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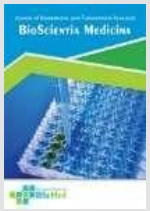

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Ocular Vascular Occlusion Following COVID-19 and Travel Vaccinations: A Systematic Review and Exploration of Immuno-Thrombotic Mechanisms

Ni Nyoman Yuniasih[1*], I Made Ary Wirawan[2], I Gusti Ayu Made Juliari[1], Ida Ayu Ary Pramita[1]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

[2]Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

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***Corresponding author:**
Ni Nyoman Yuniasih

E-mail address:
Nyomanyuniasih@gmail.com

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A B S T R A C T

Background: Ocular vascular occlusion is a rare, vision-threatening emergency. While typically associated with systemic vascular comorbidities, reports have emerged suggesting a temporal link to various vaccinations. This review aims to synthesize the evidence on ocular vascular occlusion following both COVID-19 and non-COVID travel vaccinations to characterize its clinical spectrum and explore shared pathophysiological underpinnings. **Methods:** A systematic search adhering to PRISMA 2020 guidelines was conducted in PubMed, Scopus, Cochrane Library, and ProQuest for studies published from January 1st, 2013, to August 1st, 2024. All study designs reporting ocular vascular occlusion temporally associated with COVID-19 or travel immunizations were included. Data on demographics, vaccine type, clinical presentation, and outcomes were extracted. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies and the Joanna Briggs Institute (JBI) checklist for case reports. **Results:** From an initial 1,348 records, 12 studies met the inclusion criteria, encompassing case reports, series, and large database analyses. These studies described ocular vascular occlusion in individuals aged 15 to 86 years. A significant temporal clustering was observed, with the majority of individual cases occurring within seven days post-vaccination. Central retinal vein occlusion (CRVO) was the most reported subtype. A large retrospective cohort study reported a more than two-fold increased hazard for retinal occlusion post-vaccination compared to unvaccinated cohorts (HR 2.19, 95% CI 1.85-2.59, p<0.001). Both mRNA and adenoviral vector COVID-19 vaccines, as well as various travel vaccines including Zostavax, Yellow Fever, and Meningococcal B, were implicated. **Conclusion:** This review characterizes a consistent temporal association between a diverse range of vaccines and subsequent ocular vascular occlusion, suggesting it is a rare but potential adverse event. The clustering of onset times and involvement of different vaccine platforms point towards a common underlying immuno-thrombotic mechanism. These findings highlight the need for clinical vigilance for acute visual changes post-vaccination, while underscoring that the absolute risk remains exceedingly low compared to the clear benefits of vaccination.

1. Introduction

Ocular vascular occlusion encompasses a group of acute, potentially devastating ophthalmic conditions that represent an ischemic stroke of the eye.[1] The sudden obstruction of a retinal artery or vein disrupts blood flow to the delicate neural tissue of the retina, leading to a cascade of pathological events including retinal ischemia, hypoxia, hemorrhage, and macular edema. These events frequently culminate in severe and often irreversible vision loss, marking ocular vascular occlusion as a true ophthalmic emergency.[2] The clinical presentation is typically characterized by

sudden, painless monocular visual disturbance, ranging from a partial visual field defect (scotoma) to profound loss of sight.[3]

For decades, the etiological framework for ocular vascular occlusion has been firmly anchored in the principles of cardiovascular medicine. The condition is classically understood as a complication of underlying systemic vascular disease. Well-established and powerful risk factors include advanced age, systemic arterial hypertension, diabetes mellitus, hyperlipidemia, and various hematological and thrombophilic disorders such as hypercoagulable states.[4] Consequently, the diagnostic workup for a patient presenting with ocular vascular occlusion has traditionally focused on identifying and managing these systemic contributors. The occurrence of a retinal artery or vein occlusion in a young, systemically healthy individual is therefore a clinical anomaly, a diagnostic puzzle that compels a thorough investigation into alternative or atypical triggers.[5]

In recent years, the global public health landscape has been profoundly influenced by two concurrent forces: the unprecedented scale of mass immunization campaigns prompted by the COVID-19 pandemic and the continued necessity of travel medicine for an increasingly mobile global population. Travel vaccinations, such as those for yellow fever, meningococcal disease, typhoid, and herpes zoster, are indispensable tools for preventing the spread of infectious diseases across geographical borders. Their safety profiles are overwhelmingly favorable, yet like any potent immunological intervention, they carry a theoretical risk of rare but severe adverse events. Historically, ocular complications following these vaccines have been documented, though exceedingly rarely, typically manifesting as inflammatory conditions like uveitis or optic neuritis. Retinal vascular occlusions were considered an even greater rarity, representing isolated and enigmatic events when they occurred.[6]

The COVID-19 pandemic, and the subsequent global rollout of billions of vaccine doses, created a pharmacovigilance environment of unparalleled scale and resolution, bringing extremely rare adverse events following immunization (AEFI) into statistical focus.[7] As data accumulated, reports began to surface in the scientific literature and in passive surveillance databases linking various COVID-19 vaccine platforms—including novel mRNA technologies (BNT162b2, mRNA-1273) and adenoviral vector technologies (ChAdOx1, Ad26.COV2.S)—to thrombotic events. Among these were documented cases of ocular vascular occlusion, which bore a striking resemblance in their clinical presentation and temporal proximity to the sporadic reports previously associated with traditional travel vaccines.

This convergence of observations from technologically distinct vaccines developed decades apart raised a critical scientific question: could these disparate immunizations trigger a similar, specific, and severe ocular pathology? This question forms the central impetus for the present review. The prevailing hypothesis posits the existence of a vaccine-induced immuno-thrombotic state. It is theorized that the robust immune activation necessary to generate protective immunity can, in a small subset of susceptible individuals, precipitate a pathological cascade involving endothelial inflammation (endotheliitis), platelet activation, and a transient hypercoagulable state, ultimately culminating in vascular occlusion. This proposed mechanism, potentially unifying the observations across different vaccine types, suggests a common final pathophysiological pathway for this rare but devastating ocular event.[8]

While several systematic reviews have laudably addressed the occurrence of ocular vascular occlusion following COVID-19 vaccination, and a handful of case reports have documented similar events after travel vaccines, the evidence has remained fragmented.[9] To our knowledge, a comprehensive synthesis systematically connecting these two distinct yet mechanistically related fields of vaccinology is currently absent from the literature. This gap prevents a holistic understanding of the potential phenomenon

and limits the ability of clinicians and public health officials to form a unified perspective.[10]

The aim of this systematic review is to critically evaluate and synthesize the global evidence on the temporal association between ocular vascular occlusion and both COVID-19 and non-COVID travel vaccinations. The novelty of this study lies in its integrated approach. By being the first to bridge the evidence from these two distinct categories of immunization, this review seeks to analyze the collective clinical spectrum, demographic profiles, temporal patterns, and patient outcomes across diverse vaccine platforms. Through this synthesis, we aim to elucidate potential shared pathophysiological mechanisms, primarily the immuno-thrombosis hypothesis, and to provide a unified, evidence-based perspective for clinicians, ophthalmologists, and public health authorities to enhance pharmacovigilance and inform clinical practice regarding this rare but sight-threatening event.

2. Methods

This systematic literature review was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A protocol was established prior to the commencement of the review, outlining the search strategy, eligibility criteria, and methods for data synthesis. The protocol was not registered in a public database.

A comprehensive and systematic search was performed across four major electronic databases: PubMed, Scopus, Cochrane Library, and ProQuest. The search strategy was designed to identify all relevant literature published from January 1st, 2013, to August 1st, 2024. The start date was chosen to capture contemporary evidence, while the inclusion of the pre-COVID era was essential for the primary objective of comparing events with traditional travel vaccines. A key historical paper identified during preliminary scoping searches (Study 7) was deemed foundational; therefore, the search period was formally extended from 2015 to 2013 post-hoc to ensure its inclusion based on its relevance to the review's hypothesis.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to the core concepts of ocular vascular occlusion and vaccination. The primary search string, adapted for each database's unique syntax, was: ("ocular vascular occlusion" OR "retinal vein occlusion" OR "retinal artery occlusion" OR "CRVO" OR "CRAO" OR "BRVO" OR "BRAO" OR "papillophlebitis") AND ("vaccination" OR "immunization" OR "vaccine" OR "COVID-19" OR "SARS-CoV-2" OR "travel vaccine" OR "yellow fever" OR "zostavax" OR "meningococcal" OR "influenza" OR "hepatitis" OR "typhoid"). To ensure comprehensiveness, the reference lists of all included articles and relevant narrative reviews were also manually screened to identify any additional studies.

Studies were selected for inclusion based on a predefined set of eligibility criteria established before the literature search. To be included, a study had to report on individuals of any age, gender, or ethnicity who had received one or more doses of any COVID-19 vaccine or a vaccine commonly associated with travel, such as those for yellow fever, herpes zoster, meningococcal disease, hepatitis A/B, typhoid, or influenza. The primary outcome of interest was a confirmed clinical diagnosis of any form of ocular vascular occlusion, including central or branch retinal vein and artery occlusions (CRVO, BRVO, CRAO, BRAO), as well as related conditions involving vascular compromise like papillophlebitis or vasculitis leading to occlusion. All study designs were considered eligible, from randomized controlled trials and observational studies to case series and single case reports. Furthermore, case data presented within narrative reviews were included if the information was determined to be original and not published elsewhere. The search was restricted to articles published in the English language within the specified timeframe.

Conversely, studies were excluded if the ocular vascular occlusion was explicitly attributed to direct COVID-19 infection rather than vaccination.

Publications reporting on routine, non-travel childhood immunizations (such as MMR or DTaP) were also excluded unless the vaccine in question is also used for travel purposes. Non-original research, including review articles without primary data, editorials, letters, and conference abstracts, was removed. Finally, studies were excluded if they contained insufficient data to confirm the diagnosis, the specific vaccine administered, or the temporal relationship between the two events. All non-human (animal) studies were also excluded.

The study selection process followed a rigorous two-stage screening protocol executed by two independent reviewers. In the first stage, all retrieved records underwent a title and abstract screening to identify potentially relevant articles, and those that clearly did not meet the inclusion criteria were excluded. In the second stage, the full texts of all remaining articles were retrieved and assessed against the eligibility criteria for a final decision. Any disagreements between the two reviewers at either stage were resolved through discussion and consensus; if a consensus could not be reached, a third senior reviewer was consulted.

Following the final selection, data were systematically collected from each included study using a standardized extraction form. The extracted data fields included study design and patient counts; patient demographics such as age and gender; clinically relevant comorbidities or predisposing risk factors; and specific vaccine details like the platform and dose number. Information on the ocular vascular occlusion itself was also recorded, including its type and laterality. Key temporal and clinical data were extracted, such as the time from vaccination to symptom onset, presenting and final visual acuity, and findings from diagnostic imaging. Lastly, details on management strategies and patient outcomes, including the resolution or persistence of symptoms, were collected.

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers using tools appropriate for the study design. For observational cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) was utilized. The NOS evaluates studies across the domains of study group selection, group comparability, and outcome ascertainment, with scores ranging from 0 to 9 stars. Studies were categorized as high (≥7 stars), moderate (4–6 stars), or low (<4 stars) quality. A modification was made for its application to passive surveillance database analyses from sources like VAERS; since these lack a direct unexposed cohort, the 'Comparability' domain was marked as not applicable, and the score was based on the remaining domains. While this is a recognized limitation, it provides a standardized assessment framework. For case reports and case series, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports was used. This tool assesses the clarity of reporting across eight key domains, including patient history, diagnostic certainty, and clinical timeline, with a detailed summary of this assessment provided in the Results section.

Due to the anticipated significant heterogeneity in study designs, patient populations, vaccine types, and outcome measures, a quantitative meta-analysis was deemed inappropriate and was not planned. Instead, a narrative synthesis of the findings was performed to summarize the evidence, structured around key themes including demographic profiles, clinical characteristics, temporal patterns, and outcomes. Data are presented in both narrative form and through summary tables to provide a comprehensive overview. The term "descriptive subgroup characterization" is used to refer to the categorization of findings by vaccine or occlusion type, to avoid implying statistical comparison.

3. Results

The systematic search of four databases yielded a total of 1,348 records. After the removal of 341 duplicate records, 1,007 unique records remained for screening. The title and abstract screening led to the exclusion of 975 records for reasons such as focusing on ocular vascular occlusion due to direct COVID-19

infection, addressing other adverse events, or being non-original research, like editorials. The full texts of the remaining 32 articles were retrieved and assessed for final eligibility. Of these, 20 articles were excluded during the full-text review for the following reasons: 8 were review articles that did not contain original case data, 5 had insufficient data on the diagnosis or vaccine details, 4 reported on routine non-travel childhood immunizations, and 3 were found to be duplicate reports of the same patient cohort in different publications. Ultimately, 12 studies met all inclusion criteria and were included in this systematic review. The PRISMA 2020 flow diagram detailing this identification, screening, and inclusion process is presented in Figure 1.

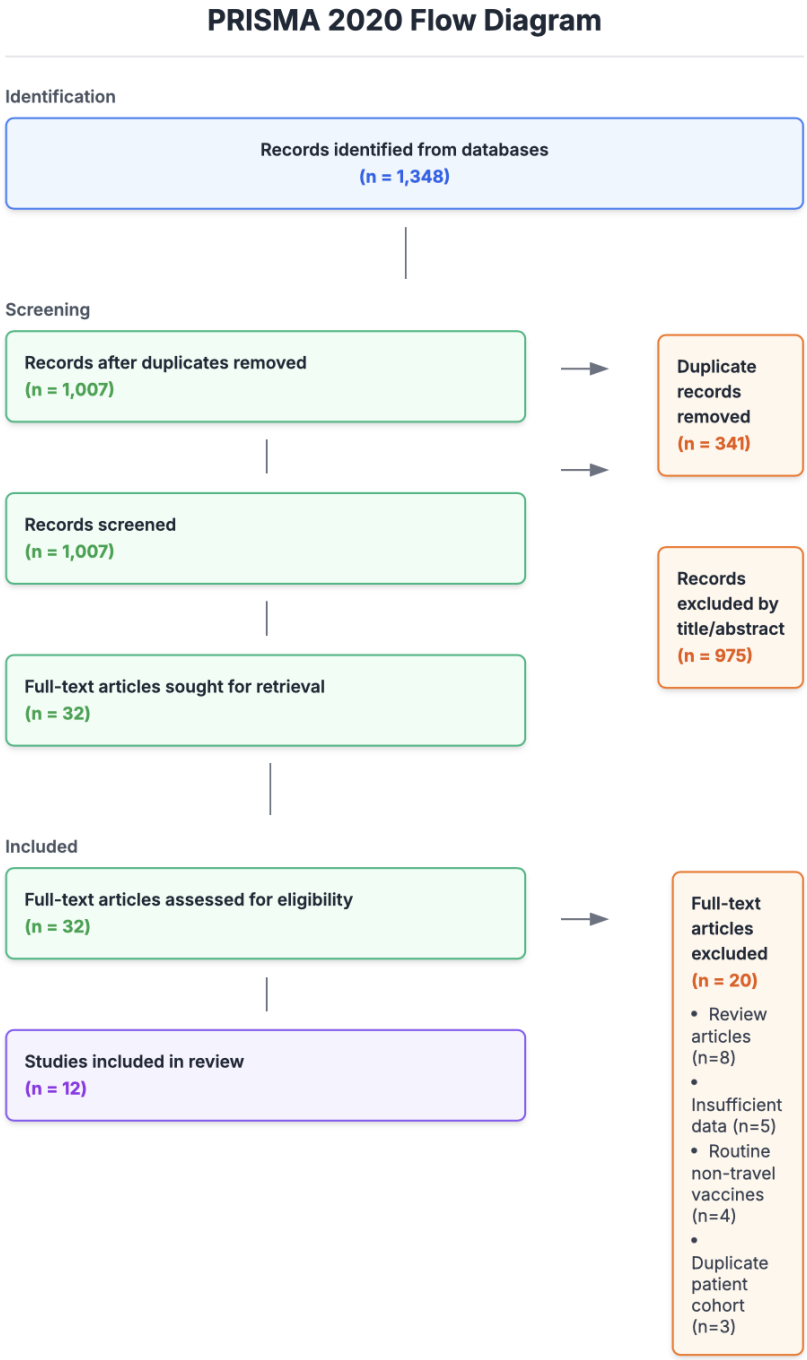

Figure 1. PRISMA 2020 flow diagram.

The 12 included studies were published between 2013 and 2024. The study designs were highly heterogeneous, comprising 7 case reports or case series, 3 large retrospective database analyses (from the Vaccine Adverse Event Reporting System [VAERS] and the TriNetX research network), and 2 narrative reviews that included original, unpublished case compilations. A detailed summary of the characteristics of each included study is provided in Tables 1a and 1b.

Table 1a. Characteristics of Studies Reporting on COVID-19 Vaccine Associated Cases

STUDY ID	STUDY DESIGN	VACCINE(S) INVOLVED	OCULAR OCCLUSION TYPE & LATERALITY	PATIENT PROFILE (AGE/SEX) & N	COMORBIDITIES	TIME TO ONSET	TREATMENT & OUTCOME
Study 1	Retrospective cohort (TriNetX)	mRNA & Adenoviral vector	Composite of RVO & RAO	Large cohort, N > 2M	Adjusted for in model	Peak risk 3-45 days	HR 2.19 (95% CI 1.85-2.59)
Study 2	Retrospective analysis (VAERS)	mRNA & Adenoviral vector	RAO & RVO	N=524 reports	Not systematically reported	Majority within 7 days	Temporal association noted
Study 3	Retrospective analysis (VAERS)	Pfizer, Moderna, Janssen	Retinal hemorrhage, BRVO, CRVO	N=397 reports; Mostly Female	Not systematically reported	Majority within 7 days	Higher reporting with Moderna & Janssen
Study 4	Case report	ChAdOx1 nCoV-19 (Dose 1)	CRVO (Left Eye)	31 / Male, N=1	None reported	7 days	Vision improved to 6/9
Study 5	Case series	BNT162b2 (Pfizer) (Dose 2)	BRVO (Unilateral)	50/F, 56/F, N=2	Mild hypertension (Case 1)	3 days	Both recovered to 20/20
Study 6	Case report	BNT162b2 (Pfizer) (Dose 3)	Combined CRVO, CRAO, Papillitis (Left)	68 / Female, N=1	Type 2 Diabetes	5 days	Vision improved from HM to 20/200

Table 1b. Characteristics of Studies on Travel/Other Vaccines & Reviews

STUDY ID	STUDY DESIGN	VACCINE(S) INVOLVED	OCULAR OCCLUSION TYPE & LATERALITY	PATIENT PROFILE (AGE/SEX) & N	COMORBIDITIES	TIME TO ONSET	TREATMENT & OUTCOME
Travel & Other Vaccine Associated Cases							
Study 7	Case series	Pandemrix, DTP, Hep A, Typhoid	Retinal vasculitis with BRAO	63 / Male, N=2	Hyperlipidemia (Case 2)	4 weeks & 2 months	Gradual vision improvement
Study 8	Case report	Yellow Fever + N. meningitidis	Small vessel vasculopathy with BRAO (Left)	41 / Male, N=1	None	4 days	Partial recovery, persistent dropout
Study 9	Case report	Herpes Zoster (Zostavax)	CRAO secondary to ARN (Right)	76 / Male, N=1	Chronic Lymphocytic Leukemia	2 days	Severe vision loss (Light Perception)
Study 10	Case report	Meningococcal B (Bexsero)	Papillophlebitis + Cilioretinal Artery Occlusion (Right)	15 / Male, N=1	None	2 weeks	Improved to 20/30 vision
Reviews with Case Compilation							
Study 11	Review with case compilation	Various (COVID-19, Zostavax)	CRAO, CRVO, Combined	27-86 / Mixed, N=18	Mixed	2-61 days	Generally poor to partial recovery
Study 12	Narrative review with case compilation	mRNA & Adenoviral vector	CRAO, CRVO, Vasculitis	17-52 / Mixed, N=9	Often none	3-21 days	Mixed outcomes

The methodological quality of the included studies was variable, which is typical for evidence concerning rare adverse events. The quality assessment scores are detailed in Table 2 (JBI Checklist for Case Reports/Series) and Table 3 (NOS for Observational Studies). The large database analyses, assessed with the modified NOS, scored between 5 and 8, indicating moderate-to-high quality. Their primary methodological strength was their large sample size, while their main limitation was the passive nature of data reporting and the lack of clinical adjudication for reported events. The case reports and series, which form the bulk of the evidence base, were assessed using the JBI checklist (Table 2). Overall, these reports were methodologically strongest in providing clear diagnostic evidence and detailed timelines. They were generally weaker in comprehensively ruling out alternative causes and reporting on concurrent interventions.

Table 2. Methodological Quality Assessment

Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Included Case Reports and Case Series

STUDY ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Study 4	✓	✓	✓	✓	✓	✓	✓	✓
Study 5	✓	✓	✓	✓	✓	✓	✓	✓
Study 6	✓	✓	✓	✓	✓	✓	✓	✓
Study 7	✓	✓	✓	✓	✓	✓	✓	✓
Study 8	✓	✓	✓	✓	✓	✓	✓	✓
Study 9	✓	✓	✓	✓	✓	✓	✓	✓
Study 10	✓	✗	✓	✓	✓	✓	✓	✓

JBI Checklist Questions Key

Q1: Were the patient's demographic characteristics clearly described?
Q2: Was the patient's history clearly described and presented as a timeline?
Q3: Was the current clinical condition of the patient on presentation clearly described?
Q4: Were diagnostic tests or methods and the results clearly described?
Q5: Was the intervention(s) or treatment procedure(s) clearly described?
Q6: Was the post-intervention clinical condition clearly described?
Q7: Were adverse events or unanticipated events identified and described?
Q8: Does the case report provide takeaway lessons?

Table 3. Methodological Quality Assessment

Newcastle-Ottawa Scale (NOS) for Included Observational Studies

STUDY ID	STUDY DESIGN	SELECTION (MAX 4)	COMPARABILITY (MAX 2)	OUTCOME (MAX 3)	TOTAL SCORE	QUALITY LEVEL
Study 1	Retrospective cohort	★★★★	★★	★★★	9	High
Study 2	Retrospective analysis (VAERS)	★★★☆	N/A*	★★☆	5	Moderate
Study 3	Retrospective analysis (VAERS)	★★★☆	N/A*	★★☆	5	Moderate

***Note on NOS scores for VAERS analyses:** These studies are descriptive analyses of a passive surveillance system and lack a direct, unexposed cohort for comparison, making the 'Comparability' domain not applicable (N/A). The total score is based on the 'Selection' of cases (representativeness of the patient population) and 'Outcome' (ascertainment and reporting of the adverse event), providing a standardized, albeit modified, assessment of methodological quality.

The review documented ocular vascular occlusion events across a vast age range, from a 15-year-old male who developed papillophlebitis with an associated cilioretinal artery occlusion following a meningococcal B vaccine (Study 10), to an 86-year-old individual included in a case compilation (Study 11) (Figure 2). The majority of cases, however, were concentrated in adults between 40 and 70 years of age. A critical finding was the occurrence of ocular vascular occlusion in many otherwise healthy individuals with no known pre-existing vascular risk factors, suggesting the vaccine may have acted as an independent trigger in these instances. In other cases, patients did have underlying comorbidities such as hypertension, diabetes, or an immunocompromised state, for instance, a 76-year-old with chronic lymphocytic leukemia who developed CRAO (Study 9). A noteworthy pattern emerged in gender distribution. While ocular vascular occlusion cases associated with traditional travel vaccines showed a slight male predominance, the large database analyses of COVID-19 vaccines in Study 3 revealed a higher frequency of reported events in females, particularly those in the 40–59 age group.

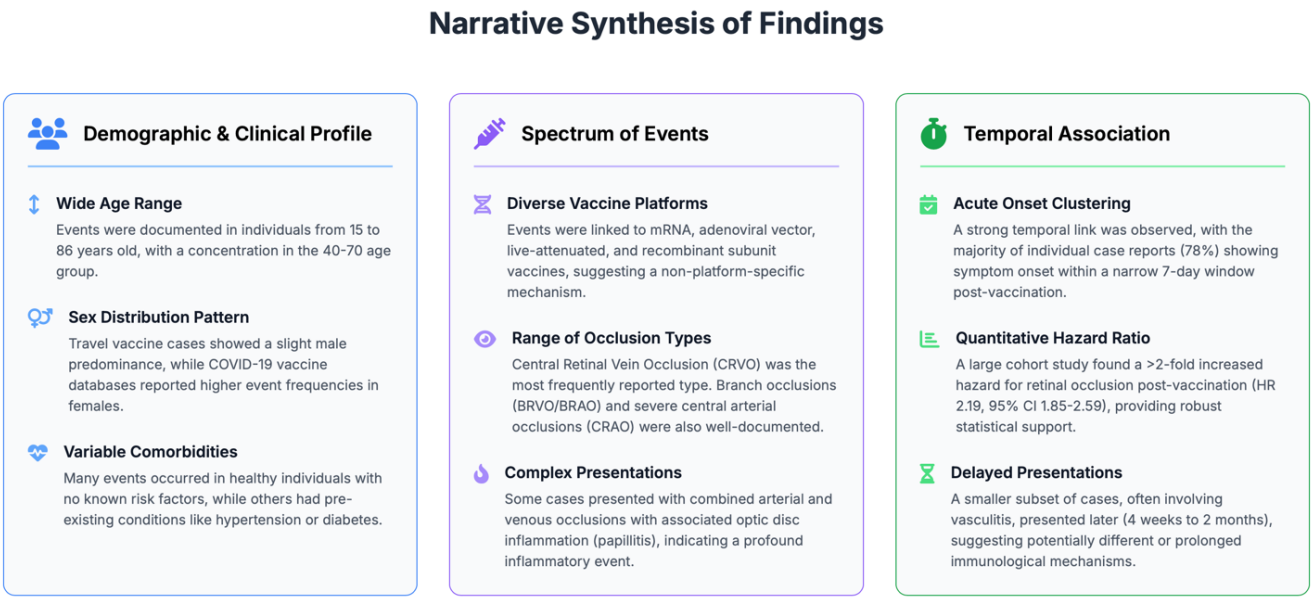

Figure 2. Narrative synthesis of findings.

A wide array of vaccine types and platforms was implicated across the 12 studies, a finding that supports the hypothesis of a shared, non-platform-specific mechanism. For COVID-19 vaccines, events were reported following administration of both mRNA platforms, such as BNT162b2/Pfizer-BioNTech and mRNA-1273/Moderna, and adenoviral vector platforms, including ChAdOx1/AstraZeneca and Ad26.COV2.S/Janssen. The implicated non-COVID travel immunizations were similarly diverse, encompassing live-attenuated vaccines like Herpes Zoster (Zostavax) and Yellow Fever, recombinant subunit vaccines such as Meningococcal B (Bexsero), and various others reported in combination, including Hepatitis A and Typhoid.

Central retinal vein occlusion (CRVO) was the most frequently reported single diagnosis, described in 8 of the 12 included publications. Branch retinal vein occlusion (BRVO) was also common, with some cases showing excellent visual recovery following prompt

anti-VEGF therapy, such as the two patients reported in Study 5. Arterial occlusions, including the more visually devastating central retinal artery occlusion (CRAO) and the more localized branch retinal artery occlusion (BRAO), were also well-documented after both vaccine categories and were often associated with poorer visual prognoses. A few complex cases presented with combined occlusions, such as concurrent CRAO and CRVO with associated optic disc inflammation (papillitis), suggesting a diffuse and profound inflammatory vascular event.

A striking finding of this review is the strong temporal clustering of ocular vascular occlusion events shortly after vaccination. This tight temporal link strongly suggests an acute biological trigger rather than a coincidental background event. Across the individual case reports where precise timing was available (encompassing 9 patients from 7 reports), the median time from vaccination to symptom onset was 5 days. A clear majority of these index cases (7 of 9, or 78%) presented within a narrow 7-day window post-immunization. Examples include CRAO occurring two days after Zostavax vaccination (Study 9) and BRVO appearing three days after an mRNA COVID-19 vaccine (Study 5). The most robust quantitative evidence supporting this association came from the large retrospective cohort study (Study 1), which utilized the TriNetX global research network. After adjusting for potential confounders, including age, gender, race, and systemic vascular comorbidities (hypertension, diabetes), the study reported a statistically significant, more than two-fold increased hazard for a composite outcome of retinal vascular occlusion in the vaccinated cohort compared to a matched unvaccinated cohort. This elevated risk was observed in the 3 to 45-day post-vaccination window (Hazard Ratio [HR] 2.19, 95% Confidence Interval [CI] 1.85-2.59, $p<0.001$). While the majority of cases occurred acutely, a smaller subset presented with a more delayed onset. For instance, the case series in Study 7 reported retinal vasculitis leading to occlusion developing 4 weeks to 2 months post-vaccination, and the compilation in Study 11 included cases with onsets up to 61 days later. These delayed presentations may point towards different or more prolonged immunological mechanisms, such as adaptive autoimmune responses.

A descriptive characterization of subgroups was performed to identify patterns based on vaccine type, occlusion type, and outcome. The key findings are summarized in Table 4. Venous occlusions (CRVO/BRVO) were the most frequent diagnoses overall and were reported after all vaccine platform types. Arterial occlusions (CRAO/BRAO), while also seen with all platforms, were more often associated with poor visual outcomes, particularly in older patients or those with pre-existing risk factors. Good visual recovery was most strongly linked to early intervention with corticosteroids or anti-VEGF therapy, especially in cases of BRVO and papillophlebitis (Table 4).

4. Discussion

This systematic review synthesizes the global evidence on the rare but clinically significant phenomenon of ocular vascular occlusion occurring in temporal proximity to both COVID-19 and traditional travel vaccinations.[11] The primary finding is not that vaccination is a common cause of ocular vascular occlusion—indeed, it remains an exceedingly rare reported event in the context of billions of vaccine doses administered worldwide—but that a consistent clinical and temporal pattern exists across a diverse spectrum of vaccine technologies. This convergent evidence, drawn from multiple countries and different study designs, provides a signal that warrants moving the discussion from one of likely coincidence to one of plausible, shared pathophysiology. This discussion will focus on dissecting these potential biological mechanisms, framing them within a unified hypothesis of vaccine-induced immuno-thrombosis, while critically acknowledging the inherent limitations of the available data.

Table 4. Descriptive Subgroup Characterization

Summary of Key Findings Across Ocular Vascular Occlusion Events

CATEGORY	SUBGROUP	PUBLICATIONS REPORTING	COMMON OCCLUSION TYPES	ASSOCIATED VACCINE PLATFORMS	KEY DESCRIPTIVE FINDINGS
Vaccine Type	COVID-19	7	CRVO, CRAO, BRVO	mRNA, Adenoviral Vector	Higher event reporting in large databases (VAERS, TriNetX). One study reported HR > 2.0 for occlusion.
	Travel & Other	5	CRAO, BRAO, Papillophlebitis	Zostavax, Yellow Fever, Meningococcal B	Events occurred in both older individuals with comorbidities and younger, healthy individuals.
Occlusion Type	Venous (CRVO/BRVO)	8	CRVO, BRVO	All platforms	CRVO was the most frequent single diagnosis. BRVO cases often showed good response to anti-VEGF therapy.
	Arterial (CRAO/BRAO)	7	CRAO, BRAO	All platforms	CRAO was associated with the poorest visual outcomes. Often seen in older patients or those with risk factors.
Outcome	Full/Partial Recovery	8	BRVO, Papillophlebitis	Mixed	Recovery strongly linked to venous occlusions. Positively associated with early intervention (anti-VEGF/corticosteroids).
	Persistent Impairment	5	CRAO, severe CRVO	COVID-19, Zostavax	Strongly associated with arterial occlusions. Linked to cases with severe macular ischemia at presentation.

The central hypothesis emerging from this comprehensive review is that ocular vascular occlusion post-vaccination is a localized manifestation of vaccine-induced immuno-thrombosis.[12] This term describes a complex pathological state where the intended, robust immune response to vaccination inadvertently triggers a pro-thrombotic and inflammatory cascade within the vascular system. The delicate, high-flow, and anatomically unique vasculature of the retina may represent a particularly vulnerable target for such a systemic insult.[13] This overarching hypothesis can be deconstructed into several interconnected and potentially synergistic pathways (Figure 3).

All vaccines, by design, function by potently activating the innate immune system to prime a durable adaptive response. Modern vaccines, particularly the highly immunogenic mRNA and adenoviral vector platforms, are powerful inducers of this first-line defense, triggering pattern recognition receptors (PRRs) like Toll-like receptors (TLRs), leading to a robust type I interferon response and the production of a host of pro-inflammatory cytokines, notably Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[14] While essential for developing immunity, an overzealous or dysregulated cytokine storm can lead to systemic or localized inflammation.

The vascular endothelium is a primary target of this inflammatory milieu. Pro-inflammatory cytokines can directly activate endothelial cells, causing a profound shift in their function from an anti-thrombotic to a pro-thrombotic surface.[15] This state, often termed endotheliitis, is characterized by the upregulation of adhesion molecules (like VCAM-1 and ICAM-1) that promote leukocyte binding, the expression of pro-coagulant tissue factor, and the

downregulation of natural anticoagulant mechanisms, such as the thrombomodulin-protein C system. Within the confined anatomy of the optic nerve head, particularly at the lamina cribrosa where the central retinal artery and vein pass, or at arteriovenous crossings in the retina, even mild endothelial swelling and inflammation can lead to vascular compression, turbulent blood flow, and venous stasis. This fulfills all three components of Virchow's triad (endothelial injury, stasis, and hypercoagulability), creating a perfect storm for thrombus formation and precipitating a venous occlusion (CRVO/BRVO).[16]

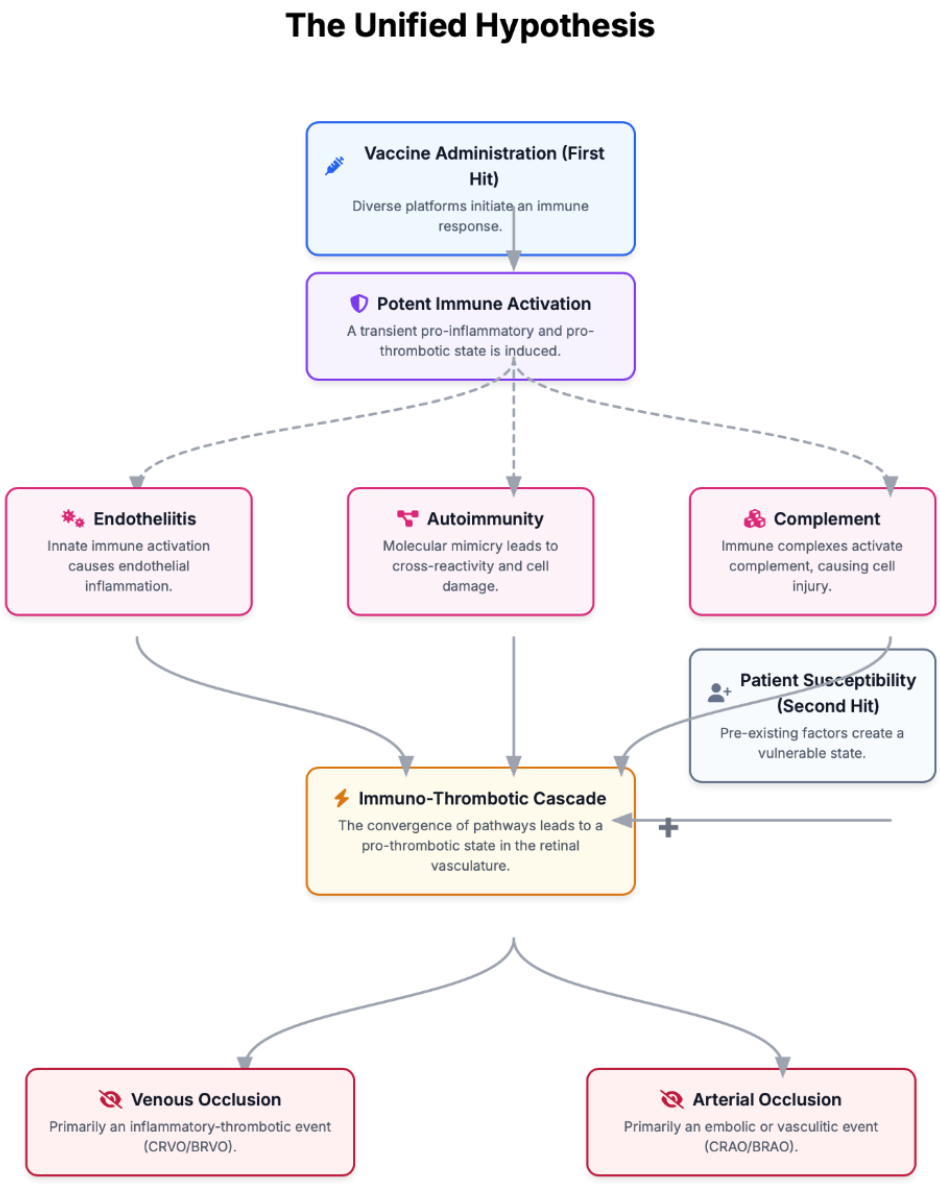

Figure 3. The unified hypothesis.

A second, more delayed pathway may involve adaptive immunity through molecular mimicry. This mechanism posits that structural similarities between vaccine components (such as the SARS-CoV-2 spike protein antigen, viral vectors, or adjuvants) and host proteins present on the surface of platelets or

endothelial cells could lead to an off-target, autoimmune response.[17] The immune system, primed by the vaccine to attack a foreign antigen, may then cross-react with these "look-alike" self-proteins, leading to antibody-mediated or T-cell-mediated endothelial damage, platelet activation, and vasculitis. This process is analogous to the mechanisms underlying many systemic autoimmune vasculitides. The variable latency observed in some of the included cases, with onset occurring weeks to months after vaccination, could be explained by the time required to mount such a misguided adaptive autoimmune response.[18] The cases reported in Study 7, which presented as a frank retinal vasculitis with secondary occlusion, are prime clinical examples supporting this mechanistic pathway.

The inflammatory milieu created by vaccination can also directly activate platelets, causing them to aggregate and release pro-thrombotic mediators. Furthermore, the formation of antigen-antibody immune complexes following vaccination can potently activate the classical complement pathway. This activation cascade leads to the generation of powerful anaphylatoxins (C3a, C5a), which further amplify inflammation and recruit immune cells, and culminates in the formation of the Membrane Attack Complex (MAC, C5b-9). The MAC can directly insert into the membranes of endothelial cells and platelets, causing lytic injury and triggering thrombosis. This complement-driven thrombotic mechanism is thought to be central to the pathophysiology of the more severe, systemic syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT), which has been linked to some adenoviral vector vaccines. It is highly plausible that a less severe, localized, or forme fruste version of this immuno-thrombotic process could manifest as an isolated ocular vascular occlusion without the systemic hallmark of thrombocytopenia.[19]

The extreme rarity of these events, despite the widespread administration of billions of vaccine doses, strongly implies that the vaccine itself is not a sufficient cause. A more compelling model is the "two-hit" hypothesis, elegantly proposed in Study 4 in the context of a post-vaccine CRVO case. The first hit is the vaccination event itself, which induces a transient, systemic pro-inflammatory and pro-thrombotic state in nearly all recipients. This is the intended and necessary response to generate immunity. The second hit is a pre-existing, patient-specific susceptibility factor that renders an individual vulnerable to the transient systemic challenge of the first hit. This second hit could be a known systemic comorbidity like poorly controlled hypertension or diabetes, which may have already caused subclinical endothelial dysfunction. It could be an anatomical variant, such as a crowded optic disc ("disc at risk") or anomalous arteriovenous crossings. It could also be a subclinical or undiagnosed condition, such as a genetic predisposition to thrombosis, such as Factor V Leiden or a prothrombin gene mutation, or a specific genetic background, including specific HLA subtypes, that primes the individual for an aberrant autoimmune response.

This two-hit model provides a robust framework for understanding why millions can be vaccinated without incident, while a few uniquely susceptible individuals experience these rare but severe events. The case reported in Study 9, where a 76-year-old with leukemia (a clear immunocompromising second hit) developed a devastating CRAO after the Zostavax vaccine, is a powerful clinical illustration of this concept in action.

While the underlying immuno-thrombotic trigger may be similar, the clinical manifestation as either an arterial or a venous occlusion likely depends on the dominant downstream effect and the site of injury. The evidence suggests retinal vein occlusion (CRVO/BRVO) is primarily an inflammatory-thrombotic event. The inflammation and endotheliitis are most consequential at sites of anatomical constriction and high shear stress—the lamina cribrosa for CRVO or an arteriovenous crossing for BRVO. Here, endothelial swelling, leukocyte adhesion, and local hypercoagulability lead to compression, stasis, and ultimately, thrombosis of the less rigid

vein. Retinal artery occlusion (CRAO/BRAO) appears to be more of an embolic or severe vasculitic event. The systemic immuno-thrombotic state could lead to the formation of small platelet-fibrin aggregates (white thrombi) in the heart or carotid arteries that then embolize to the retinal circulation. Alternatively, intense, focal vasculitis could cause such severe swelling of the arterial wall that it completely occludes the lumen. This vasculitic pathway is strongly suggested in the cases presented in Study 8 and Study 7, which described features of vasculopathy and vasculitis. The often permanent and profound vision loss associated with CRAO highlights the severity of this arterial pathway.[20]

It is imperative to interpret the findings of this review within the context of its significant methodological limitations. The conclusions drawn are based on evidence that, while suggestive, does not permit the establishment of definitive causality. The foundation of this review is built upon data from the lower tiers of the evidence pyramid, primarily case reports, case series, and descriptive analyses of passive surveillance databases. These study designs are excellent for hypothesis generation but are unable to definitively prove causation. Passive surveillance systems like VAERS are subject to well-known and significant biases, including under-reporting, over-reporting stimulated by media attention, and a lack of clinical verification for reported events. This makes it impossible to calculate a true incidence rate from this data. While the large cohort study (Study 1) adjusted for several major confounders, residual confounding cannot be excluded. For the case reports, it is impossible to definitively rule out that the ocular vascular occlusion was a coincidental event that would have occurred regardless of the vaccination, particularly in older patients with existing vascular risk factors. Given the scale of global vaccination, some temporal associations will occur by chance alone. Due to the limitations described above, particularly the lack of reliable denominator data, this review cannot and does not calculate the true incidence or absolute risk of ocular vascular occlusion post-vaccination. However, based on the number of reported cases relative to the billions of vaccine doses administered, it is clear that this risk remains exceedingly low.

5. Conclusion

This systematic review consolidates and characterizes the published global evidence of a rare but consistent temporal association between the administration of both COVID-19 and non-COVID travel vaccines and the subsequent onset of ocular vascular occlusion. The notable clustering of events within the first week following immunization, observed across a wide spectrum of vaccine platforms, strongly suggests a shared pathophysiological basis rather than widespread coincidence, with vaccine-induced immuno-thrombosis being the most plausible unifying mechanism.

While the absolute risk of this adverse event remains extremely low, and the established public health benefits of vaccination in preventing infectious disease unequivocally outweigh this potential risk, the severity and potential for irreversible vision loss make ocular vascular occlusion a clinically significant consideration. The most critical implication for clinical practice is the need for heightened vigilance and a high index of suspicion. Ophthalmologists, primary care physicians, immunologists, and travel medicine specialists should consider ocular vascular occlusion in the differential diagnosis for any patient presenting with acute, painless vision loss, scotoma, or a visual field defect within days to weeks of receiving any vaccine. Prompt referral for an urgent ophthalmologic evaluation is paramount, as early diagnosis and intervention with therapies like anti-VEGF or corticosteroids can, in some cases, lead to meaningful visual recovery. Ultimately, these findings underscore the vital importance of robust, ongoing global pharmacovigilance and highlight the need for further research to identify potential biomarkers or risk factors that may predispose a small subset of individuals to these rare but devastating ocular complications.

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