# Chronic Urticaria Associated with Covid-19 Vaccination: A systematic review

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## INTRODUCTION

- Food and Drug Administration (FDA) approved the "Emergency Use" of Pfizer-BioNTech BNT162b2, Moderna mRNA-1273, and Janssen Johnson & Johnson (J&J) COVID-19 vaccines in 2020
- Pfizer vaccine was most frequently administered (>366 million people), followed by Moderna (232 million), and J&J (19 million)[1]
  - Pfizer booster vaccine (36 million) and Moderna (20 million)[1]
- Randomized controlled trials for vaccines reported cutaneous adverse events
  - 164,669 Pfizer vaccines were administered & the most frequent adverse events occurred after the second dose[2]
    - Reactions: injection-site pain (62.8%), fatigue (50.5%), headache (40.7%), myalgia (37.2%), fever (22.5%), chills (22%), inability to perform normal activity (20.5%), and joint pain (20.3%)[2]
  - 175,816 Moderna vaccines also demonstrated a higher percentage of adverse reactions with the second dose[2]
    - Reactions: injection-site pain (74.6%), fatigue (61.1%), headache (52.1%), myalgia (50.6%), chills (37.3%), fever (37.2%), joint pain (30.8%), inability to do normal activity (32.8%), and swelling (24.2%)[2]
  - 13,725 J&J vaccines is a single dose vaccine[3]
    - headache (34%), fever (34%), chills (33%), injection-site pain (26%), and fatigue (24%)[3]
- Delayed or chronic spontaneous urticaria (CSU) reporting during clinical trials:
  - Pfizer: Not reported nor included in the package insert[4]
  - Moderna: 2% of participants who received the 50 ug dose developed an unspecified "rash"[5]
  - J&J: 0.0228% of participants developed immediate non-serious urticarial reaction & 0.0046% of participants developed serious adverse event of hypersensitivity with delayed urticaria[6,7]
- A possible factor of vaccine hesitancy among patients: fear of developing chronic urticaria and suffering from its uncertain prognosis
  - Variability in remission rates may be due to differences in the definition and etiologies of spontaneous remission across studies as well as variances in patient populations in each study[8]
- The mechanism underlying the development of chronic urticaria following COVID-19 vaccination is not well characterized
- Patients who suffer from chronic urticaria for long periods post-vaccination may worry and choose to defer or omit the vaccine series or booster doses to prevent disease exacerbation[9]

## METHOD

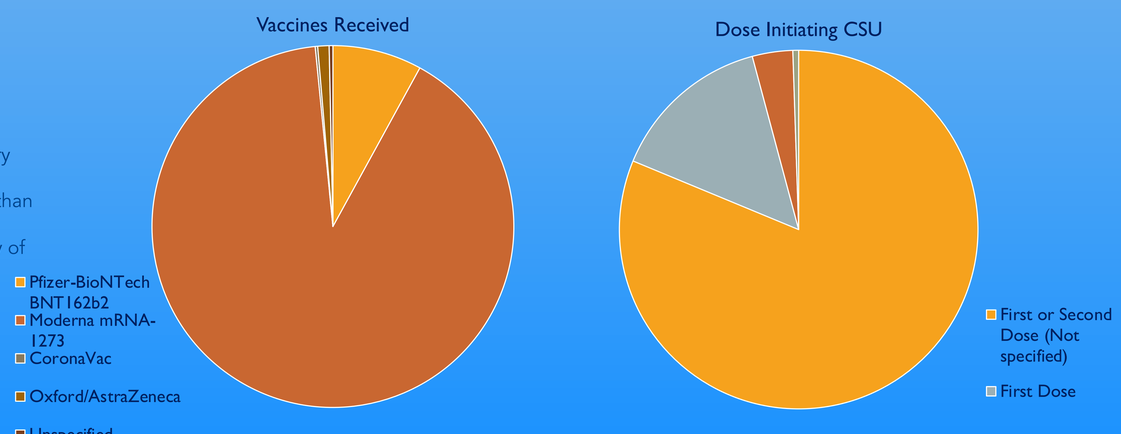
- Databases: PubMed, Embase, Cochrane
- Date of Search: Through 8 June 2023
- Keywords: "COVID-19 vaccine" & "urticaria"
  - Limited to primary data sources
- Titles and abstracts were reviewed before data abstraction
- Search produced 39 results
- Inclusion criteria: Chronic urticaria post COVID-19 vaccination and primary data source
  - Chronic urticaria = recurrent urticaria lasting for a period of greater than six weeks
- Exclusion criteria: No chronic urticaria post COVID-19 vaccination, history of urticaria, not a primary data source
- 8 papers included after a full text review

## RESULTS

- Total # of patients among eight studies: 898
- Patient ages: 24 to 78 years old
- Some patients had a history of autoimmune or allergic disease, but zero had a history of urticaria
  - Systemic lupus erythematosus (SLE), asthma, dysthyroidism, sulfa allergies, environmental allergies: 2.69%, unspecified drug allergies
  - However, the study with the largest number of participants did not report patient history regarding allergies or autoimmune conditions, which poses a limitation[11]
- CSU onset: ranged from 1 to 20 days post-vaccination
  - Lasting months to years
  - Average duration: 7.82 months (weighed by sample size across all studies)
- Physical exam was not specified for 865 (96.3%) of the patients
  - 33 (3.7%) patients' presentation aligned with urticaria
  - 48.28% developed angioedema
- Gender: 60% female
- 20% of patients developed CSU after the first dose, with an average delay in onset of symptoms of 10.83 days
- 29% of patients had concomitant autoimmune diseases (of the 6/8 that reported)
- 92% of patients had concomitant allergies (of the 6.5 of 8 reported)

| | Total CSU | % Female | Age AVG | % first dose activation | Delay of onset (D) | Concomitant AI disease | Allergy/Asthma | Duration (Months) |
|---|---|---|---|---|---|---|---|---|
| **Choi JH[12]** | 12 | 0.58 | 41.6 | 0.66 | 8.58 | Not listed | 0.58 | 8.58 |
| **Ben-Fredj N[13]** | 10 | 0.7 | 41.5 | Not listed | 1.18 | 0.1 | 0.3 | 3.7 |
| **de Montjoye L[14]** | 8 | 0.75 | 56.5 | 0.75 | 8.63 | 0.13 | Not listed | 8.25 |
| **Suan D[15]** | 1 | 0 | 39 | 0 | 14 | 0 | 0 | 6 |
| **Mahjoubi Y.[16]** | 3 | 0.66 | 48 | 1 | 5 | 0.67 | 0 | Not listed |
| **Thomas J.[17]** | 1 | 0 | 20 | 0 | 7 | 0 | 1 | 2 |
| **Brooks S.G.[18]** | 1 | 0 | 60 | 1 | 5 | 1 | 1 | 3 |
| **Duperrex O.[11]** | 80 | 0.7 | 41 | 0.1 | 10 | Not listed | 0.41 | 2.87 |
| **Duperrex O.[11]** | 782 | 0.58 | 39 | 0.19 | 11 | Not listed | Not listed | 3.27 |
| **Combined Means** | 898 | 0.59 | 39.4 | 0.20 | 10.83 | 0.29 | 0.92 | 7.82 |

Table 1. *Reported data and mean values from studies that met inclusion criteria.*




## DISCUSSION & CONCLUSION

- The exact mechanism of CSU induced by vaccination is not clear
  - Vaccination may induce a type I hypersensitivity reaction in some individuals, which is then followed by CSU within days or weeks after vaccination[19]
  - Additional etiology is thought to be incited through toll-like receptors which activate pathogen-associated molecular patterns (PAMPs) through either SARS-CoV-2 infection or vaccination[19, 20]
    - Activation of the innate immune system leads to mast cell degranulation by the complement pathway or angiotensin-converting enzyme 2[19, 20]
  - An additional hypothesized mechanism is molecular mimicry
    - SARS-CoV-2 vaccination has the potential to target host molecules that are similar to viral epitopes, causing activation of autoreactive T or B cells in an individual who is susceptible[20. 21, 22, 23, 24]
- Patients who have a history of allergic or AI diseases may be more likely to develop CSU post-vaccination
  - This systematic review demonstrates a trend of associations with concomitant AI disease
    - Concomitant occurrence of SLE in one of our patients possibly supports the theory of molecular mimicry
      - The binding of SARS-CoV-2 antibodies to human tissue may cause a reaction in patients who have a genetic predisposition to AI conditions.[20]
- Allergens and asthma may be associated with CSU development
  - Aeroallergen sensitization causes an IgE-mediated response and activation of mast cells after exposure, which has been associated with CSU development[25]
  - There may be an association of allergic rhinitis and CSU[24, 25, 26]
  - Of those reported, 92% of patients in this review had history of an allergy
- Urticaria has a female-to-male ratio of about 2-4:1[27]
  - Physiologic concentrations of estradiol cause the activation of mast cells and release of histamine [28]
  - Low concentrations of estrogens can trigger mast cell degranulation, impacting mast cell-dependent diseases like CSU[28]
- Most studies reported the average population as middle-aged
  - Aging populations may be more prone to certain autoimmune conditions[30]
  - Autoimmune diseases have numerous tolerance checkpoints, but checkpoint failures can accumulate over time or be induced by the aging process[31]
  - This leads to increased self-reactivity and transition of self-reactive native T cells to effector memory cells, facilitating chronic inflammation in older patients[30]
  - T cell proliferation and replenishment during adulthood increases susceptibility to autoimmunity and decline of self-tolerance, increasing risk of CSU

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