Investigating a Signal of Acquired Hemophilia Associated with COVID-19 Vaccination: A Systematic Case Review

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Abstract

Acquired hemophilia A (AHA), a rare but life-threatening disorder, most commonly occurs in older people and during pregnancy. During the coronavirus disease 2019 (COVID-19) vaccination campaign, an unexpected number of newly diagnosed AHA patients have been identified in clinical practice that were temporally related to COVID-19 vaccination. We present the result of a signal detection analysis aimed at exploring a possible association between COVID-19 immunization and occurrence of AHA. A disproportionality analysis on the World Health Organization (WHO) database was performed to investigate the presence of a signal of risk for AHA associated with COVID-19 vaccines. Reports of AHA associated with any COVID-19 vaccine included in the WHO database were then integrated with those available on the Food and Drug Administration Vaccine Adverse Events Reporting System and those published in the medical literature. The WHO database included 146 reports of AHA. The information component (IC) was significant for the association of AHA with all COVID-19 vaccines (IC025: 1.1) and with the vaccine product BNT162b2 (IC025: 1.6). After duplicate exclusion, 96 unique cases of AHA following COVID-19 vaccines have been reviewed. Median time to diagnosis was 18 days and 40% of cases documented the occurrence after the second dose. Overall, in 57% of the investigated cases, a preexisting condition predisposing to AHA was excluded. About 22% of cases occurred in subjects with age $\leq$65 years and there was no case associated with pregnancy. Mortality was 11%. Although we cannot exclude that the unexpected frequency of AHA diagnosis can be explained by a detection bias, the signal for COVID-19 vaccine-related AHA is robust and deserves further investigations.

Keywords
- acquired haemophilia A autoimmunity
- COVID-19
- mRNA vaccines
- BNT162b2
- mRNA-1273

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Acquired hemophilia A (AHA) is a rare, but often life-threatening, bleeding disorder caused by autoantibodies which neutralize the activity of coagulation factor VIII (FVIII) and/or accelerate its clearance.[1,2] The incidence of AHA has been estimated at approximately 1.5 cases per million/year, displaying increased burden with age (being significantly more frequent after the age of 65[3]) but without significant gender difference.[4,5] In women, a second, lower incidence peak is observed between 20 and 40 years in association with pregnancy.[6,7] Bleedings are the most frequently presenting symptoms although approximately 10% of cases are asymptomatic.[5] Prolonged activated partial thromboplastin time (aPTT), reduced plasma clotting FVIII levels, and detection of anti-FVIII autoantibodies represent the conclusive diagnostic elements.[8] Around 50% of cases do not have an identifiable causative agent (idiopathic AHA). Secondary AHA is instead associated with solid and hematological malignancies (6–22%), autoimmune diseases (9–17%), infections, skin disorders, and pregnancy. Drugs, particularly antibiotics and interferon, have been reported as potential causative agents.[9–12]

Vaccine-associated AHA has been very rarely described before the coronavirus disease 2019 (COVID-19) pandemic. To the best of our knowledge, only three cases (two for influenza vaccine and one for tuberculosis vaccine), have been published in the medical literature in the pre-COVID-19 period, thought it cannot be excluded that these figures may have been biased by a substantial under-diagnosis before COVID-19.[13–15] Since COVID-19 vaccines were approved and rolled out in mass vaccination campaigns, a substantial number of AHA cases have been reported in temporal association with an mRNA vaccination.[16–25] Concomitantly, concerns were reported by several authors about a possible increase in the expected frequency of AHA in the population. In Switzerland, Cittone et al[22] reported a fourfold yearly increase in the number of AHA cases in 2021 compared with the expected frequency recorded in previous years. In Italy, Leone et al[21] observed six cases in the first 8 months of 2021, corresponding to approximately 17 cases per million inhabitants/year, compared with 1.9 cases per million inhabitants/year observed in the previous years. Many of these cases were reported in a close temporal relationship with COVID-19 vaccination. However, identifying a causal relationship is particularly challenging for several reasons, including the lack of a definition for vaccine-associated AHA by the Brighton Collaboration.

In this article, we have investigated COVID-19 vaccine-related AHA incidence using a disproportionality analysis in the World Health Organization (WHO) database of spontaneous reports of adverse drug reactions (ADRs) and adverse events following immunization (AEFIs) (VigiBase). We have then systematically reviewed all identified cases of suspected COVID-19 vaccination-related AHA, integrating VigiBase information with those available in cases published in medical literature or recorded in the U.S. Vaccine Adverse Events Reporting System (VAERS) database.

Methods

The analysis was conducted in two steps. In the first step, we performed a quantitative assessment of the signal of risk in the VigiBase database by disproportionality analysis. In the second step, we made a case-by-case qualitative assessment by systematically reviewing all cases of AHA associated with any of the COVID-19 vaccines identified in VigiBase, and integrated it with information and possible other cases from other data sources including the medical literature.

Patient Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Disproportionality Analysis

The disproportionality analysis was conducted using VigiBase (https://who-umc.org/vigibase/). VigiBase is the largest and most comprehensive database of spontaneous reports of ADRs and AEFIs in the world. It is hosted by the Uppsala Monitoring Centre (Sweden), WHO Collaborating Centre for International Drug Monitoring, and it contains over 30 million Individual Case Safety Reports (ICRSs) from 170 countries (full members and associate countries) over five continents (data cutoff on February 28, 2022).

The disproportionality analysis is the most common approach used in signal detection to identify signal of risk in spontaneous reporting databases of adverse events. It consists of the identification of unexpectedly higher frequency of reports for a specific event (case) associated with a specific medicinal product (index) compared with a reference standard, usually the frequency of the event of interest in the entire database for all the medicinal products.[26] As a measure of disproportion, we have used in this analysis the information component (IC). The IC measures the effect size of the association of a drug or vaccine with the probability of reporting a certain adverse event.[27] The lower limit of the 95% confidence interval is indicated as IC025. A positive IC025 is usually used as a threshold for signal detection and it means that a specific adverse event is significantly over-reported for a certain drug compared with a reference (expected frequency). In the present analysis, we considered IC025 >1 as a threshold for confirming a signal of risk. A positive IC does not necessarily imply a causal relationship between a medicinal product and an adverse event: it simply reflects an increased trend in report that can be explained by many causes (for instance, a positive IC can be generated by a cluster of reports during an intensive surveillance program for specific medicinal product-related events performed in a specific hospital ward). On February 28, 2022 we searched VigiBase for each report containing the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term "Acquired hemophilia," in which the suspect vaccine was a COVID-19 vaccine. We searched also reports for preferred terms that have been considered suggestive of a possible diagnosis of AHA ("factor VIII inhibition," "acquired von Willebrand's disease," "acquired factor VIII deficiency"). The IC was calculated for each preferred term in association

with any COVID-19 vaccines and with specific vaccine products. The expected frequency[27] was calculated considering the frequency of each preferred term in VigiBase.

Systematic Case Review

For the identification and qualitative assessment of cases of suspected COVID-19 vaccine-related AHA, we started by creating a dataset of cases identified in VigiBase. With the aim of implementing the quality of information available for each case, we performed a systematic research in the medical literature to identify published cases of AHA in which a COVID-19 vaccine was indicated as a suspected causative agent. Furthermore, we have also included all openly accessible cases reported to the U.S. VAERS.

Medical Literature Search

A literature search of the MEDLINE (through PUBMED) was performed from September 1, 2020 to February 28, 2022, using English language as the only restriction. Only articles published in peer-reviewed journals were included in the final analysis. The Medical Subject Heading (MeSH) and key words used were: ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("vaccine" OR "vaccination") AND ("Acquired haemophilia" OR "factor VIII inhibition" OR "acquired von Willebrand's disease" OR "acquired factor VIII deficiency"). We also screened the reference list of reviewed articles for additional studies not captured in our initial literature search. Literature cases were also identified using U.S. VAERS and WHO VigiBase and the full texts of original articles retrieved, if missed in the initial research. We included case report and case series of acquired hemophilia reporting detailed individual patient-level data in which a COVID-19 vaccine was indicated as the suspected causative agent. We excluded review articles, meta-analysis, and original research articles reporting only aggregate data. Articles underwent a blind evaluation for inclusion by two assessors (G.V. and E.C.); disagreements were resolved by a third senior assessor (M.T.). A flowchart of the literature reviewing process is available in ►**Supplementary Fig. S1**.

U.S. VAERS Research

The VAERS database is a national spontaneous reporting system jointly administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration established in 1990 as a U.S. vaccine safety surveillance program (https://vaers.hhs.gov/). The CDC Wonder tool (https://wonder.cdc.gov/controller/datarequest/D8) reports that as of March 11, 2022, VAERS contains more than 2 million records of AEFIs. The system collects reports from vaccine manufacturers, health care providers, and the public. AEFIs that come to the attention of vaccine manufacturers must be reported by law to the VAERS system.[28]

Using the National Vaccine Information Center web page (https://medalerts.org/), which provides access to ICRS information in the database, we searched the VAERS database for reports of AHA as AEFI from the beginning of the vaccination campaign with COVID-19 vaccines (i.e., December 27, 2021) through February 28, 2022. As search keys for events, we used the MedDRA preferred terms "Acquired Haemophilia," "factor VIII inhibition," "acquired von Willebrand's disease," and "acquired factor VIII deficiency." As search keyword for vaccines, we used all currently approved COVID-19 vaccine names (see ►**Supplementary Table S1**, available in the online version).

Dataset Creation

Cases extracted from VigiBase, VAERS, and those identified by literature review were pooled in a unique dataset. Each case included was processed for identification of possible duplicate. A case was classified as a duplicate when age, gender, country of origin, MedDRA preferred term, and suspected vaccine were identical to those of another case. For literature cases, references reported in the databases supported the identification of duplicates. For cases included in VigiBase, the VAERS code was also reported and it was used to identify duplicates. When a duplicate was identified, information was checked and gathered to obtain a unique case, reporting all the available data. The process of duplicate identification and information gathering was performed blindly by two separate assessors and possible disagreements were resolved by a third assessor.

For each case we collected the following information: data source, country, age, gender, number of the dose (first, second, or third), type of vaccine (medicinal product), time from vaccine dose to final diagnosis, seriousness (death, life-threatening, hospitalization, permanent disability, medically significant, not serious), outcome (complete resolution, resolution with consequences, recovering, not resolved yet, death), signs and symptoms at presentation, concomitant drugs, pre-existing hemophilia or other coagulation disorders, history of autoimmune disease, concomitant autoimmune disease, history of cancer, concomitant cancer, concomitant illnesses (other than coagulation disorders, cancer, and autoimmune diseases), history of illnesses (other than coagulation disorders, cancer, and autoimmune diseases), anti-FVIII antibody level, FVIII level, aPTT values, and treatment for AHA. Information was generally classified as: (1) reported (when clearly stated in at least one of the data sources); (2) not available (when never stated in any of the data sources), and (3) excluded (when the exclusion of the information was clearly stated in at least one data source). Each reported disease of treatment was classified as: concomitant, when the presence of disease was clearly stated as ongoing at the moment of vaccination in at least one data source; or history, when the report clearly stated that disease or treatment was not ongoing at the moment of vaccination in at least one data source; or not specified, when treatment or disease was not clearly stated as concomitant or history for the report in at least one data source. Descriptive statistics (mean, standard deviation, median, interquartile range, percentage) was used to describe or summarize the demographic and clinical characteristics of the cases. The information was stratified by data source and by specific vaccine product.

Data Sharing Statement

Original dataset is available upon request to the corresponding author.

Table 1 Information component (IC) estimated for preferred term suggesting acquired hemophilia associated with COVID-19 vaccines and stratified by vaccine product

Active ingredient—S/I	*Preferred Term*	$N_{observed}$	$N_{expected}$	N_{drug}	$N_{reaction}$	IC_{025}	IC
COVID-19 vaccines (overall)	Acquired hemophilia	146	57	3,473,555	495	1.1	1.3
	Acquired factor VIII deficiency	4	1		6	0.2	1.9
	Acquired Von Willebrand disease	6	5		47	−1.2	0.1
	Factor VIII inhibition	18	141		1 219	−3.7	−2.9
BNT162b2	Acquired hemophilia	112	29	1,767,713	495	1.6	1.9
	Acquired factor VIII deficiency	3	0		6	−0.0	2.0
	Acquired von Willebrand disease	5	3		47	−0.8	0.7
	Factor VIII inhibition	14	72		1 219	−3.2	−2.3
mRNA-1273	Acquired hemophilia	26	11	682,505	495	0.6	1.2
	Acquired factor VIII deficiency	1	0		6	−2.6	1.2
	Acquired von Willebrand disease	1	1		47	−3.9	−0.1
	Factor VIII inhibition	4	28		1 219	−4.4	−2.7
ChAdOx1 nCOV-19	Acquired hemophilia	8	12	754,832	495	−1.8	−0.6

Abbreviation: IC, information component.

Results

Using extraction criteria, we were able to identify 150 cases (174 events reported) of suspected AHA associated with COVID-19 vaccines (146 included the preferred term "acquired haemophilia"; 4 the preferred term "acquired factor VIII deficiency"; 6 the preferred term "acquired Von Willebrand's disease," and 18 the preferred term "factor VIII inhibition"). Only three vaccine products have been reported as suspected causative agents for AHA. ►**Table 1** reports the number of observed cases, the number of expected cases, and the IC025 and IC values globally and stratified by specific COVID-19 vaccines. A signal of significant over-reporting emerged for the preferred term "acquired haemophilia" and COVID-19 vaccines as a class and for the mRNA-based vaccine BNT162b2.

The literature search led to the identification of 14 published cases[16–25] (the flowchart reported in ►**Supplementary Fig. S1** [available in the online version] describes the reviewing and the selection process). The VAERS research led to the identification of 64 cases, including 1 published case not identified with our literature review. The process resulted in the identification of 96 unique cases that were included in the qualitative analysis dataset (flowchart reported in ►**Fig. 1**).

►**Table 2** reports demographics and clinical findings in the 96 AHA patients: ►**Supplementary Table S2** (available in the online version) reports the same parameters stratified by COVID-19 vaccine type. ►**Table 3** (available in the online version) reports the event details; ►**Supplementary Table S3** reports the same parameters stratified by COVID-19 vaccine product. ►**Table 4** identifies the 14 published cases with extracted details.[16–25] Additional details of all cases are provided in ►**Supplementary Tables S4–S9** (available in the online version).

Overall, 75 reports (79%) described patients with age ≥65 years. Of interest, in females below 65 years, there was no report of vaccine-associated AHA observed during pregnancy or postdelivery period. There were 20 patients (21%) with at least one pre-existing condition that can be considered a risk factor for AHA (history of AHA, cancer, autoimmune disorder). Among the most frequently reported concomitant medications (>4 reports), there was no drug for which AHA is among the possible adverse events.

Most frequently reported signs and symptoms at presentation included hematoma ($n = 35$, 37%), decreased hemoglobin level ($n = 26$, 27%), and anemia ($n = 18$, 19%). The detection of anti-FVIII autoantibodies was disclosed in only 39 cases (41%), suggesting poor quality of reports, with a mean of 69.0 (± 137.3) Bethesda Units (BU). Reduced plasma clotting FVIII activity was documented in 45 cases (47%), with a mean activity of 9.1% (± 34.7%). Prolonged aPTT was reported in only 36 patients (38%), again suggesting a poor quality of reports, with a mean of 83 (± 37) seconds. Median time from vaccine dose to diagnosis was 18 (interquartile range: 5–32) days. In 93% of cases ($n = 89$), the imputed COVID-19 vaccine was an mRNA-based vaccine, as expected from their massive deployment worldwide. Vaccine dose number was reported in 67 cases (70%), and AHA was described most frequently after the second dose of the primary vaccination cycle ($n = 30$, 40%). Outcome was available in 71 cases (74%), yielding death in 10 cases (11%). Complete resolution was described in 15 reports (16%). Spontaneous resolution (no AHA treatments) was documented in one case (1%), where 2 months after the event, the level of aPTT and FVIII normalized spontaneously.[25]

Discussion

AHA following immunization with non-COVID-19 vaccine has been an exceedingly rare entity, with only three cases reported to date in the medical literature.[13–15] After the authorization of the first COVID-19 vaccine and in parallel with the global vaccination campaign, several authors documented an increase in the expected frequency of diagnosis of

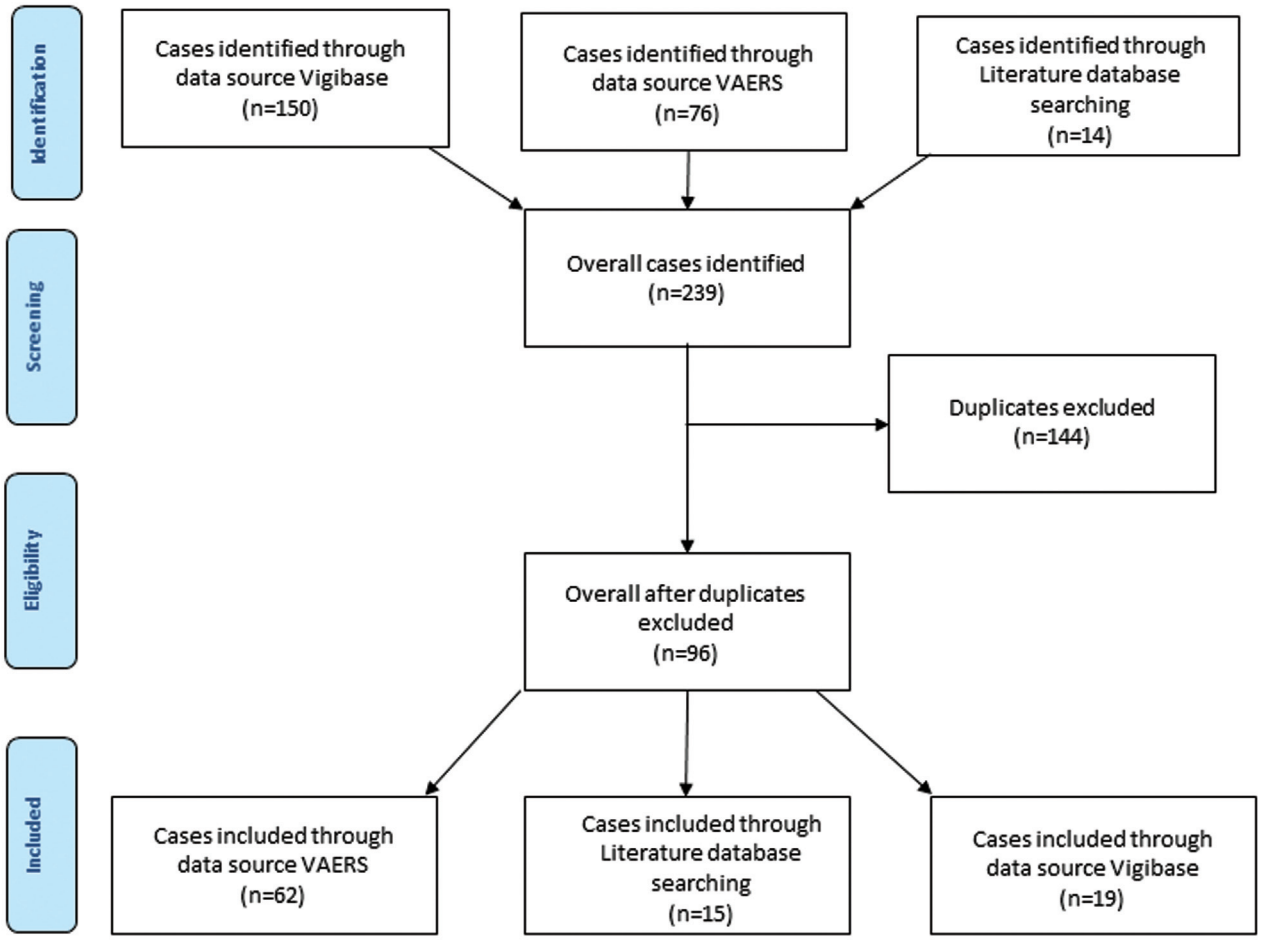

Fig. 1 Flowchart of dataset creation.

AHA that occurred closely after immunization.[21,22] Our analysis confirmed an unexpected over-reporting of COVID-19 vaccine-related AHA in the WHO database of spontaneous reporting of adverse events to drugs and vaccines (VigiBase). Since this over-reporting occurred in the exceptional circumstance of a pandemic, this signal of risk must be evaluated with caution. Indeed, it does not necessarily reflect a casual association, which should be further investigated in a qualitative analysis of clinical information available in documented cases. In particular, we cannot exclude that this signal was generated by intense activity of monitoring of vaccinated subjects (detection bias). This situation is particularly plausible following the identification of rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) for the ChAdOx1 nCOV-19 vaccine in March 2021.[29,30] Regardless of the specific COVID-19 vaccine used, the related communication of this risk and recommendations by regulatory authorities[29,31] triggered a global media claim surrounding possible hematological adverse events (notoriety bias),[32,33] thus persuading health care professionals and patients to intensify monitoring of hemostasis including coagulation factors. It is also likely that this monitoring could have occurred particularly in postimmunization periods, thus supporting the perception of a causal relationship with vaccines. Of note, to the best of our knowledge neither notoriety bias nor detection bias has been documented in the medical literature for the adenoviral vaccine ChAdOx1-related VITT. Nevertheless, the identification of a possible detection bias would not exclude a causal relationship between exposure to vaccines and occurrence of AHA that deserves to be investigated in the case-by-case review.

Temporal and biological plausibilities are likely the most important elements to consider in attempting causality assessment. The majority of AHA cases were diagnosed after 5 days, with a median of 18 days. Considering a latency period that is required to achieve a definite diagnosis (symptom occurrence followed by laboratory investigations), this temporal relationship is plausible with development of anti-FVIII antibodies. The most obvious mechanism could involve serological cross-reactivity between SARS-CoV-2 Spike protein (the active ingredient and common denominator for all COVID-19 vaccines associated with AHA) and FVIII. This mechanism was explored by Hirsiger and coworkers using blood samples from three patients developing AHA following COVID-19 immunization. Their analysis was unable to identify a role of the polyclonal response induced by vaccines in inhibition of FVIII.[34] These authors hypothesized a different mechanism. Sequences of SARS-CoV-2 Spike protein that overlap with particularly immunogenic FVIII sequences have

Table 2 Demographic and clinical characteristics of patients with acquired hemophilia in which a COVID-19 vaccine was reported as suspected causative agent in the United States Vaccine Adverse Event Reporting System (VAERS) database, the World Health Organization (WHO) VigiBase Database, and in the medical literature (see ►**Supplementary Table S2** for data stratified by vaccine product)

	Overall (N = 96)	Medical literature (N = 15)	VAERS (excluding peer-reviewed literature) (N = 62)	WHO VigiBase (excluding VAERS and peer-reviewed literature) (N = 19)
Vaccine product, *n* (%)				
BNT162b2	70 (73%)	10 (67%)	50 (81%)	10 (52%)
mRNA-1273	19 (20%)	5 (33%)	12 (19%)	2 (11%)
ChAdOx1 nCOV-19	7 (7%)	0	0	7 (37%)
Gender, *n* (%)				
F	47 (49%)	7 (47%)	32 (51%)	8 (42%)
M	49 (52%)	8 (53%)	30 (49%)	11 (58%)
Age category (y), *n* (%)				
5–14	0	0	0	0
15–44	8 (8%)	2 (13%)	5 (10%)	1 (5%)
45–54	3 (3%)	0	3 (5%)	0
55–64	10 (10%)	0	9 (15%)	1 (5%)
65–79	33 (35%)	9 (60%)	15 (24%)	9 (47%)
>80	42 (44%)	4 (27%)	30 (48%)	8 (42%)
Reported pre-existing hemophilia or others coagulative disorders, *n* (%)				
Reported	3 (3%)	0	3 (3%)	0
Excluded	74 (77%)	15 (100%)	59 (95%)	0
Not reported	19 (20%)	0	0	19 (100%)
Reported at least one pre-existing autoimmune disease (activity), *n* (%)				
Reported	12 (13%)	5 (33%)	9 (15%)	0
Current	9 (9%)	4 (27%)	5 (8%)	0
History	4 (4%)	2 (13%)	2 (3%)	0
Not specified	3 (3%)	0	3 (5%)	0
Excluded	61 (64%)	10 (67%)	51 (82%)	0
Not available	22 (23%)	0	1 (2%)	19 (100%)
Most frequently reported pre-existing autoimmune disease (type), *n* (%)				
Rheumatoid arthritis	4 (4%)	1 (7%)	3 (3%)	0
Polymyalgia rheumatica	4 (4%)	2 (13%)	2 (3%)	0
Crohn's disease	1 (1%)	0	1 (2%)	0
Horton's disease	1 (1%)	0	1 (2%)	0
Granulomatosis with polyangiitis	1 (1%)	0	1 (2%)	0
Pulmonary sarcoidosis	1 (1%)	1 (7%)	0	0
Sjogren's syndrome	1 (1%)	1 (7%)	0	0
Arthropathy psoriatic	1 (1%)	0	1 (2%)	0
Systemic lupus erythematosus	1 (1%)	0	1 (2%)	0
Raynaud's phenomenon	1 (1%)	1 (7%)	0	0
Reported at least one pre-existing cancer (activity), *n* (%)				
Reported	14 (15%)	3 (20%)	11 (18%)	0

Table 2 (*Continued*)

	Overall (N = 96)	Medical literature (N = 15)	VAERS (excluding peer-reviewed literature) (N = 62)	WHO VigiBase (excluding VAERS and peer-reviewed literature) (N = 19)
Concomitant	7 (7%)	1 (7%)	6 (10%)	0
History	9 (9%)	2 (13%)	7 (11%)	0
Not specified	2 (2%)	0	2 (3%)	0
Excluded	63 (66%)	12 (80%)	51 (82%)	0
Not available	19 (20%)	0	0	19 (100%)
Most frequently reported pre-existing cancer (type), *n* (%)				
Prostate cancer	5 (5%)	1 (7%)	4 (6%)	0
Breast cancer	5 (5%)	1 (7%)	4 (6%)	0
Kidney cancer	1 (1%)	0	1 (2%)	0
Larynx cancer	1 (1%)	0	1 (2%)	0
Relapsing bladder cancer	2 (2%)	1 (7%)	1 (2%)	0
Diffuse large B cell lymphoma	1 (1%)	0	1 (2%)	0
B cell lymphoma	1 (1%)	0	1 (2%)	0
Myelodysplastic syndrome transformation	1 (1%)	0	1 (2%)	0
Not specified cancer	1 (1%)	0	1 (2%)	0
Cases with at least one risk factor for AHA (pre-existing hemophilia or coagulative disorders, autoimmune disease, cancer), *n* (%)				
Reported	20 (21%)	6 (40%)	14 (23%)	0
Excluded	57 (59%)	9 (60%)	48 (77%)	0
Not reported	19 (20%)	0	5 (8%)	19 (100%)
Reported at least one pre-existing other illnesses (activity), *n* (%)				
Reported	50 (53%)	9 (60%)	41 (66%)	0
Concomitant	40 (42%)	10 (67%)	30 (48%)	0
History	12 (13%)	0	12 (85%)	0
Not specified	3 (3%)	0	3 (3%)	0
Excluded	25 (26%)	6 (40%)	19 (31%)	0
Not available	21 (22%)	0	2 (3%)	19 (100%)
Most frequently reported pre-existing other illnesses (type), *n* (%)				
Arterial hypertension	21 (22%)	4 (27%)	17 (27%)	0
Diabetes mellitus 2	9 (9%)	1 (7%)	8 (13%)	0
Coronary artery disease	6 (6%)	3 (20%)	3 (3%)	0
Dyslipidemia	5 (5%)	1 (7%)	4 (6%)	0
Chronic renal failure	3 (3%)	0	3 (3%)	0
Chronic kidney disease	3 (3%)	0	3 (3%)	0
Chronic obstructive pulmonary disease	3 (3%)	0	3 (3%)	0
Asthma	3 (3%)	1 (7%)	2 (3%)	0
Hypothyroidism	3 (3%)	0	3 (3%)	0
Most frequently reported concomitant medications, *n* (%)				
Acetylsalicylic acid	10 (11%)	0	9 (15%)	1 (5%)
Bisoprolol	9 (9%)	0	7 (11%)	2 (11%)
Pantoprazole	7 (7%)	0	6 (10%)	1 (5%)

(*Continued*)

Table 2 (*Continued*)

	Overall (N = 96)	Medical literature (N = 15)	VAERS (excluding peer-reviewed literature) (N = 62)	WHO VigiBase (excluding VAERS and peer-reviewed literature) (N = 19)
Ramipril	7 (7%)	0	5 (8%)	2 (11%)
Furosemide	5 (5%)	1 (7%)	3 (5%)	1 (5%)
Paracetamol	5 (5%)	1 (7%)	3 (5%)	1 (5%)
Prednisone	5 (5%)	1(7%)	4 (6%)	0
Allopurinol	4 (4%)	0	3 (5%)	1 (5%)
Cholecalciferol	4 (4%)	0	4 (6%)	0
Levothyroxine	4 (4%)	0	4 (6%)	0

Abbreviations: AHA, acquired hemophilia A; VAERS, Vaccine Adverse Event Reporting System.

Table 3 Clinical characteristics of events of acquired hemophilia in which a COVID-19 vaccine was reported as suspected causative agent in the United States Vaccine Adverse Event Reporting System (VAERS) database, the World Health Organization (WHO) VigiBase Database, and in the medical literature (see ►**Supplementary Table S3** for data stratified by vaccine product)

	Overall (N = 96)	Literature (N = 15)	VAERS (N = 62)	WHO VigiBase (excluding VAERS) (N = 19)
Vaccine product, *n* (%)				
BNT162b2	70 (73%)	10 (67%)	50 (81%)	10 (52%)
mRNA-1273	19 (20%)	5 (33%)	12 (19%)	2 (11%)
ChAdOx1 nCOV-19	7 (7%)	0	0	7 (37%)
Vaccine dose, *n* (%)				
First	25 (26%)	7 (47%)	18 (29%)	0
Second	38 (40%)	8 (53%)	30 (48%)	0
Third	4 (4%)	0	4 (6%)	0
Not available	29 (30%)	0	10 (16%)	19 (100%)
Time to diagnosis, d				
Median (IQR)	18 (5–32)	14 (7–21)	18 (4–32)	18 (2–32)
Seriousness, *n* (%)				
Death	10 (11%)	2 (13%)	3 (5%)	5 (26%)
Life-threatening	4 (4%)	0	3 (5%)	1 (5%)
Hospitalization	70 (73%)	13 (87%)	48 (77%)	9 (47%)
Permanent disability	2 (2%)	0	1 (2%)	1 (5%)
Medically significant	2 (2%)	0	1 (2%)	1 (5%)
Not serious	0	0	0	0
Not specified	8 (8%)	0	6 (10%)	2 (11%)
Outcome, *n* (%)				
Complete resolution	15 (16%)	6 (41%)	7 (11%)	2 (11%)
Recovering	24 (25%)	5 (33%)	15 (24%)	4 (21%)
Not resolved yet	22 (23%)	0	19 (31%)	3 (16%)
Death	10 (10%)	2 (13%)	3 (5%)	5 (26%)
Not available	25 (26%)	2 (13%)	18 (29%)	5 (26%)

Table 3 (*Continued*)

	Overall (N = 96)	Literature (N = 15)	VAERS (N = 62)	WHO VigiBase (excluding VAERS) (N = 19)
Most frequently reported MedDRA Preferred Term-related signs and symptoms (*n*, %)				
Hematoma	35 (36%)	10 (67%)	21 (34%)	4 (21%)
Hemoglobin decreased	26 (27%)	5 (33%)	21 (34%)	0
Anemia	18 (19%)	4 (27%)	14 (23%)	0
Hemorrhage	8 (8%)	0	7 (11%)	1 (5%)
Bruise	7 (7%)	3 (20%)	4 (6%)	0
Ecchymosis	7 (7%)	3 (20%)	3 (5%)	1 (5%)
Contusion	7 (7%)	0	7 (11%)	0
Quantitative VWF deficiency	1 (1%)	1 (7%)	0	0
No symptoms codified	19 (20%)	0	10 (16%)	9 (47%)
Reported anti-FVIII Ab (*n*, %)				
Overall	39 (41%)	15 (100%)	24 (39%)	0
Mean (SD), BU	69.0 (±137.3)	45.8 (± 83.0)	93.9 (± 178.6)	0
Reported altered FVIII (*n*, %)				
Overall	45 (47%)	15 (100%)	30 (48%)	0
Mean (SD), IU/dL	9.1 (±34.7)	3.8 (± 5.9)	11.9 (± 42.9)	0
Reported aPTT prolonged (*n*, %)				
Overall	36 (38%)	15 (100%)	21 (34%)	0
Mean (SD), s	83 (±37)	94 (± 42)	66 (± 23)	0
Most frequently reported treatment for acquired hemophilia, *n* (%)				
Steroids	33 (34%)	14 (93%)	19 (31%)	0
Prothrombin-activated complex	13 (14%)	4 (27%)	9 (15%)	0
Rituximab	13 (14%)	7 (47%)	6 (10%)	0
Cyclophosphamide	10 (10%)	3 (20%)	7 (11%)	0
Recombinant FVIII	8 (8%)	1 (7%)	7 (11%)	0
No treatment	0	0	0	0
Not reported	57 (59%)	0	38 (61%)	19 (100%)

Abbreviations: AB, antibody; aPTT, activated partial thromboplastin time; BU, Bethesda Unit; IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; VAERS, Vaccine Adverse Event Reporting System; VWF, von Willebrand factor.

been identified. These sequences are part of the antigenic component of the vaccine and could interact with not completely deleted autoreactive T cell clones specific for endogenous FVIII. These T cell clones have been identified in subjects susceptible to AHA development[35] and can stimulate the maturation and activation of B cell clones, responsible for production of natural anti-FVIII antibodies.[36] This mechanism appears plausible even considering the temporal relationship between immunization and AHA diagnosis.

Concomitant diseases and risk factors should be considered in the exclusion of alternative causes. Approximately half of the AHA cases recognize an underlying condition triggering the hemorrhagic disorder, in the majority of cases being autoimmune or oncologic diseases.[37] Pregnancy is also associated with development of AHA, and drug-associated AHA occurs only rarely (<5% of AHA cases).[7] In our population, despite a male/female ratio which is similar to that reported in most important AHA registries,[4,10,11] the age distribution and the clinical characteristics are somewhat different from those observed in general AHA populations. Indeed, among the 96 AHA cases reported here, 21% (20/96) were below the age of 65 years. Pregnancy was never reported as a concomitant condition. The presence of a pre-existing underlying disease that can explain the occurrence of AHA is documented only in 20 cases (21%) and excluded in 57 cases (59%).

AHA mortality rate is 10 to 20% in previous literature, with most favorable outcomes being associated with postpartum

Table 4 COVID-19 vaccine-associated acquired hemophilia A: cases from literature review

First author (reference)	Age, sex	Correlation between SARS-CoV-2 vaccine and AHA	Symptoms	FVIII inhibitor titer (BU)	FVIII activity (%)	Comorbidities	Treatment	Outcome
Al Hennawi[16]	75, M	Onset 3 months after second dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	318	<1	Hypertension, dyslipidemia, CAD, BPH	Bleeding: rFVIIa Inhibitor eradication: STD, RTX, CPH, CSP	FVIII 20% with no evidence of active bleeding
Radwi[17]	69, M	Onset 9 days after first dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	80	1	Diabetes, hypertension, prostate adenocarcinoma	Bleeding: none Inhibitor eradication: STD	FVIII 5%, FVIII inhibitor 2 BU with no evidence of major bleeding
Lemoine[18]	70, M	Onset 8 days after first dose of mRNA-1273 SARS-CoV-2 (Moderna) vaccine	Multiple-site hematoma	39.9	3	Polymyalgia rheumatica, HCV	Bleeding: APCC Inhibitor eradication: STD, CPH	FVIII 7%, FVIII inhibitor 11.4 BU with no evidence of active bleeding
Farley[19]	67, M	Onset 19 days after second dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	110	<1	Hypertension, pulmonary sarcoidosis	Bleeding: APCC Inhibitor eradication: STD, RTX	CR (FVIII 171% with undetectable FVIII inhibitor)
Portuguese[20]	76, F	Onset 4 days after second dose of mRNA-1273 SARS-CoV-2 (Moderna) vaccine	Multiple-site hematoma, melanotic stool	11.2	<3	Asthma, Raynaud's phenomenon	Bleeding: VWF/FVIII replacement therapy Inhibitor eradication: STD, IVIg	CR (FVIII normalization and FVIII inhibitor <0.5 BU)
Leone[21]	86, M	Onset 14 days after second dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	2.1	6	Rheumatic polymyalgia	Bleeding: none Inhibitor eradication: STD	CR (FVIII within normal reference range with undetectable FVIII inhibitor)
	73, F	Onset 14 days after first dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	0.8	5	Rheumatoid arthritis, Sjogren's syndrome	Bleeding: none Inhibitor eradication: STD	CR (FVIII 163% with undetectable FVIII inhibitor)
	67, M	Onset 49 days after second dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	2.5	6	Unremarkable	Bleeding: rFVIIa Inhibitor eradication: STD	CR (FVIII 121% with undetectable FVIII inhibitor)
	77, M	Onset 52 days after second dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma, hematuria	6.9	2	Bladder cancer	Bleeding: rFVIIa Inhibitor eradication: STD, RTX	CR (FVIII 96% with undetectable FVIII inhibitor), death for infectious complications
Cittone[22]	85, M	Onset 1 week after first dose of mRNA-1273 SARS-CoV-2 (Moderna) vaccine	Multiple-site hematoma, joint bleeding	2.2	<1	Hypertension, CAD, PAD	Bleeding: rFVIIa, APCC Inhibitor eradication: STD, RTX	Death due to hemorrhagic complications
	86, F	Onset 3 weeks after second dose of mRNA-1273 SARS-CoV-2 (Moderna) vaccine	Hemothorax following injury	1	23	AVS	Bleeding: rFVIIa, APCC Inhibitor eradication: STD	CR (FVIII 178% with undetectable FVIII inhibitor)
	72, F	Onset 2 weeks after first dose of mRNA-1273 SARS-CoV-2 (Moderna) vaccine	Multiple-site hematoma	12.4	<1	CAD	Bleeding: rFVIIa, TA Inhibitor eradication: STD, RTX	FVIII 5%, FVIII inhibitor 5.6 BU with improvement of bleeding tendency
Murali[23]	95, F	Onset 1 week after first dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Multiple-site hematoma	5.4	<1	Dementia, hypertension, CHF	Bleeding: rFVIII, TA Inhibitor eradication: STD, RTX	CR (FVIII 68% with undetectable FVIII inhibitor)
Gonzalez[24]	43, F	Onset 3 weeks after second dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Hematoma with swelling	78.4	<5	G1P1A0	Inhibitor eradication: RTX, STD	No information available
Soliman[25]	39, F	Onset 10 days after first dose of mRNA BNT162b2 SARS-CoV-2 (Pfizer/BioNTech) vaccine	Hematuria, abdominal pain	17.2	2	No	Bleeding: no treatment Inhibitor eradication: no treatment	Spontaneous resolution

Abbreviations: AVS, aortic valve sclerosis; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; CHF, chronic health failure; HCV, hepatitis C virus; IVIg. Intravenous immunoglobulin; PAD, peripheral arterial disease; rFVIII, recombinant factor VIII.

or drug-induced AHA. In our population, AHA-related mortality was 11% (10/96 cases). In one case only, retrieved from the systematic literature review, the autoantibody disappeared spontaneously[25]: such a phenomenon is typical of drug-induced AHA, where the removal of the triggering factor results in disease remission.

Taken together, the available information does not allow excluding that a causal relationship exists between COVID-19 vaccines and AHA.

This study has two main limitations. First of all, the signal detection analysis included duplicate cases. However, since disproportionality analysis included duplicated reports also for the reference group, this could represent a problem only if there would be a reason for a differential distribution of duplicates. Moreover, previous studies demonstrated that the inclusion of duplicated reports leads to identification of false signals only in situation of multiple suspected drugs, or when suspected drugs are generics.[38,39] This is because of extreme duplication due to multiple reports by different marketing authorization holders. Theoretically, false signals due to duplicates can occur in case of signals generated by a small number of reports (i.e., two or three reports).[40] In our opinion, the risk that duplicate reports could have generated a false signal for AHA and COVID-19 vaccines for one or more of the above-mentioned reasons is very limited. The second limitation could be the heterogeneity in accuracy of information provided in individual case reports, with consequent risk of misclassification. However, we believe that the number of good-quality reports is quite high to support a probable causal relationship, to such an extent to consider the generation of a signal of risk that deserves discussion.

Among the strengths of our analysis, we can certainly report the completeness of the available evidence. The use of VigiBase, the largest database of spontaneous reporting of ADRs, grants the inclusion of almost all the available cases reported globally. The integration of information with VAERS and medical literature implemented the quality of our dataset and allowed us to hypothesize a causal relationship at least for the more well-documented cases.

Conclusions

The present analysis identified a signal of risk of AHA associated with COVID-19 vaccines. This signal could be explained by a detection bias for which more patients could have been tested for hemostasis parameters including coagulation factors, particularly in the postimmunization period. This explanation could not exclude a causal relationship, as it could have simply disclosed an underdetected phenomenon. The case review analysis identified several good-quality reports of AHA for which the role of COVID-19 immunization could not be excluded. In our opinion, this signal deserves to be refined and confirmed in well-designed observational studies. In case of confirmation, the identification of risk factors for the event should be a priority, with the aim of issuing appropriate risk minimization measures.

Author Contributions

M.F., M.T., and D.F. conceived and developed the presented idea. M.F. and D.F. wrote the first draft. U.M. curated ►**Table 1**. E.C., G.V., and M.B. curated ►**Fig. 1**, ►**Tables 2**–**4**, and supplementary data. M.T. wrote the paper with input from all the authors.

Conflict of Interest

None declared.

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