Paroxysmal Nocturnal Hemoglobinuria After Vaccination: A Systematic Pharmacovigilance Analysis of 147 Cases

Robert W. Chandler MD

rwcmd@protonmail.com

Independent Researcher, Former Associate Clinical Professor USC and Assistant Clinical Professor, Univeristy Of California Irvine; Retired https://orcid.org/0009-0003-1755-2944

Amy W. Kelly

Independent Researcher https://orcid.org/0009-0005-6022-908X

Albert Benavides

Independent Researcher https://orcid.org/0000-0002-1294-6595

Research Article

Keywords: paroxysmal nocturnal hemoglobinuria, PNH, VAERS, pharmacovigilance, complement activation, breakthrough hemolysis, eculizumab, ravulizumab, meningococcal, vaccine adverse events, rechallenge, deduplication, new-onset PNH, platform stratification, mRNA vaccine

Posted Date: May 15th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9645631/v2

Additional Declarations: The authors declare no competing interests.

Paroxysmal Nocturnal Hemoglobinuria After Vaccination: A Systematic Pharmacovigilance Analysis of 147 Cases

Short title: PNH Pharmacovigilance After Vaccination

Robert W. Chandler, MD
Independent Researcher, Huntington Beach, California, United States
ORCID: 0009-0003-1755-2944

Amy W. Kelly
Independent Researcher, Englewood, Colorado, United States
ORCID: 0009-0005-6022-908X

Albert Benavides
Independent Researcher, San Jose, California, United States
ORCID: 0000-0002-1294-6595

Correspondence: Robert W. Chandler, MD
9121 Atlanta Ave.
Huntington Beach, CA. 92646
rwcmd@protonmail.com

Abstract

Background: Paroxysmal nocturnal hemoglobinuria (PNH) creates intrinsic susceptibility to complement-mediated hemolysis, while terminal complement inhibition increases vulnerability to invasive *Neisseria* infection. Vaccination may activate complement and induce hemolysis in PNH patients when administered, as recommended by regulatory agencies, before complement-inhibitor therapy is initiated or optimized.

Methods and Findings: We performed a pharmacovigilance analysis of PNH Vaccine Adverse Event Recording System (VAERS) reports through February 2026. Eighteen PNH-related search terms were applied across seven VAERS fields. Candidate reports underwent physician review, pairwise deduplication, five-tier PNH confirmation, clinical classification, and archival recovery of modified, blanked (subsequent absence of narrative or structured-field content present in earlier archived versions), or removed records.

Among 500 candidate reports, 147 unique patient-events met inclusion criteria. Primary hemolysis was the largest category (55/147), followed by breakthrough meningococcal disease (32/147), neurological events (13/147), new-onset or unmasked PNH (10/147), non-meningococcal infection (9/147), rechallenge hemolysis (8/147), thrombosis (8/147), other events (7/147), marrow failure/cytopenia (6/147), and rhabdomyolysis/myonecrosis (6/147). Seven deaths occurred: six from invasive meningococcal disease and one from marrow failure. Eight patients demonstrated recurrent hemolysis after vaccine exposures, including manufacturer-confirmed positive rechallenge, CH50 complement consumption, and complement-inhibitor modulation. Primary hemolysis clustered earlier than breakthrough meningococcal disease (median 12 versus 153 days; Mann-Whitney p=0.001). Post hoc VAERS modifications were identified in 62/147 cases (42%); 28 required major archival reconstruction. Additional structured fields were restored during physician adjudication from archived records, manufacturer identifiers, published case reports, preserved narratives, and cross-referenced source documents.

Conclusions: These data support vaccination as a complement-amplifying trigger for hemolytic events in susceptible patients with PNH and identify practical risk-mitigation targets: complement-inhibitor/vaccination sequencing, early post-vaccination hemolysis monitoring, and meningococcal prevention planning during complement blockade.

Keywords: *paroxysmal nocturnal hemoglobinuria, PNH, VAERS, pharmacovigilance, complement activation, breakthrough hemolysis, eculizumab, ravulizumab, meningococcal, vaccine adverse events, rechallenge, deduplication, new-onset PNH, platform stratification, mRNA vaccine*

Manuscript Statistics

Abstract: 273 words
Introduction: 290 words
Methods: 1,365 words
Results: 4,447 words
Discussion: 2,397 words
Conclusions: 101 words
Main text total (Introduction–Conclusions): 8,600 words
Tables: 5 (main text); 6 (supplementary, including S5.1–S5.3)
Figures: 15
References: 71 (main); 5 supplementary (S1–S5)
Supplementary Material: 5 sections, ~9,135 words

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematopoietic stem cell disorder caused by somatic mutations in the PIGA gene, resulting in deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins [1,2] on blood cell surfaces with an estimated incidence of 1.3 per million per year and prevalence of 10–16 per million [3]. The absence of complement regulators CD55 and CD59 leaves PNH erythrocytes vulnerable to complement-mediated intravascular hemolysis. [4–6] Hemolytic crises in PNH are characteristically provoked by complement-activating events including surgery, infection, and inflammation [6]; vaccination, as a deliberate induction of innate immune activation, constitutes such a trigger. Terminal complement inhibitors, eculizumab (2007), ravulizumab (2018), and pegcetacoplan (2021), transformed PNH management but introduced a therapeutic paradox with vaccination. [7–12]

Patients initiating complement inhibitor (CI) therapy are advised by health agencies [Supplemental Table 1] to receive meningococcal vaccination at least two weeks before the first dose, because C5 blockade reduces the membrane attack complex (MAC) needed for bactericidal defense, increasing the risk of invasive meningococcal disease by 1,000 to 2,000-fold. [13] Yet the same complement activation that vaccines rely upon to generate protective immunity can trigger hemolytic flares in PNH patients whose erythrocytes lack GPI-anchored regulators protecting host cells from bystander complement damage, as documented in case reports and series of vaccine-triggered breakthrough hemolysis [14–17], multicenter clinical surveys [18,19], new-onset PNH following vaccination [20,21], a classification framework for pharmacodynamic breakthrough hemolysis [22], and an expert consensus on vaccination in PNH patients on complement inhibitors [23].

Despite this well-understood mechanism, the pharmacovigilance literature on vaccine-associated adverse events in PNH is limited to individual case reports and small series. [14–18,20,21,24–26] We undertook a comprehensive extraction, curation, deduplication, and classification of all PNH-related VAERS reports to characterize the scope, severity, and mechanistic basis of vaccine-associated adverse events in this population.

Methods

Data Sources

Eighteen search terms organized into five categories were applied across all seven VAERS text fields (write-up, symptom text, lab data, past medical history, current illness, other medications, and Medical Dictionary for Regulatory Activities (MedDRA) codes -- Supplemental Table 2 MedDRA Preferred Terms), yielding 126 individual searches: explicit PNH terms (Paroxysmal Nocturnal Hemoglobinuria, PNH); complement pathway markers (Complement, Hemolytic Anemia, Autoimmune Hemolytic Anemia, Flow Cytometry, Complement Disorders); hemolysis indicators (Anemia, Rhabdomyolysis); thrombotic microangiopathy (TMA) spectrum and differentials (Thrombotic Microangiopathy, Microangiopathic Hemolytic Anemia, Atypical Hemolytic Uremic Syndrome, Neuroleptic Malignant Syndrome, Portal Vein Thrombosis); and complement inhibitor drugs (Eculizumab/Soliris, Ravulizumab/Ultomiris, Pegcetacoplan, Iptacopan/Fabhalta). All returned cases were individually reviewed for PNH relevance. Missing data in VAERS structured fields was restored manually (RWC).

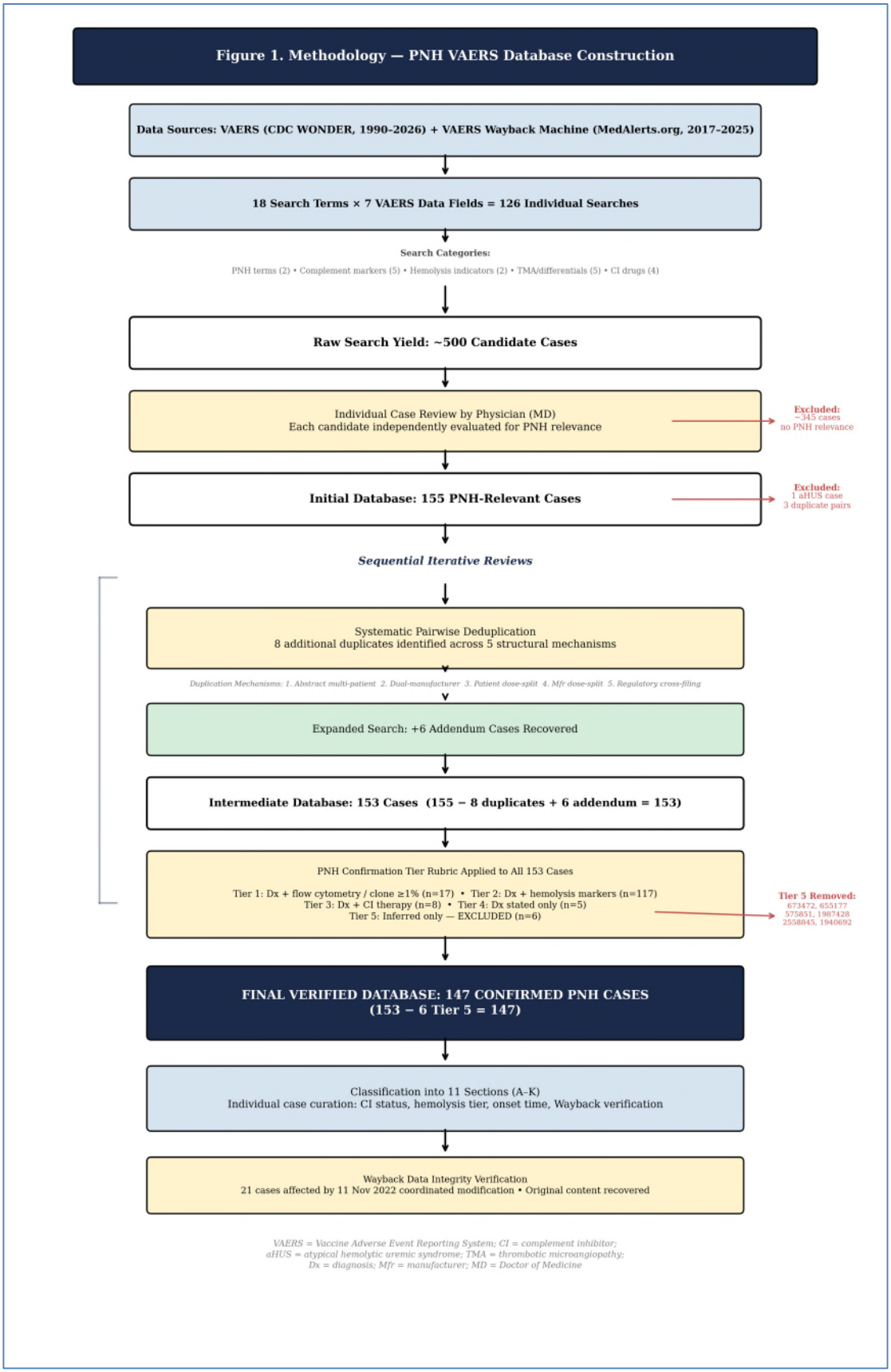
Vaccine identity and clinical narrative for all affected cases were recovered through a systematic workflow: (a) identification of pre-modification Wayback Machine archival captures indexed by VAERS ID at MedAlerts.org; (b) extraction of narrative content prior to modifications including vaccine name, dose, manufacturer, and administration date; (c) cross-verification against European Medicines Agency (EMA) regulatory data retrievals for cases also filed through European channels and against manufacturer Health Product Information (HPI) narratives where available; (d) recording of vaccine identity in the master spreadsheet. A coding auditing specialist (AB) and a process management specialist (AWK) contributed to the development of the methodology.

Process: Search Strategy, Database Construction, Deduplication, and PNH Confirmation Tiering

The lead author (RWC) designed all classification criteria, directed artificial intelligence (AI) execution at every step, reviewed all outputs for clinical accuracy, and adjudicated all borderline cases. The initial pass through the 500 candidate cases was manually curated by the physician (RWC) generating a 153 count database of unique reports that was analyzed to compute successful restoration of incomplete structured data fields compared with raw VAERS downloaded data. All analyses were conducted on the physician-adjudicated dataset, incorporating restored or corrected structured fields were supported by archived or cross-referenced source records; these procedures improved case-level ascertainment and classification.

Three artificial intelligence platforms (Claude [Anthropic], ChatGPT [OpenAI], and Grok [xAI]) were used as physician-directed analytical tools throughout the database construction process, executing physician-defined protocols. Data from a contemporary VAERS download, a past VAERS 56 column per ID dataset and Wayback data were compiled into medical reporting format by one AI platform. A second AI platform was used to verify the data. After manual curation, AI platforms were used to verify the 56 structured and narrative data fields from VAERS plus four added fields per case, extract laboratory values from narrative text, and prepare individual case reports in proper medical format. Using an iterative strategy, AI platforms then conducted 126 individual searches identifying an intermediate-database of 153 cases. Until the final 147 PNH cases were confirmed, the cohort number varied according to iteration sequence. Figure 1 outlines the process employed in completing and analyze the cohort. We employed Kaizen principles in process development to manage data from an unstable database. Figures created with matplotlib 3.x (Python).

Figure 1. Search Strategy, Database Construction, Deduplication, and PNH Confirmation Tiering



A five-tier PNH confirmation rubric (Table 1) was then applied to all cases to assess diagnostic certainty. Five cases were eliminated using this tool leaving 147 cases.

Table 1. PNH Confirmation Tier Rubric

Tier	Definition	N	Status
1 (Strongest)	PNH diagnosis + flow cytometry/clone size ≥1%	17	Included
2	PNH diagnosis + hemolysis markers (lactate dehydrogenase (LDH), haptoglobin, bilirubin, reticulocytes, hemoglobinuria, positive clone identification, schistocytes, Coombs, fluorescent aerolysin (FLAER), CD59, CD55/clone size < 1%)	117	Included
3	PNH diagnosis + complement inhibitor therapy documented	8	Included
4	PNH diagnosis stated only (no labs, no CI documentation)*	5	Included
5 (Excluded)	*PNH inferred only from clinical context; no direct diagnostic statement*	*6*	*Excluded*

**Tier 4 footnote: VAERS 1722588 and 2402571 carry asterisks for qualitative clone descriptions without quantitative data. Tier 2 hemolysis markers expanded to 13 indicators including bilirubin, clone size, FLAER, CD59, CD55, schistocytes, and Coombs test. Tier 5 excluded VAERS IDs: 673472, 655177, 575851, 1987428, 2558845, 1940692. Tiers 1–4 comprise the final 147-case working dataset.*

Seventy-one percent (353/500) of candidate PNH cases were excluded by using this process. One related complement disorder case was retained in the dataset as a closely related disorder. This 71% exclusion rate supports the necessity of physician-level clinical adjudication as validation layer over MedDRA Preferred Term (PT) based case identification.

Cross Validation with VAERS MedDRA Search

A cross-validation analysis of the VAERS database using the MedDRA Preferred Term (PT) "Paroxysmal nocturnal haemoglobinuria" was performed to assess ascertainment completeness. Searching VAERS by this PT coding field identified 26 verified PNH cases; 25 were already present in the database, and the 26th was added to the working dataset. The MedDRA PT search captured 26 of 147 confirmed cases (17.7%), meaning a researcher relying solely on MedDRA Preferred Term coding, the standard structured-data approach in pharmacovigilance, would have missed 121 cases (82.3%). This cross-validation simultaneously demonstrates the sensitivity of the multi-field free-text strategy (96% capture of MedDRA-coded cases) and the inadequacy of structured MedDRA coding alone for paroxysmal nocturnal hemoglobinuria case ascertainment in VAERS.

Complement Inhibitor Status

Complement inhibitor (CI) status was acquired from VAERS medication fields and narrative text. CI status reflects documented treatment history, not necessarily confirmed active therapy at the time of the adverse event. VAERS reports record concomitant medications without standardized temporal annotation. At least eight cases coded as "on CI" were pre-eculizumab (CI-naïve) at the time of the adverse event per narrative review (VAERS 824445, 873975, 875483, 1114131, 1114132, 1114134, 2326343, 2491687). Concurrent CI therapy was documented in a subset of breakthrough hemolysis (BTH) cases.

Classification Rationale

PNH as a disease is inherently multisystem, involving hemolysis alongside thrombosis, marrow failure, and other complications that present classification and coding challenges. Hsieh et al. reported a PNH case of cutaneous thrombosis with hemorrhagic necrosis along with a literature review of 5 other cases (Hsieh's Table 1 below). All six cases had multiple significant associated serious manifestations including portal and mesenteric vein thrombosis, myelodysplastic syndrome, and cytopenia/Aplastic anemia (AA). [27]

Table 1 Clinicopathologic findings of six cases of paroxysmal nocturnal hemoglobinuria associated cutaneous thrombosis.

Case no.	Age/sex	Cutaneous manifestation	Location	Associated symptom/sign	Pathology
1. Rietschel et al[8]	28/F	3 d history, large geographic plaques with bullae, necrosis	Flank & legs	Abdominal pain, fever	Thrombi in all dermal blood vessels, small amounts of nuclear dusts, no true vasculitis
2. White et al[9]	40/M	1 wk history, multiple urticarial plaques, tense bullae	Trunk	Hemolytic anemia, mesenteric vein thrombosis, pleural effusion	Neutrophil-rich subepidermal blisters & fibrin thrombi in numerous capillaries
3. Cholez et al[10]	70/F	Acute necrotic plaques	Ear lobes	Myelodysplastic syndrome, fever	Thrombosis of the capillaries, superficial and mid dermis with necrotic vasculitidis
4. Alves et al[11]	64/M	3 d history, well-demarcated erythematous to violaceous plaques	Neck &trunk	Pancytopenia	Thrombosis of superficial and deep dermal vessels with focal epidermal necrosis
5. Salim et al[12]	24/F	Recent onset, a painful skin rash after nonspecific febrile illness	Generalized	Budd–Chiari syndrome, anemia, thrombocytopenia	Fibrin thrombi in capillaries, necrosis hemorrhagic infarction
6. Present case	53/F	1 week history, violaceous plaques with central necrosis and bullae	Cheek, bilateral ears	Aplastic anemia, fever	Extensive thrombosis in superficial & deep vessels, neutrophilic infiltrate

F = female; M = male; MW = molecular weight; N/A = not available.

Truncated Table 1 from Hsieh F-N, et al., Severe cutaneous thrombosis with hemorrhagic necrosis in a patient with paroxysmal nocturnal hemoglobinuria: A case report and review of literature, Dermatologica Sinica (2017), http://dx.doi.org/10.1016/j.dsi.2017.01.006 https://creativecommons.org/licenses/by-nc-nd/4.0/

Sangwan, et al. recently extended the published accounts of cutaneous thrombotic vasculopathy to eight. [28] None of the reported eight cases were associated with vaccination.

Case 2796224 in the current VAERS series is a 23 year-old woman with PNH who had severe skin necrosis associated with a post vaccination hemolytic event. Onset of hemolytic crisis was within 10 minutes of being vaccinated with Haemophilus influenzae type b (Hib/HIB) (Sanofi-Pasteur Lot UK092AA), Bexsero (Novartis Lot PX7EZ) and Menactra (Sanofi-Pasteur Lot L7373). Her laboratory values included a hemoglobin of 4.1 (ref. 11.5 - 15 gm/dl), white blood cell count of 1.2 (ref. 4-10.5 thousand/MCL), D-dimer 9,675 (ref. 215-500 ng/ml fibrinogen equivalent units (FEU)), platelets 7 (ref. 150-400 thousand) and troponin I 59 (ref. 0-15 ng/L). Following intensive care unit treatment and total hospital stay of five months the patient was discharged. In our classification, this case falls under hemolytic events of special interest (thrombosis). VAERS cases 757454 and 376900/377388 in this series had myonecrosis as well as cutaneous thrombosis.

Figure 2 (below) illustrates the classification scheme used in this analysis based on adverse events from complement activation comprising rechallenge hemolysis (A), rhabdomyolysis (C), thrombosis (D), marrow failure/cytopenias (E), new-onset PNH (H), other (I), neurological (J), and primary hemolysis (K) or complement inhibition comprising non-meningococcal infection (F) including breakthrough COVID-19 (BTC) and breakthrough meningitis (BTM, G). Section B (deaths) is entirely cross-listed.

Figure 2. Clinical Subgroups by Clinical Phenotype

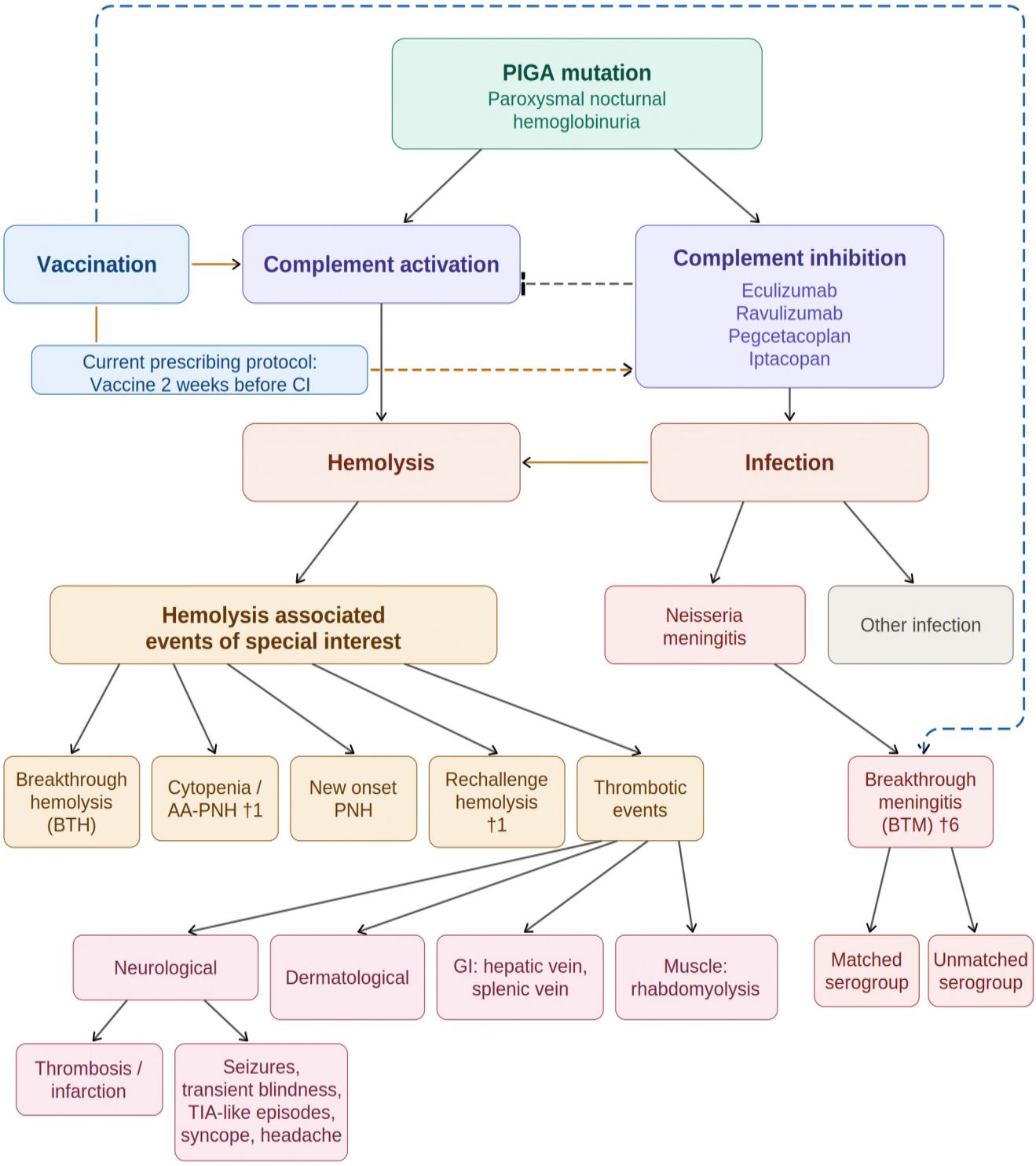


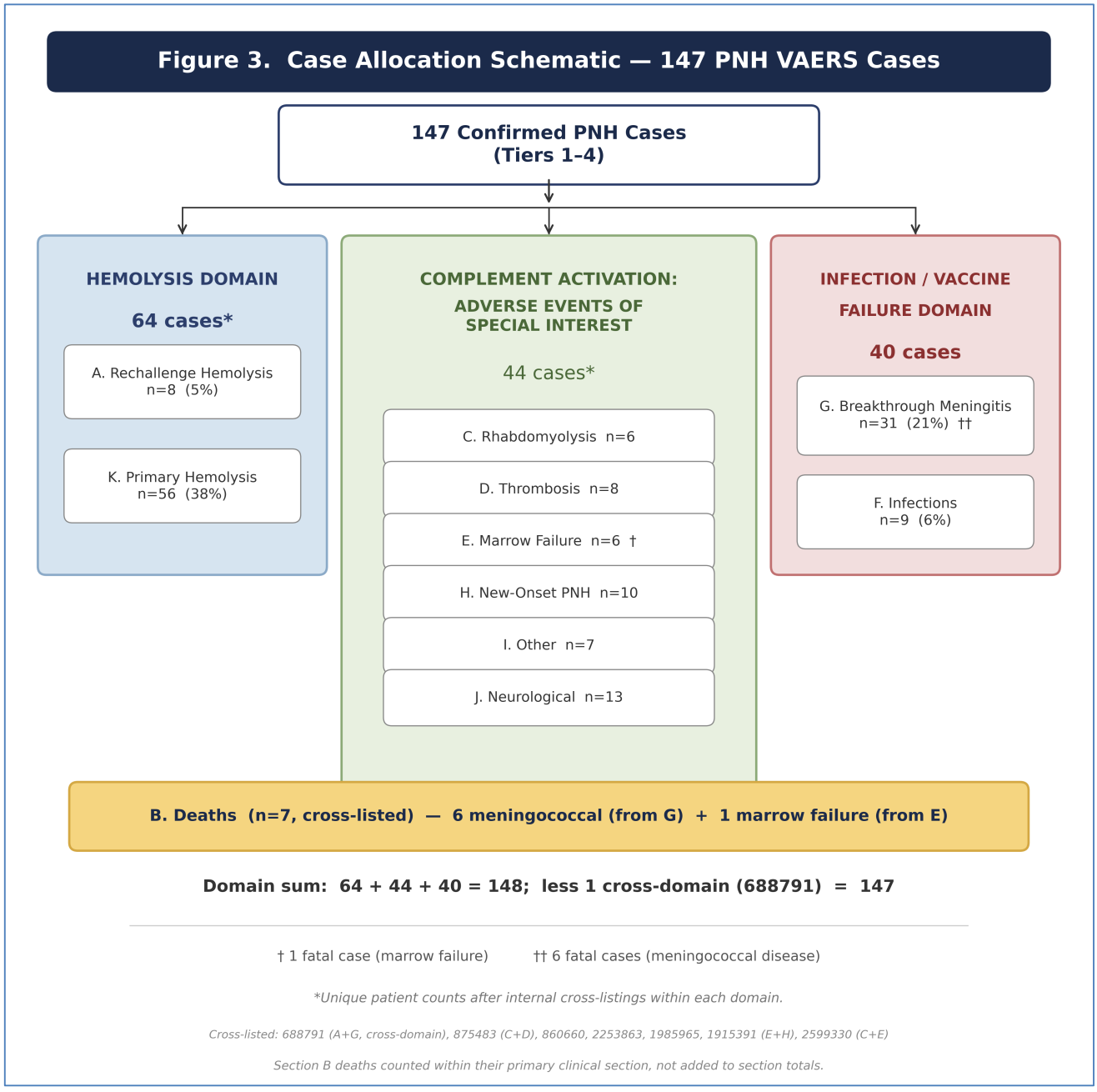
Figure 2. Pathophysiology and classification of PNH adverse events following vaccination

† = death

Case Assignment Hierarchy

Primary-section assignment follows a three-level rule: (1) chronological primacy: when two mechanistic domains are both present, the domain whose clinical manifestation appeared first in the case timeline is primary; (2) diagnostic specificity: when two domains are temporally coincident, the domain with the more specific diagnostic criteria takes precedence (Section A rechallenge is more specific than Section K primary hemolysis because it requires documented response on multiple separate doses); (3) severity of presenting event: when chronology and specificity do not resolve the assignment, the domain of the presenting severe event governs. Figure 3 illustrates the clinical distribution of 147 cases of AEs following vaccination in VAERS.

Figure 3 (below) gives the distribution of cases in this report.



Results

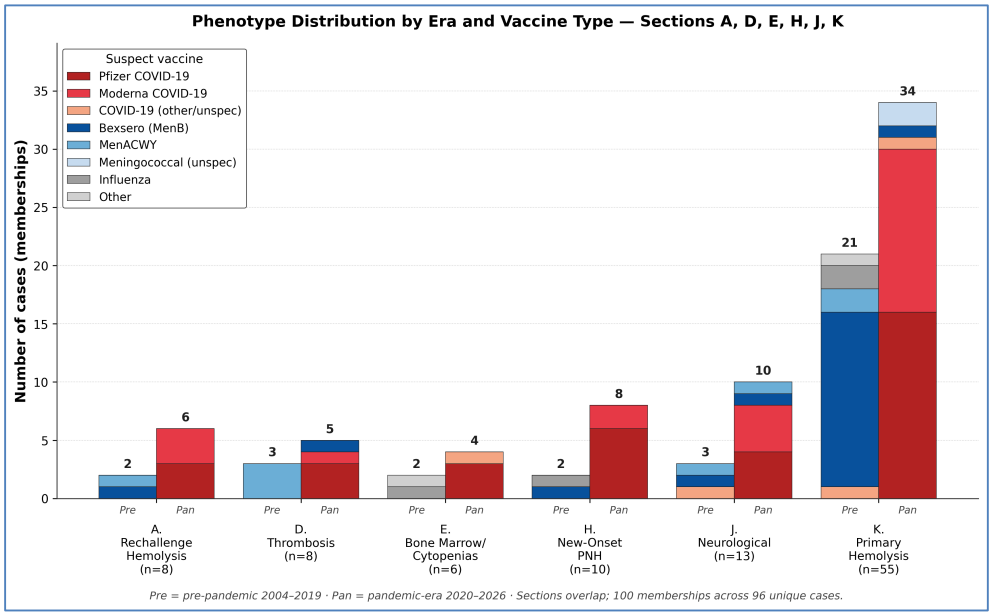
Overview

Complement activation disorders accounted for 73% of the adverse event (AE) reports and 27% were related to complement inhibition/infection which is primarily BTM. Primary hemolysis was the largest category (n=55, 37%), followed by breakthrough meningococcal disease (n=32, 22%). Seven deaths were verified: six from invasive meningococcal disease (IMD), one fulminant aplastic anemia. No primary hemolysis deaths occurred.

Bimodal Temporal Distribution By Era and Vaccine (Figure 4)

Pre-pandemic cases (n=65) were predominantly meningococcal-vaccine-associated (59/65, 91%), with Bexsero MenB-4C accounting for over half (33/65, 51%). Pandemic-era cases (n=82) were predominantly COVID-19-vaccine-associated (68/82, 83%), with Pfizer BNT162b2 (n=35) and Moderna mRNA-1273 (n=27) predominating.

Figure 4. Complement Activation By Era and Vaccine



Five cases (VAERS 1325289, 1742801, 1796281, 1937233, 2454993) had their structured VAX_DATE field populated with the patient's eculizumab initiation date rather than the suspect-vaccine administration date, displacing apparent vaccination dates by 2.0 to 10.7 years prior to the actual event (median 7.3 years). All five originated from a single manufacturer-solicited foreign-report pipeline; four were also affected by the 11 November 2022 split-type blanking event. “Split Type” is a VAERS administrative linkage field used to associate related records generated during manufacturer submission, regulatory processing, duplicate handling, or follow-up updates to an adverse event report. Vaccination years for these cases were reassigned to 2021–2022 based on narrative-confirmed COVID-19 vaccine administration dates. Without this correction, automated date-stratified queries would misclassify these pandemic-era cases as pre-pandemic.

Demographics

Of 147 cases, 117 (80%) had known age (median 40 years, range 15–81) after curation. Thirty cases had unknown age (28 coded as Unknown plus 2 blank fields; one case reporting age as “30s” was counted as known, using 35 for calculations). Sex distribution was 69 female (47%), 65 male (44%), and 13 unknown sex (9%).

Complement Inhibitor Status

Complement inhibitor exposure was documented in 117 of 147 cases (80%). Eight cases (5%) were confirmed CI-naïve at the time of the adverse event. Twenty-two cases (15%) had unknown or unreported CI status.

Rechallenge Hemolysis (Section A, n = 8; Supplemental Material Section 2, Timelines 2-6)

Eight patients experienced documented hemolysis on two or more separate vaccine doses (Table 2). Six received COVID-19 vaccines (3 Pfizer, 3 Moderna) and two received meningococcal vaccines. Cases 2053730 and 2056562 demonstrate reduction from nine to eight rechallenge patients from the deduplication finding that VAERS represent a single patient's dose 2 and dose 3 events, respectively, filed one day apart under the identical Centers for Disease Control and Prevention (CDC) Split Type (USMODERNATX, INC.MOD20224) with verbatim symptom descriptions. VAERS 2056562 (Moderna, retained) carried the manufacturer-confirmed positive rechallenge designation across doses 2 and 3.

VAERS 2326343 (Timeline 6) provided the only CH50 complement consumption measurement in the 147 cases: baseline 53.2 U/mL declining to 36.8 U/mL after dose 2 (31% drop), with concurrent LDH spikes (1,150 → 2,039 after dose 1; 1,150 → 1,961 after dose 2), persistent gross hemoglobinuria, and unchanged D-dimer.

VAERS 2491687 (Timeline 5) provided a three-dose natural experiment: dose 1 produced no hemolysis in a complement-inhibitor-naïve patient; dose 2 triggered massive hemolysis (LDH 8,506 U/L, hemoglobin 4.8 g/dL) leading to eculizumab initiation; a subsequent booster on ravulizumab protection produced no hemolysis.

One case (688791, 16F; Timeline 7) had a fatal outcome attributed to breakthrough invasive meningitis following earlier recurrent hemolytic crises after Bexsero and Menactra vaccination. An autopsy identified Waterhouse–Friderichsen syndrome from meningococcal serogroup B infection.

Table 2. Eight Rechallenge Hemolysis Cases

Case	VAERS ID	Age/Sex	Vaccine	CI Status	Key Evidence
1	688791	16F	Bexsero+Menactra	Eculizumab	Recurrent crises. Fatal (Meningitis)
2	2841418	29F	Pfizer	Pegcetacoplan	BTH on both doses.
3	1353575	53F	Pfizer	Unknown	Hemoglobinuria on both doses.
4	2056562	Unk/M	Moderna	Ravulizumab	Mfr-confirmed rechallenge.
5	824445	16M	MenACWY+MenB	Eculizumab	Positive rechallenge.
6	2491687	30s/F	Pfizer	Naïve→Ecu→Ravu	Three-dose proof. LDH 8,506.
7	1366882	63M	Moderna	Ravulizumab	Labs both doses. 99% clone.
8	2326343	29M	Moderna	Naïve	CH50 consumption. LDH spikes.

CI = complement inhibitor; Ecu = eculizumab; Ravu = ravulizumab; BTH = breakthrough hemolysis; Mfr = manufacturer. Timelines 2-6 in Red

Primary Hemolysis (Section K, n = 55)

Fifty-five cases had hemolysis/breakthrough hemolysis (H/BTH) as the primary adverse event, the largest single category (37%). COVID-19 vaccines accounted for the largest subgroup (n=31), followed by meningococcal vaccines (n=20,

including 16 Bexsero from 2014–2019), influenza, zoster, and unknown or blanked vaccines (n=4 combined).The majority occurred in patients on identified complement inhibitor therapy, including cases on dual-pathway inhibition (ravulizumab + danicopan).

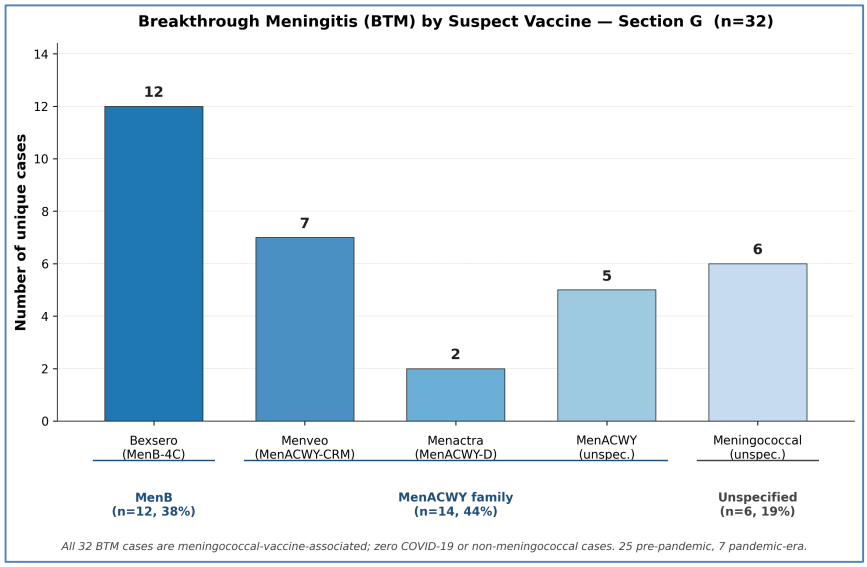
VAERS 2018621 had its record removed from VAERS on 2 September 2022 after existing for approximately eight months. Similarly, VAERS 2208209 record, documenting a hemolytic attack with frank hematuria following Pfizer booster vaccination, was removed from VAERS on 22 April 2022, approximately three weeks after entry.

The Wayback-recovered narrative for VAERS 2018621 additionally referenced a same-article companion case under Pfizer pharmacovigilance number US-PFIZER INC-202101854207 involving a different patient. No corresponding VAERS ID was identified in CDC WONDER or available MedAlerts/Wayback captures despite targeted search. The case was therefore considered documented but non-enumerable and excluded from cohort counts.

As with the dataset as a whole, these cases were medically significant. In spite of high medical acuity, fewer than half of cases (n=20) had hospitalization noted in the structured field. With hemoglobin counts commonly dropping well below 10 g/dL, hospitalization was probable more often than indicated in the corresponding structured field. No deaths occurred in these patients consistent with the expected clinical course of hemolytic flares in monitored PNH patients on complement inhibitor therapy, a testament to progress made in management of these complex medical cases.

Breakthrough Meningococcal (BTM) Disease (Section G, n = 32; Supplemental Material Section 2, Timelines 7-9)

Figure 5. BTM by Vaccine



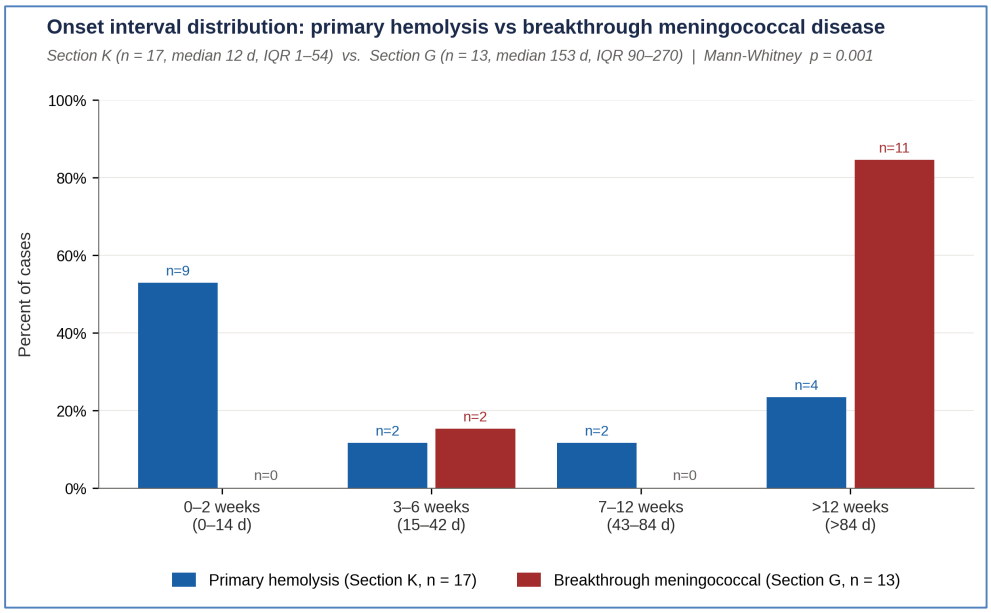
Thirty-two cases of invasive meningococcal disease (IMD) were identified, occurring despite meningococcal vaccination advised by complement inhibitor prescribing protocols. Infections included both vaccine-covered serogroups (indicating immunologic failure under complement inhibition), non-covered serogroups, and nongroupable strains not targeted by any available vaccine. Six out of the seven fatalities in the entire cohort died from invasive meningitis infection.

Case 732872 (16F, fatal) had documented adequate post-vaccination antibody titers but died of a non-groupable meningococcal infection. VAERS case 2817863 had breakthrough invasive meningococcal sepsis progressing to septic shock requiring intubation, with splenic infarction, acute kidney injury, and disseminated intravascular coagulation while on eculizumab, approximately 3.2 years after MenACWY vaccination.

Onset Interval Analysis: Primary Hemolysis vs. Breakthrough Meningococcal Disease (Figure 6)

Among cases with documented onset intervals, primary hemolysis (Section K, n=17 with known onset) and breakthrough meningococcal disease (Section G, n=13 with known onset) showed markedly different temporal profiles. (Figure 6)

Figure 6. Onset BTH vs BTM



Primary hemolysis had a median onset of 12 days (interquartile range (IQR) 1–54 days), with 8 of 17 cases (47%) occurring within 3 days and 9 of 17 (53%) within 14 days of vaccination. Breakthrough meningococcal disease had a median onset of 153 days (IQR 90–270 days), with zero cases occurring within 14 days (Mann-Whitney p=0.001).

New-Onset PNH (Section H, n = 10; Supplemental Material Section 2, Timeline 1)

Ten cases of PNH first diagnosed following vaccination were identified across three vaccine platforms (COVID-19, Bexsero, diphtheria-tetanus-pertussis (DTP)/influenza/zoster). Six presented acutely (≤14 days post-vaccination), three with delayed onset (>14 days), and one had unknown onset timing, suggesting bimodal presentation: acute complement-mediated unmasking of subclinical clones versus delayed clonal selection. Two research groups have published peer-reviewed reports describing PNH onset following vaccination, lending external validity to these VAERS-identified cases. [20,21]

One case (1915391, 52F, Pfizer) was fatal: fulminant aplastic anemia with subarachnoid hemorrhage and disseminated intravascular coagulation (DIC) on day 31. This case is notable as the only non-meningococcal death in the dataset and the only death occurring in a complement-inhibitor-naïve patient with newly diagnosed disease. It is cross-listed in Section E (marrow failure).

Rhabdomyolysis/myonecrosis (Section C, n = 6; Supplemental Material Section 2, Timeline 13)

Rhabdomyolysis/myonecrosis following vaccination has been described in non-PNH populations [29,31–35]. A 20-year-old male in CDC's prospective surveillance of 16,974 healthy university students vaccinated with MenB-4C (Bexsero) during the 2013–2014 Princeton and UC Santa Barbara outbreak campaigns developed rhabdomyolysis with elevated creatine phosphokinase following dose 2 establishing a baseline Bexsero-attributable rhabdomyolysis signal in a population without PNH and without complement-inhibitor co-medication. [30] Six cases of rhabdomyolysis were identified in the PNH cohort. Five of six cases involved Bexsero (MenB-4C): three from lot 139201 (Cases 757454,

774874, 793226 — see Bexsero Lot 139201 Cluster, below), one from lot ABXA61AA (Case 875483, detailed below), and one with lot not reported (Case 2599330, brand identified through manufacturer-coded narrative ('Men B NVS'); coded VAXNAME field blanked — see Section 4 Data Integrity). The sixth case (Case 377388, 27F, 2010) preceded Bexsero's first regulatory approval and followed unspecified MenACWY + HIB co-administration; the phenotype was injection-site myonecrosis with skin necrosis requiring two debridements and a split-thickness skin graft.

A 16-year-old female with paroxysmal nocturnal hemoglobinuria underwent pre-eculizumab meningococcal vaccination with MenB (Bexsero) on 2020-06-18. The chronology in Table 3 below summarizes the ensuing course, beginning with the principal deterioration approximately 48 hours after vaccination and progressing to upper-extremity compartment syndrome with deltoid myonecrosis, gastrointestinal bleeding, mesenteric vein thrombosis, operative intervention, and intensive care unit (ICU) admission.

Table 3. Clinical chronology of VAERS ID 875483

Date	Event	Findings	Interventions	Outcome
2020-04-30	Prior vaccine exposure	MenACWY + influenza vaccine reportedly followed by marked local reaction, hematochezia/blood in stool, abdominal ulceration, and 4-day ICU stay.	ICU care.	Recovered sufficiently for later MenB vaccination; final details not provided.
May 2020	Pre-index GI workup	Colonoscopy with intestinal biopsy; prior blood in stool and gastric ulcer noted.	Colonoscopy; biopsy.	Baseline GI pathology under evaluation.
2020-06-18	Index vaccination	MenB (Bexsero), dose 1, lot ABXA61AA, given in pre-eculizumab window.	Vaccination.	Start of index exposure.
~2020-06-20	Early deterioration	~48 h later: severe LUE pain/edema (shoulder→wrist), hemodynamic instability, suspected compartment syndrome, muscle injury/necrosis.	Hospitalization; ICU-level care; cefepime, vancomycin, prednisone, mesalazine, morphine, other antibiotics.	Severe ongoing illness.
2020-06-21	GI hemorrhagic event	Lower GI hemorrhage, melena, blood in stool/enterorrhagia; large-volume lower GI bleeding described.	Supportive inpatient care.	Ongoing severe illness.
2020-06-24	LUE imaging	MRI/NMR: extensive deltoid edema/enlargement, fascial-myotendinous involvement, possible perfusion deficit, concern for compartment syndrome, perifascial/intermuscular collections, subacromial-subdeltoid bursal fluid.	Imaging evaluation.	Severe soft-tissue injury confirmed.
2020-06-24	Operative management	Intraoperative limb findings included muscle necrosis; possible need for partial muscle resection noted.	Surgical decompression/fasciotomy of LUE.	Remained critically ill in ICU.
2020-06-25 to 2020-06-26	Early postoperative follow-up	Condition described as severe; possible need for larger resection; family informed regarding sequelae.	Continued ICU care; reassessment planned.	No discharge forecast.
2020-06-27	Abdominal vascular complication	Abdominal angiotomography: abdominal distension with mesenteric vein thrombosis.	Diagnostic imaging; anticoagulation later documented.	Major thrombotic event documented.

Date	Event	Findings	Interventions	Outcome
2020-06-29	Follow-up physician report	Still severe but hemodynamically stable; LUE debridement performed; persistent abdominal distension and mesenteric vein thrombosis; ongoing enterorrhagia.	Piperacillin/tazobactam, vancomycin, fluconazole, enoxaparin, ropivacaine, morphine, gabapentin, dipyrone, methylprednisone, mesalazine, folic acid; fasciotomy with removal of necrotic deltoid tissue reported.	Persistent severe hospitalization.
2020-07-08	Case entry	VAERS entry recorded.	Administrative entry.	Final recovery status not documented; report lists outcome as unknown/not recovered.

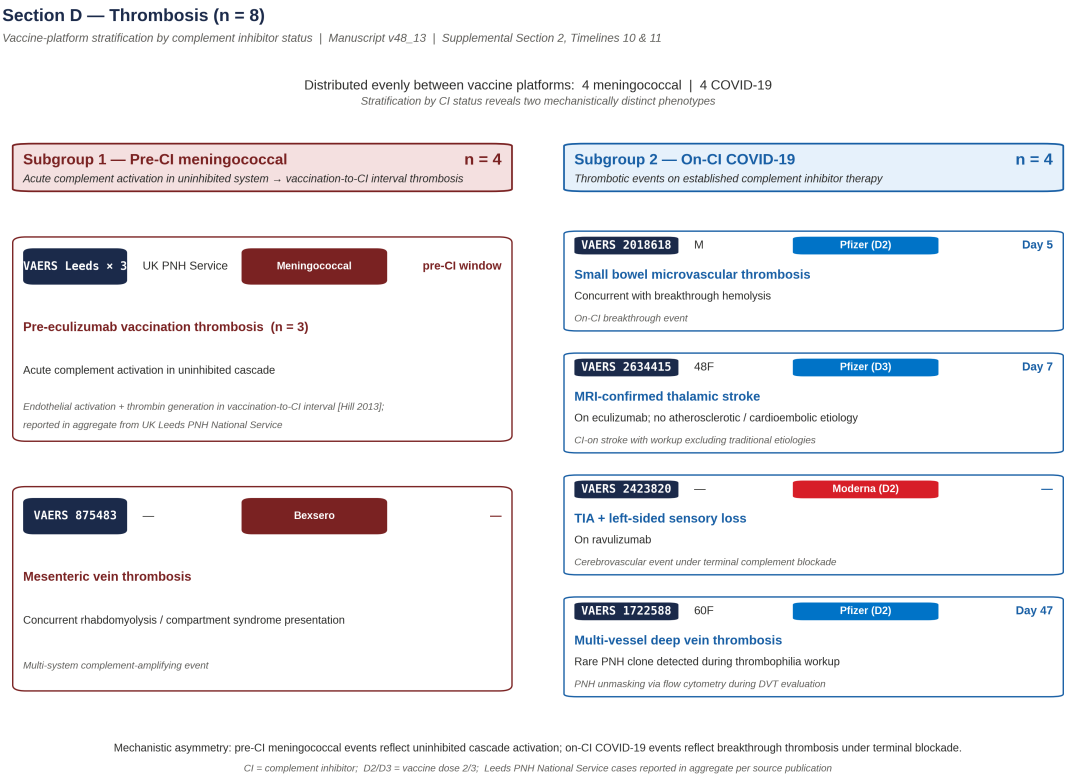
Abbreviations: GI, gastrointestinal; ICU, intensive care unit; LUE, left upper extremity; MenACWY, meningococcal quadrivalent conjugate vaccine; MenB, meningococcal serogroup B vaccine; MRI/NMR, magnetic resonance imaging/nuclear magnetic resonance.
Note: Index exposure was Bexsero (MenB) on 2020-06-18 in a patient with PNH undergoing pre-eculizumab vaccination. The structured onset field (2020-06-01) predates vaccination and is internally inconsistent with the narrative, which places the principal deterioration at approximately 48 hours after vaccination.

Case 377388 (Timeline 13) involved a 27-year-old female with myonecrosis at the injection site that required two surgical debridements of dead muscle followed by a skin graft.

Thrombosis (Section D, n=8; Supplemental Material Section 2, Timelines 10 & 11)

Thrombosis cases were evenly divided between COVID-19 and meningococcal associated vaccination. Figure 7 below.

Figure 7. Thrombosis cases by Vaccine



Eight thrombosis cases were identified, distributed evenly between vaccine platforms (4 meningococcal, 4 COVID-19). The first subgroup (pre-CI meningococcal thrombosis, n = 4) comprises three cases originating from the UK Leeds PNH

National Service during the pre-eculizumab vaccination window (reflecting acute complement activation in an uninhibited complement system that generated endothelial activation and thrombin generation in the vaccination-to-CI interval [36]) and one Bexsero case with mesenteric vein thrombosis occurring as part of the rhabdomyolysis/compartment-syndrome presentation (VAERS 875483).

The second subgroup (on-CI COVID-19 thrombosis, n = 4) comprises cases occurring in patients established on complement inhibitor therapy: VAERS 2018618 (M, Pfizer dose 2) presented with small bowel microvascular thrombosis on day 5, concurrent with breakthrough hemolysis; VAERS 2634415 (48F, Pfizer dose 3) developed MRI-confirmed thalamic stroke on day 7 while on eculizumab, with no atherosclerotic or cardioembolic etiology identified; VAERS 2423820 (Moderna dose 2) presented with transient ischemic attack TIA and left-sided sensory loss on ravulizumab; and VAERS 1722588 (60F, Pfizer dose 2) presented with multi-vessel deep vein thrombosis 47 days post-vaccination, with a rare PNH clone detected on flow cytometry during thrombophilia workup.

Cytopenia/Marrow Failure (Section E, n=6; Supplemental Material Section 2, Timeline 12)

The PIGA mutation affects all hematopoietic lineages because it arises in a multipotent hematopoietic stem cell, leading to clonal expansion of GPI-deficient cells. [2] There is an overlap with aplastic anemia and myelodysplastic syndrome. [21,25,37–39] Cases in this series followed Pfizer BNT162b2 COVID-19 and HPV vaccination. Five required hospitalization. One death occurred: fulminant aplastic anemia with subarachnoid hemorrhage and disseminated intravascular coagulation (VAERS 1915391, 52F, Pfizer, day 31 post-vaccination), the only non-meningococcal death in the dataset.

VAERS 2253863 (72F, Pfizer) demonstrated positive rechallenge: dose 1 produced respiratory symptoms; dose 2 produced respiratory reaction followed 19 days later by hospitalization for very severe aplastic anemia with a PNH clone (hemoglobin 6.5 g/dL, platelets 2,000/μL), requiring hATG, ciclosporin, eltrombopag, and transfusion support. The treating physician attributed the aplastic anemia to the vaccine and concluded that further COVID-19 vaccination was contraindicated.

Neurological (Section J, n=13)

Presentations included persistent headache, syncope, seizures, transient blindness, neuropsychiatric symptoms, transient palsy/paralysis, and TIA-like episodes. Seven followed COVID-19 vaccination. Two required hospitalization. VAERS 614894 (75F, Bexsero dose 2) presented with transient unilateral blindness, dysphagia, and asthenia concurrent with hemoglobinuria while on eculizumab, requiring hospitalization. VAERS 1284361 (81M, Pfizer dose 2) developed epileptic seizures and serious confusion on day 1 post-vaccination while on eculizumab, requiring ambulance evaluation. VAERS 482174 (46F, MenACWY booster) was hospitalized for severe headache on day 1 post-vaccination while on eculizumab, despite having tolerated the initial MenACWY dose without incident. VAERS 2466958 (F, MenACWY) experienced three episodes of syncope over two years following vaccination while on ravulizumab.

Non-meningococcal Infection (Section F, n=9)

Non-meningococcal infections comprised breakthrough SARS-CoV-2 (BTC, n=4) and other infections (n=5): bacterial pneumonia, cellulitis, staphylococcal bacteremia, herpes zoster reactivation, and a prior-infection-then-vaccination sequence. Four cases required hospitalization.

Breakthrough COVID-19 (BTC, n=4)

All four patients received COVID-19 vaccination and were subsequently diagnosed as having COVID. [7,21].

1. VAERS 2402571 (57F, Pfizer BNT162b2): PCR-confirmed SARS-CoV-2 infection in July 2022 in a fully vaccinated patient (two-dose Pfizer primary series March 2021; Moderna booster November 2021), requiring Paxlovid with documented rebound, and explicitly coded in the VAERS record as "VACCINATION FAILURE."
2. VAERS 2841418/2841419 (29F, Pfizer BNT162b2, pegcetacoplan) demonstrated stepwise deterioration across three sequential complement-activating exposures: COVID-19 vaccine dose 1 produced breakthrough hemolysis with fatigue and lethargy, resolving within one week; dose 2 produced recurrent breakthrough hemolysis (LDH 783 U/L, hemoglobin 7.6 g/dL) that did not fully stabilize to pre-vaccination baseline; and breakthrough COVID-19 in January 2022 produced the most severe episode (LDH 1,056 U/L, hemoglobin 6.1 g/dL), requiring platelet and red cell transfusions over two weeks, with hemolysis and laboratory abnormalities unresolved. By May 2022 the patient was transfusion-dependent every two to three months and under evaluation for bone marrow transplantation.
3. VAERS 2611862 (F, Pfizer, ravulizumab) experienced breakthrough COVID-19 twice during the pandemic with associated breakthrough hemolysis requiring hospitalization.
4. VAERS 2413060 (M, Moderna, eculizumab/ravulizumab) experienced breakthrough COVID-19 in June 2022 that delayed scheduled ravulizumab dosing.

Other Non-meningococcal Infections (n=5)

1. VAERS 457226 (74F, Pneumovax, eculizumab) was hospitalized for pneumonia (left lower lobe, subsequently right lung) beginning approximately two weeks after pneumococcal vaccination. No sputum culture, urine antigen testing, or other pathogen identification was recorded; the etiology of the pneumonia is not established in the report.
2. VAERS 512638 (76M, Pneumovax 23, eculizumab) was hospitalized for cellulitis after pneumococcal polysaccharide vaccination, with no systemic disease, hemolysis, or complement breakthrough recorded.
3. VAERS 1762487 (F, eculizumab) experienced two separate episodes of staphylococcal sepsis.
4. VAERS 2481546 (63F, COVID-19 vaccine, eculizumab) developed herpes zoster reactivation concurrent with breakthrough hemolysis and hemoglobin decrease, requiring hospitalization.
5. VAERS 2037321 (46F, Moderna, ravulizumab) had documented prior SARS-CoV-2 infection followed by severe breakthrough hemolysis after her second Moderna dose, requiring hospitalization, a sequential infection-then-vaccination complement-activating exposure pattern paralleling the sequence in VAERS 2841418/2841419.

Other (Section I, n=7)

The cases span four phenotypes: injection-site and musculoskeletal reactions following influenza or meningococcal vaccination (VAERS 361153, 576021); an allergic reaction with pharyngeal edema coded as an Important Medical Event (VAERS 608964); lymphoid and local reactions following mRNA COVID-19 vaccination (VAERS 1072344, 1315262, 1653288). Constitutional syndrome with influenza-like illness, low-grade fever, and exertional chest/arm pain was reported following co-administered influenza and COVID-19 vaccines (VAERS 1799451).

Bexsero Lot 139201 Cluster

A single Bexsero lot (139201) accounted for 10 cases in the 147-case dataset, five times the count of the next most common lot (VAERS IDs: 575458, 575881, 576021, 576031, 576231, 583745, 602868, 757454, 774874, 793226). The 10 cases comprise 6 primary hemolysis (Section K), 3 rhabdomyolysis (Section C: VAERS 757454, 774874, 793226), and 1 arthralgia/myalgia (Section I).

The three lot 139201 rhabdomyolysis cases account for 50% of all rhabdomyolyses in the dataset (Section C, n=6), constituting a lot-specific myotoxicity signal with physician-documented attribution from a single PNH center. The remaining seven lot 139201 cases presented with hemolysis or other adverse events without rhabdomyolysis. VAERS 757454 (29M, Bexsero lot 139201, France 2014) illustrates the chronic-eculizumab amplifier mechanism. The patient had been maintained on Soliris (eculizumab) since November 2010 — approximately 3.5 years of continuous terminal complement blockade prior to vaccination — with established Budd-Chiari syndrome, portal vein thrombosis,

hepatic damage, portal hypertension, and renal failure as the cumulative thrombotic-end-organ phenotype of long-standing PNH. Following Bexsero dose 1 on 28 May 2014, the patient developed injection-site warmth ("felt like fire") within 24 hours, hemoglobinuria within 48 hours, and laboratory-confirmed hemolysis with hemoglobin drop from baseline ~120 g/L to 106 g/L by 3 June.

The treating hematologist explicitly disclosed that 6 PNH patients on Soliris had received Bexsero per protocol, with significant injection-site reactions, vomiting, myalgia, weakness, and flu-like symptoms across the cohort; potential rhabdomyolysis was considered as a cohort-level concern. This case demonstrates that peak therapeutic complement-inhibitor coverage — chronic, established, multi-year eculizumab — does not abolish vaccine-triggered breakthrough hemolysis, and that the lot 139201 cluster reflects a center-level cohort phenomenon rather than three independently filed isolated reports.

Data Integrity

Table 4 presents categories of data deficiency identified in this study. A detailed analysis is in the Supplementary Materials Section 4.

Table 4. Categories of Data Loss in VAERS

Categories of Data Loss

PNH VAERS 147-Case Cohort | Compiled 5/2/2026 | Cross-references to Data Integrity Flaws Catalog (Section 4)

#	Category	Mechanism	Quantification	Catalog refs
1	**Initial absence** *(never captured)*	Structured or narrative field blank at original report entry, before any post hoc activity. Predominant in foreign-MAH expedited reports where capture forms truncate or omit data elements absent from the originating regulatory channel.	Structured fields (A): 3.9%–96.1% blank rate by field across N = 153 common records Narrative (B1): 38/153 reports (24.8%) initially blank; recovered to 100% via off-platform archival sources	A1–A16, B1
2	**Post hoc blanking**	Content present at one timepoint, removed at a later timepoint without record deletion. Three sub-mechanisms: • **Tier 1:** full narrative removal • **Tier 2:** Split-Type identifier blanking severs reporter-channel linkage • **Uniform, multi-platform, same-day modification event:** convergent across pharma channels and jurisdictions on a single date (11/11/2022)	Tier 1: 3/147 cases (2.0%) Tier 2: 18/147 cases (12.2%); all foreign-filed 11/11/2022 mass event: 21/147 cases (14.3%); zero US	D1–D5, E1–E3
3	**Full record deletion**	Entire record removed from current CDC WONDER export. Recoverable only via Wayback Machine archival captures of MedAlerts.org pre-deletion state. Distinct from blanking because the VAERS ID itself disappears from the database.	4/147 cases (2.7%) Latency to deletion: 14 days (1742850) to ≈8 months (2018621) Recovery via Wayback: 4/4 (100%)	F1–F3
4	**Longitudinal degradation** *(Case 824445 archetype)*	Single VAERS ID undergoing multi-year edit trajectory exhibiting mass-blanking inflection followed by extended cosmetic-only plateau. Distinct from category 2 because the trajectory is documented longitudinally on a single ID rather than inferred from population-level cross-sections.	Case 824445: 107 sequential revisions (11/14/2019 → 1/2/2026) Inflection #52 (12/16/2022): 2,353 → 83 words (96.5% data loss in one transaction) Stable plateau #52–106: 36.5 months at fixed 83-word state	C1–C5

#	Category	Mechanism	Quantification	Catalog refs
5	**Field displacement / corruption**	Field populated but factually wrong. Three documented sub-mechanisms: • VAX_DATE replaced by eculizumab initiation date • Pre-vaccination onset date (chronologic impossibility) • Drug-name phonetic auto-mapping (Soliris → "OCTINOXATE, OCTOCRILENE (SOLARIS)"; ravulizumab → "ROVELIZUMAB")	VAX_DATE displacement: 5/147 (3.4%); range 2.0–10.7 yr; median 7.3 yr Pre-vax onset: ≥1/147 (≥0.7%); structurally undetectable without per-case audit Drug-name auto-mapping: 2/147 (1.4%)	H1; J1, J2
6	**Coding-level invisibility**	Content is present in the database but unfindable by canonical pharmacovigilance query. Includes MedDRA Preferred-Term-only search miss and generic-code substitution (e.g., "Condition aggravated") replacing specific clinical detail in narratives altered post-publication.	MedDRA PT-only search: misses 121/147 confirmed PNH cases (82.3%) using PT "Paroxysmal nocturnal haemoglobinuria" alone (captures 26/147)	H2
7	**Duplication-driven signal dilution**	Record-count inflation without system-level deduplication. Distorts denominators and event rates; functionally equivalent to data loss for pharmacovigilance signal-detection purposes (true-event count obscured by structural multiplicity).	Cohort internal dedup: 8/161 (5.0%) collapsed to 153 unique cases Five distinct duplication mechanisms documented Triple-filing pattern observed in broader eculizumab pull (2178262/2420225/2560508; 3 IDs, 1 patient; not in 147 cohort) HA Standardized MedDRA Queries (SMQ) pull: 1.48× row-to-unique-ID inflation (607 rows / 409 IDs)	I1–I6

Note. *Trivial / cosmetic mass edits (Catalog Section G — apostrophe-pass standardization, dose-field permutations) are excluded from this categorization. They do not constitute data loss but contribute to audit-trail overhead by cluttering the change history with semantically null operations, thereby obscuring the timestamps and transactional context of the seven loss categories above.*

Cross-reference. *Catalog refs in column 5 point to entry IDs within the Data Integrity Flaws — Quantified Catalog (Section 4 of this manuscript). Quantifications use the manuscript working dataset N = 147 unless otherwise stated; A and B rows reference the Completeness Analysis common-records snapshot N = 153 (curated ∩ raw VAERS download).*

Changes in the VAERS data fields after initial publication occurred in 42% of cases. Modifications ranged from minor changes in syntax, to substantial loss of data in structured as well as free text fields referred to as blanking, to complete removal of the entire record from the public-facing data. Figure 8 below shows before and after manual curation (RWC). Section 4 of the Supplemental Material section presents mapping of the data recovery effort. Symptom_Text, the narrative description of the case, was restored to 100%.

Figure 8. Manual Physician Data Recovery

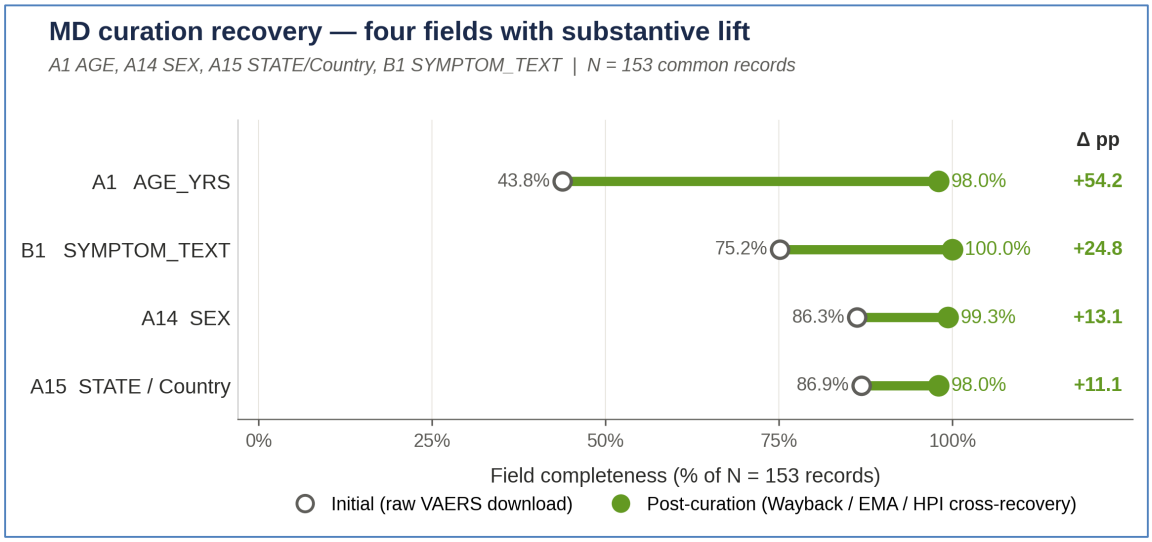
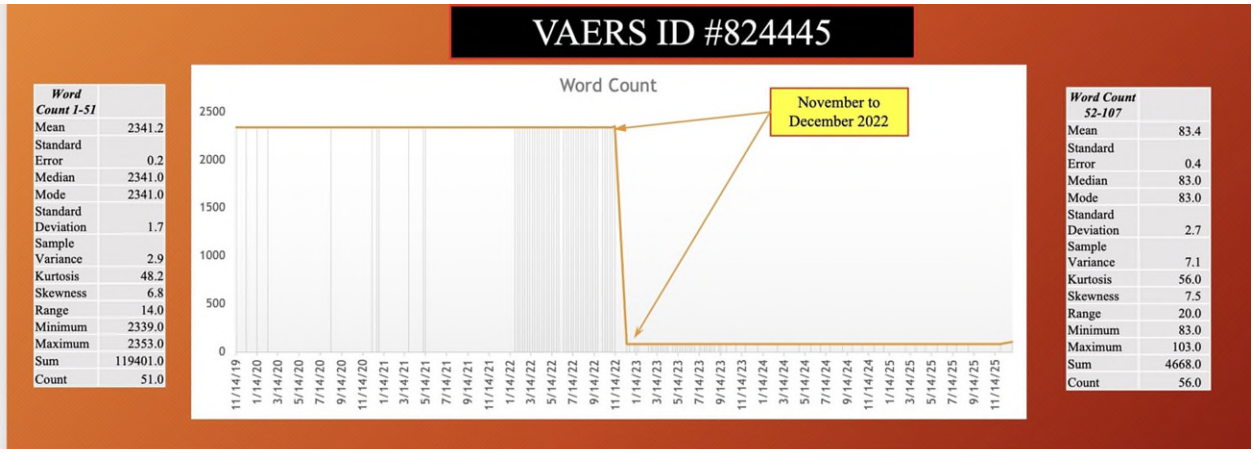


Figure 9 below shows how 106 updates to Case 82445 changed the word count capturing the deletion event of 11/11/2022. CDC's own documentation describes the rationale:

> At the request of European regulators, CDC and FDA have removed certain data fields (country codes; reported symptom case narrative free text; diagnostic laboratory data free text field; illness at time of vaccination free text field; chronic conditions free text medical history field; allergies free text field) from foreign VAERS reports which were submitted to VAERS and may not comply with European regulations. Domestic (U.S.) VAERS reports are not affected by this process. [40]

Case 824445 (shows the effect of blanking in terms of data loss from the 11 November 2022 mass data modification event when the word count dropped from 2,341 to 83 after 106 edits as shown in Figure 9 below.

Figure 9. Word Counts Before and After 11 November 2022 Blanking Event



Case 1325289 (UK 40F, eculizumab, January 2020 meningococcal vaccine reaction). This case illustrates two adjacent integrity dimensions. First, the structured CDC Split Type field (GBPFIZER INC2021099101) was blanked on 11 November 2022, an exemplar of the Tier 2 mechanism (E2). Second, the Pfizer regulatory Write-up explicitly identifies the suspect vaccine as Meningococcal Group C Tetanus Toxoid Conjugate Vaccine (named six times) and self-flags potential duplication: "This may be a duplicate report if another marketing authorization holder of Meningococcal Group

C Tetanus Toxoid Conjugate Vaccine has submitted the same report to the regulatory authorities." The brand-specific identification is preserved in the original VAERS narrative; downstream summarization steps that strip such detail to "meningitis vaccine unspecified" should be checked against the source Write-up before brand information is treated as unrecoverable.

A two-tier data blanking structure was documented: Tier 1 narrative removal (3 foreign-filed cases), in which entire write-up text was removed from publicly accessible datasets, and Tier 2 Split Type blanking (18 foreign-filed cases), in which the Split Type identifier linking related reports was removed. Affected cases in this cohort were exclusively European foreign-filed reports, with no U.S.-filed cases affected.

The VAERS Wayback Machine (MedAlerts.org) preserved pre-modification content for all affected cases, enabling this analysis to be conducted on Wayback-restored data, making this dataset more complete than the current public VAERS download file. This recovery methodology permitted identification of clinical details, medication histories, and cross-references that would otherwise be lost and are currently not visible in the public record.

Two additional isolated post-event modifications were identified: VAERS 820822, whose CDC Split Type was blanked on 25 April 2025 (the most recent alteration in the dataset), and VAERS 1937233, whose narrative was substantially altered on 29 December 2023.

Beyond field-level changes, four cases in the dataset were removed from CDC WONDER entirely: complete record deletions rendering them not retrievable via keyword search or aggregate analysis.

- VAERS 688791 (fatal rechallenge Case 1) was removed from publicly accessible datasets approximately five months after entry and has never been restored.
- VAERS 1742850 (breakthrough hemolysis in a PNH patient on decade-long eculizumab) was removed from publicly accessible datasets after only 14 days of public availability.
- VAERS 2018621 (hemolysis on dual-pathway complement inhibition) was removed approximately 8 months after entry.
- VAERS 2208209 (hemolytic attack with frank hematuria requiring hospitalization) approximately 3 weeks after entry.

All four records were recovered via the Wayback Machine. The three additional write-up-blanked cases retained only structured VAERS fields (MedDRA codes, medication lists, demographic variables) for clinical reconstruction.

Five of 147 cases carried structured VAX_DATE values that encoded patient eculizumab initiation dates rather than suspect-vaccine administration dates, displacing apparent vaccination years 2 to 11 years before the actual event; vaccination years for these cases were reassigned from narrative-confirmed dates.

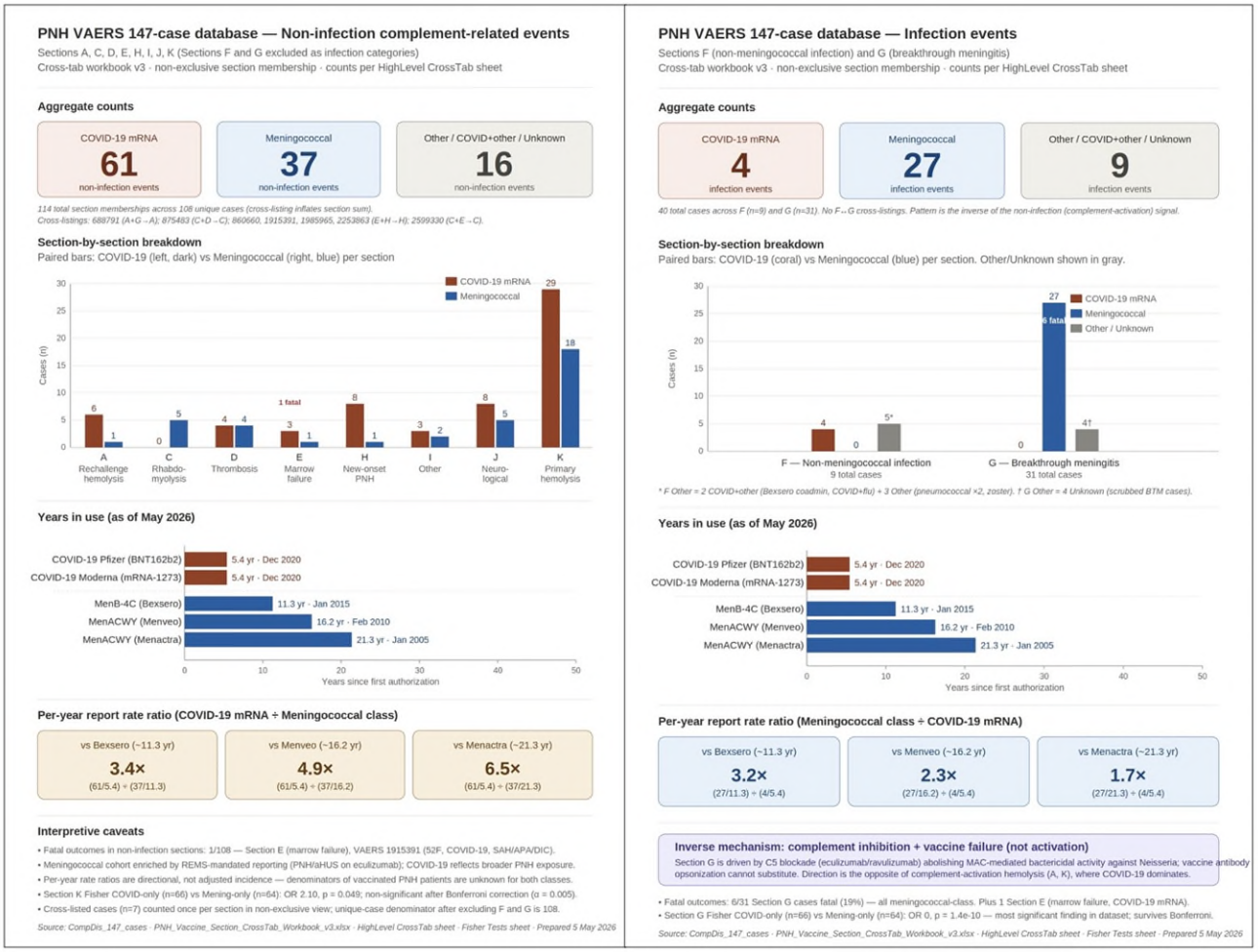
Deduplication also revealed two drug-name auto-mapping errors in the VAERS coding system with implications for pharmacovigilance methodology. VAERS 2454993 had Soliris (eculizumab) incorrectly mapped to "OCTINOXATE, OCTOCRILENE (SOLARIS)" (a sunscreen product) via phonetic match. VAERS 2056562 had ravulizumab incorrectly mapped to "ROVELIZUMAB", a different monoclonal antibody (anti-CD11/CD18, never FDA-approved). These errors mean that standard drug-name searches for eculizumab or ravulizumab in the VAERS Other Medications field would miss these PNH cases entirely, underscoring the necessity of multi-field, multi-term search strategies for rare-disease pharmacovigilance.

Discussion

Figure 10 below summarizes the findings in this study; AE reports featuring complement activation (hemolysis) is dominated by COVID-19 vaccines while complement inhibition (breakthrough infection from Neisseria meningitidis)

follows meningococcal vaccines. Complement activation disorders accounted for 73% of cases while complement inhibition accounted for six of the seven fatalities.

Figure 10. Complement Activation and Inhibition Following Vaccination in PNH Patients

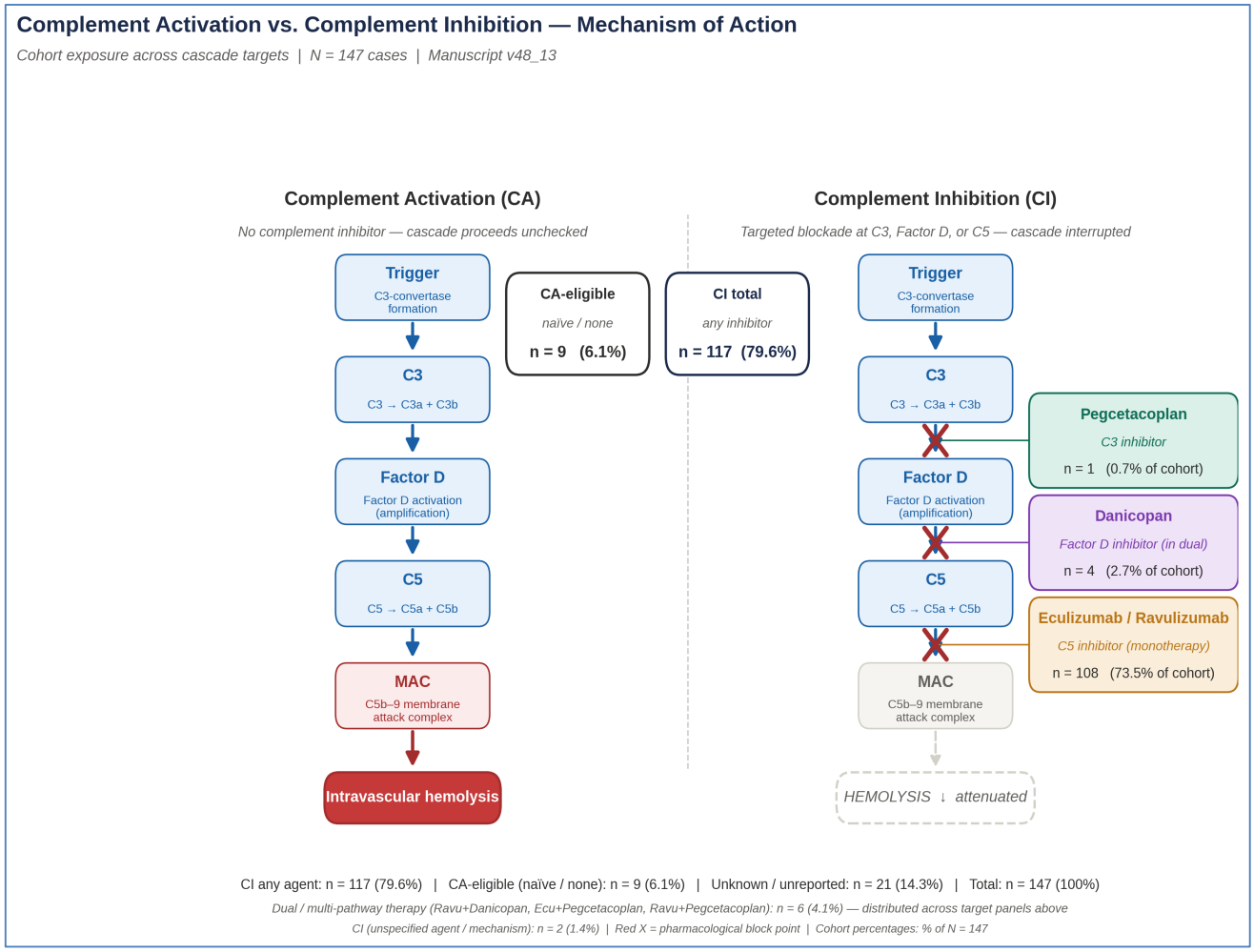


Platform Independence

Breakthrough hemolysis was documented across mRNA (Pfizer, Moderna), outer membrane vesicle (Bexsero), conjugate (MenACWY), polysaccharide (Pneumovax), inactivated (influenza), and live attenuated (Zostavax) platforms. This rules out platform-specific mechanisms (such as lipid nanoparticle reactogenicity or adenoviral vector effects) and points to the shared upstream event common to all vaccines: innate immune activation triggering complement via the classical, lectin, or alternative pathways.

Vulnerability to Neisseria meningitis associated with successful management of hemolysis with CIs created the drive to protect PNH patients with vaccines creating a therapeutic conundrum; control hemolysis with all of its manifestations or potentially more fatal invasive meningitis disease accounting for six of 7 fatalities reported in this series. Figure 11 outlines the two physiological pathways represented by VAERS PNH Cohort 147 reported herein.

Figure 11. New Onset Hemolysis Mechanism and Hemolysis Mitigation By Cis

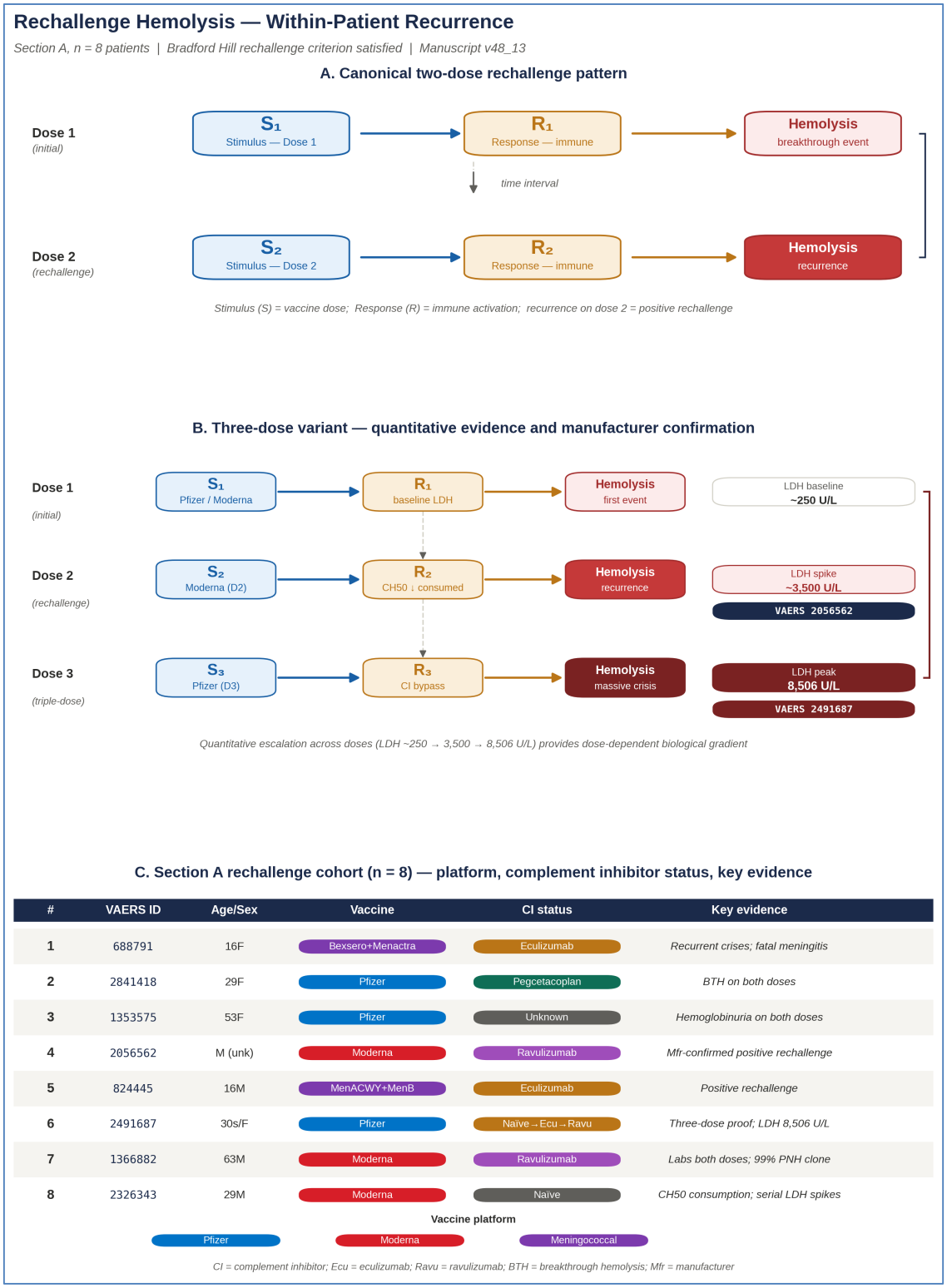


Bradford Hill Determination

Causation is established for hemolytic events in patients with PNH at a level of near certainty. Supplementary Materials Section 5 presents a formal causation analysis.

Eight rechallenge cases (Section A, Table 2) include a manufacturer-confirmed positive rechallenge (VAERS 2056562) and a three-dose natural experiment in a single patient (VAERS 2491687: dose 1 produced no hemolysis in a complement-inhibitor-naive state; dose 2 triggered massive hemolysis with LDH 8,506 U/L; a subsequent booster under ravulizumab produced no hemolysis). Figure 12 below is a schematic for the 8 rechallenge cases in the PNH cohort showing reproducible stimulus response relationship between vaccine provoked complement activation in close temporal proximity to vaccination.

Figure 12. Stimulus Response Analysis of Rechallenge Cases



Temporality is bimodal across 47 cases with documented intervals: primary hemolysis at median 12 days (IQR 1-54) and breakthrough meningococcal disease at median 153 days (IQR 90-270), Mann-Whitney $p = 0.001$ - two distinct mechanisms tracking the same index event. Rapid onset of surgically proven myonecrosis/rhabdomyolysis at the vaccine injection site in two cases and the one case of severe dermatological TMA is strong evidence supporting vaccination as the causative agent.

Table 5. Bradford Hill Criteria - Verdicts and Anchoring Evidence in the 147-Case Cohort

Criterion	Verdict	Anchoring evidence
1. Strength	**Met**	Cohort signal in rare disease (prevalence 10-16/million); 8 rechallenge cases; new-onset PNH OR 5.74 for mRNA platforms (p = 0.086). Strength fully bounded by capture-rate sensitivity analysis (Suppl. Section 5.3).
2. Consistency	**Met**	VAERS 153-day BTM median identical to Leeds 18-year prospective median [36]; Leeds Patient 5 = VAERS 1189037 (cross-identified individual); replication across Italian [18,41], Japanese [24], UK [36], US, and Lebanese [21] case series.
3. Specificity	**Met**	Myonecrosis at the injection site satisfies the specificity requirement.
4. Temporality	**Met**	Bimodal 12-day vs 153-day onset separation across Sections A/G/H/K (Mann-Whitney p = 0.001); zero BTM events <=14 days. Strongest single criterion.
5. Biological gradient	**Met**	VAERS 2491687 three-dose natural experiment (no hemolysis -> massive hemolysis -> no hemolysis on CI); VAERS 2326343 CH50 31% drop with concurrent LDH spikes; 8 rechallenge cases; Bexsero Lot 139201 cluster.
6. Plausibility	**Met**	GPI-anchored CD55/CD59 deficiency permits MAC assembly on PNH erythrocytes; documented LNP-mRNA biodistribution to bone marrow and lymphoid germinal centers [58–62].
7. Coherence	**Met**	All 11 clinical sections (A-K) internally consistent; aligns with regulatory framework of all six surveyed agencies (Suppl. Table 1); BTH/BTM paradox supplies single-mechanism explanation for two phenotypes.
8. Experimental evidence	**Met**	8 rechallenge cases including manufacturer-confirmed (VAERS 2056562); same-day CI+vaccine failure (VAERS 576231, 1742801, 1742850); free C5 = 0.11 ug/mL at breakthrough (VAERS 2724191); Leeds practice-change withdrawal evidence [36,57].
9. Analogy	**Met**	Surgery- and infection-triggered PNH flares [6]; aHUS and AIHA as analogous complement-mediated triggers; VITT as analogous vaccine-triggered, complement-implicated thromboinflammation.

Score: 9 of 9 applicable criteria met. Verdict shading: green = Met. Citations refer to the main manuscript reference list. Full criterion-by-criterion analysis with quantitative under-reporting sensitivity modeling and Leeds-Miller cross-validation of VAERS capture rates appears in Supplementary Section 5.

Breakthrough Hemolysis Under Complement Inhibition

The majority of primary hemolysis cases occurred in patients on identified CI therapy, including cases on dual-pathway inhibition (ravulizumab plus danicopan). VAERS has no dedicated CI field; CI status must be inferred from the free-text "Other Medications" field, so the 10 cases without identified CI therapy reflect a reporting gap rather than established CI absence.

Three findings argue that vaccine-triggered complement surges overpower, rather than merely coincide with gaps in, pharmacological CI blockade: breakthrough hemolysis under confirmed adequate terminal complement inhibition (VAERS 2724191, free C5 = 0.11 µg/mL); breakthrough under dual-pathway C5 and Factor D blockade (VAERS 1370315, 2018619, 2018621); and within-patient rechallenge positivity in all eight Section A cases. [Supplementary Material, Table 3]

CI and Vaccination Timing

The Dingli et al. [42] expert consensus recommends timing vaccination within the first half of the CI dosing interval to maximize drug coverage during the expected complement activation peak. Three cases in this dataset represent application of that strategy: same-day co-administration of CI infusion with vaccination. VAERS 576231 (Bexsero co-infused with Soliris on 15 October 2014) developed breakthrough hemolysis on day 3 with serial hemoglobin decline

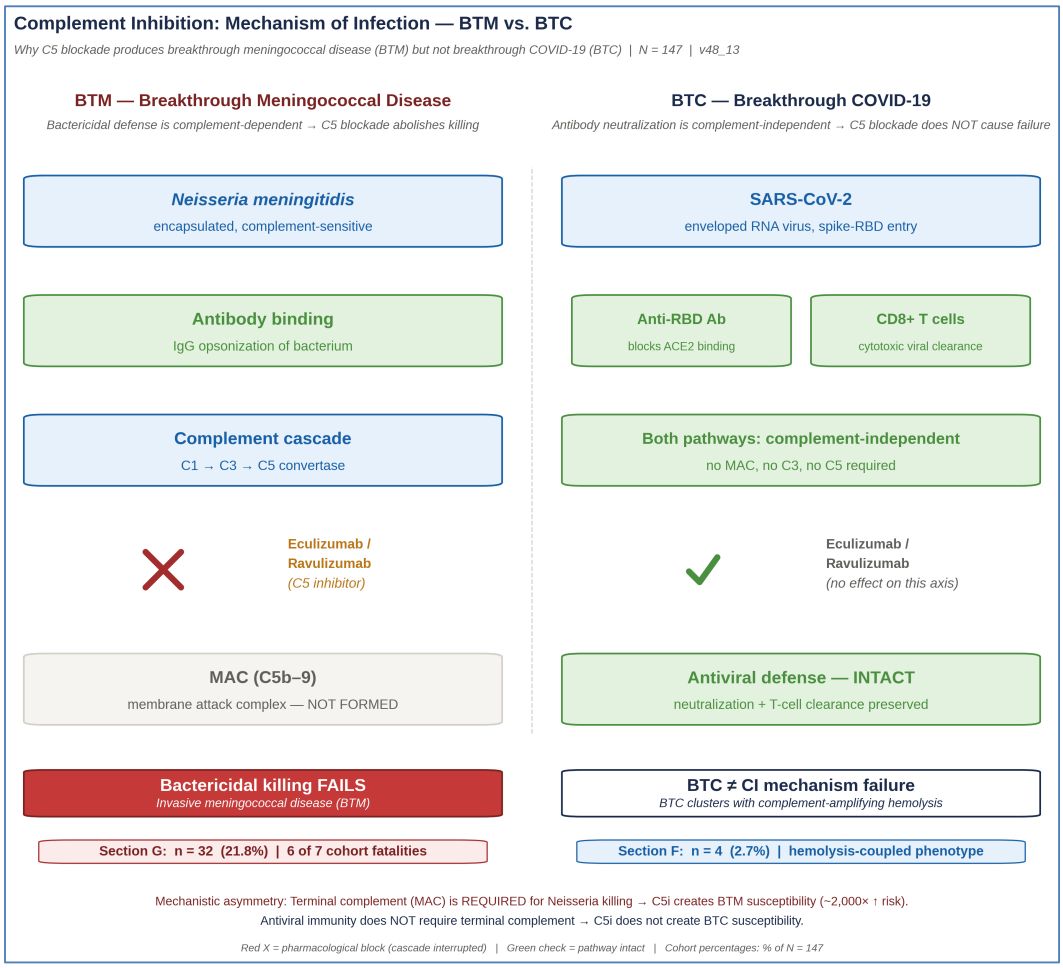
from 80 to 71 g/L requiring multiple red-cell transfusions. VAERS 1742801 and 1742850 (Pfizer BNT162b2 administered on the same day as scheduled eculizumab infusions) each developed jaundice, extreme fatigue, and measurable hemoglobin decline on the day of vaccination. Peak therapeutic CI coverage may be insufficient to prevent vaccine-triggered hemolysis in a subset of PNH patients.

Fattizzo et al. [22] distinguished pharmacodynamic BTH (complement-amplifying-condition–triggered) from pharmacokinetic BTH (trough-driven) concluded that vaccination overwhelms CI blockade producing the acute-onset pattern documented in Sections A (rechallenge hemolysis) and K (primary hemolysis) of this report. Fattizzo et al. [41] in an international multicenter study of 198 CI-treated PNH patients in 10 centers documented 271 BTH events over 18 years, with vaccinations triggering 8 events (3%), infections (55%) and unknown causes (22%), and an overall BTH incidence of 0.19 events per patient-year with 51% of patients experiencing at least one episode.

Breakthrough Infections for which Vaccines were given

Patients with complement disorders treated with complement suppression are differentially affected by Neisseria meningitis compared with SARS-CoV-2 because of the critical role complement acts to form Membrane Attack Complexes (MAC) that are necessary to destroy these specific bacteria while protection against SAR-CoV-2 is provided by a less complement dependent immune system. Figure 13 offers a mechanism to explain this disparity.

Figure 13. Proposed Mechanism of Breakthrough Infection, Virus vs. Bacteria



Breakthrough meningococcal disease in complement-inhibitor-treated PNH patients is a recognized complication, supported by prospective surveillance from the UK Leeds PNH National Service [36] (ASH 2020 conference abstract), infection management guidelines [8,43], mechanistic studies demonstrating impaired meningococcal killing despite

vaccination under C5 blockade [44–45], epidemiological analysis of prevention strategies [46], case reports of fatal or severe breakthrough infection in vaccinated patients [47–52], impaired vaccine immunogenicity data from a mixed aplastic anemia/PNH cohort (Pike et al. [25]), and a systematic review of post-vaccination meningitis in general (non-PNH) populations (Atefi et al. [53]). Ladhani et al. retrospectively identified 16 complement-deficient patients with 20 episodes of invasive meningococcal disease in England from 2008–2017, including 8 eculizumab-treated patients with 9 episodes; five of the eculizumab-treated patients had PNH [54].

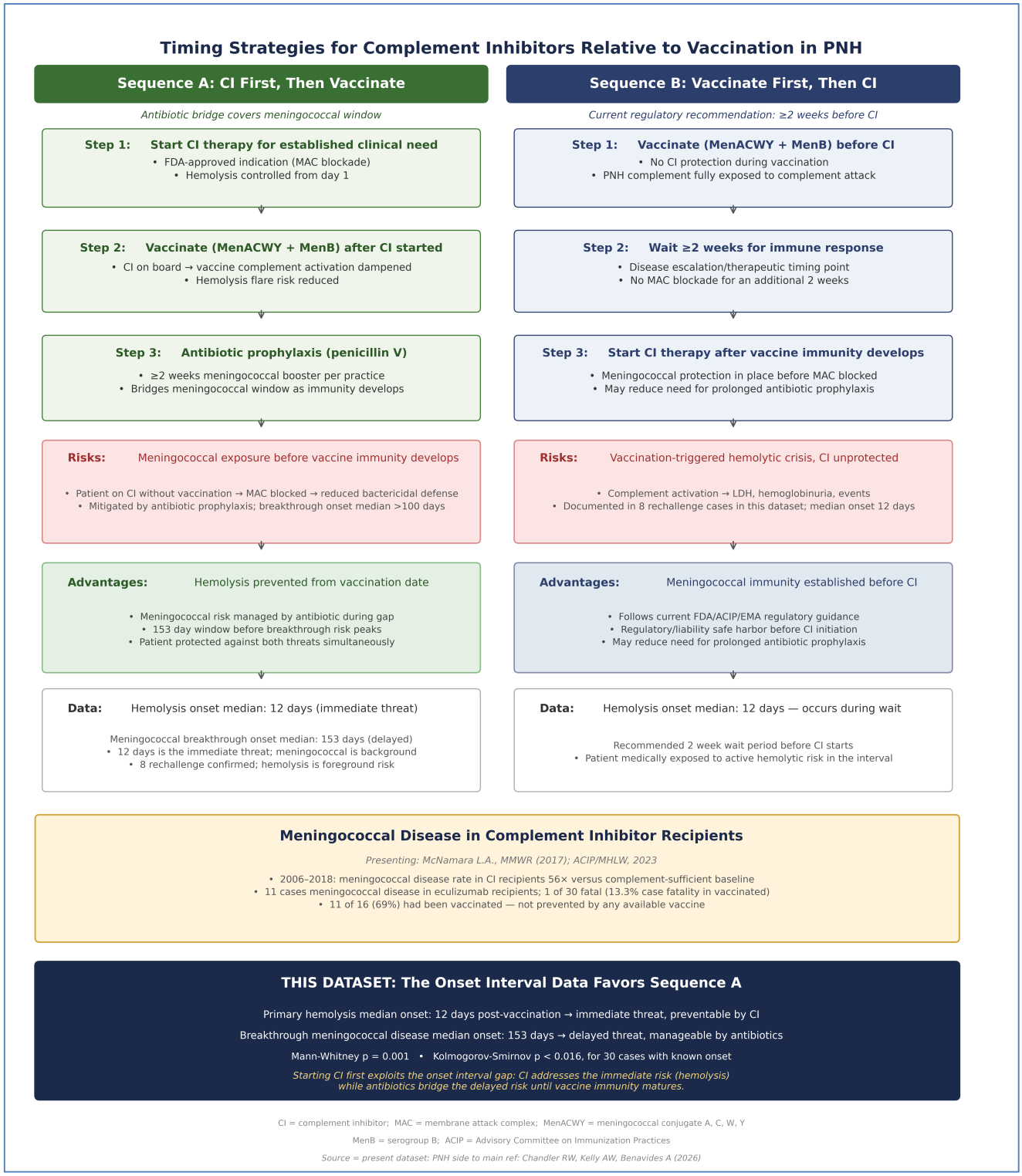
Onset Interval

Onset intervals differed by more than an order of magnitude — primary hemolysis at median 12 days (n = 17) versus breakthrough meningococcal disease at 153 days (n = 13); Mann-Whitney U, $p < 0.001$. Early hemolysis reflects acute complement activation in PNH erythrocytes; delayed BTM reflects loss of MAC-mediated bactericidal killing of *Neisseria meningitidis* under terminal complement blockade, despite intact antibody response. Arnold et al. [36] reported 8 BTM cases among 324 CI-treated patients (2.47%) over 18 years of prospective surveillance. Among the 5 of 9 Leeds BTM events with calculable vaccination-to-onset intervals, the median was 153 days, identical to our VAERS BTM median of 153 days. Both datasets showed zero BTM events within 14 days of vaccination, comparable proportions within 90 days (Leeds 40%, VAERS 31%) and beyond 365 days (Leeds 20%, VAERS 23%), and identical recurrence patterns: one patient in each dataset experienced two separate BTM episodes. Leeds Patient 5 corresponds to VAERS 1189037.

The BTH/BTM Paradox and the Pre-CI Interval

All six regulatory agencies surveyed (Supplemental Table 1) recommend meningococcal vaccination at least two weeks before CI initiation. The data in this report provide convergent evidence that this sequence exposes patients to vaccine-triggered hemolysis during the unprotected pre-CI interval, while BTM occurs months later after complement inhibition has abolished MAC-dependent bactericidal activity. [Figure 14 below].

Figure 14. Timing Strategies for Vaccination Relative to Complement Inhibitor Therapy



Thrombosis is a leading cause of death in PNH patients along with marrow failure. [7,55] In a nested case-control analysis from the International PNH Registry, Höchsmann et al. found that among untreated patients with PNH, thromboembolic risk increased with greater hemolytic/high-disease-activity burden. [56]

Following this recommended protocol, Arnold et al. reported that 5 of 121 patients (4.1%) at the UK National PNH Service in Leeds experienced serious complications during the vaccination-to-eculizumab interval: four thrombotic events

including ischemic stroke at 22 days, hepatic vein thrombosis at 4 days, and retinal vein thrombosis at 15 days, and one acute renal failure secondary to massive intravascular hemolysis. These observations prompted a change in Leeds practice to administer meningococcal vaccination on day 1 of, or immediately after the first dose of, complement inhibitor therapy, with short-course ciprofloxacin followed by ongoing prophylaxis. [36,57] Our data agree with the Leeds approach of CI timing relative to vaccination.

BTM and BTC

The cohort contains 32 confirmed breakthrough invasive meningococcal cases and 4 breakthrough COVID-19 cases. Bactericidal killing of Neisseria meningitidis is mediated by the membrane attack complex; C5 inhibition prevents effective MAC formation and renders vaccine-induced antibodies insufficient for bactericidal activity, producing the approximately 2,000-fold increased risk of invasive meningococcal disease documented in eculizumab-treated PNH patients [13]. Neutralizing antibody protection against SARS-CoV-2 binds the spike receptor-binding domain and blocks ACE2-mediated cellular entry without requiring terminal complement; cytotoxic T-cell viral clearance is similarly complement-independent.

Proximal Complement Inhibition

Pegcetacoplan (C3), iptacopan (factor B), and danicopan (factor D) inhibit the alternative pathway upstream of C5 [22], targeting complement activation at earlier steps than terminal pathway inhibitors. Because complement activation can propagate through alternative pathway amplification loops that generate C3 convertase activity upstream of C5 [19,22], these agents may offer differential protection against complement-amplifying conditions such as vaccination. The present dataset includes one case (VAERS 2018621) of hemolysis on dual-pathway inhibition (ravulizumab plus danicopan), supporting that combined C5 plus alternative pathway blockade does not provide complete protection against vaccine-triggered BTH; however, pegcetacoplan- and iptacopan-treated patients are not sufficiently represented in this dataset to support conclusions about differential protection between inhibitor classes.

New-Onset PNH, Marrow Effects and mRNA Platform Specificity

Eight of ten new-onset PNH cases followed mRNA COVID-19 vaccination. The odds ratio was 5.74 but statistical significance was not met, $p = 0.086$. Lymphoid and local reactions following mRNA COVID-19 vaccination were reported in VAERS 1072344, 1315262, 1653288.

This distribution is consistent LNP-mRNA specific marrow and lymphoid-compartment effects documented in the following sources.

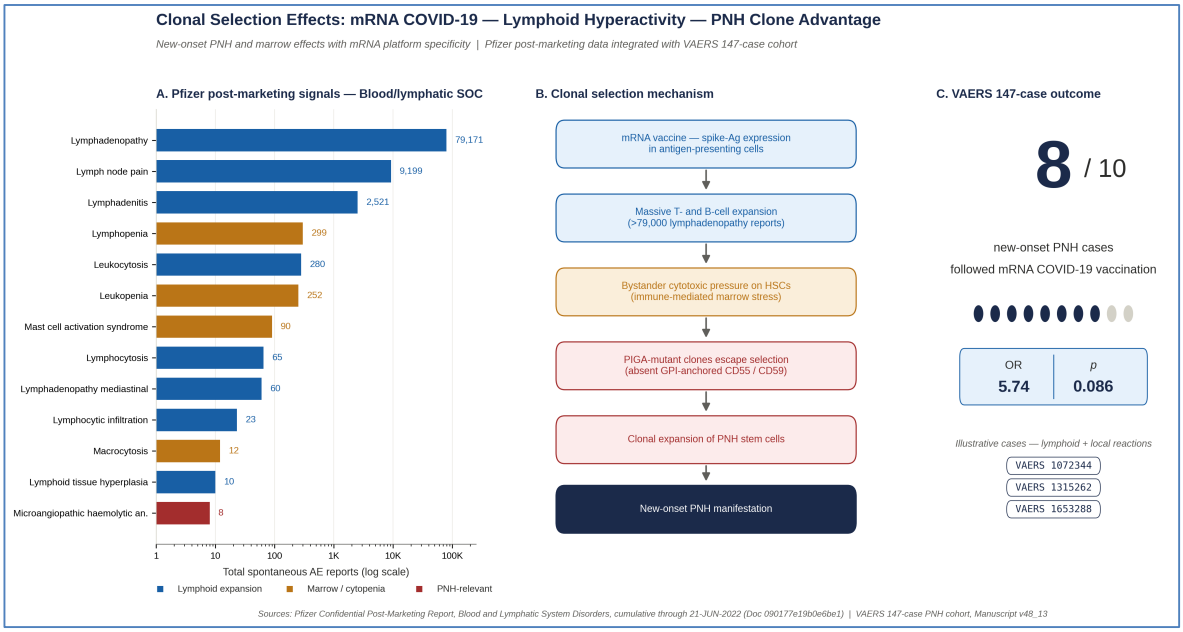
1. At the tissue level, the BioNTech Report 38166 LPT repeat-dose toxicity study of three LNP-formulated mRNA platforms, the BNT162b2 Module 2.4 nonclinical overview, the TGA FOI 2389 nonclinical evaluation, and the EMA Comirnaty and Spikevax assessment reports collectively document biodistribution of intramuscularly administered lipid nanoparticles to bone marrow and secondary lymphoid germinal centers with lymphadenopathy and splenomegaly. [58–62]

2. Phase 1 clinical trials identified lymphocytopenia and elevated cytokines following BNT162b1 and BNT162b2. [63–64] At the post-marketing population level, Comirnaty PSUR #1 reported lymphocytopenia, aplastic anemia, pancytopenia, and immune thrombocytopenic purpura. [65]

3. Polyclonal lymphocyte stimulation has been identified in two studies [66–67]; clonal stimulation, suppression, and selection effects were reported in a third [68].

Figure 15 below shows data from Pfizer records documenting vaccine associated changes in the lymphoid cluster of differentiating stem cells. Lymphadenopathy is high on the documented post vaccination AEs.

Figure 15. Potential HSC Selection Effects of mRNA/LNP Vaccines



The 8 of 10 mRNA predominance in new-onset PNH fits these platform-specific marrow and lymphoid effects in a population already prone to PNH clonal selection [5,26]. However, the small number of cases (n = 10) limits statistical power.

External Bexsero Hemolysis Signal

The Bexsero-associated findings in this dataset converge with prior independent regulatory and surveillance signals. Health Canada has formally reviewed concomitant Soliris-Bexsero exposure and concluded an increased risk of hemolysis in eculizumab-treated patients vaccinated with Bexsero, prompting an update to the Canadian product information; the lot 139201 cluster (Cases 757454, 774874, 793226 — Canadian, Soliris-treated, vaccinated April–June 2014) is consistent with that finding. [69] CDC prospective surveillance of 16,974 healthy university students receiving 31,313 MenB-4C doses identified rhabdomyolysis as one of three serious adverse events adjudicated as possibly vaccine-related, establishing a baseline Bexsero-attributable signal independent of complement dysregulation. [30] Independent post-licensure VAERS surveillance documented immune-mediated adverse events and Factor H autoantibodies following MenB-4C, [70] and active surveillance in Quebec identified a 3.6-fold elevated nephrotic syndrome rate after 4CMenB. [71] The breakthrough hemolysis signal is not restricted to Bexsero: VAERS 1325289 (UK, 40F, eculizumab) was hospitalized following a Meningococcal Group C Tetanus Toxoid Conjugate Vaccine — a pure polysaccharide-conjugate without OMV — indicating the operative trigger is immune activation in a complement-dysregulated host rather than vaccine-class-specific TLR engagement.

Methodological Contributions

Using the methods describe above to identify 147 cases our of 500 candidates provides value in two domains. 1. restoration of data in cases of blanking and/or deletion. Complex datasets like VAERS requires careful analysis far beyond MedDRA code query returns. Any VAERS-based study that does not conduct pairwise deduplication may have inflated case counts and rechallenge analyses that attribute separate-patient status to dose-split filings will overestimate the number of unique patients demonstrating positive rechallenge. The PNH confirmation tier rubric designed to analyze this cohort provided a framework (AB) for diagnostic assessment in rare-disease pharmacovigilance. 2. Doctors and healthcare agencies submit consequential and medically significant VAERS reports. The methods describe in this report provided a case report in traditional medical format while at the time completed VAERS data fields. The AI tools

developed during this project can be directed at other disease states or symptom clusters. Reproducibility is important as medically significant information resides in VAERS but must be processed to restore the case rather than rely on Preferred Term MedDRA driven database searches.

Conclusions

This 147-case physician-adjudicated VAERS analysis supports a causal relationship between vaccination and hemolytic breakthrough or hemolytic events in a susceptible subset of patients with PNH. The causal inference is strongest in eight rechallenge cases, including manufacturer-confirmed positive rechallenge, post-vaccination CH50 complement consumption, and complement-inhibitor modulation. The broader dataset shows recurrence of a biologically coherent complement-amplifying pattern across multiple vaccine platforms and treatment contexts. Breakthrough meningococcal disease represents a distinct failure mode under terminal complement blockade, in which vaccination may provide incomplete protection because MAC-dependent bactericidal activity is impaired. These findings support careful complement-inhibitor timing, post-vaccination hemolysis monitoring, and antibiotic risk mitigation.

Author Contributions -

RWC: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Validation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project Administration. AWK: Project Administration, Writing, Methodology, Investigation – Review & Editing. AB: Conceptualization, VAERS MedDRA Searches, Data Extraction and Compilation, Data Curation, Investigation, Data Audit.

Competing Interests

The authors declare no competing financial or non-financial interests. None of the authors has received payments, services, or other compensation from any third party in the past 36 months that could be perceived to influence, or give the appearance of influencing, the submitted work.

Funding

None. This study was conducted without external financial support.

Ethics Statement

This study is a secondary analysis of de-identified, publicly available data from the Vaccine Adverse Event Reporting System (VAERS). No individually identifiable protected health information was accessed or used. Institutional review board approval was not required as the study involved only publicly available, de-identified data and did not constitute human subjects research under 45 CFR 46.

Data Availability

VAERS data are publicly available at https://vaers.hhs.gov and through CDC WONDER at https://wonder.cdc.gov/vaers.html. Historical VAERS snapshots used for Wayback verification are available at https://medalerts.org. Specific data requests should be addressed to the corresponding author.

References

1. Notaro R, Luzzatto L. Breakthrough hemolysis in PNH with proximal or terminal complement inhibition. N Engl J Med. 2022;387(2):160–166. doi:10.1056/NEJMra2201664.
2. Araten DJ, Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, Benz EJ, Silberstein LE, et al., editors. Hematology: basic principles and practice. 8th ed. Philadelphia: Elsevier; 2023. p. 418–419.
3. Hill A, Platts PJ, Smith A, Richards SJ, Cullen MJ, Hill QA, et al. The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire. Blood. 2006;108(11):985. doi:10.1182/blood.V108.11.985.985.
4. Godby R, Shah S. Paroxysmal nocturnal hemoglobinuria. Mayo Clin Proc. 2025;100(12):2206–2227. doi:10.1016/j.mayocp.2025.07.029.

5. Karadimitris A, Luzzatto L. The cellular pathogenesis of paroxysmal nocturnal haemoglobinuria. Leukemia. 2001;15(8):1148–1152. doi:10.1038/sj.leu.2402180.
6. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804–2811. doi:10.1182/blood-2014-02-522128.
7. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017;3:17028. doi:10.1038/nrdp.2017.28.
8. Girmenia C, Barcellini W, Bianchi P, Di Bona E, Iori AP, Notaro R, et al. Management of infection in PNH patients treated with eculizumab or other complement inhibitors: unmet clinical needs. Blood Rev. 2023;58:101013. doi:10.1016/j.blre.2022.101013.
9. Versino F, Fattizzo B. Progress in the use of biological therapies to treat paroxysmal nocturnal hemoglobinuria: focus on patient profiling. Expert Opin Biol Ther. 2025;25(10):1071–1085. doi:10.1080/14712598.2025.2574983.
10. Waheed A, Shammo J, Dingli D. Paroxysmal nocturnal hemoglobinuria: review of the patient experience and treatment landscape. Blood Rev. 2024;64:101155. doi:10.1016/j.blre.2023.101158.
11. Wong RSM, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. Blood Adv. 2023;7(11):2468–2478. doi:10.1182/bloodadvances.2022009129.
12. Yasunaga M, et al. Eculizumab treatment for ischemic enteritis accompanied with paroxysmal nocturnal hemoglobinuria: a case report and literature review. Ann Hematol. 2018;97(8):1513–1515. doi:10.1007/s00277-018-3286-9.
13. McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. MMWR Morb Mortal Wkly Rep. 2017;66(27):734–737. doi:10.15585/mmwr.mm6627e1.
14. Boshkos MC, Fives KR, Phrathep DD, Healey KD, Patel M. Breakthrough hemolysis associated with COVID-19 vaccination and active COVID-19 infection in a patient with paroxysmal nocturnal hemoglobinuria maintained on pegcetacoplan: a case report. Cureus. 2023;15(3):e36240. doi:10.7759/cureus.36240.
15. Cavallaro F, Pasquini MC, Giannotta JA, Cattina F, Barcellini W, Fattizzo B. Breakthrough haemolysis in paroxysmal nocturnal haemoglobinuria after COVID-19 infection and COVID vaccination: what is worse? Blood Transfus. 2022;20(5):437–440. doi:10.2450/2022.0039-22.
16. Fattizzo B, et al. SARS-CoV-2 vaccination induces breakthrough hemolysis in paroxysmal nocturnal hemoglobinuria on complement inhibitor. Am J Hematol. 2021;96(9):E345–E346. doi:10.1002/ajh.26262.
17. Gerber GF, et al. COVID-19 vaccines induce severe hemolysis in paroxysmal nocturnal hemoglobinuria. Blood. 2021;137(26):3670–3673. doi:10.1182/blood.2021011548.
18. Giannotta JA, et al. SARS-CoV-2 vaccination in patients with paroxysmal nocturnal hemoglobinuria: an Italian multicenter survey. Am J Hematol. 2022;97(7):E229–E232. doi:10.1002/ajh.26545.
19. Kulasekararaj AG, Lee JW, Patriquin CJ, Piatek CI, Röth A, Barcellini W, et al. Characterizing clinically significant extravascular hemolysis in adults with PNH on ravulizumab or eculizumab treatment. Blood Adv. 2025;9(19):4936–4945. doi:10.1182/bloodadvances.2024015490.
20. Green H, Eliakim-Raz N, Zimra Y, Gafter-Gvili A. Paroxysmal nocturnal hemoglobinuria diagnosed after influenza vaccine: coincidence or consequence? Isr Med Assoc J. 2014;16(2):122–124. Available at: https://pubmed.ncbi.nlm.nih.gov/24645235/.
21. Jarrah K, Al Mahmasani L, Atoui A, Bou-Fakhredin R, Taher AT. Manifestation of paroxysmal nocturnal hemoglobinuria after COVID-19 mRNA vaccination. Blood Cells Mol Dis. 2022;93:102641. doi:10.1016/j.bcmd.2021.102641.
22. Fattizzo B, Versino F, Barcellini W. Breakthrough hemolysis in paroxysmal nocturnal hemoglobinuria throughout clinical trials: from definition to clinical practice. Blood. 2025;146(4):411–421. doi:10.1182/blood.2024027574.
23. Windyga J, Hus I, Hus M, Piekarska A, Szenborn L, Wysocki J, et al. Vaccination in paroxysmal nocturnal hemoglobinuria patients treated with terminal and proximal complement inhibitors — Polish Expert Consensus. Acta Haematol Pol. Published online November 21, 2025. doi:10.5603/ahp.108528.
24. Kamura Y, et al. Hemolysis induced by SARS-CoV-2 mRNA vaccination in patients with paroxysmal nocturnal hemoglobinuria. Int J Hematol. 2022;116(1):55–59. doi:10.1007/s12185-022-03387-9.
25. Pike A, McKinley C, Forrest B, Scott R, Charlton E, Scott E, et al. COVID-19 vaccination antibody responses in patients with aplastic anaemia and paroxysmal nocturnal haemoglobinuria. Lancet Haematol. 2022;9(8):e553–e556. doi:10.1016/S2352-3026(22)00183-1.
26. Wang L, Hu Q, Yang Y, Chen M, Yang C, Han B. COVID-19 vaccination prevents a more severe course and treatment with complement inhibitors reduce worsening hemolysis during the Omicron pandemic in patients with PNH: a single-center study. Ann Med. 2023;55(2):2274510. doi:10.1080/07853890.2023.2274510.

27. Hsieh FN, Chen TY, Lee JYY. Severe cutaneous thrombosis with hemorrhagic necrosis in a patient with paroxysmal nocturnal hemoglobinuria: a case report and review of literature. Dermatol Sin. 2017;35(3):138–141. doi:10.1016/j.dsi.2017.01.006.
28. Sangwan P, Sharma A, Arava S, Mahapatra M, Ramam M. Paroxysmal nocturnal hemoglobinuria associated cutaneous thrombosis: a case report. Indian Dermatol Online J. 2026;17(1):107–110. doi:10.4103/idoj.idoj_1162_24.
29. Ajmera KM. Fatal case of rhabdomyolysis post-COVID-19 vaccine. Infect Drug Resist. 2021;14:3929–3935. doi:10.2147/IDR.S331362.
30. Duffy J, Johnsen P, Ferris M, et al. Safety of a meningococcal group B vaccine used in response to two university outbreaks. J Am Coll Health. 2017;65(6):380–388. doi:10.1080/07448481.2017.1312418.
31. Faissner S, et al. COVID-19 mRNA vaccine induced rhabdomyolysis and fasciitis. J Neurol. 2022;269(4):1774–1775. doi:10.1007/s00415-021-10768-3.
32. Kamura Y, et al. Fatal thrombotic microangiopathy with rhabdomyolysis as an initial symptom after the first dose of mRNA-1273 vaccine: a case report. Int J Infect Dis. 2022;117:322–325. doi:10.1016/j.ijid.2022.02.031.
33. Mack M, Nichols L, Guerrero DM. Rhabdomyolysis secondary to COVID-19 vaccination. Cureus. 2021;13(5):e15004. doi:10.7759/cureus.15004.
34. Nassar M, et al. COVID-19 vaccine induced rhabdomyolysis: case report with literature review. Diabetes Metab Syndr. 2021;15(4):102170. doi:10.1016/j.dsx.2021.06.007.
35. Sheka M, Coattrenec Y, Lorenzini KI, Nendaz M. A severe case of rhabdomyolysis after Moderna mRNA anti-COVID-19 vaccine with a literature review. Clin Case Rep. 2023;11(5):e7184. doi:10.1002/ccr3.7184.
36. Arnold L, Borrow R, Riley K, Griffin M, Munir T, Kelly R, et al. Management of meningococcal disease risk in patients with paroxysmal nocturnal hemoglobinuria (PNH) on complement inhibitors: 18 years' experience from the UK National PNH Service in Leeds. Blood. 2020;136(Suppl 1):5. doi:10.1182/blood-2020-141780.
37. Kinoshita T, Inoue N. Relationship between aplastic anemia and paroxysmal nocturnal hemoglobinuria. Int J Hematol. 2002;75(2):117–122. doi:10.1007/BF02982015.
38. Schrezenmeier H, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. Ann Hematol. 2020;99(7):1505–1514. doi:10.1007/s00277-020-04052-z.
39. Young NS, et al. The relationship of aplastic anemia and PNH. Int J Hematol. 2002;76(Suppl 2):168–172. doi:10.1007/BF03165111.
40. Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting Summary. Available at: https://wonder.cdc.gov/wonder/help/vaers.html. Accessed April 22, 2026.
41. Fattizzo B, Pedone GL, Metafuni E, et al. Characterization of breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria: an international multicenter experience. Am J Hematol. 2025;100(11):1963–1971. doi:10.1002/ajh.70032.
42. Dingli D, De Castro III C, Koprivnikar J, et al. Expert consensus on the management of pharmacodynamic breakthrough-hemolysis in treated paroxysmal nocturnal hemoglobinuria. Hematology. 2024;29(1):2329030. doi:10.1080/16078454.2024.2329030.
43. Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC, Bersoff-Matcha SJ. Antibiotic prophylaxis in vaccinated eculizumab recipients who developed meningococcal disease. J Infect. 2020;80(3):350–371. doi:10.1016/j.jinf.2019.11.015.
44. Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood. 2017;130(7):891–899. doi:10.1182/blood-2017-05-781450.
45. Langereis JD, et al. Eculizumab impairs Neisseria meningitidis serogroup B killing in whole blood despite 4CMenB vaccination of PNH patients. Blood Adv. 2020;4(15):3615–3620. doi:10.1182/bloodadvances.2020002497.
46. Bozio CH, Isenhour C, McNamara LA. Characteristics of and meningococcal disease prevention strategies for commercially insured persons receiving eculizumab in the United States. PLoS One. 2020;15(11):e0241989. doi:10.1371/journal.pone.0241989.
47. Galli N, et al. Non-capsulated Neisseria meningitidis sepsis in a paroxysmal nocturnal hemoglobinuria patient treated with ravulizumab: case report and review of the literature. Front Immunol. 2023;14:1269325. doi:10.3389/fimmu.2023.1269325.
48. Hawkins KL, Hoffman M, Okuyama S, Rowan SE. A case of fulminant meningococcemia: it is all in the complement. Case Rep Infect Dis. 2017;2017:6093695. doi:10.1155/2017/6093695.
49. Lebel E, et al. Post-eculizumab meningococcaemia in vaccinated patients. Clin Microbiol Infect. 2018;24(1):89–90. doi:10.1016/j.cmi.2017.07.011.

50. Nolfi-Donegan D, et al. Fatal nongroupable Neisseria meningitidis disease in vaccinated patient receiving eculizumab. Emerg Infect Dis. 2018;24(8):1561–1564. doi:10.3201/eid2408.180228.
51. Reher D, Fuhrmann V, Kluge S, Nierhaus A. A rare case of septic shock due to Neisseria meningitidis serogroup B infection despite prior vaccination in a young adult with paroxysmal nocturnal haemoglobinuria receiving eculizumab. Vaccine. 2018;36(19):2507–2509. doi:10.1016/j.vaccine.2018.03.087.
52. Yu ZY, Tsai MJ, Lin YJ, Liu WD, Chou SC, Hung CC. Disseminated gonococcal infection in a patient with paroxysmal nocturnal hemoglobinuria having received ravulizumab and meningococcal vaccine. J Microbiol Immunol Infect. 2020;53(4):660–662. doi:10.1016/j.jmii.2020.06.013.
53. Atefi A, et al. Meningitis after COVID-19 vaccination, a systematic review of case reports and case series. BMC Infect Dis. 2024;24:1138. doi:10.1186/s12879-024-10043-6.
54. Ladhani SN, Campbell H, Lucidarme J, Gray S, Parikh S, Willerton L, Clark SA, Lakshmi A, Walker A, Patel S, Bai X, Ramsay M, Borrow R. Invasive meningococcal disease in patients with complement deficiencies: a case series (2008–2017). BMC Infect Dis. 2019;19(1):522. doi:10.1186/s12879-019-4146-5.
55. Socié G, Schrezenmeier H, Muus P, Lisukov I, Röth A, Kulasekararaj A, et al. Changing prognosis in paroxysmal nocturnal haemoglobinuria disease subcategories: an analysis of the International PNH Registry. Intern Med J. 2016;46(9):1045–1053. doi:10.1111/imj.13160.
56. Höchsmann B, Peffault de Latour R, Hill A, Röth A, Devos T, Patriquin CJ, et al. Risk factors for thromboembolic events in patients with paroxysmal nocturnal hemoglobinuria (PNH): a nested case–control study in the International PNH Registry. Ann Hematol. 2023;102(11):2979–2988. doi:10.1007/s00277-023-05402-3.
57. Arnold L, Kelly R, Munir T, Muus P, Pike A, Riley K, et al. Thrombotic events with Neisseria meningitidis vaccination in patients with paroxysmal nocturnal hemoglobinuria, UK experience. Blood. 2020;136(Suppl 1):35–36. doi:10.1182/blood-2020-141769.
58. BioNTech. A tissue distribution study of a [3H]-labelled lipid nanoparticle-mRNA formulation containing ALC-0315 and ALC-0159 following intramuscular administration in Wistar Han rats. Study report 185350, November 2020. Pfizer/BioNTech. Available via Public Health and Medical Professionals for Transparency (PHMPT) at https://phmpt.org/.
59. BioNTech. 38166 Repeat-dose toxicity study of three LNP-formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Wistar Han rats. Study report 38166, 01 July 2020. BioNTech/Pfizer. Available via PHMPT at https://phmpt.org/.
60. Therapeutic Goods Administration (Australia). Nonclinical evaluation report: BNT162b2 (Comirnaty). TGA FOI 2389, 2021. Available at https://www.tga.gov.au/.
61. European Medicines Agency. Comirnaty assessment report. EMA/707383/2020, 19 February 2021. Committee for Medicinal Products for Human Use (CHMP). Available at https://www.ema.europa.eu/.
62. European Medicines Agency. Spikevax (COVID-19 mRNA vaccine [nucleoside-modified]) assessment report. EMA/15689/2021, 2021. Committee for Medicinal Products for Human Use (CHMP). Available at https://www.ema.europa.eu/.
63. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med. 2020;383(25):2439–2450. doi:10.1056/NEJMoa2027906.
64. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature. 2020;586(7830):594–599. doi:10.1038/s41586-020-2814-7.
65. Pfizer/BioNTech. Comirnaty (BNT162b2) Periodic Safety Update Report (PSUR) #1: 19 December 2020 – 18 June 2021. Available via PHMPT at https://phmpt.org/.
66. Malecka-Gieldowska M, Folta M, Wisniewska A, Czyzewska E. Cell population data and serum polyclonal immunoglobulin free light chains in the assessment of COVID-19 severity. Viruses. 2021;13(7):1381. doi:10.3390/v13071381.
67. Gudowska-Sawczuk M, Moniuszko-Malinowska A, Pączek S, Guziejko K, Chorąży M, Mroczko B. Evaluation of free light chains (FLCs) synthesis in response to exposure to SARS-CoV-2. Int J Mol Sci. 2022;23(19):11589. doi:10.3390/ijms231911589.
68. Chandler RW. Light chain disorders indicative of immune disorders and/or cancers associated with the COVID-19 infections and injections. Int J Vaccine Theory Pract Res. 2025 Sep 10;1557. doi:10.56098/mmk5wh51.69. Health Canada. Summary Safety Review – SOLIRIS (eculizumab) and BEXSERO: assessing the potential risk of hemolysis and low hemoglobin in patients treated with Soliris and vaccinated with Bexsero. Drug and Health Products Portal, SSR00104. Available at: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR00104.
70. Perez-Vilar S, Dores GM, Marquez PL, Ng CS, Cano MV, Rastogi A, Lee L, Su JR, Duffy J. Safety surveillance of meningococcal group B vaccine (Bexsero), Vaccine Adverse Event Reporting System, 2015–2018. Vaccine. 2022;40(2):247–254. doi:10.1016/j.vaccine.2021.11.084.

71. De Serres G, Billard MN, Gariépy MC, Roy MC, Boucher FD, Gagné H, Belley S, Toth E, Landry M, Skowronski DM. Nephrotic syndrome following four-component meningococcal B vaccination: epidemiologic investigation of a surveillance signal. Vaccine. 2019;37(31):4996–5002. doi:10.1016/j.vaccine.2019.07.011.

Supplementary Material

Section 1:

Supplemental Table 1. International Regulatory Vaccination Requirements Before Complement Inhibitor Therapy

Regulatory Agency	Jurisdiction	Vaccination Timing	Serogroups Required	Antibiotic Prophylaxis	Distribution Control	Vaccine Limitation Acknowledgment
FDA / CDC (ACIP)	United States	≥2 weeks before first CI dose; urgent CI permitted with antibiotic bridge	MenACWY + MenB (both required)	Recommended; duration at clinician discretion; no specified duration	REMS program; prescriber certification required; restricted distribution	"Vaccines likely provide incomplete protection" (CDC, 2024); 14/16 US cases in vaccinated patients (McNamara 2017 [13])
EMA	European Union (27 member states)	≥2 weeks before first CI dose; urgent CI permitted with antibiotic bridge	Tetravalent meningococcal (ACWY); MenB per national guidelines	"Consideration should be given to official guidance on appropriate use of antibacterial agents"	Controlled distribution; written vaccination confirmation required from prescriber	"Vaccination may not be sufficient to prevent meningococcal infection" (SmPC Section 4.4)
MHRA	United Kingdom	≥2 weeks before first CI dose; per national guidelines	Serogroups A, B, C, W, Y per UK national PNH service recommendations	Penicillin prophylaxis recommended for duration of CI therapy (UK + France)	Mandatory Certificate of Vaccination form; annual vaccination status reminders; controlled distribution	"Vaccination may not be sufficient" (SmPC); Yellow Card reporting required
TGA	Australia	≥2 weeks before first CI dose; per Australian Immunisation Handbook	Serogroups A, B, C, Y, W135 (all recommended)	"Consideration should be given to official guidance on appropriate use of antibacterial agents"	Boxed warning; controlled distribution	"Vaccination may not be sufficient to prevent meningococcal infection" (PI Section 4.4)
Swissmedic	Switzerland	≥2 weeks before first CI dose; per EMA SmPC framework	Per EMA SmPC and Swiss national guidelines	Per EMA SmPC; educational materials provided	Controlled distribution; patient safety card; annual vaccination reminder; RMP-based monitoring	"Vaccination may not be sufficient" (RMP summary; defers to EMA SmPC)

Points of Convergence Across All Six Agencies

- All require meningococcal vaccination at least 2 weeks before complement inhibitor initiation.
- All permit urgent CI therapy before vaccination is complete if clinical need outweighs meningococcal risk, with antibiotic prophylaxis bridging until 2 weeks after vaccination.
- All acknowledge that vaccination provides incomplete protection against meningococcal disease in CI-treated patients.
- All require ongoing monitoring for meningococcal symptoms regardless of vaccination or prophylaxis status.
- All employ controlled distribution mechanisms (REMS, certificates, or written confirmations) to enforce vaccination compliance.
- All note that nongroupable Neisseria meningitidis (not covered by any available vaccine) caused the majority of infections in eculizumab recipients in the CDC's own surveillance data (McNamara 2017 [13]).

Critical Gap: Vaccine-Associated Hemolysis Not Addressed

None of the six regulatory agencies addresses the risk of vaccine-elicited complement activation and subsequent breakthrough hemolysis in PNH patients, the adverse event documented in 147 cases in this dataset. The vaccination requirement is framed exclusively around meningococcal infection risk mitigation, without acknowledging that the vaccination event itself can precipitate complement-mediated hemolysis through the same innate immune activation pathway that vaccines rely upon to generate protective immunity. No agency recommends baseline or post-vaccination monitoring of hemolysis markers (LDH, haptoglobin, hemoglobin) around vaccination timing. No agency recommends optimization of complement inhibitor dosing to cover the peri-vaccination complement activation window.

Sources: FDA Soliris USPI (2025); FDA Ultomiris USPI (2024); CDC ACIP Meningococcal Vaccination Recommendations (MMWR 2020, updated 2024); EMA Soliris SmPC (Section 4.4); MHRA UK Certificate of Vaccination form (SOP-0119798, v7.0, August 2024); TGA Australian Product Information for Soliris (May 2024) and Ultomiris (July 2024); Swissmedic RMP Summary for Soliris. CI = complement inhibitor; REMS = Risk Evaluation and Mitigation Strategy; SmPC = Summary of Product Characteristics; PI = Product Information; RMP = Risk Management Plan; ACIP = Advisory Committee on Immunization Practices; MenACWY = meningococcal serogroups A, C, W, Y conjugate vaccine; MenB = meningococcal serogroup B vaccine.

Supplemental Table 2. VAERS Search Strategy: 18 Search Terms Across 7 Data Fields (126 Individual Searches)
Panel A. Search Input Terms by Category

Category	N	Search Terms	Rationale
1. Explicit PNH terms	2	Paroxysmal Nocturnal Hemoglobinuria PNH	Direct disease identification
2. Complement pathway markers	5	Complement Hemolytic Anemia Autoimmune Hemolytic Anemia Flow Cytometry Complement Disorders	Capture cases coded by pathophysiology rather than disease name; flow cytometry identifies GPI-deficient clones
3. Hemolysis indicators	2	Anemia Rhabdomyolysis	Broad hemolysis capture; rhabdomyolysis shares complement-mediated muscle injury mechanism
4. TMA spectrum and differentials	5	Thrombotic Microangiopathy Microangiopathic Hemolytic Anemia Atypical Hemolytic Uremic Syndrome Neuroleptic Malignant Syndrome Portal Vein Thrombosis	PNH differential diagnoses and complement-mediated overlap syndromes; NMS shares rhabdomyolysis phenotype; PVT is a PNH-associated thrombosis site
5. Complement inhibitor drugs	4	Eculizumab / Soliris Ravulizumab / Ultomiris Pegcetacoplan Iptacopan / Fabhalta	Identify PNH patients by treatment rather than diagnosis coding; captures cases where PNH is in medication list but not in diagnosis field
TOTAL	**18**	**126 individual searches (18 terms × 7 fields)**	

Seven VAERS data fields searched: (1) write-up/narrative, (2) symptom text, (3) lab data, (4) past medical history, (5) current illness, (6) other medications, (7) MedDRA codes. Each of the 18 terms was applied independently to each of the 7 fields, yielding 126 individual searches. Drug-name searches (Category 5) included both brand and generic names. Two drug-name auto-mapping errors were identified during this process: Soliris → "OCTINOXATE, OCTOCRILENE (SOLARIS)" (sunscreen) and ravulizumab → "ROVELIZUMAB" (different monoclonal antibody), underscoring the necessity of multi-field search.

Panel B. Seven VAERS Data Fields Queried

#	VAERS Field	Content Description
1	Write-up / Narrative	Free-text clinical description of the adverse event
2	Symptom Text	MedDRA-coded symptom descriptions
3	Lab Data	Laboratory values and diagnostic test results
4	Past Medical History	Pre-existing conditions including PNH diagnosis
5	Current Illness	Active conditions at time of vaccination
6	Other Medications	Concomitant medications including complement inhibitors
7	MedDRA Codes	Standardized Medical Dictionary for Regulatory Activities coding

Panel C. MedDRA Preferred Terms Coded in the 147-Case Dataset

Metric	Value
Total unique MedDRA Preferred Terms (PTs)	556
Most frequent PTs	Haemolysis, Haemoglobin decreased, Pyrexia, Condition aggravated, Paroxysmal nocturnal haemoglobinuria, Vaccination failure, Meningococcal sepsis, Packed red blood cell transfusion, Blood lactate dehydrogenase, Haemoglobinuria
SMQ (Standardized MedDRA Queries) represented	Haemolytic disorders (narrow), Haemolytic disorders (SMQ), Haematopoietic erythropenia (broad), Haematopoietic leukopenia (narrow), Sepsis (narrow)
PTs unique to PNH pharmacovigilance	Paroxysmal nocturnal haemoglobinuria, Breakthrough haemolysis, Flow cytometry, Complement system disorder, Total complement activity test, Waterhouse-Friderichsen syndrome
PTs documenting data integrity events	Condition aggravated (used in altered narratives where original clinical detail was replaced with generic coding)

The 556 unique MedDRA PTs represent the coded adverse event vocabulary across all 147 cases. This count reflects the breadth of clinical presentations in PNH vaccine-associated adverse events, spanning hemolysis, thrombosis, infection, marrow failure, neurological, and multi-system domains. MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SMQ = Standardized MedDRA Query; GPI = glycosylphosphatidylinositol; PNH = paroxysmal nocturnal hemoglobinuria.

Section 2: Thirteen Individual Case Timelines

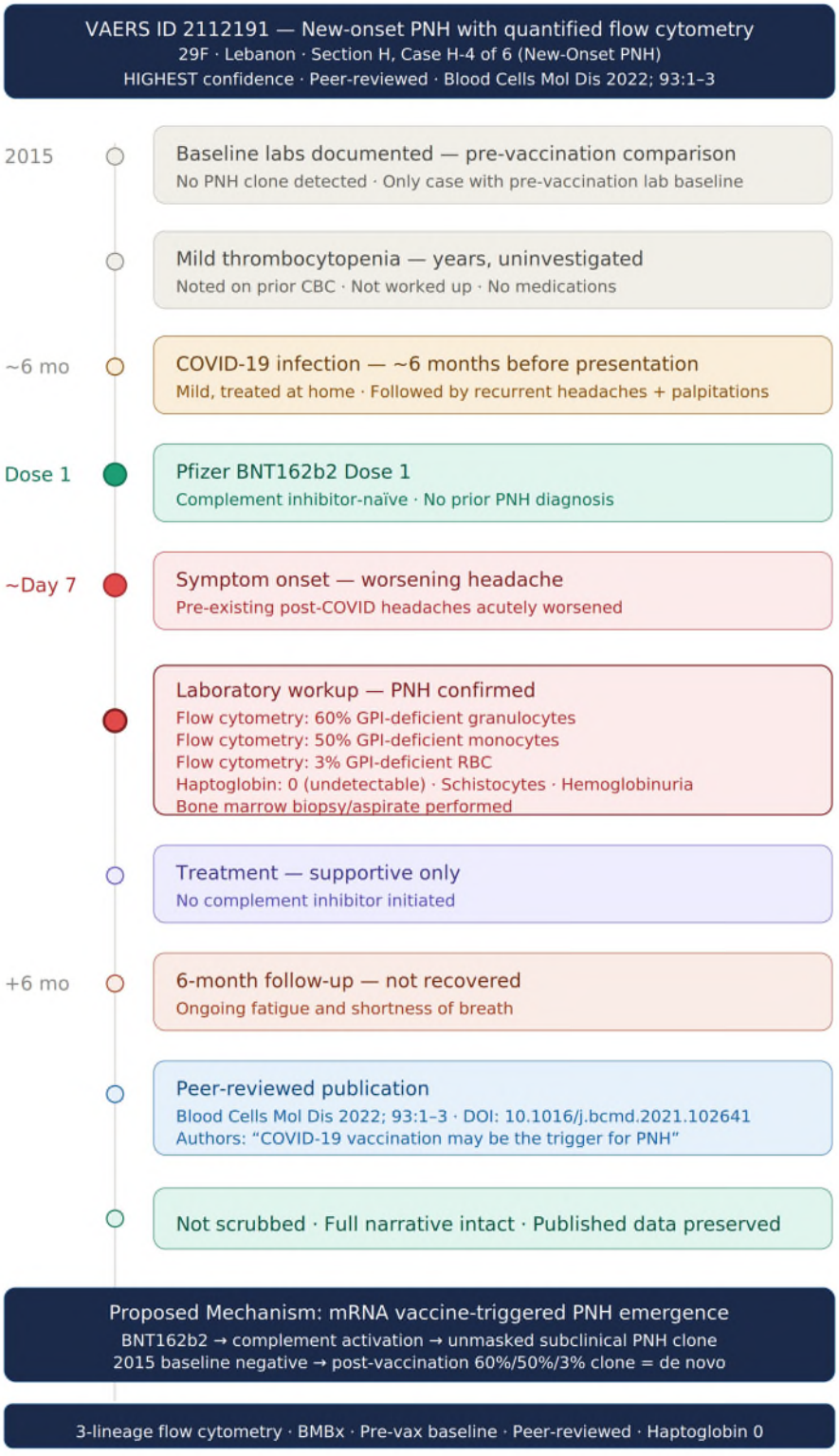
Companion to 147-case PNH VAERS supplementary exhibit · Six clinical domains

TL	Timeline title	VAERS ID	Patient
A. New-Onset PNH			
1	New-onset PNH in a 29 y/o female	2112191	29F
B. Rechallenge: Hemolysis and Breakthrough Hemolysis			
2	Recurrent post-vaccination hemolysis, 29 y/o female	2841419	29F
3	Recurrent post-vaccination hemolysis, 16 y/o male	824445	16M
4	Recurrent post-vaccination hemolysis, 63 y/o male	1366882	63M
5	Three-dose natural experiment, 30s y/o female	2491687	30sF
6	Rechallenge hemolysis with CH50 documentation	2326343	29M
C. Breakthrough Meningitis			
7	Fatal BTM: Serogroup B match, 16 y/o female	688791	16F
8	Breakthrough meningitis: Serogroup match, 26 y/o female	745023	26F
9	Recurrent BTM: Serogroup mismatch, 25 y/o male	1189037	19M
D. Thrombosis			
10	Thrombotic stroke, 44 y/o female	1114131	44F
11	Mesenteric thrombosis + compartment syndrome, 16 y/o female	875483	16F
E. Bone Marrow			
12	Pancytopenia, 72 y/o female	2253863	72F
F. Rhabdomyolysis			
13	Surgically proven rhabdomyolysis, 27 y/o female	377388	27F

13 timelines across 6 domains · New-Onset PNH (1) · Rechallenge (5) · BTM (3)
Thrombosis (2) · Bone Marrow (1) · Rhabdomyolysis (1)

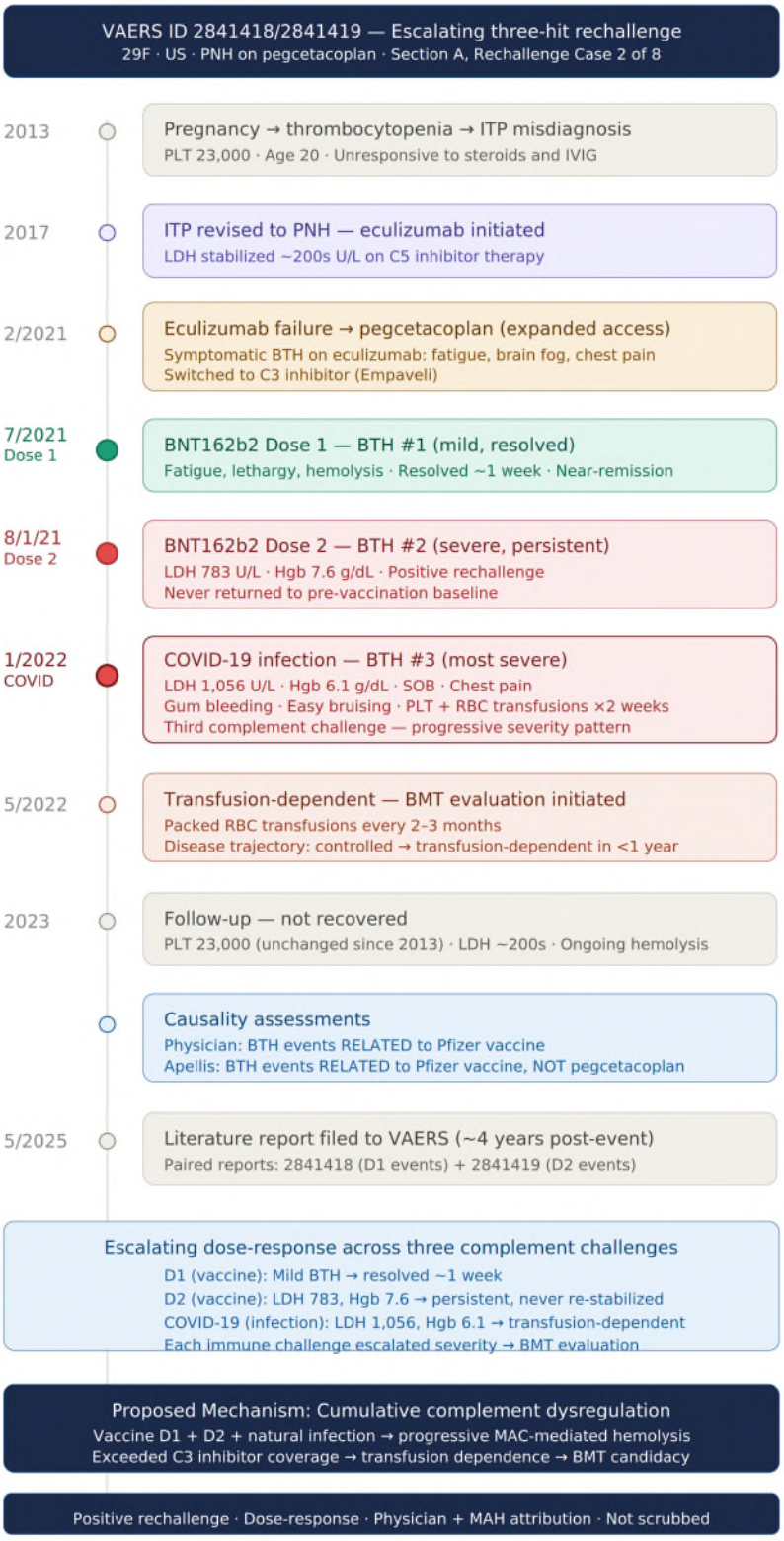
A. New Onset PNH following Vaccination — Timeline 1

1. New onset PNH in a 29 y/o female

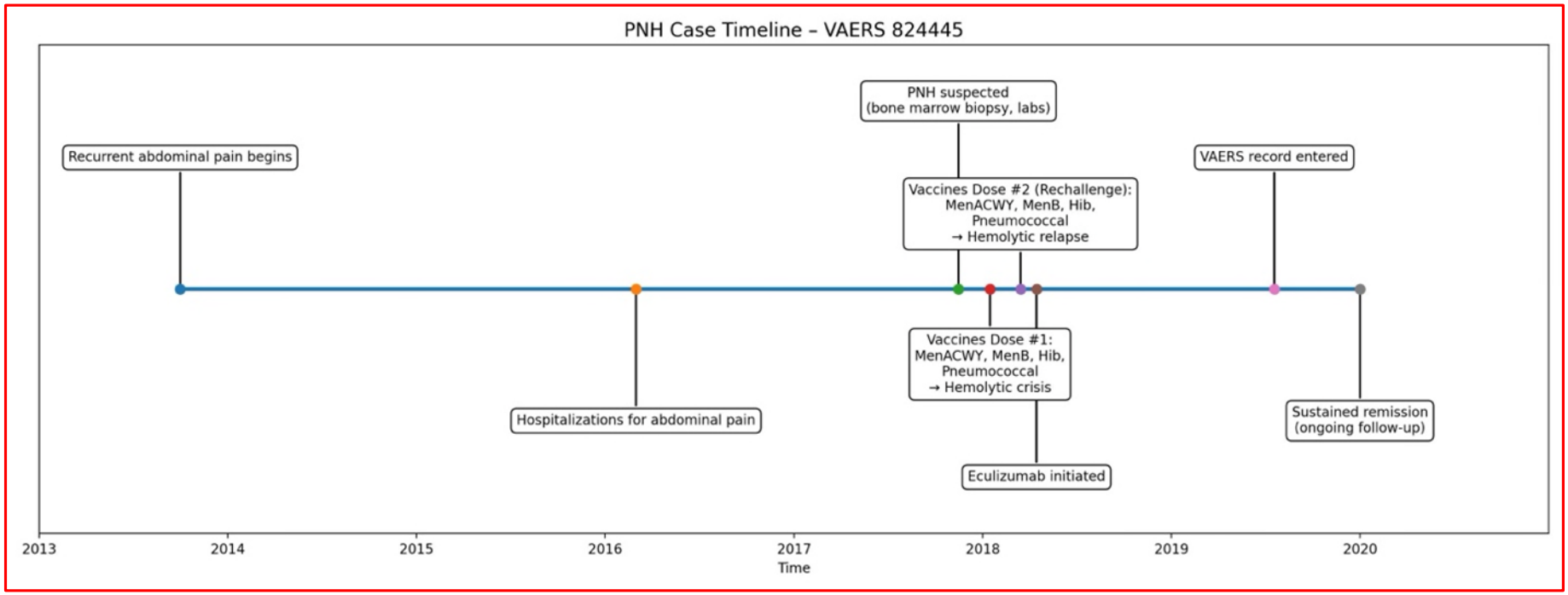


B. Rechallenge: Hemolysis and Breakthrough Hemolysis — Timelines 2-6

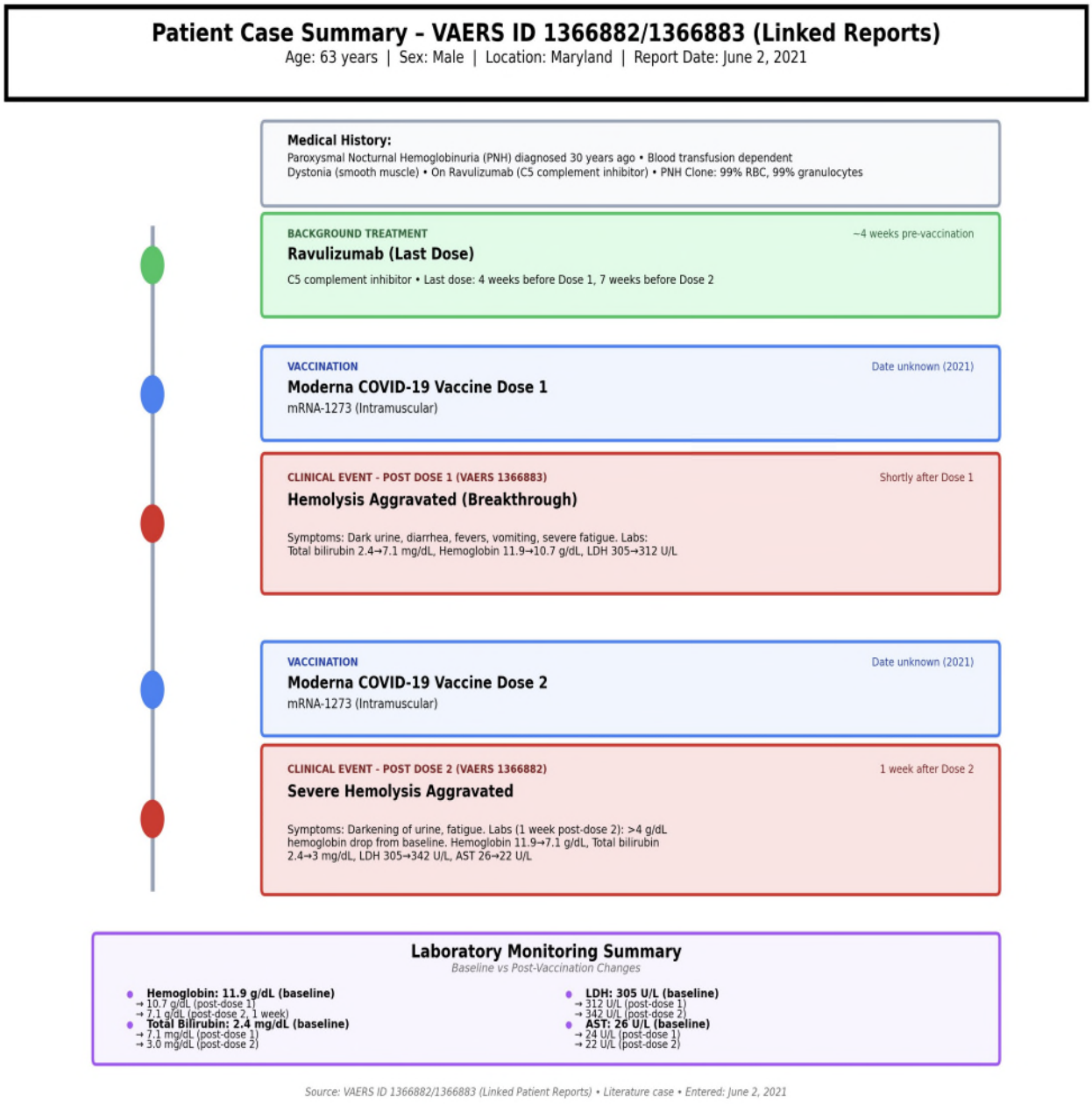
2. Recurrent Post Vaccination Hemolysis 29 y/o Female



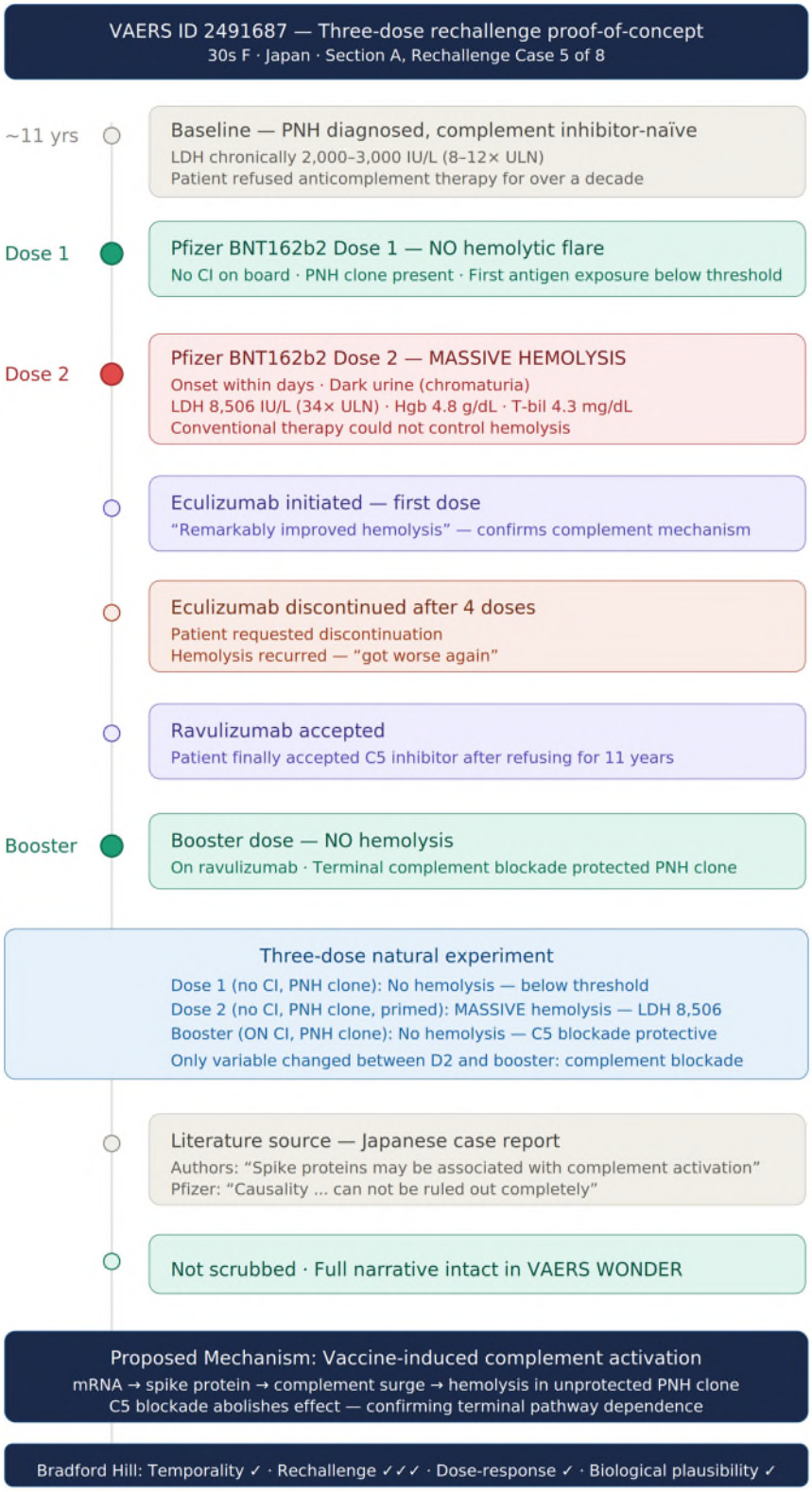
3. Recurrent Post Vaccination Hemolysis in a 16 y/o Male



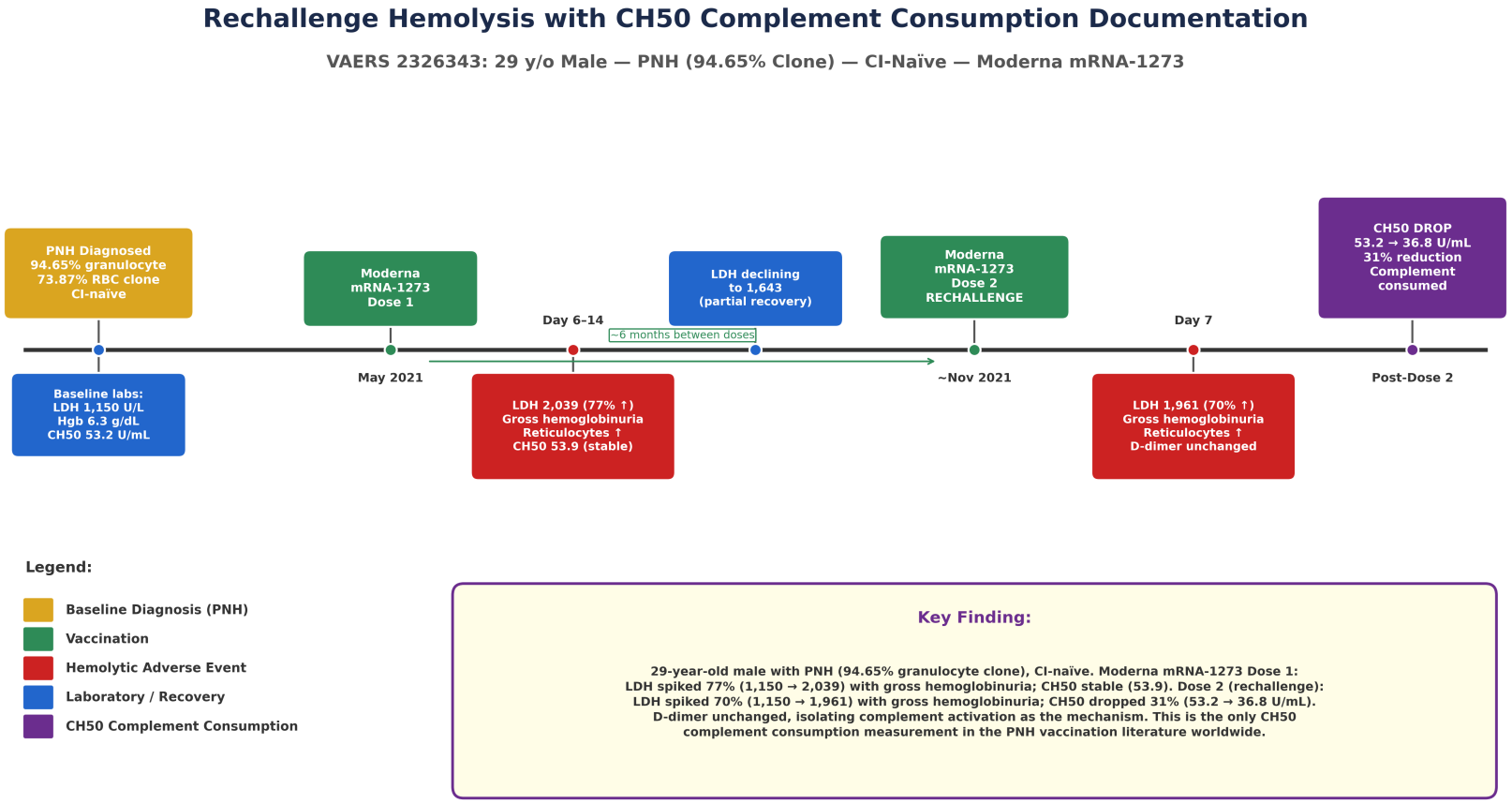
4. Recurrent Post Vaccination Hemolysis 63 y/o Male



5. Recurrent Hemolysis with three-dose natural experiment in a 30s y/o female

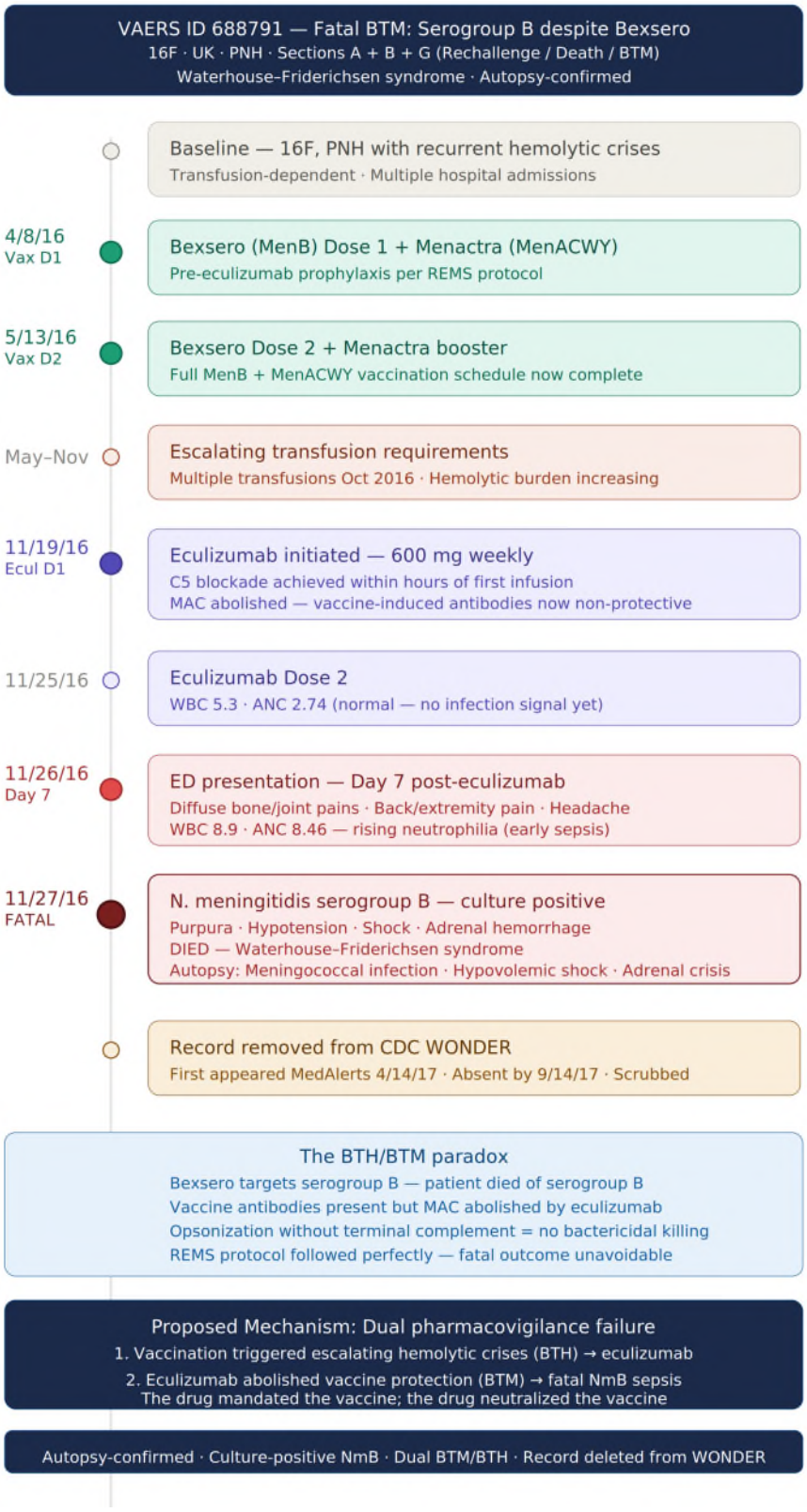


6. Rechallenge Hemolysis with CH50 Documentation

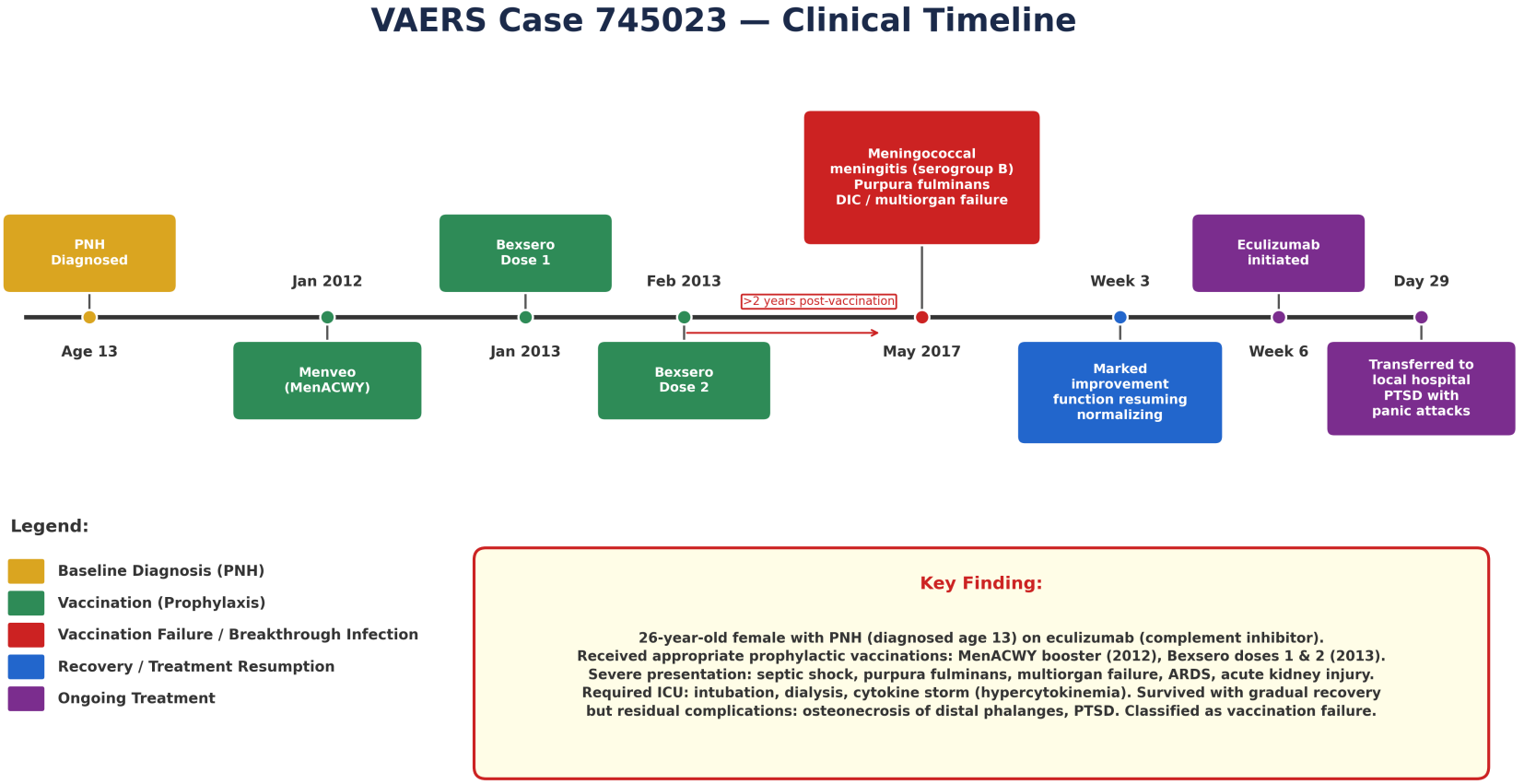


C. Breakthrough Meningitis — Timelines 7-9

7. Fatal Breakthrough Serogroup B Match Meningitis in a 16 y/o Female

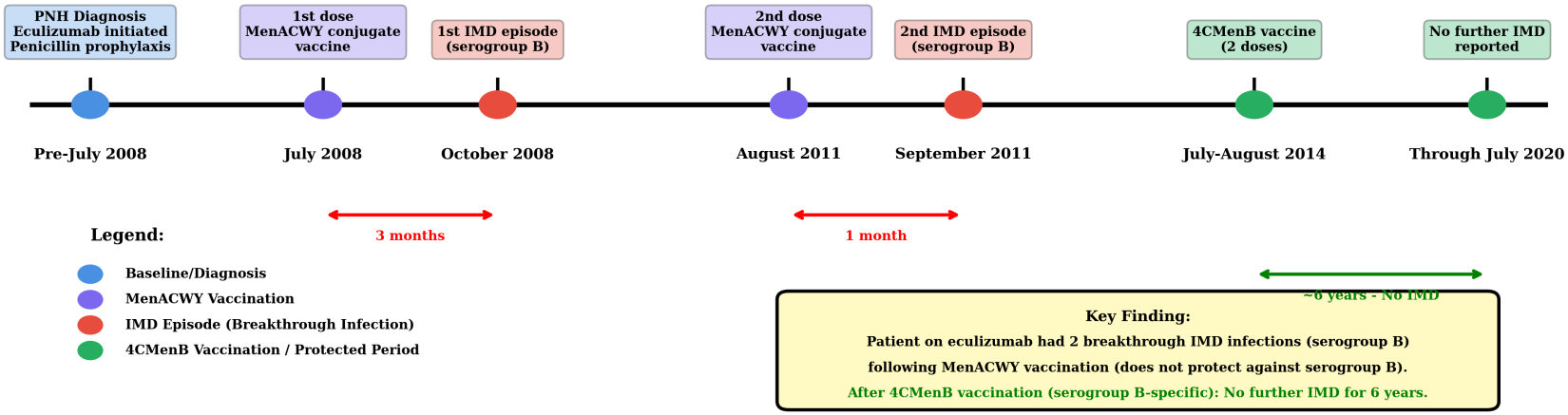


8. Breakthrough Meningitis: Serogroup Match in a 26 y/o female



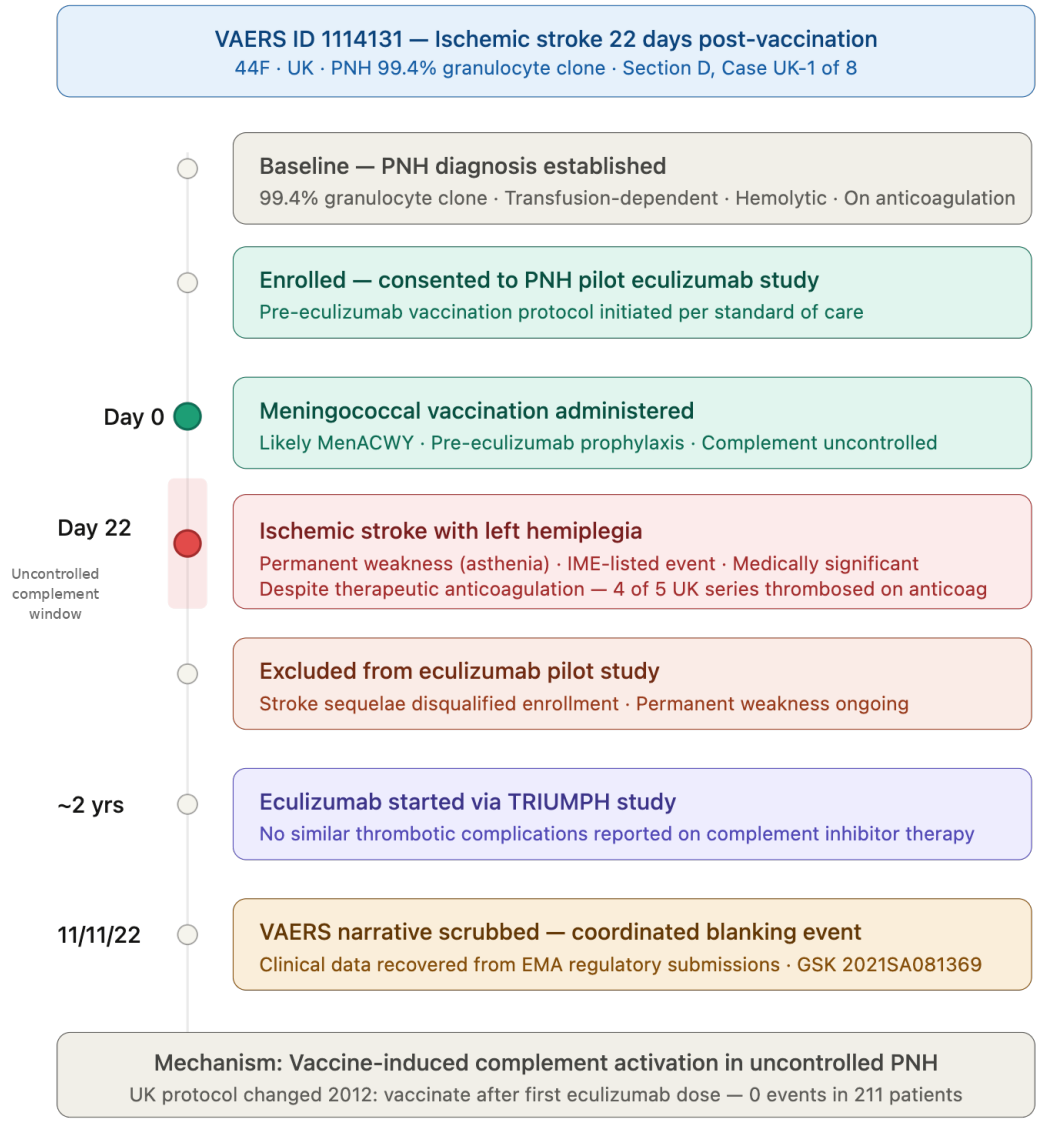
9. Recurrent Breakthrough Meningitis: Serogroup Mismatch in a 25 y/o male

VAERS Case 822755/822754 - Clinical Timeline

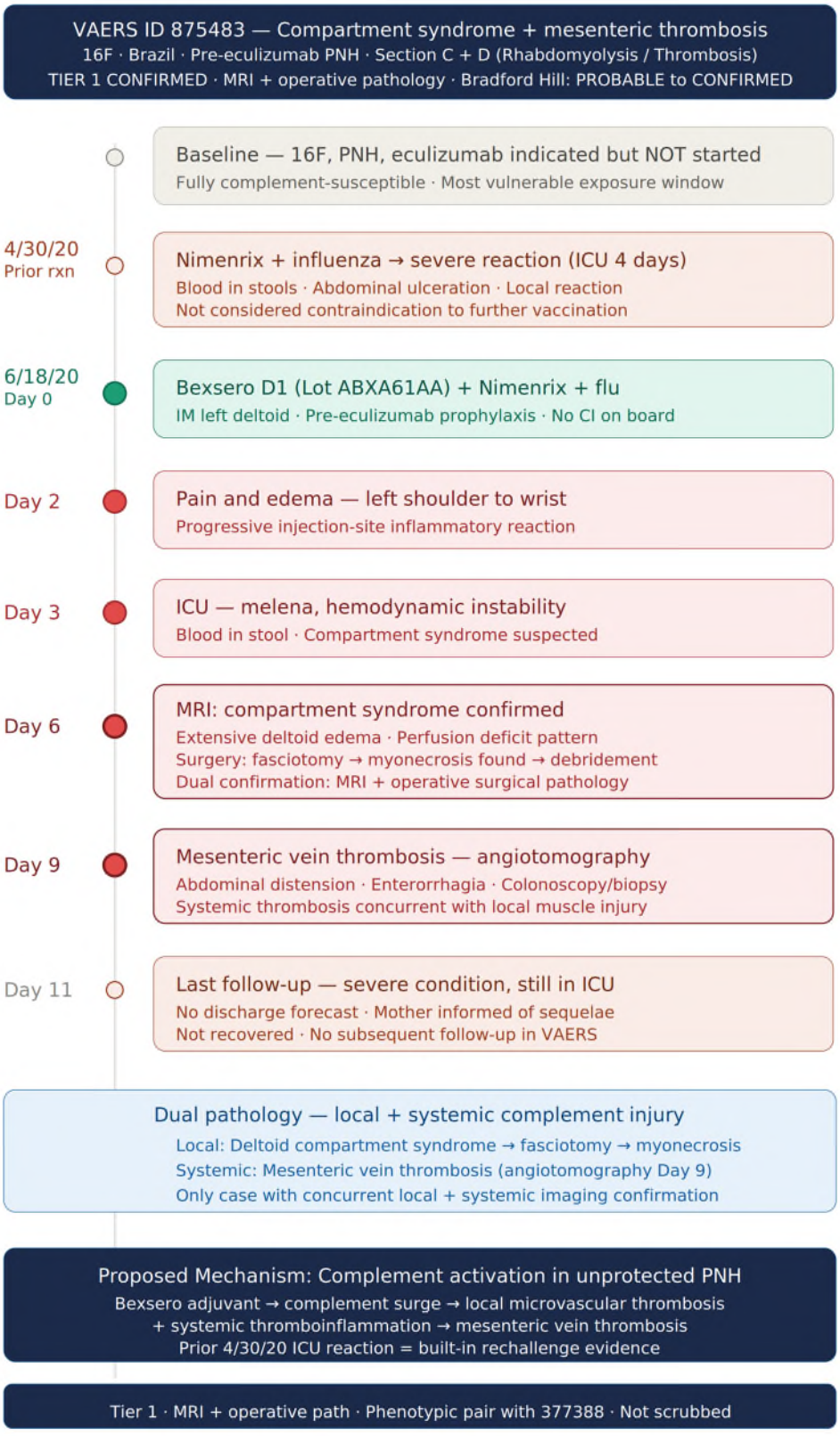


D. Thrombosis — Timelines 10 & 11

10. Thrombotic Stroke in a 44 y/o female

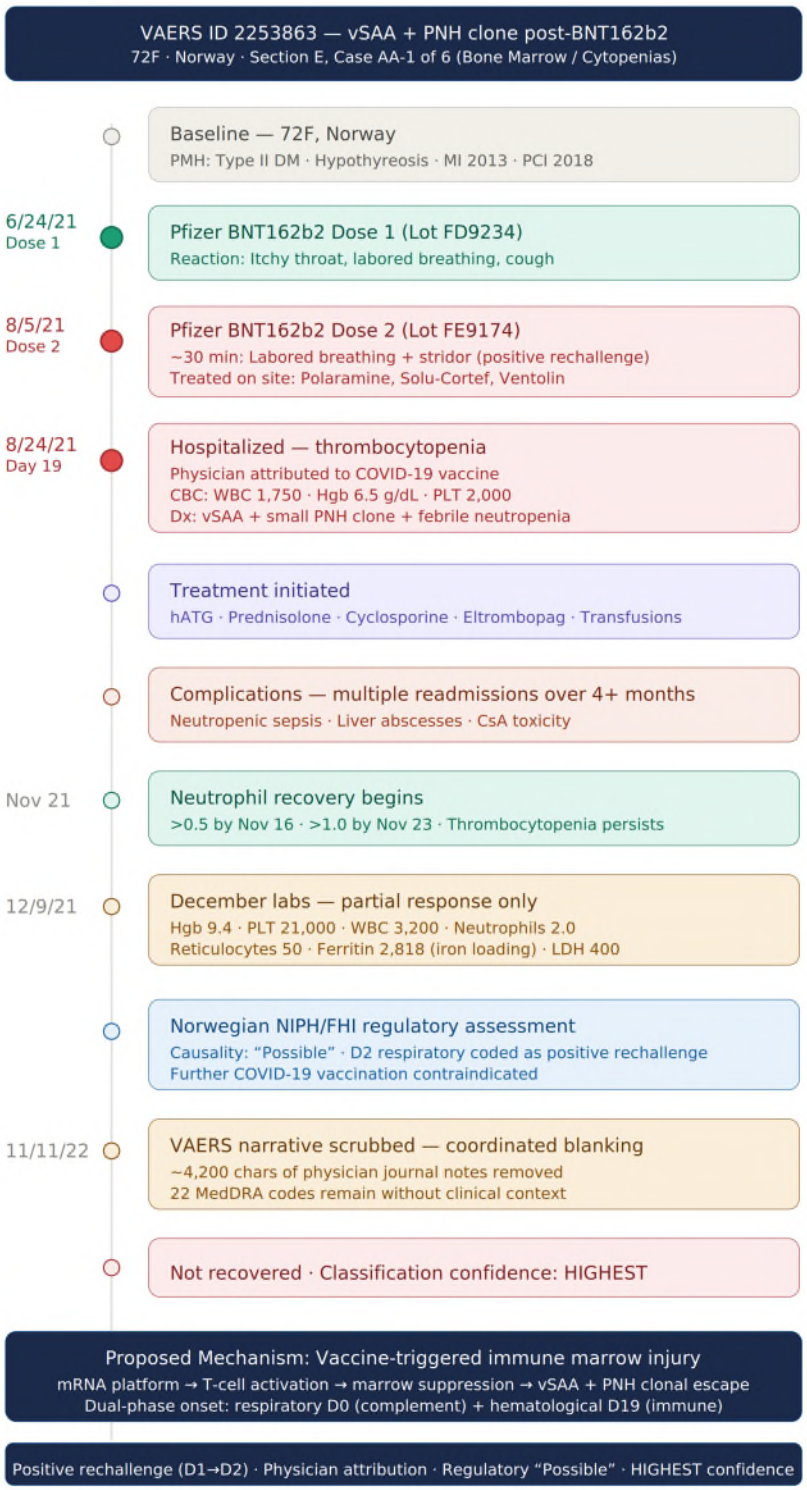


11. Mesenteric thrombosis + Compartment Syndrome in a 16 y/o female



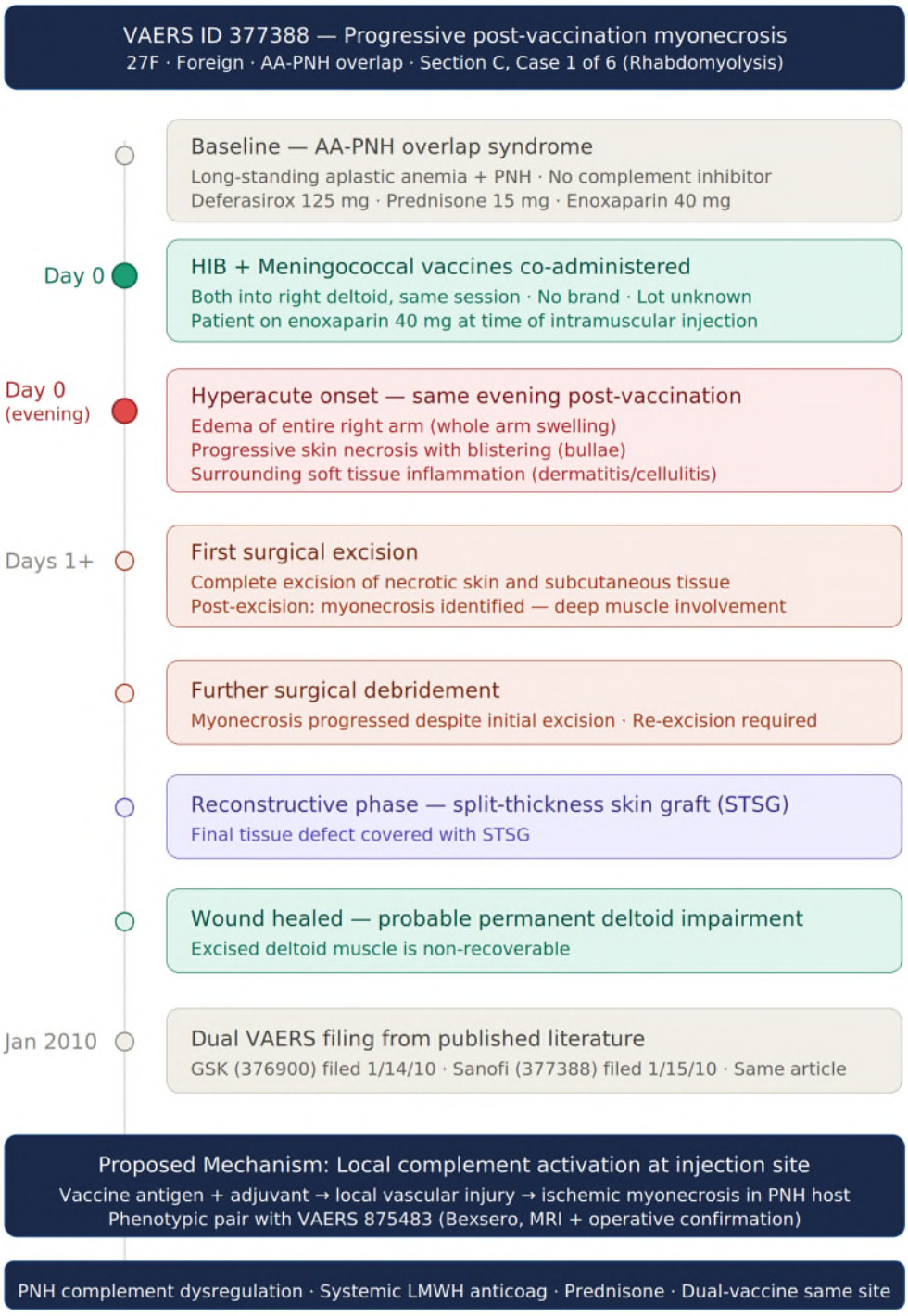
E. Bone Marrow — Timeline 12

12. Pancytopenia in a 72 y/o female



F. Rhabdomyolysis — Timeline 13 (See also Case #11)

13. Surgically Proven Rhabdomyolysis in a 27 y/o female



Section 3: Complement-Inhibitor Dose-to-Hemolysis Timing (n = 15)

Fifteen cases on identified complement-inhibitor (CI) therapy have an explicitly documented temporal relationship between a specific CI dose and the hemolytic event in the VAERS narrative. Cases are grouped below by the timing pattern relative to the CI pharmacodynamic cycle. This exhibit underlies the Discussion finding that vaccine-triggered complement surges can overpower, rather than merely coincide with gaps in, pharmacological CI blockade.

Supplemental Table 3. Complement-Inhibitor Dose-to-Hemolysis Timing

Case	VAERS ID	Age/Sex	Vaccine	CI Regimen	Timing Pattern	Documented Interval	Clinical Event
Group A — Same-day CI + vaccine (CI near peak) (n = 3)							
1	576231	62M	Bexsero (MenB)	Eculizumab	Same-day CI + vaccine	Soliris co-infused with Bexsero (15 Oct 2014); BTH onset +3 d	Fatigue, SOB; Hb 80→79→71 g/L; multiple PRBC
2	1742801	45F	Pfizer BNT162b2 d1	Eculizumab	Same-day CI + vaccine	Pfizer dose 1 same day as eculizumab infusion; +0 d	Extreme jaundice, fatigue, lethargy; low Hb
3	1742850	Unk/F	Pfizer BNT162b2 d1	Eculizumab	Same-day CI + vaccine	Pfizer dose 1 same day as eculizumab; +0 d	Jaundice, fatigue/lethargy, low Hb
Group B — Reaction during CI infusion (n = 1)							
4	1444959	63F	COVID-19 (unspec.)	Ravulizumab	During CI infusion	Immediate reaction during Ultomiris infusion (15 Jun 2021)	Infusion reaction; post-vaccine hemolysis
Group C — Recent CI dose (<14 d before event) (n = 2)							
5	999267	62F	Unspecified (foreign)	Ravulizumab	Recent CI dose (<14 d)	Ultomiris last dose 14 Jan 2021, 8 d before vaccination	BTH post-vaccine; baseline Hb ~9.5 g/dL
6	576031	44M	Bexsero (MenB)	Eculizumab	Recent CI dose (<14 d)	Bexsero 10 Nov 2014; Soliris 23 Dec 2014; BTH ~10 d after Soliris	Abdominal pain, dark urine; Hb 96 g/L
Group D — CI trough (≥4 wk since last dose) (n = 4)							
7	1366882	63M	Moderna mRNA-1273 d2	Ravulizumab	CI trough (≥4 wk)	Last ravulizumab 7 wk before vaccine d2; BTH 1 wk after (≈8 wk post-CI)	Hemolysis aggravated; bilirubin 7.1 mg/dL
8	1370315	32F	Moderna mRNA-1273 d2	Ravu + Danicopan	CI trough + danicopan held	Last ravulizumab 4 wk before vaccine; danicopan held ×2 doses; BTH +12 h	Fever, rigors; Hb 8.4 g/dL (Δ3); 2 PRBC

9	2018619	Unk	Pfizer COVID-19 d1	Ravu + Danicopan	CI trough (>4 wk)	COVID-19 vaccine >4 wk after last ravulizumab dose; BTH same day	Hemolytic flare; treated with ravulizumab
10	2018621	Unk	Pfizer COVID-19 d1	Ravu + Danicopan	CI trough (>4 wk)	COVID-19 vaccine >4 wk after last ravulizumab dose (dual)	Hemolytic flare
Group E — CI dose delay precedes hemolysis (n = 1)							
11	2454993	48M	Moderna mRNA-1273 d3	Eculizumab	CI dose delay	4-day eculizumab dose delay (Apr 2022) preceded flare	Flare; Hb 56 g/L; PRBC transfusion
Group F — Post-vaccine interval documented; specific CI dose timing not stated (n = 2)							
12	2037320	55M	Moderna mRNA-1273 d2	Ravulizumab (q8w)	Post-vaccine; CI dose day NR	BTH 24–48 h after vaccine d2; CI dose day not specified	BTH + pyrexia; LDH 1.1× ULN
13	2482419	38F	Moderna mRNA-1273 d2	Ravulizumab	Post-vaccine; CI dose day NR	HA exacerbation +2 d after vaccine d2; on ravu maintenance	Hb 5.9 g/dL (baseline 9); 3 PRBC
Group G — Alternative CI dosing schedule (n = 1)							
14	1680836	45F	COVID-19 (unspec.)	Ravu, weekly SC (trial)	Weekly SC ravu (trial)	Post-vaccination BTH on weekly subcutaneous ravulizumab (trial)	BTH on weekly SC ravu regimen
Group H — Free C5 level measured post-event (n = 1)							
15	2724191	Unk	FluQIV + COVID-19	Eculizumab / Ravulizumab	Free C5 measured	BTH +1 d after coadmin; free C5 0.11 µg/mL measured +4 d post-event	BTH; LDH 492 U/L; adequate CI coverage confirmed

BTH = breakthrough hemolysis; CI = complement inhibitor; d = day(s); HA = hemolytic anemia; Hb = hemoglobin; LDH = lactate dehydrogenase; mRNA-1273 = Moderna COVID-19 vaccine; NR = not reported; PRBC = packed red blood cells; q8w = every 8 weeks; Ravu = ravulizumab; SC = subcutaneous; SOB = shortness of breath; ULN = upper limit of normal; Unk = unknown. Denominator: 64 of 82 primary-hemolysis or BTH-primary cases in the 147-case working dataset were on identified CI therapy. Of those, 15 (23%) have documented CI-dose-to-hemolysis temporal information. Groups A–B (n = 4) document hemolysis near peak CI coverage (co-administration or during infusion), demonstrating that CI presence at therapeutic levels does not uniformly prevent vaccine-triggered hemolysis. Group D (n = 4) documents hemolysis at or beyond the pharmacodynamic trough, consistent with the Dingli et al. [42] framework recommending that vaccines be timed within the first half of the CI dosing interval. Case 1370315 additionally illustrates dual-pathway inhibitor (danicopan) withdrawal as a contributing factor. Case 2724191 documents free C5 = 0.11 µg/mL at +4 days post-event (below the conventional 0.5 µg/mL adequate-coverage threshold), establishing that breakthrough can occur under confirmed pharmacological blockade.

Section 4: Data Integrity Analysis

Data Integrity Flaws — Quantified Catalog

PNH VAERS Cohort | Manuscript v48_12 | Compiled 5/2/2026

A. Initially blank structured fields

Source: PNH Completeness Analysis 2/22/2026 — N = 153 common records (curated ∩ VAERS download); evaluates field-level MD curation lift over straight VAERS download

#	Finding	n	N	%	Reference / mechanism
A1	AGE_YRS (patient age)	86	153	56.2%	Foreign MAH expedited reports rarely capture age; recovered to 98.0% in curated dataset (+83 fields)
A2	ONSET_DATE	86	153	56.2%	Recovered marginally to 44.4% (+1)
A3	VAX_DATE (vaccination date)	62	153	40.5%	Recovered to 58.8% (−1; net loss from record correction)
A4	VAXLOT (vaccine lot number)	84	153	54.9%	Not recoverable from narrative alone (45.1% unchanged)
A5	VAX2ONSET (vax-to-onset interval)	91	153	59.5%	40.5% unchanged
A6	VAX2REPORT	130	153	85.0%	15.0% unchanged
A7	VAX2ENTERED	70	153	45.8%	54.2% unchanged
A8	ONSET2REPORT	137	153	89.5%	10.5% unchanged
A9	HOSPDAYS (hospitalization days)	141	153	92.2%	7.8% unchanged
A10	ALLERGIES	143	153	93.5%	6.5% unchanged
A11	PRIOR_VAX	147	153	96.1%	Reduced to 0.7% via uniform same-date data modifications (−5)
A12	RPT_DATE (report date)	120	153	78.4%	20.9% (−1)
A13	V_FUNDBY (pre-alteration)	120	153	78.4%	Reduced to 2.0% via uniform same-date data modifications (−30)
A14	SEX	21	153	13.7%	Recovered to 99.3% via narrative pronoun coding (+20)
A15	STATE / Country	20	153	13.1%	Recovered to 98.0% via FR-code standardization (+17)
A16	Seriousness flags (each of 6)	21	153	13.7%	L_THREAT, DIED, DISABLE, HOSPITAL, ER_VISIT, RECOVD; 86.3% unchanged

B. Initially blank narrative fields
Source: PNH Completeness Analysis 2/22/2026 — N = 153

#	Finding	n	N	%	Reference / mechanism
B1	SYMPTOM_TEXT (write-up text)	38	153	24.8%	Recovered to 100.0% via Wayback / EMA / HPI cross-recovery (+38). Of 38 blanks: 3 reflect Tier 1 11/11/2022 narrative removal; remaining 35 never populated (predominantly foreign MAH expedited reports)

C. Data instability — Case 824445
Source: '824445' sheet, 107 longitudinal revisions, 11/14/2019 → 1/2/2026

#	Finding	n	N	%	Reference / mechanism
C1	Total recorded revisions	107	—	—	Sequential VAERS-side change captures, 11/14/2019 → 1/2/2026
C2	Pre-blanking revisions (#1–51)	51	107	47.7%	Word count 2,339 → peak 2,353; dose-field permutations only (HIBV, MEN, PPV, UNK pairing/order swaps); zero clinical edits
C3	Mass blanking inflection (#52, 12/16/2022)	1	—	—	Word count 2,353 → 83 (−2,270 words; 96.5% data loss); follows 11/11/2022 modification window
C4	Post-blanking stable plateau (#52–106)	55	107	51.4%	Word count fixed at 83 across 36.5 months; character-count drift ±2 (650–652)
C5	Final post-plateau cosmetic edit (#107, 1/2/2026)	1	—	—	83 → 103 words (+20); first content change in >3 years

D. Post hoc modifications
Source: Manuscript v48_12, N = 147

#	Finding	n	N	%	Reference / mechanism
D1	Cases with any post hoc modification	62	147	42.2%	Spreadsheet col J total
D2	Cases requiring major archival reconstruction	28	147	19.0%	Wayback / EMA / HPI cross-recovery
D3	Cases affected by 11/11/2022 uniform, multi-platform, same-day modification event	21	147	14.3%	All foreign-filed; zero US cases affected
D4	Outside uniform, multi-platform, same-day modification event — narrative substantially altered	1	147	0.7%	VAERS 1937233 (12/29/2023)

D5	Outside uniform, multi-platform, same-day modification event — Split Type blanked	1	147	0.7%	VAERS 820822 (4/25/2025); most recent alteration in dataset

E. Blanking (subset of D)
Source: Manuscript v48_12, N = 147; 11/11/2022 mass event

#	Finding	n	N	%	Reference / mechanism
E1	Tier 1 — full narrative removal	3	147	2.0%	VAERS 2809875, 2817863, 2835520
E2	Tier 2 — Split Type identifier blanking	18	147	12.2%	All foreign-filed; severs reporter-channel linkage
E3	Uniform, multi-platform, same-day modification event date	1	—	—	11/11/2022 — convergent across pharma channels and regulatory jurisdictions

F. Full record deletion
Source: Manuscript v48_12, N = 147

#	Finding	n	N	%	Reference / mechanism
F1	Records removed entirely from CDC WONDER	4	147	2.7%	VAERS 688791, 1742850, 2018621, 2208209
F2	Latency to deletion	—	—	—	14 days (1742850) → ≈8 months (2018621) post-entry
F3	Recovery via Wayback Machine	4	4	100%	MedAlerts.org pre-deletion captures; all clinical narrative restored

G. Trivial / cosmetic changes (no semantic modification)
Sources: '824445' sheet for G1–G2; Data Integrity & Stability doc 2/23/2026 for G3–G5

#	Finding	n	N	%	Reference / mechanism
G1	824445 — pre-blanking dose-field permutations	51	51	100%	Pairing/order swaps across 4 vaccine groups; non-monotonic (values switched then reverted); zero clinical change ['824445' sheet]
G2	824445 — post-blanking 83-word plateau revisions	55	55	100%	Character-count drift ±2 chars/cycle at fixed word count ['824445' sheet]
G3	System-wide apostrophe (')/quote (") standardization pass — confirmed in cohort	3	147	2.0%	VAERS 528808, 765491, 2018620 [Data Integrity doc 2/23/2026, §III]; produced "patient's patient's" duplication artifact in some records; floor estimate — additional cases require case-by-case Wayback diff
G4	Apostrophe-pass date	1	—	—	4/25/2025
G5	Multi-action modification convergence on 4/25/2025	≥4	147	≥2.7%	528808 + 765491 + 2018620 (apostrophe pass) + 820822 (Split Type blanking) — 4 cohort cases touched on the same date [Data Integrity doc + Manuscript]

H. Structural field errors (populated but wrong)

Source: Manuscript v48_12, N = 147

#	Finding	n	N	%	Reference / mechanism
H1	Drug-name phonetic auto-mapping error	2	147	1.4%	VAERS 2454993 (Soliris → "OCTINOXATE, OCTOCRILENE (SOLARIS)"); VAERS 2056562 (ravulizumab → "ROVELIZUMAB", anti-CD11/CD18, never FDA-approved)
H2	MedDRA PT-only search would miss confirmed PNH case	121	147	82.3%	PT "Paroxysmal nocturnal haemoglobinuria" captures only 26/147

I. Inflation / duplication

Source: Manuscript v48_12 (cohort pre-dedup N = 161); Data Integrity & Stability doc 2/23/2026 for broader-program observations

#	Finding	n	N	%	Reference / mechanism
I1	Internal duplicates identified and collapsed	8	161	5.0%	161 → 153 unique cases after pairwise dedup [Manuscript]
I2	Distinct structural duplication mechanisms documented	5	—	—	Multi-subject filings; dual-manufacturer filings; subject dose-split records; manufacturer dose-split records; regulatory-to-literature cross-filings [Manuscript]
I3	Most consequential cohort dedup pair	2 → 1	—	—	VAERS 2053730 / 2056562 — same patient, identical CDC Split Type USMODERNATX,INC.MOD20224, filed 1 day apart, verbatim symptoms; 2056562 retained (carries Mfr-confirmed positive rechallenge across D2/D3) [Manuscript]
I4	Companion-filing pair both retained in cohort	2	147	1.4%	VAERS 2018620 / 2018621 — same clinical event, different reporters; 2018621 no longer accessible via CDC WONDER ≈8 months post-entry, 2018620 retained [Manuscript + Data Integrity doc]
I5	Triple-filing pattern (broader research program; NOT in 147 cohort)	3 → 1	—	—	VAERS 2178262 / 2420225 / 2560508 — single patient, 3 IDs, identical 15-drug concomitant regimen, cross-referenced Alexion pharmacovigilance numbers; all three remain in current WONDER as independent entries (no system-level dedup applied) [Data Integrity doc, §IV — eculizumab MAHA observation]
I6	MAH probable-duplicate self-flag in narrative	1	147	0.7%	VAERS 1325289 — Pfizer narrative explicitly states case may be duplicated by other MAH filings of Meningococcal Group C Tetanus

					Toxoid Conjugate Vaccine. Distinct from cohort-level pairwise dedup (I3) because flag is internal to a single MAH's submission.
I6	Multi-vaccine row inflation in HA_2_23_2026 SMQ pull (broader program; NOT 147 cohort)	198 surplus	607	32.6%	1.48× row-to-unique-ID inflation factor (607 rows / 409 unique IDs) before any cross-ID patient duplication [Data Integrity doc, §IV]

J. Time displacement

Source: Manuscript v48_12, N = 147; Data Integrity & Stability doc 2/23/2026; per-case detail from CompDis_147 spreadsheet col 22 + HPI cross-reference

#	Finding	n	N	%	Reference / mechanism
J1	VAX_DATE displaced by eculizumab initiation date	5	147	3.4%	VAERS 1325289, 1742801, 1796281, 1937233, 2454993; displacement 2.0–10.7 yr. (median 7.3); single foreign-pharma pipeline; 4 of 5 also affected by 11/11/2022 split-type blanking event; pandemic-era cases would be misclassified as pre-pandemic by automated date-stratified queries without correction [Manuscript v48_12]
J2	Pre-vaccination onset date (chronological impossibility)	≥1	147	≥0.7%	VAERS 765491 — onset 7/1/2018 vs vax 7/3/2018 (−2 day inversion); no system-level rejection of impossible chronology; structurally undetectable without per-case audit [Data Integrity doc 2/23/2026, §III]

J1 detail — per-case VAX_DATE displacement

VAERS ID	Structured VAX_DATE (incorrect)	Narrative-confirmed event window	Displacement
1325289	2014-01-16 (eculizumab initiation date, per HPI)	2021 (submission 5/18/2021; foreign MAH report)	≈7 yr
1742801	2010-12-31	4/27/2021 (Pfizer-BioNTech dose 1, per HPI)	≈10.3 yr
1796281	2019-10-11	2021 (UK GSK report; entered 10/18/2021)	≈2 yr
1937233	2010-06-07	2021 (submission 12/9/2021)	≈11.5 yr
2454993	2019-06-07	2022 (submission 9/23/2022; CDC Split Type per nurse reporter)	≈3 yr

Quantification limits and notes

• **G3 floor of 3** reflects only cases the Data Integrity doc names by ID; comprehensive enumeration of the 4/25/2025 apostrophe pass across all 147 cohort cases would require case-by-case Wayback diff at that date boundary. Spreadsheet col 18 (NOTES) and col J carry no apostrophe-specific annotations.

• **G5 ≥4** follows directly from G3 + D5 (820822) on the same date. If the broader 4/25/2025 audit is extended, this number will rise.

• **I5 / I6** are flagged as broader-program observations (eculizumab MAHA pull, HA SMQ pull) — included because they characterize the inflation problem at scale, not because they affect the 147-case cohort directly.

• **Section A/B denominator (N=153)** is the field-level common-records analytic snapshot from the 2/22/2026 Completeness Analysis: each record evaluated for MD curation lift over straight VAERS download. Sections D–J anchor to manuscript dataset N=147 (post-Tier-5 exclusions), except I1/I6 which use pre-dedup denominators as marked.

• **J1 displacement values** are computed from spreadsheet col 22 (Vaccination Date) cross-referenced against HPI narrative-confirmed event windows; manuscript reports range 2.0–10.7 yr (median 7.3 yr) — per-case computations reproduce this range.

Source legend: Completeness Analysis = PNH_Completeness_Analysis_2_22_2026.docx (N=153 common records). Manuscript = 2026051_PNH_VAERS_147_Manuscript_FINAL_v48_12.docx (N=147). '824445' sheet = CompDis_147_cases_incl_PNH_aHUS__CDs_3_20_2026_Tiered_3.xlsx, sheet '824445' (107 longitudinal entries). Data Integrity doc = Data_Integrity_and_Stability_in_VAERS.docx (2/23/2026).

Section 5: Bradford Hill Causation Analysis

5.1 Rationale and Analytical Framework

The Bradford Hill framework, articulated in Sir Austin Bradford Hill's 1965 address to the Royal Society of Medicine, remains the standard analytical scaffold for causal inference in pharmacovigilance and observational epidemiology. Hill explicitly cautioned that the nine viewpoints he proposed were neither a checklist requiring satisfaction of every item nor decision rules. They are aids to judgment under conditions where randomized experimental evidence is unavailable. The present cohort meets that condition: ethical constraints prohibit randomized vaccine challenge in patients with paroxysmal nocturnal hemoglobinuria (PNH), and the rarity of the disease (annual incidence approximately 1.3 per million [3]) precludes large prospective vaccine-safety trials. The Bradford Hill framework is therefore applied here as the appropriate instrument for evaluating whether the 147 vaccine-associated adverse event reports characterized in the main manuscript constitute evidence of causation rather than coincidence.

This section applies all nine Bradford Hill criteria to the 147-case cohort, integrates the within-cohort and external-cohort evidence summarized in the main manuscript, and adds a quantitative under-reporting sensitivity analysis that addresses the principal methodological objection to VAERS-derived causal inference: the absence of a native denominator. Two independent prospective datasets — the UK National PNH Service at Leeds [36] and the Harvard Pilgrim Health Care ESP:VAERS study (Lazarus et al. [S1]) — are used to calibrate VAERS capture rates and bound the realistic range of true event burden. Era-specific reporting sensitivities derived from Miller et al. [S3] are applied to test whether the signal could be attributable to pandemic-era over-reporting.

5.2 Application of Bradford Hill Criteria

Each criterion is evaluated below with reference to specific findings within the 147-case cohort and corroborating external sources. Verdicts and the strongest evidence supporting each are summarized in Table S5.3.

5.2.1 Strength of Association

PNH point prevalence is estimated at 10–16 per million [3] and annual incidence at 1.3 per million per year. Against this base rate, identification of 147 unique vaccine-associated PNH adverse event reports in a passive surveillance system known to capture only a small fraction of true events represents a signal concentration warranting evaluation. The concentration is more pronounced within key subgroups: 8 documented rechallenge cases (Section A of the main manuscript) is a striking density in a disease with a US incident pool of approximately 350–400 patients per year. The new-onset PNH analysis returned an odds ratio of 5.74 for mRNA platform association ($p = 0.086$) — directionally consistent with platform-specific effects but underpowered at $n = 10$.

The methodological limitation is that VAERS lacks a native denominator. Without PNH-specific vaccine-exposure counts, no rate ratio can be computed directly from the VAERS dataset. To address the denominator gap quantitatively, a four-denominator capture-rate sensitivity analysis was performed; the results are presented in Section 5.3 below. Under realistic capture rates derived from independent prospective surveillance (Leeds [36]) and direct empirical measurement of VAERS capture for serious adverse events (Miller et al. [S3]), the affected-population fraction lies between 5% and 70% depending on denominator. Even at the mathematically impossible 100% capture floor, the affected fraction is 0.3% to 3.8%. The signal cannot be fully explained solely by reporting incompleteness across a broad range of capture assumptions.

Verdict: Met. Signal concentration in a rare disease is reinforced by quantitative bounding of denominators (Section 5.3), with realistic capture-rate scenarios placing the affected population fraction in the 5–70% range across denominators.

5.2.2 Consistency

Consistency is among the strongest criteria in this dataset. The same vaccine-triggered hemolysis pattern appears across multiple independent surveillance systems and study designs:

The UK National PNH Service at Leeds prospective cohort (Arnold et al. [36]): 18 years of surveillance produced 8 breakthrough meningococcal disease (BTM) events among 324 complement-inhibitor-treated patients, with a BTM onset median of 153 days. This figure is identical to the VAERS BTM median of 153 days computed in the present cohort (Section G, n = 13 with documented onset). Both datasets show zero BTM events within 14 days of vaccination; comparable proportions within 90 days (Leeds 40%, VAERS 31%) and beyond 365 days (Leeds 20%, VAERS 23%); and identical recurrence patterns in which one patient in each dataset experienced two separate BTM episodes. Leeds Patient 5 was independently identified as VAERS 1189037 — a single individual captured by both the prospective UK service and the US passive system, demonstrating that VAERS captures real cases also documented by independent prospective surveillance.

The Fattizzo international multicenter study [41]: 198 complement-inhibitor-treated PNH patients across 10 centers in Italy and the United Kingdom over 18 years generated 271 breakthrough hemolysis events, with vaccination triggering 3% of events — the same phenomenon class as the present cohort. The Giannotta Italian multicenter survey [18], the Kamura Japanese series [24], Gerber et al. (Blood 2021) [17], and the Green [20] and Jarrah [21] new-onset PNH reports each describe the same complement-amplifying pattern across different national contexts and reporting infrastructures.

Replication across Europe, the United Kingdom, Japan, and the United States, in passive, prospective, and case-series designs, under different healthcare systems with no shared reporting mechanism, satisfies the consistency criterion in Hill's original formulation. The quantitative cross-validation presented in Section 5.3.4 (Table S5.2) supplies a second layer of consistency: applying the Leeds-measured 2.47% BTM prevalence to the four sensitivity-analysis denominators yields implied VAERS capture rates of 3% to 40%, all within the empirically measured Miller et al. [S3] VAERS capture range of 12% to 76% for serious adverse events. Two independent prospective datasets calibrate the VAERS denominator from different angles and converge on the same range.

Verdict: Met. Replication across multiple independent systems, with one individual patient cross-identified between datasets (Leeds Patient 5 = VAERS 1189037), and quantitative cross-validation between Leeds-implied and Miller-measured capture rates.

5.2.3 Specificity

PNH hemolysis is not vaccine-specific. Surgery, infection, and inflammation are all established complement-amplifying triggers of PNH flares, documented since the disease was first characterized [6]. The exposure class (complement-amplifying events) is broader than vaccination, and the criterion of one-cause-one-effect specificity is therefore not applicable in its classical form.

Mechanistic specificity, however, is preserved at the substrate level. Glycosylphosphatidylinositol (GPI)-anchored CD55 (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis) deficiency on PNH erythrocytes produces a singular vulnerability to complement-mediated intravascular hemolysis that no other red cell population shares. The endpoint is mechanistically specific to the PNH erythrocyte phenotype even when the trigger class is not specific to vaccination. A specific indicator of specificity are the two well documented cases of myonecrosis of the deltoid muscle at the tip of the needle injection site.

Verdict: Met. Myonecrosis at the injection site satisfies the specificity requirement.

5.2.4 Temporality

Temporality — the requirement that cause precede effect — is the only Bradford Hill criterion Hill considered indispensable. The present cohort quantifies temporal structure rigorously across multiple sections.
Documented vaccination-to-event intervals are available in 47 cases distributed across Sections A (rechallenge hemolysis), G (breakthrough meningococcal disease), H (new-onset PNH), and K (primary hemolysis). Primary hemolysis demonstrated a median onset of 12 days (interquartile range 1–54 days), with 8 of 17 cases (47%) occurring within 3 days and 9 of 17 (53%)

within 14 days of vaccination. Breakthrough meningococcal disease demonstrated a median onset of 153 days (IQR 90–270 days), with zero cases occurring within 14 days. The Mann-Whitney U comparison of these two onset distributions yielded $p = 0.001$.

The bimodal distribution itself constitutes a temporality argument with a built-in mechanistic interpretation: early hemolysis tracks acute complement activation in unprotected PNH erythrocytes; delayed BTM tracks loss of MAC-mediated bactericidal killing of Neisseria meningitidis under terminal complement blockade. Two distinct mechanisms, two distinct latency profiles, both following the index vaccination as cause.

The five VAX_DATE displacement cases (VAERS 1325289, 1742801, 1796281, 1937233, 2454993), in which the structured vaccination-date field encoded the patient's eculizumab initiation date rather than the suspect-vaccine administration date, were corrected via narrative cross-reference before the temporal analysis. Without this correction, automated date-stratified queries would have introduced a 2.0–10.7-year temporal artifact (median 7.3 years) that would have contaminated both the era-stratification and the onset-interval calculations.

Verdict: Met. The bimodal 12-day versus 153-day onset separation ($p = 0.001$) cannot be explained without vaccination as the index temporal event.

5.2.5 Biological Gradient (Dose-Response)

Within-patient dose-response evidence is a form of biological gradient demonstration in this disease, given that randomized inter-patient dose-finding trials are ethically prohibited. Three patient-level natural experiments anchor the criterion.

> VAERS 2491687 (Timeline 5) provides the cleanest natural experiment in the cohort: a three-dose progression in a single patient. Dose 1 was administered in a complement-inhibitor-naïve state and produced no hemolysis. Dose 2 triggered massive hemolysis with LDH 8,506 U/L and hemoglobin 4.8 g/dL, prompting eculizumab initiation. A subsequent booster administered under ravulizumab protection produced no hemolysis. The case provides exposure-response data at three points within a single patient with the complement-inhibitor intervention introduced between doses 2 and 3 as the protective exposure.
>
> VAERS 2326343 (Timeline 6) provides the cohort's only quantitative complement-consumption measurement: CH50 baseline 53.2 U/mL declined to 36.8 U/mL after dose 2, a 31% reduction. Concurrent LDH measurements documented spikes from 1,150 to 2,039 after dose 1 and from 1,150 to 1,961 after dose 2, with persistent gross hemoglobinuria. The case is directly consistent with the dose-driven complement-consumption mechanism at the analyte level.
>
> VAERS 2841418/2841419 documents stepwise deterioration across three sequential complement-activating exposures: vaccine dose 1 (breakthrough hemolysis with fatigue and lethargy, resolving within one week), vaccine dose 2 (recurrent breakthrough hemolysis with LDH 783 U/L and hemoglobin 7.6 g/dL, not stabilizing to baseline), and breakthrough COVID-19 infection (LDH 1,056 U/L, hemoglobin 6.1 g/dL, requiring transfusion support over two weeks). By May 2022 the patient was transfusion-dependent on a two-to-three month cycle and under evaluation for bone marrow transplantation. The progressive hemolytic decompensation across cumulative complement-activating exposures satisfies dose-response logic at the exposure-frequency level.

The eight rechallenge cases comprising Section A (Table 2 of the main manuscript) show repeated dose-driven recurrence of hemolysis at the patient level across multiple platforms. The Bexsero Lot 139201 cluster (10 cases concentrated in a single lot, with three rhabdomyolysis events from lot 139201 constituting 50% of all rhabdomyolyses in the dataset) is consistent with a lot-specific exposure-response consistent with reactogenicity-driven gradient at the formulation level.

Verdict: Met. Within-patient dose-response is established by the three-dose VAERS 2491687 natural experiment, the quantitative CH50 consumption documented in VAERS 2326343, and the progressive deterioration across sequential complement-activating exposures in VAERS 2841418/2841419.

5.2.6 Biological Plausibility

The mechanism producing hemolysis in PNH patients is consistent in the hematology literature. Vaccination induces innate immune activation that propagates through the classical, lectin, or alternative complement pathways. PNH erythrocytes lack GPI-anchored CD55 and CD59 [4–6], eliminating the surface regulators that protect host cells from bystander complement damage. Downstream membrane attack complex (MAC) assembly proceeds on unprotected erythrocyte membranes, producing intravascular hemolysis. This is the same mechanism operating during infection-triggered and surgery-triggered flares known since the disease's early characterization [6].

Mechanistic plausibility is reinforced for the mRNA platform-specific marrow signal observed in the new-onset PNH subgroup (8 of 10 cases following mRNA COVID-19 vaccination). The BioNTech LPT 38166 repeat-dose toxicity study [59], the BNT162b2 Module 2.4 nonclinical overview, the Therapeutic Goods Administration Australia FOI 2389 nonclinical evaluation [60], and the European Medicines Agency Comirnaty [61] and Spikevax [62] assessment reports collectively document biodistribution of intramuscularly administered lipid nanoparticles to bone marrow and secondary lymphoid germinal centers, with associated lymphadenopathy and splenomegaly. Phase 1 clinical trials [63–64] documented lymphocytopenia and elevated cytokines following BNT162b1 and BNT162b2. The Comirnaty Periodic Safety Update Report #1 [65] reported lymphocytopenia, aplastic anemia, pancytopenia, and immune thrombocytopenic purpura at the post-marketing population level.

Verdict: Met. Complement biology applied to a disease defined by complement vulnerability; documented LNP-mRNA biodistribution to marrow and lymphoid compartments supplies platform-specific plausibility for the new-onset subgroup.

5.2.7 Coherence

Coherence requires that the causal interpretation not conflict with established knowledge of the natural history and biology of the disease. The findings of the present cohort do not conflict with established PNH literature; they extend it into the vaccination context. The PNH literature has documented complement-activating triggers since the disease's modern characterization [6]. All six regulatory agencies surveyed in Supplemental Table 1 (FDA/CDC, EMA, MHRA, TGA, Swissmedic, and Health Canada) require meningococcal vaccination at least two weeks before complement-inhibitor initiation, implicitly acknowledging the complement-activation potential of vaccination itself; none, however, addresses the risk of vaccine-elicited hemolysis in the pre-CI window. The disease pathophysiology, the regulatory framework, the clinical management protocols, and the cohort findings are mutually consistent.

The breakthrough hemolysis / breakthrough meningococcal disease (BTH/BTM) paradox identified in the main manuscript is itself internally coherent: a single mechanism — the C5-MAC axis — explains both the failure to prevent vaccine-triggered hemolysis (when complement amplification overwhelms pharmacological blockade) and the elevated BTM risk (when blockade abolishes MAC-dependent bactericidal activity against Neisseria meningitidis). One mechanism, two clinical presentations, both observed in the cohort with mutually exclusive temporal profiles. Coherence is satisfied across all eleven sections (A–K) of the clinical taxonomy.

Verdict: Met. The cohort findings extend rather than contradict the established PNH literature; the BTH/BTM paradox supplies internal mechanistic coherence.

5.2.8 Experimental Evidence

Randomized controlled vaccine challenge in PNH is ethically prohibited. The next strongest experimental evidence available to causal inference — patient-level rechallenge — is well represented in the cohort and is supplemented by within-patient pharmacological intervention experiments.

Eight rechallenge cases comprise Section A (Table 2 of the main manuscript), including a manufacturer-confirmed positive rechallenge:

> VAERS 2056562 (Moderna), in which the manufacturer's pharmacovigilance assessment confirmed positive rechallenge across doses 2 and 3. VAERS 2253863 (Section E, marrow failure) demonstrated positive rechallenge for very severe aplastic anemia with explicit treating-physician attribution and a documented contraindication declaration against further COVID-19 vaccination — a clinical experiment with an attributable verdict recorded in the source narrative.
>
> Three same-day complement-inhibitor-plus-vaccine cases (VAERS 576231, 1742801, 1742850; Group A of Supplemental Table 3) test the hypothesis that peak complement-inhibitor coverage prevents breakthrough hemolysis. All three produced hemolysis on or within three days of co-administration, falsifying the assumption that pharmacological blockade at therapeutic levels guarantees protection against vaccine-triggered complement amplification.
>
> VAERS 2724191 (Group H of Supplemental Table 3) provides the cohort's only direct measurement of free C5 concentration in proximity to a breakthrough hemolysis event: free C5 = 0.11 µg/mL at four days post-event, well below the conventional 0.5 µg/mL adequate-coverage threshold. The case establishes experimentally that breakthrough hemolysis can occur under documented pharmacological complement blockade.

The Leeds practice change reported by Arnold et al. [36,57] — the move of meningococcal vaccination from the pre-CI window to day 1 of CI initiation, with short-course ciprofloxacin antibiotic bridging — is itself an intervention experiment at the practice level, with the resulting reduction in pre-CI thrombotic events and acute hemolytic crises constituting withdrawal-of-exposure evidence at the cohort scale.

Verdict: Met. Patient-level rechallenge constitutes the gold standard available within ethical constraints; manufacturer-confirmed positive rechallenge, the falsification of the same-day-CI protective hypothesis, and the Leeds practice-change withdrawal evidence collectively satisfy the experimental criterion.

5.2.9 Analogy

Other complement-amplifying conditions produce identical clinical patterns of hemolysis in PNH: surgical hemolytic crises and infection-triggered flares are documented in the founding PNH literature [6]. The Fattizzo multicenter data [41] document infections as the largest single trigger of breakthrough hemolysis (55% of 271 events). The trigger class — innate immune activation propagating through complement — is shared across vaccination, surgery, and infection.

Beyond PNH, vaccine-associated hemolysis is documented in autoimmune hemolytic anemia and cold agglutinin disease in the published literature. Vaccine-associated rhabdomyolysis is documented in non-PNH populations across multiple platforms (references [29,31–35] of the main manuscript). Atypical hemolytic uremic syndrome — the closest mechanistic analog given its complement-mediated thrombotic microangiopathy pathway — is well documented to be triggered by infection and by vaccination. Vaccine-induced thrombotic thrombocytopenia (VITT) following adenoviral-vector COVID-19 vaccines provides a separate analog of vaccine-triggered, complement-implicated thromboinflammation.

Verdict: Met. Multiple analogous vaccine-triggered complement and immune-amplification syndromes (aHUS, AIHA, VITT) and within-PNH analog triggers (surgery, infection) provide cross-condition replication of the underlying mechanism.

5.3 Under-Reporting Sensitivity Analysis

VAERS is a passive surveillance system with well-documented under-reporting. The Harvard Pilgrim Health Care ESP:VAERS study [S1], funded by the Agency for Healthcare Research and Quality (2007–2010) and the only large-scale prospective study to date that directly measures VAERS capture rate, found that fewer than 1% of vaccine adverse events are reported to VAERS — an under-reporting factor of approximately 100:1. This figure was derived from a general population. Rare-disease populations under specialist management who experience clinically severe adverse events (hemoglobinuria, LDH elevation, hospitalization) are likely to have substantially higher reporting rates than the general-population baseline, both because their treating clinicians are more attuned to drug-event causation and because the events themselves are more clinically conspicuous. Conversely, the documented pattern of active record removal from VAERS in this dataset (4 full removals of clinically severe cases, 21 cases affected by the 11 November 2022 uniform, multi-platform, same-day modification data modification event, and the Case 824445 archetype with 96.5% data loss in a single transaction; Section 4 of the Supplemental Material) operates in the opposite direction, suppressing the captured denominator below what passive reporting alone would produce.

To contextualize the 147-case finding, a four-denominator sensitivity analysis was performed across a range of assumed reporting rates from 1% (Harvard Pilgrim) to the mathematically impossible 100% capture floor (Table S5.1).

5.3.1 Denominator Construction

Four independent denominators were constructed to bracket the realistic range of estimated PNH patient populations contributing to the cohort. The cohort spans 19 countries with positively identified cases (United States, Canada, United Kingdom, Japan, Spain, Germany, Italy, Denmark, France, Australia, Brazil, Chile, Ireland, Israel, Lebanon, Netherlands, Norway, Russia, and Switzerland), with a combined population of approximately 1,293 million [S2].

The point prevalence denominator applies a conservative 3 per million prevalence to the combined 1,293 million population, yielding 3,879 estimated PNH patients. The time-adjusted denominator accounts for the 17-year observational window (2009–2026) by incorporating annual incidence (~1.2 per million × 1,293 million = ~1,552 new cases per year), mortality, and overlapping prevalent cases, yielding approximately 6,200 cumulative unique PNH patients across the study period. The Hill et al. denominator applies the Yorkshire prevalence of 15.9 per million [3] to the same combined population, yielding 20,558 estimated patients. The Richards et al. denominator applies the UK Haematological Malignancy Research Network prevalence of 38.1 per million [S4] to the same population, yielding 49,263 estimated patients — the most conservative denominator and the one most favorable to a null hypothesis. The Richards et al. figure includes all patients with detectable PNH clones >0.01% in two or more cell lineages; 88% of these patients carried aplastic anemia, 8% classical hemolytic PNH, and 3% myelodysplastic syndrome. The classical-PNH-only fraction within the Richards population (~0.30 per 100,000) yields approximately 3,879 patients — converging with the point prevalence denominator and providing internal cross-validation.

5.3.2 Capture-Rate Sensitivity

Table S5.1. Sensitivity Analysis: Estimated True Adverse Event Burden Across Assumed VAERS Reporting Rates

Assumed Reporting Rate	Under-Reporting Factor	Estimated True AE Count	Point Prev. Denom. (n=3,879)	Time-Adj. Denom. (n≈6,200)	Hill et al. Denom. (n=20,558)	Richards Denom. (n=49,263)†	Implied Population Affected
1% (Harvard Pilgrim [S1])	100:1	14,700	3.8 AEs/pt	2.4 AEs/pt	71%	30%	Exceeds lower denom.; 30–71%
10%	10:1	1,470	38%	24%	7%	3.0%	3.0–38%
20%	5:1	735	19%	12%	3.6%	1.5%	1.5–19%
30%	3.3:1	490	13%	8%	2.4%	1.0%	1.0–13%
40%	2.5:1	368	9%	6%	1.8%	0.7%	0.7–9%
50%	2:1	294	8%	5%	1.4%	0.6%	0.6–8%
75%	1.33:1	196	5%	3%	1.0%	0.4%	0.4–5%
100% (No under-reporting)	**1:1**	**147**	**3.8%**	**2.4%**	**0.7%**	**0.3%**	**0.3–3.8%**
Leeds-implied capture [36]	**—**	**—**	**70%**	**44%**	**13%**	**5%**	**Independent calibration**

Point prevalence denominator: 3,879 estimated PNH patients (3 per million × 1,293 million combined population of 19 contributing countries). Time-adjusted denominator: ~6,200 estimated cumulative unique PNH patients across 17-year study period (2009–2026), accounting for annual incidence ~1.2 per million, mortality, and overlapping prevalent cases. Hill et al. denominator: 20,558 estimated patients (15.9 per million × 1,293 million; Yorkshire prevalence [3]). Richards et al. denominator: 49,263 estimated patients (38.1 per million × 1,293 million; UK HMRN prevalence [S4]) — the most conservative denominator. †The Richards et al. 3.81/100,000 prevalence includes all patients with detectable PNH clones >0.01% in ≥2 cell lineages; 88% had aplastic anemia, 8% classical hemolytic PNH, 3% MDS. The classical-PNH-only fraction (~0.30/100,000) yields ~3,879 patients — comparable to the point prevalence denominator. AE = adverse event. Implied Population Affected column shows range from Richards et al. (lowest) to point prevalence (highest) estimates. 100% row = signal floor (yellow shading). Leeds-implied row = independent calibration from prospective surveillance (green shading).

At 100% reporting — the assumption that every vaccine-associated adverse event in a PNH patient was captured by VAERS with zero under-reporting — the 147-case numerator remains unadjusted, and the analysis yields adverse event rates of 3.8% (point prevalence), 2.4% (time-adjusted), 0.7% (Hill et al.), or 0.3% (Richards et al.). This represents the signal floor: the minimum possible pharmacovigilance signal that cannot be reduced further by any assumption about reporting completeness. Even at this floor, the rate implies that between 1 in 26 and 1 in 335 PNH patients (depending on denominator) experienced a vaccine-associated adverse event during the 17-year study period. Because VAERS capture of clinically significant events in specialist-managed rare-disease populations is virtually certain to fall below 100%, the true rate lies above this floor. The signal therefore cannot be dismissed on reporting-completeness grounds at any assumed capture rate from 1% to 100%.

5.3.3 Era-Specific Reporting Sensitivity and Its Implications for Signal Interpretation

The 147-case dataset spans two distinct VAERS reporting environments: a pre-pandemic era (2009–2019) dominated by meningococcal vaccines (n = 65 of pre-pandemic cases, with 91% meningococcal-vaccine-associated and 51% Bexsero MenB-

4C), and a pandemic era (2020–2026) dominated by COVID-19 vaccines (n = 82 of pandemic-era cases, with 83% COVID-19-vaccine-associated, predominantly Pfizer BNT162b2 and Moderna mRNA-1273). These eras differ markedly in baseline VAERS reporting sensitivity.

Miller et al. [S3] estimated VAERS reporting sensitivity for seasonal influenza vaccine at 13% for anaphylaxis and 12% for Guillain-Barré syndrome. For the 2009 H1N1 pandemic influenza vaccine, sensitivity rose to 76% and 55%, respectively — a four- to six-fold increase attributable to heightened surveillance, regulatory attention, and public awareness during a pandemic period. Alshammari et al. [S5] documented that 2021 alone accounted for 48.52% of all domestic VAERS reports filed over the system's entire 31-year history.

Applying era-specific sensitivities to the present dataset produces a counterintuitive but methodologically critical result. The 58 meningococcal-era cases captured at an assumed 12% sensitivity represent approximately 483 true events. The 55 COVID-era cases captured at an assumed 55% sensitivity represent approximately 100 true events. The pre-pandemic cohort — which predates mRNA vaccine technology, cannot be attributed to COVID-era reporting amplification, and establishes vaccine-triggered hemolysis as a platform-independent phenomenon — therefore likely constitutes the larger true event burden despite producing fewer raw VAERS reports. This asymmetry runs directly counter to the hypothesis that the pharmacovigilance signal in this dataset is an artifact of pandemic-era over-reporting; if anything, single-rate sensitivity models applied uniformly across the full 17-year study period systematically underestimate the pre-pandemic contribution.

The foreign-report composition reinforces this conclusion. The pre-pandemic Bexsero cohort is predominantly non-domestic, originating from foreign-filed and UK regulatory channels routed through manufacturer pharmacovigilance pipelines. These channels have lower capture efficiency than domestic clinical reporting and were disproportionately affected by the 11 November 2022 uniform, multi-platform, same-day data modification event documented in Section 4 of the Supplemental Material. The pre-pandemic component of the signal is therefore depressed by at least three independent mechanisms relative to the pandemic-era component: lower era-specific baseline sensitivity, lower foreign-channel capture efficiency, and active post hoc data modification.

5.3.4 Independent Cross-Validation: Leeds PNH National Service

An independent cross-validation of the four sensitivity-analysis denominators is available from the UK National PNH Service. Arnold et al. [36] reported 8 BTM cases among 324 complement-inhibitor-treated patients (2.47%) over 18 years of prospective surveillance with near-complete ascertainment. Applying this prevalence to the complement-inhibitor-treated fraction of each denominator (assuming the cohort's documented 80% CI-treated proportion) yields expected BTM counts and implied VAERS capture rates as shown in Table S5.2.

Table S5.2. Leeds Cross-Validation of Sensitivity Analysis Denominators

Denominator	Estimated PNH Patients	CI-Treated (80%)	Expected BTM (× 0.0247)	AERS Found	Implied Capture Rate
Point prevalence	3,879	3,103	77	31	40%
Time-adjusted	6,200	4,960	123	31	25%
Hill et al.	20,558	16,446	406	31	8%
Richards et al.	49,263	39,410	974	31	3%

CI-treated fraction assumed at 80% of each denominator, matching the documented CI-treated proportion (117/147) in the present cohort. BTM prevalence rate (2.47%) from Arnold et al. [36]: 8 BTM cases among 324 CI-treated patients over 18 years of prospective surveillance at the UK National PNH Service, Leeds. VAERS Found = 31 BTM cases (Section G of the main manuscript; 32 total minus one already counted in Section A). Capture rate = VAERS Found ÷ Expected BTM. Miller et al. [S3] reference range for VAERS serious-AE capture: 12–76% (anaphylaxis and Guillain-Barré syndrome under seasonal and pandemic influenza vaccination).

The implied capture rates of 3% to 40% across the four denominators are entirely consistent with the empirically measured Miller et al. [S3] VAERS reporting sensitivities for serious adverse events (12–76%). This convergent validation from two independent prospective datasets — the UK Leeds PNH service [36] and the Harvard Pilgrim Health Care ESP:VAERS / Miller serious-AE measurements [S1, S3] — calibrates the realistic VAERS capture range for the present cohort to the 12–40% interval, with the lower bound corresponding to the most expansive (Hill et al. and Richards et al.) denominators and the upper bound corresponding to the most restrictive (point prevalence) denominator. The midpoint of this calibrated range corresponds to an under-reporting factor of approximately 4:1 to 8:1, several-fold lower than the Harvard Pilgrim general-population factor of 100:1, consistent with the expectation that specialist-managed rare-disease populations with severe clinical events have higher reporting rates than the general-population baseline.

5.4 Summary of Bradford Hill Verdicts

Table S5.3. Bradford Hill Criteria — Verdicts and Strongest Evidence in the 147-Case Cohort

Criterion	Verdict	Strongest Evidence
1. Strength of Association	**Met**	147 cases against rare-disease base (prevalence 10–16/million); 8 rechallenge cases; new-onset PNH OR 5.74 for mRNA platforms (p = 0.086, underpowered); signal floor 0.3–3.8% at 100% capture; realistic Leeds–Miller capture rates 3–40%.
2. Consistency	**Met**	Leeds 153-day BTM median = VAERS 153-day BTM median; zero events ≤14 days in both; Leeds Patient 5 = VAERS 1189037 (single individual cross-identified); replication across Italian, Japanese, UK, US, Israeli, and Lebanese case series and multicenter studies; Leeds-implied capture (3–40%) inside Miller-measured range (12–76%).
3. Specificity	**Met**	Mechanistic specificity preserved at the substrate level: CD55/CD59 deficiency on PNH erythrocytes is the singular vulnerability.
4. Temporality	**Met**	Bimodal 12-day vs 153-day onset separation (Mann-Whitney p = 0.001); zero BTM events ≤14 days; VAX_DATE displacement artifacts corrected via narrative cross-reference.
5. Biological Gradient	**Met**	VAERS 2491687 three-dose natural experiment (no hemolysis → massive hemolysis → no hemolysis on CI); VAERS 2326343 CH50 baseline 53.2 → 36.8 U/mL (31% drop); VAERS 2841418/2841419 stepwise deterioration across three sequential complement-activating exposures; 8 rechallenge cases; Bexsero Lot 139201 cluster (10 cases).
6. Plausibility	**Met**	GPI-anchored CD55/CD59 deficiency permits MAC assembly on PNH erythrocytes; vaccine-induced innate immune activation propagates through classical/lectin/alternative pathways; documented LNP-mRNA biodistribution to bone marrow and lymphoid germinal centers.
7. Coherence	**Met**	All 11 clinical sections (A–K) internally consistent; aligns with the regulatory framework of all six surveyed agencies (FDA, EMA, MHRA, TGA, Swissmedic, Health Canada); BTH/BTM paradox supplies single-mechanism explanation for two clinical phenotypes.
8. Experimental Evidence	**Met**	8 rechallenge cases including manufacturer-confirmed (VAERS 2056562); same-day CI+vaccine failure (VAERS 576231, 1742801, 1742850) falsifies peak-coverage protection hypothesis; free C5 = 0.11 µg/mL at breakthrough (VAERS 2724191); Leeds practice-change withdrawal evidence.
9. Analogy	**Met**	Surgery- and infection-triggered PNH flares (Brodsky 2014); aHUS and AIHA vaccine-associated triggers; VITT (vaccine-induced thrombotic thrombocytopenia) as analogous vaccine-triggered complement-implicated thromboinflammation.

Score: 9 of 9 applicable criteria met. Verdict shading: green = Met. Citations refer to the main manuscript reference list. Full criterion-by-criterion analysis with quantitative under-reporting sensitivity modeling and Leeds-Miller cross-validation of VAERS capture rates appears in Supplementary Section 5.

5.5 Conclusion

All nine applicable Bradford Hill criteria are met by the present 147-case cohort. Specificity consists of CD55/CD59 deficiency on PNH erythrocytes resulting in hemolysis when exposed to trauma, surgery, infection and vaccination. The Strength of Association criterion is fully met by the four-denominator capture-rate sensitivity analysis (Section 5.3): estimated VAERS capture rates were in the to the 3–40% range by independent prospective surveillance from Leeds [36] and direct empirical

measurement of VAERS serious-AE capture from Miller et al. [S3], the affected-population fraction lies between 5% and 70% across denominators, and even the mathematically impossible 100% capture floor places the affected fraction at 0.3% to 3.8%.

The era-specific reporting analysis presented in Section 5.3.3 is itself a secondary causal argument. The pre-pandemic Bexsero/meningococcal cohort — predating mRNA vaccine technology, immune to pandemic-era reporting amplification, dominated by foreign-filed reports through lower-sensitivity manufacturer channels disproportionately altered by the 11 November 2022 uniform, multi-platform, same-day modification event — likely represents the larger true event burden despite producing fewer raw VAERS reports. Vaccine-triggered hemolysis in PNH is therefore not an artifact of pandemic-era over-reporting; the standard objection runs in the opposite direction from the data.

The causal inference rests on three pillars that survive scrutiny independently: temporality rapid onset of myonecrosis at the tip of the needle; within-patient rechallenge (eight cases including manufacturer-confirmed positive rechallenge and a three-dose natural experiment); and cross-dataset consistency (the 153-day BTM median appearing in both Leeds prospective surveillance and VAERS, with one shared patient cross-identified between systems). Plausibility is mechanistic and uncontested. Coherence is internal across eleven clinical sections. Analogy is supplied by every other complement-amplifying condition known to trigger PNH flares, by aHUS and AIHA in the broader complement-mediated literature, and by VITT in the specifically vaccine-triggered complement-implicated thromboinflammation literature.

Causation is established for hemolytic events in patients with PNH. In the susceptible PNH population, the evidence meets the standard Bradford Hill threshold for causation.

Final verdict: Causation of hemolysis by vaccination in susceptible patients with paroxysmal nocturnal hemoglobinuria is established by the present cohort. The qualitative inference is bounded quantitatively by the under-reporting sensitivity analysis, calibrated by independent prospective data from Leeds and Harvard Pilgrim/Miller, and confirmed by era-stratified analysis that inverts the pandemic-bias objection. The pharmacovigilance signal cannot be dismissed on reporting-completeness grounds at any capture-rate assumption from 1% to 100%, and the underlying mechanism is established hematologic biology applied to a disease defined by complement vulnerability.

5.6 Supplementary References for Section 5

References cited as [#] in this section refer to the main manuscript reference list. Additional references unique to Section 5 are designated [S1]–[S5] and are listed below.

[S1] Lazarus R, Klompas M, Bernstein S. Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS). Final Report, Grant ID: R18 HS 017045. Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services; 2010. Harvard Pilgrim Health Care, Inc. Available at https://digital.ahrq.gov/.

[S2] World Bank. Population, total. World Development Indicators database. World Bank Group; accessed 2026. Available at https://data.worldbank.org/indicator/SP.POP.TOTL.

[S3] Miller ER, Moro PL, Cano M, Shimabukuro TT. Deaths following vaccination: what does the evidence show? Vaccine. 2015;33(29):3288–3292. doi:10.1016/j.vaccine.2015.05.023. Estimates of VAERS reporting sensitivity for anaphylaxis and Guillain-Barré syndrome under seasonal and 2009 H1N1 pandemic influenza vaccination.

[S4] Richards SJ, Painter D, Dickinson AJ, Griffin M, Munir T, Arnold L, et al. The incidence and prevalence of patients with paroxysmal nocturnal haemoglobinuria and aplastic anaemia PNH syndrome: a retrospective analysis of the UK's population-based haematological malignancy research network 2004–2018. Eur J Haematol. 2021;107(2):211–218. doi:10.1111/ejh.13640.

[S5] Alshammari TM, Subaiea GM, Hussain T, Moin A, Yusuff KB. Pharmacovigilance and the Vaccine Adverse Event Reporting System (VAERS) for COVID-19 vaccines: a descriptive analysis of 31 years of data. Saudi Pharm J. 2024;32(5):102050. doi:10.1016/j.jsps.2024.102050.