Review

Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: A systematic review and meta-analysis

Bin Wang [a,b,1], Xiaoqing Shao [a,b,1], Dan Wang [c,d], Donghua Xu [e], Jin-an Zhang [a,b,*]

[a] Department of Rheumatology and Immunology, Jinshan Hospital of Fudan University, Shanghai 201508, China
[b] Department of Endocrinology, Jinshan Hospital of Fudan University, Shanghai 201508, China
[c] Department of Epidemiology and Biostatistics, School of Public Health, Hebei Medical University, Shijiazhuang 050017, China
[d] Department of Library, Hebei Medical University, Shijiazhuang 050017, China
[e] Department of Rheumatology and Immunology, The Affiliated Hospital of Weifang Medical University, Weifang 261000, China

ARTICLE INFO

ABSTRACT

Background: In the past several years, more and more studies proposed some concerns on the possibly increased risk of autoimmune diseases in individuals receiving vaccinations, but published studies on the associations of vaccinations with risks of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) reported conflicting findings. A systematic review and meta-analysis was carried out to comprehensively evaluate the relationship between vaccinations and risk of SLE and RA.
Methods: Pubmed, Web of Science and Embase were searched for observational studies assessing the associations of vaccinations with risks of RA and SLE. Two authors independently extracted data from those eligible studies. The quality of eligible studies was assessed by using the Newcastle-Ottawa Scale (NOS). The pooled relative risk (RR) with 95% confidence intervals (CIs) was used to measure the risk of RA and SLE associated with vaccinations, and was calculated through random-effect meta-analysis.
Results: Sixteen observational studies were finally considered eligible, including 12 studies on the association between vaccinations and SLE risk and 13 studies on the association between vaccinations and RA risk. The pooled findings suggested that vaccinations significantly increased risk of SLE (RR = 1.50; 95%CI 1.05–2.12, P = 0.02). In addition, there was an obvious association between vaccinations and increased risk of RA (RR = 1.32; 95%CI 1.09–1.60, P = 0.004). Meta-analysis of studies reporting outcomes of short vaccinated time also suggested that vaccinations could significantly increase risk of SLE (RR = 1.93; 95%CI 1.07–3.48, P = 0.028) and RA (RR = 1.48; 95%CI 1.08–2.03, P = 0.015). Sensitivity analyses in studies with low risk of bias also found obvious associations of vaccinations with increased risk of RA and SLE.
Conclusion: This study suggests that vaccinations are related to increased risks of SLE and RA. More and larger observational studies are needed to further verify the findings above and to assess the associations of vaccinations with other rheumatic diseases.

© 2017 Elsevier B.V. All rights reserved.

Contents

1. Introduction

Vaccination is the most effective way of preventing infectious diseases [1]. However, recent studies suggested that it's also possibly associated with some adverse events including autoimmunity [2–6]. To increase human immune response to vaccines, adjuvants are usually added to vaccines, but they can result in the development of some autoimmune events [7,8]. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA), also named as Shoenfeld's syndrome and first presented by Shoenfeld and Agmon-Levin in 2011, is a well-defined autoimmune condition caused by adjuvants [9–12]. In the past several years, more and more studies have proposed concerns about the possibly increased risk of autoimmune diseases associated with vaccinations [13–15].

Rheumatic diseases are a group of immune mediated disorders which mainly affect joints and muscles, and they have become common causes of chronic illness worldwide [16]. Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are two common rheumatic diseases, both of which obviously impair the life quality of affected patients and are associated with higher risk of mortality [17–19]. Though the prevalence of rheumatic diseases is relatively low, some studies suggested that the incidence rates of RA and SLE have increased in recent years [20,21]. Identifying risk factors of RA or SLE not only leads to a better understanding of their pathogenesis, but also helps us to develop some effective interventions to reduce risk of RA or SLE in those high-risk individuals.

Severe cases reports of SLE or RA following vaccinations were frequently reported in the literature, which indicated that vaccinations might be causal factors of those rheumatic diseases [22–36]. There were also a number of epidemiological studies on the associations of vaccinations with risk of RA or SLE, but they reported conflicting findings [37–49]. Some studies reported that vaccinations could increase the risk of RA or SLE [38,40,44,48,49], but other studies found that vaccinations had no obvious impact on the risk of RA or SLE [37,39,41,45, 46]. Therefore, there is no definite conclusion on the relationship between vaccinations and risk of RA and SLE. To get a better understanding of the impact of vaccinations on risk of RA and SLE, a systematic review and meta-analysis was performed. The present meta-analysis was performed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, and was registered at PROSPERO website (CRD42017059866) [50].

2. Methods

2.1. Search strategy

Pubmed, Web of Science and Embase were searched for observational studies assessing the associations of vaccinations with risk of RA and SLE. The search strategy used in Pubmed was as following: (vaccinations OR vaccination OR vaccines OR vaccine) AND (rheumatic diseases OR rheumatic disease OR rheumatoid arthritis OR lupus OR systemic lupus erythematosus OR SLE). The last time of literature search was February 15, 2017, and no language restriction was used. The bibliographies of relevant reviews and included studies were checked to find additional studies.

2.2. Selection criteria

Eligible studies must meet the following selection criteria: (1) Cohort studies or case-control studies; (2) The exposure was vaccinations, such as HBV vaccination and HPV vaccination; (3) The controls were those individuals without receiving vaccinations; (4) The outcome of interest was the risk of RA and SLE associated with vaccinations; (5) Reporting risk estimates with 95% confidence intervals (CIs) of rheumatic diseases caused by vaccinations, such as relative risk (RR), hazard ratio (HR), odds ratio (OR) and incidence rate ratios. Studies with overlapping data or without usable data were all excluded.

2.3. Data extraction

Two authors extracted data independently from those eligible studies using a predesigned form, and disagreements were resolved by discussion among all authors. Data extracted from included studies mainly contained authors' name, publication year, study design, country, characteristics of participants, selection of controls, source of information about vaccinations, length of follow-up, definitions of SLE or RA, confounding factors used for adjustment analysis, matched factors used to select controls, and risk estimates with 95%CIs of rheumatic diseases. For studies provided both unadjusted and adjusted risk estimates, only the latter one was used in the meta-analysis.

2.4. Quality assessment

We assessed the study quality according to the Newcastle Ottawa Scale (NOS). According to the NOS criteria, risk of bias of included studies was assessed on three domains: selection of participants, comparability between exposed and non-exposed participants, and the ascertainment of outcomes. Four stars, two stars and three stars were scored for those three domains respectively, and studies with total stars of <6 were deemed to have high risk of bias. Studies with 6 or more stars were deemed to have low risk of bias.

2.5. Statistical methods

The pooled RR with 95%CI was used to measure the risk of RA and SLE associated with vaccinations. To account for heterogeneity among those eligible studies, data were pooled using a random-effect meta-analysis (DerSimonian-Laird method) [51]. I^2 statistic and Cochran's Q test were utilized to test the heterogeneity [52,53]. When I^2 was >50%, meta-regression analysis was carried out to identify potential sources