Review Article

Human parvovirus B19 research concerning the safety of blood and plasma derivatives in China

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Abstract: Human parvovirus B19 (B19V) is a common human pathogen which is associated with a broad spectrum of clinical manifestations. Since B19V can be transmitted via blood and plasma derivatives, it has been considered to pose great risk in transfusion safety. Since the early 21st century, European Pharmacopoeia, the Plasma Protein Therapeutics Association and U.S. Food and Drug Administration have proposed a list of guidelines to reduce the risk of B19V transmission by plasma derivatives. In terms of blood, some countries implement management measures on B19V to maximize the safety of blood transfusion. In China, no related documentation for monitoring B19V has been issued. The aim of this review is to discuss the risk for B19V transmission through blood and plasma derivatives in China. The issues raised with the intention to contribute to further development of risk management measures.

Keywords: Human parvovirus B19 (B19V); blood safety; plasma derivatives; China

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Human parvovirus B19 (B19V) was discovered in the sera of normal blood donors while screening for hepatitis B virus in 1975 (1). Although B19V infection generally runs its course without any problems in healthy individuals, it can result in serious complications in patients with underlying hematological disorders or immunodeficiency (2,3). Due to its pathogenicity and risk of transmission through blood and plasma derivatives, great concerns have been raised on this virus (4). In some countries, guidelines have been developed and proposed for screening tests or eliminating B19V in order to maximize the safety of blood and plasma derivatives. While in China, no regulations or recommendations for monitoring B19V are available at present. However, great efforts have been made to investigate the epidemic status and characterization of B19V circulating in China, thus abundant data are being accumulated for further assessment of the viral safety of blood and plasma derivatives, as well as for policy making. In this report, we reviewed the prevalence and the level of B19V in Chinese blood donors and plasma donations as well as plasma derivatives.

Features of human parvovirus B19

B19V belongs to the *Erythroparvovirus* genus within the *Parvoviridae* family. It is a small (around 20 nm diameter), non-enveloped single-stranded DNA virus of approximately 5,600 nucleotides (5,6). The capsid consists of two structural proteins: viral protein 1 (VP1) and 2 (VP2). VP2 is the major capsid protein and constitutes 95% of the capsid composition. VP2 alone can assemble virus-like particles. VP1 is the minor capsid protein and it is not necessary for capsid formation. But VP1 has an additional 227 aa at the N terminus compared with VP2, known as

VP1 unique region (VP1u), which contains critical elements for virus entry, especially an original phospholipase A2 (PLA2) domain. B19V also encodes non-structure protein NS1, a multiple functional protein that is essential for the replication of B19V DNA and regulation of gene expression that is cytotoxic to host cells (7,8). In addition, the genome also encodes three smaller nonstructural proteins, i.e., 7.5, 9 and 11 kDa.

B19V is currently classified into 3 genotypes (genotype 1, 2, 3), which were defined as having greater than 10% divergence in overall DNA sequence (9). Within genotypes 1 and 3, two distinct subgroups were identified by phylogenetic analyses, respectively (10,11). All these three genotypes appear to circulate. However, their relative frequencies are strikingly different and their spatial and temporal distribution is not uniform (12). Genotype 1 circulates worldwide and can be found in most parts of the world (13). Genotype 2 is relatively rare. It has only been reported sporadically in several European countries, Brazil and the United States (14-18). Genotype 3 seems to be endemic in Ghana but has also been identified in Brazil, North India, China and the United States (9,19-23). Despite the genome-wide variations among them, these three B19V genotypes are assumed to have similar biological properties, transmission routes, and pathogenic capacities. In the clinical setting, they pose a similar diagnostic challenge (24,25).

B19V is a common virus that spreads worldwide. It is normally transmitted through the respiratory route. It can also be transmitted vertically and through bone marrow and organ transplantations as well as via transfused blood and plasma derivatives (26-28). Viremia occurs 1 week after exposure to the virus and virus titers peak within the first 2 days. Viremia usually lasts about 5 days. In acute infection, the virus titer could reach 10^{14} IU/mL in peripheral blood (29). B19V specific IgM antibodies are detectable 10 to 14 days after infection and can generally persist for 5 months. However, in some patients, the IgM antibodies can last even longer. IgG antibodies against B19V usually appear about 15 days after infection, remain high for several months and persist long-term. The seroprevalence of B19V is age dependent, increasing from 15% in preschool children to 50% in younger adults and to about 85% in the elderly (30).

B19V is the first parvovirus demonstrated to be pathogenic in humans. It causes diverse clinical manifestations, whose characteristics and outcomes mostly depend on the immune and physiological status of the infected individuals: asymptomatic or just some self-limiting illnesses in the normal population, transient aplastic crisis in patients with hematological problems, chronic anemia in immunodeficient patients, and abortion or non-immune hydrops fetalis in pregnant women. B19V could be also involved in the induction or pathogenesis of numerous autoimmune diseases, notably rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (3).

Human parvovirus B19: relevance with transfusion safety

B19V can be transmitted through blood and plasma derivatives. In fact, B19V transmission by transfusion of blood is rare due to its low prevalence in blood donors. Thus, screening of blood donors for B19V infection is not routine. Some countries including Japan, Germany, and Netherland implemented relative measures to mitigate the risk of B19V transmission so as to make blood transfusions as safe as possible.

In September 1997, Japanese Red Cross (JRC) introduced a receptor-mediated hemagglutination assay as a screening test for B19V. This assay has been used for all donated blood until 2007. Since 2008, with an aim to improve assay sensitivity, the hemagglutination test has been replaced by chemiluminescent enzyme immunoassay, with the sensitivity of approximately $10^{6.3}$ IU/mL with the genotype samples and $10^{6.4}$ IU/mL with B19V DNA-positive donor samples, respectively (31).

In Germany, screening for B19V DNA in blood donors began in the year 2000. Minipool real-time NAT (testing in a minipool format of up to 96 donations) was introduced to do such screening. Blood products with B19V DNA virus load $\geq 10^5$ IU/mL were discarded. In contrast, minipools with B19V DNA virus load $<10^5$ IU/mL were not resolved, and all blood products contained were released. In any case, donors were not informed about their B19V infection and were allowed to give subsequent donations (32).

In Netherlands, Health Council proposed a high-risk-group approach for cellular blood products, meaning that "B19V safe" cellular blood products (ones from a donor in which B19V specific IgG antibodies have been detected in two separate blood samples, one taken at least 6 months after the other) be administered to risk groups: pregnant women (except in the case of transfusions given during birth), patients with congenital or acquired hemolytic anemia who have no detectable B19V specific antibodies and patients with cellular immunodeficiency who have no

detectable B19V specific antibodies (33).

Since source plasma pools for manufacturing plasma derivatives are consisted of thousands of plasma derivatives, even one donation with B19V could contaminate the entire pool. In some cases, acutely infected blood donors, with extremely high viremic levels of B19V but without symptoms, are not recognized and thus allowed to donate blood or plasma, resulting in a considerable risk of B19V transmission via plasma derivatives. What's more, because of its small size and lack of envelope, B19V is difficult to be completely inactivated and/or removed. Therefore, limiting the viral load of B19V in the source plasma pools is crucial for reducing the risk of B19V transmission via plasma derivatives (34,35).

In order to counteract the transmission of B19V via plasma derivatives, since the early 21st century, U.S. Food and Drug Administration (FDA), European Pharmacopoeia (Ph. Eur.) and the Plasma Protein Therapeutics Association (PPTA) have issued a list of guidelines, proposing a limit of 10^4 IU/mL for levels of B19V DNA in manufacturing pools destined for making some or all kinds of plasma derivatives (36-39). Since all B19V genotype variants can be contaminants, the NAT assay for screening B19V DNA is required to be able to detect all three genotypes of B19V (40,41).

In China, neither specific documentation nor technical guidelines for monitoring B19V have been issued.

Human parvovirus B19 in Chinese blood donors

To our knowledge, Cai *et al.* presented the first report on the detection of B19V infection among Chinese blood donors in Zhaoqing in 1999 (42). Since then, abundant data with respect to the prevalence of B19V are being accumulated in different parts of China, especially in Southwest China, South China and Central China.

Data regarding the prevalence of B19V specific IgG and IgM among Chinese blood donors are shown in *Table 1*. The rate of B19V IgG-positive blood donors serves for the assessment of the rate of donors who have had a past infection.

The seroprevalence differs between 10.53% and 55.43% in different cities with the lowest incidence been found in Liuzhou (43) and the highest incidence in Changchun (56). However, Hou *et al.* detected B19V IgG in 41.38% of 58 blood donors in Liuzhou (44), showing significantly different incidence rate in the same city. There was the same scenario for Luoyang: Ke *et al.* detected B19V IgG in 43.40% of 106 blood donors (43), while Hou *et al.* detected only in 13.79% of 58 (44). Since testing for B19V specific antibodies was performed with the same commercial assay kit of parvovirus IgG/IgM in these studies, the significant different incidence rate in the same city might be partly due to the differences in the size of the study population and the years of sample collection. In Chinese blood donors, the prevalence of IgG antibodies against B19V increases with age (47,49,53,57). In most studies, approximately 30% of 18- to 30-year-old subjects have detectable IgG, while about 60% of around 50-year-old subjects are seropositive (57). However, the B19V IgG prevalence of blood donors in Xiamen seems lower than that of blood donors at the same age in other cities (53).

The rate of B19V IgM-positive blood donors serves for the assessment of the rate of donors who were infected with B19V recently. In China, the prevalence of B19V IgM in healthy blood donors varies from 0.54% (51) to 15.22% (46) in different cities, except Chongqing in Hou Y's study (none of 60 samples tested was B19V IgM positive) (44), with the lowest incidence found in Foshan and the highest incidence in Shenyang. The current studies showed an insignificant effect of age on the incidence of seropositive IgM.

Studies have also been carried out to determine the prevalence of B19V DNA in blood donors. An overview about the prevalence and levels of B19V DNA in blood donations are provided in *Table 2*. In most studies, the prevalence of B19V DNA is usually very low, varies from 0.02% (58) to 6.80% (52), except in Wuhan study (20.91%, 23/110) (60); and DNA concentration in these positive samples has been detected to be low ($<4.89\times10^5$ IU/mL plasma). Acute B19V infections with high DNA concentrations in Chinese blood donors seemed to be rarely detectable. Using phylogenetic analysis, Ke *et al.* demonstrated the circulation of B19V Genotype 1 in Chinese blood donors. Genotype 2 and 3 have not been detected in their study (43).

The prevalence of B19V IgM and B19V DNA in blood donors is usually lower than that of IgG in these studies, suggesting that acute B19V infection in Chinese blood donors is in the minority.

Human parvovirus B19 in Chinese pooled plasmas and plasma derivatives

In China, all the plasma for manufacturing into plasma derivatives are collected from plasma donors. The plasma recovered from the whole blood collected from blood

Table 1 The prevalence of human parvovirus B19 reported in blood donors

Region	Province	City/county	Yr(s) of sample collection	Seroprevalence of B19V				Reference
				IgG (%)	IgM (%)	IgM and IgG (%)	No of investigated donors	
Northwest China	Xinjiang	Urumqi	Apr. 2008–Aug. 2009	24.78	7.96	2.65	113	(43)
			Jan. 2013–Feb. 2014	22.41	1.72	–	58	(44)
Southwest China	Yunnan	Kunming	Apr. 2008–Aug. 2009	20.87	1.74	0	115	(43)
	Sichuan	Chengdu *et al.*	2009	32.61	7.61	2.17	92	(45)
		Mianyang	Jan. 2013–Feb. 2014	0	1.72	–	58	(44)
	Guizhou	–	–	52.50	15.00	–	40	(46)
	–	Chongqing	Oct. 2012–Sep. 2013	36.68	5.07	1.90	1,104	(47)
			Oct. 2012–Sep. 2013	36.70	5.59	1.86	752	(47)
			Jan. 2013–Feb. 2014	41.67	0	–	60	(44)
Central China	Henan	Luoyang	Apr. 2008–Aug. 2009	43.40	10.38	5.66	106	(43)
			Jan. 2013–Feb. 2014	13.79	1.72	–	58	(44)
		Zhengzhou	Mar. 2015–Mar. 2016	32.98*		–	1,046	(48)
	Hubei	Wuhan	–	47.69	10.65	–	216	(46)
		Yichang *et al.*	Sep. 2013–Nov. 2013	43.36	2.46	–	934	(49)
South China	Guangxi	Liuzhou	Apr. 2008–Aug. 2009	10.53	7.89	1.75	114	(43)
			Jan. 2013–Feb. 2014	41.38	3.45	–	58	(44)
	Guangdong	Guangzhou	Mar. 2004–Feb. 2005	38.58	1.88	0.28	1,760	(50)
		Foshan	–	25.00	0.54	–	368	(51)
		Lianshan and Liannan	–	29.26	–	–	–	(52)
East China	Fujian	Xiamen	May 2013–Nov. 2013	16.79	4.64	–	1,078	(53)
		–	–	38.10	3.57	–	56	(54)
	Shandong	Jining	2013–2014	36.15	5.94	4.69	960	(55)
North China	–	Tianjin	–	31.60	7.36	–	326	(46)
Northeast China	Jilin	Changchun	Mar. 2005–Apr. 2005	55.43	–	–	–	(56)
	Liaoning	Shenyang	–	24.28	15.22	–	276	(46)

*, positive samples were B19V IgG or IgM positive.

donors are not allowed for manufacturing. Data about the prevalence of B19V in Chinese plasma donors are lacking. However, the prevalence of B19V in plasma donors seems to be similar to that in blood donor population. Han *et al.* compared the prevalence of B19V between plasma donors and blood donors, and results showed that the prevalence of B19V DNA was 0.06% in blood donors and 0.079% in source plasma donors, respectively and there was no significant difference between them (58).

There are 29 manufacturers for plasma derivatives in China. NAT screening of source plasma pools for B19V has not yet been implemented in the manufacturing. According to the reports listed in *Table 3*, there were great differences among the positive rates of industrial plasma

Table 2 The prevalence of human parvovirus B19 DNA reported in blood donors

Region	Province	City/county	Yr(s)of sample collection	Prevalence of B19V DNA (%)	No of investigated donations	Viral load among positive samples	Reference
Northwest China	Xinjiang	Urumqi	Apr. 2008–Aug. 2009	0.72	836	2.13×10^3–4.93×10^4 IU/mL	(43)
			Jan. 2013–Feb. 2014	2.42	413	2.66×10^2–7.20×10^4 copies/mL	(44)
Southwest China	Yunnan	Kunming	Apr. 2008–Aug. 2009	0.28	1,075	7.90×10^2–1.56×10^4 IU/mL	(43)
	Sichuan	Chengdu *et al.*	2009	0	92	–	(45)
		Mianyang	Jan. 2013–Feb. 2014	0	479	0	(44)
		–	Jul. 2012–Dec. 2012	0.02	5,030	4.89×10^5IU/mL	(58)
	–	Chongqing	Oct. 2012–Sep. 2013	0.40	752	1.10×10^2–2.80×10^3 copies/mL	(47)
	–		Jan. 2013–Feb. 2014	0.37	1,611	3.73×10^2–1.59×10^3 copies/mL	(44)
South China	Guangdong	Foshan	–	4.26	94	–	(51)
		Lianshan and Liannan	–	6.80	147	–	(52)
		Zhaoqing	Nov. 1996–Dec. 1997	5.08	374	–	(42)
		–	Dec. 2013–Dec. 2014	0.27	6,000	–	(59)
	Guangxi	Liuzhou	Apr. 2008–Aug. 2009	0.28	1,075	7.90×10^2–1.56×10^4 IU/mL	(43)
			Jan. 2013–Feb. 2014	0.60	667	3.68×10^2–1.45×10^3 copies/mL	(44)
Central China	Hubei	Wuhan	Mar. 2000	20.91	110	–	(60)
	Henan	Luoyang	Jan. 2013–Feb. 2014	0.16	624	2.72×10^2 copies/mL	(44)
			Apr. 2008–Aug. 2009	1.24	1,051	2.48×10^2–4.65×10^4 IU/mL	(43)
North China	Jiangsu	–	Jul. 2001	2.67	600	–	(61)
	Fujian	Xiamen	May 2013–Nov. 2013	0.06	10,452	3.59×10^2–1.07×10^4 IU/mL	(53)
East China	Shandong	Jining	2013–2014	2.23*	359	–	(55)
		Linyi	Jan. 2009–Jun. 2009	6.65	632	–	(62)
		–	Oct. 2006–Oct. 2007	6.33	300	–	(63)

*, prevalence of B19V DNA in B19V IgG or IgM positive blood donors.

pools in China, ranging from 5.45% (9/165) (59) to 100% (10/10) (64). Such diversities are likely to reflect geographic differences in the circulation of B19V in diverse parts of China, methodological differences in screening procedures, differences in sample size, or differences in number of plasma units within each pool sample.

In previous reports, we investigated the prevalence and genotypic characterization of B19V in plasma pools used in the manufacture of plasma derivatives. By using an in-house qPCR assay for simultaneous detection of all three genotypes of B19V, 71.91% (169/235) of plasma pools were confirmed to be contaminated by B19V DNA, with the concentrations of 5.18×10^2–1.05×10^9 IU/mL. Approximately 31.95% of the B19V DNA-positive samples were $<10^4$ IU/mL, while 68.05% contained $>10^4$ IU/mL (34). Further phylogenetic analysis of B19V DNA derived from source plasma pool samples showed that there were B19V 1a, 1b and 3b, putative 1a/3b recombinants and unclassified strains circulating in China (23).

Because of the resistance of B19V to most viral inactivation procedures used in manufacturing of plasma derivatives, B19V DNA can always be detected in various

Table 3 The prevalence of B19V DNA in plasma donors, plasma pool samples for fractionation, and plasma derivatives

Study author and year of publication	Prevalence of B19V DNA								
	Plasma donors	Plasma pools	F VIII	PCC	IVIG	Fibrinogen	Thrombin	Albumin
Wu Y, 2009 (64)	–	100% (10/10)	75% (12/16)	–	–	–	–	–
Hou JF, 2012 (65)	0.09% (6/6,505)	82.41% (89/108)	67.86% (38/56)	78.79% (26/33)	0 (0/84)	45.83% (11/24)	–	–
Zhang W, 2012 (66)	–	54.23% (77/142)	54.29% (19/35)[b]	70.59% (12/17)[b]	6.45% (10/155)[a], 38.9% (21/54)[b]	85.71% (6/7)[b]	–	30% (3/10)[a], 0 (0/50)[b]
Zheng RB, 2015 (59)	–	5.45% (9/165)	7.41% (4/54)	10.34% (6/58)	0(0/55)	5.66% (3/53)	–	–
Han T, 2015 (58)	0.04% (2/5,040)	–	–	–	–	–	–	–
Zeng FX, 2015 (67)	0.03% (3/10,150)	23.73% (14/59)	–	–	0 (0/4)[c], 0 (0/16)	–	–	0 (0/4)[c], 0 (0/15)
Jia JT, 2015 (68)	–	59.49% (116/195)	93.55% (29/31)	88.89% (8/9)	–	100% (10/10)	85.71% (6/7)	–
Jia JT, 2015 (34)	–	71.91% (169/235)	–	–	–	–	–	–

[a], samples collected in the period 1993–1995; [b], samples collected in the period 2009–2011; [c], samples were produced from pooled plasma with B19V DNA positive plasma pools sample.

plasma derivatives, particularly in coagulation factors.

Table 3 summarizes the prevalence of B19V DNA in Chinese plasma derivatives. In most reports, factor VIII, prothrombin complex concentrate (PCC), fibrinogen and thrombin were found to be highly contaminated with B19V DNA, with the prevalence rates of 54.29–93.55%, 70.59–88.89%, 45.83–100%, and 85.71%, respectively. However, an extremely lower prevalence in factor VIII, PCC, and fibrinogen produced by 2 manufactures located in South China has been reported by Zheng *et al.* This unexpected finding might be attributed to the lower prevalence of B19V DNA in these regions (59).

Intravenous immunoglobulin (IVIG) and albumin are comparatively safe, and B19V DNA is less frequently detected in these products and, when detected, the levels are usually low. In Zhang W's study, low levels of B19V DNA were detected in 3 of 10 batches of albumin produced during 1993 to 1995, while no B19V DNA was detected in 50 batches of albumin produced during 2009 to 2011. For IVIG, although the ratio of B19V DNA positive IVIG produced during 2009 to 2011 was significantly higher than that produced during 1993 to 1995, IVIG were moderately contaminated with low levels of B19V DNA (66).

Future and perspective

Despite the frequent detection of B19V DNA in blood donors and pooled plasmas, as well as plasma derivatives, there is no suspected transfusion-transmitted B19V infections in China. This could be explained by the fact that most recipients already have B19V specific antibodies due to previous infections and that many B19V DNA-positive plasma derivatives were also positive for the presence of B19V specific antibodies, resulting in neutralization of the virus. Another possible explanation is that B19V infections were underreported, because many of the infections are clinically inapparent, or because the role of B19V infection in the etiology of some diseases was not recognized. Thus, the risk for B19V transmission through blood and plasma derivatives in China should not be neglected.

Despite abundant data regarding the prevalence of B19V in Chinese blood donors and plasma derivatives have been reported, continued evaluation of the incidence and genotypic characterization of B19V are also required to support decision making on whether limit for blood and plasma derivatives should be proposed in China.

In the case of blood, it might cost much time and money to test all blood donors for the presence of B19V. According

to Netherland's measure (33), a less expensive option is the risk-group approach, in which "B19V safe" blood would only be given to those patients for whom infection with B19V would pose a serious health risk. Adoption of this differentiated approach would obviate the need to test all blood donors for infection with B19V.

In the case of plasma derivatives, the implementation of a universal B19V NAT screening as an in-process test for source plasma is highly recommended. If the introduction of screening for B19V is under consideration or required by a national authority regulating blood program, it is necessary to establish a cutoff level for screening. In addition, since the co-existence of B19V 1a, 1b and 3b, as well as putative B19V 1a/3b recombinants in Chinese plasma donations, B19V NAT assay used in the manufacturing of plasma derivatives must be able to detect all B19V variants circulating in China.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob.2019.01.01). The authors have no conflicts of interest to declare.

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