A systematic review of vaccine-induced immune thrombosis and thrombocytopenia triggered by non-adenoviral vector vaccination: ultra-rare or non-existent?

Vaccine-induced immune thrombosis and thrombocytopenia (VITT) is classically associated with adenoviral vector vaccination.[1] VITT is part of a wider group of diseases known as PF4-associated immunothrombosis with thrombocytopenia (PITT), which includes heparin-induced thrombocytopenia (HIT). PITT can also manifest in individuals without either proximate vaccine or heparin exposure, most notably following adenoviral infection.[2] Although we are aware of reports of VITT following non-adenoviral vector vaccination, it is unclear whether those attributed to mRNA-based vaccination truly represent VITT, or whether they reflect the background incidence of spontaneous syndromes coupled with heightened awareness.

This systematic review aimed to identify and collate cases of PITT that are related to non-adenoviral vector vaccines using wide search terms, then systematically assess the likelihood of VITT using recognized criteria. Of 42 included cases, only 5 met criteria for "definite" VITT; however, none were wholly convincing. VITT triggered by non-adenoviral vector vaccination, therefore, appears very rare or possibly non-existent.

A literature search was completed on 11th October 2025 using the terms outlined in *Online Supplementary Table S1*. We also searched abstracts from major hematology meetings and reference lists. The searches were restricted to studies published from 1st January 2008 onwards as this is the year of the first report of a spontaneous HIT-like syndrome.[3]

Search results were uploaded to Rayyan (Cambridge, MA, USA), an artificial intelligence (AI)-powered systematic review management platform. After automated removal of duplicate and clearly irrelevant records, titles, abstracts, and full texts were screened by 2 reviewers (Figure 1). The inclusion criteria were: 1) clinical case reports, cohort studies, or trials reporting clinical information about patient presentations; 2) studies reporting presentation with

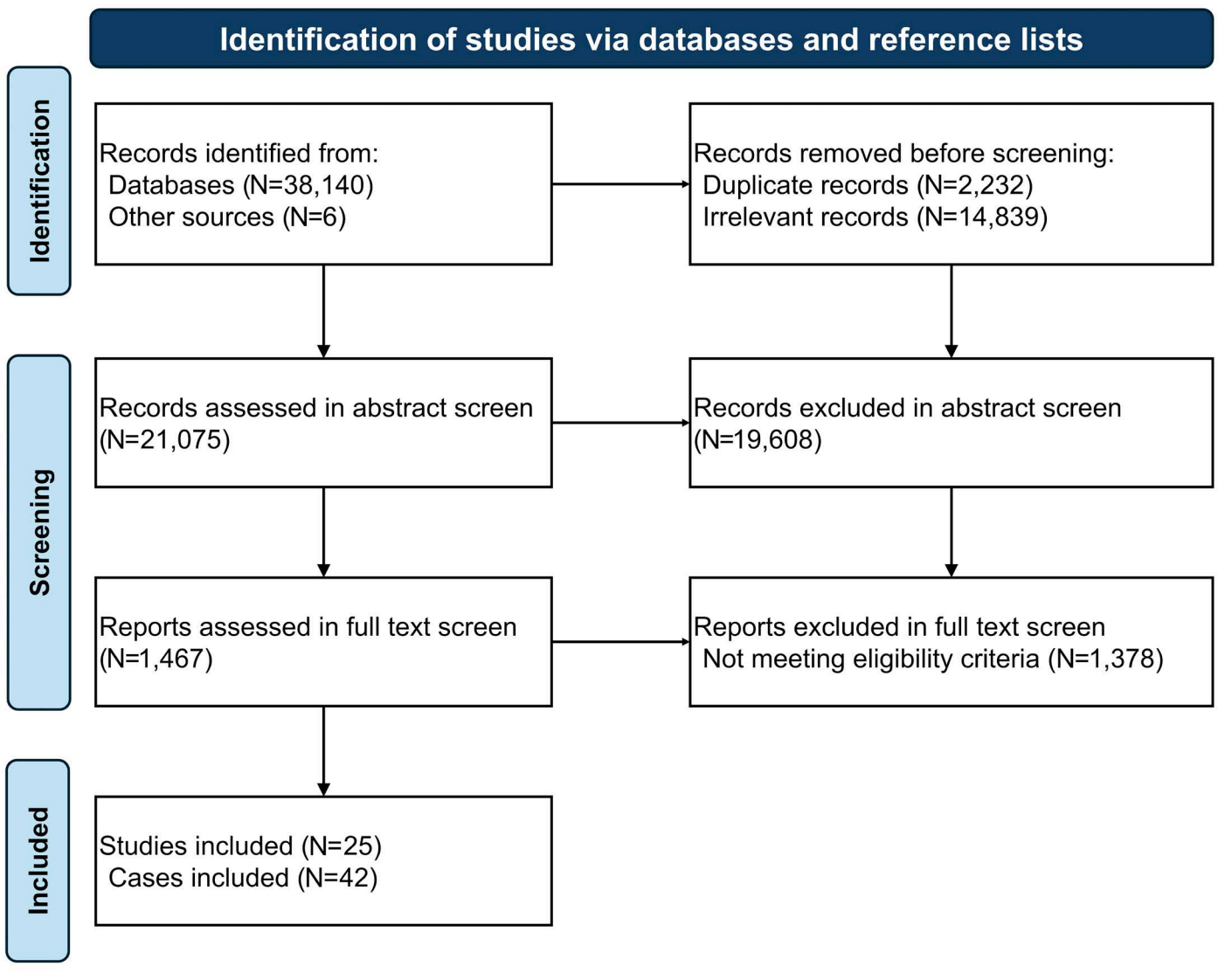


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA): flow diagram.

any thrombotic event with or without thrombocytopenia with a positive antibody test for anti-PF4 antibodies or a positive platelet activation assay temporally related to vaccination; 3) studies reporting thrombocytopenia without thrombosis with a positive antibody test for anti-PF4 antibodies or a positive platelet activation assay temporally related to vaccination. To keep inclusion criteria wide, we did not define the length of time for temporal relation to vaccination and only required that the authors made this link.

Demographic and clinical data were manually extracted from records and cases that met inclusion criteria were graded as either "definite", "probable", or "possible" according to three internationally accepted systems (summarized in *Online Supplementary Table S2*).[4,5] Ethical approval was not required for this systematic review, as it involved analysis of previously published case reports and did not include the collection of new data or direct patient involvement.

The search identified 38,146 studies. After screening, 25 studies consisting of 42 individual patient cases were included in this review (Figure 1). The demographics, presenting features, and investigation findings of the cases are summarized in Table 1. The clinical history, laboratory investigations, and fulfilment of diagnostic criteria for individual cases are shown in *Online Supplementary Table S3*. According to the Brighton TTS case definition,[5] 38/42 (90.5%) were considered "definite" cases. The Brighton definition is intentionally broad and not specific to VITT, encompassing any presentation of thrombosis with thrombocytopenia regardless of the underlying mechanism. This inclusivity is purposeful, as it allows capture of potential VITT cases even where confirmatory laboratory testing (e.g., anti-PF4 antibodies or functional assays) is unavailable or incomplete, often due to resource constraints.

Four cases met our inclusion criteria but not met the TTS case definition. According to the Brighton VITT Classification and the UK Expert Consensus Criteria, only 5 (11.9%) cases could be classified as a "definite" case of VITT. According to the Brighton VITT Criteria, 6 (14.6%) were classified as "probable", 21 (51.2%) as "possible", and 9 (22.0%) as "not meeting criteria". According to the UK Expert Consensus Criteria, 9 (22.0%) were classified as "probable", 19 (46.3%) "possible", and 6 (14.6%) as "not meeting criteria".

Johansen *et al*. reported the case of a 25-year-old woman presenting ten days after Gardasil HPV-9 vaccination, with internal iliac vein thrombosis and pulmonary embolism (PE), severe thrombocytopenia, markedly elevated D-dimer, hypofibrinogenemia, and a strongly positive anti-PF4 ELISA.[6] However, a HemosIL AcuStar HIT-IgG assay was moderately positive, which is generally not the case in VITT and suggests that this case is more HIT-like. Sangli *et al*. reported a 65-year-old man who developed DVT, PE, and CVST ten days after a second Moderna mRNA vaccine dose.[7] This patient had a strongly positive anti-PF4 ELISA and serotonin release assay, findings more consistent with HIT than VITT. Su *et al*. described a 70-year-old man presenting with stroke and thrombocytopenia seven days after a first Moderna dose, with hypofibrinogenemia, very high D-dimer, but only weakly positive anti-PF4 ELISA.[8] Two further reports described younger patients developing thrombocytopenia and venous thrombosis 7-21 days after a third Pfizer-BioNTech dose, with very high D-dimer, normal fibrinogen, weak anti-PF4 ELISA positivity, and negative functional testing, suggesting possible milder or alternative VITT-like phenotypes.[9,10] Thus, of the 5 cases that are classified as "definite", our clinical judgement is that none are wholly consistent with VITT.

Among reported cases, several are highly consistent with VITT despite failing to meet definite criteria on technical grounds. Chen *et al*. reported a 42-year-old woman presenting with CVST, profound thrombocytopenia, markedly elevated D-dimer, and a strongly positive anti-PF4 ELISA.[11] The timing of presentation at 32 days downgrades this case from "definite" to "probable" but this was the only case where a VITT-like pattern of platelet activation was documented. Hosseinzadeh *et al*. reported an 85-year-old man who developed splenic vein thrombosis and severe thrombocytopenia five days after a first dose of inactivated Sinopharm BBIBP-CoV vaccine.[12] Anti-PF4 ELISA was strongly positive, and the clinical presentation was otherwise entirely consistent with VITT, although no functional testing was performed. The case was classified as "probable" rather than "definite" solely because the reported D-dimer (>3,200 ng/mL) did not clearly exceed the Brighton threshold of 4,000 ng/mL. Sung *et al*. and Tejaswi *et al*. reported cases of patients who developed venous thrombosis with thrombocytopenia and very high D-dimer levels four and 30 days post-vaccination, respectively.[13,14] However, anti-PF4 antibody testing was not performed.

Esefeld *et al*. recently published a case series reporting the clinical and laboratory characteristics of patients presenting with a VITT-like syndrome after mRNA-based COVID-19 vaccination but in whom anti-PF4 antibodies were not found.[15] However, on further work-up, they found that serum from 12 patients still activated platelets through FcγRIIA (as is the case in HIT and VITT) and discovered that 7 of 12 patients had anti-histone antibodies. Similarly, other reports have described patients with features typical of VITT but with negative anti-PF4 antibody testing (*Online Supplementary Table S3*).

In this systematic review, we used broad search terms to identify reported cases of possible VITT following non-adenoviral vector vaccination. This approach aimed to capture cases not explicitly labeled as VITT by the original authors. We identified 25 studies describing 42 unique cases, allowing critical appraisal of the existence and biological plausibility of VITT in this setting.

A notable feature of this cohort was that fewer than half of cases occurred following first exposure to the implicated

Table 1. Baseline characteristics, laboratory findings, diagnostic classification, and outcomes of the study cohort.

Variable	N=42	Missing, N (%)
Median age, years (IQR)	58.0 (37-71)	0
Female sex, N (%)	16 (38.1)	0
Possible trigger, N (%)		0
Pfizer-BioNTech mRNA COVID-19 vaccine	26 (61.9)	
First dose	12 (46.2)	
Subsequent dose	14 (53.8)	
Moderna mRNA COVID-19 vaccine	10 (23.8)	
First dose	3 (30.0)	
Subsequent dose	7 (70.0)	
Sinopharm COVID-19 vaccine	4 (9.5)	
First dose	2 (50)	
Subsequent dose	1 (25)	
Unknown dose type	1 (25)	
Covacin COVID-19 vaccine	1 (2.4)	
Unknown dose type	1 (100)	
Gardasil 9 HPV vaccine	1 (2.4)	
First dose	1(100)	
Time from trigger to presentation, days, median (IQR)	7 (4-20)	2 (4.8)
D-dimer, ng/mL, median (IQR)	18,150 (7,554-29,275)	18 (42.9)
Fibrinogen, g/L, median (IQR)	3.15 (1.71-4.31)	28 (66.7)
Platelet nadir, x10^9/L, median (IQR)	57 (17-112)	1 (2.4) (reported as normal)
Testing, N (%)		
Anti-PF4 antibody testing, N (%)	34 (81.0)	
ELISA	32 (76.2)	
OD: <0.40‡	1 (3.1)	
OD: 0.40-0.99	7 (21.9)	
OD: 1.00-1.99	0	
OD: ≥2.00	4 (12.5)	
'Positive', otherwise undefined	1 (3.1)	
'Negative', otherwise undefined	19 (59.4)	
CLIA	2 (4.8)	-
<1 U/mL	1 (50.0)	
1-5 U/mL	1 (50.0)	
EIA	1 (2.4)	
OD: 1.00-1.99	1 (100.0)*	
OD: ≥2.0	1 (100.0)*	
Gel agglutination assay	1 (2.4)	
Negative	1 (100.0)	
PF4 antibody test, not defined	2 (4.8)	
Negative	2 (100.0)	
Functional platelet activation testing, N (%)	23 (54.7)	
HIPA - WP	1 (2.4)	
Negative	1 (100.0)	
SRA - WP	1 (2.4)	
Positive - 51% release with low concentration heparin, inhibited by high concentration heparin	1 (100.0)	
LTA† - PRP	1 (2.4)	
Positive - 39% aggregation in presence of low concentration heparin	1 (100.0)	-
Flow cytometry - WP	19 (45.2)	
Negative	6 (31.6)	
Positive - defined as mean + 3 SD of negative control for phosphatidylserine exposure	12 (63.2)	
Positive - 66% P-selectin expression	1 (5.2)	
Functional platelet activation assay, not defined	1 (2.4)	
Negative	1 (100.0)	

Continued on following page.

Variable	N=42	Missing, N (%)
Thrombosis, N (%)	40 (95.2)	
Site of thrombosis		
Deep vein thrombosis	18 (42.9)	
Pulmonary embolism	17 (40.5)	
Cerebral venous sinus thrombosis	8 (19.0)	
Ischemic stroke	6 (14.3)	
Portal vein thrombosis	2 (4.8)	
Superior mesenteric vein thrombosis	2 (4.8)	
Splanchnic vein thrombosis (otherwise undefined)	2 (4.8)	-
Splenic vein thrombosis	1 (2.4)	
Axillary vein thrombosis	1 (2.4)	
Internal iliac vein thrombosis	1 (2.4)	
Budd-Chiari syndrome	1 (2.4)	
Splenic infarction	1 (2.4)	
Disseminated intravascular coagulation	1 (2.4)	
Acral necrosis	1 (2.4)	
None	1 (2.4)	
VITT diagnostic classification, N (%)		
Brighton TTS		
Definite	38 (90.5)	
Probable	0 (0.0)	
Possible	0 (0.0)	
Did not meet criteria	4 (9.5)	
Brighton VITT		
Definite	5 (11.9)	
Probable	6 (14.3)	-
Possible	22 (52.4)	
Did not meet criteria	9 (21.4)	
UK Expert		
Definite	5 (11.9)	
Probable	11 (26.2)	
Possible	20 (47.6)	
Did not meet criteria	6 (14.3)	
Fatal outcome, N, (%)	4 (16.0)	17 (40.5)

*Platelet count at presentation was assumed to be platelet nadir if that is the only platelet count provided. †Light transmission aggregometry (LTA) reported as heparin-induced platelet activation (HIPA). ‡Normal range reported as <0.3. #Assay results are from the same case. CLIA: chemiluminescent immunoassay; COVID-19: coronavirus disease 2019; EIA: enzyme immunoassay; ELISA: enzyme-linked immunosorbent assay; HPV: human papillomavirus; IQR: interquartile range; OD: optical density; PF4: platelet factor 4; PRP: platelet rich plasma; PS: phosphatidylserine; SD: standard deviation; SRA: serotonin release assay; TTS: thrombosis with thrombocytopenia syndrome; VITT: vaccine-induced immune thrombotic thrombocytopenia; WP: washed platelets.

vaccine, a pattern that is highly inconsistent with classical adenoviral vector-associated VITT, where first exposure overwhelmingly predominates. As expected, thrombosis was reported in nearly all cases but the relatively low number of cases with CVST is again suggestive that this cohort is dissimilar to classical VITT.

Although 5 cases fulfilled formal criteria for “definite” VITT,[6-10] none were wholly convincing. In contrast, in our clinical judgement, the cases reported by Chen *et al*. and Hosseinzadeh *et al*., both classified as “probable”, represent the most convincing examples of VITT in this cohort. However, the lack of functional testing in both limits our conclusions about these cases. This is indicative of the inconsistent diagnostic evaluation across cases. Testing for anti-PF4 antibodies was performed in most cases but functional platelet activation assays were performed in only a small minority. Several cases demonstrated weak anti-PF4 ELISA positivity or functional assay patterns more consistent with HIT. This raises the possibility of coincident HIT or other causes of thrombosis with thrombocytopenia occurring alongside low-level anti-PF4 antibodies, which are known to be part of the physiological immune response. The findings of Esefeld *et al*., suggesting alternative antigenic targets such as histones,[15] are also consistent with ELISA-negative cases that were reported at the outset of VITT.[1]

This study is limited by reliance on published case reports and is likely to underestimate true incidence. Cases may have been missed if mild, rapidly fatal, unrecognized, or not reported. Most reports originated from high-income settings with greater awareness and access to specialized testing. Incomplete reporting of platelet counts, coagulation parameters, anti-PF4 testing, and functional assays limited definitive classification. Conversely, several reports describing VITT were excluded due to absence of thrombocytopenia or immunological testing, highlighting variability in application of diagnostic criteria during the pandemic.

Given the billions of non-adenoviral vector vaccine doses administered worldwide, the small number of biologically plausible cases identified here suggests that VITT in this context is exceedingly rare. A proportion of reported cases likely reflect misclassification, spontaneous PITT, or HIT-like syndromes coinciding with vaccination rather than a distinct vaccine-specific phenomenon. Corroborating this conclusion, a recent study that systematically evaluated all cases of thrombosis reported in an Italian registry after vaccination for COVID-19 found no cases of VITT among 210 recipients of non-adenoviral vector vaccination.[16] PF4-associated immunothrombosis with thrombocytopenia encompasses a wide spectrum of presentations and should, therefore, be suspected in patients with thrombosis and thrombocytopenia irrespective of vaccine exposure. Access to appropriate testing by anti-PF4 ELISA and, importantly, functional testing is key to rapid diagnosis and management.

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Contributions

YK and AG designed the study, extracted and analyzed data, and wrote the manuscript; SJM and PLRN reviewed and edited the manuscript, and provided clinical and diagnostic context; RJB conceived and designed the study, and wrote the manuscript.

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Data-sharing statement

All relevant data are presented in this manuscript and in the *Online Supplementary Appendix.*

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