Impact of Parvovirus B19 infection on transfusion safety

Preliminary analysis of epidemiological data and indications for donor management

October 2024

CENTRO NAZIONALE SANGUE
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Technical Document

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Objective

The purpose of this technical document is to assess the national epidemiological data of Parvovirus B19 (B19V) infection in the donor population as well as the implications for transfusion safety, based on currently available scientific evidence, with respect to the increased incidence of positivity that was detected by fractionation companies on national plasma donations in the first quarter of 2024.

Preamble

In May 2024, the European Centre for Disease Prevention and Control (ECDC) reported that, as of the end of 2023, nine EU/EEA countries have reported a significant increase in Parvovirus B19 (B19V) positivity on the European surveillance portal for infectious diseases (EpiPulse). The increase is detected mainly in the paediatric age population and pregnant women[1].

As early as April 2024 the ECDC had requested information from the National Focal Points (NFPs) of the ECDCSoHO blood transfusion network regarding the performance of screening tests for B19V on blood and blood component donations and whether they observed an increase in cases of B19V infection in the donor population. Of the 18 countries that provided feedback, a large proportion reported that they do not routinely screen for B19V on donations; in addition to the very few countries that test for labile blood products, however, a not insignificant number of Member States claim to have information on NAT positive testing for B19V through tests performed by pharmaceutical companies that process plasma collected by blood establishments within a "toll manufacturing" system. Ten countries (Finland, Hungary, Luxembourg, Lithuania, the Netherlands, the Czech Republic, Denmark, France, Germany and Slovakia) reported increased reactivities to B19V in blood donors or plasma donations intended for industrial fractionation collected in early 2024, compared with the same period in 2023. More recently, Italy shared preliminary data indicating a significant increase in plasma units intended for fractionation tested positive for B19V from the end of December 2023 to the first six months of 2024.

1 European Centre for Disease Prevention and Control. Risks posed by reported increased circulation of human parvovirus B19 in the EU/EEA – 5 June 2024. ECDC: Stockholm; 2024.

Italian Context

In Italy the level of quality and safety of blood components is guaranteed by prevention and control measures, including the use of voluntary and regular donors, who belong to low-risk categories being selected and individually assessed for risk factors related to communicable diseases based on the eligibility criteria provided by current legislation, as well as for the performance of biological qualification tests on each individual donation.

As for the biological qualification tests of blood components, it should be pointed out that Directive 2004/33/EC[2] requires mandatory HBsAg, anti-HCV and anti-HIV 1/2 serological tests, while in Italy, for many years, molecular tests for HBV DNA, HCV RNA and HIV1/2 RNA and the serological test for *Treponema pallidum* have been mandatory on every single donation. With the introduction of serological testing for combined anti-HIV 1/2 antibody and HIV 1 antigen (Generation IV test), the profile of biological qualification tests has been expanded in order to improve the safety level of blood components[3].

With regard to plasma for fractionation, plasma donations flow into production pools, whose volumes are defined in the Plasma Master Files (PMFs) of each company holding national plasma manufacturing agreements with the lead regions of interregional agreements. In compliance with the provisions of the European Pharmacopoeia, the following tests must be repeated in the first plasma thawing pool: anti-HIV1/2 antibody detection, HBsAg antigen detection, and NAT test for HCV[4]. In addition, due to voluntary adherence to procedures that ensure higher levels of quality and safety, fractionation companies have also introduced the performance of NAT tests for HBV, HIV, HAV and B19V. Moreover, for plasma intended for solvent-detergent (SD) viral inactivation treatment[5], the Pharmacopoeia requires the following additional tests to be performed on the thawing homogeneous pool: HAV RNA, B19V DNA and HEV RNA because of the non-enveloped characteristics of the aforementioned viruses that make them unresponsive to viral inactivation procedures.

Finally, the Pharmacopoeia requires that the NAT B19V test is performed also in the case of plasma pools intended for the production of Anti-D (Rh) Immunoglobulins[6,7].

The introduction of testing for HAV RNA and B19V DNA on plasma for fractionation introduces safety features that blood components for clinical use do not benefit from. Against of the minimum prescription introduced at the European level, in Italy it was deemed necessary to extend the testing of donations to molecular testing first for HCV and then for HBV and HIV, because of national and international epidemiological evidence and

2 Directive 2004/33/CE of the Commission of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components was transposed with Ministerial Decree of March 2005 “Protocols for assessing the suitability of donor" and "Characteristics and methods for donating blood and blood components”. Official Journal of the European Union L 91/25 of 30.3.2004.
3 Ministerial Decree of 2 November 2015 “Provisions relating to the quality and safety requirements of blood and blood components. Official Journal General Series no. 300 of 28.12.2015 - Ordinary Supplement no. 69.
4 *European Pharmacopoeia.* 2020. Human Plasma for Fractionation (*Plasma humanun ad separationem*). Monograph 01/2020:0853. 10th ed. Strasburg: Council of Europe; 2020.
5 *European Pharmacopoeia.* 2020. Human Plasma (Pooled and treated for virus inactivation) (*Plasma humanun coagmentatum conditumque ad exstinguendum virum*). Monograph 01/2020:1646. 10th ed. Strasburg: Council of Europe; 2020.
6 *European Pharmacopoeia*. 2020. Human anti-D Immunoglobulin (*Immunoglobulinum humanum anti-D*). Monograph 01/2020:557. 10th ed. Strasburg: Council of Europe; 2020.
7 *European Pharmacopoeia*. 2020. Human anti-D Immunoglobulin for intravenous administration (*Immunoglobulinum humanum anti-D ad usum intravenosum*). Monograph 01/2020:1527. 10th ed. Strasburg: Council of Europe; 2020.

the demonstrated ability of these tests to significantly reduce the so-called *window period* of these infections, allowing the interception of a significant proportion of asymptomatic infected donors.

The screening for B19V by NAT method, which was aimed at detecting donations with high levels of viremia in mini-pools of plasma intended for industrial fractionation, was introduced after the description of seroconversions for B19V (in the absence of disease) in volunteers enrolled in a pharmacovigilance study on SD plasma. Some batches of this blood component medicinal product had caused the transmission of B19V because they contained high titre loads of it (B19V DNA > 10^7 IU/mL).

The introduction of testing for B19V DNA on industrial mini-pools, which is carried out by pharmaceutical companies, allows the detection thus elimination of potentially infected plasma units before the formation of the industrial pool. Therefore, the aforementioned screening is considered as a control of the manufacturing process of plasma-derived medicinal products and not as a screening of donations[8]. It is performed because of the need to prevent that the sum of viral loads > 10^4 IU/mL in the individual donations placed in the plasma pools can, by overcoming the dilution effect, nullify the effectiveness of the neutralizing antibodies (derived from donations made by immunized donors) present in the same pools and reduce the effect of the subsequent steps of viral removal and inactivation present in the industrial fractionation process[9].

Consequently, it can be stated that the volume of the industrial processing pool combined with the sum of significant viral loads present in it, as well as the reduced effects of viral inactivation and removal procedures on non-enveloped viruses have a considerable impact on the risk of contamination of the thousands of units of medicinal products produced from that raw material and intended for thousands of recipients. As for the assessment of transmissibility risk in the context of clinical use of labile blood components not tested for non-enveloped viruses, the impacts of such risk, where present, are reduced to a one to a few unit relationship.

In view of what was reported in the preamble on the ECDC questionnaire, the Italian National Blood Centre launched a survey involving fractionation companies holding agreements with the Regions and Autonomous Provinces (RAPs) for national plasma manufacture.

In order to assess the epidemiological trend of B19V, an analysis was performed taking into consideration the regional data from 2018 - 2024 recorded by each of the fractionation companies regarding plasma units both collected by blood establishments and blood collection units of the RAPs and intended to industrial processing for the manufacturing of blood-derived medicinal products and virus-inactivated plasma.

The B19V positivity rate detected through plasma units sent to the company was calculated using as denominator the number of total donations made in each month between January 2018 and June 2024. Positivity results refer to units detected positive for B19V with viral titres above the acceptable limits defined by the companies and therefore no longer processed. In this context, it is therefore useful to point out that the epidemiological data presented here may be underestimated with respect to the real prevalence of the virus in the Italian donor population since it reports what for each fractionation company is detected during

8 Nucleic Acid Testing to Reduce the Possible Risk of Parvovirus B19 Transmission by Plasma-Derived Products: Guidance for Industry. Food and Drug Administration, 2009. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatory Information/Guidances/default.htm. Last access: 15 June 2024.
9 QSEAL NAT Testing Standard, Version 2.0. Plasma Protein Therapeutics Association - PPTA. Annapolis, Maryland, June 13, 2013. Available at: https://cdn.prod.website-files.com/638f893112c6eac0e46ac576/64517906a60bdb04ed8c3b74_NATTestingV2-3.pdf. Last access: 15 June 2024.

the testing stage and, consequently, considered as positive, concealing all those units possibly positive but with viral titres below the aforementioned acceptability limits.

A preliminary data analysis showed two peaks in 2018 and 2019 (with 46 and 86 positive units, respectively) and a maximum peak of 138 positive units in March 2024.

The ratio of B19V-positive units on the date of donation to total units donated (and subsequently sent to fractionation companies) in the related month shows two peaks in May 2018 and June 2019 with 19.8 and 39.4 positive units per 100,000 donations, respectively. An additional peak was recorded in June 2020, with 14 positive units per 100,000 donations, and more recently, 10.3 and 59.4 positive units per 100,000 donations were observed in June 2023 and March 2024, respectively (Figure 1).

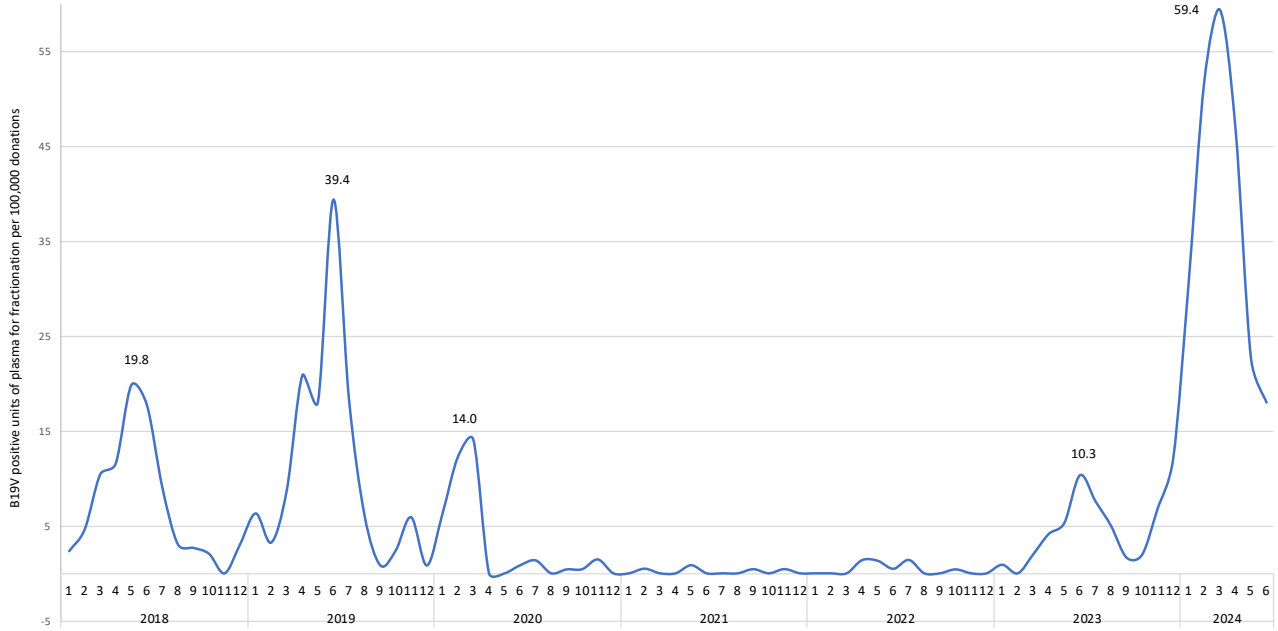

Figure 1. B19V positive units of plasma for fractionation per 100,000 units donated in the related month in Italy between 2018 - 2024.

The distribution of B19V-positive units by geographic area (Figure 2), which was made according to ISTAT coding[10], shows a fluctuating trend between 2018 and 2020 with significant peaks especially in the Islands, where values of 59.7 and 62.1 positive units per 100,000 donations were recorded in the years 2018 and 2019, respectively. In the period between 2020 and 2022, these curves declined reaching values close to zero, increasing again only from the year 2023.

10 Description of boundaries geographical data of administrative units for statistical purposes. Version 26/02/2019. ISTAT, Rome 2018. Available at: https://www.istat.it/it/files/2013/11/2019.28.06-Descrizione-dei-dati.pdf. Last access 5 May 2024.

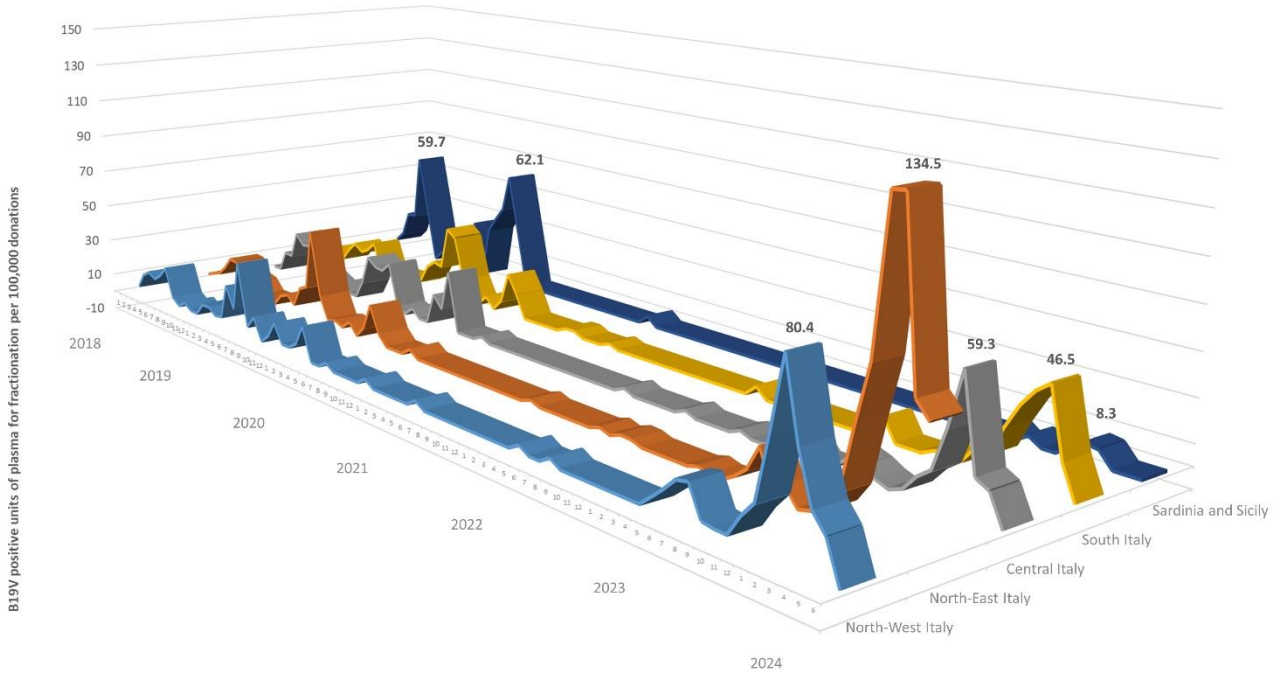

Figure 1. B19V positive units of plasma for fractionation per 100,000 units donated in the same month in Italy, per geographical area, between 2018 - 2024.

In the first semester of 2024, during the testing procedure, each of the fractionation companies detected 82.3 positive units per 100,000 donations in the Northeast geographic area and 39 positive units per 100,000 donations in the Northwest area. The South and Central areas recorded 29.9 and 28.3 positive units per 100,000 donations, respectively. As for Sardinia and Sicily, the number of positive units per 100,000 donations was 3.8 (Figure 3).

In particular, in March and April 2024 two maximum peaks of 133.9 and 134.5 positive units per 100,000 donations were recorded in the Northeast area, respectively.

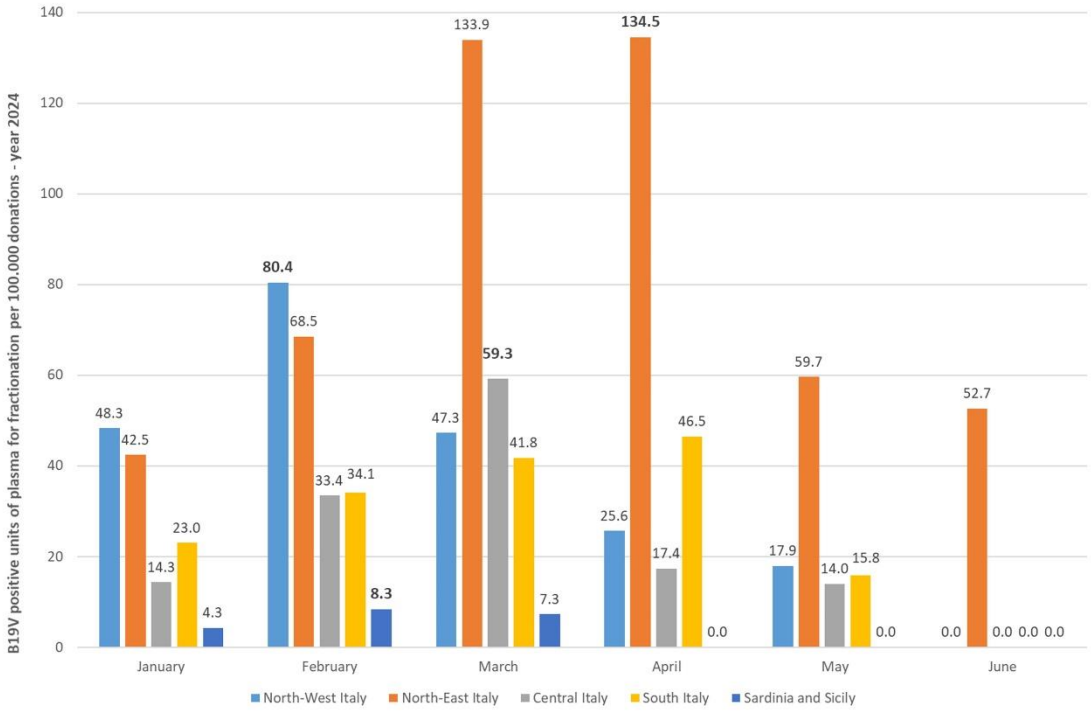

Figure 2. B19V positive units of plasma for fractionation per 100,000 units donated in Italy, per month and per geographical area, between 2018 - 2024.

Regional data analysis shows that in the first six months of 2024, B19V-positive units were found in the majority of Italian RAPs: 12/21 in January (with a minimum recorded in Sicily of 5.5 and a maximum in the Autonomous Province of Bolzano with 150.7 B19V-positive units per 100,000 units donated in the same month), 18/21 in February (with a minimum recorded in Sicily of 5.5 and a maximum in Piedmont with 171.1 B19V-positive units per 100 000 units donated in the same month), 16/21 in March (with a minimum recorded again in Sicily of 9.7 and a maximum in Umbria with a value of 363.3 B19V-positive units per 100,000 units donated during the same month), 9/21 in April (with a minimum recorded in Marche of 25.8 and a maximum in the Autonomous Province of Bolzano with 357.4 B19V-positive units per 100,000 units donated in the related month), 7/21 in May (with a minimum recorded in the Autonomous Province of Bolzano of 51.9 and a maximum in Liguria with 168.9 B19V positive units per 100,000 units donated in the same month). Eventually, in June (preliminary data) there are currently B19V-positive units only in Emilia-Romagna with a value of 245.5 B19V-positive units per 100,000 units donated during the reporting month.

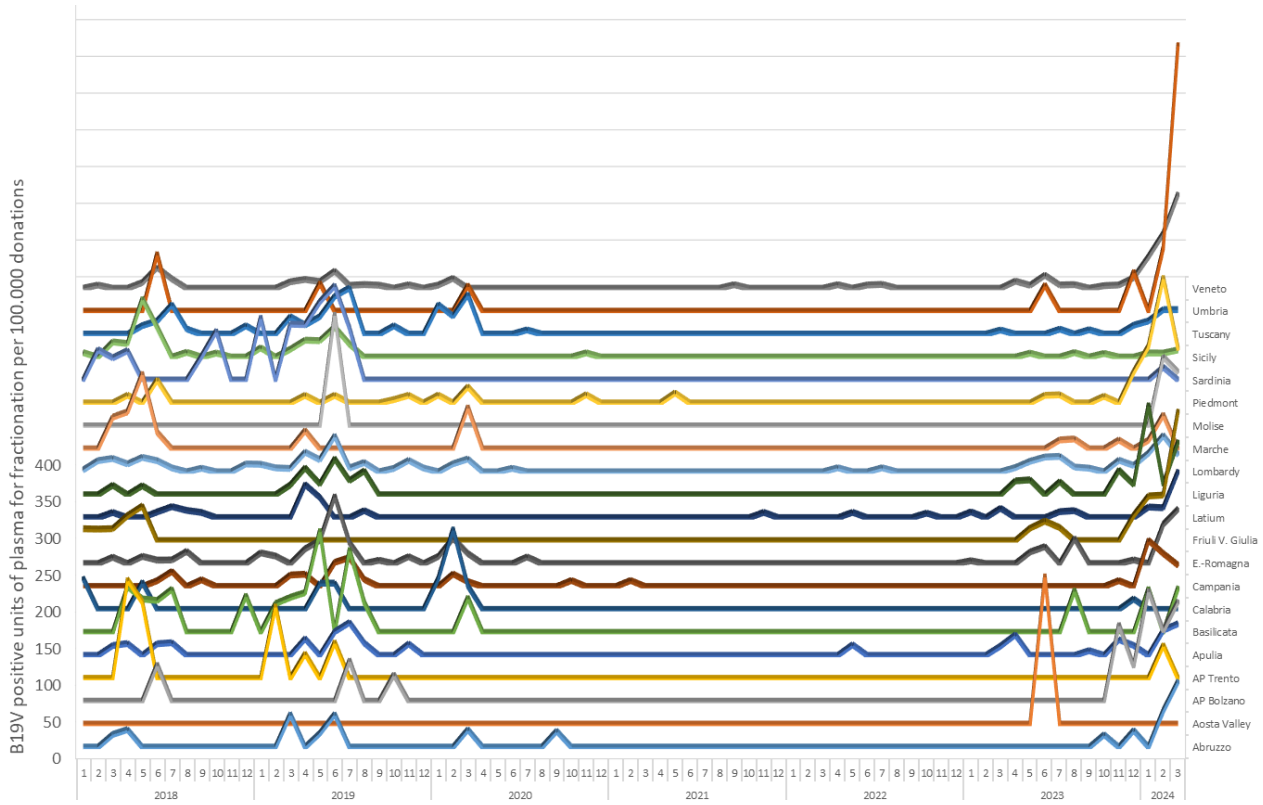

Figure 3. B19V positive units of plasma for fractionation per 100,000 units donated in Italy, per month and per Region and Autonomous Province, between 2018 - 2024.

Clinical impact assessment of Parvovirus B19 infection

B19V is a linear single-stranded DNA (ssDNA) virus (genome of about 5,000 bases) belonging to the family *Parvoviridae*, genus *Erythrovirus*; the non-envelope virion has an 18-25 nanometers diameter. To date, three different genotypes have been identified. The predominance of genotype 1 is observed on all continents, followed by genotypes 2 and 3. All three genotypes have been found in symptomatic and asymptomatic individuals and have been reported in several countries worldwide [1-10].

Several studies suggested that after primary infection in both symptomatic and asymptomatic individuals and in both immunocompromised and immunocompetent hosts, viral genomic DNA is detectable in tissues. Genotype 1 replicates restrictively in human bone marrow erythroid progenitors producing high viral load viremia. In contrast, the high viral load viremia of genotypes 2 and 3 has been identified only occasionally. The infection is generally benign in nature, especially in immunocompetent individuals, and possible sequelae, including haematologic sequelae, are extremely rare. Immunocompromised patients can take advantage of the availability of effective therapy by administering intravenous polyvalent human immunoglobulins [2,6-11].

During the acute phase of infection, which occurs about a week after transmission and persists for a very short time (about 5 days), viral DNA is present at high titres (up to 10^{14} IU/mL) in the blood, while IgG and IgM antibodies are absent. At the onset of symptoms, specific IgM begins to become positive, which is followed 13-18 days after infection by the production of specific IgG. IgM persists for 1-3 months (sometimes longer) and then stabilises; IgG generally persists for a lifetime. Viremia may persist months in immunocompromised individuals or in pregnant women with physiological immunodepression [1,2,4,6,9].

The incidence of B19V infection is typically seasonal. Infection induces an immune response that usually confers lifelong protection against reinfection. The likelihood of infection after exposure depends on previous immunity to B19V. Seroprevalence studies report a prevalence of 5-10% antibody positivity in young children, 50% in young adults, and more than 90% in the elderly; therefore, the probability of infection decreases with age [1,4,8-12].

Transfusion field

B19V transmission through Substances of Human Origin (SoHO) has been described in the literature through transfusion of red blood cells and platelets, treatment with plasma-derived medicinal products and haematopoietic stem cells (HSCs), and solid organ transplantation[1].

However, clinically significant B19V infection transmitted by transfusion appears to be a rare or undetected event, as indicated by data from several European countries. As an example, in the United Kingdom, only one case was reported between 1996 and 2022, and in Germany, no transfusion-transmitted B19V infection was reported between 1997 and 2017, in the absence of routine testing for this virus on donors during this period[1].

For the decade 2013-2023, Italian haemovigilance data report no cases of transfusion transmission by B19V. Literature data report a single documented case of transfusion transmission of B19V in a patient with major thalassemia in the 1990s [13].

Studies in blood donors have detected persistence of B19V DNA for months or years thanks to the use of more sensitive methods. High DNA concentrations have been detected as a viraemic peak in acute infection;

after the acute stage, the DNA concentration decreases rapidly, accompanied by the formation of potentially neutralizing IgG antibodies. Persistence of B19V DNA has been demonstrated in various tissues (liver, heart, tonsils, synovium) and it has been suggested that, after the acute phase, naked DNA is released from the tissues into the plasma. Therefore, positivity for B19V DNA detected in plasma collected from blood donors at 6 months after acute infection would detect only naked DNA strands, which may persist even years after infection, and not mature, infectious virions. Based on this assumption, most B19V-positive DNA donations, i.e., those with low DNA concentrations, might not be infectious to recipients, and the persistence of B19V DNA in donors after peak acute phase might be irrelevant [14-16].

Literature data report that transfusion transmissibility for B19V is at DNA levels of 10^5 IU/mL, and the concentration of DNA in blood products is often too low to infect the recipient (B19V DNA < 10^4 IU/mL). Moreover, after acute infection, the presence of B19V DNA in the donor is accompanied by presumably neutralising antibodies that also play a protective role for the recipient of his or her donation [9,15-20].

However, a Japanese study reports transmission of B19V infection through an erythrocyte concentrate with DNA levels of 5.1×10^3 IU/mL and the presence of IgG and IgM antibodies in donor plasma. In contrast, no B19V infection was observed after transfusion of 15 blood component units (eight red blood cell concentrates, four platelet concentrates, and three fresh frozen plasma samples) from donors with B19V DNA concentrations between 10^3 and 10^4 IU/mL of plasma [15].

Finally, although IgM is generally expected to appear during acute infection, in the case of B19V infection it is not always detectable during the viraemic peak. Therefore, screening for anti-B19V IgM would not seem to be suitable for identifying blood donations at risk of transmission of B19V infection [15].

Risk assessment

Given the exceptionally high number of B19V cases reported in the population in 14 EU/EEA countries, the ECDC conducted an infection risk assessment primarily on four population groups[1]:

- Risk for general population: assessed as low, as most infections result in mild childhood exanthematous disease, although the occurrence of some complications is not excluded.
- Risk for pregnant women: below 20 weeks' gestation is assessed as low to moderate, considering uncertainties about the circulation of the virus, the fact that an estimated 30-40% of women of childbearing age are susceptible to infection, and that serious outcomes occur in a small percentage of pregnancies with infection.
- Risk for immunocompromised individuals, including transplant patients: moderate, as these patients do not undergo viral clearance and may suffer from chronic anaemia, pancytopenia, graft loss or dysfunction, and organ-specific complications.
- Risk for individuals with chronic haematologic diseases (e.g., sickle cell anaemia, thalassemia, etc.): moderate, as B19V infection may cause transient aplastic crisis.

Differently from HBV, HCV and HIV 1/2 viruses, B19V infections have a substantially marginal public health impact in terms of transmission through clinical transfusion; it appears, however, to be more significant for plasma-derived medicinal products, because of both the potential "cumulative" risk that may arise in the composition of industrial pools consisting of thousands of units and the documented partial efficacy of viral inactivation methods (particularly the SD method) against non-capsulated viruses [21-25].

Indications for transfusion safety

On the basis of the aforementioned considerations made, which are supported by significant scientific literature, the introduction of the NAT B19V test on individual blood and blood component donations collected by blood establishments and blood collections units does not appear justified to date, without prejudice to the validity of the testing strategy of industrial mini-pools intended for the manufacturing of blood-derived medicinal products and SD virus-inactivated plasma.

Although B19V DNA has been detected for more than 6 months after seroconversion, the measured concentration appears to be low and the detection is probably based on naked DNA strands; moreover, it is accompanied by the presence of protective antibodies in at least all donors with ongoing B19V infection. In addition to this, there is also the assessment of the recipient's immune status, which, in about 70% of cases, would already be immune to B19V infection [14,15].

With reference to the above and in relation to the measures for labile blood component donation, the literature reports the experience of the Netherlands: blood components from a single donor can be considered "safe for B19V" if they come from donors tested positive for IgG B19V antibodies in two separate samples taken in an interval of at least 6 months. This approach would provide both greater protection of at-risk patient groups against potential transmission of B19V infection from donor detected positive and eligibility for donation after 6 months deferral[1][15].

The Guidelines in use in the United Kingdom[11], in addition to the deferral of donors who report close contact with B19V-infected individuals, report less restrictive criteria for the readmission of a positive donor: the donor is eligible to donate if more than 4 weeks have elapsed since both the resolution of systemic symptoms (fever, malaise, headache, nasal discharge, abdominal pain, sore throat) and a positive result for B19V DNA, where testing has been performed.

The indications on donor and recipient management made in the following paragraph aim at ensuring transfusion safety to protect donors' and recipients' health. The Working Group made these indications through an accurate analysis of both the available scientific evidence related to epidemiological trends in B19V infection and the guidance provided by international agencies.

Management of positive donor

Without prejudice to what is already stated in the Italian Ministerial Decree of November 2nd, 2015 and the EDQM Guide for the Preparation, Use and Quality Assurance of Blood and Blood Components with regard to the donor's history reporting contact with individuals with contagious diseases (exanthematous diseases, infectious mononucleosis, hepatitis A or others) in the past 4 weeks, having due regard to literature data, as an extremely precautionary approach to the recipient, the Working Group recommends to apply a deferral period of 6 months from the date of donation or in case of infection from donor history in absence of tests, for donors who turned out to be viraemic upon investigations conducted by the fractionation company or for donors reporting confirmed acute infection, respectively.

11 Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Parvovirus B19. Available at: https://www.transfusionguidelines.org/dsg/wb/guidelines/parvovirus-b19#:~:text=Must%20not%20donate%20if%3A, diagnosed%20through%20blood%20donation%20screening. Last access: 15 June 2024.

With reference to the aforementioned donor history of contact with B19V-infected individuals, deferral should be applied on the basis of the medical assessment, which will also take into account any previous history of B19V infection in the donor or the possibility that any contact occurred in the post-infectious stage (after the appearance of the rash).

Algorithm for look back activities following positivity reported by the fractionation company

In case of B19V positive plasma unit sent to the fractionation company, it is recommended to trace the recipient(s) of the labile blood components derived from the same transfusion unit from which the plasma subsequently sent for fractionation was obtained, recording the event within the management systems in use in the blood establishment.

Given that 70 percent of the adult population is already immunised against the virus and that the eventual course of infection in immunocompetent individuals is mostly benign or asymptomatic, it is not considered necessary to recommend further investigation; however, if the recipient belongs to moderate-risk categories according to ECDC indications (i.e. a. pregnant women; b. immunocompromised individuals; c. individuals with chronic hematologic diseases), it is recommended to collect evidence of any adverse events attributable to B19V transmission, in collaboration with the physician in charge of the recipient. Such evidence must be supported by documented and proven cause-and-effect relationship detectable through assessment of the immunologic status of the recipient(s) before and after the transfusion of labile blood components derived from the donation whose plasma was found to be viraemic.

If the above documented assessment leads to potential imputability, further investigation of the recipient is recommended, without prejudice to the obligation to notify on the National Blood Information System (*Sistema Informativo dei Servizi TRAsfusionali*, SISTRA).

In order to enable periodic monitoring of the epidemiological situation of B19V in the transfusion setting, the outcomes of positivity notifications, recordings and any subsequent documentary investigation should be reported every three months to the Regional Blood Coordinating Centres (RBCCs) for the purpose of making an overall regional report to be sent to the Italian National Blood Centre. The latter will then forward the aggregated data to the Ministry of Health.

Having due regard of the development of the epidemiological situation and the findings from other research studies, it is recommended that the Ministry of Health, through the Italian National Blood Centre, ensures a regular update of this technical document.

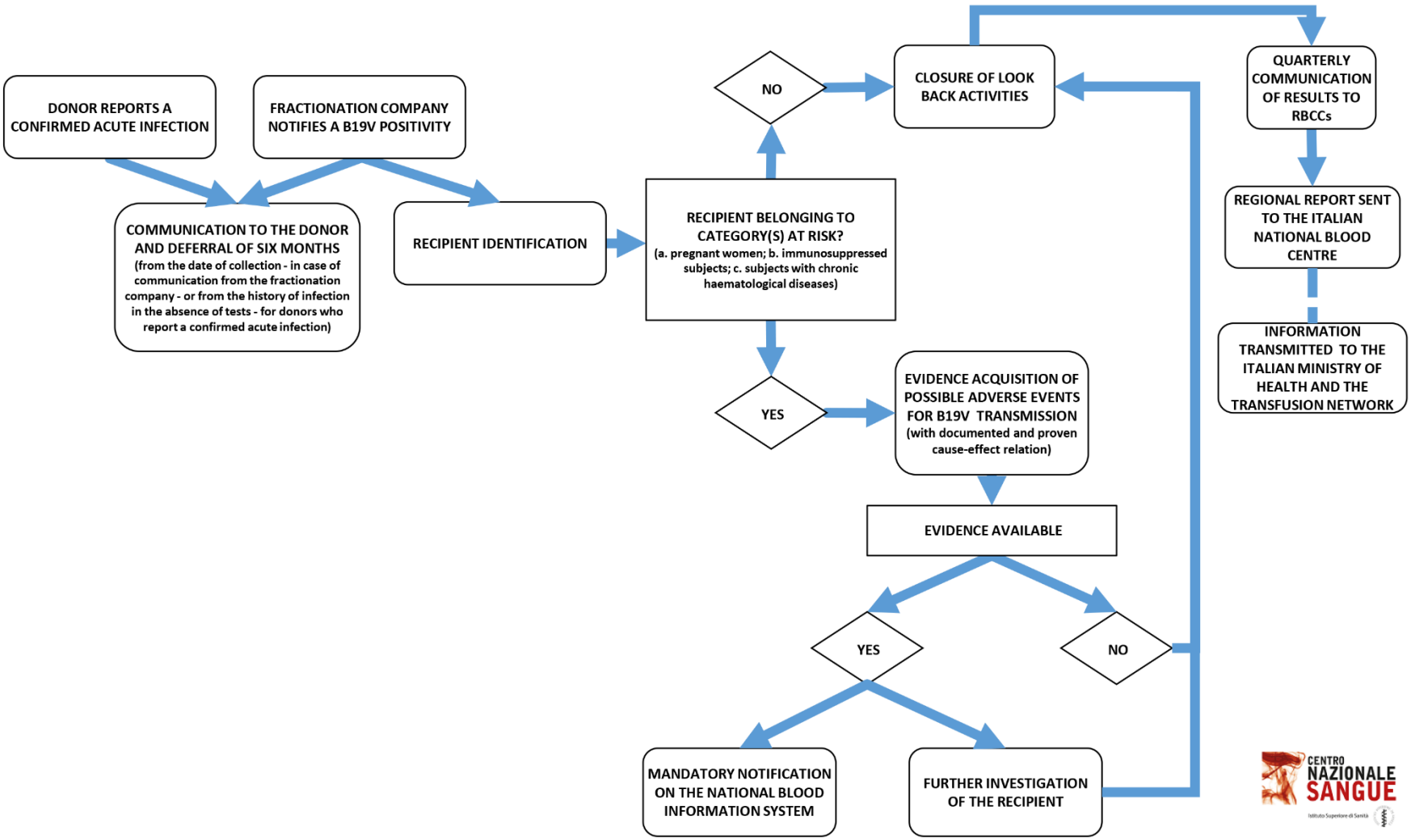

Figure 4. Algorithm for look back activities following a reported B19V positivity.

Medical-legal evaluations

A medical-legal analysis of the issue is also considered appropriate in order to elaborate useful indications for the best management of both the current epidemiological contingency and the individual positive cases of the material intended for fractionation obtained from a donor whose labile blood components have been transfused. Where possible, an attempt will also be made where to suggest indications about the readmission to donation of the B19V positive donor.

The appropriateness of this analysis is suggested by several normative assumptions, all aimed at recalling the overriding interest of the State in ensuring the healthcare safety[12], including the right of the citizen to be informed about the state of his or her health and to express an informed and valid consent to transfusion therapy, also in accordance with EU directives and guidelines. The consent takes into account the relationship between the expected benefits of the therapy and the correlated risks, considering that it is scientifically certain that transfusion therapy, however safe, can never be zero risk[13]. The efforts adopted for the prevention of such risks should obviously be commensurate with their predictability and preventability[14].

It is necessary to consider that the current situation (as better elucidated elsewhere in the document) does not yet have sufficient evidence to predict the future progress and spread of B19V infection, except for the evidence of cyclicality with infection rates that may reach an epidemic level every 3-4 years.

These characteristics show the need to follow precautionary and suitable recommendations to ensure transfusion activities safety according to Law No. 24 of 2017 and applying an **up-to-date** evidence-based scientific approach as well as carrying out an accurate surveillance of the phenomenon. Moreover, where possible, further investigations (e.g. autopsy, immunological, histopathological, etc.) on reported cases of transmission should be made in order to understand the real risk to patients, researching correlation and pathogenicity and/or any degree of severity in recipients at high risk of serious complications (pregnant women and immunocompromised individuals).

These recommendations can (and should) be updated on the basis of scientific knowledge on the phenomenon and its global and national trends evolution.

With reference to European and national legislation and according to the very recent ECDC-Threat Assessment Brief "Risk posed by reported increased circulation of human parvovirus B19 in the EU/EEA" dated June 5, 2024, there is no recommendation to perform NAT testing with regard to labile blood components. NAT testing is recommended and performed only on pools intended for fractionation for and only for reasons of systemic risk. It should be considered that, to date, no European authority has

12 Law No. 24 of 2017 (Provisions regarding the safety of healthcare and of the assisted person, as well as the professional responsibility of those practicing healthcare professions. Official Journal No. 64 of 17-3-2017) states at article 1: “The safety of healthcare is part of the right to health and is pursued in the interest of the individual and the community. The safety of healthcare is also achieved through implementation of all activities aimed at preventing and managing the risk associated with the provision of healthcare services and the appropriate use of structural, technological and organizational resources. (…)”.
13 Ministerial Decree of 2 November 2015 “Provisions on safety and quality requirement of blood and blood components” includes, among other indications, informed consent for transfusion, and instructions for signing: “(…) The patient candidate for the transfusion of blood components, informed in advance that this procedure may not be completely risk-free, is required to express his/her consent or dissent in writing, using the form referred to in paragraph G".
14 Article 40 of penal code relating to legal responsibility states: “Not avoiding an event, which one has the legal obligation to prevent, is equivalent to causing it", this provision is applied only to situations in which the risk of the event is foreseeable and preventable through the action, otherwise such provision would be inapplicable in a general context.

recommended a change in this analysis approach or given different and more restrictive indications on this point, so - at this time - it does not seem strictly mandatory to adopt a plan to perform NAT testing on all blood components intended for clinical use.

This consideration is also reached by examining the risk assessment carried out in the population of 14 EU countries showing a low risk for the general population also considering that in the majority of adult subjects (70-80%) anti-B19V antibodies are detected (of IgG class); this is an expression of previous exposure to the virus. In addition, there is an extreme rarity of cases of post-transfusion transmission of B19V infection and the benign nature of the disease, especially in immunocompetent subjects.

According to the ECDC, different considerations can be made for particular risk groups such as: pregnant women, immunosuppressed people, transplant patients, patients with chronic blood diseases such as hemolytic diseases who have a moderate risk. For these subjects, it seems possible to indicate that the scientific data currently available and the ECDC reports[1] recommend, in compliance with the Italian legislation on information and consent: firstly, an adequate information towards healthcare personnel also aimed at reporting doubtful or suspected cases with the objective of collecting as much information as possible on the phenomenon and, secondarily, a specific communication to the groups of patients at risk. In consistency with this logical construction, it appears useful to recommend that blood establishments that receive a notification of a positivity detected by the fractionation company (a notification that necessarily occurs after the transfusion of labile blood components) collect data regarding any patient transfused with the blood components derived from the notified units (documentary traceability). If the recipients belong to the risk groups indicated by ECDC, it is recommended to verify (also by recalling the patient) whether the recipient has experienced adverse events attributable to the post-transfusion infection and, if so, to report it as a possible adverse event to the transfusion, thus taking the necessary actions to confirm, or vice versa exclude the cause correlation.

As for to viraemic donors, in the presence of a potential persistent viremia of uncertain clinical significance, it appears appropriate to adopt a decision-making algorithm for the re-admissibility of the donor. This approach is recommended in order to prevent an objectively avoidable and foreseeable risk pursuant to *art. 40 of the penal code*, with particular regard to high-risk patients for whom the complications of a transfusion-transmitted infection can be severe.

Next actions

Given the absence of epidemiological data from B19V on the general population, the monitoring of the trend of positivity of plasma donations intended for fractionation was approved by the Working group established *ad hoc* by the Italian National Blood Centre.

Moreover, in order to better understand the epidemiology of B19V infection in the donor population, it is appropriate to carry out the molecular characterization of a statistically significant portion of B19V positive samples and to initiate a seroprevalence study on donors to better understand the distribution of the immunisation in different age groups.

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