

Chadox1 Ncov-19 Vaccination: A Clinico-Pathological Review of Coagulation Derangement in Four Cases

Adekoya A. O.

Lagos State University Teaching Hospital, Ikeja, Lagos
Lagos State University college of Medicine, Ikeja, Lagos

Adelekan-Popoola F.

Next Haematology Medicare, Lagos

Fabamwo A. O.

Lagos State University Teaching Hospital, Ikeja, Lagos
Lagos State University college of Medicine, Ikeja, Lagos

Abayomi E. A.

Lagos State Ministry of Health

Ajibare A. O.

Lagos State University Teaching Hospital, Ikeja, Lagos
Lagos State University college of Medicine, Ikeja, Lagos

Odugbemi B.

Lagos State University Teaching Hospital, Ikeja, Lagos
Lagos State University college of Medicine, Ikeja, Lagos

Soyemi S. S.

Lagos State University Teaching Hospital, Ikeja, Lagos
Lagos State University college of Medicine, Ikeja, Lagos

ABSTRACT

BACKGROUND: Mass vaccination of the populace was one of the responses to mitigate the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) pandemic. Some minor and major adverse effects have been reported. **METHODS:** This study reviewed the clinico-pathologic parameters of 4 patients with clinical and biochemical coagulation abnormalities following the administration of the Oxford AstraZeneca COVID-19 (ChAdOx1 nCoV-19) vaccination. Their clinical, laboratory and radiological parameters were retrieved and documented. **RESULTS:** All the patients had abnormality of coagulation with thrombus formation. Two of the reported patients had several risk factors for thrombosis and thus their diseases may not have causal relationship with the vaccination while the other 2 patients had no plausible clinical explanation for their coagulation abnormality. Mortality was recorded in two of the patients. **CONCLUSION:** Severe adverse effect of ChAdOx1 nCoV-19 Vaccination may not be rare. Physicians should have a high index of suspicion and there is also a need to upscale adverse events monitoring.

Keywords: ChAdOx1 nCoV-19, Covid 19, Covid Vaccination, Astrazeneca, Johnson and Johnson.

INTRODUCTION

Presently, over two hundred and sixty million positive cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARs CoV-2) have been reported with over five million Coronavirus disease 19 (COVID19) related deaths globally. [1] As part of the response to this pandemic, Nigeria, through the National Primary Health Care Development Agency (NPHCDA), started the administration of the Oxford AstraZeneca COVID-19 (ChAdOx1 nCoV-19) vaccination in March 2021. The initial round of vaccinations lasted approximately 4 weeks. Priority for the first phase of the vaccination was targeted at frontline workers as well as other vulnerable groups. As of April 19th, 2021, 317,916 doses of vaccines have been administered as first dose representing approximately 1% of the 24 million population in the megacity of Lagos. [1] Of this number, 14 cases of severe and 419 cases of mild adverse effects associated with the vaccination were reported.

Internationally, there have been reports of adverse events following vaccination with the Oxford/Astra Zeneca as well as Johnson and Johnson vaccines. We report four cases of severe adverse events of coagulation defects among those who received AstraZeneca COVID19 vaccination in Lagos, Nigeria. The importance of this report is to verify the clinico-pathological features of these cases and determine if there is a causative relationship with the vaccine. To the best of our knowledge, this is the first documentation of coagulation related severe side effects of Oxford AstraZeneca COVID-19 (ChAdOx1 nCoV-19) in Nigeria.

METHODS

This is a case series of 4 patients who were admitted in our hospitals on account of suspected severe adverse reaction (abnormality of coagulation with thrombus formation) to covid-19 vaccine. We reviewed their clinical presentations, treatment modalities and analysed their various results including the autopsy report. Investigation results and characteristics of the patients were presented in tables. Consent for publication was obtained from the patients or their next of kin.

RESULTS

Case Summary

Patient 1 was an 80-year old female, known hypertensive and diabetic of 20 years duration with poor drug compliance. She presented at the Medical Emergency on the 25th March 2021 with a history of right-sided limb weakness of 3-hours duration. There was associated speech impairment, facial asymmetry and altered sensorium. She had no previous history of cerebrovascular accidents (CVA). This event occurred at rest. She had received AstraZeneca COVID-19 vaccination 2 days prior to presentation after which she was said to have had a mild headache. An assessment of Left Hemispheric Ischaemic CVA with Right Hemiparesis was made, image confirmed (Figure 1A).

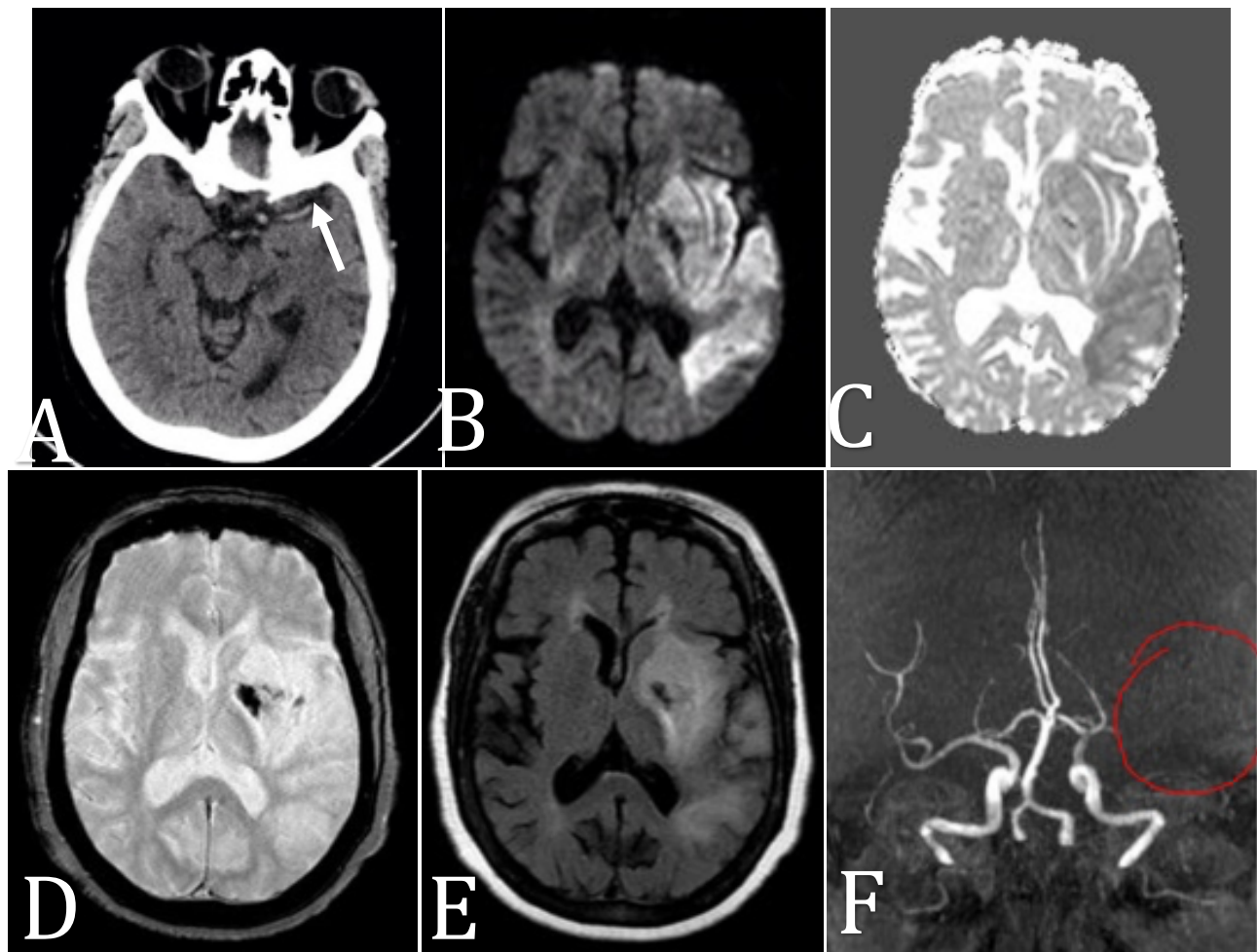


Figure 1 – Brain CT (patient 1) on admission (A) showing a left dense MCA sign with no evidence of haemorrhage. Brain MRI done 3 days post thrombolysis showed restricted diffusion in left MCA territory (B, C) with T2 FLAIR hyperintensity (E) and blooming on the T2* FFE (D) suggesting acute infarct with Type 1 haemorrhagic conversion. MRA showed a left MCA occlusion (F).

The identified risk factors were hypertension, diabetes mellitus, black race as well as old age. She was thrombolysed with intravenous Alteplase (door to needle time was 6hours). Investigation findings on the day of admission and subsequent days were as shown below. (Table 1).

Table 1: Investigation results of patient 1

	INVESTIGATION	REFERENCE VALUE	Day 0	Day 2	Day 3	Day 5	Day 6	Day 10	Day 11
1	PCV (%)	35-48	36.6				39.1		
2	WBC (10 ⁹ /L)	4-11	7.6				8.8		
3	Platelet (10 ³ /uL)	150-450	307				254		
4	ESR (mm/hr)	Up to 20	36						
5	Urea (mmol/L)	2.5-6.4	4.4		8.4				
6	Creatinine (umol/L)	53-115	115		119				
7	Bicarbonates (mmol/L)	22-30	29		32				
8	Sodium (mmol/L)	135-145	139		139				
9	Potassium (mmol/L)	3.5-5.5	3.5		3.0			4.1	
10	Chloride (mmol/L)	98-110	97		95				
11	INR	0.8-1.2	1.27	1.03					
12	PTT (Secs)	26.5-40.0	28.3	25.7					
13	PT (Secs)	11.5-14.5	17.3	14.4					
14	Total Cholesterol (mmol/L)	<5.18	5.4						
15	HDL mmol/L	0.91-2.21	2.1						
16	LDL mmol/L	<3.0	3.0						
17	Triglycerides (mmol/L)	<1.7	0.71						
18	Globulin (g/L)	20-35	45						
19	Total Protein (g/L)	64-83	85						
20	Serum Albumin (g/dL)	35-50	40.3						
21	Total Bilirubin (umol/L)	2-20	7.2						
22	Direct Bilirubin (umol/L)	0-3.4	1.8						
23	ALT (U/L)	10-40	16						
24	AST (U/L)	10-42	28						
25	ALP (U/L)	40-120	135						
26	GGT (U/L)	5-43	60						
27	D-Dimer (ng/mL)	1-500		5679.73					9735.95
28	Troponin (ng/mL)	0-0.1		<0.10		<0.05			
29	CK-MB	0-4.3		3.1		4.40			
30	LDH (IU/L)	110-220		237					
31	Myoglobin (ng/mL)	0-95		137.0		91.09			
32	HbA1C (%)		5.7						

A Brain MRI done 3 days after admission revealed an acute ischaemic infarct with haemorrhagic transformation. Ten (10) days later, patient was noticed to have bilateral pedal swelling (Right>Left) extending to the lower 1/3 of the right leg with associated differential warmth and tenderness. A repeat D-Dimer done on that same day showed an increase from a prior 5679.73ng/dL to 9735.95ng/dL. She was subsequently started on subcutaneous enoxaparin 40mg daily. Furthermore, venous Doppler scan of both lower limbs done on day 15 of admission showed bilateral lower limb deep venous thrombosis (DVT) with right subcutaneous swelling. Subsequently, she developed sudden onset difficulty in breathing same day and died despite attempt at resuscitation.

The post post-mortem findings showed features of hypertensive heart disease, tricuspid valve dilatation, deep vein thrombosis, generalised petechiae as well as chronic passive congestion of the liver. Samples were taken from all organs for histology.

Final Diagnosis: Ischaemic CVA, complicated by bilateral Deep Venous Thrombosis and Pulmonary Embolism.

Patient 2 was a 34-year-old man who was referred to a private hematology center on account of a 3-day history of hematuria, bleeding into the skin and gums. He had been otherwise well prior to onset of these symptoms. The only significant exposure in the past month was AstraZeneca COVID 19 vaccine which he had received 7 days prior to onset of symptoms. Significant examination findings revealed petechial rashes on arms and bleeding gums. His blood pressure was 143/92mmHg. Investigation results at presentation showed a hematocrit of 41%, white blood cell count of $6.41 \times 10^9/L$, Platelet count of $2 \times 10^9/L$. Erythrocyte sedimentation rate (ESR) of 35mm/hr., D-dimer of 0.32 (0-0.5mcg/ml), bleeding time of 1min 30sec (1-4mins), Clotting time of 5min 47 sec (4-8min), International normalized ratio of 0.98 (0.9-1.2), Alanine transaminase level of 64.5U/L (0-45), Aspartate transaminase level of 75.5IU/L (0-40), Alkaline phosphatase level of 82IU/L (40-129) and gamma glutamyl transaminase level of 107.6IU/L (8-78). Total Bilirubin and renal function were normal. Urine microscopy culture and sensitivity showed albumin ++, RBC+++ , leucocytes + and no red cell casts. A repeat full blood count done 2 days later showed a lower platelet count of $1 \times 10^9/L$. Peripheral blood film showed normochromic, normocytic red cells, adequate on film, no schistocytes observed, normal white blood cell morphology, adequate on film and no platelet clumps or platelets were seen on film.

Patient was admitted and started on IV Methylprednisolone 1g once daily for 3 days, IV Omeprazole 80mg 12hourly, oral Amlodipine 10mg once daily, oral Carvedilol 12.5mg twice daily and intravenous levofloxacin 500mg once daily. He was transfused with 3 therapeutic units of apheresis platelets (Dose $150 \times 10^9/L$) on same day. The hematuria stopped about 2 hours after receiving the platelet transfusion; however repeat platelet count about 12hrs post-transfusion remained $1 \times 10^9/L$. This confirmed the suspicion of immune mediated platelet consumption. Patient was commenced on intravenous immunoglobulins at 0.5g/Kg/day for 2 days. Platelet count was $28 \times 10^9/L$ and $80 \times 10^9/L$ on day 1 and 2 respectively following intravenous immunoglobulin infusion. D-dimer remained within normal limits though the liver function remained slightly deranged while renal function remained normal. Venous doppler scans and abdominopelvic CT scans were all normal and excluded thrombosis. Patient has

remained stable and was discharged for follow up and has remained well. Platelet Factor 4 antibodies and Enzyme linked Immunosorbent Assay (PF4 ELISA) were negative.
Final Diagnosis: Immune Thrombocytopenic Purpura.

Patient 3 was a 36-year-old female who presented at a private facility on account of left lower limb swelling of two weeks duration. The swelling was said to have been gradual in onset. It began as a puffy ankle which progressively increased in size, was initially non-tender but later associated with pain after a week. The swelling was localised to the left calf and medial thigh. She had urinary symptoms and no history suggestive of heart failure. She was ambulant and well prior to the onset of this illness but she however received COVID 19 vaccine at a Primary Healthcare Centre six days prior to the onset of illness. She subsequently developed rash, swelling and discoloration at the injection site. Complete blood count done at presentation showed Haemoglobin of 7.4 g/dL, MCV of 46.4 fl (76-96), MCH of 18pg (27-32), MCHC of 27.2 g/dL(31-36), total white cell count of 5,800/L, Neutrophil 63.6%, Lymphocytes 27.4%, Eosinophil 2.9%, Basophil 0.3% and platelets of 311,000 mm³. D-dimer was elevated above 3000ng/ml (repeat >10,000ng/ml) while her renal function was within normal limits. She had an abdominal CT scan which showed large uterine fibroid in proximity and compressing the left common iliac vessel and the doppler ultrasound of the left leg showed clots in the left iliac vein extending to the popliteal vein. A diagnosis of obstructive deep venous thrombosis with underlying iron deficiency anaemia secondary to menorrhagia from uterine fibroid was made. Patient was treated with anticoagulation and iron replacement therapy and referred for further management of uterine disorder and the iron deficiency anaemia.

Final Diagnosis: Deep Venous Thrombosis secondary to iliac vein compression.

Patient 4 was a 48-year-old man, admitted via the medical emergency on referral from a secondary healthcare facility in Lagos. He presented with easy fatigability and weight loss of one-month duration, cough and breathlessness of two weeks duration. There was associated history of high-grade fever, drenching night sweats and gum bleeding. He was also noted to have generalized throbbing headache and had passed 5 episodes of non-bloody diarrhea. There was no history of visual blurring, no bleeding from any other orifices. No history of recurrent chest pain, no haemoptysis and no reduction in urine output. Symptoms was said to have started three days after taking COVID-19 Vaccine. His social history is significant for consumption of 14units of alcohol per week for more than 10 years and he had 13.5 pack years of cigarette. No significant past medical history. Before presentation at LASUTH, he had 7 pints of blood transfused at the referring hospital on account of low packed cell volume (PCV). The full blood count (CBC) from the referring hospital showed a PCV of 12%, WBC of 80.8 X 10⁹/L, platelet count of 22,000 mm³ with myeloid blast cells suggestive of acute myeloid leukaemia M₄. On general examination, he was chronically ill-looking and dyspnoeic. Respiratory system examination revealed coarse crepitations on the right side with an oxygen saturation of 85% in room air. Investigations done at presentation included a Chest X-ray which showed patchy opacities in the right hemi thorax. A repeat FBC (post transfusion) showed PCV of 20.2%, WBC of 88.6X10⁹/L and severe thrombocytopenia with a platelet count of 900mm³. An assessment of suspected acute myeloid leukaemia complicated by sepsis was made and his management included parenteral antibiotics, intravenous fluids, fresh whole blood transfusion, oxygen therapy and other supportive treatments. He was reviewed by haematologists but his condition deteriorated and he died on the following day after presentation at our facility.

Final Diagnosis: Acute Myeloid Leukaemia.

Table 2. Characteristics of the patients

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age (yr.)	80	34	36	48
Sex	Female	Male	Female	Male
Premorbid state	HTN, DM	Fit and well	Fit and well	Fit and well
Symptoms	Right sided limb weakness	Hematuria, ecchymosis, gum bleeding	Left lower limb swelling	Gum bleeding, fever
Time from vaccination to admission(days)	2	7	7	3
Location of thrombosis	Cerebral vessel		Left iliac to popliteal vein	
Platelet count nadir (x 10 ⁹ /L)	254	1		22
D=dimer peak (mg/liter)	>35	Normal	>35	
Anticoagulation treatment	LMWH		LMWH	
Platelet units transfused	0	3	0	7
Other treatments	Alteplase	Methylprednisolone(1mg/kg), IVIG (0.5g/kg)		Antibiotics, antipyretics
Outcome	Fatal	Full recovery	Full recovery	Fatal
Remark	Autopsy done. No link with vaccination	Followed up on antiplatelet	CT Abdomen showed fibroid resting on the left common iliac vessel	

DISCUSSION

Internationally, there have been reports of adverse events following vaccination with both the Oxford/Astra Zeneca and Johnson and Johnson vaccines. An adverse event following immunization (AEFI) is defined as any untoward medical occurrence which follows immunization. Such events may occur in healthy individuals and it may not have a causal link with the use of the vaccine. [2] The most severe of reported AEFIs following COVID-19 vaccination involved thrombo-embolic events. [3,4] This have resulted in the suspension of rolling-out of certain vaccines or the restriction of their use to certain age groups. [5] There is a near absence of literature on such events in Africa, although there is a slower vaccine roll-out process and consequent poor vaccine coverage in Africa, relative to high income countries.

We report 4 cases of individuals who presented with features suspected to be AEFI following Oxford/AstraZeneca COVID 19, ChAdOx1 nCoV-19 Vaccination in Lagos, Nigeria.

Patient 1 did not suggest a causal relationship between the vaccine and the thrombotic events experienced. Prior to vaccination the patient had several risk factors for cerebrovascular disease including her advanced age, long-standing hypertension, and diabetes. Furthermore, a comprehensive post-mortem examination did not show any convincing association. Discussion around the association of COVID 19 vaccine with neurological complication started late in 2020 when 2 patients developed transverse myelitis after receiving the vaccine. [6] One of these was later reported as not related to the vaccine administration. [7] Furthermore, the original data from the mRNA vaccine trial showed that 7 out of the 37,000 vaccine recipients developed Bell's palsy but this was later reported as not significantly different when compared with the general population. [8] The subsisting advisory from competent authorities as regards the balance between the risks of neurologic complications and the benefits of the vaccine significantly tilt towards the benefits. [9] Previously reported cases of post vaccine thrombosis were characterized by thrombocytopenia, [4,10-12] which was not found in patient 1, though she had a mild drop in her platelet count after six days on admission. Immunoglobulin G (IgG) assay against PF-4 heparin complex was reported in cases of post vaccine thrombosis and is recommended for patients who present with features of thrombosis or thrombocytopenia following vaccine administration. [10,13] This assay was not done in patient 1 because of lack of facility. Therefore, apart from a temporal relationship with the vaccine administration, there was not enough evidence to conclude that the ischaemic stroke or venous thromboembolism that occurred was due to the vaccine. Additionally, the patient did not fit the demographic and there were multiple confounders that could better explain her presentation. Limitations in patient 1 include the lack of extensive evaluation for prothrombotic state and a screening for SARS-CoV-2. However, our suspicion and subsequent investigations into this case was necessary because little or no data is available in our environment as regards neurological manifestations following ChAdOx1 nCoV-19 Vaccination.

Patient 2 presented with features suggestive of a syndrome referred to as Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or Vaccine induced immune thrombotic thrombocytopaenia (VITT). This same syndrome is now simply referred to as Thrombosis with Thrombocytopenia Syndrome (TTS). [14] This rare disorder is characterized by COVID 19 vaccination (Oxford/AstraZeneca or Johnson and Johnson 4 to 30 days previously), thrombocytopenia, positive anti platelet factor 4 (PF4) / poly-anion complex antibody, venous or arterial thrombosis; often cerebral or abdominal. [4,14] This patient had the vaccine 7 days previously and had thrombocytopenia but the PF4 antibody was not assessed due to non-availability. These are significant limitations in this case. However, it is noteworthy that this patient was successfully treated with IV immunoglobulin and prednisolone. The bleeding episode resolved promptly following platelet transfusion but the platelet count remained at $1 \times 10^9/L$. This confirmed the suspicion of an autoimmune origin. This patient recovered fully following treatment and was followed up in the outpatient clinic. Conversely, Schultz et al reported high mortality in VITT patients who had platelet transfusion as part of their treatment modalities. [15] Though rare, TTS is being increasingly associated with ChAdOx 1 nCoV-19 Vaccination. [4]

Patient 3 developed deep vein thrombosis 6 days after ChAdOx1 nCoV-19 Vaccination. In addition, she had markedly high D-dimer. However, a contrast enhanced abdominal CT showed a large fibroid compressing the left common iliac vein. The fact that the patient was fit and well until after vaccination suggest a pro-thrombotic nature of the vaccine. [16]

The last patient had a smouldering illness and developed thrombocytopenia 3 days after ChAdOx1 nCoV-19 Vaccination. He received 7 units of whole blood from the referral centre and never had any platelet transfusion or definitive treatment with steroid/immunoglobulin as he passed on shortly after presentation at our facility. Though his clinical features are highly suggestive of leukemia on presentation, his thrombocytopenia may have been covid vaccination induced. New onset acute immune thrombocytopenia purpura (ITP) have been reported following SARS nCoV-2 vaccination. [17,18] The severity of thrombocytopenia is mostly less than 10,000/ μ L. The American Society of Haematology recommends that treatment with IVIG and/or steroid be initiated while awaiting a negative anti PF4 result to exclude TTS in this type of case. [14] This underscores the need for high index of suspicion and early initiation of treatment after clinical suspicion.

CONCLUSION

In conclusion, events in these 4 cases suggest that the discussion around the association of ChAdOx1 nCoV-19 Vaccination with clot formation in Europe should not be considered alien to Africa and thus the guiding principle should be a high index of suspicion. There is a need for intense adverse events monitoring and further studies on these adverse events, especially in this part of the world is essential.

References

1. Dadax. Wordometer-Real time world statistics. <https://www.worldometersinfo/coronavirus/>. 2021.
2. https://www.who.int/vaccine_safety/initiative/detection/AEFI/en/. Adverse Events Following Immunization (AEFI). 2021.
3. Tobaigy M, Elkout H, MacLure K. Analysis of Thrombotic Adverse Reactions of COVID-19 AstraZeneca Vaccine Reported to EudraVigilance Database. *Vaccines*. 2021;9(4).
4. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *The New England journal of medicine*. 2021.
5. Maas D, Kramers C, Smit H, Middeldorp S, Helsloot I. [Temporary suspension of AstraZeneca's vaccine; a reconstruction]. *Nederlands tijdschrift voor geneeskunde*. 2021;165.
6. Allen A SL, Kaiser Health News. NIH "Very Concerned" about Serious Side Effect in Coronavirus Vaccine Trial. *Health News*. 2020.
7. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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.
8. Ledford H. US authorization of first COVID vaccine marks new phase in safety monitoring. *Nature*. 2020;588(7838):377-8.
9. Goss AL, Samudralwar RD, Das RR, Nath A. ANA Investigates: Neurological Complications of COVID-19 Vaccines. *Annals of neurology*. 2021;89(5):856-7.
10. Wolf ME, Luz B, Niehaus L, Bhogal P, B  zner H, Henkes H. Thrombocytopenia and Intracranial Venous Sinus Thrombosis after "COVID-19 Vaccine AstraZeneca" Exposure. *Journal of Clinical Medicine*. 2021;10(8):1599.

11. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *New England Journal of Medicine*. 2021.
12. Muir K-L, Kallam A, Koepsell SA, Gundabolu K. Thrombotic Thrombocytopenia after Ad26. COV2. S Vaccination. *New England Journal of Medicine*. 2021.
13. Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, et al. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. *Hamostaseologie*. 2021.
14. Hematology ASo. Thrombosis with Thrombocytopenia Syndrome. <https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia>. 2021.
15. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *The New England journal of medicine*. 2021.
16. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. *BMJ* (Clinical research ed). 2021;372:n699.
17. Helms JM, Ansteatt KT, Roberts JC, Kamatam S, Foong KS, Labayog JS, et al. Severe, Refractory Immune Thrombocytopenia Occurring After SARS-CoV-2 Vaccine. *Journal of blood medicine*. 2021;12:221-4.
18. Lee EJ, Cines DB, Gernsheimer T, Kessler C, Michel M, Tarantino MD, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *American journal of hematology*. 2021;96(5):534-7.

