Review Article

COVID-19 VACCINES: ADVERSE EVENTS FOLLOWING IMMUNISATION

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ABSTRACT

Patients rely on healthcare providers as their most credible and frequent source of vaccine information. It is therefore crucial that healthcare providers are informed and have evidence-based, objective and clear guidance on vaccine efficacy and specific adverse events following immunisation (AEFI). Reported serious AEFIs are extremely rare for the COVID-19 vaccines. This article discusses the main AEFIs attributed to COVID-19 vaccines, including neurological complications of Guillain-Barré syndrome (GBS) and acute transverse myelitis (ATM), thrombosis; cardiac complications, including myocarditis, pericarditis and cardiomyopathy; and allergic reactions such as anaphylaxis, urticaria and skin rashes. The benefits of COVID-19 vaccination outweigh the risks; however, it is important that healthcare providers are aware of the risks and know how to recognise and manage them.

Keywords: COVID-19 vaccine, adverse events, Guillain-Barré syndrome (GBS), acute transverse myelitis (ATM), thrombosis, cardiac complications, myocarditis, pericarditis, cardiomyopathy, vaccine allergy, urticarial, skin rash

INTRODUCTION

Vaccines continue to save millions of lives and are considered among the greatest public health achievements in the history of medicine. COVID-19 vaccines are following in their predecessors' footsteps; and with development at a breathtaking speed, which has been called a scientific triumph.[1] By 28 September 2021, the pandemic had claimed 4 752 988 lives. It has altered the way in which society performs work, travels, educates and socialises.[2] The COVID-19 vaccination has already been shown to prevent severe COVID-19 disease and deaths, to protect people with a high work-related risk of infection, to prevent disease transmission to a large extent, and ultimately to limit the emergence of new variants.[3–10]

Many patients who are vaccine-hesitant rely on healthcare providers as their most credible and frequent source of vaccine information. It is therefore crucial that healthcare providers are informed and have evidence-based, objective and clear guidance to offer on vaccine efficacy and specific adverse events following immunisation (AEFI).[11]

By 11 October 2021, 6 364 million vaccine doses had been administered globally.[2] The South African national vaccine rollout commenced on 17 May 2021, with both the Comirnaty (Pfizer-BioNTech) vaccine and the COVID-19 Vaccine Janssen. Since the official national rollout of COVID-19 vaccines, at least 19 million South Africans have received their first vaccine; ten million South Africans are fully vaccinated.[12] The South African Health Products Regulatory Authority (SAHPRA) had received 1 473 reports of AEFIs by 31 July 2021, most of which were mild, non-serious and already listed in the internationally approved product information. These reports account for a 0.02% reporting rate of the almost 7.1 million doses of COVID-19 vaccines administered in South Africa at that point in time.[13,14]

ADVERSE EVENTS ASCRIBED TO COVID-19 VACCINES

It is important to distinguish between serious AEFIs and expected side-effects. Side-effects are usually mild and include local injection reactions and systemic symptoms such as fevers, chills, fatigue, myalgia and headache. These are attributed mainly to an early innate immune response and occur in the first day or two following vaccine administration. Late local reactions have been reported, characterised by a well-demarcated area of erythema appearing at the injection site approximately a week after mRNA COVID-19 vaccination, with recurrence occurring in some individuals after repeat vaccination. This is not a contraindication to vaccination.[15,16]

Reported serious AEFIs are extremely rare for the COVID-19 vaccines.[17,18] Serious AEFIs are defined as those that:

- require hospitalisation or prolong an existing hospitalisation;

- may be life-threatening;
- result in a congenital anomaly/birth defect; or
- result in death.

Rare serious adverse events have been reported after COVID-19 vaccination; they include, but are not limited to, thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome (GBS), acute transverse myelitis (ATM), capillary leak syndrome (Janssen COVID-19 vaccine) and myocarditis (mRNA – Pfizer-BioNTech and Moderna COVID-19 vaccines). Severe allergic reactions and anaphylaxis are rarely reported with the mRNA vaccines and much less frequently with the Janssen viral vector vaccine. The perceived risk of COVID-19 vaccines triggering autoimmunity could not be substantiated with robust evidence.[19] In this review we discuss briefly some of these AEFIs and the approach to their diagnosis and management.

NEUROLOGICAL COMPLICATIONS OF COVID-19, INCLUDING GUILLAIN-BARRÉ SYNDROME AND ACUTE TRANSVERSE MYELITIS

An increased risk of GBS is reported following the administration of the Janssen vaccine. The risk of developing GBS after receiving the Janssen vaccine is reported as 8.1 per million doses administered and after the Pfizer-BioNTech vaccination as 1.05 per million doses administered.

In a population of one billion people, it could be expected that 17 000 cases of GBS would occur sporadically per annum, of which 1 962 would occur in any six-week period. When considering a more optimistic four-billion-person immunisation programme conducted over one year, 68 000 cases of GBS could be expected to occur naturally within this period of time, irrespective of any vaccination programme. Of these GBS cases, 13 076 would occur in the ten-week window following double-dose vaccination. It is therefore inevitable that thousands of sporadic cases of GBS caused by other factors will appear to be associated temporally with COVID-19 vaccination.[20,21]

Although the available evidence suggests an association between the Janssen vaccine and increased risk of GBS, it is still insufficient to establish a causal relationship.[22]

Cases of GBS, including recurrent cases, are also reported in the setting of SARS-CoV-2 infection.[23,24] The Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) has been revised to include a warning about GBS. The Fact Sheet for Recipients and Caregivers notes the following: vaccine recipients should seek medical attention immediately if they develop any of the following symptoms after receiving the Janssen COVID-19 vaccine. The symptoms include:

- weakness or tingling sensations, especially in the legs or arms, that worsens and spreads to other parts of the body;
- difficulty with walking;
- difficulty with facial movements, including speaking, chewing or swallowing;
- double vision or an inability to move the eyes; or difficulty with bladder control or bowel function.[25]

GBS occurs more commonly in males than in females, and the incidence increases with age. Patients might require admission to an intensive care unit (ICU) and ventilator support; and although most patients recover, GBS can result in permanent paralysis or death.[26]

Diagnostic criteria for GBS include progressive motor weakness in at least one extremity, which can range from weakness to complete paralysis, and areflexia.

A lumbar puncture should be performed in patients with suspected GBS. Importantly, this procedure is done to exclude other diagnoses rather than to confirm GBS. A combination of an elevated protein level and a normal cell count in the CSF (termed 'albuminocytological dissociation') is considered a hallmark feature of GBS. It is however, not always present; only 64% of patients with GBS have this feature. Nerve conduction studies (NCS) can help to support the clinical diagnosis of GBS and discriminate between axonal and demyelinating subtypes. Ganglioside antibodies should be tested for, because the results may help to differentiate between the variants of GBS. Ganglioside antibody tests are commercially available; unfortunately though, the negative predictive value of ganglioside antibody tests is low; therefore, a negative test finding does not exclude GBS as a diagnosis.[26]

GBS evolves to a nadir typically within four weeks before improving. Patients need regular neurological monitoring with assisted ventilation if clinically indicated. Immunotherapy with either intravenous immune globulin (IVIG) or plasma exchange (PLEX), is effective for disease-modifying treatment in GBS. GBS patients need to be on DVT prophylaxis and often need pain management.[27,28]

For individuals with a documented history of GBS, adenovirus vector COVID-19 vaccines should preferably be avoided. If only an adenovirus vector vaccine is available, the decision should be individualised and based on that person's risk for severe COVID-19 and their GBS history.[29]

Other neurological adverse events reported after COVID-19 vaccinations include acute transverse myelitis, acute disseminated encephalomyelitis, post-vaccinal encephalitis and Bell's palsy. The temporal relationship between vaccination and these disorders, together with the absence of clues pointing to an alternative diagnosis, might suggest a role for an anti-SARS-CoV-2 vaccine as a immunological trigger, although a causal relationship has yet to be established and the preliminary observations suggest caution.[30–35]

The findings of investigations suggest the possibility that autoimmune neurological responses are triggered by the reactions between anti-SARS-CoV-2 spike protein antibodies and tissue proteins, and also the interaction between spike proteins and angiotensin-converting enzyme 2 receptors.[34,36]

THROMBOSIS ASSOCIATED WITH COVID-19 VACCINATION

Several disorders may be associated with thrombocytopenia and thrombosis, including antiphospholipid syndrome, thrombotic thrombocytopenia purpura and some viral diseases (especially retroviral disease). In February 2021, however, the first reports of the development of a prothrombotic state presenting with

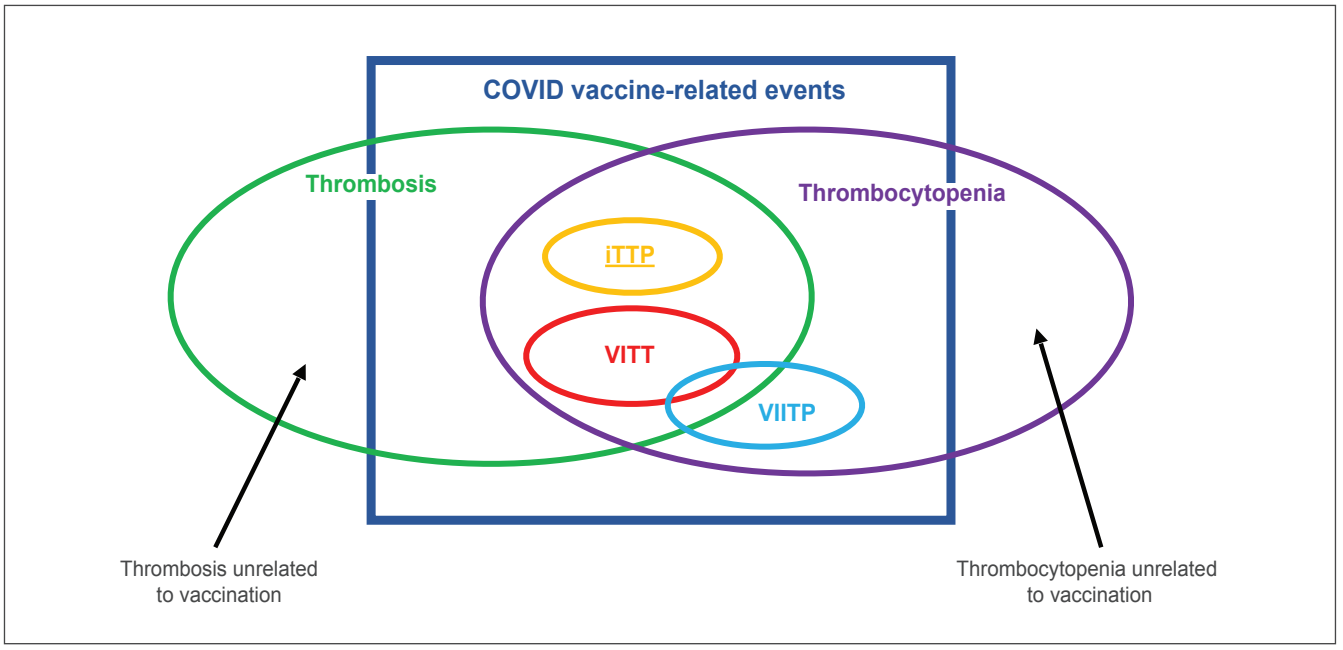

Figure 1: Adapted from 'The SCC platelet immunology register of VITT and VIITP: towards standardisation of laboratory and clinical parameters'[41]

thrombosis and thrombocytopenia post-COVID-19 vaccination emerged.[37] Initially, it was mostly reported in a small number of patients who received the ChAdOx1 Cov-19 vaccine (Astra Zeneca), but subsequently reports emerged of the same prothrombotic state occurring after vaccination with the adenoviral vector vaccine, Ad26.COV2.S vaccine[38] (Janssen/ Johnson & Johnson). This syndrome is now known as vaccine-induced immune thrombotic thrombocytopenia (VITT) or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). This is a potentially life-threatening disorder and early detection with appropriate management is necessary.

Reports of possible acquired/immune thrombotic thrombocytopenic purpura (aTTP/iTTP) post-vaccination have also been published. The first report of this *different thrombotic complication* was in a patient who received the ChAdOx1 Cov-19 vaccine (Astra Zeneca).[39] Subsequent reports also followed after vaccination with the BNT162b2 vaccine (Pfizer).[40] Some of these patients had a history of TTP.

It should be kept in mind that patients may develop both thrombocytopenia and thrombosis post-vaccination for other reasons not relating to the vaccination (see Figure 1); and that not all thrombotic events or thrombocytopenia should be ascribed to vaccination in the post-vaccination period.

VITT is extremely rare and the true incidence is unknown. Estimates vary between 1 : 100 000 among patients 50 years of age or older and at least 1 : 50 000 among patients in the younger group (< 50 years of age).[42] Millions of people have been vaccinated and although pharmacovigilance should be thorough, it may be underreported. Females of younger age (< 60 years old) were reported to be more affected, but this may be due to in the initial vaccination rollouts, as large numbers of vaccination were done in young female healthcare workers. VITT is now being reported in equal numbers in older patients and males in keeping with vaccines being administered in these groups.

Platelet factor 4 (PF4), a tetrameric, highly positive charged protein, is normally released from alpha granules in platelets. In a syndrome similar to VITT, called heparin-induced thrombocytopenia with thrombosis (HITT), a small number of patients make antibodies against PF/heparin complexes when they are given heparin.[43] These antibodies bind to PF4 on platelet surfaces and activate platelets and also neutrophils, monocytes and endothelial cells, leading to clot formation. Spontaneous HITT (no heparin exposure) has been described in medical and post-surgical patients. The same pathophysiology is present in VITT, although it is unclear whether the vaccine components form a new epitope with PF4 or, as a result of negatively charged vaccine components, they cause PF4 to form higher-order structures with the creation of neoantigens and the formation of anti-PF4 antibodies.

The interval between vaccination and the thrombotic event is usually between four and 28 days. The most common affected vessel sites are the cerebral veins, but thrombosis occurs in the lower extremities, the pulmonary arteries and splanchnic vessels. Both arterial and venous thrombosis can occur and multiple sites may be involved. It is important to remember that, especially as patients have thrombocytopenia, cerebral venous sinus thrombosis may present with intracranial bleeding. Patients may also show minor platelet defect type bleeding (petechiae/ purpura) and, rarely, more serious bleeding.

Patients presenting with thrombosis will routinely have a *full blood count* (FBC) done, which in VITT reveals thrombocytopenia. Careful examination of the blood smear is necessary to exclude other causes of thrombocytopenia. If previous platelet counts of the patient are available, comparing the current value with the patient's normal baseline count may give an early indication of the development of thrombocytopenia. *D-dimer* values are high (often very high with values > 3.0 mg/L). *PT and aPTT* are normal or mildly increased and *fibrinogen levels* are often low. *Anti-PF4 antibodies* are positive (ELISA method) and a modified *Heparin-*

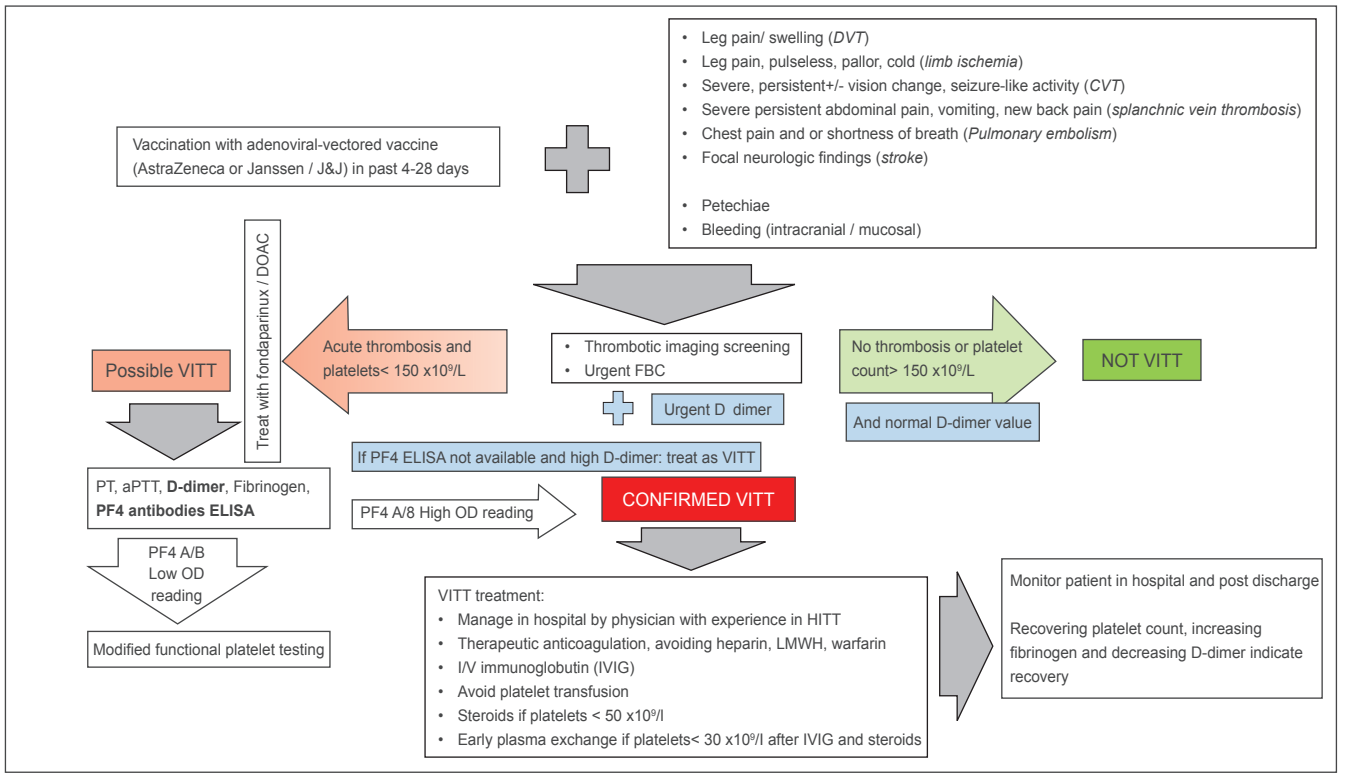

Figure 2: Diagnosis and management of VITT. Adapted from the ISTH guideline. (https://academy.isth.org/isth/document_library?dc_id=9915&f=menu%3D8%2Abrowseby%3D8%2Asortby%3D2%2Alabel%3D19794). In view of the evolving spectrum of the disorder and more heterogenous presentation, the importance of the triad of thrombosis, thrombocytopenia and high D-dimer is highlighted.[44] iTTP: immune/ acquired thrombotic thrombocytopenic purpura; VITT: vaccine-induced immune thrombotic thrombocytopenia; VIITP: vaccine-induced immune thrombocytopenia.

induced platelet aggregation (HIPA) test (showing hyper-reactive platelets in the presence of PF4) may be done (in South Africa, this test is done only at the Haematology Department of the University of the Free State). ELISA PF4 testing is available from many of the laboratories and with a strongly positive ELISA test functional platelet testing is unnecessary. A high index of suspicion is necessary and the mnemonic ***VITT*** (Warkentin) in Table I can be handy in this regard.[43]

Management principles of VITT:[45,46]

1. Urgent management of patients in hospital by a physician with knowledge of or experience in managing HITT. After discharge of patients, follow-up platelet counts should be done twice weekly for at least 2–3 weeks (recovery of platelet count if > 150 × 10^9/L).
2. Therapeutic anticoagulation should be given, unless contraindicated, while awaiting a confirmatory PF4 ELISA result. Although many patients' platelets do not show hyper-reactivity with heparin in functional testing, heparin is avoided (including heparin flushes) and fondaparinux is given. Direct oral anticoagulants (rivaroxaban or apixaban) have also been given to patients (in South Africa we do not have other suggested drugs such as argatroban, danaparoid or bivalirudin). Therapeutic anticoagulation is continued for three months after platelet count recovery.
3. High-dose intravenous immunoglobulin is given for two days (1 g/kg).
4. Platelet transfusions should not be given unless critical bleeding occurs.
5. Cryoprecipitate may be needed for bleeding in a patient with hypofibrinogenemia.
6. Plasma exchange and immunosuppression are suggested for refractory VITT.
7. In the setting of vaccines requiring a second dose, the culprit vaccine should not be re-administered.

Common clinical dilemmas surrounding COVID-19 vaccination and thrombosis:

1. Patients with a strong family history of thrombosis or a previous thrombosis should get vaccinated. The pathophysiology in VITT differs from normal VTE. The risk of thrombosis in COVID-19 infection is much higher than with vaccination.
2. Patients who are not on an anticoagulant or an antiplatelet drug, should not start taking these drugs around the time of vaccination (including aspirin).
3. Patients with a previous history of TTP should be managed cautiously. In view of recent reports of iTTP, care should be taken to do ADAMTS13 levels in these patients before and after vaccination.[41] These patients should be managed by clinical haematologists.

MYOCARDITIS, PERICARDITIS AND CARDIOMYOPATHY AFTER COVID-19 VACCINATION

Over the past year, there has been a growing international list of reports of the rare occurrence of myocarditis and/or pericarditis within the first week after receiving an mRNA COVID-19 vaccine

TABLE I: VITT MNEMONIC[43]
Vaccination done
Interval four to 28 days between vaccination and thrombosis/ thrombocytopenia
Thrombotic event (venous/arterial)
Thrombocytopenia (< 150 × 10^9/L or 50% decrease in baseline platelet count)

– usually after the second dose. The reports were mainly of male patients, particularly young adults and adolescents.[47] According to the data in the US Vaccine Adverse Events Reporting System (VAERS), in persons 12–29 years of age approximately 40.6 cases of myocarditis occurred per million second doses of mRNA COVID-19 vaccines among males. In contrast, 4.2 cases occurred per million second doses among females in the same age group. For persons over 30 years of age, the reporting rates were 2.4 and 1.0 per million second doses respectively for males and females. The vast majority of cases were mild and the patients recovered quickly.[48,49]

The risk of developing myocarditis is 18 times greater in the 12–29 age group following natural infection with SARS-CoV-2 – a much more significant risk than is observed following vaccination.[50]

Myocarditis may present with chest pain, dyspnoea, palpitations or syncope. Infants and children < 12 years may present with irritability, vomiting, poor feeding, tachypnoea or lethargy.[51] Other causes of myocarditis should also be considered and excluded as part of the differential diagnosis, such as infection (including SARS-CoV-2 infection), existing autoimmune conditions or ischaemic disease.

Biomarkers of cardiac injury may be elevated in patients with acute myocarditis and may help to confirm the diagnosis. Troponin I has high specificity (89%) but limited sensitivity (34%) in the diagnosis of myocarditis. Increased levels of cardiac troponin I are more common than increased levels of creatine kinase MB in acute myocarditis. Patients may have abnormal findings on electrocardiogram, echocardiogram or cardiac magnetic resonance imaging.[51] Cardiac diagnoses made post-COVID-19 vaccine require urgent specialist clinical management. The mainstay of treatment is supportive therapy that may include the use of nonsteroidal anti-inflammatory drugs, the occasional use of intravenous immune globulin, glucocorticoids when clinically indicated, and the use of targeted cardiac medications or interventions as required.[47] Patients who developed myocarditis post-COVID-19 vaccination mostly experienced the resolution of their symptoms with conservative management. Exercise restriction is recommended until the heart recovers.[48]

For individuals who develop myocarditis or pericarditis following a first dose of an mRNA vaccine, the second dose should be deferred. If the risk for severe COVID-19 is high due to underlying comorbidities, it is reasonable for such an individual to choose to receive a second dose once the episode has completely resolved. SAHPRA approved the Pfizer-BioNTech mRNA vaccine, Comirnaty, for individuals 12–17 years, and vaccination commenced on 20 October 2021. The Medical Advisory Committee recommended the delay in administering the second dose in this age group due to concerns about rare cases of myocarditis while studies are ongoing.[52,53]

Individuals with a history of resolved myocarditis or pericarditis unrelated to COVID-19 vaccination can receive an mRNA vaccine.[54]

ALLERGIC REACTIONS TO COVID-19 VACCINES

An increase in vaccine-associated anaphylaxis was reported during the early stages of the rollout of mRNA vaccines in Europe and the United States. An estimate of 2.5–11.1 cases of anaphylaxis per million doses has been reported from recent surveillance data.[55] The reported anaphylaxis rate in response to adenoviral vector vaccines has been fewer than 0.5 cases per million, which is similar to the anaphylaxis rate in response to other viral vaccines currently in use.[58] No fatal cases of anaphylaxis have yet been reported to COVID-19 vaccines. The approach to patients with a history of, or a high risk for, anaphylaxis to COVID-19 vaccines has been discussed in detail in a recent review article published in *Current Allergy and Clinical Immunology*.[55]

More recently, the focus has shifted from anaphylaxis to cutaneous reactions after COVID-19 vaccination. Urticarial eruptions and angioedema are the most common cutaneous reactions reported in patients undergoing mRNA COVID-19 vaccinations.[57]

A recent article published in *JAMA Dermatology* describing adverse events after mRNA COVID-19 vaccination in a cohort of 50 000 healthcare employees reported cutaneous reactions in 1.9% after the first dose of vaccine and 2.3% after the second dose of vaccine. More than 600 employees who reported a cutaneous reaction after their first dose received their second dose of vaccine and 83% did not have a recurrence of cutaneous reactions. Cutaneous reactions were mostly mild, the most frequently reported symptom being an itchy rash.[58]

Another recent research study among healthcare workers in Milan vaccinated with mRNA COVID-19 vaccines reported urticaria or angioedema in 1.8% of vaccine recipients. This study demonstrated a threefold increased risk for urticaria or angioedema in healthcare workers using ACE-inhibitors, which may allude to the role of bradykinin in these reactions. Of note, all the reported reactions were mild and self-limiting.[59]

Urticaria or angioedema usually develops hours to days after vaccination. In contrast, the majority of potentially serious systemic reactions after mRNA vaccination occur within 30 minutes of administration. The time course of cutaneous reactions corresponds to the normal immunological or inflammatory response to vaccination, which suggests that cytokines and other immunological molecules may lead to non-IgE-mediated mast cell and basophil degranulation.[60]

The mechanism of anaphylactic reactions to COVID-19 vaccines has not yet been fully characterised. The mRNA vaccines contain polyethylene glycol (PEG), which has rarely been implicated as an allergen in anaphylactic reactions to other PEG-containing

products and medications. The viral vector vaccines contain polysorbate, which is structurally related to PEG, and has also rarely been implicated in anaphylactic reactions. There are no egg proteins or gelatins in the currently available COVID-19 vaccines.[60]

The recommended management of patients with suspected allergic reaction to COVID-19 vaccines:[60]

- Take a good history, including previous reactions, timing and types of reaction, as well as previous episodes of anaphylaxis to COVID-19, other vaccines and injectable medication.
- Patients with a history compatible with COVID-19 vaccine anaphylaxis should be referred to an allergy clinic for SPT/intradermal tests to PEG/polysorbate, if available. Basophil activation tests (BAT) or CAST tests are available to PEG but, although very specific, the sensitivity of these tests has not yet been established and they are best used in combination with other tests in a research setting.
- In high-risk patients, an alternative vaccine could be considered for boosting. Boosting should be offered in a setting equipped to manage anaphylaxis. A graded challenge of 10% dosing, followed by 90% dosing after 30 minutes if no serious effects are observed, is recommended. Non-sedating antihistamine cover should be considered prior to administering the vaccine.
- Patients with a previous cutaneous reaction to a COVID-19 vaccine should also consider taking a non-sedating antihistamine prior to vaccination. Vaccination can take place without additional precautions, but a 30 min observation period is recommended after vaccination.
- If a patient should develop a severe allergic reaction or anaphylaxis after receiving a dose of COVID-19 vaccine, a clotted blood sample (SST tube) should always be taken between 30 min and four hours after the reaction for mast cell tryptase measurement. A baseline mast cell tryptase should also be requested at least 24 hours after the initial measurement, because a fourfold increase above baseline is diagnostic.

CONCLUSION

Global safety monitoring data suggest that life-threatening serious adverse events are rare following vaccination and that the benefits of COVID-19 vaccination, at both the individual and the population level, far outweigh the risks.

It is important to ensure that healthcare providers and vaccine recipients are aware of the risks and that patients should seek care if they experience concerning symptoms after COVID-19 vaccination. All events should be investigated, followed up on and reported; however, temporal associations do not necessarily imply causality.

Members of the public and health professionals are encouraged to report AEFIs to the health facility delivering the vaccine either on the Med Safety App (which can be downloaded from App Stores for Android and iOS phones), or by calling the COVID-19 hotline on 0800 029 999.[13,14]

It is essential that COVID-19 vaccination proceed safely with as few barriers as possible, because widespread vaccination is a key intervention in the control of this pandemic. To achieve this aim, both doctors and patients need to have access to reliable information and reassurance.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Marlene Buitendach's technical assistance and Mark Cruz da Silva for proofreading the script.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

REFERENCES

1. O'Callaghan KP, Blatz AM, Offit PA. Developing a SARS-CoV-2 vaccine at warp speed. JAMA. 2020;324(5):437–438. https://doi.org/10.1001/jama.2020.12190.
2. World Health Organization. WHO Coronavirus Covid-19 Dashboard. 2021. https://covid19.who.int/ (accessed 14 October 2021).
3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet (London, England). 2021;397(10269):99–111. https://doi.org/10.1016/S0140-6736(20)32661-1.
4. Polack FP, Thomas SJ, Kitchin N, et al. C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–2615. https://doi.org/10.1056/NEJMoa2034577.
5. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med. 2020;383(25):2439–2450. https://doi.org/10.1056/NEJMoa2027906.
6. Thomas SJ, Moreira ED, Kitchen N, Absalon J, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med. 2021;385(19):1761–1773. https://doi.org/10.1056/NEJMoa2110345.
7. Frenck RWJ, Klein NP, Kitchen N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med. 2021; 385(3):239–250. https://doi.org/10.1056/NEJMoa2107456.
8. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585–594. https://doi.org/10.1056/NEJMoa2108891.
9. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384(23):2187–2201. https://doi.org/10.1056/NEJMoa2101544.
10. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. N Engl J Med. 2021;385:1355–1371. https://doi.org/10.1056/NEJMoa2110362.
11. Dudley M. The state of vaccine safety science: Systematic reviews of evidence. Lancet Infect. 2020;20(5):80–89. https://doi.org/10.1016/S1473-3099(20)30130-4.
12. Department of Health. COVID-19 vaccination Summary as at 17:00 13Oct 2021, 5. [Internet]. https://sacoronavirus.co.za/latest-vaccine-statistics/ (accessed 13 October 2021).
13. South African Health Products Regulatory Authority. SAHPRA statement on adverse events following immunisation (AEFIS) with COVID 19 vaccines. [Internet]. Press release 20 August 2021. https://www.sahpra.org.za/press-releases/sahpra-statement-on-adverse-events-following-immunisation-aefis-with-covid-19-vaccines/ accessed 13 October 2021).
14. South African Health Products Regulatory Authority. How to report adverse events following immunisation (AEFIS). [Internet] http://aefi-reporting.sahpra.org.za/report-aefi.html (accessed 13 October 2021).
15. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. N Engl J Med. 2021;384(13):1273–1277. https://doi.org/10.1056/NEJMc2102131.
16. Centres for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. [Internet] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (accessed 13 October 2021).
17. Gee J, Marquez P, Su J, et al. First month of COVID-19 vaccine safety monitoring-United States. Morb Mortal Wkly Rep. 2021;70:283–288. https://doi.org/10.15585/mmwr.mm7008e3.
18. Shay DK, Gee J, Su JR, et al. Safety monitoring of the Janssen (Johnson

& Johnson) COVID-19 vaccine. Morb Mortal Wkly Rep. 2021;70:680–684. https://doi.org/10.15585/mmwr.mm7018e2.
19. Peter J. COVID-19 vaccination: recommendations for management of patients with allergy or immune-based disease. SAMJ. 2021;111(4):291–294. https://doi.org/10.7196/SAMJ.2021.v111i4.15576.
20. Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barré syndrome: Let's not leap to associations. Brain. 2021;144(2):357–360. https://doi.org/10.1093/brain/awaa444.
21. Abramowicz M, Zuccotti G, Pflomm J, et al. Guillain-Barré syndrome with the Johnson and Johnson COVID-19 vaccine. The Medical Letter on Drugs and Therapeutics. 2021;63(1630):121–22.
22. Rosenblum H, Hadler SC, Moulia D, et al. Use of COVID-19 vaccines after reports of adverse events among adult recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on immunisation Practices – United States. July 2021;70(32):1094–1099. https://doi.org/10.15585/mmwr.mm7032e4.
23. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: An up-to-date systematic review of 73 cases. J Neurol. 2021;268:1133–1170. https://doi.org/10.1007/s00415-020-10124-x.
24. McDonnell EP, Altomare NJ, Parekh YH, et al. COVID-19 as a trigger of recurrent Guillain-Barré syndrome. Pathogens. 2020;9(11):965. https://doi.org/10.3390/pathogens9110965.
25. U.S. Food and Drug Administration. Coronavirus (COVID-19) [Internet]. News release 12 July 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-july-13-2021 (accessed 13 October 2021).
26. Van den Berg B, Walgaard C, Drenthen J, et al. Guillain-Barré syndrome: Pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol. 2014;10:469–482. https://doi.org/10.1038/nrneurol.2014.121.
27. Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré Syndrome. Lancet. 2021;397(10280):1214–1228. https://doi.org/10.1016/S0140-6736(21)00517-1.
28. Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barré Syndrome. Cochrane Database Syst Rev. 2017;2:CD001798. https://doi.org/10.1002/14651858.CD001798.pub3.
29. Edwards KM, Orenstein WA. COVID-19: Vaccines to prevent SARS-CoVf-2 infection. UpToDate: [updated 27 September 2021] https://www.uptodate.com/contents/covid-19-vaccines-to-prevent-sars-cov-2-infection?sectionName=Myocarditis&search=myocarditis%20covid%20vaccine&topicRef=12 (accessed 7 October 2021).
30. Vegezzi E, Ravaglia S, Buongarzone G, et al. Acute myelitis and ChAdOx1 nCoV-19 vaccine: Casual or causal association? J Neuroimmunol. 2021;359:577686. https://doi.org/10.1016/j.jneuroim.2021.577686.
31. Vogrig A, Janes F, Gigli GL, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 vaccination. Clin Neurol Neurosurg. 2021;208:106839. https://doi.org/10.1016/j.clineuro.2021.106839.
32. Kenangil GO, Ari BC, Guler C, Demir MK. Acute disseminated encephalomyelitis-like presentation after an inactivated coronavirus vaccine. Acta Neurol Belg. 2021;121(4):1089–1091. https://doi.org/10.1007/s13760-021-01699-x.
33. Zuhorn F, Graf T, Klingebiel R, Schäbitz WR, Rogalewski A. Postvaccinal encephalitis after ChAdOx1 nCov-19. Ann Neurol. 2021;90(3):506–511. https://doi.org/10.1002/ana.26182.
34. Gao JJ, Tseng HP, Lin CL, et al. Acute transverse myelitis following COVID-19 vaccination. Vaccines. 2021;9(9):1008. https://doi.org/10.3390/vaccines9091008.
35. Román GC, Gracia F, Torres A, et al. Acute transverse myelitis (ATM): Clinical review of 43 patients with COVID-19-associated ATM and 3 post-vaccination ATM serious adverse events with the ChAdOx1 nCoV-19 vaccine (AZD1222). Front Immunol. 2021;12:653786. https://doi.org/10.3389/fimmu.2021.653786.
36. Goss AL, Samudralwar RD, Das RR, Nath A. ANA investigates: Neurological complications of COVID-19 vaccines. Ann Neurol. 2021;89(5):856–857. https://doi.org/10.1002/ana.26065.
37. Carli G, Nichele I, Ruggerin M, Barra S, Tosetto A. Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. Intern Emerg Med. 2021;16(3):803–804. https://doi.org/10.1007/s11739-021-02685-0.
38. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021;384:2092–2101. https://doi.org/10.1056/NEJMoa2104840.
39. Al-Ahmad M, Al-Rasheed M, Shalaby NAB. Acquired thrombotic thrombocytopenic purpura with possible association with Astra Zeneca-Oxford COVID-19 vaccine. eJHaem. 2021;2:534–536. https://doi.org/10.1002/jha2.219.
40. Maayan H, Kirgner I, Gutwei O, et al. Acquired thrombotic thrombocytopenic purpura: A rare disease associated with BNT162b2 vaccine. J Thromb Haemost. 2021;19:2314–2317. https://doi.org/10.1111/jth.15420.
41. Choi PY, Grace RF, Ahlen AT, et al. The SSC platelet immunology register of VITT and VIITP: Toward standardization of laboratory and clinical parameters. J Thromb Haemost. 2021;19(8):2094–2095. https://doi.org/10.1111/jth.15402.
42. Pavord S, Scully M, Hunt BJ, et al. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. N Engl J Med. 2021;385:1680–1689. https://doi.org/10.1056/NEJMoa2109908.
43. Warkentin T. Covid-19: Vaccine-induced immune thrombotic thrombocytopenia. UpToDate: [updated 30 September 2021] https://www.uptodate.com/contents/covid-19-vaccine-induced-immune-thrombotic-thrombocytopenia-vitt (accessed 7 October 2021).
44. Lavin M, Elder PT, O'Keeffe D, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT) – a novel clinico-pathological entity with heterogeneous clinical presentations. Br J Haematol. 2021;195:76–84. https://doi.org/10.1111/bjh.17613.
45. Jacobson BF, Schapkaitz E, Mer M, et al. Recommendations for the diagnosis and management of vaccine-induced immune thrombotic thrombocytopenia. S Afr Med J. 2021;111(6):535–537.
46. Bussel JB, Connors JM, Cines DB, et al. Thrombosis with Thrombocytopenia Syndrome (also termed vaccine-induced Thrombotic Thrombocytopenia). American Society of Haematology: [updated 12 August 2021] https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia (accessed 7 October 2021).
47. Pepe S, Gregory AT, Denniss AR. Myocarditis, pericarditis and cardiomyopathy after COVID-19 vaccination. Heart Lung Circ. 2021;30(10):1425–1429. https://doi.org/10.1016/j.hlc.2021.07.011.
48. Gargano J, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: Update from the Advisory Committee on immunisation Practices – United States June 2021. MMWR. 2021;70(27). https://doi.org/10.15585/mmwr.mm7027e2.
49. Gubernot D, Jazwa A, Niu M, et al. US population-based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021;39(28):3666–3677. https://doi.org/10.1016/j.vaccine.2021.05.016.
50. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in a Nationwide setting. N Eng J Med. 2021;385:1078–1090. https://doi.org/10.1056/NEJMoa2110475.
51. Cooper LT Jr. Myocarditis. N England J Med. 2009;360:1526–1539. https://doi.org/10.1056/NEJMra0800028.
52. South African Government News Agency. Children aged between 12 and 17 to be vaccinated. [Internet]. Republic of SA. SA News.gov.za. [15 October 2021] https://www.sanews.gov.za/south-africa/children-aged-between-12-and-17-be-vaccinated (accessed 20 October 2021).
53. Malan M, Karim AA, van Dyk J. Joining the COVID vaccine queuer: Why SA's teen will have to wait for the jab. [Internet]. Health 24. News 24. [13 September 2021] https://www.news24.com/health24/medical/infectious-diseases/coronavirus/joining-the-covid-vaccine-queue-why-sas-teens-will-have-to-wait-for-the-jab-20210913-2 (accessed 20 October 2021).
54. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. [Internet] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (accessed 23 July 2021).
55. Day C, Peter J. Approaching COVID-19 vaccination and anaphylaxis from 2 directions. Curr Allergy Clin Immunol. 2021;34(3):122–127.
56. Shay DK, Gee J, Su JR, et al. Medline® Abstract for Reference 3 of 'COVID-19: Allergic reactions to SARS-CoV-2 vaccines. MMWR Morb Mortal Wkly Rep. 2021;70(18):680.
57. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. J. Am. Acad. Dermatol. 2021;85:46–55. https://doi.org/10.1016/j.jaad.2021.03.092.
58. Robinson LB, Fu X, Hashimoto D, et al. Incidence of cutaneous reactions after messenger RNA COVID-19 vaccines. JAMA Dermatol. 2021;157(8):1000–1002. https://doi.org/10.1001/jamadermatol.2021.2114.
59. Cugno M, Consonni D, Lombardi A, et al. Increased risk of urticaria/angioedema after BNT162b2 mRNA COVID-19 vaccine in healthcare workers taking ACE inhibitors. Vaccines (Basel). 2021;9(9):1011. https://doi.org/10.3390/vaccines9091011.
60. Kelso JM. COVID-19: Allergic reactions to SARS-CoV-2 vaccines. UpToDate: [updated 20 August 2021] https://www.uptodate.com/contents/covid-19-allergic-reactions-to-sars-cov-2-vaccines" https://www.uptodate.com/contents/covid-19-allergic-reactions-to-sars-cov-2-vaccines (accessed 20 October 2021).