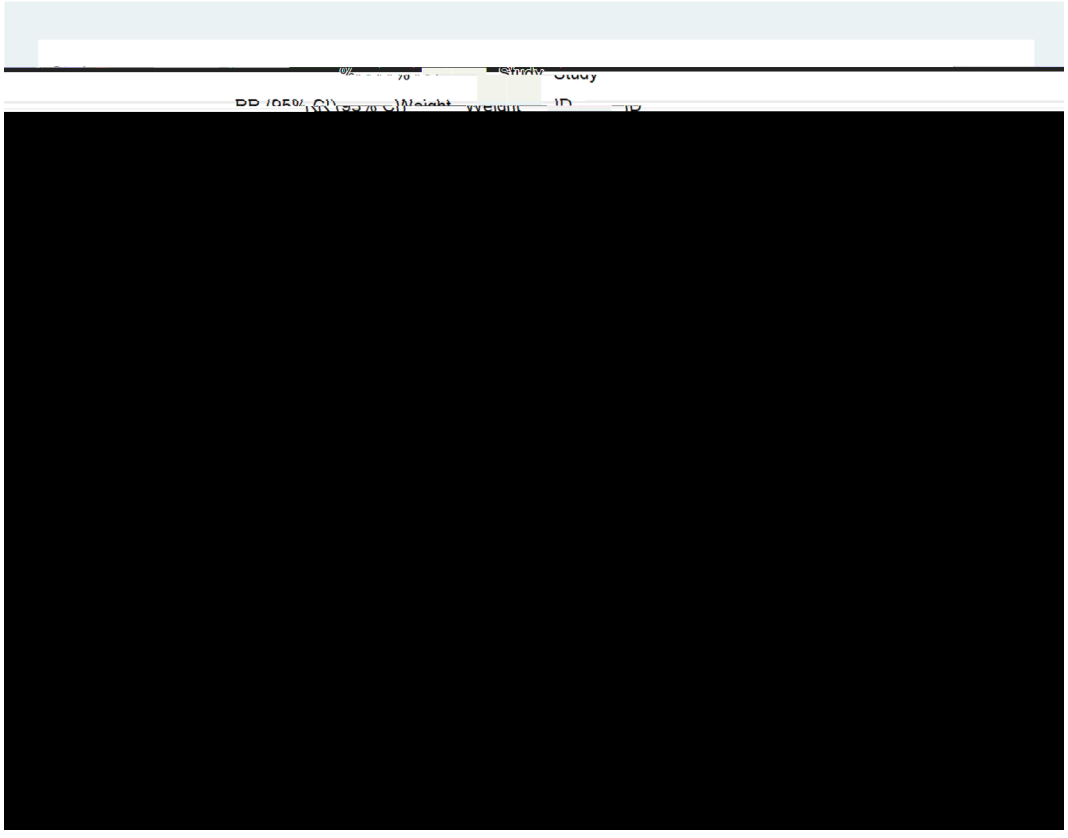

Fig. 2 Forest plot for the association between vaccinations and RA risk

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%,

be in uenced by other factors, such as environmental or genetic factors, which may explain why the overall analysis did not show a signi cant association. e number of studies with comprehensive short-term follow-up is limited, and there is considerable heterogeneity. Di erences in study types may have obscured the true association between vaccination and RA, highlighting the need for larger and higher-quality studies to con rm our ndings. To reinforce the reliability of our ndings, we have consulted existing research. Multiple studies support the idea that the COVID-19 vaccine does not signi cantly 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 speci c vaccine-type subgroups demonstrates their safety, tolerability, and e cacy 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 ndings 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

Strengths and limitations

Our review's strengths include its large sample size and

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.

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Data availability
This study is a systematic review and meta-synthesis that utilizes data extracted from previously published research. All data supporting the □ndings 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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