# Diagnostic Performance of a Particle Gel Immunoassay in Vaccine-Induced Immune Thrombotic Thrombocytopenia

Günalp Uzun[1] Karina Althaus[1,2] Stefanie Hammer[1] Yvonne Wanner[1] Stefanie Nowak-Harnau[1] Sigrid Enkel[1] Tamam Bakchoul[1,2]

[1] Centre for Clinical Transfusion Medicine, University Hospital of Tuebingen, Tuebingen, Germany
[2] Institute for Clinical and Experimental Transfusion Medicine, Medical Faculty of Tuebingen, University Hospital of Tuebingen, Tuebingen, Germany

Address for correspondence Tamam Bakchoul, MD, Department of Transfusion Medicine and Coagulation Disorders, Institute for Clinical and Experimental Transfusion Medicine, Medical Faculty of Tuebingen, Otfried-Müller-Straße 4/1, 72076 Tübingen, Germany (e-mail: tamam.bakchoul@med.uni-tuebingen.de).

Hamostaseologie 2023;43:22–27.

## Abstract

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare but serious complication of adenoviral vector-based COVID-19 vaccines. Similar to heparin-induced thrombocytopenia (HIT), antibodies reacting to platelet factor 4 (PF4) are responsible for platelet activation in VITT. The diagnosis of VITT includes the detection of anti-PF4 antibodies. Particle gel immunoassay (PaGIA) is one of the rapid immunoassays that is commonly used in the diagnosis of HIT to detect anti-PF4 antibodies. The aim of this study was to investigate the diagnostic performance of PaGIA in patients suspected of VITT. In this retrospective, single-center study, the correlation between PaGIA, enzyme immunoassay (EIA), and modified heparin-induced platelet aggregation assay (HIPA) in patients with findings suggestive of VITT was investigated. A commercially available PF4 rapid immunoassay (ID PaGIA H/PF4, Bio-Rad-DiaMed GmbH, Switzerland) and an anti-PF4/heparin EIA (ZYMUTEST HIA IgG, Hyphen Biomed) were used according to manufacturer's instructions. Modified HIPA was accepted as the gold standard test. Between March 8 and November 19, 2021, a total of 34 samples from clinically well-characterized patients (14 males, 20 females, mean age: $48.2 \pm 18.2$ years) were analyzed with PaGIA, EIA, and modified HIPA. VITT was diagnosed in 15 patients. Sensitivity and specificity of PaGIA were 54 and 67%, respectively. Anti-PF4/heparin optical density values were not significantly different between PaGIA positive and negative samples ($p = 0.586$). The sensitivity and specificity of EIA, on the other hand, were 87 and 100%, respectively. In conclusion, PaGIA is not reliable in the diagnosis of VITT because of its low sensitivity and specificity.

**Keywords**
- diagnostic test
- platelet factor 4
- rapid immunoassay
- platelet immunology

## Introduction

The global vaccination campaign showed great success in containing the COVID-19 pandemic by reducing the number of severely ill patients as well as the mortality rate.[1] More than 5.2 billion people have already received at least one dose of vaccine, and the global vaccination campaign continues, albeit at a slower pace.[2] Rare cases of unusual thrombosis and thrombocytopenia have been reported after administration of adenoviral vector-based vaccines against

**received**
October 14, 2022
**accepted after revision**
November 22, 2022


Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-1986-1556.
ISSN 0720-9355.

SARS-CoV-2.[3–6] This phenomenon was later termed "vaccine-induced immune thrombotic thrombocytopenia (VITT)." To date, several hundred people with VITT have been reported. Although the mortality rate has decreased dramatically following recognition of the phenomenon and increased awareness among medical personnel, it nonetheless remains at approximately 20%.[7,8] Early therapeutic intervention with intravenous high-dose immunoglobulin and anticoagulation might be live saving in VITT patients.[9–11] For a timely treatment, it is important to make the diagnosis in a short time after clinical suspicion.

Similar to heparin-induced thrombocytopenia (HIT), antibodies reactive to platelet factor 4 (PF4) play a central role in the pathophysiology of VITT.[3,12] PF4, which is released from platelet α granules on activation, is a cationic protein and interacts with negatively charged molecules such as heparin and glycosaminoglycans. Anti-PF4 antibodies induce platelet activation and aggregation by cross-linking the Fcγ receptor IIA on platelets.[3,4] The diagnosis of VITT includes the detection of anti-PF4 antibodies.[13,14] Besides enzyme immunoassays (EIAs) for PF4/heparin antibodies, rapid immunoassays such as particle gel immunoassay (PaGIA), chemiluminescence immunoassay (CLIA), latex-enhanced immunoturbidimetric assay (LIA), and lateral flow assay (LFA) are implemented in diagnostic algorithms for HIT and widely used in clinical practice.[15,16] Compared with EIAs, rapid tests can be performed in every laboratory and delivers a result within a short period of time.

The ID-PaGIA heparin/PF4 antibody test kit was developed to detect antibodies directed against heparin/PF4 complexes and is used as a rule-out test in the diagnosis of HIT.[17] The test suspension includes red-colored, high-density synthetic polymer beads coated with heparin/PF4 complexes. Anti-PF4/heparin antibodies of any class bind antigen-coated beads and initiate agglutination of the particles. After centrifugation, agglutinated beads stay at the top of the gel column and are evaluated as a positive reaction. The test is negative if the colored beads stay at the bottom of the gel after centrifugation.

In clinical studies, PaGIA showed a high negative predictive value of over 95% for HIT.[18,19] Early case series reported false-negative results with rapid tests in VITT patients.[5,20,21] Although recently published expert opinions recommend against the use of rapid immunoassays, their diagnostic performance in VITT has not been investigated systematically earlier.[15] The aim of the current study was to investigate the diagnostic performance of a PaGIA in patients suspected of VITT.

## Methods

### Study Cohort

In this single-center study, we retrospectively reviewed the medical records of patients referred to our laboratory between March 8 and November 19, 2021, for the detection of anti-PF4 antibodies because of clinical suspicion of VITT. Samples were first tested for anti-PF4 antibodies using PaGIA, which was routinely used in our laboratory for the diagnosis of HIT. Regardless of the test result, the samples were then further analyzed with an EIA and a modified functional platelet activation test, heparin-induced platelet activation assay (HIPA). We included patients who received adenovirus-based COVID-19, ChadOx1 nCoV-2 (AstraZeneca-Oxford), or Ad26.COV2-S (Johnson & Johnson/Janssen) vaccine. Patients who developed thrombocytopenia and/or thrombosis after receiving an mRNA-based COVID-19 vaccine were not included in this study. In addition, samples which were not investigated with the rapid test were excluded. More than one sample was available for some patients. We included only the first sample from each patient in this analysis. The diagnosis of VITT was confirmed if the anti-PF4/heparin EIA and modified HIPA were positive.

### Laboratory Measurements

All parameters were measured in the central laboratory of the university Hospital of Tuebingen on an Atellica COAG 360 coagulation platform (Siemens Healthcare Diagnostics, Marburg, Germany) as reported elsewhere.[22] The following reagents from Siemens Healthcare Diagnostics, Marburg, Germany were used: Dade Actin FS for activated partial thromboplastin time (aPTT), INNOVANCE D-dimer assay for D-dimer, and Dade thrombin for fibrinogen.

### Particle Gel Immunoassay

A commercially available PaGIA was used (ID-PaGIA heparin/PF4 antibody test, Bio-Rad-DiaMed GmbH, Switzerland). The assay was performed according to manufacturer's instructions. The test suspension includes red-colored, high-density synthetic polymer beads coated with heparin/PF4 complexes. If the sample includes anti-PF4/heparin antibodies, they bind to these antigen-coated beads and initiate agglutination of the particles. Patient serum (10 µL) was carefully pipetted into the upper chamber of the microtube without touching to gel supernatant. The vortexed particle suspension (50 µL) was pipetted into the same tube. The gel card was incubated 5 minutes at room temperature and centrifuged thereafter for 10 minutes in a special centrifuge. For the validation of the test results, a positive and a negative control were included in each test. The reaction is considered positive if the aggregated beads remain on top of the gel column after centrifugation. The reaction is considered negative if the colored beads reach the bottom of the gel and no aggregation occurs on or within the gel column. The results were read visually by two independent observers.

### Enzyme Immunoassay

We measured IgG antibodies to PF4/heparin using a commercial EIA (ZYMUTEST HIA IgG, Hyphen Biomed, Neuville sur Oise, France) according to manufacturer's instructions. Two hundred microliters of diluted patient sample (1:100) and 50 µL of platelet lysate containing PF4 were added to empty wells of a microtiter plate coated with protamine sulfate and unfractionated heparin. The plate was incubated at room temperature for 1 hour. After a wash step to remove the unbound antibody, the plate was incubated for 1 hour at room temperature after adding horseradish peroxidase

 

coupled to a polyclonal antibody (200 µL) to the wells. During the second wash step, unbound immunoconjugate was removed. Immediately following washing, 200 µL of tetramethylbenzidine substrate was added to the wells. To stop the color development, 50 µL of 0.45 M sulfuric acid was added. The optical density (OD) was measured at 450 nm using a microplate reader. An OD of 0.5 or greater was considered positive according to the manufacturer's instructions.

### Modified Heparin-Induced Platelet Aggregation Assay

The ability of sera to activate platelets was tested using a modified HIPA, as previously described.[3] In brief, serum was tested with washed platelets from four different healthy donors in the absence (buffer alone) or in the presence of heparin at different concentration or with PF4. For PF4 test, washed platelets were preincubated with PF4 for 10 minutes at room temperature; 20 µL of patient serum and 75 µL of washed platelets ($300 \times 10^3$ platelets/µL) were placed in microtiter wells. Final concentration in the wells was 0.2 IU/mL heparin, 100 IU/mL heparin, or 10 µg/mL PF4. Microtiter wells containing spherical stir bars were stirred at ~500 rpm. Wells were examined optically at 5-minute interval for loss of turbidity. A serum was considered reactive (positive) if a shift from turbidity to transparency occurred within 30 minutes in at least two platelet suspensions. Observation time was 45 minutes. Each test included a diluted serum from a patient with HIT as a weak positive control, collagen (5 µg/mL) as strong positive control, and a serum from a healthy donor as a negative control. Before testing, all patient sera were heat-inactivated in a water bath at 56 °C for 30 minutes.

### Statistics

Statistical analyses were performed using Prism, version 9 (GraphPad, La Jolla, the United States). Data were presented as median (min–max) or *n* (%). The Kolmogorov–Smirnov test was used to assess sample distributions. The *t*-test or Mann–Whitney's *U*-test was used for the comparison of two independent samples. We calculated the receiver operating characteristic (ROC) curve and the respective areas under the ROC curve (AUROC). Sensitivity, specificity, and the positive and negative predictive values were determined. A *p*-value $<0.05$ was assumed to represent statistical significance.

## Results

### Study Cohort

Thirty-four patients (20 females, 14 males) were included into the analyses. Median age of the patients was 48 years (range: 20–80). Median duration between vaccination and the laboratory investigation was 12 days (range: 4–60). Median platelet count at presentation was $79 \times 10^3$/µL (range: 10–438). Seven (20%) patients had only thrombocytopenia, 7 (20%) patients had a thrombotic event after vaccination, 14 (41%) patients had both thrombocytopenia and thrombosis, and 6 (19%) patients had neither thrombocytopenia nor thrombose. Thirty-three patients received ChadOx1 nCov19 and 1 patient received Ad26.COV2-S. Four patients developed symptoms after second vaccination with ChadOx1 nCov19. VITT was confirmed with modified HIPA in 15 patients. Clinical and demographic characteristics of patients with and without VITT are presented in ►Table 1.

### Particle Gel Immunoassay

A positive reaction was seen in 15 samples and a negative reaction in 18 samples. In three samples, a doubtful reaction was seen. Sensitivity and specificity of PaGIA were calculated using modified HIPA as gold standard test (►Table 2). Doubtful results in PaGIA were excluded from this analysis. PaGIA had a moderate sensitivity (54%) and specificity (67%) for detection of platelet activating anti-PF4 antibodies. Anti-PF4/heparin OD values were not significantly different between PaGIA-positive and -negative samples (OD 0.20 [0.09–3.69] vs. OD 0.49 [0.08–3.48], $p = 0.586$, ►Fig. 1A). Overall agreement between PaGIA and EIA was 54% and between PaGIA and HIPA was 61% (►Table 3). We also investigated

**Table 1** Clinical and demographic characteristics of patients with suspected VITT

| | Non-VITT | VITT | *p* |
|---|---|---|---|
| *n* | 19 | 15 | |
| Age, years | 63 (20–80) | 39 (20–62) | 0.004 |
| Gender (M/F) | 9/10 | 5/10 | 0.410 |
| Platelet count, $10^3$/µL | 194 (19–438) | 52 (18–79) | <0.001 |
| D-dimer, µg/mL FEU | 1.55 (0.2–9.0) | 33 (10–73) | <0.001 |
| Fibrinogen, mg/dL | 343 (202–480) | 189 (50–416) | 0.049 |
| aPTT, seconds | 22 (18–32) | 23 (21–43) | 0.172 |
| PF4-EIA, ODs | 0.14 (0.08–0.27) | 2.91 (0.49–3.69) | <0.001 |
| Thrombocytopenia, *n* (%) | 11 (57%) | 13 (100%)[a] | <0.001 |
| Thrombosis, *n* (%) | 7 (36%) | 14 (93%) | <0.001 |

Abbreviations: aPTT, activated partial thromboplastin time; EIA, enzyme immunoassay; OD, optical density; PF4, platelet factor-4; VITT, vaccine-induced immune thrombotic thrombocytopenia.
Note: Data are presented as median (range) or *n* (%).
[a]Platelet count was not available in two patients with VITT.

 

**Table 2** Diagnostic performance of PaGIA and PF4/heparin EIA for the diagnosis of VITT

| | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|
| PaGIA | 54 | 67 | 54 | 67 |
| EIA | 87 | 100 | 100 | 90 |
| PaGIA(+) and thrombocytopenia ($<150 \times 10^3/\mu L$) | 46 | 83 | 67 | 68 |
| PaGIA(+) or thrombocytopenia ($<150 \times 10^3/\mu L$) | 93 | 42 | 56 | 89 |
| Thrombocytopenia ($<150 \times 10^3/\mu L$) | 100 | 58 | 62 | 100 |

Abbreviations: EIA, enzyme immunoassay; PaGIA, particle gel immunoassay; PF4, platelet factor-4; VITT, vaccine-induced immune thrombotic thrombocytopenia.

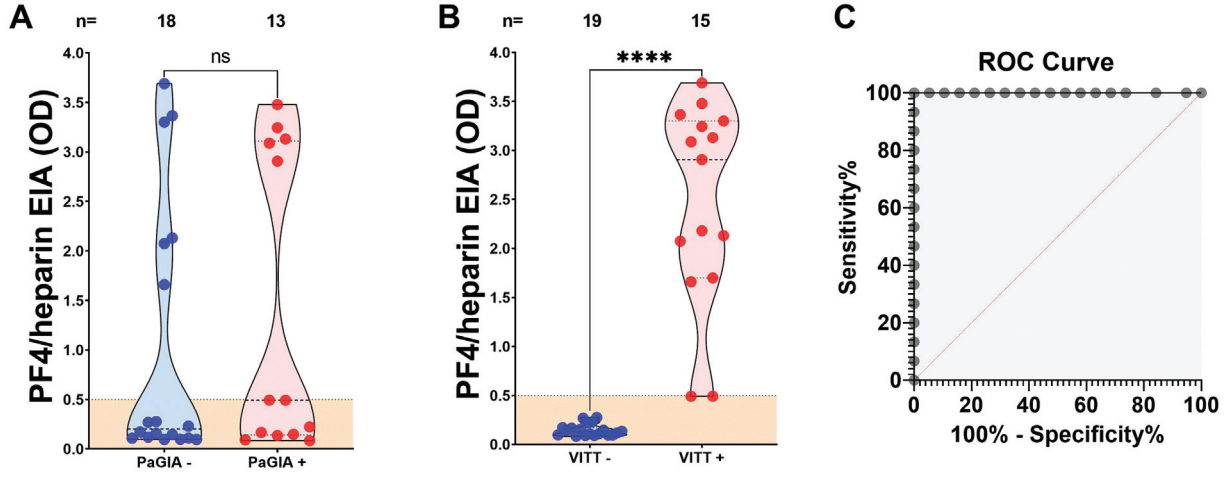


**Fig. 1** Anti–platelet factor 4 (PF4)/heparin antibody levels measured by enzyme immunoassay (EIA). Anti-PF4/heparin optical density (OD) values were compared in patients according to particle gel immunoassay (PaGIA) result (**A**) and vaccine-induced immune thrombotic thrombocytopenia (VITT) diagnosis (**B**). Receiver operating characteristic (ROC) curve of PF4/heparin EIA for the diagnosis of VITT (**C**). The optimal cut-off was OD 0.384 with a sensitivity of 100% (79–100%) and a specificity of 100% (83.2–100%). Area under the curve was 1.0 with a $p < 0.001$. ns = not significant. $^{****}p < 0.001$.

**Table 3** Comparison of PaGIA, PF4/heparin EIA, and modified HIPA

| | Neg/Neg | Pos/Pos | Neg/Pos | Pos/Neg | Overall agreement |
|---|---|---|---|---|---|
| PaGIA/EIA | 12 | 5 | 6 | 8 | 17 (54%) |
| PaGIA/HIPA | 12 | 7 | 6 | 6 | 19 (61%) |
| mHIPA/EIA | 13 | 19 | 2 | 0 | 32 (94%) |

Abbreviations: EIA, enzyme immunoassay; mHIPA, modified heparin-induced platelet activation assay; PaGIA, particle gel immunoassay; PF4, platelet factor-4; VITT, vaccine-induced immune thrombotic thrombocytopenia.

whether the combination of PaGIA with other clinical characteristics of the disease would improve the diagnostic performance of PaGIA (►Table 2). However, performance of combination of PaGIA with thrombocytopenia was lower than that of thrombocytopenia alone for the diagnosis of VITT (►Table 2).

### Enzyme Immunoassay

PF4/heparin EIA was positive in 13 samples. Anti-PF4/heparin OD values were significantly higher in VITT patients (►Table 1, ►Fig. 1B). Sensitivity (87%) and specificity (100%) of EIA were markedly higher compared with PaGIA (►Table 2). Overall agreement between EIA and HIPA was 94% (►Table 3). The calculated optimal cut-off was OD 0.384 with a sensitivity of 100% (79–100%) and a specificity of 100% (83.2–100%). Area under the curve was 1.0 with a *p*-value <0.001 (►Fig. 1C).

## Discussion

VITT is a rare but serious prothrombotic condition caused by anti-PF4 antibodies after administration of an adenoviral vector vaccine for SARS-CoV-2.[3,23] The prompt diagnosis is of paramount importance in the management of patients with

 

VITT. In this study, we investigated the performance of PaGIA for the diagnosis of VITT. We found that PaGIA has a low sensitivity and specificity for the detection of anti-PF4 antibodies.

Several studies investigated the performance of rapid immunoassays in patients with VITT earlier. Platton et al investigated the ability of commercially available laboratory assays to identify anti-PF4 antibodies.[24] In general, rapid immunoassays performed significantly worse than EIAs. Among rapid immunoassays, however, PaGIA had the highest sensitivity (45%) but the lowest specificity (66.7%). Reilly-Stitt et al performed an international interlaboratory comparison exercise to test the performance of regular HIT assays for suspected VITT samples.[25] Participating centers have received five positive and one negative serum samples. PaGIA was one of the most commonly used rapid immunoassays among participating centers (72 of 385 participating centers). The sensitivity of PaGIA calculated for each positive sample ranged between 7 and 69% and the specificity was 99% for the negative sample. On the other hand, the sensitivity of CLIA and LIA was 0 to 2% and their specificity was 85 to 98%.[25]

A recent interlaboratory comparison study using 12 samples showed a sensitivity of 25% for PaGIA.[20] Similar to previous reports, the diagnostic performance of PaGIA was better than other rapid immunoassays (0% for CLIA and 8% for LFA). On the other hand, the sensitivity of EIAs was 100 and 91.6%. They concluded that rapid immunoassays are useless alone as an initial screening test for suspected VITT cases. However, they also suggested a combination of negative CLIA and a positive sensitive PF4 EIA for VITT diagnosis in the absence of confirmatory functional assays.[20]

The difference between EIAs and rapid immunoassays in the detection of PF4 antibodies in HIT and VITT is not completely understood. A possible explanation is that HIT and VITT antibodies target different epitopes on PF4.[26] Although binding of VITT antibodies is restricted to heparin-binding site on PF4, HIT antibodies target antigens outside of heparin-binding site.[26] We showed that heparin at therapeutic concentration can dissociate VITT antibodies from PF4 ex vivo.[27] It has been suggested that EIA microtiter plates can bind free, unbound PF4 in addition to PF4/heparin complexes, and that this interaction could expose antigens recognized by VITT antibodies by altering the conformation of the protein.[15]

This study has several limitations. First, we did not test the samples with other commonly used rapid immunoassays. However, previous studies have shown that PaGIA performs significantly better than CLIA, LIA, and LFA. Second, because of the retrospective nature of the study, we could only include patients who were tested with PaGIA at initial presentation. This could lead to selection bias. In addition, the sample size of the study was small. Prospective multicenter studies are needed to overcome these limitations.

Despite the recent decline in the use of adenovirus-based vaccines against SARS-CoV-2, they continue to be used especially in developing countries.[28,29] Considering that PF4-EIA is not widely available as first-line diagnostic assay and only a handful of centers perform functional testing, the diagnosis of VITT is a challenge for clinicians. Clinical suspicion is important in determining which samples should be subjected to these extensive tests. Due to the limited sensitivity, negative results of rapid tests should be interpreted with caution and in cases where clinical suspicion is high, cotreatment with intravenous immunoglobulin and anticoagulation should be initiated without waiting for the results of immunologic or functional testing.

In conclusion, PaGIA is not a reliable test for the diagnosis of VITT because of its low sensitivity and specificity. There is still a need for a rapid immunoassay that can be used in the diagnostic workup of patients with suspected VITT when enzymatic immunoassays are not readily available. Further studies are needed to understand the poor diagnostic performance of rapid immunoassays in VITT and to develop new diagnostic tests.

## Authors' Contributions

G.U., K.A., and T.B. designed the study. G.U., K.A., S.H., Y.W., S.N-H., and S.E. collected the clinical data and analyzed the test results. G.U., K.A., and T.B. performed the statistical analyses, interpreted the results, and wrote the manuscript. All authors read and approved the manuscript.

## Funding/Acknowledgments

This work was supported by grants from the German Research Foundation and from the Herzstiftung to T.B. (BA5158/4 and TSG-Study), by special funds from the state of Baden-Württemberg for coagulation research and blood donation service of German Red Cross to T.B. This study was partially presented as a poster contribution at the 17th Annual Meeting of the German Society for Clinical Chemistry and Laboratory [17. Jahrestagung der Deutschen Gesellschaft für Klinische Chemie und Laboratoriumsmedizin], October 13–14, 2022, in Mannheim, Germany. We thank Barbara Gubitz for her help during patient chart review.

## Conflicts of Interest

T.B. has received research funding from CoaChrom Diagnostica GmbH, DFG, Robert Bosch GmbH, Stiftung Transfusionsmedizin und Immunhämatologie e.V.: Ergomed, DRK Blutspendedienst, Deutsche Herzstiftung, Ministerium fuer Wissenschaft, Forschung und Kunst Baden-Wuerttemberg; has received lecture honoraria from Aspen Germany GmbH, Bayer Vital GmbH, Bristol-Myers Squibb GmbH & Co., Doctrina Med AG, Meet The Experts Academy UG, Schoechl Medical Education GmbH, Stago GmbH, Mitsubishi Tanabe Pharma GmbH, Novo Nordisk Pharma GmbH, Leo Pharma GmbH, Swedish Orphan Biovitrum GmbH; has provided consulting services to Terumo; has provided expert witness testimony relating to heparin-induced thrombocytopenia (HIT) and non-HIT thrombocytopenic and coagulopathic disorders. All of these are outside the current work. Other authors declare no competing financial interests.

 

## References


1 Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 2022;399(10328):924–944
2 World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Published December 15, 2021. Accessed December 15, 2021 at: https://covid19.who.int/
3 Althaus K, Möller P, Uzun G, et al. Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia. Haematologica 2021;106(08):2170–2179
4 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384(22):2092–2101
5 Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021; 384(23):2202–2211
6 Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384(22):2124–2130
7 van de Munckhof A, Krzywicka K, Aguiar de Sousa D, et al. Declining mortality of cerebral venous sinus thrombosis with thrombocytopenia after SARS-CoV-2 vaccination. Eur J Neurol 2022;29(01):339–344
8 Pavord S, Scully M, Hunt BJ, et al. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. N Engl J Med 2021;385(18):1680–1689
9 Bourguignon A, Arnold DM, Warkentin TE, et al. Adjunct immune globulin for vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med 2021;385(08):720–728
10 Lentz SR. Cooling down VITT with IVIG. Blood 2021;138(11): 921–922
11 Uzun G, Althaus K, Singh A, et al. The use of IV immunoglobulin in the treatment of vaccine-induced immune thrombotic thrombocytopenia. Blood 2021;138(11):992–996
12 Marini I, Uzun G, Jamal K, Bakchoul T. Treatment of drug-induced immune thrombocytopenias. Haematologica 2022;107(06): 1264–1277
13 Nazy I, Sachs UJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost 2021;19(06):1585–1588
14 Oldenburg J, Klamroth R, Langer F, et al. Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH. Hamostaseologie 2021;41(03):184–189
15 Warkentin TE, Greinacher A. Laboratory testing for VITT antibodies. Semin Hematol 2022;59(02):80–88
16 Favaloro EJ. Laboratory testing for suspected COVID-19 vaccine-induced (immune) thrombotic thrombocytopenia. Int J Lab Hematol 2021;43(04):559–570
17 Meyer O, Salama A, Pittet N, Schwind P. Rapid detection of heparin-induced platelet antibodies with particle gel immunoassay (ID-HPF4). Lancet 1999;354(9189):1525–1526
18 Pouplard C, Gueret P, Fouassier M, et al. Prospective evaluation of the '4Ts' score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia. J Thromb Haemost 2007;5(07):1373–1379
19 Schallmoser K, Drexler C, Rohde E, et al. The particle gel immunoassay as a rapid test to rule out heparin-induced thrombocytopenia? J Thorac Cardiovasc Surg 2009;137(03):781–783
20 Sachs UJ, Cooper N, Czwalinna A, et al. PF4-dependent immunoassays in patients with vaccine-induced immune thrombotic thrombocytopenia: results of an interlaboratory comparison. Thromb Haemost 2021;121(12):1622–1627
21 Tiede A, Sachs UJ, Czwalinna A, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccination. Blood 2021;138 (04):350–353
22 Hörber S, Lehmann R, Fritsche L, et al. Lifestyle intervention improves prothrombotic coagulation profile in individuals at high risk for type 2 diabetes. J Clin Endocrinol Metab 2021;106 (08):e3198–e3207
23 Greinacher A, Langer F, Makris M, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): update on diagnosis and management considering different resources. J Thromb Haemost 2022;20(01):149–156
24 Platton S, Bartlett A, MacCallum P, et al. Evaluation of laboratory assays for anti-platelet factor 4 antibodies after ChAdOx1 nCOV-19 vaccination. J Thromb Haemost 2021;19(08):2007–2013
25 Reilly-Stitt C, Jennings I, Kitchen S, et al. Anti-PF4 testing for vaccine-induced immune thrombocytopenia and thrombosis (VITT): results from a NEQAS, ECAT and SSC collaborative exercise in 385 centers worldwide. J Thromb Haemost 2022;20(08): 1875–1879
26 Huynh A, Kelton JG, Arnold DM, Daka M, Nazy I. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. Nature 2021;596(7873):565–569
27 Singh A, Toma F, Uzun G, et al. The interaction between anti-PF4 antibodies and anticoagulants in vaccine-induced thrombotic thrombocytopenia. Blood 2022;139(23):3430–3438
28 Fortner R. AstraZeneca's COVID-19 (mis)adventure and the future of vaccine equity. BMJ 2022;379:o2592
29 Factbox: Vaccines delivered under COVAX sharing scheme for poorer countries. Accessed November 19, 2022 at:https://www.reuters.com/business/healthcare-pharmaceuticals/vaccines-delivered-under-covax-sharing-scheme-poorer-countries-2022-01-03/