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Transfusions of Blood Products Derived from Genetic Vaccine Recipients: Safety Concerns and Proposals for Specific Measures

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Abstract: The World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic in 2020, following which a global genetic vaccination program has been rapidly implemented as a fundamental solution. However, it has been reported worldwide that the modified mRNAs encoding spike proteins and lipid nanoparticles, which are used as drug delivery systems, not only cause thrombosis and cardiovascular disorders post vaccination, but might also cause diverse diseases involving all organs and systems, including the nervous system. Furthermore, the toxicity and pathogenicity of spike proteins may necessitate defining these proteins as nonbiological infective material. Based on these reports and the abundant evidence that has come to light in the past few years, this paper aims to draw the attention of medical professionals to the various risks associated with transfusion using blood products derived from long COVID patients or from genetic vaccine recipients, and to make proposals regarding specific inspection items, testing methods, regulations, etc. This paper provides insights to address the post-vaccination syndrome and its consequences following such genetic vaccination programs.

Keywords: COVID-19 vaccine; genetic vaccine; blood product; blood transfusion; spike protein; post-vaccination syndrome; harm–benefit assessment; prion; spikeopathy; inspection standard; diagnostic criteria

1. Introduction

On March 11, 2020, the Director-General of the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) pandemic, caused by severe-acute-respiratory-syndrome-related coronavirus (SARS-CoV-2) [1], and countries worldwide actively implemented classical public health measures, including quarantine, isolation, disinfection, and lockdowns. However, hopes for a vaccine grew as the general consensus was that rapid herd immunity was the best solution to overcome the pandemic. Therefore, since 2021, as a means to combat SARS-CoV-2 infection, several global pharmaceutical companies have developed various genetic vaccines that use the spike protein

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of the Wuhan strain of SARS-CoV-2 as an antigen, following which rapid vaccination has been promoted on a global scale [2,3]. During this period (2020-2022), virological studies on SARS-CoV-2 have been intensively conducted, and the pathogenic mechanism of this virus has been elucidated in detail [4,5]. In brief, the key pathogenic processes include binding of the spike protein of SARS-CoV-2 to the angiotensin-converting enzyme 2 receptor on vascular endothelial cells, allowing viral entry and amplification [6]; triggering of red blood cell and platelet aggregation by the spike protein [7–11]; and formation of microthrombi [12,13].

Genetic vaccines, such as mRNA vaccines that encode spike proteins, have caused a wide variety of diseases in all organs and systems of the human body, including the nervous system, in addition to thrombosis, which has resulted in cardiovascular disorders in vaccine recipients [14–21]. Thrombosis is induced in the vaccine recipient by the spike proteins produced from the mRNA or DNA introduced via the genetic vaccine when the foreign gene is introduced into autologous cells using gene-transfer capable lipid nanoparticles (LNPs) or other means. Although evidence for specific problems has been reported individually, Parry et al. have proposed the theory of spikeopathy (spike disease) as a hypothesis that synthesizes all of the evidence for this problem [22]. Furthermore, two general mechanisms are proposed by which a modified gene introduced into the body by genetic vaccination as well as some of the antigens produced by its expression can be transmitted throughout the body. First, LNPs encapsulating modified mRNA can spread throughout the body via the bloodstream from the injection site and can accumulate in specific organs, such as the liver, spleen, ovaries, testes, and bone marrow [22,23]. Second, pseudouridinated mRNA molecules and synthesized spike proteins can be released as extracellular vesicles, or exosomes, from cells that have incorporated the LNPs. These exosomes are transported in the circulation throughout the body to reach various organs [24–27]. Furthermore, spike proteins produced by cells that have taken up the modified gene travel throughout the body in the bloodstream (Figure 1) [28,29]. Thus, the risk of inducing various health conditions can be attributed to the transport, distribution, and expression of the components of the genetic vaccine beyond the administration site to organs and tissues of the whole body.

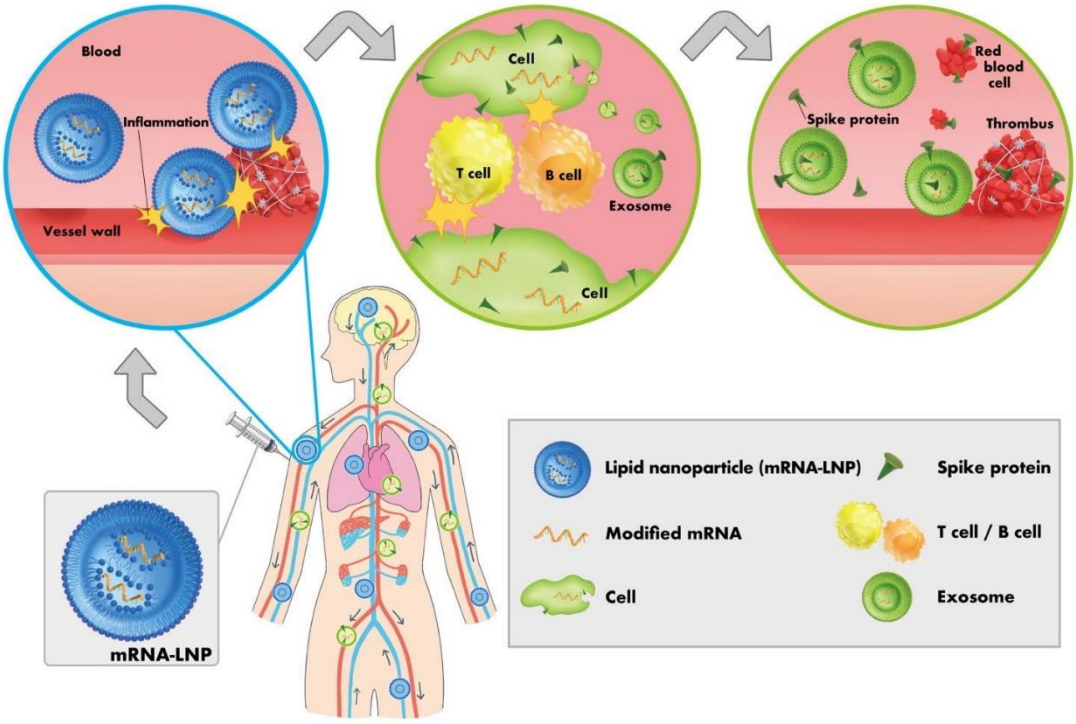

Figure 1. Possible mechanisms for spread of spike proteins and modified RNAs throughout the body. Lipid nanoparticles (LNPs) are transported via the bloodstream to various tissues and organs.

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Cells that take up the LNPs are thought to produce spike proteins, and some of the spike proteins and modified RNA are released into the blood as exosomes. Exosomes containing spike proteins are transported to various tissues and organs via the bloodstream. LNPs are known to cause inflammation, and spike proteins are known to aggregate red blood cells and platelets, which may pose a risk of microthrombus formation. Note that LNPs and exosomes are drawn large in this figure for clarity.

Although the Director-General of the WHO declared the end of the COVID-19 public health emergency on May 5, 2023, post-vaccination syndrome (PVS) caused by genetic vaccines has become a major global problem [19,21,27,30], requiring a reasonable harm–benefit assessment of the global use of such vaccines [27,31–33]. Since the beginning of the coronavirus pandemic and following vaccination with genetic vaccines, the safety of blood products and their use in transfusions has been debated [34–39]. However, owing to a lack of understanding of the pathology of SARS-CoV-2 at the beginning of the pandemic, specific discussions, based on the data or on the analysis of the problem and its risks, were not attempted; only concerns were expressed, and no clear conclusions or policies were drawn. For example, Jacobs et al. stated that hospitals were not required to collect the genetic vaccination status of blood donors or to inform patients about the same [37] because, until 2021, health issues arising from vaccination with genetic vaccines had not been reported. Contrary to initial expectations, genes and proteins from genetic vaccines were found to persist in the blood of vaccine recipients for prolonged periods of time [22,28,40–45], causing a variety of adverse events. Roubinian et al. reported that transfusions of plasma and platelet blood components collected before and after COVID-19 vaccination were not associated with increased adverse outcomes in transfusion recipients who did not develop COVID-19 [39]. However, they only evaluated plasma and platelet preparations, not red blood cell or whole blood preparations. Moreover, the study only followed up recipients to the point of 30-day readmission rates; therefore, the long-term effects remain unclear.

Genetic vaccines are the equivalent of biomedicine (i.e. immune therapeutics) rather than conventional vaccines in terms of their mechanism of action [46,47]. The various genetic vaccines currently treated as vaccines should originally have been treated as biomedicine; however, because they were classified as vaccines, huge numbers of people were inoculated with them [2,3]. As a result, extensive areas of medicine are now beginning to be affected because most of the population in many countries has been vaccinated [19,21,27,30,48], which possibly indicates that blood products for transfusion have been affected by these genetic vaccines. Considering the volume of evidence that has recently come to light, this paper aims to raise awareness among relevant parties and suggest specific recommendations regarding the use of blood products derived from genetic vaccine recipients, including those who have received mRNA vaccines. Furthermore, this paper examines the current risks of blood transfusions when genetic vaccines are administered in large quantities. The vaccine recipients described in this paper are limited to genetic vaccine recipients.

2. Overview of Cases of Blood Abnormalities after Vaccination with Genetic Vaccines

A wide variety of diseases related to blood and blood vessels, such as thrombosis, have developed after vaccination with genetic vaccines, including many cases of serious health injuries. For example, a PubMed search on diseases such as thrombocytopenia, thrombotic disorders with thrombocytopenia, deep vein thrombosis, thrombocytopenic purpura, cutaneous vasculitis, and sinus thrombosis combined with the essential keywords "COVID-19 vaccine" and "side effects" yielded several hundred articles in the two years since the rollout of genetic vaccines [14,17,20,21,49]. Microscopic observation has revealed that in addition to abnormally shaped red blood cells, amorphous material has been found floating in the blood of mRNA-vaccinated individuals, some of which has shown grossly abnormal findings (Table 1, point 2 and 5) [7–11,50]. The spike protein has amyloidogenic potential [51–55], is neurotoxic [56–58], and can cross the blood–brain barrier [59–61], which suggests that the spike protein used as an antigen in genetic vaccines might itself be toxic [22,62,63].

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Table 1. Major concerns with the use of blood products derived from genetic vaccine recipients.

	Concerns	Description	References
1	Spike protein contamination	The spike protein, which is the antigen of SARS-CoV-2 and genetic vaccines, has already been found to have various toxicities, including effects on red blood cells and platelet aggregation, amyloid formation, and neurotoxicity. It is essential to recognize that the spike protein itself is toxic to humans. It has also been reported that the spike protein can cross the blood–brain barrier. Therefore, it is essential to remove the genetic vaccine-derived spike protein itself from blood products.	[22,29,45,56–61]
2	Contamination with amyloid aggregates and microthrombi formed by spike proteins	Amyloid aggregation and development of microthrombi formed by the spike proteins into visible thrombi is yet unknown. However, once formed, amyloid aggregates may not be readily cleared and therefore need to be removed from blood products. These amyloid aggregates have been shown to be toxic.	[52,53,131]
3	Events attributable to decreased donor immune system and immune abnormalities due to immune imprinting or class switch to IgG4, etc., resulting from multiple doses of genetic vaccines	In cases where the immune function of a donor is impaired by vaccination with genetic vaccines, there is a risk that the donor might have an (subclinical) infectious disease or has developed viremia or other conditions after being infected with a pathogenic virus, even in the absence of subjective symptoms. Therefore, healthcare professionals who perform surgical procedures, including blood sampling and organ transplantation, as well as use blood products, should exercise caution while handling the blood of genetic vaccine recipients to prevent infections through blood. All healthcare professionals should be informed of these risks.	[64–68,71–76,81–85,87–92]
4	Presence of lipid nanoparticles (LNPs) and pseudouridinated mRNA (mRNA vaccines only)	If the blood donated by recipients of mRNA vaccines is collected without a sufficient deferral period after genetic vaccination, LNPs and pseudouridinated mRNA may remain in the blood. LNPs are highly inflammatory and have been found to be thrombogenic, posing a risk to transfusion recipients. Furthermore, LNPs have potent adjuvant activity and pose a risk of inducing Adjuvant-Induced Autoimmune Syndrome (ASIA syndrome). An additional risk is that if the pseudouridinated mRNA is incorporated into the recipient's blood while still packaged in LNPs, further spike protein may be produced in the recipient's body. Additionally, if modified mRNAs persist in the body for a prolonged period of time, they can cause a decrease in immune functions.	[23,40,44,76,106–111,167,169]
5	Contamination with aggregated red blood cells or platelets	The spike protein causes red blood cells and platelets to aggregate; these aggregates will be carried into the recipient's blood unless they are physically removed from the blood product before transfusion.	[7–11,50]
6	Memory B cells producing IgG4 as well	Large amounts (serum concentration typically above 1.25–1.4 g/L) of non-inflammatory IgG4-positive plasma	[78–80,173,174]

 doi:10.20944/preprints202403.0881.v2

as IgG4 produced from them	cells can cause chronic inflammation, such as fibroinflammatory disease.

Individuals who have received multiple doses of a genetic vaccine may have multiple exposures to the same antigen within a brief period, thereby being imprinted with a preferential immune response to that antigen [64–67]. This phenomenon, called original antigenic sin or immune imprinting, may have caused COVID-19 vaccine recipients to become more susceptible to contracting COVID-19 [68]. Moreover, such vaccine recipients are also at a risk of antibody-dependent enhancement of infection, whereby antibodies produced by vaccination promote viral infection and symptoms [69,70]. In contrast, repeated administration of genetic vaccines may result in immune tolerance because of a class switch to non-inflammatory immunoglobulin G4 (IgG4) [71–76], whereby the immune system of the recipient does not mount an excessive response such as cytokine storm [27,77], as evidenced by case reports of IgG4-related disease [78–80]. Such alterations in immune function due to immune imprinting and immunoglobulin class switching to IgG4 occurring in genetic vaccine recipients is a cause for concern as these may increase the risk of serious illness due to opportunistic infections or pathogenic viruses that would not pose a problem in a normal immune system [81–87]. Therefore, from the perspective of traditional containment of infectious diseases, greater caution is required in the collection of blood from genetic vaccine recipients and in the subsequent handling of blood products, as well as during solid organ transplantation and even during surgical procedures [88–92] to avoid the risk of accidental blood-borne infections (Table 1, point 3) [89–92]. Although the phenomenon of immune imprinting can occur even when spike protein is not used as an antigen or when another antigen is used (e.g., inactivated influenza vaccine) [93], in case of genetic vaccines, which produce an antigen within the body, the period of exposure to the same antigen might be prolonged, resulting in the risk of immune imprinting being higher than with conventional inactivated vaccines. The duration for which vaccine components remain in the body after a person has received a genetic vaccine is yet unknown [22,40,43]; however, it is expected that they remain in the body for a longer period than that originally thought, partly based on reports of spike protein being detected in vaccinated individuals several months post vaccination (Table 1, point 1) [22,28,41,42]. In addition, the immune dysfunction of genetic vaccine recipients is expected to be prolonged owing to immunoglobulin class switching to IgG4 [71,73,76] due to long-term exposure to a specific identical antigen (in this case, spike protein), and also because some of the B cells that produce IgG4 are likely to differentiate into memory B cells that survive in the body for a sustained period [73,94] (Table 1, point 3 & 6). In contrast, modified (N1-methyl-pseudouridylated) mRNAs cause a decrease in immune function if they remain in the body for an extended period of time [76].

In summary, receiving blood products derived from blood collected in, at least, a brief deferral period after vaccination with genetic vaccines might pose a health risk for some patients. Although occurrence of secondary damage caused by transfusion of blood products derived from genetic vaccine recipients is yet unknown, it is vital that medical institutions and administrative organizations respond and investigate cooperatively keeping various possibilities in mind, especially considering that mechanisms such as the toxicity of the spike protein itself and the effects of LNPs and modified mRNA on the immune response have not been fully elucidated. A significant proportion of the COVID-19 PVS in mRNA vaccine recipients is due to toxic spike proteins, and the inclusion of structures in the receptor-binding domain within these proteins might induce prion disease, as Seneff et al. and Perez et al. have reported [51,95–101]. Furthermore, prion similarity in the receptor-binding domain exists not only in the spike protein of the Wuhan strain, which is still used as an antigen in genetic vaccines, but also in that of variants of SARS-CoV-2, such as the Delta strain, with the exception of the Omicron strain [98,102]. Further studies are required to ascertain whether uniform vigilance is required for the spike protein of all coronavirus strains or just the spike protein of certain variants, such as the Wuhan strain.

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3. Specific Proposals for Blood Sampling and Use of Blood Products from Vaccine Recipients

In the previous section, blood-related abnormalities that have occurred following vaccination with genetic vaccines were discussed. In this section, specific proposals on how to respond to these health conditions are provided. Blood contamination affects several areas of health care; therefore, it is crucial to plan beforehand and be vigilant to avoid these occurrences [100,101,103–105].

3.1. Additional Requirements for Blood Collection (Donation)

Currently, in Japan, the Japanese Red Cross Society (https://www.jrc.or.jp/english/) plays a central role in blood collection activities, and its blood products are used for blood transfusions and other purposes. The current rules of the Japanese Red Cross Society state that blood can be collected from genetic vaccine recipients after a deferral period (48 hours for mRNA vaccine recipients and 6 weeks for AstraZeneca DNA vaccine recipients); however, the data and rationale for such rules have not been specified. Similar to procedures for infections such as human immunodeficiency virus and prion diseases, a history of genetic vaccination (DNA and/or mRNA type), including timing and number of doses, should be obtained by interview when blood is collected, and maintained in the official record (Figure 2, Table 2). Additional caution is warranted, particularly in cases where sufficient number of days have elapsed since the genetic vaccine was administered, because LNPs [23,106–109] and spike protein mRNA, which can induce inflammation, may continue to remain in the blood (Table 1, point 4) [22,40,43,44]. In cases where certain events such as anaphylactic shock occurred immediately after genetic vaccination, the effects of LNPs should also be suspected [110]. Negatively charged LNPs themselves interact with fibrinogen to form thrombi [111], and because LNP induces inflammation, it may cause thromboinflammation by itself [112]. Therefore, the presence of LNPs may in itself be a factor that should be viewed with caution when using transfusion products.

Table 2. Tests needed to confirm the safety of blood products.

	Concerns	Description	References
1	Spike protein content in blood	Immunochemical techniques include enzyme-linked immunosorbent assay, immunophenotyping, mass spectrometry, liquid biopsy, and a combination of liquid biopsy and proteomics. We propose initially conducting mass spectrometry because it can directly measure the protein itself.	[28,29,124–127,129]
2	Spike protein mRNA in blood	PCR and/or liquid biopsy are the options. If mRNA for the spike protein is detected, lipid nanoparticles (LNPs) may be present (mRNA vaccines only).	[127,128,130]
3	Spike protein DNA in blood	PCR and liquid biopsy are the options. This test is necessary because AstraZeneca's viral vector is a DNA vaccine. For mRNA vaccines, it is believed that pseudouridinated mRNA is not reverse transcribed, but this test is required if the spike protein remains in the body for a prolonged period.	[127,128]
4	Autoimmune disorders	Long-term persistence of the spike protein in the blood increases the risk of autoimmune disease. Therefore, it would be useful to assess for autoimmune disease using antinuclear antibodies as biomarkers in people who are positive for the spike protein, taking into account the results of interviews regarding the subjective symptoms.	[27,169,171,172]
5	Post-vaccination syndrome (PVS)	A history of vaccination with genetic vaccines and COVID-19, current and previous medical history, and	[15,175,176]

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		presence of subjective symptoms (e.g., headache, chest pain, shortness of breath, malaise) should be obtained from blood donors and formally recorded. The type of questions included in the interview are critical to facilitate diagnosis and treatment of COVID-19 PVS, as more people are complaining of psychiatric and neurological symptoms after genetic vaccination.	
6	Proteins resulting from frameshifting of pseudouridinated mRNA	Although it is not yet clear whether proteins other than the spike protein are translated from pseudouridinated mRNAs, mass spectrometry may be useful in confirming this.	[166]
7	Amyloid aggregates and thrombi	Common markers of thrombosis, such as D-dimer, should be first used. Once the major components of amyloid aggregates and thrombi have been identified, their use as biomarkers is proposed. Understanding the composition of amyloid aggregates will be important in the future, as amyloid aggregates have been reported to be toxic. Understanding the composition of amyloid aggregates may provide clues to how amyloid is broken down.	[52,53,131,177]
8	Origin of spike protein	This test will help determine whether the spike protein is from the genetic vaccine or from SARS-CoV-2. Potential candidates include nucleocapsid.	[4,5,41,128]
9	Immunosuppression	It may be necessary to analyze immunoglobulin subclasses (such as the amount of IgG4) if immunosuppression from multiple doses of the genetic vaccine is a concern.	[71–74]
10	Anti-nucleocapsid antibodies	The presence or absence and amount of anti-nucleocapsid antibodies as well as antibody isotypes may be an indicator(s) for distinguishing whether these are caused by genetic vaccines or long COVID.	[141–143]
11	Others	Occurrence of myocarditis and pericarditis after genetic vaccination has been reported in various countries. Therefore, those with subjective symptoms should also be assessed for myocarditis markers, such as cardiac troponin T.	[18,19,29,144,178,179]

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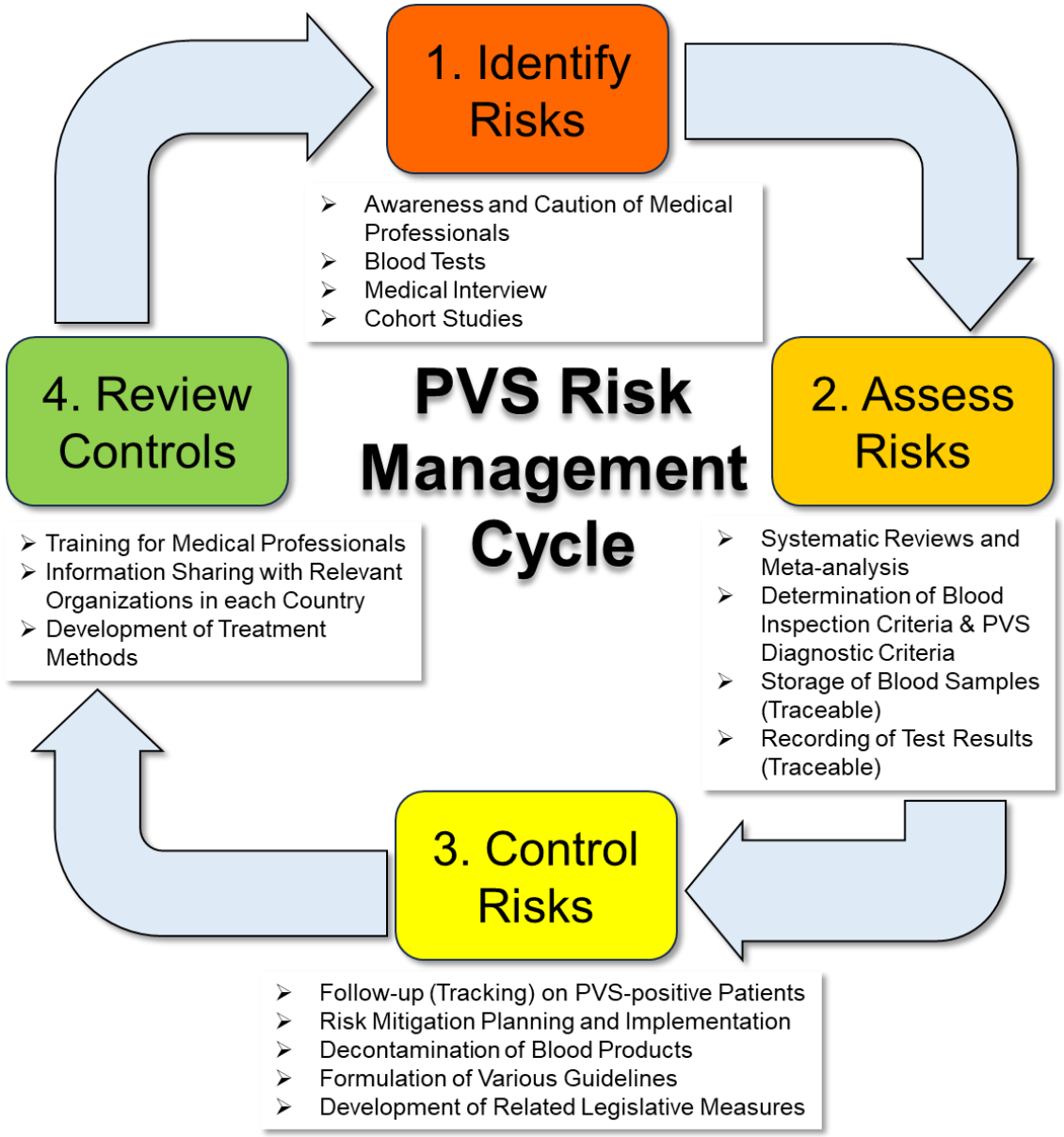


Figure 2. Proposed PVS risk management cycle. Summary of items and procedures required for management of blood products derived from genetic vaccine recipients or those affected with spike protein and modified genes. As with any risk management exercise, it is important to constantly revise policies and procedures as risks and problems are identified. PVS, post-vaccination syndrome.

In contrast, in cases where individuals underwent long COVID without receiving a genetic vaccine, the likelihood of the spike protein remaining in their body is possible; therefore, maintaining official records of the occurrence of long COVID is essential [52,113–115]. The degradation rates of pseudouridinated mRNA and spike protein in the body are yet unknown; therefore, blood products derived from genetic vaccine recipients should be used with extreme caution, considering that cases of AIDS, bovine spongiform encephalopathy (BSE), and variant Creutzfeldt-Jakob disease (vCJD), caused by the use of contaminated blood products, have occurred earlier [105,116–123].

3.2. Handling of Existing Blood Products

Currently, the genetic vaccination status of blood donors is not confirmed or controlled by organizations, including medical institutions, and the use of blood collected from such donors for transfusions may pose risks to patients. Therefore, when blood products derived from genetic vaccine recipients are used, it is necessary to confirm the presence or absence of spike protein or modified

 doi:10.20944/preprints202403.0881.v2

mRNA as performed in tests for pathogens (Figure 2, Table 2). Presence of spike protein or modified mRNA should be quantified by an immunochemical enzyme-linked immunosorbent assay, immunophenotyping, direct mass spectrometry of the protein itself, exosome-based liquid biopsy as used in cancer screening, or PCR [28,29,124–130]. For protein assays, mass spectrometry could be used as an initial step to identify and quantify the spike protein itself in blood [28,126] as it may take time to generate a good-quality anti-spike protein antibody or a positive control for a recombinant spike protein to be compared with, and to sort and distribute them to each laboratory. Concurrently, the components of the spike protein-induced amyloid material should be analyzed [52,131], and once identified, these could be used as biomarkers in future studies. Furthermore, exosome analysis could also be used for these investigations because spike proteins and the genes encoding them are circulated throughout the body by exosomes (Figure 1) [24–27].

Although it is essential to remove the spike protein or a modified gene derived from the genetic vaccine if found in a blood product, currently, there is no reliable way to do so. The presence of a prion-like structure within the spike protein molecule [96,100,101] suggests that this molecule may be a persistent, sparingly soluble, heat-resistant, and radiation-resistant protein [132,133]. The prion protein can be inactivated by thiocyanate, hydroxide, and hypochlorite [134–136]; however, whether these methods can be applied to the spike protein and the resulting amyloid materials is not yet known. Notably, Nattokinase, an alkaline protease, degrades spike proteins *in vitro* [137]. Although further studies are needed to determine whether such enzymes are indeed effective in degrading spike proteins, it is worth noting that Nattokinase is already known as an alternative in the prevention and treatment of cardiovascular diseases [138–140]. Currently, however, there are no methods to reliably remove the pathogenic protein or mRNA; therefore, it might not be prudent to use all such blood products until a definitive solution is found. Some medical facilities might not be able to dispose of blood products immediately; therefore, in such cases, the transfusion consent form provided to the patient should include the possibility of blood products being contaminated with spike protein or other foreign substances. In any case, to prevent and reduce medical accidents caused by contaminated blood, it is imperative to underscore the importance of confirming the history and frequency of vaccination with genetic vaccines at the time of blood collection; this information should be documented as an official record, managed and stored by both medical and governmental organizations (see Figure 2, Table 2).

3.3. Need for Regular Checkups and Cohort Studies to Gain a Complete Picture of Blood Components

The residual status of spike protein or modified gene fragments derived from genetic vaccines in the blood of vaccinated individuals is currently unknown; it might be useful to include the measurement of these molecules in routine health checkups. It would also be prudent to include a section in the routine medical checkup questionnaire to check genetic vaccination status and the number of vaccinations received to obtain an overall picture of the residual status of spike proteins in the blood. A variety of conditions following genetic vaccination involve thrombosis and immunological conditions [12,14,16,17,21,22,71,73]; therefore, abnormalities in blood components related to these events should also be analyzed.

Transmission of spike protein was observed when mice that had not been vaccinated with the genetic vaccine were administered exosomes collected from vaccine recipients [25], thus proving that the spike protein and its modified genes can be transmitted through exosomes. Therefore, full testing should be done initially, regardless of genetic vaccination status, and a cohort study should be conducted to quickly identify all components derived from genetic vaccines (Figure 2). Although such measures involve steady, labor-intensive efforts that require collaboration between all parties involved, the subsequent analyses may lead to the development of diagnostic criteria and testing for COVID-19 PVS. In addition, even those individuals who have not been vaccinated with the genetic vaccine, but have had long COVID, may have residual spike proteins or fibrin-derived microthrombi in their bodies; therefore, the same testing and follow-up as that for genetic vaccine recipients should be conducted for such individuals. [52,53,113–115]. The presence or absence and amount of anti-nucleocapsid antibodies as well as that of antibody isotypes may be an indicator(s) in distinguishing

 doi:10.20944/preprints202403.0881.v2

whether vaccination with genetic vaccines or long COVID resulted in the presence of residual spike proteins or fibrin-derived microthrombi in their bodies (Table 2, point 10) [141–143]. Further, these cohort studies would help establish cutoff values for blood levels of spike protein and other substances to determine the safety of blood products. Faksova et al. conducted a large cohort study of 99 million people using a multinational Global Vaccine Data Network™ and found a significantly increased risk of myocarditis, pericarditis, Guillain-Barre syndrome, and cerebral venous sinus thrombosis in genetic vaccine recipients [144]. Such studies will be increasingly necessary in the future.

3.4. Need for Expedited Development of Clinical Practice Guidelines and Diagnostic Criteria for COVID-19 PVS

Although the spectrum of COVID-19 PVS is diverse, it is mostly characterized by a high prevalence of hematologic and immune-related diseases [21]. Thus, regardless of the transfusion issues discussed in this paper, blood tests are likely to be the first step in the diagnosis of COVID-19 PVS. The ability to rapidly develop highly accurate testing systems, particularly blood tests, will be critical in treating patients with COVID-19 PVS. Additional meta-analysis of data from systematic reviews and cohort analyses will be needed to prevent bias in diagnostic criteria and to develop appropriate clinical practice guidelines (Figure 2) [145–147].

4. Effects of Blood Transfusion from Genetic Vaccine Recipients and the Need for Traceability of Blood Products for Transfusion

There has been considerable debate regarding the safety of blood products for transfusion prepared from blood donated by vaccine recipients [36–39]. However, the effect of a genetic vaccine, such as an mRNA vaccine, on the human body is yet unknown, although cases of encephalitis caused by blood transfusion from dengue vaccine recipients have been reported as recently as 2023 [148], indicating that the current system for managing and tracking blood products is not adequate. Unless accurate tests are established, no conclusions can be drawn about the risk or safety of blood transfusions using blood products from genetic vaccine recipients. Therefore, thorough and continuous investigation is necessary, which can be accomplished by registering all potential donors, ensuring traceability of blood products, and maintaining rigorous recipient outcome studies and meta-analysis. Furthermore, it is essential to rigorously obtain a history of vaccination and COVID-19 infection from donors, preserve official records, and store samples of blood products for later detection and verification of substances such as spike proteins and exosomes (Figure 2). Given the wide variety of tests and records, the movement of people around the world, and the import/export of blood products, it may be necessary in the future to establish traceability by introducing blockchain technology into the management of blood products while maintaining anonymity [149,150].

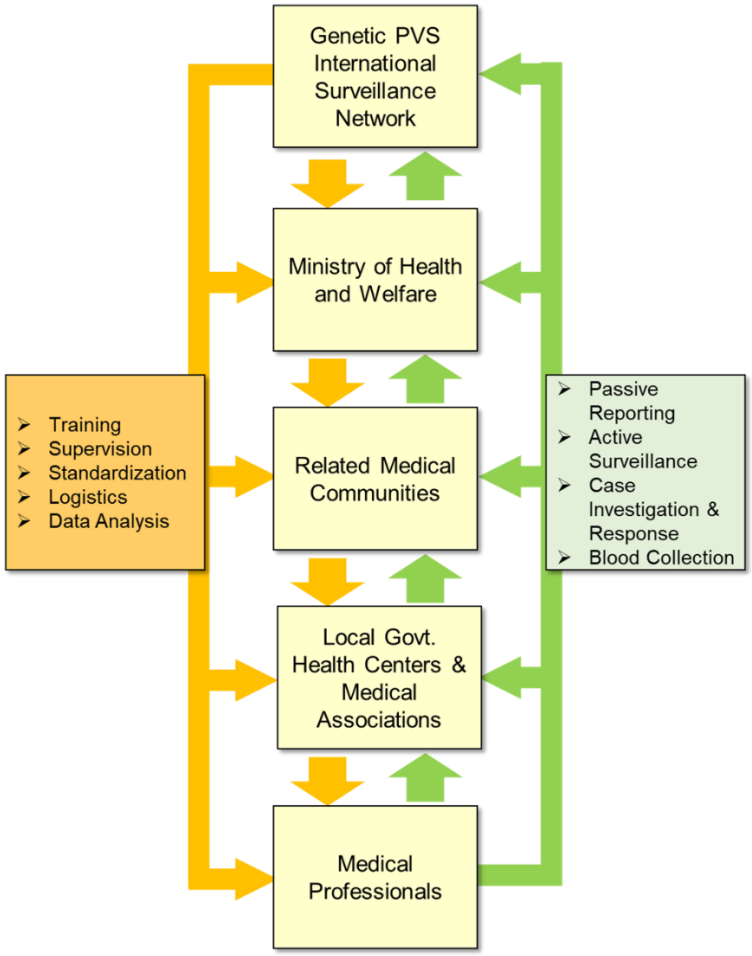
5. Need for the Development of Relevant Legislation

In Japan, the "Act on Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases" (https://www.japaneselawtranslation.go.jp/en/laws/view/2830/en) and "Act on Organ Transplantation" have been enacted to prevent the spread of infectious diseases through blood products and to handle organ transplants, respectively. The Ministry of Health, Labour and Welfare has issued the "Guidelines for Blood Transfusion Therapy" regarding blood transfusions. These laws and guidelines specify the responsibilities of the public, physicians, and national and local governments and protect the rights of citizens. However, the spike protein, used as an antigen, or its gene, are not organisms; therefore, certain legal decisions are required, such as how to legally define the pathogenicity of the spike protein. Thus, a new definition of the spike protein—as a nonbiological infection, may be necessary with increasing clarity on its toxicity and pathogenicity [22,62]. Subsequently, when the risks of and health injuries caused by blood products derived from genetic vaccination recipients have been roughly clarified (Table 2), it will be essential to formulate regulations to reduce and prevent risks and contamination. This can be achieved by developing

 doi:10.20944/preprints202403.0881.v2

related laws with the participation of the legislative branch, legal experts, medical administration personnel, healthcare providers, and medical researchers, and by taking measures such as checking vaccination status and dates and legally regulating the import/export of blood products (Figure 2). The entire process requires coordination between agencies and healthcare professionals from the outset.

In contrast to previous drug programs, vaccination with genetic vaccines was implemented simultaneously for a substantial number of people on a global scale [2,3]; therefore, legislation and international treaties need to urgently and explicitly elucidate bilateral and multilateral agreements among countries regarding the management of blood products. These legal frameworks should delineate regulations governing the handling of blood products and establish protocols for governmental compensation and response to issues and hazards associated with these products, including penalties and prohibitions. The International Health Regulations 2005 [151,152] could be used for this purpose; however, considering the WHO's strong push for vaccination with genetic vaccines [153], another framework may be needed. As described in Section 3.3 of this article, it might also be necessary for countries to conduct active epidemiological surveys [154], as was the case with COVID-19, compile the results of these surveys, and establish an international organization tasked with monitoring response efforts and assessing damages within each country (Figure 3). For such decisions, it is vital to incorporate not only the perspective of infectious diseases but also that of biosafety and biosecurity [152,155]. Thus, there is an urgent need for an international conference of various experts, including policymakers, legal experts, historians, and ethicists, to discuss in a transparent manner what problems and challenges might arise from genetic vaccines and beyond [156–159].



A mechanism is needed to raise information directly to the Genetic PVS International Surveillance Network in the event of an emergency.

 doi:10.20944/preprints202403.0881.v2

Figure 3. An example of a system for managing health injuries among genetic vaccine recipients. Given the global nature of vaccination with genetic vaccines and the movement of vaccine recipients and blood products between countries, an international surveillance network to establish coordination among countries is needed. PVS, post-vaccination syndrome.

In Japan, Article 15 (2) of the Infectious Disease Act (https://www.japaneselawtranslation.go.jp/ja/laws/view/2830/en#je_ch3at5) stipulates that the Japanese government is responsible for conducting epidemiological studies. Considering the significant health risks associated with COVID-19 PVS, we urge the Japanese government to prioritize the analysis and safety verification of blood products derived from genetic vaccine recipients.

6. Further Considerations

To address the need for developing methods to identify and remove spike proteins and modified genes derived from genetic vaccines from blood products, the Japanese Society of Hematology (http://www.jshem.or.jp/modules/en/index.php?content_id=1), the Japanese Society of Transfusion and Cell Therapy (http://yuketsu.jstmct.or.jp/en/), and related organizations need to develop guidelines on how to handle blood products that contain residual spike proteins or their modified genes ensuring that a uniform inspection standard is developed. Additionally, as noted earlier, vaccination with genetic vaccines has been promoted on a global scale [2,3], which will necessitate coordination and exchange of information with national administrations and relevant international medical societies (Figure 2). Furthermore, international guidelines on the handling of blood products and the establishment of an international investigatory organization will be necessary (Figure 3). There is an urgent need to share the risks of transfusion of blood products derived from genetic vaccine recipients among the parties concerned, and prompt investigation and response by all parties concerned is essential.

During the course of the development of various guidelines, previous responses to such health emergencies should be considered; for example, when the transmission of BSE and vCJD, also through blood transfusion, was a health issue (e.g., the Creutzfeldt-Jakob Disease International Surveillance Network in https://www.eurocjd.ed.ac.uk/) [105,116,117,123,160]. In the case of BSE in the United Kingdom, the mode of transmission of prion protein was unknown; therefore, leukodepletion of blood products was conducted universally. Whether this action was effective in preventing transmission of BSE and vCJD through blood products is controversial [105,122,123,161]; however, removing white blood cells from all blood products was not common at that time, as is now routinely done with collected blood. Nevertheless, because of leukodepletion, the safety of blood products has increased [162]. In the case of the spike protein, which causes abnormalities such as agglutination of red blood cells and platelets [8–11,50], leukodepletion alone will not resolve the issue. Thus, it is worth confirming whether washing of red blood cells can be effective [163,164]; in urgent cases, autotransfusion may be an option [165].

Recent studies have shown that RNA pseudouridylation can result in frameshifting [166]; however, whether a portion of the pseudouridinated mRNA for the spike protein is translated into another protein of unknown function in vaccine recipients is yet unknown. Moreover, if these proteins are also pathogenic, additional testing for such frameshift proteins may be needed in the future. Even if a frameshift protein is not toxic, it is foreign to the body and could cause an autoimmune reaction. In addition, as described in Section 3.1, LNPs themselves are highly inflammatory substances [23,106,107,109,110]; however, LNPs exhibit stronger adjuvant activity than the adjuvants used in conventional vaccines [167], and could result in autoimmune diseases (Table 1, point 4) [168,169]. Thus, although the causative agent of autoimmune disease is not yet known, the large number of reported cases of autoimmune disease following genetic vaccination is a concern [15,21,27,30,169,170]. The very mechanism of genetic vaccines that induces one's own cells to produce antigens of the pathogen carries the risk of inducing autoimmune diseases, which cannot be completely avoided even if mRNA pseudouridylation technology is used. Thus, individuals with a

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positive blood test for spike protein may need to undergo interviews and additional tests for autoimmune disease indicators, such as for antinuclear antibodies (Table 2, point 4) [27,169,171,172]. Alternatively, if the amino acid sequence of the protein resulting from such a frameshift is predictable, these candidate proteins could be included in the initial mass spectrometry assay (Table 2, point 6). Thus, it is particularly important to develop tests and establish medical care settings in anticipation of these situations.

7. Conclusion

Finally, the use of genetic vaccines, such as pseudouridinated mRNAs and mRNA-LNP platforms [47,108], should be reviewed critically to avoid further risks similar to those described in this paper. The impact of these genetic vaccines on blood products and the actual damage caused by them are unknown at present. Furthermore, the issues discussed in this paper pertain to all organ transplants, including bone marrow transplants, and not just blood products. Therefore, in order to avoid these risks and prevent further expansion of the potential for blood contamination and complication of the situation, we suggest that the vaccination campaign using genetic vaccines should proceed with caution and that a harm–benefit assessment be carried out, as called for by Fraiman et al. and Polykretis et al. [27,31–33]. Moreover, as Parry et al. stated [22], it is critical and timely to reevaluate the pseudouridinated mRNA based technology before the advent of other genetic vaccines that are being developed. The health injuries caused by vaccination with genetic vaccines cannot be ignored; therefore, countries and relevant organizations should take concrete steps together to identify the risks and to control and resolve them.

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