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.

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