Safety Platform for Emergency vACcines

D2.2.7 Companion Guide for Acute Aseptic Arthritis

V1.0 – [17 Jul 2024]

Authors: Barbara Law, Miriam Sturkenboom, Matthew Dudley, Marta Rojo Villaescusa

TABLE OF CONTENTS

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DEFINITIONS & ACRONYMS

A/C	Acute / Convalescent
AEFI	Adverse event following immunization
AESI	Adverse events of special interest
Ag	Antigen
ANA	Antinuclear antibodies
ANCA	Antineutrophil cytoplasmic antibodies
BC	Brighton Collaboration
BCG	Bacille Calmette-Guérin
CBC	Complete blood count
CCP	Cyclic citrullinated peptide
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CI	Confidence interval
CM	Clinical modification (Relates to numbered versions of ICD codes)
CRP	C-reactive protein
C&S	Culture and sensitivity
CT	Computed tomography
CUI	Concept unique identifier
DOI	Digital object identifier
EBV	Epstein Barr virus
ESR	Erythrocyte sedimentation rate
ENA	Extractable nuclear antigen
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GU	Genitourinary
HBV	Hepatitis B vaccine
HBC	Hepatitis C virus
HIV	Human immunodeficiency virus
HPF	high power field
IA	Inflammatory arthritis
ICD	International Classification of Diseases
IOM	Institute of Medicine
IQR	Interquartile range
LFT	Liver function test
MCP	Metacarpal phalangeal joints
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Mumps Measles Rubella vaccine
MRI	Magnetic resonance imaging
OR	Odds ratio
PCR	Polymerase chain reaction
PFU	Plaque forming unit
PJI	Prosthetic joint infection
PIP	Proximal interphalangeal joints
PMN	Polymorphonuclear white blood cell
PPD	Purified protein derivative
ReA	Reactive arthritis

RF	Rheumatoid factor
rVSV	Recombinant vesiculostomatitis virus
SF	Synovial fluid
SpA	Spondyloarthritis
SPEAC	Safety Platform for Emergency vACcines
Td	Tetanus toxoid
TSH	Thyroid stimulating protein
UA	Urinalysis
uL	Microliter
UMLS	Unified Medical Language System
US	Ultrasound

INTRODUCTION

1. Background

CEPI has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI prioritized epidemic diseases. Having identified relevant AESI, SPEAC then works to ensure tools and resources are available to facilitate a standard approach to global vaccine safety research and pharmacovigilance activities.

The AESI resources include tabulation of relevant medical codes as well as background incidence data and risk factors. The tools include new case definitions if no published Brighton Collaboration case definition exists, case report forms for standard data collection that would support meeting the case definition levels of certainty and algorithms for assessing level of certainty based on available evidence for each case.

Initially these resources and tools were developed as separate documents but starting in 2021 they were pulled together into a single 'Companion Guide' for each published Brighton Collaboration Case Definition. All Companion Guides are available in the SPEAC website. In addition, since the summer of 2022, all SPEAC Companion Guides are published on the SPEAC community portion of the Zenodo public website. This enables all Companion Guides to have a citable DOI.

The focus of this document is to provide a new Companion Guide to the Acute Aseptic Arthritis Case Definition.[1] The guide also incorporates relevant evidence from a systematic review of acute aseptic arthritis as an AEFI published by the Brighton CD working group as background to the case definition.[2]

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for Acute Aseptic Arthritis.

3. Methods

The methods used are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. As for all Companion Guides, medical codes were obtained using Codemapper[3-7], described in Appendix 6. In addition, any new methodology, relevant to the content of this Guide, is also provided in appendix 6.

4. Results

4.1 Literature search

As noted in Appendix 6, two separate search strategies were used to identify articles on epidemiology, incidence and risk factors for acute aseptic arthritis. The two strategies yielded a total of 119 articles. There were 2 articles found in both reviews, so after removing duplicates 117 articles remained. Based on screening of title and abstract, 54 articles were excluded for the following reasons: 41 did not address incidence or risk factors, 7 were on topics unrelated to acute arthritis, 5 focused on therapy or diagnosis and 1 was the Brighton case definition for acute aseptic arthritis. An additional 33 articles were excluded after full text review because they were non-contributory to the content for the Companion Guide. A total

of 30 articles were included and are referenced in the appropriate sections of this guide (Appendices 2, 3 or 4) along with 34 articles retrieved by hand search of the citations.[8-71]

While the intended scope of the Companion Guide is acute aseptic arthritis, based on the evidence in the literature review, the final scope was expanded to cover entities that could also present as acute inflammatory arthritis since final diagnoses are rarely achieved at the time of first presentation and diagnostic workup. Thus, medical codes, background incidence, risk factors and recommendations for real time investigation are presented for acute inflammatory arthropathies, undifferentiated inflammatory arthritis, reactive arthritis, viral arthritis and septic arthritis as well as, where appropriate, on crystalline arthropathies and chronic inflammatory arthropathies (rheumatoid arthritis, ankylosing spondylitis).

The outputs are provided as separate appendices to simplify printing as needed. These include:

1. Acute inflammatory arthritis diagnostic Codes for: ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT
2. Acute inflammatory arthritis background rates
3. Acute inflammatory arthritis risk factors
4. Acute Aseptic Arthritis Case Definition key caveats for diagnosis, data analysis and presentation of safety data as well as guidance on 'real time' investigation of any possible cases of acute inflammatory arthritis that may be identified as part of clinical trials or active surveillance.
5. Acute Aseptic Arthritis data abstraction and interpretation form with algorithms for assessing level of certainty and a glossary of relevant terms.
6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to Acute Aseptic Arthritis as well as other acute onset inflammatory arthritides, including ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT codes for data entry or database searching, background rates, risk factors and guidance for real time investigation. It also provides updated tools, which are in the same format as the online versions, for collecting and interpreting clinical data to apply the Brighton Acute Aseptic Arthritis case definition and determine the level of diagnostic certainty.

It is important to emphasize key conclusions based on the evidence presented in this guide including:

- A clinical diagnosis of arthritis should be supported by objective, physician confirmed signs of arthritis (swelling, erythema, warmth, reduced range of motion of affected joints) and radiographic confirmed joint effusion (by ultrasound or MRI).
- New onset acute arthritis has a very broad differential diagnosis and requires initial investigation for several possibilities that would require specific therapy, including septic arthritis, rheumatoid arthritis and crystalline arthritis.
- When acute arthritis is reported as an AEFI, particularly in the context of a clinical trial or emerging vaccine safety signal, follow-up is critical since the final diagnosis may change over time. The acute aseptic arthritis case definition requires that there be full resolution of symptoms and signs in <6 weeks. Accordingly, 6 weeks is the minimum follow-up time. However, since it has also been shown in longitudinal studies that there may be recurrences, 6 – 12 months follow-up is preferable.
- The Brighton CD working group noted that acute aseptic arthritis should be distinguished from reactive arthritis. However, there is no accepted working case definition of reactive arthritis. Further, the scope of etiologies of reactive arthritis has expanded in recent years and includes several vaccines although these are, as yet only temporal associations.

SPEAC recommends that the data collection form and algorithms be used to assign level of certainty for all identified AEFI with features of Acute Aseptic Arthritis.

Further, SPEAC recommends that cases of acute inflammatory arthritis that are temporally associated with vaccination but don't meet the BC CD, should also be reported, investigated and followed to resolution.

Finally, SPEAC recommends in settings where acute aseptic arthritis is a specified AESI, such as pre- and post-marketing clinical trials as well as pharmacovigilance signal evaluation studies, that:

- Plans be in place for rapid notification and MD evaluation of all cases of acute arthritis following immunization
- Where possible, ultrasound imaging should be done to confirm joint effusion (or MRI if available).
- For all cases with signs of joint effusion, arthrocentesis should be done to obtain synovial fluid for WBC and differential, bacterial gram stain and culture and examination for crystals. When arthritis follows administration of live viral vaccines or vector platforms, synovial fluid should be tested for presence of the vaccine strain.
- All confirmed cases of acute inflammatory aseptic arthritis should be followed for 6 – 12 months. Where possible, engage rheumatologic experts to conduct the follow-up and further investigation over time.
- All post-immunization cases of acute inflammatory aseptic arthritis should be classified, at the end of follow-up, as level 1, 2, 3, 4 or 5 of acute aseptic arthritis. For each case there should be a summary description of the criterion values that contributed to the final classification, including any that led to Level 5, such as presence of fever or synovial fluid WBC differential showing >50% PMNs (The tools in Appendix 5 or the digital version of the data collection form can be used to facilitate this. Any level 4 or 5 case(s) should also be classified according to the final most likely diagnosis (e.g., reactive arthritis, rheumatoid arthritis, undifferentiated arthritis). Any cases classified as reactive arthritis should be further described in terms of the inciting etiology, if known (GI, GU, RTI, skin infection) or suspected (e.g., vaccine administration).

This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

6. References

1. Woerner A, Pourmalek F, Panozzo C et al. Acute aseptic arthritis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2019; 37:384-391. https://doi.org/10.1016/j.vaccine.2017.08.087 PMID 30342899
2. Panozzo CA, Pourmalek F, Pernus YB et al. Arthritis and arthralgia as an adverse event following immunization: A systematic literature review. Vaccine 2018; 37:372-383. https://doi.org/10.1016/j.vaccine.2018.06.067 PMID 30502066
3. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors J. CodeMapper: Semi-automatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 2017 (8) 26: 998-1005. http://Doi.org/10.1002/pds.4245 PMID 28657162
4. McCray AT, Burgun A, Bodenreider O. Aggregating UMLS semantic typesfor reducing conceptual complexity. Studies H ealth Technology Information, 2001 84(Pt 1): 216-20. PMID: 11604736; PMCID: PMC4300099.
5. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.
6. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety, 1999. 0(2):109-17. http://Doi.org/10.2165/00002018-199920020-00002 .
7. Schuemie MJ, Jelier R, Kors JA. Peregrine: Lightweight gene name normalization by dictionary lookup. In: Proc of the Second BioCreative Challenge Evaluation Workshop., 2007. 131–133.
8. Savolainen E, Kaipiainen-Seppänen O, Kröger L, Luosujärvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 arthritis survey. J Rheumatol. 2003;30(11):2460-2468. PMID 14677193
9. Isomäki H, Raunio J, von Essen R, Hämeenkorpi R. Incidence of inflammatory rheumatic diseases in Finland. Scand J Rheumatol. 1978;7(3):188-192. http://doi.org/10.3109/03009747809095652 PMID 310157
10. Kononoff A, Arstila L, Pussinen P, et al. Incidence of inflammatory joint diseases in Finland: results from a population-based epidemiological study. Rheumatol Int. 2017;37(10):1693-1700. http://doi.org/10.1007/s00296-017-3779-1
11. Söderlin MK, Börjesson O, Kautiainen H, Skogh T, Leirisalo-Repo M. Annual incidence of inflammatory joint diseases in a population based study in southern Sweden. Ann Rheum Dis. 2002;61(10):911-915. http://doi.org/10.1136/ard.61.10.911
12. Hočevar A, Potočnik Pucelj N, Ješe R, Pavič-Nikolič M, Tomšič M, Rotar Z. The incidence of spondyloarthritis in Slovenia. Medicine (Baltimore). 2019;98(26):e16177. http://doi.org/10.1097/MD.0000000000016177
13. Rohekar S, Pope J. Epidemiologic approaches to infection and immunity: the case of reactive arthritis. Curr Opin Rheumatol. 2009 Jul;21(4):386-90. http://doi.org/10.1097/BOR.0b013e32832aac66 . PMID: 19373091
14. Hitchon CA, Peschken CA, Shaikh S, El-Gabalawy HS. Early undifferentiated arthritis. Rheum Dis Clin N Am 2005; 31:605-626. http://doi.org/10.1016/j.rdc.2005.07.006 PMID 16287587.
15. Berthelot JM, Saraux A, Maugars Y, Prost A, Le Goff P. The nosology-taxonomy of recent-onset arthritis: The experience of early arthritis clinics. Semin Arthritis Rheum 2001;30:354-65. http://doi.org/10.1053/sarh.2001.19820 PMID 11303308
16. Hulsemann JL, Zeidler JL Undifferentiated arthritis in an early synovitis out-patient clinic. Clin Exp Rheum 1995; 13:37-43 PMID 7774101
17. Sieper J, Rudwaleit M, Baraliakos X, et al. The assessment of spondyloarthritis international society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68(Suppl 2):ii1–44. http://doi.org/10.1136/ard.2008.104018 PMID 19433414
18. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24. http://doi.org/10.1002/art.1780310302 PMID 3358796
19. Kay J, Upchurch KS. Rheumatology 2012; 51 Suppl 6: vi5-9. https://doi.org/10.1093/rheumatology/kes279 PMID 23221588

20. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8. http://doi.org/10.1002/art.1780270401 PMID 6231933
21. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73. http://doi.org/10.1002/art.21972 PMID 16871531
22. Petty RE, Southwood TR, Baum J et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban 1997; J Rheumatol 1998; 25:1991-4. PMID 9779856
23. Bentaleb I, Abdelghani KB, Rostom S et al. Reactive Arthritis: Update Current ClinMicroReports 2020; 7:124-32. https://doi.org/10.1007/s40588-020-00152-6 PMID 33014690
24. Duba AS, Mathew SD. The seronegative spondyloarthropathies. Prim Care Clin Office Pract 2018; 45:271-287. http://doi.org/10.1016/j.pop.2018.02.005 PMID 29759124
25. Zochling J, Smith EU. Seronegative spondyloarthritis. Best Pract Res Clin Rheumatol 2010; 24:747-56. http://doi.org/10.1016/j.berh.2011.02.002 PMID 21665123
26. McGill PE, Oyoo GO. Rheumatic disorders in Sub-saharan Africa. East Afr Med J. 2002 Apr;79(4):214-6. http://doi.org/10.4314/eamj.v79i4.8882 . PMID: 12625680.
27. Stolwijk C, Boonen A, van Tubergen A, Reveille JD. Epidemiology of Spondyloarthritis. Rheum Dis Clin North Am 2012; 38(3): 441-476. http://doi.org/10.1016/j.rdc.2012.09.003 PMID 23083748
28. Hannu T. Reactive arthritis. Best Pract&ResClinRheum 2011; 25:347-57. http://doi.org/10.1016/j.berh.2011.01.018 PMID 22100285
29. Zeidler H, Hudson AP. Reactive Arthritis Update: Spotlight on new and rare infectious agents implicated as pathogens. Current Rheum Reports 2021; 23:53. https://doi.org/10.1007/s11926-021-01018-6 PMID 34196842
30. Tugelbayeva A, Ivanova R, goremykina M et al. Reactive arthritis in children (review). Georgian Medical News 2021; 2(311): 130-135. PMID 33814406
31. Mathew AJ, Ravindran V. Infections and arthritis. Best Pract&ResClinRheum 2014; 28:935-959. http://dx.doi.org/10.1016/j.berh.2015.04.009 PMID 26096095
32. Bawazir Y, Towheed T, Anastassiades T. Post-streptococcal reactive arthritis. Curr Rheum Rev 2020; 16:2-8; http://doi.org/10.2174/1573397115666190808110337 PMID 31393253
33. Rueda JC, Crepy MF, Mantilla RD. Clinical features of Poncet's disease. From the description of 198 cases found in the literature. Clin Rheumatol 2013; 32:929-3. https://doi.org/10.1007/s10067-013-2270-y PMID 23624588
34. Goedvolk CA, von Rosenstiel IA, Bos AP. Immune complex associated complications in the subacute phase of meningococcal disease: incidence and literature review. Arch Dis Child 2003; 88:927-30. http://doi.org/10.1136/adc.88.10.927 PMID 14500317
35. Edington F, Varjao D, Melo P. Incidence of articular pain and arthritis after chikungunya fever in the Americas: A systematic review of the literature and meta-analysis. https://doi.org/10.1016/j.jbspin.2018.03.019 PMID 30053609
36. Bekaryssova D, Yessirkepov M, Zimba O et al. Reactive arthritis before and after the onset of the COVID-19 pandemic. Clin Rheum 2022; 41:1641-52. https://doi.org/10.1007/s10067-022-06120-3 PMID 35247132
37. Roseti L, Grigolo B. COVID-19 and rheumatic diseases: a mini-review. Frontiers in Medicine 2022; 9:997876. https://doi.org/10.3389/fmed.2022.997876 PMID 36226148
38. Kocyigit BF, Akyol A. Reactive arthritis after COVID-19: a case-based review. Rheum Intl 2021; 41:2031-39. https://doi.org/10.107/s00296-021-04998-x PMID 34550429
39. Amissah-Arthur MB, Poller B, Tunbridge A, Adebajo A. Musculoskeletal manifestations of Ebola virus. Rheumatol 2018; 57:28-31. http://doi.org/10.1093/rheumatology/kex082 PMID 28379487
40. Adwan MH. An update on drug-induced arthritis. Rheumatol Int 2016; 36:1089-1097. https://doi.org/10.1007/s00296-016-3462-y. PMID 27000044
41. Adverse effects of vaccines: Evidence and Causality. In: Stratton K, Ford A, Rusch E, Clayton EW, editors. Committee to review adverse effects of vaccines; Institute of Medicine. Washington (DC): National Academies Press (US); 2011.

42. Bell D, Manchal N, et al. Reactive arthritis from influenza vaccination: a novel presentation that mimics prosthetic joint infection. A Case Report. J Bone & Joint Surg Case Connect 2021; 11:e21.00207. http://dx.doi.org/10.2106/JBJS.CC.21.00207 PMID 35102026
43. Kesiktaş FN, Yemisen M, Gün K, Uludağ M, Dernek B. A Case of Reactive Arthritis Developed After Tetanus Vaccine. İstanbul Kanuni Sultan Süleyman Tıp dergisi. 2015. pp. 147– 149. http://doi.org/10.5222/iksst.2015.147
44. Rahimi SS, Osstrov BE, Lopez-Pena M. Inflammatory arthritis following hepatitis B vaccination in an infant. Case Reports in Rheumatology 2021; 5598217; https://doi.org/10.1155/2021/5598217 PMID 33880198
45. Dudley MZ, Halsey NA, Omer SB et al. The state of vaccine safety science: systematic reviews of the evidence. Lancet ID 2020; 20(5): e80-e89 https://doi.org/10.1016/S1473-3099(20)30130-4. PMID 32278359
46. Anis O, Yogev D, Dotan A et al. Autoimmune disorders caused by intravesical bacillus Calmette-Guerine treatment: A systematic review. Autoimmunity Rev 2023; 22. https://doi.org/10.1016/j.autrev.2023.103329 PMID 37961015
47. Abdelghani KB, Nacef L, Miladi S et al. Reactive arthritis following BCG therapy for bladder cancer: a systematic literature review. Curr RheumReports 2021; 23:39. https://doi.org/10.1007/s11926-021-01004-y PMID 33913026
48. Tinazzi E, Ficarra V, Simeoni S, Artibani W, Lunardi C. Reactive arthritis following BCG immunotherapy for urinary bladder car- cinoma: a systematic review. Rheumatol Int. 2006;26(6):481–88. http://doi.org/10.1007/s00296-005-0059-2 . PMID: 16220289
49. Agnandji, S.T., Huttner, A., Zinser, M.E., Njuguna, P., Dahlke, C., Fernandes, J.F., Yerly, S., Dayer, J.A., Kraehling, V., Kasonta, R. and Adegnika, A.A., 2016. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe. New England Journal of Medicine, 374(17), pp.1647-1660. http://doi.org/10.1056/NEJMoa1502924 PMID 25830326
50. Huttner, Angela, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. The Lancet Infectious diseases 15.10 (2015): 1156-1166. http://doi.org/10.1016/S1473-3099(15)00154-1 PMID 26248510
51. Heppner DG, Kemp TL, Martin BK et al. Safety and immunogenicity of the rVSVrG-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomized, multicentre, double-blind,placebo-controlled, dose-response study. Lancet Infect Dis 2017; 17:854-866. https://doi.org/10.1016/S1473-3099(17)30313-4
52. Halperin SA, Arribas JR, Rupp R et al. Six-month safety data of recombinant vesicular stomatitis virus-Zaire ebola virus envelope glycoprotein vaccine in a phase 3 double-blind, placebo-controlled randomized study in healthy adults. JID 2017; 215:1789-98. https://doi.org/10.1093/infdis/jix189 PMID 28549145
53. Liu J, Wu H, Xia S-L. New-onset arthritis following COVID-19 vaccination: a systematic review of case reports. Vaccines 2023; 11, 665. https://doi.org/10.3390/vaccines11030665 PMID 36992249
54. Nahra V, Makandura M, Mattar M, Anthony DD. A case series on the COVID-19s vaccines and possible immune-related adverse events: a new challenge for the rheumatologists. Cureus 2022; 14: e12492 http://doi.org/10.7759/cureus.29660 PMID 36321010
55. Roux N, Poussing S, Maurier F. Case of reactive sacroiliitis possibly induced by an mRNA coronavirus disease vaccine. BMJ Case Rep 2022; 15:3249063. https://doi.org/10.1136/bcr-2022-249063 PMID 35798496
56. Vanaskova E, Kelbich P, Novotny T. Reactive synovitis of the knee joint after COVID-19 vaccination: the first ultrastructural analysis of synovial fluid. IntlJRheumDis 2022; 00:1-4. http://DOI.org/10.1111/1756-185X.14411 PMMID 35929362
57. Koh S, Chen H, Hsu C. Prolonged peripheral seronegative spondyloarthritis following BioNTech coronavirus diseas 2019 vaccination: a case report Int J Rheum Dis 2022; 1-4. https://doi.org/10.1111/1756-185X.14512 PMID 36482057
58. Rim Park Y, Ben-Artzi A. New onset of inflammatory arthritis following moderna COVID-19 vaccination. Isr Med Assoc J 2022; 24-333-4. PMID 35598060
59. Nune A, Sapkota HR, Iyengar KP. The emergence of rheumatic immune-mediated inflammatory disease manifiestations following SARS-CoV-2 vaccination. Ind J Rheum 2022; 17:214-215.
60. An Q-J, Qin D-A, Pei J-X. Reactive arthritis after COVID-19 vaccination. HumVaccines & Immunotherapeutics 2021; 17(9):2954-6. http://doi.org/10.1080/21645515.2021.1920274 PMID 34033732

61. Enginar AU. Arthritis following COVID-19 vaccination: report of two cases. Intn'l Immunopharm 2021; 101:108256. https://doi.org/10.1016/j.intimp.2021.108256 PMID 34673298
62. Baimukhamedov C. Arthritis of the left elbow joint after vaccination against SARS-CoV-2 infection. Int J Rheum Dis 2021; 24:1218-1220. http://doi.org/10.1111/1756-185X.14202 PMID 34363344
63. Wojturska W, Nowakowski J, Pilch W et al. Reactive arthritis after vaccination against SARS-CoV-2: A case series and a mini-review. Human Vaccines and Immunotherapeutics 2023; 19(1): 2173912. https://doi.org/10.1080/21645515.2023.2173912 PMID 36746791
64. Schoenardie BO, Schoenardie AO, Damke JP. Monoarthritis induced by the Oxford-AstraZenecaR SARS-CoV-2 vaccine. Rev Colomb Reumatol 2022; 29(S1):S77-S79. https://doi.org/10.1016/j.rcreu.2022.01.002
65. Turk SM, Ozturk Z, Karatas D, Gonullu E. Inactivated COVID-19 vaccine can induce reactive polyarthritis in older patients: Report of two cases. Georgian Med News 2021; 10(319): 101. PMID 34749331
66. Alalem N, Yousaf N. A Case report of Reactive arthritis after COVID-19 AstraZeneca Vaccination. Cureus 2023; 15(2): e35544. http://DOI.org/10.7759/cureus.35544 PMID 37007315
67. Shokraee K, Parsaei A, Masoumi M. Reactive arthritis after Gam-COVID-Vac vaccination: a case report. Modern Rheumatology Case Reports Jan 2023; http://doi.org/10.1093/mrcr/rxad002 PMID 36715083
68. National Academies of Sciences, Engineering, and Medicine. 2024. Evidence review of the adverse effects of COVID-19 vaccination and intramuscular vaccine administration. Washington, DC: The National Academies Press. https://doi.org/10.17226/27746
69. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Research & Therapy 2017; 19: 18. https://doi.org/10.1186/s13075-017-1229-9
70. Mau W, Raspe H-H, Mersjann H. Early arthritides: nosography, nosology, and diagnostic criteria. Scan J Rheumatology 1989; Suppl. 79:3-112. http://doi.org/10.3109/03009748909092606 PMID 2595336
71. Zeidler H, Hudson AP. Quo vadis reactive arthritis? Curr Opin Rheumatol 2022; 34(4): 218-224. http://doi.org/10.1097/BOR.0000000000000880 PMID 35699331

APPENDIX 1.

ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT Codes for Acute Aseptic Arthritis

1.1 Acute Aseptic Arthritis Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMEDCT [3-7]

TABLE 1.1 NARROW SEARCH TERMS FOR Acute Aseptic Arthritis

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD-9-CM	ICD-10-CM	SNOMEDCT
C0276308	Arthritis due to rubella	Arthritis due to rubella		056.71		19431000
		Rubella arthritis			B06.82	
		Arthritis rubella	10003270			
C0152083	Transient arthropathy	Transient arthropathy		716.4		66191007
		Transient arthropathy, site unspecified		716.40		
C0157805	Arthropathy involving hand associated with other viral diseases	Arthropathy associated with other viral diseases, hand		711.54		
C0409548	Arthropathy associated with other viral diseases, other specified sites			711.58		
C0409549	Arthropathy associated with other viral diseases, multiple sites			711.59		
C0409550	Arthropathy associated with other viral diseases, ankle and foot			711.57		
C0409551	Arthropathy associated with other viral diseases, lower leg			711.56		
C0409552	Arthropathy associated with other viral diseases, pelvic region and thigh			711.55		
C0409554	Arthropathy associated with other viral diseases, forearm			711.53		
C0409555	Arthropathy associated with other viral diseases, upper arm			711.52		
C0409556	Arthropathy associated with other viral diseases, shoulder region			711.51		
C0157801	Arthropathy associated with other viral diseases, site unspecified	Arthropathy associated with other viral diseases		711.5		
		Arthropathy associated with other viral diseases, site unspecified		711.50		
C3892044	Oligoarticular Arthritis	Oligoarthritis	10082100			
C0477550	Other specified arthritis	Other specified arthritis			M13.8	
		Other specified arthritis, unspecified site			M13.80	
C0837950	Other specified arthritis, multiple sites				M13.89	
C0837954	Other specified arthritis, hand				M13.84	
C0837957	Other specified arthritis, ankle and foot				M13.87	
C0837958	Other specified arthritis, other site				M13.88	

TABLE 1.2 BROAD SEARCH TERMS FOR Acute Aseptic Arthritis

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD-9-CM	ICD-10-CM	SNOMEDCT
C0003864	Arthritis	Arthritis	10003246			3723001
C3892044	Oligoarticular Arthritis	Oligoarthritis	10082100			
C0477550	Other specified arthritis	Other specified arthritis			M13.8	
		Other specified arthritis, unspecified site			M13.80	
C0837950	Other specified arthritis, multiple sites	Other specified arthritis, multiple sites			M13.89	
C0837954	Other specified arthritis, hand	Other specified arthritis, hand			M13.84	
C0837957	Other specified arthritis, ankle and foot	Other specified arthritis, ankle and foot			M13.87	
C0837958	Other specified arthritis, other site	Other specified arthritis, other site			M13.88	
C0022408	Arthropathy	Arthropathy	10003285			399269003
		Joint disorders	10023213			
		Arthropathy, unspecified		716.9	M12.9	
		Arthropathy, unspecified, site unspecified		716.90		
		Unspecified disorder of joint		719.9		
		Joint disorder, unspecified			M25.9	
		Unspecified disorder of joint, site unspecified		719.90		
C0152083	Transient arthropathy	Transient arthropathy		716.4		
		Transient arthropathy, site unspecified		716.40		

TABLE 1.3 SEARCH TERMS FOR Events that would exclude acute aseptic arthritis

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD-9-CM	ICD-10-CM	SNOMEDCT
C0003869	Arthritis, infectious	Pyogenic arthritis		711.0	M00	
		Pyogenic arthritis, unspecified			M00.9	
		Unspecified infective arthritis		711.9		
		Unspecified infective arthritis, site unspecified		711.90		
		Infectious arthritis	10021904			
		Infective arthritis				396234004
		Arthritis infective	10060968			
		Pyoarthrosis				372939007
C0003873	Rheumatoid arthritis	Rheumatoid arthritis	10039073	714.0		69896004
		Rheumatoid arthritis, unspecified			M06.9	
C0152087	Crystal arthropathies	Crystal arthropathies		712		
		Crystal arthropathy	10061419			18834007
		Crystal arthropathy, unspecified			M11.9	
		Unspecified crystal arthropathy		712.9		
		Unspecified crystal arthropathy, site unspecified		712.90		
C0018099	Gout	Gout	10018627		M10	
		Gout unspecified			M20.9	
C0003868	Arthritis, gouty	Gouty arthritis	10018634			

APPENDIX 2.

Acute Aseptic Arthritis Background Rates

2.1 Acute Inflammatory Arthritis Background Rates[8-22]

Only one study presented below, provided data on the incidence of viral arthritis[8] and the case definition was based on clinical or serologic evidence of viral infection. Table 2.2 describes the methodology and Table 2.3 the classification used for all entities in Table 2.1. Notably the definitions of reactive arthritis varied. Except for viral arthritis, the other entities tend to be chronic in nature, although reactive arthritis may resolve within the timeframe defined by the working group for acute aseptic arthritis (< 6weeks). The rationale for including these data, is that all the studies in Table 2.1 focused on incident cases of proven inflammatory arthritis that were assessed by rheumatologists during the acute presentation of the disease. As such they provide an approximation of expected cases of new onset inflammatory arthritis. Table 2.4 provides a breakdown of specific diagnostic entities included in each study, if provided by the authors. It is notable that undifferentiated arthritis makes up a large portion of the total entities included in each study. Further, it has been established, via several long-term follow-up studies of new onset inflammatory arthritis, that the initial diagnosis often changes over time.[13-16] The minimal follow-up time for cases of possible acute aseptic arthritis is 6 weeks given that complete resolution must occur within this timeframe to meet any level of diagnostic certainty for the Brighton case definition. While the case definition suggests that reactive arthritis is not within the scope of acute aseptic arthritis, many cases of reactive arthritis have been temporally associated with a variety of vaccines (see Appendix 3 on Risk Factors for acute inflammatory arthritis). Accordingly, any cases of clinical arthritis persisting ≥6 weeks should be followed to resolution or to determination of a specific final diagnosis.

TABLE 2.1. ACUTE NEW ONSET INFLAMMATORY ARTHRITIS BACKGROUND RATES BY GEOGRAPHIC REGION

NOTE: Study methods, arthritis classification criteria and distribution are provided in Tables 2.2, ,2.3 and 2.4 respectively.

Country	Study years	Population Age and Type of Arthritis	Incidence per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA None					
AMERICAs None					
ASIA None					
AUSTRALIA/OCEANIA None					
MIDDLE EAST None					
EUROPE					
Finland[8]		All ages All Arthritides Reactive arthritis Viral arthritis Undifferentiated arthritis Adult: all arthritides Child: juvenile arthritis	229.7 [198.9-263.9] (199) 10.1 [4.1-20.8] (7) 7.2 [2.3-16.8] (5) 148.5 [121.2-180.1] (103) 271.1 [233.7-312.7] (103) 63.6 [33.1-118.8] (11)	129.6 [97.1-169.5] (53) 15.3 [5.0-35.8] (5) 6.1 [0.7-22.1] (2) 52.1 [30.4-83.5] (17) 153.3 [113.8-202.8] (50) 36.2 [7.5-105.8] (3)	319.1 [269.4-375.2] (146) 5.4 [0.7-19.7] (2) 8.2 [1.7-23.9] (3) 234 [187.2-289] (86) 375.5 [315.5-443.7] (138) 88.8 [38.3-174.9] (8)
Finland[9]	1974-1975	≥16 years All arthritis Reactive arthritis Non-defined arthritis	218 (332) 14 (22) 48 (73)	182(133) 12 (9) 39 (28)	250 (199) 16 (13) 57 (45)
Finland[10]		>16 years All Inflammatory joint disease Reactive arthritis Undifferentiated arthritis	130.4 [127.1-133.8] (292) 7.9 [7.1-8.8] (16) 38.1 [36.5-39.9] (80)	136.4 [131.5-141.5] (142) 7.4 [6.3-8.7] (7) 27.2 [25.0-29.5] (29)	141.5 [127.1-133.8] (150) 8.3 [7.2-9.6] (9) 48.3 [45.5-51.3] (51)
Sweden[11] (Växjö)	1999-2000	>16 years All New Onset Inflammatory Joint Disease Reactive arthritis Undifferentiated arthritis	115 [97-134] (151) 28 [20-39] (37) 41 [31-54] (54)	96 [74-123] (63) 21 [12-36] (14) 41 [27-60] (27)	132 [106-163] (88) 35 [22-52] (23) 41 [27-59] (27)
Slovenia[12]	2014-2016	≥18 years All spondyloarthropathies Reactive arthritis Undifferentiated spondyloarthropathy	14.3 [12.8-16.0] 1.0 [0.7-1.6] 4.3 [3.5-5.3]		

TABLE 2.2. METHODOLOGY FOR INCIDENCE STUDIES OF ACUTE INFLAMMATORY ARTHRITIS

Country	Finland[9]	Finland[8]	Finland[10]	Sweden[11]	Slovenia[12]
Location (Population)	City of Heinola and surrounding 29 counties (260,000)	City of Kuopio (86,651)	Northern Savo Province (includes city of Kuopio) (206,441)	Kronenberg county (132,000)	Country (704,342)
Study period	1974/1975	Jan1-Dec31, 2000	Jan1-Dec31, 2010	May1/1999-May1/2000	Jan1, 2014 to Dec 31, 2016
Case Ascertainment	Referrals of eligible patients, stimulated by letters to all practicing MDs and notices posted in all health centres	Referrals for inflammatory arthritis	Referrals for undiagnosed inflammatory joint disease, to outpatient clinics or hospitals	Referrals for acute onset inflammatory arthritis of unknown cause or acute or subacute new onset polyarthritis; reviewed records of all hospitalized patients with joint fluid aspiration	Medical record search for ICD10 codes: M02*(post-infective and reactive arthropathies), M07*(enteropathic arthropathies), M45*(ankylosing spondylitis), M46.1*(sacroiliitis, not elsewhere classified), K50*, K51*, L40*
Inclusion criteria	≥16 years; swelling of ≥1 joint with duration of ≤6 months	All ages; ≥1 joint with peripheral synovitis or signs of inflammation in sacroiliac, glenohumoral or hip joints assessed by US, MRI or scintography		>16 years; new joint inflammation with swelling of ≥1 joint	Clinical features consistent with SpA found on throrough review of electronic and paper records; and meeting ASAS criteria[17] for axial and peripheral SpA
Exclusion criteria	None specified	Traumatic joint condition; prior osteoarthritis; presence of only tenosynovitis or bursitis	Traumatic joint condition; prior osteoarthritis; SA; solitary tenosynovitis or bursitis; established prior diagnosis or therapy for inflammatory joint disease.	≤16 years; osteoarthritis, SA, crystal arthropathy; patients with history of joint swelling before May 1999;	None specified
Diagnostic workup	Not specified	All: CBC, ESR, CRP, LFTs, Cr, RF, HLA-B27; UA Children: serology for Camylobacter, Salmonella, Yersinia, Borrelia, Sindbis (Pogosta virus), parvovirus Clinical indication: SF, bacterial/viral serology; stool C&S; XRays/US of involved joints.	All: basic lab tests (not specified), fasting plasma glucose, lipid panel, RF, anti-CCP, HLA-B27, UA. MD discretion: SF, blood / urine/ stool C&S; infectious disease serology; Xrays/US of affected joints.	Not specified	Not specified

TABLE 2.3. CLASSIFICATION CRITERIA FOR ACUTE INFLAMMATORY ARTHROPATHIES INCLUDED IN INCIDENCE STUDIES

NOTE: greyed out cells indicate diagnostic category not included in study

STUDY	Finland[9]	Finland[8]	Finland[10]	Sweden[11]	Slovenia[12]
Rheumatoid Arthritis	American Rheumatology Association (ARA) criteria[18]	≥4 ARA criteria[18]	≥4 ARA criteria[18] or ≥6 ACR/Eular criteria[19]	ARA criteria[18], number not specified	
Ankylosing Spondylitis	≥grade 2 bilateral sacroiliitis AND (back pain or limitation of back mobility)	Back pain >3 months + radiographic signs of spinal involvement (≥grade 2 bilateral sacroiliitis or signs of spondylitis)			Modified New York criteria[20]
Psoriatic Arthritis	Joint inflammation in patients with psoriasis excluding RF+ polyarthritis	Peripheral arthritis with psoriasis, excluding RF-positive polyarthritis or spondylitis with psoriasis		Psoriasis in association with arthritis and RF-	2006 CASPAR criteria[21]
Unspecified SpA*		Inflammatory back pain & scintigraphic or MRI-defined sacroiliitis/arthritis in glenohumeral, hip or peripheral joint(s)			
CTD		Arthritis & evidence for specific Ct disease (biopsies, Xrays, lab tests)			
Sarcoid Arthritis	Arthritis & evidence of acute sarcoidosis				
Crystalline Arthritis	Specified 'Gout': typical clinical picture or sodium urate crystals in SF	Typical clinical picture with elevated serum uric acid level or with monosodium urate, calcium pyrophosphate or dihydroxyapatite crystals in SF or with typical erosions or chondrocalcinosis in radiographs			
JIA**		Meets Durban classification[22]			
Reactive Arthritis	Peripheral synovitis and recent or present GI or GU infection, but lacking symptoms of urethritis or eye inflammation.	Prior GI or GU tract infection and peripheral synovitis or inflammatory signs in sacroiliac, glenohumeral, or hip joints and positive: stool C&S, ligase chain reaction (LCR) test for C. trachomatis or serology for enteric bacteria causing ReA.	Prior skin, RT, GI or GU tract infection and peripheral synovitis or inflammatory signs in sacroiliac, glenohumeral, or hip joints.	Inflammatory arthritis with prior infection verified by culture or serology; OR in absence of history of infection, by culture or serology alone	SpA preceded by GI or GU tract infection caused by bacteria commonly associated with ReA.
Reiter's disease	Peripheral synovitis & urethritis or eye inflammation or both				
Enteric Arthritis					Acute arthritis & existing proven IBD
Viral Arthritis		Typical clinical picture with rash or elevated anti-viral IgM or IgG			
Osteoarthritis	Isolated synovitis of osteoarthritic joint				
Undifferentiated Arthritis	Arthritis not meeting any defined entity	Other mono-, oligo- or polyarthritis: ± RF+ [8]; ± RF or anti-CCP+ [10].		Arthritis not meeting any defined entity	SpA not meeting any defined entity

*Spondyloarthropathy; **Juvenile Inflammatory Arthritis

TABLE 2.4. DISTRIBUTION OF DIAGNOSTIC RHEUMATOLOGIC ENTITIES INCLUDED IN INCIDENCE STUDIES

Country	Finland[9]	Finland[8]	Finland[10]	Sweden[11]	Slovenia[12]
Incident cases (%)	**332 (100%)**	**199 (100%)**	**292 (100%)**	**151 (100%)**	**302 (100%)**
Diagnostic subsets:					
Rheumatoid Arthritis	75 (22.6%)	25 (12.6%)	86 (29.4%)	31 (21%)	
Ankylosing Spondylitis	15 (4.5%)	4 (2.0%)	18 (2.7%)	2 (1.3%)	62 (20.5%)
Psoriatic Arthritis	11 (3.3%)	16 (8.0%)	32 (11.0%)	11 (7%)	115 (38.1%)
Unspecified Spondyloarthritis		9 (4.5%)	21 (7.2%)		
Connective tissue disease	11 (3.3%) [6 systemic lupus erythematosus, 3 mixed connective tissue disease, 1polymyositis, 1 Wegener's granulomatosis]	6 (3.0%)		3 (2.0%) [2 systemic lupus erythematosus, 1 mixed connective tissue disease]	
Sarcoidosis	4 (1.2%)		3 (1.0%)	3 (2.0%)	
Crystalline arthritis	Gout: 9 (2.7%)	13 (6.5%)	31 (10.6%)		
Juvenile arthritis		11 (5.5%)			
Reactive arthritis	22 (6.6%)	7 (3.5%)	16 (5.5%)	37 (24%)	22 (7.3%)
Enteropathic arthritis					12 (4.0%)
Viral arthritis		5 (2.5%)	None found		
Other	29 (8.7%) [21 Osteoarthritis or trauma with synovitis; 2 septic arthritis; 2 rheumatic fever; 2 rheumatic tenosynovitis; 1 juvenile rheumatoid arthritis, 1 chondromatosis]		5 (1.7%) [4 enteropathic arthritis; 1 arthropathy with thyroid disease;]	12 (7.9%) [3 Lyme arthritis, 3 Henoch Schonlein purpura, 2 polymyalgia rheumatica, 2 ankylosing spondylitis, 1 temporal arteritis, 1 osteoarthritis with synovitis]	
Undifferentiated arthritis	148 (44.6%) [includes 75 with probable but unconfirmed rheumatoid arthritis]	103 (51.8%)	80 (27.4%)	54 (36%)	91 (30.1%)

APPENDIX 3

Risk Factors for Acute Aseptic Arthritis

New Onset Inflammatory Arthritis Risk Factors There are many possible causes of acute inflammatory arthritis.[23-26] The Working Group limited acute aseptic arthritis to entities where there are no infectious pathogens within the joint and the course is transient, with full resolution within 6 weeks of onset.[1] However, at the time of first presentation it is impossible to know what the time course to resolution will be. Furthermore, published follow-up studies of acute arthritis have shown that the diagnosis after months of follow-up, may change as new clinical features emerge that fit established classification criteria.[12-15] A thorough approach to initial investigation, including synovial fluid aspiration and analysis, as well as follow-up for >6 weeks is essential. (see Appendix 4 for recommendations on real-time investigation of acute arthritis). Accordingly, the risk factors for new onset acute inflammatory arthritis are presented in two separate tables: Table 3.1 focuses on acute inflammatory arthritis where inflammation is not caused by microbial invasion of the joint space; Table 3.2 focuses on arthritis due to inflammation caused by intraarticular infection, including septic arthritis. Non-inflammatory arthritides such as degenerative osteoarthritis are beyond the scope of this guide.

TABLE 3.1 Risk Factors for New Onset Inflammatory Arthritis [1, 2, 23-68] (excluding Septic arthritis and other intra-articular infectious causes of arthritis – these are presented in Table 3.2)

Age	Juvenile onset spondyloarthritis: onset in children and adolescents aged <16 years
Genetics	HLA-B27 increases risk of several spondyloarthropathies including Reactive Arthritis; marked variation in prevalence geographically: reviewed by Stolwijk et al[27]: Papua New Guinea Pawaia tribe – 53%; Haida indigenous people, Queen Charlotte Islands, Canada – 50%; Chukotka people in East Russia – 40%; Northern Scandinavian countries 15-25%; Western European populations 4-13%; USA 6.1%; Arabic countries 2-5%; Japan 1%; South American Indians, Australian aborigines 0-<1%; also reviewed by Zochling 2010: Norway Samis – 24%; Norway overall 16%; Iceland 15%; Finland 12-16%; Czech Republic 10%; Germany 9.5%; Greece 5.4%; China 2-9%; Africa <1% (Congo, Nigeria), Japan 0.5%, Australian aborigines 0%
Geography	Reactive arthritis is more frequent in countries with a high prevalence of HLA-B27 (see Genetics)
Behavioral	• Alcohol abuse • High dietary intake of purines (red meat, shellfish, fructose containing beverages, beer, other alcohol) which break down into uric acid (Crystal arthropathies like gout)
Trauma	• Joint trauma or surgery
Comorbidity	• Enteropathic arthritis: may occur in the context of Inflammatory Bowel Disease • Psoriasis: 20-30% of patients with psoriasis develop arthritis; 15% of PsA cases present prior to skin changes • Crystal arthropathies (e.g., gout): untreated high blood pressure, diabetes, obesity, metabolic syndrome, chronic heart or kidney disease • Autoimmune Systemic disorders that may present as acute arthritis: Rheumatoid arthritis, SLE, sarcoidosis • Malignancy: leukemia, metastatic cancer

Extra-articular Infection as causes of Reactive arthritis	• **Established causes of Reactive Arthritis**[23-31] – infection precedes onset of arthritis by 3 days to 6 weeks
	  • **Urogenital infection:** *Chlamydia trachomatis*
	  • **Gastrointestinal infection:** *Yersinia enterocolitica* O3, O8 and O9; *Yersinia pseudotuberculosis, Campylobacter jejuni, Salmonella enterica (serovars Typhimurium enteritidis Paratyphi B and C, others), Shigella flexneri, Shigella sonnei, Shigella dysenteriae*

	• **Respiratory infection:** *Chlamydiae pneumoniae*
	• **Atypical causes of Reactive Arthritis**[31]
	  • **Urogenital tract:** *Gardnerella vaginalis, Mycoplasma genitalium, Mycoplasma hominis, Mycoplasma orale, Ureaplasma urealyticum, Neisseria gonorrhoea*
	  • **Gastrointestinal tract:** *Blastocytosis, Clostridium difficile, Cyclospora cayetanensis, E. coli, Hafnia alvei, Helicobacter pylori, Microsporidia, Strongyloides stercoralis, Tropheryma whippelii, Vibrio parahaemolyticus, Helicobacter cinaedi, B cereus, Lactobacillus*
	  • **Amoebae:** *Cryptosporidium, Entaboeba histolytica, Entamoeba hartmanni, Giardia lamblia*
	  • **Respiratory tract:** *Beta-haemolytic streptococci*[32]*, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Neisseria meningitidis*
	  • **Other (skin, soft tissue infection**): *Bartonella henselae, Borrelia burgdorferi (Lyme disease), Brucella abortus, Brucella mellitensis, Coxiella burneti Leptospira, Orientia tsutsugamushi, Propionibacterium acnes, Pseudomonas aeruginosa, Rickettsia conorii, Rickettsia rickettsii, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus lugdunensis*
	• **Other extra-articular infections that may be complicated by arthritis alone or spondyloarthritis (enthesitis, tendonitis, tenosynovitis) during the acute infection or during convalescence.**[31] Microbial antigens may be identified in synovial fluid or biopsy, but infectious agent is usually not recovered by culture of synovial fluid
	  • *Mycobacterium sp.* Reactive Arthritis may complicate Tuberculosis[33] and Leprosy[26]
	  • *Meningococcal sp.* Acute aseptic arthritis has been observed within 4 to 10 days of starting antibiotic therapy for invasive meningococcal infections; pathogenesis is thought to be circulating immune complexes[34]
	  • Parvovirus B19
	  • Alphaviruses[26,35]: Chikungunya, Ross River, Barmah forest, O'nyong nyong, Mayaro, Sindbis, Karelian fever (Western Russia), Ockelbo agent (Sweden), Pogosta (Finland)
	  • Retroviruses: HIV
	  • SARS-Coronavirus-2[36-38]
	  • Hepatitis viruses: Hepatitis A, Hepatitis B, Hepatitis C
	  • Other viruses: Rubella, Mumps, Adenovirus, Varicella virus, EBV, Coxsackie viruses (A9, B2, B3, B4), Zika virus, Ebola[39]

Drugs	• Based on a non-systematic review[40], drugs that have been temporally associated with arthritis include certain antimicrobials (tetracyclines, quinolones, rifampicin, quinupristin-dalfopristin, voriconazole), dipeptidyl peptidase-4 inhibitors, isotretinoin, chemotherapeutic agents (aromatase inhibitors, paclitaxel, docetaxel, cabazitaxel), alpha interferon and serotonin receptor 2A antagonists. Nothing was presented in the review to support that these are proven causal associations. It is beyond the scope of this work to systematically review the literature for all drugs that may cause arthritis.
Vaccine	• As a prelude to developing the Acute Aseptic Arthritis case definition, the Working Group did a systematic review of arthritis and arthralgia as an AEFI.[2] The literature search included articles published up to Dec 3, 2017. Among the included 343

studies were 206 clinical trials, 90 observational studies and 47 case reports. The study concluded that evidence linking incident arthritis or worsening of arthritic conditions was too heterogeneous and incomplete to infer a causal association. Some key issues were lack of consistent outcome definitions for arthritis or arthralgia, and inclusion in many studies of arthritis/arthralgia as a composite outcome.

- The Institute of Medicine report on childhood vaccines[41] examined the epidemiologic and mechanistic evidence for a link between several vaccines and arthropathy. They concluded the following:
    - **HBV vaccine:** the evidence was inadequate to establish causation for Reactive arthritis, Psoriatic arthritis, Rheumatoid arthritis or Juvenile Inflammatory Arthritis
    - **Diphtheria toxoid, tetanus toxoid, acellular pertussis containing vaccines:** evidence was inadequate to establish causation for arthropathy
    - **Influenza seasonal vaccines:** evidence inadequate to establish causation for new onset or exacerbation of arthropathy
    - **MMR:** the evidence supported acceptance of a causal relationship between MMR and transient arthralgia, but not transient arthritis, in both women and children; the evidence was inadequate to establish causation for arthropathy in men, for chronic arthropathy in children or for chronic arthritis in women.
    - **VZV:** evidence inadequate to establish causation for onset or exacerbation of arthropathy
- **Since the IOM review, three new case reports of arthritis following quadrivalent influenza vaccine[42], tetanus toxoid[43] and Hepatitis B vaccine[44] have been published.** While these are temporal associations only, details are presented in Table 3.3 as illustrative of a more extensive investigation than was done in older case reports.
- **An updated systematic review of evidence published since the 2011 IOM report for a similar range of vaccines concluded that rubella-containing vaccines can cause mild, acute transient arthralgia or arthritis in adult women but rarely in children**[45] No new evidence was presented beyond those reviewed by IOM. No evidence was found to implicate other vaccines.
- **BCG intravesical instillation for bladder cancer:** systematic reviews of reports of autoimmune disorders[46] or Reactive Arthritis[47,48] have been inconclusive in terms of establishing a causal association. A review of the evidence is beyond the scope of this Companion Guide to acute aseptic arthritis.
- **rVSVrG-ZEBOV-GP Ebola virus vaccine:** acute oligoarthritis was observed in several clinical trials, summarized below. The likely mechanism was direct viral invasion of the joint space as a result of viremia following vaccination, based on positive rVSV PCR in 4 of 8 tested synovial fluid samples.
    - **Phase I vaccine trial in Geneva**[49] 22% (11 of 51) of subjects given a single dose of 10 or 50 million PFU developed oligoarthritis a median of 11 (Interquartile range 9-13) days that lasted for a median of 8 (range 2-109) days. Arthritis was confirmed by ultrasound in 7 and MRI in 2. Imaging was not done in 1 and had nonspecific findings in 1. One had recurrent arthritis 82 days after vaccination which fully resolved after 10 days. There were 2 others with recurrent arthralgia without arthritis. Synovial fluid was obtained in only one case revealing 7190 leukocytes/ml

which were 80% monocytes; rVSV was detected by PCR but viral culture was negative. This one case provided evidence for viral invasion of the joint space as the cause of acute arthritis.

- **Phase 1/2 vaccine trial in Geneva**[50] With the observation of oligoarthritis the Geneva trial cited above was stopped and then re-instituted using a lower dose (300,000 PFU) of vaccine. 25% (13 of 51) of subjects given the lower dose developed arthritis a median of 10 (IQR 9-14) days after vaccination, confirmed clinically in 12 and by ultrasound in 1. Among the cases where arthrocentesis was performed, 2 were PCR positive for rVSV. In this trial an increased risk for arthritis was observed for older subjects with an Odds Ratio of 2.43 (95% Confidence Interval 1.44-4.78) for every 10 additional years in age. A similar analysis done for the 13 cases after doses of 10 – 50 PFU failed to find an association with older age (OR 0.76; 95% CI 0.43-1.35 per 10 additional years).
- **Phase 1b vaccine trial in USA**[512] In a dose-response study, 4.5% (19 of 418) of subjects given a single dose of vaccine with various PFU (3000 in 64; 10,000 in 64; 300,000 in 64; 3 million in 84; 9 million in 47; 20 million in 47; 100 million in 48). Arthritis was observed in 1 – 4 subjects at each dose level (2.1-6.3%) and there was no correlation between the size of the dose and frequency of arthritis. Arthritis was also observed in 3.2% (3 of 94) subjects given placebo. Arthritis onset a median of 12.0 (IQR 10-14; range 0-23) days after vaccination and lasted a median of 8.0 (IQR 6-15; range 2-47) days. There was no correlation between arthralgia occurring within 1 week after immunization and arthritis later on. Joint tenderness or swelling was objectively confirmed in all vaccine associated cases and 2 of the 3 placebo cases. No cases had radiologic imaging or arthrocentesis performed.
- **Phase 3 vaccine trial in USA, Canada, Spain**[52] In a randomized, double-blind, placebo-controlled study of 3 different lots of vaccine, arthritis, defined as joint swelling or effusion, occurred in 5.1% (40 of 790; onset median 11.0 and range 1-25 days after vaccine; duration median 7.0 and range 0.4-44 days) of subjects given a lot containing 20 million PFU; in 4.2% (11 of 260; onset median 10.0 and range 2-14 days after vaccine; duration median 5.0 and range 1-156 days) of subjects receiving 100 million PFU and in 0% (0 of 133) of subjects given placebo. Imaging was not done. Synovial fluid was obtained from 4 cases with 1 positive by PCR. All subjects with arthritis were followed for 6 months and all but 2 had complete recovery. The two with persistent arthritis beyond 6 months both had pre-existing degenerative osteoarthritis.

- **Reports of acute arthritis following COVID-19 vaccines** A recent systematic review identified 31 reports involving 45 patients with new-onset arthritis following COVID-19 vaccination[53]. Among these were 23 cases that fall within the spectrum of acute aseptic arthritis or acute reactive arthritis [54-62] An additional 6 case reports were identified in a case series with literature review[63-65] and 2 in a hand search of citations[66,67] All original citations were retrieved and case details are presented in Table 3.4 below. Although these are temporal associations only, they are presented because arthropathy was not included in the scope of the recently completed evidence review by the National Academies of Sciences, Engineering and Medicine (previously IOM). [68]

TABLE 3.2 Risk Factors for intra-articular infection, including septic arthritis[1, 31]

Age	• Extremes of age (young children, geriatric)
Behavioral	• Intravenous drug use
Animal exposure	• Bites can result in direct inoculation of bacteria into joint space (Dog or cat: *S. aureus, Pasteurella multocida, Pseudomonas sp., Moraxella sp., Haemophilus sp.;* Rat: *S. aureus, Streptobacillus moniliformis, Spirillum minus)*
Occupational	• Occupational exposure to animals increases risk of *Brucella sp.* infection
Recreational	• Intravenous drug abuse • Chronic alcohol abuse
Surgery / other trauma	• Recent joint surgery especially prosthetic joint implants (knee, hip) • Arthroscopy • Direct joint trauma • Open reduction of fractures • Human bite (Typical infecting organisms from oral flora: *Eikenella corrodens, S. aureus,* group b streptococci, oral anaerobes) • Wound infection contiguous to joint
Comorbidity	• Pre-existing joint disease: acute or chronic diseases which damage joints (e.g., osteoarthritis, rheumatoid arthritis) • Diabetes mellitus • Chronic renal failure • Malignancy • Immunocompromised – increased risk of Mycobacterial infection
Infection with microbes that invade joint	• **Bacterial:** *S. aureus,* Group A and Group B beta-hemolytic streptococci*, Neisseria gonorrhoeae, Haemophilus influenzae, Kingella kingae, Moraxella osloensis, Pseudomonas aeruginosa, Shigella sp., Salmonella sp., Streptococcus pneumoniae, Mycoplasma hominis, Ureaplasma urealyticum, Arcanobacterium haemolyticum, Brucella sp. Nocardia asteroids, Enterobacter sp., Serratia marcescens,* anaerobic bacteria *(Bacteroides sp., Propionibacterium acnes, gram positive cocci), E. coli* (primarily in neonates), • **Mycobacterial:** *Mycobacterium tuberculosis,* atypical mycobacteria *(M. avium-intracellulare complex, M fortuitum, M Haemophilum, M terrae, M kansasii, M marinum, M chelonae)* • **Fungal:** *Sporothrix schenckii, Coccidioides immitis, Blastomyces dermatitidis, Candida albicans, Paracoccidioides brasiliensis, Pseudallescheria boydii* • ~~**Parasitic:** *Dracunculus medinensis*~~ • **Viral:** Adenovirus, Coxsackieviruses, EBV, Hepatitis A, Hepatitis B, Hepatitis C, HIV, Mumps, Parvovirus B19, Rubella, Varicella Zoster virus.

TABLE 3.3 Recent case reports of acute, new-onset, inflammatory arthritis following vaccines included in the 2011 IOM review[41]

Abbreviations in Table: anti-CCP – anti-cyclic citrullinated peptide; ANA – antinuclear antibody; ANCA - Antineutrophil cytoplasmic antibodies; CRP – C-reactive protein, in mg/dL; DM – Diabetes Mellitus; EBV – Epstein Barr Virus; ENA – extractable nuclear antigen; ESR – erythrocyte sedimentation rate in mm/hour; F – female; HBV - hepatitis B virus; HCV – hepatitis C virus; IA – inflammatory arthritis; L – left; M – male; MRI – magnetic resonance imaging; PMN – polymorphonuclear cells; R – right; ReA – reactive arthritis; RF – rheumatoid factor; SF – synovial fluid; Td – tetanus toxoid; UA – urinalysis; uL – microliter; US – ultrasound; WBC – white blood cells X 10^9.

Author Country	Age Sex	Medical History	Vaccine Dose	Vaccine to Onset	Clinical Diagnosis	Confirmation of Arthritis	Laboratory Testing	Final Diagnosis	Duration
Bell[42] Australia	50 F	Bilateral total knee arthroplasty 3 years prior to episode; R great toe gout in past, controlled with allopurinol; Type 2 DM; obese; dilated cardiomyopathy; sleep apnea; severe asthma	Quadrivalent influenza	2 days	R&L knee arthritis	SF: R knee 190,000 WBC; 85% PMNs L knee: 252,000 WBC, 89% PMNs Both negative for bacterial gram stain, PCR; culture negative but samples taken in OR, after antibiotic started; no crystals	ESR 68; CRP 62; HLA-B27+; Negative RF, anti-CCP, ANCA.	ReA; Couldn't rule out PJI but considered unlikely given complete resolution with only 7 days antibiotic and no relapse when discontinued	Surgical debridement of both knees with implant retention and exchange of polyethylene bearing; Completely resolved by 2 weeks post-op
Kesiktas[43] Türkeye	29 F	Unremarkable	Td	2 days	R ankle swelling	Not done	ESR 37; CRP 42.3; Normal uric acid, renal function, UA; negative RF, ANA, HLA-B27, HBV, HCV, Brucellosis.	ReA	4 weeks
Rahimi[44] USA	w-born F	Born at 36 weeks after induction of labor due to maternal preeclampsia	HBV Dose 1	10 days	R knee swelling	SF: Bacterial C&S negative MRI – R knee effusion	ESR 18; HLA-B27+; Negative ANA, Lyme disease, Parvovirus	IA	> 2 months; not clear when total resolution because family moved; definitely <1 year

TABLE 3.4 Case reports of acute, new-onset, inflammatory arthritis following COVID-19 vaccination[54-67]

Abbreviations in Table: anti-CCP – anti-cyclic citrullinated peptide; ANA – antinuclear antibody; ANCA - Antineutrophil cytoplasmic antibodies; ASOT – anti-streptolysin O titer; CBC – complete blood count; CMV – cytomegalovirus; Cr – creatinine; CRP – C-reactive protein, in mg/dL; C&S – Culture and sensitivity; CT – computed tomography; DIP – distal interphalangeal joints; DM – Diabetes Mellitus; EBV – Epstein Barr Virus; ENA – extractable nuclear antigen; ESR – erythrocyte sedimentation rate in mm/hour; F – female; GERD – Gastroesophageal reflux disease; GU – genitourinary; HBV - hepatitis B virus; HCV – hepatitis C virus; HIV – human immunodeficiency virus; hpf – high power field; IA – inflammatory

arthritis; L – left; LFT – liver function test; M – male; MCP – metacarpal phalangeal joints; MRI – magnetic resonance imaging; PIP – proximal interphalangeal joints; PCR – polymerase chain reaction; PJI – prosthetic joint infection; PMN – polymorphonuclear cells; PPD – purified protein derivative (TB skin test); R – right; ReA – reactive arthritis; RF – rheumatoid factor; SF – synovial fluid; SpA – spondyloarthritis; Td – tetanus toxoid; uL – microliter; UA – urinalysis; US – ultrasound; WBC – white blood cells.

Author Country	Age Sex	Medical History	Vaccine Dose	Vaccine to Onset	Joint Involved	Confirmation of Arthritis	Laboratory Testing	Final Diagnosis	Duration
Nahra[54] USA	71 M	Stroke Brain aneurysm Dyslipidemia	Pfizer Dose 2	1 day 3 months	Diffuse arthralgia Arthritis R MCP 4&5	Rheumatologist consult 3 months after onset	ESR 89; CRP 12.5; ANA 160; Negative: RF, anti-CCP, ENA.	IA	5-6 months
Roux[55] France	30 F	Unremarkable	Pfizer Dose 2	3 days	R sacroiliitis	**SF:** negative for crystals, bacteria **CT:** sacroiliitis Bony erosion	CRP 70; Normal: kidney/liver function; Negative: HLA-B27, HIV, EBV, CMV, chlamydia.	ReA	2 months
Vanaskova[56] Czech Rep	53 M	Type 2 DM Hypertension	Pfizer Dose 1	3 days	Arthritis L knee	**SF:** 4680 WBC/uL; 89% PMN; No bacteria or crystals. **US:** L knee effusion	CRP 91.8	ReA	<6 weeks
Koh[57] Taiwan	17 F	Unremarkable	Pfizer Dose 1	7 days	Arthritis R&L knee	**SF:** 89,600 WBC/uL; predominantly PMNs; bacterial culture negative/no crystals. **MRI:** R&L knee effusions.	ESR 85; CRP 57.9; HLA B-27+; Negative RF, ANA.	SpA	2 months after therapy; ~ 3 months overall
Rim-Park[58] USA	73 F	Bronchiectasis Osteoarthritis cervical spine	Moderna Dose 2	19 days	Dactylitis R 2nd digit	**US:** tendonitis but no synovitis	Normal: CBC, ESR, CRP; Negative: HLA-B27.	IA	≥5.5 weeks
	64 M	Hypertension GE reflux	Moderna Dose 2	1 day	Arthritis L PIP2	**US:** synovitis	Not stated	IA	≥9 weeks
Wojturska[63] Poland	39 M	Hyperchol-esterolemia GERD	Moderna Dose 3	7 days	Polyarthritis R knee, R+L MCPs, PIPs, DIPs	**SF:** increased WBC and PMNs (no numbers provided); culture and crystal negative. **US:** R knee effusion	ESR 69; CRP 90; Slight elevation(≤4x) LFTs; Negative: RF, anti-CCP, ANA, ANCA, HLA-B27, GU bacteria, Borrelia hepatotropic viruses.	ReA	≤6 months

	67 F	Hypothryoid Gallstones Hyperchol-esterolemia	ChAdOx 1 Dose 2	10 days	Polyarthritis R&L knees, wrists, PIPs, DIPS, elbows	Clinical findings of arthritis; **X-ray hand:** normal.	Normal: CBC, ESR, CRP, LFTs, Cr; Negative: RF, anti-CCP, ANA, HLA-B27, GU bacteria, hepatotropic viruses, Lyme disease.	ReA	not stated
	33 M	URTI 1 week pre-vaccine (COVID negative)	ChAdOx 1 Dose 2	1 day	Arthritis L knee	Clinical findings of arthritis; **Xray:** normal	ESR 17; CRP 28; pyuria, urine C&S 10^6 *E. coli* (not treated); Negative: HIV, HBV, HCV, Borrelia, GU bacteria	ReA	≤1 month
Schoenardie[64] Brazil	25 F	GERD	ChAdOx 1 Dose 2	4 days	Arthritis 4th L PIP	Case photo confirmed joint swelling and erythema. **Xray:** normal	Normal: ESR, CRP, CBC, kidney/liver function; Negative: HLA-B27, RF, ANA, HIV, HBV, HCV, syphilis	ReA	<2 weeks
Alalem[66] Saudi Arabia	24 M	Healthy except for avulsion injury to R knee in childhood	ChAdOx 1 Dose 2	3-4 days	Arthritis R knee	**SF:** 2425 WBC, 45% PMNs; negative gram and acid-fast stains; no crystals. **MRI:** small joint effusion.	CRP 5.7; Negative: HLA-B27, RF, anti-CCP, ANA, ASOT, blood C&S.	ReA	Persisted 10 months;
Nune[59] UK	44 F	Not provided	ChAdOx 1 Dose 1	2 days	Swollen R ankle	Nothing reported	CRP 78; Negative: RF, anti-CCP, serum urate.	ReA	Not stated
An[60] China	23 F	ReA episode after a cold 2 years earlier; otherwise unremarkable	Sinovac Dose 1 +14 days Sinovac Dose 2	7 days 2 days	L knee pain and swelling Arthritis L knee	**SF:** 20-25 wbc/hpf; 90% PMNs; negative gram stain & culture; no crystals. **MRI:** L knee effusion	ESR 32; CRP 15; Negative: RF, anti-CCP, ANA, HLA-B27, ASOT, HIV, hepatitis, syphilis, mycoplasma.	ReA	<1 month
Enginar[61] Türkiye	74 F	Hypertension Type 2 DM	Sinovac Dose 1	2 days	Polyarthritis R wrist, MCP 2,3,4, PIP 2,3,4	Clinical exam only. Photos confirm swelling	ESR 84; CRP 20.2; Normal: CBC, uric acid; Negative: RF, anti-CCP, aNA, HLA-B17, Brucella, HBV, HCV.	ReA	Improved after 1 week; Time to resolution not clearly stated
	76 M	Ankylosing Spondylitis for 30 years	Sinovac Dose 2	7 days	Polyarthritis All L hand MCPs, PIPs	Clinical findings of arthritis; Case photos confirm swelling.	ESR 85; CRP 11.2 ; HLA-B27+, Normal: CBC, uric acid, UA;	ReA	Resolved but no timelines given.

							Negative: RF, anti-CCP, ANA, Brucella, HBV, HCV.		
Turk[65] Türkiye	79 F	Healthy	Sinovac Dose 2	5 days	Arthritis R&L hands; L ankle	Clinical findings of arthritis; Case photos confirm swelling, erythema, both hands, L ankle.	ESR 77; CRP 215; Negative RF, anti-CCP, ANA, brucella.	ReA	Not stated
	72 F	Healthy	Sinovac Dose not stated	3 weeks	Arthritis L elbow, R&L knees, R ankle	Nothing reported	ESR 75; CRP 237; Negative RF, anti-CCP, ANA, Brucella HBV, HCV, HIV, chlamydia, Parvovirus B19, urine C&S.	ReA	2 weeks
Shokraee[67] Iran	41 M	Unremarkable	SputnikV Dose 1	20 days	Arthritis L elbow	**SF:** 22,000 WBC; 90% PMN; Bacterial/Fungal cultures negative; No crystals **US:** thickened synovium, moderate effusion	ESR 51; CRP 21; Negative RF, anti-CCP, ANA, HLA-B27, Brucella, PPD, UA, urine C&S.	ReA	Improved after 2 weeks; no clear timeline for full resolution
Baimukhamedov[62] Kazakhstan	58 M	Unremarkable	SputnikV Dose 2	5 days	Arthritis L elbow, shoulder	**SF:** no crystals **US:** moderate L elbow effusion; L shoulder synovitis;	ESR 18; CRP 2.2; Negative: RF, anti-CCP, ASOT, chlamydia, ureaplasma.	Post-vaccine arthritis	Resolved after 1 week

APPENDIX 4

Acute Aseptic Arthritis Case Definition
Key Caveats for Diagnosis, Data Analysis and Presentation

Acute Aseptic Arthritis Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1 Key elements of Case Definition (CD)

4.1.1 To meet any level of certainty the case definition requires:

- Absence of recent trauma to the joint
- ≥1 classic feature of arthritis objectively confirmed by a health care provider. These include:
  - swelling or erythema of the joint or peri-articular structures
  - increased warmth palpable over the joint capsular contour
  - restricted range of motion of the affected joint.
  - joint effusion
- complete resolution in <6 weeks from onset

4.1.2 The time to resolution criterion, while essential to meeting the CD, should only drive duration of follow-up, not investigation. The differential diagnosis of new-onset, acute arthritis is extremely broad (see Table 4.1) and thorough investigation as soon as arthritis is diagnosed (based on the classic features outlined above) is essential to guide treatment and classification. It is particularly important to rule out intra-articular infection as soon as possible so appropriate antimicrobial therapy can be started.

4.1.3 Aspiration of synovial fluid (SF) is required to meet Level 1 or Level 2 of diagnostic certainty

- For Level 1, SF analysis must include:
  - WBC count and differential
  - Attempt to identify microrganisms by Gram stain or PCR or microscopy
  - Bacterial culture
  - Examination for any pathologic cells (e.g. cells indicative of leukemia)
- For Level 2, SF must be sent for bacterial culture
- For both Level 1 and 2, in addition to negative bacterial culture, the SF sample, must be obtained before the first dose of antibiotic

4.1.4 Both Levels 2 and 3 require absence of fever, defined as ≥1 measured temperature of ≥38.0° Centigrade. (provide link to BC Fever CD)

4.1.5 Level 2 requires a blood culture to be done AND to be negative for bacteria.

4.2 Recommendations for real time assessment

As noted in section 4.1, the Brighton acute aseptic arthritis case definition applies to a very narrow category of acute aseptic arthritis that may follow immunization. A key component of investigation is aspiration and analysis of synovial fluid. However, the specific tests noted in 4.1.3 above, are specific to the case definition, but fall short of what should be done to thoroughly investigate a case of acute, new-onset, arthritis (See Table 4.2).

A case of new onset, acute inflammatory arthritis, has a broad differential diagnosis (see Table 4.1). Several important observations were made in studies that recruit patients with new-onset arthritis and investigate with long term follow-up.[13-16]

- At the onset of acute arthritis, classification is difficult, in part due to specific duration requirements for meeting disease classification criteria: Rheumatoid arthritis - > 6 weeks; Reactive arthritis - ≥1 month; spondyloarthropathies – back pain >3 months. This difficulty is reflected in the classification seen in the 5 incidence studies presented in Appendix 2. The largest category of disease classification was undifferentiated arthritis in 4 studies, making up: 30.1[12]%, 36%[11], 44.6%[9] and 51.8%[8]of all cases. In the fifth study[9] only rheumatoid arthritis (29.4% of cases) was more prevalent than undifferentiated arthritis (27.4% of cases).
- When cohorts of acute onset arthritis patients are followed up over several months, the initial diagnosis often changes.[13-16] An initial diagnosis of rheumatoid arthritis may be questioned if the arthritis completely

resolves over time; an initial undifferentiated arthritis may meet the classification criteria for rheumatoid or psoriatic or other spondyloarthritis over time.

- All cases of arthritis should be seen by experienced rheumatologists ≤1 year after first signs and symptoms (ideally as soon as possible after arthritis is objectively documented).
- Synovial fluid should be analyzed whenever possible
- Follow up should be over a minimum of 1 year, with regular visits during that time frame.

Reactive arthritis (ReA) is a specific category that requires mention. The WG noted that ReA is "commonly defined by an aseptic peripheral arthritis occurring within four weeks of a primary gastrointestinal or genitorurinary infection, mostly associated with *Yersinia, Campylobacter, Salmonella, Shigella and Chlamydia trachomatis*". However, as discussed in Appendix 3 on Risk factors for acute inflammatory arthritis, the list of etiologies for ReA has been greatly expanded and has been reported following vaccination – most notably after instillation of BCG to treat bladder cancer[46-48] and following several COVID-19 vaccines[53-67]. While causality has not been established for the latter, it is notable that investigation and follow-up were inadequate in many reports. Arthritis was also observed following the rVSVrG-ZEBOV-GP Ebola virus candidate vaccine.[49-52] While the cases seen in clinical trials were better documented than those reported following COVID-19 vaccination, none would have met the acute aseptic arthritis case definition based on information presented in the publication and supplemental material – albeit the case definition was published after the trials. Of 26 cases reported during phase 1 or 2 trials[49, 51], 22 were confirmed by ultrasound or MRI but none had synovial fluid collected. Duration exceeded 6 weeks in 5 of 22 (23%). A phase 3 trial[52] identified 51 cases with joint swelling and effusion but only 4 had synovial fluid collected, specifically for vaccine virus culture, of which 1 was positive. All were reported as resolved at the 6-month follow-up visit, but it was impossible to discern how many lasted >6 weeks following the onset.

It may be that the acute aseptic arthritis case definition needs to be updated to enable capture of cases that last >6 weeks. In the meantime, particularly for trials of vaccine platforms like rVSV which have been associated with acute arthritis, investigation should be thorough, and follow-up extended for at least 6 months if not a full year. Where possible, early referral to physicians with rheumatologic expertise should be done. The rheumatologic entities to be considered are outlined in Table 4.1 and proposed investigation in Table 4.2.

TABLE 4.1 Causes of acute, new-onset, arthritis

Category	Entities
Chronic arthropathies	Rheumatoid arthritis, Juvenile inflammatory arthritis, Psoriatic arthritis, Enteropathic arthritis (occur in context of established inflammatory bowel disease – Crohn's disease or ulcerative colitis), Ankylosing spondylitis.
Autoimmune or connective tissue disease that can present as acute arthritis	Systemic lupus erythematosus, Sjogren's syndrome, scleroderma,mixed connective tissue disease, sarcoidosis, Wegener's granulomatosis, polymyositis, celiac disease.
Episodic arthritis without systemic involvement	Crystalline arthropathies: monosodium urate (gout), calcium pyrophosphate or dihydroxyapatite crystals in synovial fluid
Intra-articular infection	Pyogenic bacteria, mycobacteria, fungi, bacteria (see table 3.2 for a detailed list of possible etiologies)
Joint inflammation that follows 3 to 4 weeks after an extra-articular infection	**Classic Reactive Arthritis:** with a proven preceding infection involving the: gastrointestinal tract (*Yersinia enterocolitica 03, 08 or 09; Yersinia pseudotuberculosis; Campylobacter jejuni; Salmonella typhi / enteriditis / paratyphi B or C; Shigella sp.);* genitourinary tract (Chlamydia trachomatis); or respiratory tract *(Chlamydia pneumoniae).* **Atypical causes of Reactive Arthritis:** See Table 3.1 for a list of bacteria, fungi, parasites and viruses and vaccines that have been reported to cause reactive arthritis.
Acute synovitis complicating chronic osteoarthritis	Synovitis is a common feature of osteoarthritis and may present as an acute episode of inflammatory arthritis with effusion.[69]

TABLE 4.2 Approach to cases of acute, new-onset arthritis in a vaccine clinical trial setting or as part of a safety signal investigation. Compilation of recommendations from multiple sources [1, 70, 71]

Category: Note – for items marked by an asterisk (*), document those that were confirmed by a physician	
History	**Past medical history:** hospitalizations, underlying diseases/disorders, medications. In particular prior diagnosis of acute, recurrent or chronic arthritis, autoimmune disease, inflammatory bowel disease, diabetes mellitus, or within prior 4 weeks: • gastrointestinal, genitourinary, respiratory tract or skin infection. If present, document what if any investigation was done to determine etiology • joint trauma, joint surgery, arthroscopy Family history: any arthropathies **Articular features*:** symptoms (pain, swelling, decreased range of motion); specific joints involved – peripheral and axial; unilateral or bilateral; **Para-articular features*:** enthesitis, tenosynovitis, dactylitis, bursitis **Extra-articular features*:** psoriasis, erythema nodosum, keratoderma blennorrhagica, oral / mucosal ulcers, uveitis, corneal ulcers, vasculitis, photosensitivity, butterfly rash, Raynaud's **Time course of arthritic events**: time from vaccination (if given) to onset of arthritic features; duration of arthritic symptoms before physician assessment; if arthrocentesis performed, indicate if this was done before or after starting antibiotics for possible septic arthritis;
Physical examination	**Articular signs***: swelling, warmth, erythema, reduced range of motion; all involved joints should be documented **Para-articular signs*:** bursitis, tendonitis, tenosynovitis, enthesiopathy, dactylitis **Extra-articular signs*:** features of diseases associated with arthritis: uveitis, conjunctivitis, colitis, urethritis, enteritis, pharyngitis, carditis, nephritis, cerebritis, mouth or genital ulcers, butterfly rash, raynaud's syndrome, scleroderma; infection. Noting absence of any extra-articular

Consultation	Consultation may not be necessary at the time of initial symptoms and signs of arthritis. Most critical, is to rule out septic arthritis which requires aspiration of synovial fluid for gram stain and bacterial culture. Infectious disease or rheumatology consultation may help with this. Rheumatology consultation should definitely be obtained, if available, if arthritis persists more than 6 weeks. Ideally, in settings where acute arthritis is an identified adverse event of special interest that will be investigated and followed, the availability of referral services in participating study sites should be identified before the study starts.	
Assessment	**Should be done in all cases**	**Do if clinically indicated**
General Bloodwork	CBC + differential, ESR, CRP, uric acid, calcium, HLA-B27	
Immunologic bloodwork	RF/anti-CCP (specific for Rheumatoid arthritis); ANA	Serology for GU or GI pathogens if recent history of infection. Serology for viral infection
Synovial Fluid analysis	WBC + differential; crystals (using polarized light microscopy); gram stain, bacterial culture;	Microscopy/culture for virus (including vaccine virus if live vaccine), fungi, mycobacterium
Microbiologic testing (other than synovial fluid)	Blood culture.	• Genitourinary infection: urethral/cervical swab for gonococcus, chlamydia • Gastroenteritis: stool culture for yersinia, salmonella, shigella, campylobacter • Respiratory tract infection: nasopharyngeal swab for virus, Chlamydia pneumoniae • Other system infection: cultures as appropriate to the system(s)
Radiographic imaging	Ultrasound of involved joints to detect effusion; plain x-rays may show any chronic damage to the joints such as osteoarthritis	MRI – detects synovitis, erosions, sacroiliitis as well as helps to identify bony deformities, soft tissue or ligamentous injuries, tumor
Disease Course		
Treatment	Document any drugs given to treat the arthritis and their duration	
Follow-up	**Total duration of follow-up:** should be a minimum of 6 weeks since that is the threshold, beyond which, acute aseptic arthritis case definition is ruled out. Even if arthritis has resolved, longer follow-up, from 6-12 months, is preferred to monitor for any recurrences. If arthritic symptoms and signs are still present at 6 weeks, follow-up should be continued to full resolution. It would be appropriate, if not already done, to refer any cases that continue beyond 6 weeks, to a rheumatologist for follow up and continued management.	

4.3 Data Collection Guidelines

All Working Group recommendations for data collection related to the adverse event are captured in Table 4.2 along with other published recommendations for assessment, investigation and follow-up of cases of acute-onset new arthritis.

4.4 Data Analysis Guidelines

4.4.1 Classify reported events in one of five categories:

1. Level 1 Acute Aseptic Arthritis
2. Level 2 Acute Aseptic Arthritis
3. Level 3 Acute Aseptic Arthritis

4. Level 4: reported event of Acute Aseptic Arthritis but insufficient evidence to meet Level 1, 2, 3 or 5 of the case definition
5. Level 5: Not a case of Acute Aseptic Arthritis: this should only be used when there is documentation of evidence contradicting the case definition criteria:
    a) Recent articular trauma that could explain the joint signs and symptoms
    b) Culture confirmed septic arthritis
    c) Certainty that ≥1 sign of arthritis (joint swelling, erythema, warmth, decreased range of motion) was not confirmed by a physician OR imaging for joint effusion (US, MRI, CT).
    d) >6 weeks duration of arthritic signs and symptoms
    e) Documentation of fever (temperature ≥38.0° Centigrade) for cases that didn't meet level 1 but had other criteria needed to meet level 2 or 3.

NOTE: while cases that meet (d) and (e) above, should be classified as Level 5 with respect to acute aseptic arthritis, they should continue to be followed until resolution of arthritis, or until a specific diagnosis is made (such as rheumatoid arthritis). Cases that are diagnosed as reactive arthritis, with no confirmed etiology (typical or atypical microbial pathogens) (see Table 3.1) should be counted as possibly vaccine-associated.

4.4.2 **Interval from immunisation (day 0) to onset of arthritis:** if multiple cases are being analysed, classify as proportion falling into one of the following categories:

- ≤ 3 days
- 4 - 7 days
- 8 - 14 days
- 15 - 21 days
- > 3 to ≤6 weeks
- > 6 weeks

4.4.3. Duration of Arthritis

- < 6 weeks
- ≥ 6 weeks to ≤ 3 months
- > 3 months to ≤ 6 months
- > 6 months to < 1 year
- ≥ 1 year

APPENDIX 5

Acute Aseptic Arthritis
Data Abstraction and Interpretation Forms
With Algorithms for Assessing Level of Certainty
And Glossary of Terms

5.1. Acute Aseptic Arthritis Data abstraction and interpretation form with algorithms for assessing level of certainty

The form is organized in a series of Steps presented as tables.

- **Step 1** guides the collection of data needed to meet the case definition criteria for Acute Aseptic Arthritis. Depending on the specific criterion, data are collected using two formats:
    - as mutually exclusive answers of YES, NO or UNKNOWN to a series of questions
    - as a checklist of specific things that were noted to be present (i.e. YES) like signs or symptoms, or lab test results.

  Relatively simple criteria used in the case definition may be defined directly in step 1. Others may require formulae to define – as done in Step 2.
- **Step 2** uses some or all of the data entered in Step 1 to assign values (YES, NO or UNKNOWN) to each case definition criterion.
- **Step 3** is a small tabular summary of the assigned value (YES, NO or UNKNOWN) for each criterion in the case definition.
- **Step 4** provides a tabular algorithm to assign the Level of certainty that meets the case definition (Level 1, 2 or 3) or that does not meet the case definition (Levels 4 and 5).
- A Pictorial algorithm is presented that presents, in a single page, all the relevant criteria needed to meet the case definition and a flow diagram that shows the path to each level of diagnostic certainty depending on the criterion values.
- A Glossary of Terms is also included. Any terms defined in the glossary are yellow highlighted in the Step 1 data form.

The abstraction form can be used in several settings:

- As a case report form for data abstraction from a hospital/other institutional chart as part of epidemiologic studies of background incidence or to test for causal association between vaccine (s) and Acute Aseptic Arthritis
- Guide data collection for case validation (all or a subset) in studies where electronic health data were used for case ascertainment based on selected medical codes (ICD9/10, SNOMEDCT, MedDRA)
- Serve as a supplement to a prospective clinical trial case report form where one or more cases of Acute Aseptic Arthritis may be observed during the trial. In such settings it may also serve as a guide for the type of data to be collected and investigations to be done at the time a possible case is identified.
- Supplement national pharmacovigilance AEFI report forms in case of the occurrence of a safety signal related to Acute Aseptic Arthritis
- Help to organize the data available in an Adverse Event Following Immunization Report form relative to what is needed to assign a level of certainty. Equally important the form will make it clear what data are missing and help to guide case follow-up when feasible.

The same data form will also be available online as part of an Automated Brighton Classification (ABC) Tool.

TABLE 5.1 Acute Aseptic Arthritis KEY CASE DEFINITION CRITERIA AND LIKELY SOURCES OF RELEVANT INFORMATION. Space is also provided to record the actual sources of information.

Criterion	Criterion category	Likely sources of information	Actual sources of Information
A	Clinical signs & symptoms of arthritis assessed by a physician	Outpatient clinic, emergency room or hospital admission history and physical examination notes by physician.	
B	Time course from onset to resolution of arthritis	Course in hospital or status at follow-up visits to outpatient clinics	
C	History of recent joint trauma	History of current illness (clinic, Emergency Room or hospital notes)	
D	Synovial fluid analysis	Clinic, Emergency Room, hospital or specialist consultation notes indicating arthrocentesis performed. Laboratory reports for synovial fluid analysis (including leukocyte count and differential; microscopy for pathologic cells (e.g., malignant cells); microbiology tests (gram stain and bacterial, fungal, mycobacterial or viral culture; microscopy for parasites); examination for presence of crystals.	
	Timing of arthrocentesis for synovial fluid sample for testing relative to start of antibiotic therapy for possible infectious arthritis	Clinic, Emergency Room or hospital notes relative to date and time of arthrocentesis for synovial fluid as well as date and time of first dose of antimicrobial therapy (if given).	
E	Bacterial blood culture	Microbiology laboratory reports for blood culture results	
F	Fever	Clinic, Emergency Room or hospital history and physical exam notes; temperature chart if in hospital; nursing notes for vital signs (usually include measured temperature)	

Step 1. Complete the case data entry form choosing the most appropriate answer as defined below: Terms with a glossary definition

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent, OR nothing was documented about the criterion.
- Questions regarding criteria marked with an asterisk* must be answered.

Criterion	Question	Possible Answers		
Criterion A: Clinical Illness signs and symptoms that were assessed by a health care provider				
A0.1*	Clinical signs & symptoms of acute arthritis were assessed by a health care provider. **If YES, check each of the findings that were present in A1**	☐ YES	☐ NO	☐ UNKNOWN
A1	☐ 1. Articular swelling ☐ 3. Periarticular swelling ☐ 5. Articular effusion ☐ 2. Articular erythema ☐ 4. Periarticular erythema ☐ 6. Restricted range of movement	☐ 7. Increased warmth palpable over capsular contour of the joint		
Criterion B: Time from symptom onset to complete resolution				
B*	Symptoms completely resolved within < 6 weeks from time of onset.	☐ YES	☐ NO	☐ UNKNOWN
Criterion C: Recent articular trauma				
C*	History of articular trauma within the 6 weeks prior to symptom onset	☐ YES	☐ NO	☐ UNKNOWN
Criterion D: Synovial fluid examination consistent with aseptic arthritis				
D0.1*	Synovial fluid was aspirated from one or more joints for laboratory examination. **If YES answer D1-6**	☐ YES	☐ NO	☐ UNKNOWN
D1	Synovial fluid for routine bacterial culture obtained before starting antimicrobial therapy OR no antimicrobial therapy given	☐ YES	☐ NO	☐ UNKNOWN
D2	> 2000 leukocytes/mm^3 in aspirated synovial fluid	☐ YES	☐ NO	☐ UNKNOWN
D3	< 50% of synovial fluid leukocytes are polymorphonuclear cells (PMN)	☐ YES	☐ NO	☐ UNKNOWN
D4	Synovial fluid examination **negative** for pathologic cells	☐ YES	☐ NO	☐ UNKNOWN
D5	Synovial fluid gram stain, microscopy or PCR examination **negative** for bacteria	☐ YES	☐ NO	☐ UNKNOWN
D6	Routine culture of synovial fluid **negative** for bacteria	☐ YES	☐ NO	☐ UNKNOWN
Criterion E: Bacterial blood culture				
E0.1*	Blood sample sent for bacterial culture. If YES, choose most correct result: E1 or E2 or E3	☐ YES	☐ NO	☐ UNKNOWN
E	☐ 1. Bacterial blood culture was **negative** (no bacteria recovered)			
	☐ 2. Bacterial blood culture was **positive** (1 or more bacteria recovered; e.g., *Staphylococcus aureus, Streptococcus pyogenes)*			
	☐ 3. Bacterial blood culture results unavailable or unknown			

Criterion F: Fever				
F*	Fever was present (at least one documented temperature of ≥38.0° Centigrade)	☐ YES	☐ NO	☐ UNKNOWN

Step 2. Based on clinical data entered in Step 1, assign a value to criteria A, D and E1 using the rules in the Criterion Options column.

CRITERION					Criterion value: compare data entered in step 1 table to formulae in the YES, NO and UNKNOWN columns to determine FINAL VALUE for each MAJOR and Minor Criterion		
Clinical Category	**Name**	**FINAL VALUE (Circle/Highlight)**			**YES (Y)**	**NO (N)**	**Unknown (U) if**
Health care provider assessed and reported ≥1 sign of arthritis	**A**	Y	N	U	A0.1 = YES AND ≥1 of A1(1, 2, 3, 4, 5, 6 or 7) = YES	A0.1 = NO OR A0.1 = YES, but none of A1 (1, 2, 3, 4, 5, 6 & 7) = YES	A0.1 = Unknown
Synovial fluid exam consistent with aseptic arthritis	**D**	Y	N	U	(D1, D2, D3, D4, D5 AND D6) ALL = YES	ANY of (D1, D2, D3, D4, D5 OR D6) = NO	D0.1 = NO or Unknown OR (D1, D2, D3, D4, D5 OR D6) = YES or Unknown*
Negative bacterial blood culture	**E1**	**Y**	**N**	**U**	E0.1 = YES AND E = 1	E0.1 = YES AND E = 2	E0.1 = NO or UNKNOWN OR E = 3

* NOTE: choose UNKNOWN if there is a combination of YES and Unknown with no NO's (e.g., if D1 and D2 = YES and [D3, D4, D5 and D6 = Unknown])

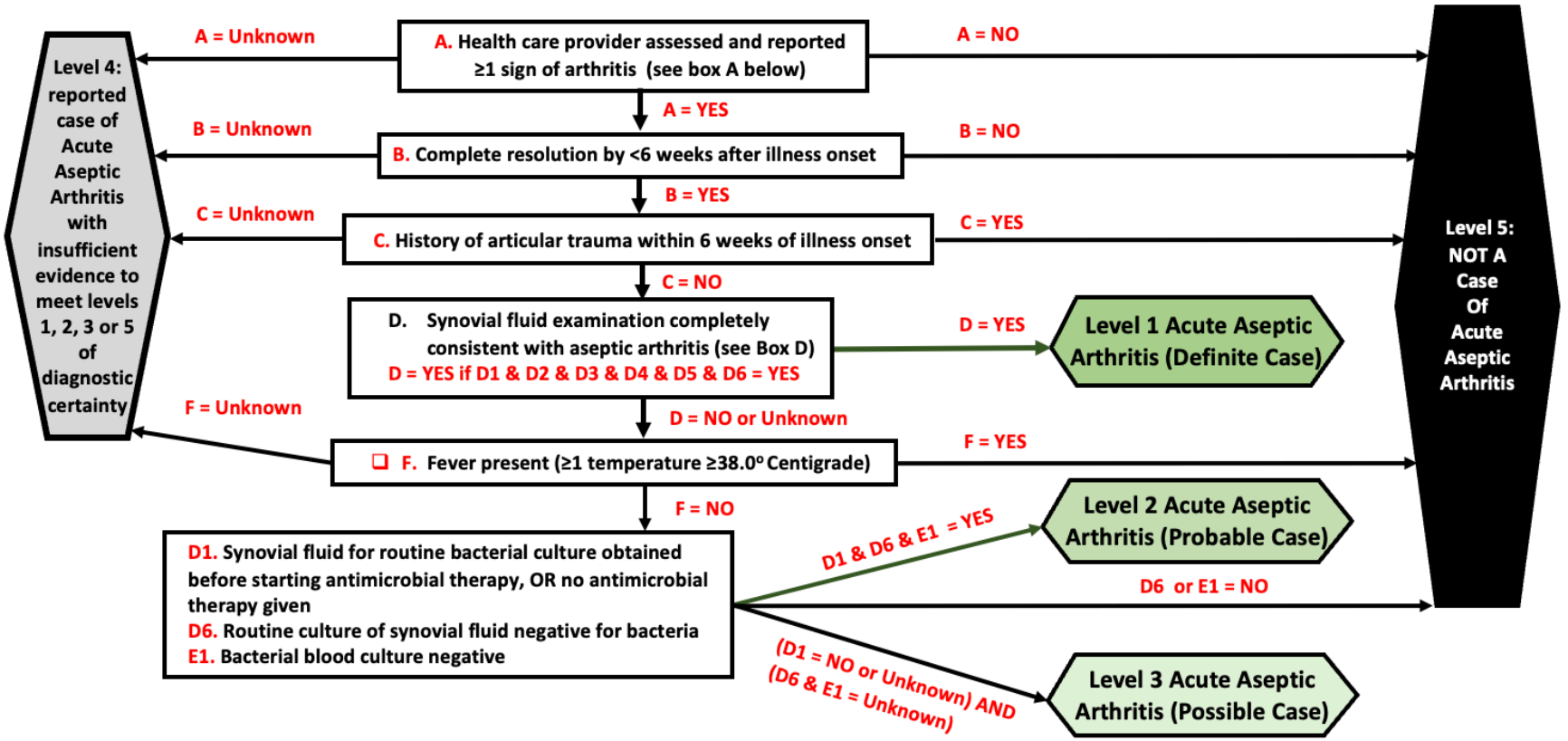
Step 3. Record the value of B, C, D1, D6 and F from Step 1 above and of A, D and E1 from step 2 above. Y = YES, N = NO, U = Unknown

Criterion	A	B	C	D	D1	D6	E1	F
Final Value								

Step 4. Use the final values of all criteria recorded in Step 3 above to determine the level of certainty for Acute Aseptic Arthritis based on the formulae below. Start with Level 1 (A, B, C, D). If not met move to Level 2 (A, B, C, D1, D6, E1, F) and if not met try Level 3 (A, B, C, D1, D6, E1, F). If none of Levels 1, 2 or 3 are met, try Level 5 (A, B, C, D6, E1, F). If Levels 1, 2, 3 and 5 not met, then assign Level 4.

Level of Certainty	
Level 1	(A AND B AND D = YES) AND (C = NO)
Level 2	(A AND B AND D1 AND D6 AND E1 = YES) AND (C AND F = NO)
Level 3	(A AND B = YES) AND (C AND F = NO) AND (D1 = NO or Unknown) AND (D6 AND E1 = Unknown)
Level 4	Reported Acute Aseptic Arthritis but fails to meet any defined level of certainty (1, 2, 3 or 5)
Level 5	(A = NO) OR (B = NO) OR (C = YES) OR (D6 = NO) OR (E1 = NO) OR (F = YES)

Figure 5.1 Pictorial algorithm for determining ACUTE ASEPTIC ARTHRITIS level of diagnostic certainty



A. Signs of arthritis: ≥1 of

- ❑ 1. Articular swelling
- ❑ 2. Articular erythema
- ❑ 3. Periarticular swelling
- ❑ 4. Periarticular erythema
- ❑ 5. Articular effusion
- ❑ 6. Restricted joint range of motion
- ❑ 7. Increased warmth palpable over capsular contour of the joint

D. Synovial fluid examination consistent with aseptic arthritis. Must have ALL of the following:

- ❑ Synovial fluid for routine bacterial culture obtained before starting antimicrobial therapy OR no antimicrobial therapy given [D1 = YES]
- ❑ ≥ 2000 leukocytes/mm ^{3} [D2 = YES]
- ❑ <50% of leukocytes were polymorphonuclear cells (PMNs) [D3 = YES]
- ❑ Synovial fluid examination negative for pathologic cells [D4 = YES]
- ❑ Synovial fluid gram stain or microscopy or PCR negative for bacteria [D5 = YES]
- ❑ Routine culture of synovial fluid negative for bacteria [D6 = YES]

GLOSSARY OF TERMS

Term	Definition
Articular	Relating to one or more joints
Articular effusion	Palpable increase in synovial fluid ora n amount of synovial fluid above the upper normal age-corrected limits as detected by ultrasound, MRI or CT
Articular erythema	An increase in skin redness over the capsular contour of the joint.
Articular swelling	Visible enlargement in articular and/or capsular volume, with or without objective measurement, and without articular trauma within the preceding 6 weeks.
CT	Computed tomography
Leukocytes	White Blood Cells (WBC) – can be polymorphonuclear cells (PMC) which include neutrophils, basophils and eosinophils; or mononuclear cells (lymphocytes, monocytes)
MRI	Magnetic Resonance Imaging
Periarticular	Relating to the tissues that surround one or more joints
Periarticular erythema	An increase in skin redness over the soft tissue surrounding the joint.
Periarticular swelling	Visible enlargement of the periarticular soft tissue volumen with or without objective measurement.
Restricted range of movement (ROM)	Restricted joint mobility in at least one movement dimensión as compared to age-corrected normal values. May be due to one or more of: pain on movement, increased synovial fluid, capsular or periarticular swelling.
Synovial fluid	Fluid secreted by the membrane which lines most joints in the body. The fluid lubricates and reduces friction between joint surfaces.

APPENDIX 6.

Methodology: Brief Summary

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

6.1. Acute Aseptic Arthritis ICD-9/10-CM, MedDRA and SNOMEDCT Codes [3-7]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[3] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[4] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[5, 6] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[7] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMEDCT, MeSH, ICPC-2 and Read-CTv3. In this updated version of the Companion Guide, the SNOMEDCT codes have been added.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the encephalitis Brighton case definitions for all Tier 1 AESI. The concepts identified for encephalitis were considered relevant for background incidence rate determination as well as to study hypotheses related to encephalitis as a vaccine-product related reaction. Most of the terms include encephalitis and acute disseminated encephalomyelitis since encephalitis may be part of these broader categories.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the Zenodo site.

6.2. Acute Aseptic Arthritis Background Incidence

A PubMed literature search was conducted by Mathew Dudley using the strategy shown below to find articles on population-based incidence of Acute Aseptic Arthritis:

("Arthritis, Reactive"[Mesh] OR "reactive arthritis"[tiab] OR "reactive arthritides"[tiab] OR "post infectious arthritis"[tiab] OR "post infectious arthritides"[tiab] OR "post-infectious arthritis"[tiab] OR "post-infectious arthritides"[tiab] OR "postinfectious arthritis"[tiab] OR "postinfectious arthritides"[tiab] OR "reiter syndrome"[tiab] OR "reiter's syndrome"[tiab] OR "reiters syndrome"[tiab] OR "reiter disease"[tiab] OR "reiter's disease"[tiab] OR "reiters disease"[tiab] OR "acute aseptic arthritis"[tiab])

AND

("Incidence"[Mesh:noexp] OR "incidence"[tiab] OR "Epidemiology"[Mesh:noexp] OR "epidemiology"[tiab])

AND

English[lang]

AND

("1900/01/01"[PDAT] : "3000/12/31"[PDAT])

AND

("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "clinical trial"[Publication Type])

NOT

("animals"[Mesh] NOT "humans"[Mesh])

NOT

("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti])

The search was conducted in PubMed on Oct 25, 2023 by Mathew Dudley.

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for acute aseptic arthritis were

extracted. Acute aseptic arthritis incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (Barbara Law). Screened in articles were then reviewed and data abstracted into an excel spreadsheet (Marta Roja Villaescusa) for inclusion in the background rate table. Additional articles were found by hand citation search of screened in articles.

The spreadsheet with all extracted background incidence data is available on the Brighton Collaboration website.

6.3. Acute Aseptic Arthritis Risk Factors

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:
1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] along with a review of arthritis and arthralgia as an adverse event following immunization[2], both prepared by the Brighton Acute Aseptic Arthritis Working Group,
were reviewed for evidence related to associated risk factors. Articles obtained by the search strategy for background incidence, shown in 6.2 above, were also screened and reviewed for evidence bearing on risk factors. In addition, a separate PubMed literature search was conducted by Mathew Dudley using the strategy shown below to identify articles that linked vaccine (s) or immunization to acute arthritis. The search was limited to articles published on or after January 1, 2017, to update the systematic searches done by the Brighton Acute Aseptic Arthritis Working Group initially done on May 28, 2015 and then updated to Dec 3, 2017.[2]

("Vaccines"[Mesh] OR "vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[Mesh] OR "vaccination"[tiab] OR "vaccinations"[tiab] OR "vaccinate"[tiab] OR "vaccinated"[tiab] OR "immunization"[mesh] OR "immunization"[tiab] OR "immunizations"[tiab] OR "immunisation"[tiab] OR "immunisations"[tiab] OR "immunize"[tiab] OR "immunized"[tiab] OR "immunise"[tiab] OR "immunised"[tiab])

AND ("Arthritis, Reactive"[Mesh] OR "reactive arthritis"[tiab] OR "reactive arthritides"[tiab] OR "post infectious arthritis"[tiab] OR "post infectious arthritides"[tiab] OR "post-infectious arthritis"[tiab] OR "post-infectious arthritides"[tiab] OR "postinfectious arthritis"[tiab] OR "postinfectious arthritides"[tiab] OR "reiter syndrome"[tiab] OR "reiter's

syndrome"[tiab] OR "reiters syndrome"[tiab] OR "reiter disease"[tiab] OR "reiter's disease"[tiab] OR "reiters disease"[tiab] OR "acute aseptic arthritis"[tiab])

AND ("2017/01/01"[PDAT] : "3000/12/31"[PDAT])

AND English[lang]

AND ("Observational Study"[Publication Type] OR "Clinical trial"[Publication Type] OR "Case report*"[Publication Type] OR "Case series"[Publication Type] OR "Causality assessment"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Protocol"[Publication Type])

NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp])

NOT ("animals"[Mesh] NOT "humans"[Mesh])

Articles were screened by a single medical reviewer (Barbara Law). Based on the title and abstract, articles were selected for full text review. Additional articles were identified by hand search of the included articles citations.

6.4. Acute Aseptic Arthritis Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for Acute Aseptic Arthritis was reviewed and key aspects identified with particular relevance to real time assessment of Acute Aseptic Arthritis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published Acute Aseptic Arthritis case definition was reviewed, and key recommendations identified for data collection, analysis and presentation specific to the adverse event reproduced or summarized.

6.5. Data Abstraction & Interpretation Form, Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration case definition for Acute Aseptic Arthritis[1] was thoroughly and repeatedly reviewed by one individual (Barbara Law) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

A data abstraction form was developed to capture information relevant to the Acute Aseptic Arthritis case definition criteria. The form uses a standard format developed to ensure harmonized approaches between paper forms (as here in the Companion Guide) and digital forms used online. The questions in the form are designed to enable one of three possible answers:

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was absent or not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent OR nothing was documented about the criterion

Step 1 involves completing the data abstraction form answering all questions. In some cases the data form will identify specific criteria used to determine Level of Certainty (LOC). In other cases, further manipulation of the available data, considered Step 2 in the process, will be needed to define criteria needed for LOC. A small summary table of all the final criterion values form the first two steps is done as Step 3. Step 4 involves a tabular algorithm that uses the values of the Case Definition Criteria (YES, NO or UNKNOWN) to determine the highest achievable LOC with Level 1 being the highest, most specific level (Definite Case). A one-page pictorial algorithm is also provided that shows the stepwise pathway to each

defined LOC based on the criterion values. This algorithm is designed for use as a stand-alone tool for LOC calculation since in addition to the pathway it also shows provides a specific definition for each criterion.

A glossary of terms relevant to the case definition criteria was developed based initially on the published case definition. Where possible, the term definition was taken directly from the published case definition (often from the footnotes provided within each published case definition). If there was no definition in the publication, then an on-line search was done to obtain definitions based on available medical dictionaries or other on-line resources. The glossary is provided for use by data-abstractors without a medical background.