Response to: 'Clarification regarding the statement of the association between the recombinant zoster vaccine (RZV) and gout flares' by Didierlaurent *et al*

We read with great interest the correspondence from Didierlaurent *et al*[1] regarding our recent report on the association between vaccination and risk of gout flares using a case-crossover design.[2] In particular, we appreciate the clarification that the authors provided regarding the unsolicited adverse events reported during the 30 days after each vaccination, including episodes of gout, with incident gout cases surpassing reports of recurrent gout flares. While this is a notable difference from our online case-crossover study which included only patients with known gout and assessed for recurrent gout flares, this raises the intriguing possibility of the vaccine 'unmasking' gout in susceptible individuals, whether mediated by the effect of the vaccine adjuvant on the inflammasome pathway or another mechanism. It is well-recognised that patients with incident gout have a history of chronic hyperuricemia that leads to the asymptomatic deposition of monosodium urate (MSU) crystals in and around joints long before the first clinically apparent flare of gout.[3] For example, studies of patients with asymptomatic hyperuricaemia, a prerequisite condition for the eventual development of gout, have demonstrated that approximately 25% of patients have evidence of asymptomatic MSU deposits when assessed with advanced imaging techniques such as ultrasound or dual-energy CT.[4] Thus, while the results of our study may not be directly applicable to these patients who reported incident gout after recombinant zoster vaccine vaccination, the available data to date collectively call for future studies including patients with and without existing gout.

We agree with the authors that the hypothesised mechanisms underlying the potential association between vaccination and gout flares involving the activation of the inflammasome are derived from *in vitro* studies[5 6] and has not been definitively demonstrated *in vivo*. The authors also raise the intriguing possibility of the risk of gout flares being mediated by serum urate change, similar to other known triggers for gout flares such as diuretics[7 8] and alcohol use,[9–11] as a result of the release of DNA material by dying innate cells after they have been recruited at the site of injection.[12] Serial measurements of serum urate before and after vaccination can be a readily implementable first step to further elucidate this possibility.

Finally, we reiterate that the benefits of vaccinations far outweigh the possible small risks of gout flares.

Chio Yokose[1,2] **Hyon Choi**[1,2,3]

[1]Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
[2]Clinical Epidemiology Program, Mongan Institute, Massachusetts General Hospital, Boston, MA, USA
[3]Arthritis Research Canada, Richmond, British Columbia, Canada

Correspondence to Dr Hyon Choi, Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, MA, United States; HCHOI@mgh.harvard.edu

Handling editor Josef S Smolen

Contributors All authors contributed equally to this work.

Funding CY is supported by the National Institutes of Health Ruth L. Kirschstein Institutional National Research Service Award [T32-AR-007258]. HC is supported by the National Institutes of Health [P50 AR060772].

Competing interests CY has no disclosures. HC reports consulting for Ironwood, Selecta, Horizon, Takeda, Kowa and Vaxart; research support from Ironwood and Horizon.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Yokose C, Choi H. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2019-216670

Received 5 December 2019
Accepted 6 December 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216639

Ann Rheum Dis 2019;**0**:1. doi:10.1136/annrheumdis-2019-216670

ORCID iD
Chio Yokose http://orcid.org/0000-0001-7557-3303

REFERENCES

1 Didierlaurent AM, Desssart C, Cunningham AL. Clarification regarding the statement of the association between the recombinant zoster vaccine (RZV) and gout flares. *Ann Rheum Dis* 2019. doi:10.1136/annrheumdis-2019-216639. [Epub ahead of print: 02 Dec 2019].
2 Yokose C, McCormick N, Chen C, *et al*. Risk of gout flares after vaccination: a prospective case cross-over study. *Ann Rheum Dis* 2019;78:1601–4.
3 Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. risks and consequences in the normative aging study. *Am J Med* 1987;82:421–6.
4 Dalbeth N, House ME, Aati O, *et al*. Urate crystal deposition in asymptomatic hyperuricaemia and symptomatic gout: a dual energy CT study. *Ann Rheum Dis* 2015;74:908–11.
5 Eisenbarth SC, Colegio OR, O'Connor W, *et al*. Crucial role for the NALP3 inflammasome in the immunostimulatory properties of aluminium adjuvants. *Nature* 2008;453:1122–6.
6 Franchi L, Núñez G. The NLRP3 inflammasome is critical for aluminium hydroxide-mediated IL-1beta secretion but dispensable for adjuvant activity. *Eur J Immunol* 2008;38:2085–9.
7 Kahn AM. Effect of diuretics on the renal handling of urate. *Semin Nephrol* 1988;8:305–14.
8 Choi HK, Atkinson K, Karlson EW, *et al*. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* 2005;165:742–8.
9 Puig JG, Fox IH. Ethanol-Induced activation of adenine nucleotide turnover. Evidence for a role of acetate. *J Clin Invest* 1984;74:936–41.
10 Lieber CS, Jones DP, Losowsky MS, *et al*. Interrelation of uric acid and ethanol metabolism in man. *J Clin Invest* 1962;41:1863–70.
11 Choi HK, Atkinson K, Karlson EW, *et al*. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* 2004;363:1277–81.
12 Kool M, Soullié T, van Nimwegen M, *et al*. Alum adjuvant boosts adaptive immunity by inducing uric acid and activating inflammatory dendritic cells. *J Exp Med* 2008;205:869–82.