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

**W H Bermingham BSc MBBS MRCP\*, M R Ardern-Jones DPhil FRCP$, A P Huissoon** **PhD, FRCP FRCPath\*+ and M T Krishna PhD, FRCP, FRCPath\*+**

*\*Department Allergy and Immunology, University Hospitals Birmingham, Birmingham, UK*

*$Clinical Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton, UK*

*+Institute of Immunology and Immunotherapy, University of Birmingham, UK*

Word count = 822; Table = 1; Figures =0

**Address for correspondence:**

Dr W. Bermingham

Department Allergy and Immunology

Heartlands Hospital

University Hospitals Birmingham

Birmingham

UK

B9 5SS

Email: william.bermingham@nhs.net

Tel: +441214241085

Fax: +441214243229

WHB has nothing to disclose.

APH has received support for attending conferences from CSL and Biotest, and payment for educational speaking and writing from ALK, Octapharma and Shire.

MTK received grants from FSA, MRC CiC, GCRF and NIHR for research outside submitted work. MTK received funds from ALK Abello to attend an international conference. MTK is clinical lead for national allergy accreditation program (IQAS, The Royal College of Physicians), co-opted steering group member of BRIT registry and chair of EDI working group for the British Society for Allergy and Clinical Immunology.

Our department in Birmingham received an educational grant from Thermofisher, ALK Abello, MEDA and other pharmaceutical companies for annual PracticAllergy course.

MAJ has acted as a speaker/consultant/advisor for Regeneron, Sanofi, Leo Pharma, AbbVie, and Pfizer. He has acted as an investigator for AbbVie, Amgen and Leo Pharma commercial clinical studies (unpaid).

No funding has been received specifically in relation to this manuscript.

Chronic spontaneous urticaria and angioedema (CSU/A) is a common condition seen worldwide with an estimated global point prevalence of 0.7% (95% C.I, 0.2‐1.4)(1) and with a higher prevalence in non-White populations. Symptoms present as an ‘allergy mimic’ but are underpinned by non-specific, non-IgE-mediated histamine release from mast cells. The combination of common population prevalence and likelihood of vaccines precipitating symptoms in those with CSU/A presents an immediate risk to the SARS-COV-2 global vaccine program.

Several novel vaccines are now licensed for use in High-Income and Low/Low-Middle Income Countries (LICs/LMICs) to combat the SARS-COV-2 pandemic. Whilst significant uncertainties remain, estimates necessitating 60-90% herd immunity to block viral transmission will require high vaccine uptake globally (2).

Public fear/perception of adverse events is a significant contributor to vaccine hesitancy(3) with low vaccine uptake amongst non-White populations in the UK. For SARS-COV-2 vaccines, latest US CDC data showed that anaphylaxis occurred in 4.7 and 2.5 per million doses of Pfizer-BionTech (9,943,247 doses) and Moderna vaccines (7,581,429) respectively(4). However, the frequency of other adverse events, including urticaria and angioedema, has not been established. For other vaccines programs, rates of urticaria as high as 5-13% are quoted for toxoid vaccines based on data from 1987(5). A recent study of the 2009 monovalent H1N1 influenza vaccine reported hives/urticaria as the most commonly reported ‘hypersensitivity reaction’ within 48 hours of vaccination(6). Such symptoms, post-vaccination, may occur through IgE-mediated or non-IgE-mediated pathways. The distinction is important as whilst IgE-mediated reactions would be a contraindication for a second dose of the same vaccine, this is not the case for non-IgE mediated responses, such as those due to CSU/A. Diagnosis can be challenging, and this is compounded by a global unmet demand for allergy specialists to support assessment, particularly in LICs and LMICs.

Clinical experience suggests that vaccines are recognised 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, including: hepatitis B, human papilloma virus, 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 under treated and associated with high healthcare use (8). Importantly, the burden of CSU/A in this study was significantly greater in Central/South American patients (compared to European), possibly due to weaker health service framework, 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/LMICs in Africa and Asia(3,8). This has important contextual relevance to the SARS-COV-2 vaccination program.

Hence, there is a clear need for a proactive approach for CSU/A during the SARS-COV-2 vaccination program. A proportion of CSU/A patients 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 projections of absolute patient numbers experiencing flares of CSU/A symptoms.

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

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

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’.
3. Recommend regular antihistamines for 2 days prior 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 setting to avoid prescribing corticosteroids for acute urticaria and/or angioedema, unless there is clear objective evidence for anaphylaxis or for a severe flare not responding to high dose antihistamines. Finally, vaccine safety surveillance programs should specifically capture and review data relating to patients with a diagnosis of CSU/A to better inform future management of this common, yet poorly understood condition.

**Table-1:** **A global projection (hypothesised) of acute flares of symptoms in patients with CSU/A based on 1% point prevalence. Population data based on UN estimates for individuals ≥18 years in 2020 (population.un.org)**

|  |  |  |
| --- | --- | --- |
| **By World Bank income groups** | **Projected number of CSU/A patients at 1% point prevalence of population ≥18yrs** | **Absolute number of patients experiencing post-vaccine flares of CSU/A symptoms based on a hypothesised incidence** |
| **0.5%** | **1%** | **5%** | **10%** |
| **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  | 1,538  | 3,075  | 15,377  | 30,754  |

**References**

1. Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy [Internet]. 2020;75(2):423–32. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/all.14037

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(10263):1614–6.

3. Finney Rutten LJ, Zhu X, Leppin A, Ridgeway JL, Swift M, Griffin JM, et al. Evidence-Based Strategies for Clinical Organizations to Address COVID-19 Vaccine Hesitancy. Mayo Clin Proc [Internet]. 2020; Available from: https://doi.org/10.1016/j.mayocp.2020.12.024

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 [Internet]. 2021 Feb 12; Available from: https://doi.org/10.1001/jama.2021.1967

5. Caubet J, Ponvert C. Vaccine Allergy. Immunol Allergy Clin N Am. 2014;34:597–613.

6. Halsey NA, Griffioen M, Dreskin SC, Dekker CL, Wood R, Sharma D, et al. Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: Reports to VAERS. Vaccine. 2013;31(51):6107–12.

7. Magen E, Shalom G, Waitman D-A, Kahan N. Chronic Spontaneous Urticaria Following Vaccination. Int J Adv Res. 2018;6(2):1434–9.

8. Maurer M, Houghton K, Costa C, Dabove F, Ensina LF, Giménez-Arnau A, 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):1–10.

9. Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. Rheumatology. 2021;(March):1–7.