# Allergic reactions to the Ad26.COV2.S Vaccine in South Africa

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**Abstract**

**Abstract** ( n=254/250 words) **Background:** The Janssen-Ad26.COV2.S vaccine is authorised for use in several countries with more than 30 million doses administered. Mild and severe allergic adverse events following immunisation(AEFI) have been reported. The aim of this report is to detail allergic reactions reported during the Sisonke phase 3B study in South Africa. **Methods:** A single-dose of the Ad26.COV2.S vaccine was administered to 477234 South African Healthcare Workers between 17 February and 17 May 2021. Monitoring of adverse events used a combination of passive reporting and active case finding. Telephonic contact was attempted for all adverse events reported as "allergy". Anaphylaxis adjudication was performed using the Brighton Collaboration (BCC) and NIAID case definitions. **Results:** A large cohort of South African healthcare workers received the Ad26.COV2.S vaccination. Only 250(0.052%) patients reported any allergic-type reaction(less than 1 in 2000), with four cases of adjudicated anaphylaxis (BCC level 1, n=3)(prevalence of 8.4 per million doses). All anaphylaxis cases had a prior history of drug or vaccine-associated anaphylaxis. Cutaneous allergic reactions were the commonest non-anaphylatic reactions and included: self-limiting, transient/localised rashes requiring no healthcare contact(n=91); or isolated urticaria and/or angioedema[n=70 median onset 48(IQR 11.5-120) hours post vaccination] that necessitated healthcare contact(81%), antihistamine(63%), and/or systemic/topical corticosteroid(16%). All immediate (including adjudicated anaphylaxis) and the majority of delayed AEFI(65/69) cases resolved completely. **Conclusions:** Allergic AEFI are rare following a single-dose of Ad26.COV with complete resolution in all cases of anaphylaxis. Though rare, isolated, delayed onset urticaria and/or angioedema was the commonest allergic AEFI requiring treatment, with nearly half occurring in participants without known atopic disease. Keywords: allergic reaction, anaphylaxis, COVID19 adenovirus vaccine; Janssen-Ad26.COV2.S vaccine, urticaria

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**Abstract** ( n=241/250 words)

**Background:** The Janssen-Ad26.COV2.S vaccine is authorised for use in several countries with over 30 million doses administered. Mild and severe allergic adverse events following immunisation(AEFI) have been reported. The aim of this report is to detail allergic reactions reported during the Sisonke phase 3B study in South Africa.

**Methods:** A single-dose of the Ad26.COV2.S vaccine was administered to 477234 South African Healthcare Workers between 17 February and 17 May 2021. Monitoring of adverse events used a combination of passive reporting and active case finding. Telephonic contact was attempted for all adverse events reported as "allergy". Anaphylaxis adjudication was performed using the Brighton Collaboration (BCC) and NIAID case definitions.

**Results:** Only 251(0.052%) patients reported any allergic-type reaction(less than 1 in 2000), with four cases of adjudicated anaphylaxis (BCC level 1, n=3)(prevalence of 8.4 per million doses). All anaphylaxis cases had a prior history of drug or vaccine-associated anaphylaxis. Cutaneous allergic reactions were the commonest non-anaphylatic reactions and included: self-limiting, transient/localised rashes requiring no healthcare contact(n=92); or isolated urticaria and/or angioedema[n=70 median onset 48(IQR 11.5-120) hours post vaccination] that necessitated healthcare contact(81%), antihistamine(63%), and/or systemic/topical corticosteroid(16%). All immediate (including adjudicated anaphylaxis) and the majority of delayed AEFI(65/69) cases resolved completely.

**Conclusions:** Allergic AEFI are rare following a single-dose of Ad26.COV with complete resolution in all cases of anaphylaxis. Though rare, isolated, delayed onset urticaria and/or angioedema was the commonest allergic AEFI requiring treatment, with nearly half occurring in participants without known atopic disease.

Keywords: allergic reaction, anaphylaxis, COVID19 adenovirus vaccine; Janssen-Ad26.COV2.S vaccine, urticaria

## Introduction

The ongoing global effort to vaccinate an estimated 60% of the human population started in December 2020. In just six months, mass vaccine campaigns have seen approximately 5 billion doses of COVID19 vaccines administered and more than a quarter of the world population having received at least one dose (1). There are currently 13 different vaccines in use, with three major emergency authorised platforms including: inactivated SARsCoV2 virus (Sinopharm and Sinovac-CoronaVac); adenoviral-vectored (ChadOx/AstraZeneca and Ad26.COV2.S); and the mRNA vaccines (Moderna mRNA 1273 and Pfizer/BionNtech Comirnaty) – the latter two technologies with either little or no prior large scale human use in other infections. The mass use of these novel vaccine technologies has meant increased reporting of uncommon and rare adverse events following immunisation (AEFI), including immune-mediated events such as Guillain-Barré syndrome and anaphylaxis (2). Large cohort studies such as Sisonke, a phase 3B study of the Ad26.COV2.S in South African (SA) Healthcare workers (HCW), are thus invaluable to provide more detailed information about these uncommon adverse events of special interest (AESI).

Allergic AEFI are well-known and reported with almost all registered vaccines, with the prevalence of anaphylaxis in most vaccine safety surveillance systems ˜1 in a million doses (3, 4). Soon after the emergency authorisation of mRNA COVID19 vaccines an increased prevalence of anaphylaxis was noted with this novel platform, with prevalence estimates from 2-100 per million doses (2, 5, 6), and self-reported allergic reactions in ˜2% of vaccine recipients (2). Few reports of anaphylaxis following ChAdOx1-S adenovirus vaccine are available, with prevalence estimates of 0.3-33 per million doses (5). No anaphylactic events occurred in the ENSEMBLE trials of the Ad26.COV2.S (7, 8), with only one post-marketing surveillance study reported to date(9). There are several reports of self-limiting, delayed, large local allergic reactions surrounding the injection site following the Moderna mRNA 1273 vaccine (10), but the prevalence, spectrum and outcomes of delayed allergic reactions to other COVID19 vaccines have not been reported. Thus, we aimed to detail the spectrum of immediate and delayed allergic AEFI reported following Ad26.COV2.S vaccination in a large

cohort of SA HCWs.

**Methods**

The Sisonke *("Together"* in isiZulu) phase 3B study is an open-label, single-arm implementation study of the Ad26.COV2.S COVID19 vaccine among adult (>18 years) HCWs in SA. The trial is sponsored by the SA Medical Research Council (SAMRC) with vaccines provided by Janssen Vaccines & Prevention B.V, a pharmaceutical company of Johnson & Johnson (NCT04838795) (http://sisonkestudy.samrc.ac.za/). The Institutional Review Boards/Ethics Committees of participating Clinical Research Sites approved the study, which was conducted under the oversight of the South African Health Products Regulatory Authority (SAHPRA).

Vaccinations were conducted in collaboration with the routine Provincial Department of Health public and private vaccination centres across all nine provinces of SA and overseen by Good Clinical Practice (GCP)-trained personnel linked to each of the ENSEMBLE trial research sites. Participants underwent informed consent before receiving a single intramuscular (IM) injection of Ad26.COV2.S at a dose level of $5\times10^{10}$ virus particles. Participants with a previous history of allergic reactions to vaccinations were observed for 30 minutes post-vaccination whereas the rest of the participants were observed for 15 minutes post-vaccination.

Safety monitoring was conducted through a combination of passive reporting and active case finding. An electronic adverse event reporting link was sent via text message on days 1, 7 and 14 post vaccination. Adverse events could also be reported either by calling a toll-free 24-hour safety line or through the completion of an adverse event report form which was available at vaccination sites and hospitals. The safety team reviewed serious adverse events and adverse events of special interest reports daily. Full details of the Sisonke pharmacovigilance and safety reporting processes are detailed elsewhere (11).

The Sisonke safety database was searched for allergic AEFI using a comprehensive list of possible allergy-related search terms (see supplementary appendix). Duplicates and clear non-allergic entries were removed and then all reports were screened by an allergist. In addition to the initial reporting, telephonic contact was attempted with all participants reporting a possible allergy AEFI where details were missing to clarify the event and collect additional information on past medical and allergy history as well as details of treatment and outcomes of mild/moderate allergic AEFI requiring treatment and healthcare contact. Suspected anaphylaxis cases were adjudicated by two physicians using the Brighton Collaboration and NIAID case definition; with cases needing to meet both definitions to be considered confirmed cases (12-14). Immediate reactions were restricted to those occurring within 6 hours post vaccination (15).

Descriptive statistics were performed using counts and proportions for categorical data, and medians and interquartile ranges for continuous variables. All statistical analyses were conducted using STATA version 14 (STATA Corp., College Station, TX, USA).

**Results**

From the 17th February to 17th May 2021 a total of 477234 [female n=357481 (74.9%)] SA HCWs received a single, open-label dose of the Ad26.COV2.S vaccine in the Sisonke phase 3B study. A total of 10,279 (2.2%) HCWs reported AEFI of which 139 (1.4%) AEFI. Searching of these AEFI identified 569 possible allergic reactions for screening, and 318 could be excluded as non-allergic AEFI (**Figure 1** ), leaving 251 (0.052%)probable allergic AEFI for an overall prevalence of 1 in 2000 doses. Thereafter, more detailed review including telephonic contact was attempted for the 251 participants with probable allergic AEFI; of which 38/251 (15%) were uncontactable. Of the 251, 139 did not require / seek medical attention.The majority [92/251 (36%)] reported a localized, transient rash (morphology undocumented) or pruritis that was self-limiting (lasting less than 24 hours), responsive to over-the-counter medications, and not requiring contact with either a family physician or emergency medical services. Six patients (2%) noted isolated worsening of existing symptoms of allergic rhinoconjuncitivitis in the 24 hours following vaccination, necessitating use of existing allergic medications. Four participants (see exclusions **Figure 1** ) reported delayed-onset of non-urticarial type rashes (one blistering, two purpuric and one eczematous) all of which were referred

to specialist dermatologists. One of these cases had a confirmed cutaneous vasculitis (on the basis of skin biopsy) and was known with underlying systemic lupus erythematous.

Four cases of immediate allergic AEFI were adjudicated as anaphylaxis, accounting for an overall prevalence of 8.4 per million doses.**Table 1** details the four adjudicated cases of anaphylaxis that met both Brighton Collaboration case definition (n=3/4 level 1, 1/4 level 3) of anaphylaxis and NIAID criteria. The median (IQR) age of patients with anaphylaxis was 50 (45-53) years, and all cases were female. The median (IQR) time to onset was 10 (9-52) minutes, with 3/4 cases having an onset of reaction within the 15 minute protocol recommended observation time. All patients had a background of atopic disease with all four giving a history of prior anaphylaxis to medication. One patient had a history of vaccine-associated anaphylaxis to a yellow fever vaccine. One of these patients had prior confirmed SARS-CoV-2 infection. All patients required emergency room treatment, with three being admitted to hospital. All patients except one received epinephrine, antihistamines, intravenous (IVI) corticosteroids and Beta-agonist therapies. All patients recovered completely. Unfortunately, only 1/4 patients had a post-reaction tryptase measurement; this single normal tryptase measurement was performed six hours post-vaccine in a 56 year old female, known with uncontrolled asthma, who presented with facial angioedema and bronchospasm 10 minutes after vaccination (**Table 1** ).

Mild/moderate allergic AEFI that necessitated treatment and contact with the medical services occurred in 107/251 (43%). The commonest allergic AEFI were delayed (>6 hours) reactions (n=69/107, 64%), with isolated urticaria and/or angioedema (n=70/107, 65%) the most frequently reported individual allergic phenotype (**Table 2** ).

**Table 2** shows demographic details, past medical and allergy history, clinical features and management of non-anaphylactic allergy AEFI needing medical attention, comparing immediate with delayed reactions, and isolated urticaria and/or angioedema. Similar to anaphylaxis cases, the majority [91/107 (85%)] of non-anaphylactic allergy AEFI occurred in females with a median(IQR) age of 37 (27-43) years. Reactogenicity was common, occurring in 67/107(63%) participants. Overall 53/88 (60%) of participants with non-anaphylactic allergy AEFI, had a history of prior anaphylaxis or atopic disease Of the 24 immediate non-anaphylactic allergy AEFI, ten occurred within 15 minutes, seven between one and three hours, and five between 4-6 hours post dosing [median(IQR) 0.75(1-3) hours)]. Amongst delayed reactions, 24/69 (35%) started within 24 hours post dosing, with 29/69 (42%) starting between 3 and 21 days post vaccination.. Only eight cases of non-anaphylactic allergy AEFI required admission to hospital with the majority successfully treated with antihistamines 62/107 (58%) and oral corticosteroids 30/107 (28%) only. Five patients in this group received epinephrine treatment for either severe bronchospasm, or angioedema of the upper respiratory tract due to concern around airway swelling.

Isolated urticaria and/or angioedema was the commonest single allergic reaction phenotype. The majority (39/70, 56%) occurred 24 hours or more after dosing, with a median (IQR) of 48(11.5-120) hours. More than half of these patients had no history of atopy. Only one patient in this group needed hospitalisation, and only four needed to receive emergency treatment.

Data on number of days of symptoms was not available; however all patients, except four, reported complete resolution of their AEFI at the time of telephonic contact (five to seven months post vaccination), with the majority indicating that symptoms resolved within a week of onset. Four patients reported urticaria and/or angioedema that was ongoing at the time of contact and these patients have been referred for further allergy care and management as chronic urticaria.

## Discussion

The tremendous global scale of COVID19 vaccination means that the cumulative number of uncommon or rare AEFIs, such as anaphylaxis, can be expected to occur in larger numbers than usual in the coming 12-18 months when compare to usual background rates In addition, . national vaccine safety groups and clinicians need published data on registered COVID19 vaccines to inform the public, create awareness of patients at risk of AEFIs, and to correctly manage mild and severe AEFIs. No severe (>grade 3) allergic AEFIs were noted in the phase I-III studies of Janssen Ad26.COV2.S (7, 8), and only one post-marketing surveillance

study from Vaccine Adverse Events Reporting System (VAERS) reported on "rash" as a non-anaphylactic allergic AEFI (9). Thus, this study provides the largest cohort with detailed allergic AEFI reporting following vaccination with the Janssen Ad26.COV2.S.

Allergic AEFI with the Ad26.COV2.S vaccine are uncommon in this large cohort with an estimated prevalence for any allergic AEFI including anaphylaxis of 1 in 2000 doses (0.052%) and 8.4 per million doses (0.0008%), respectively.. This rate for anaphylaxis is higher than the ˜1 case per million doses reported for most known vaccines (3, 4), and the <0.5 per million dose rate reported after investigation of 79 reports to the USA Vaccine Adverse Events Reporting Systems (VAERS) following 7.98 million doses of Ad26.COV2.S administered in the USA. However, when the data are disaggregated by vaccine, the majority of post-marketing datasets reporting anaphylaxis to mRNA COVID19 vaccines have an estimated prevalence of >20 anaphylaxis cases per million doses (5), while regulatory data for the ChadOx/AstraZeneca adenoviral vectored vaccine estimate rates between 0.32 to 33.4 per million doses.Of note is that there may be over-reporting in large pharmacovigilance reporting systems with inclusion of non-allergic reactions as many reports do not meetcriteria when reviewed and subjected to a more detailed allergy work-up (5). Nevertheless, although overall rates for any allergic AEFI and anaphylaxis are rare, rates of up to 1 in 50 for non-anaphylactic reactions have been reported for mRNA COVID19 vaccines (2), so overall the Ad26.COV2.S vaccine appears to to have a significantly lower risk of inducing allergic reactions when compared to the mRNA vaccines. Importantly, from an overall vaccine safety perspective, is that although four cases met case definitions for anaphylaxis, no patients died or suffered circulatory collapse requiring repeated dosing with epinephrine. Several factors support non-IgE mechanisms including that all cases were female; one recovered without epinephrine; and the single mast cell tryptase measurement performed was not elevated (**Table 1** ). Possible mechanisms include IgG against excipients (16) or complement activation related pseudoallergy (CARPA), rather than IgE-mediated anaphylaxis to a vaccine ingredient or excipient such as polysorbate 80 (17).

The commonest allergic AEFI in this cohort was a delayed urticarial rash and generalised pruritis with or without angioedema. , with onset usually a day or up to 21 days following vaccination. Eight versus five cases of urticaria were reported in active versus placebo arms of the phase III ENSEMBLE study (7). Urticaria and angioedema have been well-reported with several registered vaccines e.g. influenza and toxoid vaccines (18, 19), as well as COVID19 vaccines (20). Catala A *et al.* reported 405 cutaneous reactions following COVID vaccines in a Spanish population with the commonest being urticarial, followed by morbilliform and papulovesicular rashes. Interestingly, the only adenoviral vectored vaccine included was the ChadOx/AstraZeneca vaccine and urticaria accounted for a fifth of all cutaneous reactions reported to this vaccine (20). Urticaria is also associated with several viral infections, including adenovirus and more recently SARS-CoV-2 infections (21, 22). Furthermore, unlike the immediate allergic AEFIs, patients experiencing delayed urticarial AEFIs less commonly had a background of atopic disease. This also suggests that the mechanisms underlying these reactions relate to non-IgE pathways and the immune interaction – both innate and adaptive - with viral vector expressed viral proteins, vaccine ingredients or combinations of these.

The majority of reactions could be managed symptomatically with antihistamines/corticosteroids and were self-limiting, not requiring hospitalisation nor emergency treatment. However, in four patients vaccine-induced urticaria has not resolved, now lasting > 6 weeks post vaccination. Vaccines can rarely trigger chronic spontaneous urticaria (18) and induce urticarias such as cold urticaria (23). Some infections, including SARS-CoV-2, have also been shown to exacerbate chronic spontaneous urticaria (CSU) (24). Patients developing new or exacerbated CSU following COVID19 vaccination should be reviewed by an allergist with treatment focusing on the use of high doses of antihistamines, rather than unnecessary corticosteroids which may interfere with the development of a protective vaccine response (25). Further research is now required to examine the effects of COVID19 vaccines on cohorts of chronic urticaria, which is not uncommon(24, 26).

The major strength of this study was the large cohort size and the robust passive and active safety surveillance systems that allowed for comprehensive AEFI reporting for allergic events. However, because not all allergic AEFIs were followed up at pre-specified time points, and events were managed at hospitals across the country by non-study staff, a small amount of data could not be captured.

In conclusion, this study is the first to detail allergic AEFIs following use of the novel Ad26.COV2.S vaccine. Reassuringly, allergic AEFI were very rare with complete resolution of all cases of anaphylaxis. Self-limiting delayed urticaria was the commonest allergic AEFI and clinicians should be aware that these can occur several days after vaccination. The majority of allergic reactions were self-limiting and could be managed expectantly without ongoing problems.

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**References**

1. Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, et al. A global database of COVID-19 vaccinations. Nat Hum Behav. 2021;5(7):947-53.

2. Blumenthal KG, Robinson LB, Camargo CA, Jr., Shenoy ES, Banerji A, Landman AB, et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA. 2021;325(15):1562-5.

3. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. J Allergy Clin Immunol. 2019;143(4):1465-73.

4. McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol. 2016;137(3):868-78.

5. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C, et al. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. J Allergy Clin Immunol Pract. 2021;9(10):3546-67.

6. Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. JAMA. 2021;325(8):780-1.

7. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.

8. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384(19):1824-35.

9. Shay DK, Gee J, Su JR, Myers TR, Marquez P, Liu R, et al. Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine - United States, March-April 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):680-4.

10. Blumenthal KG, Freeman EE, Saff RR, Robinson LB, Wolfson AR, Foreman RK, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. N Engl J Med. 2021;384(13):1273-7.

11. Takuva S, Takalani A, Garrett N, Goga A, Peter J, Louw V, et al. Thromboembolic Events in the South African Ad26.COV2.S Vaccine Study. N Engl J Med. 2021;385(6):570-1.

12. Panel NI-SE, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-58.

13. Loprinzi Brauer CE, Motosue MS, Li JT, Hagan JB, Bellolio MF, Lee S, et al. Prospective Validation of the NIAID/FAAN Criteria for Emergency Department Diagnosis of Anaphylaxis. J Allergy Clin Immunol Pract. 2016;4(6):1220-6.

14. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

15. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy. 2014;69(4):420-37.

16. Warren CM, Snow TT, Lee AS, Shah MM, Heider A, Blomkalns A, et al. Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. JAMA Netw Open. 2021;4(9):e2125524.

17. Zhang B, Li Q, Shi C, Zhang X. Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms. Pharmacology. 2018;101(1-2):104-10.

18. Magen E, Shalom G, Waitman D, Kahan N. CHRONIC SPONTANEOUS URTICARIA FOLLOWING VACCINATION. Int J of Adv Res 2018 6(Feb):1434-39.

19. 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.

20. Catala A, Munoz-Santos C, Galvan-Casas C, Roncero Riesco M, Revilla Nebreda D, Sola-Truyols A, et al. Cutaneous reactions after SARS-CoV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases. Br J Dermatol. 2021.

21. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. Dermatology. 2021;237(1):1-12.

22. Wedi B, Raap U, Wieczorek D, Kapp A. Urticaria and infections. Allergy Asthma Clin Immunol. 2009;5(1):10.

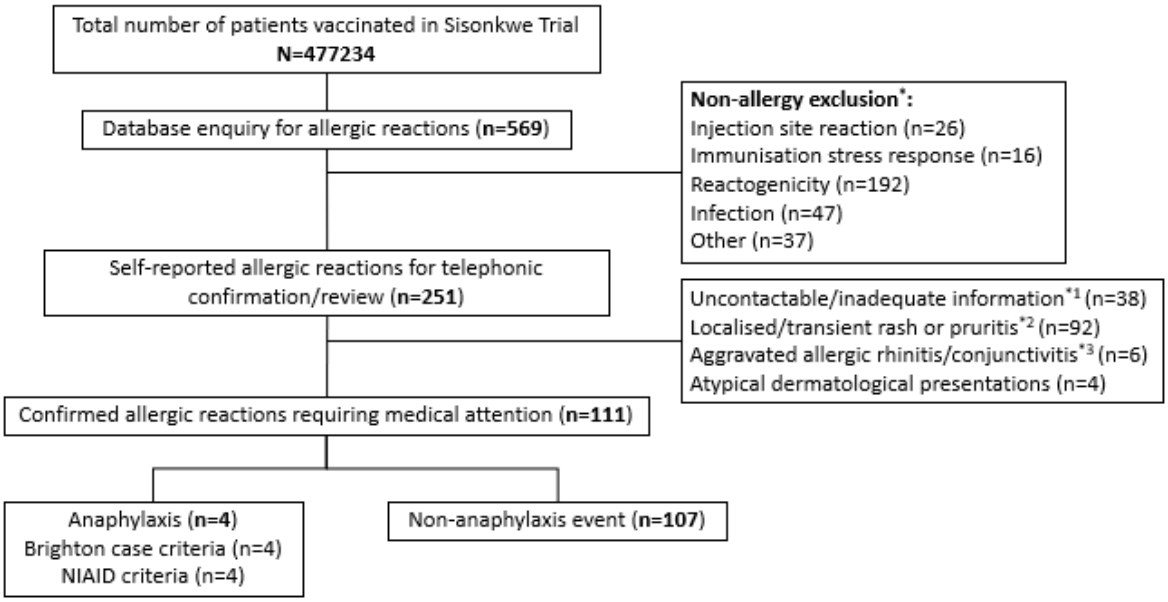
23. Raison-Peyron N, Philibert C, Bernard N, Du-Thanh A, Barbaud A, Bessis D. Cold Contact Urticaria Following Vaccination: Four Cases. Acta Derm Venereol. 2016;96(6):852-3.

24. Kocaturk E, Salman A, Cherrez-Ojeda I, Criado PR, Peter J, Comert-Ozer E, et al. The global impact of the COVID-19 pandemic on the management and course of chronic urticaria. Allergy. 2021;76(3):816-30.

25. Bermingham WH, Ardern-Jones MR, Huissoon AP, Krishna MT. Forewarned is forearmed: chronic spontaneous urticaria as a potential risk to effective SARS-CoV-2 vaccine uptake and global public health. Br J Dermatol. 2021;185(4):838-9.

26. Goncalo M, Gimenez-Arnau A, Al-Ahmad M, Ben-Shoshan M, Bernstein JA, Ensina LF, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol. 2021;184(2):226-36.

**Figure 1.** Overall summary of all allergy adverse events following immunisation with Janssen Ad26COV 2.S reported during the Sisonke phase 3B study




***Non-allergy exclusion definitions:***
***Injection site reactions*** *included swelling, redness and localized itching around the area of vaccination*
***Immunisation stress response*** *included all symptoms related to anxiety including fainting and vasovagal episodes within a few minutes post vaccination*
***Reactogenicity*** *included participants that reported one or more of: fever, rigors, muscle aches, nausea/vomiting, atypical chest pains, sore throat and/or cough within the first 72 hours post vaccination*
***Infections included****: SARsCoV2 RT-PCR positivity, tonsillitis, upper and lower respiratory tract infection, and tooth abscess.*
***Other diagnoses included****: uncontrolled hypertension, thromboembolism, neuralgia, trauma, shingles/HSV1 reactivation, uncontrolled hypertension, arthralgia and respiratory symptoms occurring >28 days post vaccination*
***1Uncontactable or inadequate information*** *meant that despite three separate phone call attempts we were unable to get sufficient information about the adverse reaction to classify it as allergy or non-allergy*
***2 Localised/transient rash or pruritis*** *needed to be a reported rash of any morphology that was self-limiting (lasting less than 24 hours), and responsive to over-the-counter medications with no requirement for any contact with either a family physician or emergency medical service*
*Suggest NIAID criteria written in full in legend for Fig 1 and Table 1*
*3 **Worsening of existing allergic rhinoconjunctivitis** Patients with previously diagnosed allergic rhinitis repoted worsened symptoms after receiving the vaccine*

| Age | Sex | Time to reaction | General symptoms | Brighton score and allergy symptoms | NIAID score | Atopy history | Anaphylaxis history | Past Medical History | Previous COVID | Hospital-ised | Adrenaline used | MC tryptase <6 hr post Rxn |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 52 | F | 10min | Nil | Level 1<br>Major:<br>• 1 Dermatological (angioedema)<br>• 1 Respiratory (bronchospasm)<br>• 1 Cardiovascular<br>• (Hypotension and loss of consciousness) | Yes | Asthma<br>Penicillin allergy | Yes (penicillin) | Systemic Lupus<br>Fibromyalgia<br>Hypothyroidism<br>Anaemia | No | Yes | Yes | ND |
| 56 | F | 10min | Headache | Level 1<br>Major:<br>• 1 Dermatological (angioedema)<br>• 1 Respiratory (bronchospasm) | Yes | Asthma/Allergic rhinitis<br>Eczema<br>Sensitised to HDM, tree pollen<br>Polysorbate 80 allergy | Yes (Yellow fever vaccine) | Hypertension<br>Glaucoma | Yes | Yes | No | 4.99µg/l (1.0-15.0) |
| 35 | F | 6 hours | Fever | Level 1<br>Major:<br>• 1 Dermatological (generalised urticaria)<br>• 2 Cardiovascular (hypotension, tachycardia)<br>• 1 Respiratory (bronchospasm) | Yes | Beta-lactam allergy, NSAID allergy | Yes (BLA, NSAID) | Nil | No | Yes | Yes | ND<br>(Elevated IgE and CRP) |
| 48 | F | 5min | Nil | Level 3<br>Minor<br>• Dermatological (generalised puritis without rash)<br>• Respiratory (non-productive cough, subjective dyspnoea, sensation of throat closure) | Yes | Allergy to latex, sodium benzoate, local anaesthetic | Yes (local anaesthetic) | Nil | No | Emergency room only | Yes | ND |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | • GIT (nausea and vomiting) | | | | | | | | |

**Table 1**.Characteristics of four cases of adjudicated anaphylaxis meeting both Brighton collaboration and NIAID case definition

Abbreviations: GIT: gastrointestinal; NSAID: Nonsteroidal anti-inflammatory drug; BLA: Beta-lactam antibiotic; MC: mast cell; ND: Not done; NIAID: National Institute of Allergy and Infectious Disease

**Table 2** Characteristics and management of non-anaphylaxis allergic AEFI stratified by timing of onset (immediate versus delayed)

| | **All cases, n=107** | **Immediate reaction ≤ 6 hours, n=24[#]** | **All Delayed reaction > 6 hours, n=69[#]** | **Isolated urticaria and/or angioedema n=70** |
|---|---|---|---|---|
| Female, n(%) | 91 (85) | 21 (88) | 57 (83) | 60 (86) |
| Age, median(IQR) yrs. | 38 (28;45) | 38 (29; 52) | 37 (27; 43) | 39 (28; 46) |
| Time to reaction, median(IQR) hrs | 24 (6;96) | 0.75 (0.1; 3) | 48 (22; 120) | 48 (11.5; 120) |
| **Allergy symptoms** | | | | |
| - Angioedema , n(%) | 26 (24) | 6 (25) | 17 (25) | 16 (27) |
| - Urticaria, n(%) | 73 (68) | 12 (50) | 54 (78) | 61 (87) |
| - Generalised pruritis, n(%) | 30 (28) | 7 (29) | 22 (32) | 18 (26) |
| - Respiratory symptoms[*1] | 35(33) | 12(50) | 17(25) | excluded |
| - Gastrointestinal symptoms[*1] | 11(10) | 3(13) | 5(7) | 3 (4) |
| - Cardiovascular symptoms[*1] | 7(7) | 3 (13) | 2(3) | excluded |
| Patients with reactogenic effects, n(%) | 67 (63) | 14 (58) | 46 (67) | 41 (56) |
| Local injection site reaction, n(%) | 34 (32) | 8 (33) | 22 (32) | 19 (27) |
| **Allergy history** | | | | |
| None, n(%) | 35 (33) | 7 (29) | 26 (38) | 30 (43) |
| Unknown, n(%) | 19 (18) | 0 | 8 (12) | 15 (21) |
| **Any atopic disease, n (%)** | | | | |
| - previous any anaphylaxis, n(%) | 6 (6)[*3] | 3 (13) | 3 (4) | 3 (4) |
| - Drug allergy | 11 (1) | 4 (17) | 7 (10) | 5 (7) |
| - Asthma | 26 (24) | 9 (38) | 16 (23) | 8 (11) |
| - Atopic dermatitis | 15 (14) | 2 (8) | 13 (12) | 8 (11) |
| **Past medical history** | | | | |
| - Unknown, n(%) | 17 (15) | 0 | 8 (12) | 14 (20) |
| - None, n(%) | 54 (50) | 10 (42) | 42 (60) | 32 (45) |
| - HIV on ART, n(%) | 3 (3) | 1 (4) | 2 (3) | 3 (4) |
| - Patients with non communicable diseases | 24 (22)[*4] | 14 (58) | 20 (29) | 24 (34) |
| - COVID19 prior to vaccination, n(%) | 6 (6) | 4 (17) | 2 (2) | 4 (6) |
| **Management** | | | | |
| Unknown, n(%) | 14 (13) | 0 (0) | 5 (7) | 13 (19) |
| Required treatment, n(%) | 90 (84) | 24 (100) | 62 (90) | 57 (81) |
| Hospitalised: Admitted, n(%) | 8 (8) | 3 (13) | 5 (7) | 1 (1) |
| Emergency Room visit, n(%) | 11 (10) | 4 (17) | 7 (10) | 4 (6) |
| Treatment(s) received | | | | |
| - Adrenaline[*6], n(%) | 5 (5) | 4 (17) | 1 (1) | 1 (1) |
| - Systemic Steroids, n(%) | 30 (28) | 12 (50) | 18 (26) | 11 (16) |
| - Antihistamines , n(%) | 62 (58) | 18 (75) | 41 (59) | 44 (63) |
| - Inhalational treatment, n(%)[*7] | 36 (33) | 9 (38) | 10 (14) | 0 |
| - Other[*8] | 16 (14) | 3 (13) | 13 (19) | 13 (19) |

[#]There were 14 participants in whom the time of reaction onset was unknown.
[*1] Respiratory symptoms included one or more of: bronchospasm, upper airway swelling, subjective dyspnoea without wheeze or stridor, persistent dry cough, hoarse voice, sensation of throat closure. Gastrointestinal symptoms included one or more of: nausea and vomiting, diarrhea, abdominal pain. Cardiovascular symptoms included one or more of hypotension, tachycardia, and decreased level of consciousness or loss of consciousness.
[*2] Reactogenicity adverse events include one or more of fever(n=49), headache(n=53), or myalgia(n=43)
[*3] Anaphylaxis to latex (n=1), anaphylaxis to beta-lactam (n=1), anaphylaxis to bee venom (n=1), unknown (n=3) however no patients reported previous vaccine anaphylaxis
[*4]Non-communicable diseases include: HPT (n= 11), Diabetes (n=5), Dyslipidaemia (n=3), Hypothyroidism (n=5), GORD (n=3), PCOS (n=2), Gilberts disease (n=1), congenital heart disease (n=1), osteoporosis (n=2), breast cancer in remission (n=2), rheumatoid arthritis (n=1), endometriosis (n=1), osteoarthritis (n=1)
[*6] Received adrenaline due to severe bronchospasm or angioedema of the face and tongue
[*7] Nebulisation (n=12), inhaled corticosteroids (n=13), Long acting beta agonist/inhaled corticosteroid (n=2), Long acting beta agonist (n=2), Short acting beta agonist (n=1)
[*8] Antibiotics (n=3), paracetamol (n=5), thiamine (n=1), intravenous fluids (n=6)

Supplementary Material

## Appendix 1: Allergy search terms for safety database

1. "rash"
2. "hives"
3. "hive"
4. "urticaria"
5. "angioedema"
6. "angiedema"
7. “swollen tongue"
8. "allergic"
9. "allergy"
10. "pruritis"
11. "pruritus"
12. "itchiness”
13. “itchy”
14. “ itchiness”
15. “itching”
16. "bronchospasm”
17. "bronchial”
18. "blocked chest”
19. "wheeze”
20. "wheezing”
21. "tightness chest”
22. "tight chest”
23. "difficulty breathing”
24. "shortness of breath”
25. "short of breath”
26. "sob”
27. "respiratory distress”
28. "dypsnoea”
29. "dyspnea”
30. "difficulty in breathing”
31. "diffculty breathing”
32. "diffculting breathing”
33. "diffcalty breathing”
34. "difficalty breathing”