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Research article

Human parvovirus B19 frequency among blood donors after an epidemic outbreak: relevance of the epidemiological scenario for transfusion medicine

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ABSTRACT

A retrospective, cross-sectional study was conducted to determine the frequency of human parvovirus B19 (B19V) infected individuals, viral loads and immunity among blood donors from Argentina, in a post-epidemic outbreak period. B19V DNA and specific IgG were tested in minimum study samples of donors attending a blood bank at Córdoba, Argentina, in 2014. Anti-B19V IgM and viral loads were determined in B19V-positive plasma samples. Seven of 731 samples (0.96%) resulted positive, corresponding to individuals aged 32–53 years, four of them repeat donnors and three first-time donors. Viral loads were $<10^3$ IU/mL. None had IgM and 6/7 had IgG, one of them at a high level (in the range of 100–200 IU/ml, and the remaining 5 at low to medium level, 5–50 IU/ml). Thus one case was classified as acute infection (DNA+/IgM-/IgG-) and six as potentially persistent infections (DNA+/IgM-/IgG+). No coinfections with other pathogens of mandatory control in the pre-transfusion screening were detected. Prevalence of IgG was 77.9% (279/358). This study provides the first data of B19V prevalence in blood donors in Argentina, demonstrating high rates of acute and persistent B19V infections and high prevalence of anti-B19V IgG in a post-epidemic period. Further research is needed to elucidate mechanisms/factors for B19V persistence as well as follow-up of recipients in the context of haemo-surveillance programs, contributing to the knowledge of B19V and blood transfusion safety.

1. Introduction

Human parvovirus B19 (B19V, *Erythroparvovirus primate 1* [1]) infection is associated with manifestations that vary depending on the host immunological and hematological status, but many infected subjects are asymptomatic or have mild, nonspecific symptoms. The virus tropism for erythroid progenitor cells, the high virus titer during the acute phase of the infection (usually 10^6–10^7 IU/ml B19V or higher) and the death of infected cells after the viral cycle is complete [2, 3, 4, 5] can lead to an acute cessation of red blood-cells production causing clinical conditions related to anemia, which can range from moderate to severe, even life-threatening [5, 6]. B19V is transmitted mainly by respiratory secretions and is mostly a childhood infection [6]. It can also be transmitted by transfusion, since there is no specific questionnaire to identify or suspect an infection in asymptomatic blood donors that could carry the virus [7]. In addition, B19V particle is extremely small and lacks an envelope, for which it is an agent difficult to eliminate by conventional methods (detergent, extreme pH, heat, filtration) [8]. Transmission, seroconversion, symptomatic and asymptomatic infections have been documented in patients treated with different blood products obtained from plasma and platelet concentrates from apparently healthy donors [9, 10, 11, 12, 13, 14].

B19V is considered a potential contaminant of blood transfusion products, since virus clearance studies have indicated that solvent detergent-treated plasma lots containing $>10^7$ IU/ml B19V DNA can transmit the virus to patients and seronegative volunteers [15]. On the other hand, in some individuals, B19V may persist and the viral genome remain detectable during many months at low ($<10^3$ IU/ml) or high titers ($>10^4$ IU/ml) [7]. Consequently, some blood donors can continue donating while carrying the virus (and potentially infectious virions) in

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their blood [3, 16, 17]. Thus, the potential risk of B19V infection for blood recipients should be surveyed.

B19V DNA prevalence varying from 0.2 to 1.9% has been reported among blood donors, and the concentrations determined are frequently $<10^4$ viral genome UI/ml [18, 19]. However, individuals with higher viral loads have also been detected [2, 19, 20, 21, 22, 23]. Thus, monitoring and characterizing the local B19V circulation can contribute to undertaking measures for safe use of blood. In Argentina, B19V epidemiology in blood banks is unknown and the screening of this agent is not routinely performed. Therefore, we aimed to determine the frequency of B19V DNA detection and the seroprevalence of B19V among local blood donors.

2. Methods

2.1. General design and ethical considerations

A retrospective, observational, cross-sectional study was accomplished, analyzing a randomly selected study sample of blood donors. The assays were performed in one plasma sample per individual (an aliquot of the blood collected at time of donation, obtained to perform pre-transfusion screening).

A minimum sample size was estimated to study B19V DNA prevalence using PCR. All PCR-positive samples were subsequently subjected to quantitative PCR and specific IgM and IgG testing to identify acute and persistent infections in the study population. Taking into account that all the individuals in the study group were asymptomatic, the following combination of immunological parameters were considered: I. DNA-positive/IgG-negative and IgM-positive or negative accounting for ongoing acute infection; II. DNA-positive/IgG-positive/IgM-positive, recent acute infection; III. DNA-positive/IgG-positive/IgM-negative was interpreted as long-term infection or potentially persistent infection.

Presence of specific IgG was also determined in a minimum study sample to estimate the seroprevalence of B19V among blood donors.

This study was performed in accordance with the principles of the Declaration of Helsinki and its supplements and was approved by the Ethics Committee of Hospital Rawson, Córdoba, Argentina (05082015).

2.2. Study sample

The study population included men and women aged 18–65 years who attended Fundación Banco Central de Sangre (FBCS) at Córdoba, Argentina, between July 1 and December 31, 2014. This period was selected for being a post-epidemic year, since during the previous year (2013) an epidemic outbreak of B19V had occurred. Considering 8,400 average donors attending FBCS in a 6-month period, a 95% confidence level, 5% error, and 10% expected loss, the maximized minimum study sample required was 408. For seroprevalence, the estimated IgG frequency was 70% [24] and the minimum sample size was 345.

2.3. Specimen collection, transport, processing, and storage

Individual plasma samples were randomly recovered from cryopreservation (-70 °C) at the blood bank and transported in biological secure packaging with ice to the Institute of Virology, where nucleic acid were extracted and then kept at -20 °C until testing. Different aliquots of each plasma sample were also conserved at -20 °C to perform serological assays and further independent DNA extraction and quantification.

2.4. B19V detection

Nucleic acids were extracted from 200 μL aliquots of plasma using guanidine thiocyanate lysis buffer and precipitation with silica [24, 25]. B19V DNA was determined in two independent repetitions by PCR, using 2-μl DNA extract in TE buffer with primers 5′CACTATGAAAACTGGGCAATAAAC and 5′AATGATTCTCCT GAACTGGTCC. The target is a 242-nucleotide NS1 fragment (2035–2276 on GenBank NC_000883.2), which was amplified at an annealing temperature set at 55 °C (35 rounds) [25]. The reaction contained 5% DMSO, 2.5 mM MgCl2, 0.8 mM nucleotide mixture, 0.2 μM each primer, and 0.02 U/μl Taq DNA polymerase in the provided buffer (Invitrogen). PCR products were visualized by electrophoresis in silver-stained 10% polyacrylamide gels [24, 25]. The technique was validated previously, using different panels of serum samples, such as 26 known B19V-positive specimens (by a nested PCR technique) [24] of which 25 were also positive with protocol used in the present study, and 35 known B19V-negative samples (25 random serum specimens and 10 serum with confirmed post-vaccine measles/rubella after MMR inoculation), all of which resulted negative, accounting for 96,2% sensitivity and 100% specificity.

2.5. B19V DNA quantification

After DNA extraction with commercially available columns following the instructions of the manufacturer (Qiagen), B19V DNA in samples identified as positive in the screening assay was tested by a quantitative real time PCR (qPCR). The procedure used a set of primers targeting a fragment of NS1 region from nucleotide 2082 through 2274 on GenBank AF162273, as described elsewere [26] and, as a reference, the international standard WHO/NIBSC UK EN63QG 1st International Standard 2000 Parvovirus B19 DNA 500,000 IU/ml (code 99/800). The qPCR assay was performed with TaqMan probes essentially as cited [26]. A linear range of quantification was established between 1×10^3 and 2×10^6 IU/ml of B19V DNA (results expressed IU as recommended [27]) in ABI PRISM 7500 (Applied Biosystems) equipment. The sensitivity (95% detection limit) of this qPCR assay was approximately 100 IU/ml. Each sample was tested in triplicate.

2.6. Serology

Ridascreen Parvovirus B19 IgG and IgM (R-Biopharm) ELISA tests for quantitative analysis of specific antibodies were used following the manufacturer's instructions.

2.7. Data analysis

Donor demographic data were obtained from donor cards. The results were described using frequencies, mean and standard deviation. Frequencies are described with odds ratio (OR) values and 95% confidence interval (95%CI). Significant differences were identified using Chi2 and Fisher's exact tests ($\alpha < 0.05$) when appropriate.

3. Results

3.1. Characteristics of the study population

Plasma samples from 731 donors were assayed by PCR. The age range of donors was 16–68 years (mean 34.6 ± 10.5, 95%CI: 33.8–35.4); 599 (82%) were <45 years old (estimated population odds 4.5, 95%CI 3.6–5.5) and 419 (57%) were male (estimated population odds 1.3, 95% CI 1.2–1.6). The sampling was distributed homogeneously through the entire study period (Figure 1).

In order to determine the seroprevalence (specific IgG), a subgroup of 358 plasma samples (randomly taken from the previous group) was analyzed by ELISA. They corresponded to blood donations between epidemiological weeks 25 and 51 of year 2014 (Figure 1) and the donor age range was 17–64 years (mean 35.0 ± 10.9, 95%CI 33.9–36.1); 289 (81%) were young adults (<45 years old, estimated population odds 4.2, 95%CI 3.2–5.4), and 192 (54%) were male (estimated population odds 1.2, 95%CI 0.9–1.4).

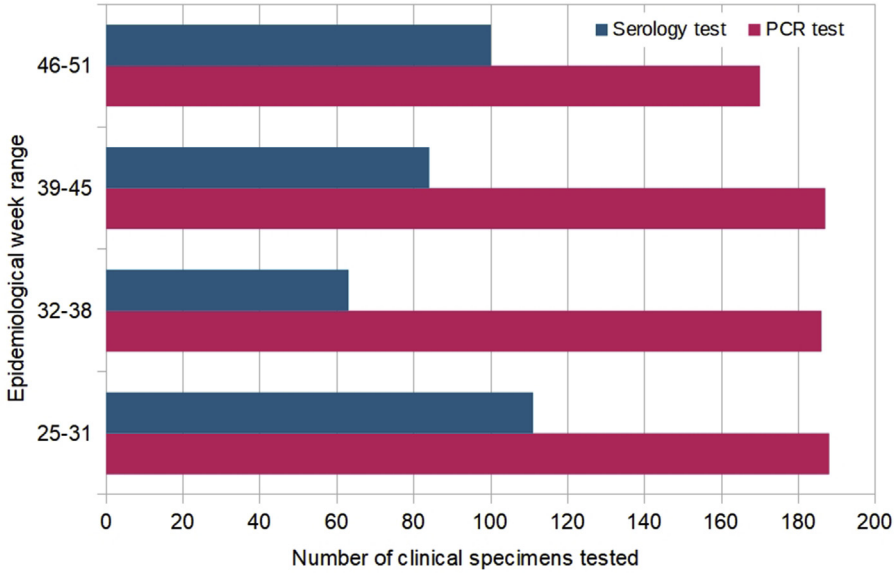

Figure 1. Number of plasma samples included per epidemiological week range for DNA (PCR) and IgG (serology) tests.

3.2. Detection of B19V, quantification and estimation of acute and persistent infections

B19V DNA was detected in seven of the 731 samples (0.96%, 95%CI 0.46–1.96%). All of them also had detectable viral DNA by qPCR, but concentrations under the limit of quantification. In addition, none had detectable anti-B19V IgM, while 6/7 were anti-B19V IgG-positive (of them, only one had high level IgG, in the range of 100–200 IU/ml, Table 1). Therefore, one donor had an ongoing acute infection and the other six were classified as long-term or potentially persistent infections (Table 1). The estimated rates of acute and long-term/persistent infections were 1.4 and 8.2 per 1000 donors, respectively. As shown in Table 1, given that none of these seven donors presented any co-infection with other pathogen of mandatory control in the pre-transfusion screening, the corresponding blood components were used for transfusion/production of blood derivatives.

3.3. Seroprevalence of B19V

Among 358 samples, 55 (15.4%) were anti-B19 IgG-negative, 279/358 (77.9%) were positive and 24/358 (6.7%) indeterminate. In the subgroup of IgG-positive individuals, 151 (54.1%) were male (estimated population odds 1.2, 95%CI 0.9–1.5) without statistically significant differences compared with positive women frequency ($p = 0.036$). There were no differences in the distribution of IgG-positive results according to age groups ($p = 0.9$) nor regarding epidemiological week ranges ($p = 0.5$), but the proportion of indeterminate results was significantly higher in older donors ($p < 0.0001$, OR 4.0, 95%CI 1.7–9.4), as shown in Figure 2.

4. Discussion

We demonstrate B19V infection by viral-DNA detection in 0.96% blood donors from Argentina, using a representative sample. Analogous frequency have been documented in Brazil (1.1%) [21], Chile (0.8%) [28], United Kingdom (0.9%) and Ghana (1.3%) [29], South Africa (0.9%) [19] and the United States (0.9%) [30]. At global level, the detection rate seems more variable: while some European countries have reported the lowest prevalence (The Netherlands, 0.06% [31] and Belgium, 0.16% [32]), the frequency depends on the series studied [18, 21, 22, 23]. Part of the differences can be assumed to be due to the primers, since the genetic diversity influences the detection of infection especially when nucleic acid based techniques are used [26, 33, 34]. But mainly the type of study and sampling and the natural variation in the circulation of B19V can be influencing the results. Being an endemic-epidemic infection, B19V incidence is shaped by spring

Table 1. Demographic and immunological features of B19V DNA-positive blood donors.

Sample number	Sex	Age (years)	IgG	[IgG] range IU/ml	IgM	Type of B19V infection	Pre-transfusion screening[1]	Type of donor		Destiny of blood components
								Repeat	First-time	
79	F	43	NEG	˂3.0	NEG	I	NEG	x		Plasma: manufacturing of blood products. Erythrocytes and platelets: transfusion.
93	F	32	POS	30.1–50.0	NEG	III	NEG		x	Donation interrupted due to bad tolerance.
101	M	50	POS	5.1–10.0	NEG	III	NEG	x		Plasma: manufacturing of blood products. Erythrocytes and platelets: transfusion.
166	M	39	POS	10.1–30.0	NEG	III	NEG	x		Plasma: manufacturing of blood products. Erythrocytes: transfusion.
353	M	53	POS	100.0–200.0	NEG	III	NEG	x		Erythrocytes and platelets: transfusion.
536	M	37	POS	30.1–50.0	NEG	III	NEG		x	Plasma: manufacturing of blood products. Erythrocytes and platelets: transfusion.
625	F	41	POS	30.1–50.0	NEG	III	NEG		x	Erythrocytes and plasma: transfusion.

[1] Pathogens included in pre-transfusion screening tests of local blood banks: Hepatitis B virus, Hepatitis C virus, HIV, HTLV, *Trypanosoma cruzi, Treponema pallidum*, and *Brucella spp*. NEG: negative; POS: positive. I. ongoing acute infection; III. long-term infection or potentially persistent infection.

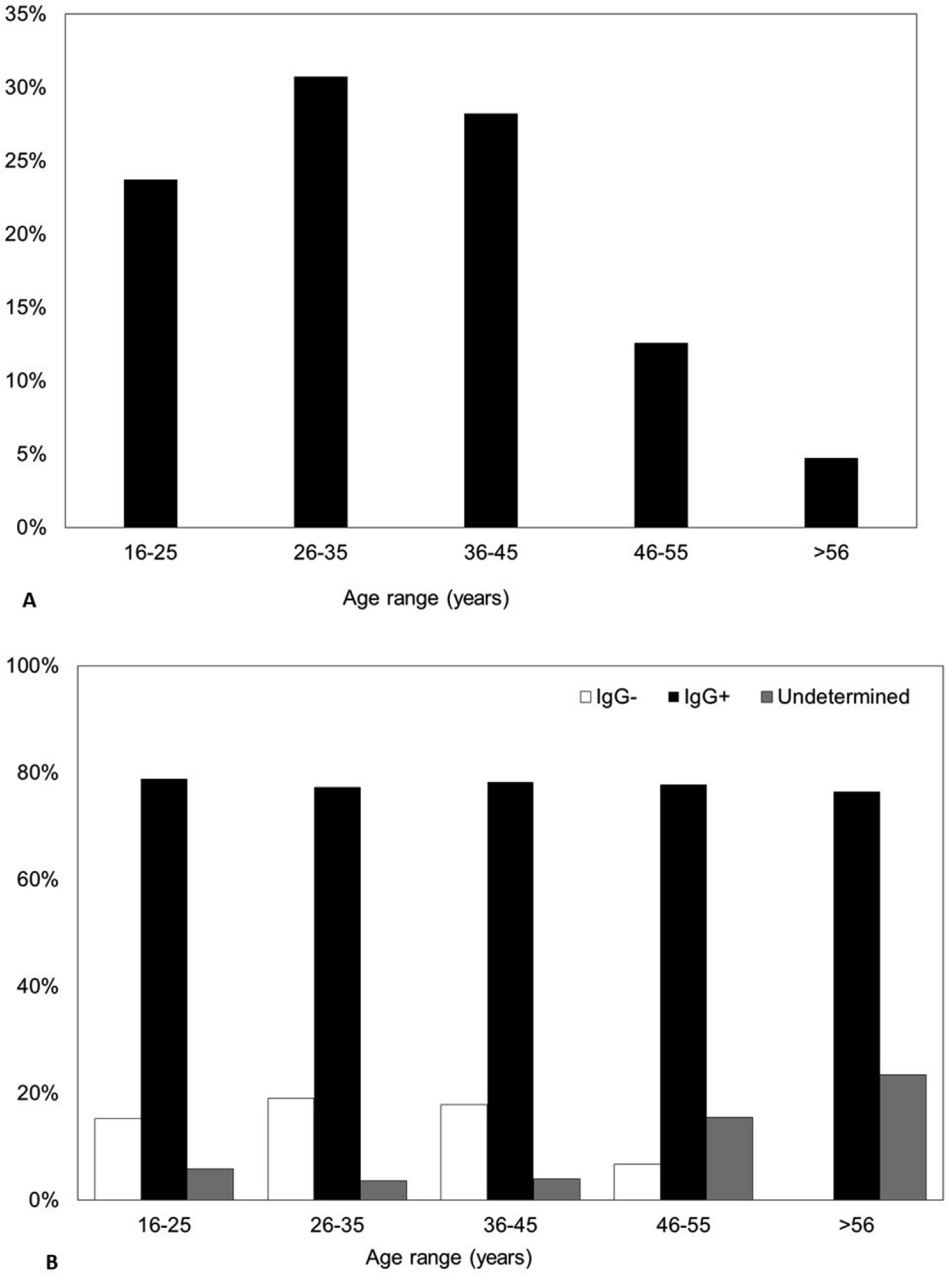

Figure 2. A. Age-range distribution of samples tested for anti-B19V-IgG. B. Age-range distribution of results.

outbreaks and major epidemics every several years [35, 36, 37]. The records in our country indicate epidemic outbreaks in the years 2007 and 2013 [24,38]. As 2014 was a post-epidemic year and B19V persistence in blood for up to two years has been confirmed [3], these factors can explain the high seroprevalence and viral DNA frequency in our study compared to others.

DNA-positive individuals were 32–53 years. This contrasts with the report from Ke et al. [39], where 21 of 23 positive donors were <35 years old. A high frequency of the virus in older donors might seem striking. However, persistent infections for long periods of time, decades and possibly life-long, have been reported [40, 41]. In line with this, in our series only one individual had ongoing acute infection while the remaining six had long-term/potentially persistent infections (all of them but one with low/medium levels of IgG). Less plausibly, the occurrence of asymptomatic re-infections could also be considered, although re-infections are rarely described events that have been confirmed in specific cases [42].

B19V was detected equally in first-time and repeat donors, which is sound given its transmission mainly through the respiratory tract (any type of donor would have a similar risk of acquiring the infection). In contrast, a higher prevalence of sexually transmitted and parenteral pathogens (HIV, *Hepatitis B virus, Hepatitis C virus*) has been demonstrated in first-time donors compared to repeat donors [43]. On the other hand, no coinfection with HIV, HBV, HCV, *Human T Lymphotropic Virus*, *Brucella* spp, *Trypanosoma cruzi*, or *Treponema pallidum* was detected in B19V-positive cases. Therefore, blood components from these individuals were considered suitable and used for transfusion or production of blood derivatives. This implies that recipient patients were exposed to a potential risk of infection through transfusion, particularly concerning direct blood transfusion.

Prevalence of specific IgG determined in a representative sample was 78%, which is higher than the local prevalence in asymptomatic controls in 2007 and 2012 [24,38] and the prevalence in Chile (55%), Brazil (60%), Australia and England (60%) [29, 44, 45, 46]. Some attribute a

higher prevalence in developing countries to widespread circulation and greater transmission of the virus in insufficient conditions of hygiene and bioprotection [21]. However a seroprevalence rate of nearly 100% in developed countries has also been reported [47], thus the differences observed can be linked to the variability in the circulation of the virus, as considered above. The local 2013 epidemic outbreak supports the high percentage of immune individuals in our 2014 epidemiological scenario.

As expected, anti-B19V IgG prevalence was not different between men and women [36, 44]. Regarding age distribution, the frequency of IgG-positive individuals was high and also not significantly different between age subgroups (76–79%). However, the frequency of individuals with an indeterminate result of IgG test increased significantly with age ($p < 0.0001$). This could indicate a decay of detectable levels of circulating antibodies in older adults long time after the primary infection, as observed by Candotti et al. [29]. In addition, given the possibility of vanishing specific immunity, we could in fact hypothesize about the possible occurrence of B19V reinfections in adults, which has been suggested by others [42, 48]. In this matter, further research on B19V-specific long-time immunity is required, since populations are increasingly long-lived accompanied by increasing probabilities of comorbidity. Consequently, older adults could be a risk-group of reinfection, both acquired in the community and by transfusion.

Among the seven B19V-positive individuals, one had no detectable specific antibodies and the rest had IgG (not IgM), which can be interpreted as one ongoing acute infection and six long-term or potential persistent infections. Thereby, local rates of acute and long-term/persistent infections found were high (1.4 and 8.2 per 1,000 donors, respectively). Viremic donors had B19V DNA under the limit of quantification (1×10^3 IU/ml). Unless it is a very early stage of infection, low viral load detected in donors having ongoing acute infections might not seem in agreement with what could be expected for this stage of infection (this applies for the one case classified as acute infection). In this regard, underestimation of viral load due to B19V genome polymorphisms leading to mismatches in primer binding regions is possible [26, 49]. Determination of viral loads should be achieved with a different molecular target assay, but currently, there is not any other available in Argentina. Moreover, the study of blood recipients should be considered in future haemo-surveillance programs in regional blood banks.

Direct transfusion of B19V-containing blood and blood components can infect a susceptible receptor. In this situation, transfusion transmission is associated to risk of anemia, particularly in vulnerable recipients (non-immune pregnant women and immunosuppressed/transplant patients) in whom different moderate to severe diseases can occur after B19V-induced depletion of erythrocyte precursors [50, 51, 52, 53]. Even when blood units from B19V viremic donors from our study might have been used for transfusion, reception of more than one blood unit dilute the virus and also passively immunize with neutralizing antibodies. In this situation the risk of B19V transfusion transmission is low, mainly due to the high IgG frequency. However, it should be reminded that is a variable scenario (specific of post-epidemic periods), and both the rate of DNA and specific IgG can fluctuate yearly.

For pooled-plasma products, FDA recommends B19V nucleic acid testing to identify and prevent the use of plasma units containing B19V DNA. No B19V transmission from pooled-plasma products has been documented when less than 10^4 IU/ml B19V DNA are present in an infused product, thus the proposed limit of 10^4 IU/ml for the production of plasma pools destined for all plasma derivatives. In contrast, measures to avoid potential B19V transmission by single donation blood products have not been established so far in many countries, although the first cases of transfusion-transmitted B19V infection were reported in the 90s [7]. Since after acute infection B19V DNA can remain detectable in blood for months to years [3], in a repeat-blood donor population this could mean that multiple consecutive B19V DNA-positive donations can be taken from a single donor. In addition, in our series all viremic donors had undetectable IgM, thus strategies to avoid transfusion-transmitted B19V cannot be based on serological screening (anti-B19V IgM is undetectable very early in the infection and in persistent infections). Taking this into account, the molecular screening of blood seems to be the most efficient method to avoid B19V.

In conclusion, this study demonstrates the occurrence of high rates of acute and long-term or persistent B19V infections, as well as a high prevalence of anti-B19V IgG, among blood donors in a post-epidemic period. It also provides the first data on the prevalence of B19V in this population in Argentina. Further research is needed to elucidate the mechanisms and factors influencing B19V persistent infection, as well as follow-up studies of recipients in the context of haemo-surveillance programs.

Declarations

Author contribution statement

M. Adamo and S. Blanco: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

H. Carrizo and S. Gallego: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

F. Viale, S. Rivadera, G. Rodríguez-Lombardi and M. Pedranti: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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