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Forewarned is forearmed: chronic spontaneous urticaria as a potential risk to effective SARS-CoV-2 vaccine uptake and global public health

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Chronic spontaneous urticaria and angio-oedema (CSU/A) is a common condition with an estimated global point prevalence of 0·7% (95% confidence interval 0·2–1·4).[1] The prevalence is higher in Latin America and Asia than in other regions. Symptoms present as an 'allergy mimic' but are underpinned by nonspecific, non-IgE-mediated mast cell histamine release. The combination of common population prevalence and the likelihood of vaccines precipitating symptoms in those with CSU/A presents an immediate risk to the SARS-CoV-2 global vaccine programme.

Several novel SARS-CoV-2 vaccines are licensed for use in high-income countries, low-income countries (LICs) and low-to-middle-income countries (LMICs). While significant uncertainties remain, estimates necessitating 60–90% herd immunity to block viral transmission will require high vaccine uptake.[2]

Public fear and perception of adverse events are significant contributors to vaccine hesitancy.[3] For SARS-CoV-2 vaccines, the latest US Centers for Disease Control and Prevention data showed that anaphylaxis occurred in 4·7 and 2·5 per million doses of the Pfizer–BioNTech (9 943 247 doses) and Moderna vaccines (7 581 429), respectively.[4] However, the frequencies of other adverse events, including urticaria and angio-oedema, are not established. For other vaccines, rates of urticaria as high as 5–13% are quoted for toxoid vaccines.[5] A study of the 2009 monovalent H1N1 influenza vaccine reported hives or urticaria as the most common 'hypersensitivity reaction' within 48 h of vaccination.[6] Such symptoms, postvaccination, may occur through IgE-mediated or non-IgE-mediated pathways. The distinction is important as while IgE-mediated reactions would be a contraindication for a second dose of the same vaccine, this is not the case for the non-IgE-mediated responses due to CSU/A. Diagnosis can be challenging, compounded by a global unmet demand for allergy specialists, particularly in LICs and LMICs.

Clinical experience suggests that vaccines are recognized precipitants of symptoms in CSU/A, although data in this area are sparse. Magen *et al.* recently reported a case series regarding development of CSU following recent receipt of a range of vaccines: hepatitis B, human papillomavirus, influenza, yellow fever, and combination DTP vaccines.[7]

The AWARE study (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) highlighted that CSU/A is often undertreated and is associated with high healthcare use.[8] Importantly, the burden of CSU/A was significantly greater in Central and South American patients than in European patients, possibly due to a weaker health service framework, and lack of access to specialist care and treatments (particularly omalizumab). It is likely that there is a similar or a higher burden of uncontrolled disease in LICs and LMICs in Africa and Asia.[3,8]

Hence, there is a clear need for a proactive approach for CSU/A during the SARS-CoV-2 vaccination programme. A proportion of patients with CSU/A can be expected to experience worsened symptoms in association with recent SARS-CoV-2 vaccination, which may be easily misinterpreted as 'vaccine allergy'. Given the relatively high prevalence of CSU/A, burden is likely to be significant. Table 1 provides hypothesized projections of absolute patient numbers experiencing flares of CSU/A symptoms.

Without intervention, the impact is likely to be multifactorial. Incorrect labelling as 'vaccine allergic' will have detrimental consequences on SARS-CoV-2 immunity at patient and population levels. Vaccine safety surveillance data may exaggerate the perceived risk of IgE-mediated reactions. Furthermore, severe urticaria or angio-oedema flares may require short-course corticosteroid treatment, which could interfere with vaccine-related immune responses. While data for CSU/A are unavailable, > 10 mg per day prednisolone (medium-to-long-term treatment) for rheumatological conditions was found to have a measurable impact on humoral immune response to vaccines.[9] However, antihistamines are a well-established, safe and relatively inexpensive therapy used both as prophylaxis and for the management of acute flares in patients with CSU/A. Some reports suggest a potential protective anti-COVID effect from antihistamines, but to date there are no data to suggest antihistamines reduce the immunogenicity of SARS-CoV-2 vaccination.

There are currently no data regarding the risk of CSU/A exacerbation after SARS-CoV-2 vaccination. However, in view of the importance of this issue, we propose the following pragmatic advice for patients with CSU/A, which the authors have previously employed to abrogate symptom flares in settings such as intercurrent infection, surgical procedures and allergen-specific immunotherapy (desensitization):

1 A diagnosis of CSU/A does not increase the risk of an IgE-mediated reaction to SARS-CoV-2 vaccination.
2 Vaccination may cause a flare of CSU/A, which may be confused with 'vaccine allergy'.

Table 1 A global projection (hypothesized) of acute flares of symptoms in patients with chronic spontaneous urticaria and angio-oedema (CSU/A) based on 1% point prevalence. Population data are based on United Nations estimates for individuals aged ≥ 18 years in 2020[10]

		Absolute number of patients experiencing postvaccine flares of CSU/A symptoms based on a hypothesized incidence of			
	Projected number of patients with CSU/A	0·5%	1%	5%	10%
By World Bank income group					
High-income countries	10 107 600	50 538	101 076	505 380	1 010 760
Middle-income countries	40 248 360	201 242	402 484	2 012 418	4 024 836
Low-income countries	4 034 480	20 172	40 345	201 724	403 448
By continent					
Africa	7 144 420	35 722	71 444	357 221	714 442
Asia	33 372 970	166 865	333 730	1 668 649	3 337 297
Europe	6 047 020	30 235	60 470	302 351	604 702
Latin America and the Caribbean	4 657 010	23 285	46 570	232 851	465 701
Northern America	2 882 310	14 412	28 823	144 116	288 231
Oceania	307 540	1538	3075	15 377	30 754

3 Recommend regular antihistamines for 2 days prior to and after receiving the vaccine in patients with CSU/A. Patients on long-term antihistamines may be advised to increase their usual dose for this period (under clinical supervision).

This should be combined with advice to clinicians managing patients in acute and emergency settings to avoid prescribing corticosteroids for acute urticaria and/or angio-oedema, unless there is clear objective evidence for anaphylaxis or for a severe flare not responding to high-dose antihistamines. Finally, vaccine safety surveillance programmes should specifically assess data relating to patients with a diagnosis of CSU/A to better inform future management of this common, yet poorly understood condition.

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References

1 Fricke J, Ávila G, Keller T *et al.* Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. *Allergy* 2020; **75**:423–32.
2 Anderson RM, Vegvari C, Truscott J, Collyer BS. Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. *Lancet* 2020; **396**:1614–6.
3 Finney Rutten LJ, Zhu X, Leppin A *et al.* Evidence-based strategies for clinical organizations to address COVID-19 vaccine hesitancy. *Mayo Clin Proc* 2021; **96**:699–707.
4 Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US – December 14, 2020 – January 18, 2021. *JAMA* 2021; **325**:1101–2.
5 Caubet J, Ponvert C. Vaccine allergy. *Immunol Allergy Clin North Am* 2014; **34**:597–613.
6 Halsey NA, Griffioen M, Dreskin SC *et al.* Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS. *Vaccine* 2013; **31**:6107–12.
7 Magen E, Shalom G, Waitman D-A, Kahan N. Chronic spontaneous urticaria following vaccination. *Int J Adv Res* 2018; **6**:1434–9.
8 Maurer M, Houghton K, Costa C *et al.* Differences in chronic spontaneous urticaria between Europe and Central/South America: results of the multi-center real world AWARE study. *World Allergy Organ J* 2018; **11**:1–10.
9 Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. *Rheumatology (Oxford)* 2021; https://doi.org/10.1093/rheumatology/keab223.
10 United Nations. Population Division. Available at: www.un.org/development/desa/pd (last accessed 10 June 2021).

Conflicts of interest: M.R.A.J. has acted as a speaker, consultant or advisor for Regeneron, Sanofi, LEO Pharma, AbbVie and Pfizer; and has acted as an investigator for commercial clinical studies (unpaid) with AbbVie, Amgen and LEO Pharma. A.P.H. has received support for attending conferences from CSL and Biotest, and payment for educational speaking and writing from ALK, Octapharma and Shire. M.T.K. has received grants from FSA, MRC CiC, GCRF and NIHR for research outside the submitted work; has received funds from ALK Abello to attend an international conference; and is clinical lead for the national allergy accreditation programme (IQAS, the Royal College of Physicians), a co-opted steering group member of the BRIT registry, and chair of the EDI working group for the British Society for Allergy and Clinical Immunology. Our department in Birmingham received an educational grant from Thermo Fisher, ALK Abello, MEDA and other pharmaceutical companies for annual PracticAllergy courses.