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Arthritis and arthralgia as an adverse event following immunization: A systematic literature review

Catherine A. Panozzo [a], Farshad Pourmalek [b], Yolanda Brauchli Pernus [c,1], Gecilmara S. Pileggi [d], Andreas Woerner [e], Jan Bonhoeffer [c,e,1,*], for the Brighton Collaboration Aseptic Arthritis Working Group [2]

[a] Harvard Pilgrim Health Care Institute/Harvard Medical School, Boston, United States
[b] University of British Columbia, Vancouver, Canada
[c] Brighton Collaboration Foundation, Basel, Switzerland
[d] School of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil
[e] University of Basel Children's Hospital, Basel, Switzerland

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ABSTRACT

Background: Arthritis and arthralgia are reported as adverse events following immunization with various vaccines.
Objective: To better understand current knowledge of arthritis and arthralgia as an adverse event following immunization.
Methods: A systematic literature review of Pubmed, Embase, and Cochrane Library was conducted. Data extraction was performed by two independent reviewers. No restrictions on dates were imposed and all types of vaccine studies with primary data were reviewed.
Results: Of 343 included studies, there were 206 clinical trials, 90 observational studies, and 47 case reports. Influenza was the most commonly studied vaccine (n = 91, 24.4%). Of the 155 (45.2%) studies addressing causality assessment, 84 studies (54.2%) revealed the assessment method. Only seven clinical trials and 12 observational studies reported a measure of association. Four of these studies examined worsening of arthritic conditions in patients with pre-existing disease. Rigorous assessment of causality was not performed in most studies and many observational studies were prone to bias.
Conclusions: The current evidence linking vaccination to incident arthritis or worsening of arthritic conditions is too heterogeneous and incomplete to infer a causal association. Recommendations for future studies include use of consistent, standardized case definitions and causality assessments, better control of confounding and minimization of bias, and inclusion of measures of associations.

1. Background

In the late 1960s, clinical studies with rubella vaccines first showed mild and transient arthralgia following rubella vaccination [1]. Similarly, arthritis was observed following natural infection with rubella virus which suggested a possible association [2]. However, a subsequent series of prospective studies designed to evaluate the potential association between rubella vaccine and arthralgia or arthritis presented conflicting evidence. In addition to rubella vaccine, hepatitis B (HBV) vaccine was associated with induction of rheumatic disorders, including arthritis, during the 1990s [3,4].

In 2011, Institute of Medicine (IOM) evaluated the causality of a series of adverse events following immunization (AEFI) [5]. The heterogeneity of arthritis definitions including acute and chronic forms, reactive, aseptic and septic arthritis as well as arthralgia presented difficulties in evaluating a potential causal association with vaccines reliably. Measles, mumps, and rubella (MMR) vaccine and the occurrence of transient arthralgia in some women and children was classified as a probable causal relationship, while there was insufficient evidence to accept or reject a causal relation with other vaccines.

The development of new Ebola vaccine candidates following the Ebola outbreaks in West Africa in 2014 resulted in renewed interest and concern about the potential relationship between vaccines and subsequent arthralgia and arthritis [6]. Since arthralgia and

* Corresponding author at: University of Basel Children's Hospital, Spitalstrasse 33, 4056 Basel, Switzerland.
E-mail address: contact@brightoncollaboration.org (J. Bonhoeffer).
[1] http://www.brightoncollaboration.org.
[2] Catherine A. Panozzo and Farshad Pourmalek contributed equally to this publication.

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arthritis remain closely monitored AEFI, the Brighton Collaboration Working Group for Aseptic Arthritis reviewed the currently available literature to prepare for developing a standardized case definition for aseptic arthritis [7].

2. Methods

This systematic review was conducted referencing the criteria set forth in the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist and Reporting Guidelines [8].

2.1. Search strategy and databases

A detailed search strategy is provided in the online Supplementary Material 1. Briefly, a literature search was performed in Embase, Medline via PubMed, and the Cochrane Libraries, using search terms related to "vaccine," "immunization," "inoculation," "arthralgia," "arthritis," and "joint pain." No date restrictions were imposed, but searches were limited to articles published in English. The literature search was conducted on May 28, 2015. Full text articles were obtained through the author's academic libraries. All references were imported and managed in EndNote X7 (Thomson Reuters Scientific LLC, Philadelphia, USA).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.06.067.

2.2. Screening and data extraction

One reviewer (CP) removed duplicate references and screened for the keywords, "arthritis," arthralgia," or conditions related to "joints," and the mention of a vaccine in the title or abstract. From this first set, two reviewers (CP; FP) selected articles reporting primary data (e.g., clinical trials, observational studies, case reports) related to preventive vaccines for further review and extracted data into a structured database. Fields included on the data extraction form created in Excel are provided in the Supplementary Material 2. Discrepancies in article selection and data extraction were discussed together and moderated in the presence of a third reviewer (JB) until agreement was reached.

2.3. Analysis

The two reviewers who performed the data extraction checked and compared their forms for completeness and coding consistency across variables during and at the conclusion of the review process. The two data extraction forms were then combined, and additional completion and consistency checks were performed in SAS version 9.3 (Cary, North Carolina, USA) and Stata version 13 (College Station, Texas, USA).

Frequencies of study characteristics (e.g., types of vaccines included, study location, ages of the population, time intervals assessed) were summarized by study type using SAS and Stata. Since the link between vaccination and arthritis or arthralgia could be limited to specific vaccines, evidence by vaccine type (e.g., influenza vaccines, HPV vaccines), focusing on clinical trials and observational studies that provided measures of association with corresponding measures of variance (e.g., confidence intervals, not just p-values), were summarized in-detail.

2.4. Post hoc analyses

To update the primary literature search conducted on May 28, 2015, two authors (CP; GP) repeated the literature search conducted previously, summarizing major articles published or indexed in English from May 29, 2015 through December 3, 2017 in PubMed. All clinical trials on the candidate Ebola vaccines identified in the search were summarized, even if they did not report measures of association.

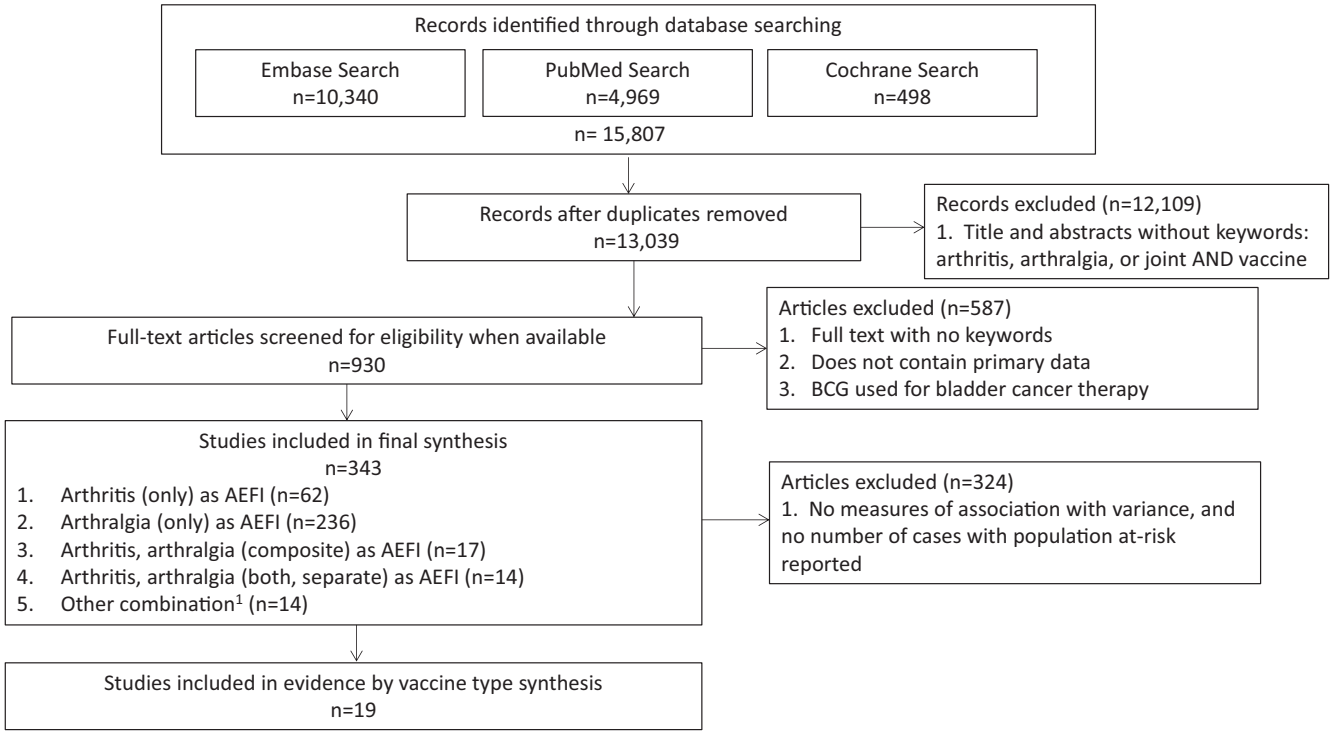

Fig. 1. Attrition diagram. [1]Other combination includes arthralgia and myalgia as a composite outcome and osteitis.

3. Results

3.1. Literature search and screening

The Embase, PubMed, and Cochrane Library searches identified 15,807 articles (Fig. 1) (Supplementary Material 3). Following removal of duplicates, 13,039 references remained. Initial screening of titles and abstracts reduced the number of relevant articles to 930. If a study abstract corresponded to a full text, the full text article was retrieved and reviewed. After completing this review, 343 articles met the inclusion criteria.

3.2. Characteristics of studies extracted

Among the 343 articles that were included for final analysis, approximately 60% of the studies were clinical trials (n = 206) and approximately one-quarter (n = 90) were observational studies (Table 1). The remaining studies were case reports (n = 47). Overall, influenza was the most frequently examined vaccine (n = 91, 24.4%), followed by rubella (n = 27, 7.2%) and hepatitis B (n = 27, 7.2%), human papilloma virus [HPV] (n = 20, 5.4%), and meningococcal (n = 19, 5.1%). Data related to *Plasmodium falciparum* and hepatitis A vaccines were based on clinical trials only. The majority of DTP (80.0%), pneumococcal (75.0%), meningococcal (73.7%), and influenza (69.2%) vaccine studies were clinical trials. In contrast, data on rubella and MMR vaccines were most commonly reported in observational studies.

Approximately one-third of the studies were conducted in the United States or Canada (n = 124, 36.2%) and another one-third of them were conducted in Europe (n = 123, 35.9%). Over half (n = 194, 56.6%) of the studies reviewed were initiated between 2000 and 2009. Approximately one third (n = 116, 33.8%) of the studies enrolled between 100 and 999 subjects, and these were mostly clinical trials. Larger studies enrolling 5,000 subjects or more were mostly observational (n = 42, 12.2%).

Three-quarters of the studies included both males and females (n = 263); most studies including only females examined HPV vaccine. Over one-third of the studies included only adults (n = 132) and over another third included various (generally meaning "all") ages (n = 135). About two-thirds of the studies included only healthy participants (n = 223) and approximately one-tenth included various diseased participants (n = 32). Clinical trials were more likely to include only healthy or only diseased subjects compared with observational studies, which tended to include both (i.e., the general population).

3.3. Types of AEFI identified

Arthralgia only was reported in 236 (68.8%) studies; arthritis only was reported in 62 (18.1%) articles; arthralgia and arthritis were both reported as separate outcomes in 14 (4.1%) studies and as a composite outcome in 17 (5.0%) studies.

3.4. Outcome definition and diagnostic criteria

The majority of studies (n = 221, 64.4%) used physician-verified patient or parent reports based on symptom diaries for case ascertainment. More than 90% (n = 203, 91.9%) of studies using symptom diaries were clinical trials, which generally focused on arthralgia without providing an explicit definition.

The most explicit outcome definition available for arthritic conditions was based on published, pre-established criteria. This approach was outlined in five studies (three observational studies, one clinical trial, and one case report). American College of Rheumatology (ACR) criteria were used in two studies on rheumatoid arthritis and reactive arthritis [9,10]. International League of Associations for Rheumatology (ILAR) criteria was used in two studies examining the worsening of Juvenile Idiopathic Arthritis (JIA) symptoms following vaccination [11,12]. American Rheumatism Association (ARA) year 1956 criteria for Rheumatoid Arthritis (RA) was used in one study [13,14].

About one-fifth of the reviewed studies (n = 74, 21.6%) provided a description of patients' clinical characteristics with or without the results of additional investigations (e.g., laboratory, histopathology, or imaging) as diagnostic criteria for the outcome. Among observational studies examining secondary data sources, International Classification of Diseases (ICD) or Medical Dictionary for Regulatory Activities (MedDRA) codes were commonly used to define the outcome, and sometimes accompanied by chart review.

3.5. Event severity

Approximately 40% of the studies mentioned the severity of arthritis or arthralgia (n = 143, 41.7.3%). About half of these studies used a standard 3-point scale for event severity (n = 65, 48.9%), of which 63 studies (56 clinical trials) used the FDA guidelines [15]. Approximately 10% of the studies (n = 18, 13.5%) that did not report event severity reported the number of serious adverse events. Most of these studies defined serious events as death, or events requiring hospitalization, resulting in significant disability, incapacity, or congenital abnormality.

3.6. Time to event

Time from vaccination to adverse event was mentioned in 300 (87.5%) studies. In approximately half of these studies (n = 145, 48.3%), the time to event ranged from 10 to 99 days.

3.7. Causal association

Approximately 45% (n = 155) of the reviewed studies (provided a causality assessment that included a specific mention or discussion of the arthralgia or arthritis findings (Fig. 2). Clinical trials had the highest proportion of studies which did not include a specific causality assessment (141/206 or 68% of clinical trials). Studies that assessed causality (n = 155, 45.2%) used different terminologies and assessment methods. In order to summarize causality assessment results, we used the terminology (not the method) of WHO's Advisory Committee on Causality Assessment [16]. The most frequent category of the causality assessment result was "certain or very likely" (n = 62, 40.0%), followed by "possible" (n = 37, 23.9%) and "unrelated" (n = 35, 22.6%). Of note, Sever et al used a case-based approach for each AEFI reported to the VAERS for anthrax vaccine in two studies [17,18].

Among the 155 (45.2%) studies addressing causality assessment, 84 studies (54.2%) revealed the assessment method. Of these, the most frequent method was based on clinical evidence and plausibility (n = 22, 29.3%). This was followed by statistical comparisons of outcomes between the vaccinated group and the comparator group (n = 20, 26.7%), providing quantification of risk and strength of association. The WHO causality assessment method and scale were used only in two studies [17,18]. Three studies made use of positive re-challenge tests [19–21]. The weakest causality assessment methods were identified in case reports (n = 6, 66.7%), two clinical trials and one passive surveillance study, relying on temporal associations [22–30].

3.8. Evidence by vaccine type

A total of 19 (5.5%) studies provided measures of association with corresponding estimates of variance and reported the number

Table 1
Characteristics of studies reviewed (n = 343).

Study characteristic	All studies (n, %)	Clinical trials (n, %)	Observational (n, %)	Case reports (n, %)
Number of studies	343 (100.0)	206 (60.1)	90 (26.2)	47 (13.7)
Vaccine[1]				
Influenza	91 (26.5)	63 (30.6)	23 (25.6)	5 (10.6)
Rubella	27 (7.9)	10 (4.9)	11 (12.2)	6 (12.8)
Hepatitis B	27 (7.9)	11 (5.3)	6 (6.7)	10 (21.3)
HPV	20 (5.8)	11 (5.3)	6 (6.7)	3 (6.4)
Meningococcal	19 (5.5)	14 (6.8)	2 (2.2)	3 (6.4)
Plasmodium falciparum	16 (4.7)	16 (7.8)	0 (0.0)	0 (0.0)
Pneumococcal	12 (3.5)	9 (4.4)	2 (2.2)	1 (2.1)
Rabies	12 (3.5)	5 (2.4)	5 (5.6)	2 (4.3)
MMR	11 (3.2)	3 (1.5)	8 (8.9)	0 (0.0)
Hepatitis A	10 (2.9)	10 (4.9)	0 (0.0)	0 (0.0)
DTP	10 (2.9)	8 (3.9)	1 (1.1)	1 (2.1)
Other	118 (34.4)	69 (33.5)	29 (32.2)	20 (42.6)
Location[2]				
USA or Canada	124 (36.2)	65 (31.6)	43 (47.8)	16 (34.0)
Europe	123 (35.9)	73 (35.4)	28 (31.1)	22 (46.8)
Southeast Asia	24 (7.3)	20 (9.7)	3 (3.3)	1 (2.1)
Latin America	22 (6.4)	12 (5.8)	6 (6.7)	4 (8.5)
Western Pacific	18 (5.2)	13 (6.3)	2 (2.2)	3 (6.4)
Africa	12 (3.5)	10 (4.9)	2 (2.2)	0 (0.0)
>1 region	9 (2.6)	8 (3.9)	1 (1.1)	0 (0.0)
Australasia	6 (1.7)	5 (2.4)	1 (1.1)	0 (0.0)
Eastern Mediterranean	5 (1.5)	0 (0.0)	4 (4.4)	1 (2.1)
Decade of study initiation[3]				
1960s/1970s	24 (7.0)	8 (3.9)	12 (13.3)	4 (8.5)
1980s	18 (5.2)	4 (1.9)	6 (6.7)	8 (17.0)
1990s	56 (16.3)	19 (9.2)	22 (24.4)	15 (31.9)
2000s	194 (56.6)	141 (68.4)	40 (44.4)	13 (27.7)
2010s	51 (14.9)	34 (16.5)	10 (11.1)	7 (14.9)
Age groups				
Children only (0–16 years)	49 (14.3)	22 (10.7)	18 (20.0)	9 (19.1)
Adults only (17–59 years)	132 (38.5)	93 (45.1)	11 (12.2)	28 (59.6)
Elderly only (60 + years)	14 (4.1)	9 (4.4)	3 (3.3)	2 (4.3)
Various	135 (39.4)	80 (38.8)	47 (52.2)	8 (17.0)
Unclear	13 (3.8)	2 (1.0)	11 (12.2)	0 (0.0)
Sex				
Both	263 (76.7)	182 (88.3)	74 (82.2)	7 (14.9)
Female only	55 (16.0)	18 (8.7)	13 (14.4)	24 (51.1)
Male only	23 (6.7)	6 (2.9)	2 (2.2)	15 (31.9)
Unclear	2 (0.6)	0 (0.0)	1 (1.1)	1 (2.1)
Population type				
Healthy	223 (65)	170 (82.5)	16 (17.8)	37 (78.7)
Healthy and diseased	84 (24.5)	14 (6.8)	65 (72.2)	5 (10.6)
Diseased	32 (9.3)	20 (9.7)	7 (7.8)	5 (10.6)
Unclear	4 (1.2)	2 (1.0)	2 (2.2)	0 (0.0)
Population size				
<10	43 (12.5)	1 (0.5)	0 (0)	42 (89.4)
10–99	94 (27.4)	83 (40.3)	7 (7.8)	4 (8.5)
100–999	116 (33.8)	88 (42.7)	28 (31.1)	0 (0.0)
1000–4999	44 (12.8)	27 (13.1)	17 (18.9)	0 (0.0)
5000+	42 (12.2)	7 (3.4)	34 (37.8)	1 (2.1)
Unclear	4 (1.2)	0 (0.0)	4 (4.4)	0 (0.0)
Adverse event type				
Arthritis and arthralgia, reported separately	14 (4.1)	4 (1.9)	10 (11.1)	0 (0.0)
Arthritis only	62 (18.1)	9 (4.4)	20 (22.2)	33 (70.2)
Arthritis and arthralgia, composite outcome	17 (5.0)	4 (1.9)	9 (10.0)	4 (8.5)
Arthralgia only	236 (68.8)	182 (88.3)	45 (50.0)	9 (19.1)
Other combinations[4]	14 (4.1)	7 (3.4)	6 (6.7)	1 (2.1)

[1] For enumeration of the vaccines, studies with more than one type of vaccine were counted separately. Therefore, the total number of vaccines is greater than the total number of individual studies. Vaccines mentioned in less than 10 studies are grouped together as "other".
[2] Classification of countries is based on WHO regions with two modifications: "Americas" is divided to "USA or Canada" and "Latin America"; Australia and New Zealand are reclassified from "Western Pacific" and grouped together as "Australasia".
[3] For studies in which it was unclear, the year prior to publication was used to classify the decade of study initiation.
[4] Includes arthralgia and myalgia as a composite outcome, and osteitis

of cases and population at-risk [10–12,31–46] (Tables 2 and 3). Seven (36.8%) of these studies were clinical trials of which two assessed arthritis, four assessed arthralgia, and one used a composite endpoint for the adverse event of interest. Of note, the two clinical trials examining arthritis as an AEFI assessed worsening of arthritic conditions in individuals with pre-existing disease; none of the seven trials assessed onset of incident arthritic disease. The remaining 12 (63.2%) studies were observational studies of which ten assessed arthritis, one assessed arthralgia, and one used a composite endpoint for the adverse event of interest. Two of the ten observational studies examining arthritis as an AEFI assessed worsening of arthritic conditions in individuals with pre-existing disease while the remaining eight studies examined incidence of arthritis in the general population. The vaccines most commonly

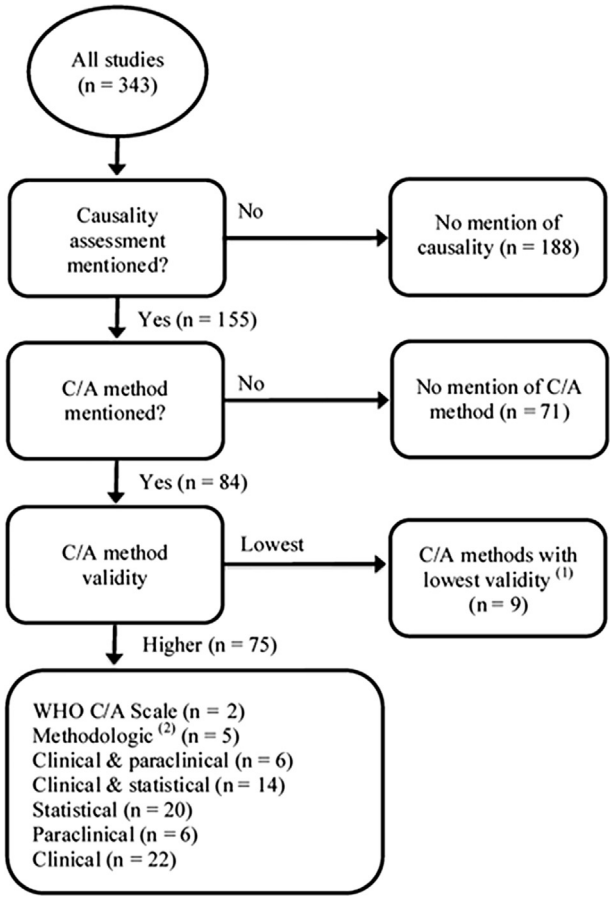

Fig. 2. Attrition diagram for causality assessment [C/A] mention and methods. [1]Causality assessment [C/A] methods with lowest validity had mere "short duration from vaccination to adverse event, (n = 1)" "lack of elements leading to different causal interpretation, (n = 1)" or mere "consistency of findings with other studies" (n = 7). [2]Lack of comparator group.

assessed among these 19 studies were influenza vaccines (n = 7), hepatitis B vaccines (n = 5), tetanus-containing vaccines (n = 3), HPV vaccines (n = 3), and MMR vaccines (n = 3). Some studies reported on multiple vaccines, compared vaccines or dose numbers to each other, or focused on concomitant administration. Detailed discussion of evidence by vaccine type and disease promotion in patients with pre-existing arthritic conditions are available in Supplementary Material 4.

3.9. Post hoc analyses

The literature search of articles published from May 29, 2015 through December 3, 2017 identified 656 publications. After scanning abstracts for keywords (arthritis OR arthralgia OR joint AND vaccine), 142 articles remained eligible. After further narrowing the articles to clinical trials investigating Ebola candidate vaccines, or to studies reporting measures of association for all other vaccines, eight articles remained and were reviewed [47–54]. These articles included studies on Ebola (n = 4) (Supplementary Material 5), HPV (n = 2), zoster (n = 1), and anthrax vaccines (n = 1). Detailed discussions of these studies are available in Supplementary Material 4.

4. Discussion

This systematic review focused on arthritis as an AEFI. The extensive literature search with sensitive inclusion criteria demonstrated heterogeneity, overlap and lack of consistent outcome definitions. This is in keeping with previous work highlighting the missed opportunity of harmonized vaccine safety assessment and the resulting challenges of data interpretation [55–57].

In this review, the majority of articles were clinical trials of which influenza vaccine was most frequently evaluated. In these trials, the most common solicited AEFI among the spectrum of arthritis outcomes was the symptom arthralgia. Observational studies were more likely to evaluate the diagnosis of arthritis than arthralgia. Many early studies included a small number of patients or were case reports, most frequently on rubella or hepatitis B vaccines. Case reports were useful for understanding a given patient's work-up, but the actual criteria for which a physician team concluded that a patient's arthritis was the result of vaccination were variable, and commonly undefined. This gap is well recognized and aimed to be addressed by the World Health Organization criteria and method for causality assessment [58]. However, this method is not widely used so far. More recently, large observational studies including those utilizing electronic medical records or administrative databases have been used to assess the association between vaccination and arthritis and have provided better powered and re-assuring safety of the vaccines in this systematic review [10,31,43,51].

4.1. Limitations

Limitations of this systematic review include restricting the literature search to articles available in the English language. Second, while literature search terms were broad, it is possible that relevant articles may have been excluded from review. Furthermore, we focused on studies that included epidemiologic measures of association rather than only clinical findings in the consideration of evidence by vaccine type in the main analysis. In addition, some important current questions, such as whether a third doses of MMR vaccine administered during a mumps outbreak is associated with arthritis or not, were not addressed in the identified literature. Finally, the authors refrained from formal meta-analysis of the data because incomplete safety data reporting, and variations in vaccine products, study populations and outcome definitions across studies, as well as limited control for bias and confounding in several observational studies question the value of direct comparisons across these studies. Well-designed clinical trials of new vaccines and high quality safety data from large observational studies on existing vaccines would strengthen the current body of evidence.

4.2. Recommendations

Based on this review, we recommend the following: Future clinical trials assessing the safety of vaccines should allow risk evaluation of potential induction or promotion of arthritis – rather than arthralgia alone. Active and adequate follow-up time of study subjects is essential. Consistent use of terminology for arthritis and arthralgia in clinical trials, observational studies, and case reports is needed to promote data comparability and scientific progress. We recommend the use of the Brighton Collaboration guidelines for clinical studies [59] and the standardized case definition of acute aseptic arthritis published in tandem with this review [7]. Arthritis and arthralgia should be reported as separate outcomes rather than a composite outcome. Every effort should be made to limit potential biases (e.g., selection bias, confounding bias) by study design or analysis, and implications of residual biases should be explored. The impact of known biases on the results should be thoroughly discussed or explored in sensitivity analyses. Appropriately powered measures of association between vaccination and arthritis along with uncertainty estimates should be provided. Subgroup analyses, including different vaccine doses (additional doses

Table 2
Summary of clinical trials estimating risk and precision of arthritis or arthralgia following immunization.

First author (year published)	Study description	Population (country, years data collected)	Vaccine (manufacturer, if specified)	Case definition, including severity + time interval assessed	Number of persons eligible	Number of cases	Type of risk(s) estimated w/estimate(s) (95% CI)
AEFI: Arthritis (in prevalent population)							
Del Porto (2006) [34]	Non-randomized, unblinded safety and immunization trial	Intervention group: adults with SLE or RA who were vaccinated; Control group: adults with SLE, RA, or who were healthy and refused vaccination. No placebo used. (Italy, 2003–2004)	Seasonal TIV (GSK)	SLE and RA defined as per the American College of Rheumatology; Flare for SLE patient defined as introduction of a new treatment in the presence of worsening of an already active system, or in response to the activation of a new system, or an increase in medication for the above reasons; Flare for RA patient defined as introduction of a new treatment or the increase of a previous treatment in presence of worsening of the disease activity or in appearance of extra-articular manifestations; Also measured SLEDAI and DAS_{28} at baseline 30, 90, and 180 days post-vaccination; Severity scale not mentioned, but severity of flares measured; Follow-up post-vaccination up to 7 days	44 (24 vaccinated of whom 14 had SLE and 10 had RA; 20 unvaccinated of whom 10 had SLE and 10 had RA; An additional 10 healthy controls	2 vaccinated SLE patients and 2 vaccinated RA patients had flares; 1 non-vaccinated SLE and 3 non-vaccinated RA patients had flares	Odds ratio. OR = 2.17 (0.1, 137.49) for flares in SLE patients who were vaccinated vs. unvaccinated; OR = 0.58 (0.04, 6.94) for flares in RA patients who were vaccinated vs. unvaccinated; OR = 1 (0.16, 6.18) for flares in SLE and RA patients who were vaccinated vs. unvaccinated
Heijstek (2013) [11]	Randomized, multicenter, open-label clinical equivalence trial.	Vaccinated and unvaccinated children 4–9 years-old with JIA. No placebo used in unvaccinated control group. (Netherlands, 2008–2011)	MMR booster (Netherlands Vaccine Institute, Sanofi Pasteur)	JIA defined according to the International League of Associations for Rheumatology Criteria; JADAS-27 with 2.0 as equivalence margin measured. Flares defined as worsening of 30% or more in at least 3/ 6 core criteria, without simultaneous improvement of $\geq$ 30% in $\geq$ 2 criteria, with $\geq$ 2 active and/or limited joints if the joint count was used as criterion of a flare; risk of flare and total flares/year following MMR measured; Severity scale as measured by JADAS-27; Follow-up post-vaccination every 3 months for 1 year	131 children of whom 63 were assigned to the vaccine booster group and 68 were assigned to the control group in modified ITT analysis	Precise numbers not reported	Mean difference; Relative risk. Mean difference = 0.4 (−0.5 to 1.2) for JADAS-27 score in JIA patients receiving MMR booster versus control; RR = 0.9 (0.4, 2.0) for a flare occurring 3 months post MMR booster versus control; RR = 1.3 (0.8, 2.1) for a flare occurring during the entire 12-month study period for MMR booster versus control. Additional estimates for subgroups taking methotrexate or biologics (95% CIs all included 1)
AEFI: Arthralgia (in healthy population)							
Barrett (2011) [32]	Phase III, multi-center, double-blind, randomized placebo-controlled safety and immunogenicity trial	Healthy adults, 18–49 years-old (USA, 2008–2009)	Seasonal influenza, vero-cell-culture-derived (Baxter)	Arthralgia as reported by the participant using diary cards; Severity scale mild, moderate, severe, and not reported; Follow-up to 21 days post-vaccination	3623 (vaccinated group, safety analyses); 3620 (placebo group, safety analyses)	224 (6%) cases of arthralgia in vaccine group; 110 (3%) cases in placebo group	Relative risk. RR = 2.0 (1.6, 2.5) for vaccine versus placebo groups
Embree (2015) [35]	Phase II, open-label, randomized, controlled, safety and immunogenicity trial	Healthy children 11–14 years-old (Canada, 1999–2000)	Tdap-IPV (Sanofi Pasteur Limited), Hepatitis B (Merck & Co., Inc.). Group 1: Tdap-IPV, followed by hepatitis B $\sim$ 1 month later. Group 2: Simultaneous Tdap-IPV and hepatitis B. Second and third	Sore joints as reported by participants using diary cards; Severity scale: any, moderate, severe; Follow-up post-vaccination for 2 weeks after each dose	144 in Group 1 and 132 in Group 2 (ITT analyses)	26 in Group 1 and 27 in Group 2 with sore joints, any severity. 6 in Group 1 and 6 in Group 2 with sore joints, moderate or severe intensity	Percent difference. For any sore joints, Group 1 vs. Group 2: 2.4% (-5.4, 10.2). For moderate or severe sore joints, Group 1 vs. Group 2: 0.4% (−3.7, 4.4)

(*continued on next page*)

Table 2 (*continued*)

First author (year published)	Study description	Population (country, years data collected)	Vaccine (manufacturer, if specified)	Case definition, including severity + time interval assessed	Number of persons eligible	Number of cases	Type of risk(s) estimated w/estimate(s) (95% CI)
			doses of hepatitis B given 1 and 6 months after the initial hepatitis B vaccination				
Frenck (2012) [37]	Phase III, multi-center, double-blind randomized placebo-controlled, safety and immunogenicity trial	Healthy adults, 50–59 years-old (USA, 2007–2008)	Pneumococcal (Pfizer), seasonal TIV (GSK). Group 1 received pneumococcal plus TIV then placebo one month later. Group 2 received placebo plus TIV then pneumococcal one month later	Self-reported, new generalized joint pain, and any aggravated generalized joint pain; Severity scale not mentioned; Follow-up 14 days after vaccination	1061 of whom 530 were vaccinated in Group 1 and 531 were vaccinated in Group 2	New joint pain: 102/309 (Group 1, Dose 1); 73/296 (Group 2, Dose 1); 78/285 (Group 2, dose 2); Any aggravated joint pain: 62/292 (Group 1, Dose 1), 51/284 (Group 2, Dose 1), 67/282 (Group 2, dose 2)	Percent difference. For new joint pain: 8.3% (1.1, 15.6) for Group 1, Dose 1 vs. Group 2, Dose 1; 5.6% (−1.8, 13.1) for Group 1, Dose 1 vs. Group 2, Dose 2. For any aggravated joint pain: 3.3% (−3.3, 9.8) for Group 1, Dose 1 vs. Group 2, Dose 1; 2.5% (−9.4, 4.4) for Group 1, Dose 1 vs. Group 2, Dose 2
Lyons (2008) [42]	Phase I, single-center, double-blind, randomized placebo-controlled safety and immunogenicity trial	Healthy adults 18–36 years-old from the Army Department Medical Center and School (USA, 2004)	Concomitant Adenovirus serotypes 4 and 7 in experimental group and placebo in control group	Self-reported daily symptom diary of adverse events, including arthralgia, for first 7 days post-vaccination and physical and laboratory evaluations on Days 7, 14, 21, 28, and 56 post-vaccination; Severity scale: unnoticed, little effect, or large effect on activity; Follow-up 56 days post-vaccination and 180 days post-vaccination for serious adverse events	30 in vaccinated group and 28 in control group	4 (13.3%) arthralgia cases in vaccinated group, 0 in control group	Odds ratio. OR = 5.38 (0.54, 263.58) for arthralgia in vaccinated versus control groups. Note: one case added to control group to make estimation of OR feasible
Tingle (1997) [45]	Randomized, double blind, placebo-controlled trial	Females who were seronegative for rubella, 18–41 years-old, and 0–12 weeks postpartum (Canada, 1989–1992)	Rubella, RA 27/3 strain, or saline placebo	Acute and persistent arthropathy (defined as arthritis or arthralgia). Acute arthritis: joint effusion or swelling with ≥ 2 of warmth, tenderness, pain on movement, or limited motion through 28 days post-vaccination in the absence of recent trauma or pre-existing joint manifestations. Acute arthralgia: joint pain without evidence of swelling, heat redness, or limited motion through 28 days post-vaccination and not attributed to other causes. Persistent arthropathy: occurrence of arthritis or arthralgia at any time 12 months post-vaccination in women who experienced acute arthropathy and for whom joint complaints not attributed to other causes. Severity scale not mentioned; Follow-up every 3 months for a total of 12 months post-vaccination	543 subjects followed up at 1 month; 456 completed 12 month assessment	81 vaccinated and 55 controls had acute arthropathy; 58 vaccinated and 41 controls had persistent arthropathy	Odds ratio. OR = 1.73 (1.17, 2.57) for acute arthropathy in vaccine versus control groups; OR = 1.58 (1.01, 2.45) for persistent (recurrent) arthropathy in vaccine versus control groups

Table 3
Summary of observational studies estimating risk and precision of arthritis or arthralgia following immunization.

Study	Study description	Population description	Vaccine	Case definition, including severity + time interval assessed	Number of persons or person-time eligible	Number of cases	Type of risk(s) estimated w/ estimate (s) (95% CI)
AEFI: Arthritis (in prevalent cases)							
Heijstek (2007) [12]	Retrospective cohort, multicenter	Patients born 1989–1996 who were vaccinated with MMR and had JIA. Sub-analysis of patients using methotrexate; (Netherlands)	MMR	International League of Associations for Rheumatology criteria used to confirm JIA (however, only approximately one-quarter B27 typed); Disease activity measured by Physician's global assessment (PGA), erythrocyte sedimentation rate (ESR), and number of flares 6 months before and after MMR; Severity scale not mentioned	173 vaccinated patients in active, limited joint, and PGA analyses, 132 in ESR analysis, and 175 in flare analysis that estimated odds ratios	40 flares in 36 patients before MMR and 56 flares in 50 patients after MMR; total number of patients with PGA > 0.3 and ESR > 15 not reported	Difference; Odds ratio, adjusted for JIA type and medication use with propensity scores. OR = 1.6 (0.8, 3.2) for limited joints >=1, OR = 1.7 (0.8, 3.6) for PGA > 0.3, OR = 1.4 (0.5, 3.7) for ESR > 15, OR = 1.6 (0.8, 3.1) for active joints >=1, OR = 1.4 (0.7, 2.9) for flare >=1, comparing disease 6 months after versus 6 months before vaccination
Smith (2012) [44]	Self-controlled case series	Females from a population-based cohort who had arthritis and were 13–15 years-old; (Canada, 2007–2009)	HPV (Merck & Co)	Arthritis identified in Ontario health database; Severity scale not mentioned; Follow-up 7, 21, 60, and 100 days post-vaccination	2519 subjects	14 cases	Rate ratio, adjusted for age and non-time varying confounders (by design). RR for 1–7 days post-vaccination could not be estimated because no cases; RR = 2.03 (0.44, 9.27) 8–21 days post-vaccination vs. control period; RR = 4.06 (1.36, 12.10) 22–60 days post-vaccination vs. control period; RR = 1.00 (0.27, 3.68) 61–100 days post-vaccination vs. control period
AEFI: Arthritis (in general population)							
Bardage (2011) [31]	Retrospective cohort, population-based	General population of individuals registered in a single county, age range 0–109 years-old; (Sweden, 2009)	Pandemic TIV H1N1 (GSK)	RA using ICD-10 codes associated with hospital admissions or specialist care; Results stratified by whether vaccine was given in the early (<45 days) or late phase ($\geq$45 days) of the vaccine campaign and whether the RA diagnosis was made $\leq$ 6 weeks post-vaccination or > 6 weeks post-vaccination in subgroup analysis of vaccinated group; Severity scale not mentioned; 90% of the population was followed 256–315 days	1,024,019 vaccinated subjects and 921,005 unvaccinated subjects	416 incident RA cases in vaccinated of whom 62 were diagnosed $\leq$ 6 weeks after vaccination (40 in early and 22 in late phase of campaign)	Hazard ratio, adjusted for age, sex, socioeconomic status, and healthcare consumption. Vaccinated vs. unvaccinated: HR = 1.01 (0.86, 1.20) (early phase of campaign) HR = 0.84 (0.69, 1.02) (late phase of campaign)
Bengtsson (2010) [10]	Case-control, matched by age, sex, and residency	General adult population from the population-based Epidemiological Investigation of RA Case-Control Study, 18–70 years-old; (Sweden, 1996–2006)	Multiple (Influenza, tetanus, diphtheria, tick-borne encephalitis, hepatitis A, B, C [composite], polio, pneumococcal)	Incident RA using 1987 American College of Rheumatology criteria; Severity scale not mentioned; vaccine history examined up to 5 years before onset of disease via interview	1851 RA cases, 1984 controls	582 cases were vaccinated and 617 controls were vaccinated	Odds ratio, adjusted by age, sex, residency, and social class. OR = 1.0 (0.9, 1.1); OR = 1.1 (0.9, 1.3) for influenza; OR = 1.0 (0.8, 1.2) for tetanus; OR = 1.0 (0.7, 1.4) for diphtheria; OR = 0.8 (0.6, 1.1) for tick-borne encephalitis; OR = 0.9 (0.7, 1.2) for hepatitis A, B, C; OR = 1.1 (0.6, 1.8) for polio; OR = 1.0 (0.5, 1.9) for pneumococcal
Chao (2012) [33]	Retrospective cohort	Privately insured females, 9–26 years-old; (USA, 2006–2008)	HPV (Merck & Co)	Primary definition employed electronic algorithm using ICD-9 codes, abnormal	189,629 females	75 electronically identified potential RA or JRA cases (37 RA, 38	Incidence rate ratio, unadjusted. IRR = 0.71 (0.39, 1.45) for RA comparing vaccinated to

(*continued on next page*)

Table 3 (*continued*)

Study	Study description	Population description	Vaccine	Case definition, including severity + time interval assessed	Number of persons or person-time eligible	Number of cases	Type of risk(s) estimated w/ estimate (s) (95% CI)
				laboratory results, or pharmacy prescriptions related to RA or JRA with medical record review by a committee that included rheumatologists; Severity scale not mentioned; Follow-up to 180 days (median for RA, 62 days; median for JRA, 55 days)		JRA); Sampling in case review so multiple imputation approach applied to IRR estimations	unvaccinated; IRR = 0.48 (0.26, 0.91) for JRA comparing vaccinated to unvaccinated. Additional estimates in sensitivity analyses (95% CIs all include 1, except for one estimate where vaccination was protective)
Fisher (2001) [36]	Cross-sectional household survey, sampled to be representative of U.S. children	Probability sample of civilian noninstitutionalized population of children < 6 years-old in the National Health Interview Survey; (USA, 1993–1994)	Hepatitis B (Merck)	Chronic conditions (e.g., arthritis) that were noticed ≥ 3 months before interview date. Self-reported and coded using ICD-9-CM; Severity scale not mentioned; Time interval of follow-up unclear	6515 subjects (in 1994)	14 cases prevalent chronic arthritis (12 in vaccinated and 2 in unvaccinated in 1994)	Prevalence odds ratio (adjusted). POR = 1.60 (0.40, 6.39) for chronic arthritis controlling for age, race, gender, education, and income in 1993 for vaccinated versus unvaccinated and POR = 5.79 (0.98–34.12) in 1994. OR = 5.91 (1.05, 33.14) when controlling for only age, race, and gender in 1994. Additional estimates reported (95% CIs all included 1, except for unadjusted OR in 1994)
Geier (2005) [38]	Described as matched case-control study	General population ≥ 7 years-old as reported to Vaccine Adverse Event Reporting System; (USA, 1990–2004)	Hepatitis B and tetanus toxoid-containing vaccines	Costart Codes for arthritis and RA; Severity scale not mentioned, but percentage disabled reported; Median time interval from vaccination to arthritis was 3 days and median onset from vaccination to RA was 11 days	232 cases of arthritis (4426 controls) and 54 cases of RA (1297 controls)	202 arthritis cases received hepatitis B and 30 arthritis cases received tetanus-containing vaccines; 53 RA cases received hepatitis B and 1 RA case received tetanus-containing vaccines	Described as odds ratio, matched by sex, age, and year, but calculations use cases and controls selected dependent on exposure and matching schema not described. OR = 2.01 (1.3, 3.1) for arthritis, hepatitis B vs. tetanus toxoid; OR = 18 (3.1, 740) for RA, hepatitis B vs. tetanus toxoid.
Ho (2012) [39]	Retrospective cohort using National Health Insurance Database	General population of nearly all those ≥65 years-old in Taiwan with no autoimmune conditions under study, e.g., RA; (Taiwan, 2008–2009)	Seasonal TIV (Novartis, Pasteur Merieux Connaught, GSK)	ICD-9 code for RA (714.0) in ambulatory and hospital settings as used by EMA in previous work; confirmed using catastrophic release dataset from National Health Insurance Research Database; Severity scale not mentioned; Follow-up at 6 then 12 months	93,049 (41,986 vaccinated; 51,063 unvaccinated)	33 (16 unvaccinated RA cases, 17 vaccinated RA cases) in 12 months	Odds ratio, adjusted using propensity score stratification. Propensity scores included age, gender, URI OPD # in prior six months, comorbidity, SES, geographic region and urbanization level of residence. OR = 2.42 (0.80, 7.30) for RA after 6 months for vaccinated versus unvaccinated; OR = 1.39 (0.69, 2.79) after 12 months for vaccinated versus unvaccinated
Ray (2011) [43]	Retrospective cohort and matched case-control	Privately insured adolescents and adults 15–59 years-old; (USA, 1997–1999)	Tetanus, or influenza, or hepatitis B	Administrative claims with medical chart review for incident RA and JRA; Severity scale not mentioned; Follow-up 90, 180, 365 days post-vaccination in cohort and follow-up 90, 180, 365, and 730 days post-vaccination in case-control analyses	Approximately 1 million individuals with 2,587,111 person-years	378 probable and definite RA cases in cohort analyses with an additional 37 cases in case-control analyses (415 total cases) with 1245 controls	Relative risk, adjusted for age, sex, race, and number of health care visits. Odds ratio, adjusted by age and clinic visits via matching and also for sex, race, and number of utilization visits. Vaccinated vs. unvaccinated at 90, 180, 365 days post-vaccination: Hepatitis B, RR = 1.44 (0.46, 4.51), RR = 1.67 (0.74, 3.77), RR = 1.23 (0.58, 2.63); Tetanus, RR = 1.36 (0.72, 2.54), RR = 1.31 (0.82, 2.09), RR = 0.93 (: 0.62, 1.37); Influenza, RR = 0.72 (0.45, 1.14), RR = 1.36 (1.03, 1.80), RR = 1.34

							(1.06, 1.69). Cases vs. Controls at 90, 180, 365, 730 days post-vaccination: Hepatitis B, OR = 1.5 (0.4, 5.2), OR = 2.0 (0.8, 5.1), OR = 1.4 (0.6, 3.1), OR = 1.0 (0.5, 2.12); Tetanus, OR = 0.8 (0.4, 1.6), OR = 1.1 (0.6, 1.8), OR = 0.8 (0.5, 1.2), OR = 0.8 (0.6, 1.12); Influenza, OR = 0.7 (0.4, 1.2), OR = 1.1 (0.8, 1.6), OR = 1.1 (0.9, 1.5), OR = 1.1 (0.8, 1.4)
Wasserman (2003) [46]	Retrospective cohort of adverse event survey data	Soldiers, 17–61 years; (USA, 1998–2000)	Anthrax (Bioport Corporation)	Self-reported incident joint aches; Severity scale used a scale going from 0 = no symptoms to 4 = symptoms not relieved by medication/can't perform activities; Survey completed 1–2 weeks post-vaccination	2849/3069 surveys returned among vaccinated subjects. 301 vaccinated and 639 unvaccinated subjects in rate ratio analysis	346 joint aches in 2849 vaccinees of which 40 were reported as 4 on the severity scale.	Rate ratio (unadjusted). RR = 0.84 (0.50–1.43) for self-reported diagnosis of arthritis in vaccinated vs. unvaccinated groups
AEFI: Arthralgia (in general population)							
Klooster (2011) [41]	Cross-sectional survey during national catch-up campaign	General adolescent female population, born 1993–1996; (Netherlands, 2009)	HPV (GSK)	Self-reported questionnaire about adverse events, including joint pain; Severity scale dichotomized (yes/no); Follow-up for 7 days with median time to onset 13 h after Dose 1, 24 h after Dose 2, and 8 h after Dose 3 for joint pain	4248 girls returned surveys; 1681 girls completed all 3 surveys	Joint pain: 13.0% (12.0, 14.1) after Dose 1, 5.4% (4.6, 6.3) after Dose 2, 4.8% (3.9, 5.8) after Dose 3	Odds ratio, adjusted for birth cohort: Dose 2 v. Dose 1: 0.38 (0.31–0.46); Dose 3 vs. Dose 1: 0.33 (0.26–0.41). Odds ratio, adjusted for birth cohort and dose number: Chronically ill vs. not: 1.17 (0.98–1.40); Sick at vaccination vs. not: 1.48 (1.21–1.80); Sick during week before vaccination vs. not: 1.53 (1.28–1.82)
AEFI: Arthritis, Arthralgia (composite, in general population)							
Klein (2015) [40]	Retrospective cohort of 8 Vaccine Safety Datalink sites. Primary analyses used stratified exact binomial tests and secondary analyses used case-centered logistic regression	Privately insured children, 12–23 months of age; (USA, 2000–2012)	MMRV vs. MMR + Varicella (V); (Merck & Co)	First ICD-9-CM code for arthritis or arthralgia (combined outcome), 714.9, 716.9, or 056.71, during the 1–42 day risk interval post-vaccination. 57–180 day comparison interval used in secondary analyses; Severity scale not mentioned	123,200 doses of MMRV administered; 584,987 doses of MMR + V administered	1 case after MMRV and 1 case after MMR + V 1–42 days post-vaccination in primary analyses; 4 cases (1 case after MMRV, 3 cases after MMR + V) 1–42 days post-vaccination in secondary analyses; 31 cases (6 cases after MMRV, 25 cases after MMR + V) 57–180 days post-vaccination in secondary analyses	Risk difference (unadjusted), adjusted relative risks (stratified by age, gender, calendar week, and VSD site in primary analyses), adjusted odds ratios, and ratio of odds ratios. RD = 0.32 (−0.91, 4.26)/ 100,000 doses administered for MMRV vs. MMR + V; RR = 12.12 (0.03, 4443.16) for MMRV vs. MMR + V in 1–42 day post-vaccination risk interval (primary analysis); Ratio of ORs = 0.22 (0 to 124.03) for MMRV cases in risk and comparison intervals vs. MMR + V cases in risk and comparison intervals (secondary analysis). Unadjusted RD per 100,000 doses in risk versus comparison intervals = -0.9 (−3.07 to 3.13) for MMRV and -1.05, (−1.88 to 0.08) for MMR + V

and boosters, or dose escalation designs), should also be reported when feasible. Standard case based causality assessment methods and terminologies should be used and the appropriate methods should be described and referenced. This is especially important when studies are not able to report measures of relative or absolute risk and corresponding precision estimates (e.g., case reports).

5. Conclusions

Overall, the evidence is too heterogeneous and incomplete to infer a causal association between vaccination and new onset of arthritis following vaccines. A possible exception may be transient arthralgia following rubella vaccine in women of childbearing age although this evidence is primarily based on case reports. In addition, among studies that reported measures of association, the majority were powered to detect only large increases in risk; thus, it is possible that small increases in risk exist but remain undetected. The evidence related to Ebola vaccines is still emerging and continued monitoring is required.

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Disclaimer

The findings, opinions and assertions contained in this document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organisation.

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