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Parvovirus B19: diagnosis, distribution and disease associations

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Citation
Russcher, A. (2025, March 11). *Parvovirus B19: diagnosis, distribution and disease associations*. Retrieved from https://hdl.handle.net/1887/4197416

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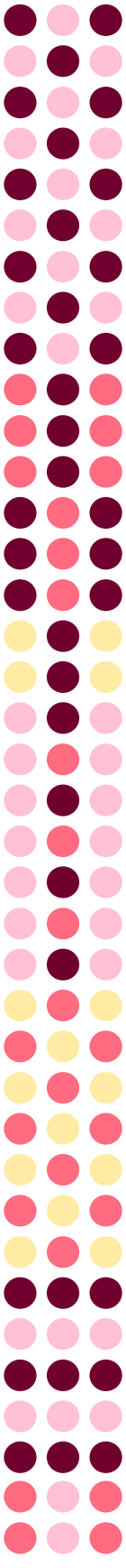

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General introduction

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STRUCTURE AND TAXONOMY

Human parvovirus B19 (B19V) is a member of the family of *Parvoviridae.* This family consists of two well established subfamilies; *Parvovirinae* and *Densovirinae*. The two subfamilies are distinguished by their ability to infect vertebrate animals and invertebrates, respectively [1]. Recently, a third subfamily *Hamaparvovirinae* has been proposed that can infect both vertebrates and invertebrates (figure 1) [1]. Members of the family *Parvoviridae* are small, non-enveloped viruses with linear, single-stranded DNA genomes of 4 - 6 Kb. Due to their small genomes, which do not encode their own replicative enzymes, most *Parvoviridae* require actively dividing host cells for replication and some viruses require helper viruses from other families.

The subfamily of *Parvovirinae* contains ten genera, which include 75 species as described in a taxonomy revision in 2019 [1]. *Parvovirinae* infect a wide range of vertebrates (birds, reptiles, mammals), although the tropism of each *Parvovirinae* species appears to be restricted to a single host species and is often tissue-specific. Viruses that infect humans are present in several genera. B19V belongs to the genus *Erythroparvovirus*, which contains seven species (B19V, seal parvovirus, simian parvovirus, rhesus macaque parvovirus, pig-tailed macaque parvovirus, chipmunk parvovirus and bovine parvovirus 3). In this genus, B19V is the only species to infect humans [1, 2].

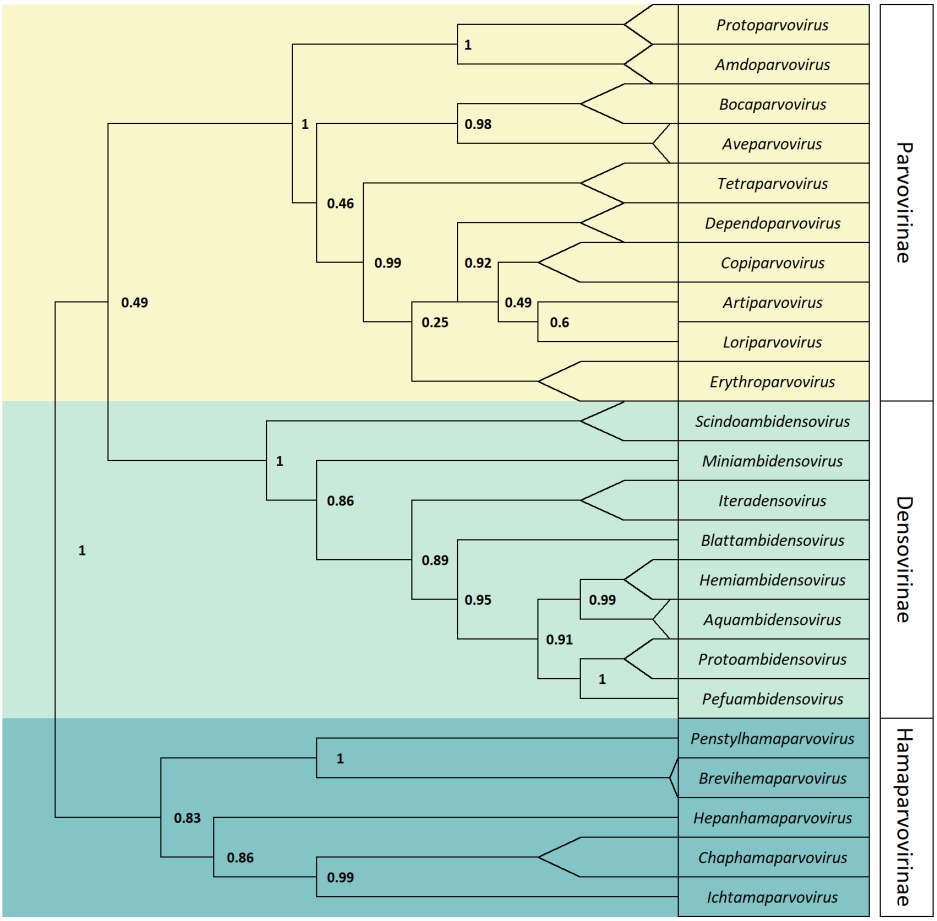


Figure 1: *Phylogenetic relationship of the Parvoviridae at the genus level, based on Bayesian inference of the tripartite helicase domain (167 amino-acids), which is conserved throughout the family Parvoviridae. The size of the last branching (most right) represents the distance from the most basal node in the genus to the branch peaks for each genus, which comprises multiple species (adapted from Pénzes et al [2])*

B19V harbors a linear, single-stranded DNA genome of 5596 nucleotides. The genome is packaged in a small (~25 nm diameter) stable capsid with an icosahedral structure and no surrounding envelope. The genome codes for 3 major proteins: Viral Protein (VP) 1, VP2 and non-structural protein 1 (NS1). VP2 is the major structural protein and accounts for 96% of the capsid structure. VP1 is the minor capsid protein. VP 1 and VP2 have overlapping sequences, but the VP1 protein differs

from VP2 by an additional 227 amino acids that make up the VP1 unique region (VP1u) (figure 2). NS1 is the major regulatory protein, which regulates the entire viral replication cycle and is capable of inducing apoptosis in infected cells. Apart from these major proteins, a 11 kDa protein is involved in DNA replication and apoptosis and a 7.5 kDa protein is expressed, of which the function is still unknown [3].

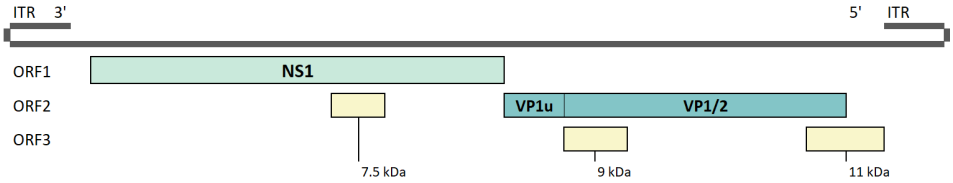


***Figure 2**: Genome organization of B19V*

B19V has 3 genotypes, which are distinct with ~10% divergence on the whole genome [4]. Within genotypes, variation is restricted to 1 to 4% and further subtypes have been described [5, 6]. Genotype 1 circulates worldwide and is now dominant in Northern Europe. Genotype 2 co-circulated with genotype 1 until half a century ago and then disappeared from circulation. As B19V DNA is able to persist in tissue life-long (a topic which will be explored further in this introduction), genotype 2 genomes are now only detected in individuals born before 1973 [7]. Genotype 3 co-circulates with genotype 1 in Africa, South-America and Asia and is occasionally detected in other regions [8-10]. Despite genome variation, capsid protein sequences are similar among genotypes which results in antibody cross-neutralization [11, 12].

CELL ENTRY AND REPLICATION

In natural infection, the virus is transmitted by respiratory secretions. The virus is subsequently carried to the bone marrow where it infects erythroid progenitor cells (EPCs). Productive infection of EPCs is dependent on the combination of the expression of specific receptors and co-receptors on the cell surface and the presence of essential cellular factors for replication. It has been shown that only certain types of EPCs in relatively late stages of differentiation are susceptible to productive infection [13-16]. Historically, globoside, or P-antigen, was regarded as the main receptor for B19V-binding and uptake, with a possible role for co-receptors, in which Ku80

and alfa5-beta-integrin have been implicated [17, 18]. More recent evidence has shown that viral uptake by the cell is mediated by interaction of VP1u with a yet unknown erythroid-specific receptor, and globoside is involved, but dispensable for uptake [19, 20]. After uptake, the presence of globoside does seem essential for endocytic trafficking. In the absence of globoside, incoming viruses are retained in the endocytic compartment and the infection is aborted [21, 22]. It has been observed that persons with a rare mutation in the globoside synthase gene who do not express globoside seem naturally resistant to infection [23]. Globoside is found on erythroblasts, but its distribution is much wider than B19V's narrow tropism, indicating that other factors are also essential for productive infection [24]. In addition to the interaction of VP1u and a cell receptor, antibody-dependent uptake has also been shown as a mechanism by which B19V is internalized in monocytes, endothelial cells and B-cells, and has been proposed as a mechanism to explain the sustained presence of B19V DNA in cells other than erythroid progenitor cells [25-27]. The exact mechanism by which respiratory epithelium is infected has not yet been elucidated, but this mechanism differs from the uptake by EPCs [28].

With regard to productive infection, the presence of erythropoietin (EPO) seems essential for B19V replication, as it is for the maturation of erythroid progenitor cells. It has been demonstrated in vitro that B19V replication does not take place in erythroid progenitor cells in the absence of EPO [13, 15]. Hypoxia has also been shown to promote viral replication [29-31]. Furthermore, it has been observed *in vitro* that parvoviruses also need actively replicating host cells for their own replication, as they depend on host enzymes for viral replication [32].

Infection of EPCs leads to cell cycle arrest and apoptosis of the cell, leading to depletion of the EPC pool in the bone marrow, until the infection is cleared. This leads to a disappearance of reticulocytes from the peripheral blood, as these are the immediate precursors of erythrocytes. This temporary halt in erythropoiesis impacts different patient populations differently. It is not clinically significant in otherwise healthy hosts, but can cause severe anemia in fetal infection or in those with underlying predisposing conditions. This will be discussed in the paragraph on disease associations.

DIAGNOSIS OF PARVOVIRUS B19

Figure 3 provides an overview of the different courses of clinical and laboratory parameters of B19V infection in different patient populations.

Serology: Availability of viral antigens has been a limiting factor for specific serology, until the development of baculovirus expression systems for this purpose [33]. Parvovirus B19 IgM and IgG testing is used as the gold standard for diagnosing recent and past infection, although it has been suggested that a combination of methods should preferably be used for most accurate diagnosis [34, 35]. In immunocompetent persons, serological profiles follow the classic pattern in which IgM becomes detectable around 10-12 days after infection and persists for several weeks up to 3 months, followed or accompanied by IgG which usually becomes detectable around two weeks after infection and remains detectable life-long [36, 37]. In severely immunocompromised individuals such as transplant patients, serologic responses may be weak and protective immunity may develop late or only after tapering of immunosuppressive treatment [38-41]. Once natural protective immunity has developed, immunity is considered to be life-long.

PCR in blood: Replicative infection is characterized by viremia with high viral levels up to 10^{14} IU/mL. In many individuals, the viral load decreases after the acute phase of infection to around 10^4 IU mL, and such levels of viral DNA may remain detectable for months. This observation was for the first time reported in 1993 when PCR remained positive during 9 months with low B19V DNA loads after infection in the presence of antibodies and has been observed many times over (42-45). This particular course with waning levels also suggests that low DNA loads can be used as indicators for late stages of infection or past infection, which underscores the need for accurate viral load quantification [35].

PCR on bodily fluids: In pregnant women, intrauterine B19V infection can be diagnosed by PCR on amniotic fluid (as a replacement for fetal blood) [46]. Saliva has been proposed as a non-invasive alternative for diagnosis of acute B19V infections, but due to its suboptimal sensitivity its use should be considered with care [47].

PCR in tissue: In tissue, B19V DNA may remain detectable by PCR for years and probably life-long. In figure 4, an overview of studies on B19V DNA persistence in different tissues (excluding cardiac tissue; which is discussed elsewhere) is presented [27, 48-91]. This figure shows that B19V DNA persistence has been unequivocally and consistently demonstrated in a very broad range of tissue types. The observed PCR positivity rates vary between studies, which can probably be explained by heterogeneous populations with differing seroprevalences (not always reported in the studies) and by differing methodologies. The prolonged detection of B19V DNA typically is not associated with any apparent disease activity and the

ability of B19V to reactivate from a latent state, as is common in Herpesviridae, has never been demonstrated. This has sparked many debates about the clinical interpretation of the tissue detection of B19V DNA. Although detected in many different tissues, it remains largely unknown what type of cells contain B19V DNA and in what form B19V DNA occurs in these cells. A crucial question in the prolonged detection of B19V DNA in both blood and tissue is whether such presence of B19V DNA originates from active replicative infection or whether the presence of B19V DNA consists of viral remnants (of a past infection), which may have been passively absorbed in a variety of tissues.

(Metagenomic) next-generation sequencing (mNGS): in recent years, the fast developments in (m)NGS assays have also contributed to the identification of B19V DNA in compartments and situations, while not primarily searched for. Examples are the presence of B19V DNA detected by mNGS in serum in (fatal) liver failure, viral encephalitis and in cardiomyopathy [92-94]. Due to the ability of B19V to persist in practically all compartments of the body, interpretation of these findings in (m)NGS only seems possible when these data are accompanied by at least reliable quantification of mNGS data, reliable evidence of viral gene expression or additional proof of any presumed disease-causing activity.

Cell culture: Due to its tropism for human erythrocyte progenitor cells, propagation in standard tissue culture is difficult. In the earliest attempts, cell culture was only possible on freshly harvested human bone marrow [13, 14, 95]. Later, certain well-established leukemic or megakaryoblastoid cell lines have been shown to support B19V replication, but these are only semi-permissive [96]. More recently, the development and expansion of erythroid progenitor cells from human hematopoietic stem cells has improved *in vitro* culture of B19V, but this culture model still requires strict *in vitro* circumstances to attain productive infection [15, 30, 97, 98]. The demanding and specialized techniques required for these cell cultures underscore the need for reliable, easily applicable methods to determine viral replicative activity.

Other methods: other diagnostic techniques have been applied to detect or visualize B19V. In acute infection, electron microscopy (EM) can show viral particles in blood and bone marrow and diseased tissue such as infected fetuses or placentas [99, 100]. Immunohistochemical staining can show viral inclusions in erythroblasts [101] and in situ-hybridization has shown B19V DNA in fetal tissue [102, 103]. These methods are not employed in routine diagnostic settings.

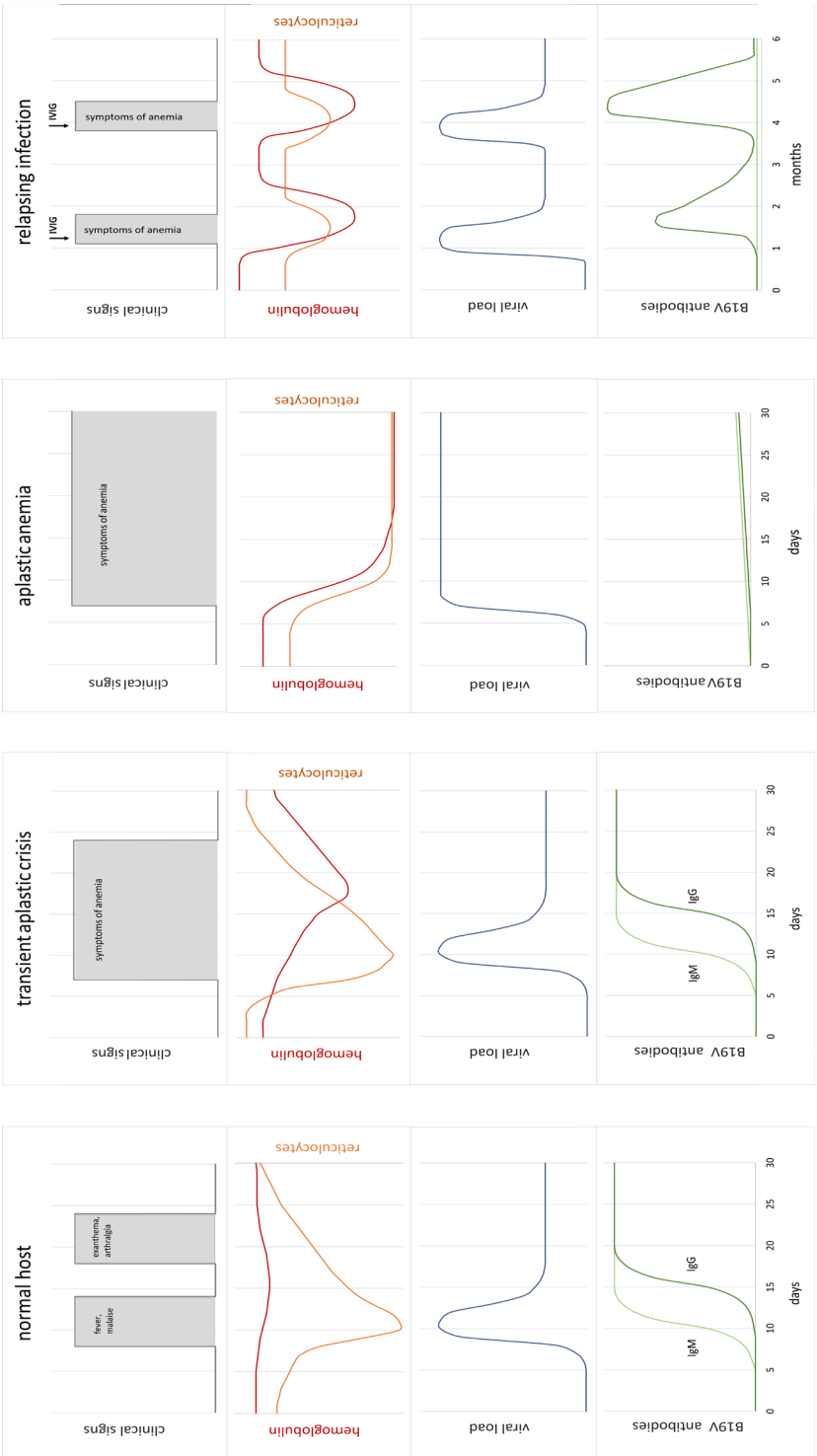


***Figure 3**: Overview of different clinical manifestations and course of laboratory parameters of B19V infections in different patient populations, from left to right: normal host; transient aplastic crisis in patients with underlying red blood cell disorders; aplastic anemia in immunocompromised patients; relapsing infection in immunocompromised patients after IVIG treatment*

TRANSMISSION DYNAMICS AND SEROPREVALENCE

Natural transmission and seroprevalence

Human-to-human transmission in the community occurs via respiratory secretions. Most B19V infections occur in childhood, when cases may be recognized as classical 'fifth disease' (see below), but infections can also pass undiagnosed as non-specific febrile illness. This is apparent from a seroprevalence of 35 to 58% in children at age ten in certain European countries, which increases to 57-73% at the age of 30 years [104]. Furthermore, seroprevalence is slightly, but significantly higher in day care workers [105]. B19V infections peak yearly in late spring and have been reported to occur in regular four-year cycles (oscillations), although divergent superimposed cycles have also been observed [106-110].

Vertical transmission

When a non-immune woman is infected in pregnancy, vertical transmission may occur. The incidence of B19V infection in seronegative pregnant women is estimated to be 1 to 5%. This may increase to 10% in epidemic periods [111, 112]. Vertical transmission occurs in 40 to 51% of pregnancies in which maternal infection occurs [113, 114]. The severity of fetal symptoms largely depends on the stage of pregnancy at infection, which will be discussed in the paragraph on disease associations.

Iatrogenic transmission: transfusion-transmitted B19V infection

Due to the persistence of B19V DNA in plasma, B19V has raised potential concerns in blood banking. Prevalence of B19V DNA in blood donations is estimated between zero and 1%, with varying DNA loads [115]. B19V transmission by blood products has been observed, but transfusion-transmitted-B19V (TT-B19V) disease primarily occurs after transfusion of high-load blood donations from acutely infected donors [116-119]. Blood donations that contain low levels of B19V DNA are not considered to be infectious and European guidelines for blood banking accept blood donations with DNA loads not exceeding 10^5 IU/mL for the production of certain plasma products [116, 120, 121]. It is unknown why low-level DNAemic blood donations are not infectious. It has been suggested that simultaneously with infectious virus, neutralizing antibodies from the donor are transmitted. Alternatively, it may be that the presence of viral DNA does not indicate that infectious viral particles are present. It could also be that TT-B19V disease may be overlooked due to a mild clinical course

[115, 116, 120, 122]. It clearly is an issue why low-level DNAemic samples do not transfer infection.

Iatrogenic transmission: transplantation-associated B19V infection

Due to their immunocompromised state, transplant patients are at risk of developing severe anemia when they become infected with B19V (see paragraph on clinical manifestations). Obviously, infection after transplantation may occur through natural transmission but proven or very probable donor-transmitted infection has been reported in case reports and case series [38, 123]. Of all solid organ transplantation (SOT) patients, B19V infection in kidney transplantation (KTx) patients has been studied most extensively. Of all symptomatic B19V infections in KTx, it is estimated that two thirds of episodes occur in the first three months following transplantation [40]. It is unknown whether this follows from a high percentage of donor-transmitted infection shortly after transplantation, or whether transplant patients are more at risk for severe B19V disease in the first months after transplantation, due to a stringent immunosuppressive regimen and often pre-existent anemia as a consequence of renal failure. The prevalence of B19V DNAemia in the first year after kidney transplantation is estimated at 7.6% (CI 3.7%-15.0%), but not all patients are symptomatic [124]. In patients with anemia, the incidence rate of B19V DNAemia is estimated at 27.4% [124]. Conversely, of B19V DNAemic patients, anemia (as a proxy for symptomatic B19V disease) can be estimated to occur in 37% at the time of B19V detection [123-126]. It is remarkable that not all severely immunosuppressed patients in which (early) B19V DNAemia after transplantation is identified, develop symptoms of B19V-disease. In addition, true donor-transmitted B19V infection seems a relatively rare event although PCR-positivity rate of kidney tissue is not rare (fig 2) and no measures are currently being taken in transplant medicine to match serostatus for donors and recipients for B19V and thus prevention of transplantation-associated B19V. These findings raise the question how to interpret B19V DNAemia after SOT.

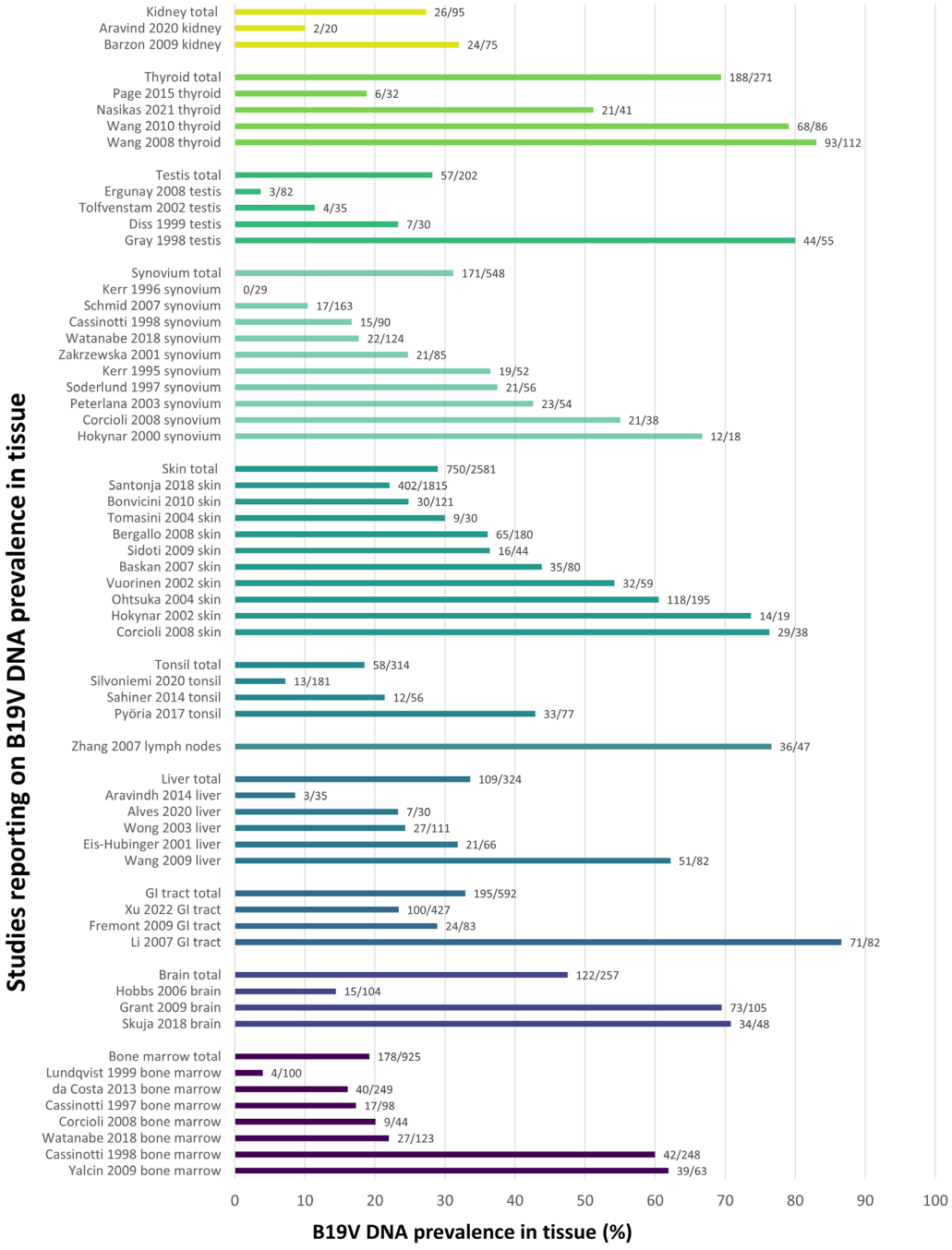


***Figure 4**: PCR positivity rates of B19V DNA in various human tissues. Numerator/denominator is displayed at the end of the bar. Studies are listed by first author and year of publication.*

PARVOVIRUS B19 AND DISEASE ASSOCIATIONS

B19V was discovered in 1975 by the Australian virologist Yvonne Cossart and her co-workers. In a comparative analysis of methods to detect hepatitis B surface antigen in sera from patients and healthy blood donors, the researchers identified viral particles that were similar to animal parvoviruses when examined by electron microscopy. The designation 'B19' originates from the coding of the microtiter plates that were used for the experiments; one of the virus-containing wells was sample number '19' in panel B (99).

In the years hereafter, B19V 'found its disease'. It was identified in a common childhood illness known as 'fifth disease' [127], and subsequently in a set of clinical syndromes that all result from the tropism of the virus for erythrocyte progenitor cells. Its manifestations and their severity are highly dependent on the immunological status of the host or whether an underlying red blood cell disorder is present. These clinical syndromes will now be briefly discussed in different patient categories.

Infection in the healthy host

As B19V is a ubiquitous pathogen, contact often occurs in early life and cases of infection usually manifest themselves in childhood. The classical clinical syndrome in an immunocompetent child is known as the historical exanthematous 'fifth disease' or erythema infectiosum and consists of a febrile illness in combination with erythema of the cheeks ('slapped cheeks'), followed by a rash on trunk and limbs with a lacy and reticular pattern. Although rare in children, adults may experience arthropathy after B19V-infection. This is estimated to occur in 30-50% of adults and is more frequent in women [128]. Arthropathy mainly manifests as symmetric joint involvement, usually of the hands and occasionally of ankles, knees and wrists. Arthropathy usually resolves spontaneously within a few weeks and joint destruction does not occur. It is believed that both rash and arthropathy are immunecomplex-mediated symptoms of the infection [129].

Infection in pregnancy

Infection of the healthy pregnant woman may run a mild course or may even go unnoticed, but when the infection is vertically transmitted to the fetus, serious fetal complications may occur. Transplacental infection of the fetus may result in a very severe anemia, followed by a high-output cardiac failure, which in turn leads

to fetal hydrops. The high output cardiac failure of fetal hydrops can be demonstrated non-invasively by measuring the middle cerebral artery blood flow (MCA flow), already in very early stages. Severity of the symptoms in the fetus strongly depends on the stage of pregnancy at infection. Before 20 weeks of gestation, the risk of fetal hydrops is 3.9 to 11.9%, but after 20 weeks of gestation, fetal hydrops hardly occurs after B19V infection [113, 114, 130]. Severe fetal hydrops is managed with intrauterine erythrocyte transfusions (IUT), which have improved survival rates considerably in the past decennia [130-132]. It is thought that long-term consequences of intrauterine B19V infection, when successfully managed with IUT, are minimal. However, this is mostly based on population studies [133-135]. More detailed evaluation in small study groups shows that neurologic sequelae might occur more frequently than previously thought [136, 137]. Further studies are needed to gain insight into the consequences of severe intrauterine infection. In addition, the true birth prevalence of B19V infection is unknown, as there are no national screening programs for B19V and infection in the healthy pregnant woman may go unnoticed. It is therefore also unknown how many fetuses suffer mild, undetected intrauterine infection with B19V and whether long-term consequences of mild infections occur and what they may consist of. Diagnosis of intrauterine B19V infection is now performed with invasive techniques during pregnancy (PCR on fetal plasma/amniotic fluid); the first step towards estimation of disease burden is development of a suitable non-invasive screening tool.

Infection in the host with underlying red blood cell disorders

The special tropism for erythrocyte progenitor cells results in a special category of patients that are vulnerable to the effects of B19V infection. In patients who suffer from either decreased red blood cell production or an increased red blood cell turnover, the halt in erythropoiesis leads to an immediate and profound drop in hemoglobulin levels, leading to the condition known as 'transient aplastic crisis' (TAC). In case of decreased red blood cell production, this can be attributed to the lack of resting progenitor cells that could be recruited to compensate for the consequences of the elimination of active cells by the wave of B19V infection. In case of an increased red blood cell turnover, the half-life of existing erythrocytes is too short to compensate for the halt in erythropoiesis. Disorders among the patients susceptible to this complication, as a non-exhaustive list, include sickle cell disease, thalassemia, spherocytosis, erythrocyte enzyme deficiencies and even malaria [129]. As

these patients are usually capable of mounting adequate immune responses, aplastic crises resolve spontaneously in a few weeks, although good supportive treatment is essential for full clinical recovery.

Infection in the immunocompromised host

In immunocompetent persons, the dip in reticulocytes is too transient to affect erythrocyte levels in a clinically relevant way. In contrast, in persons with impaired immunity, a robust immune response does not occur, resulting in prolonged infection of EPCs, leading to clinically relevant anemia (figure 3). This so-called 'pure red cell aplasia' (PRCA) has been reported to occur in patients with severe congenital or acquired immunodeficiencies, such as transplant patients and AIDS-patients [40, 129, 138-140]. In such patients, B19V infection only resolves when neutralizing antibodies become present, either by intrinsic production or external administration in the form of intravenous immunoglobulins (IVIG). This is evident from transplant patients in whom viremia and anemia resolve after treatment with IVIG, but who relapse when IVIG has been cleared from the circulation after approximately 3-4 months [141]. Lasting immunity is only obtained when the immunocompromised state improves, e.g. by tapering immunosuppressive treatment and the development of subsequent natural immunity. Although neutralizing antibodies are considered to be crucial in the clearance of infection, there is evidence for T-cell responses also playing a role in controlling infection [142-145].

B19V and its association with miscellaneous syndromes

The above-mentioned clinical syndromes are historically well-described and have a profound evidence-based pathogenetic etiology. Apart from this set of well-described clinical syndromes, B19V has also been implicated in a myriad of clinical manifestations for which the evidence is still debated. Many of these associations are only reported in case studies or case series, often solely basing the association on the detection of B19V DNA in certain tissues and lacking additional support for the association.

A presumed role of B19V in causing myocarditis or cardiomyopathy has been particularly confusing and will be discussed in some detail. Soon after PCR assays became available on a large scale, it was observed that a large proportion of both diseased and non-diseased hearts contained B19V DNA in cardiac tissues. Figure 5 presents an overview of the studies which report on the prevalence of detection

of B19V DNA in both diseased and non-diseased cardiac tissue [52, 146-181]. Most studies have looked at the prevalence of B19V DNA in diseased hearts, in particular patients with myocarditis (MC) or dilated cardiomyopathy (DCM). The distribution of PCR positivity in both diseased and non-diseased cardiac tissue has a very wide range, but suggests that positivity rates are comparable. This is confirmed by a recent meta-analysis, which shows that the relative risk ratio of B19V DNA positivity in cardiac tissue is not significantly higher in patients with cardiac disease compared to control groups [182]. Obviously, the comparable presence of viral DNA in diseased and normal hearts casts doubt on the significance of this finding as a cause of cardiac disease.

Subsequently, it has been suggested that to fully understand the capability of B19V to cause cardiac disease, other parameters such as height of viral load and measures of viral activity should be taken into account [183]. A number of studies found that DCM was associated with higher cardiac B19V viral loads [148, 176, 180], but several other studies have found no association between viral load and pathology, even reporting viral loads in non-diseased hearts that are higher than those in DCM [146, 160, 164, 179]. Other methods including detection of mRNA, immunohistochemistry, in-situ hybridization, electron microscopy and specific B19V T-cell responses have also been employed to understand the significance of the presence of B19V DNA in cardiac tissue, but these studies are often characterized by methodological shortcomings and also report conflicting outcomes [152, 169, 180, 184-186]. These divergent results and shortcomings of diagnostic techniques do not support a clear role for B19V in myocarditis and cardiomyopathies, but above all underline the importance of reliable methods to evaluate the nature of the B19V DNA detected in such syndromes.

Based on the detection of B19V DNA, B19V has also been implicated in hepatitis, skin diseases, thyroid diseases, rheumatoid disease and vasculitis [72, 82, 91, 187, 188], while other studies have failed to confirm a causal relationship in all these syndromes [62, 73, 77, 189].

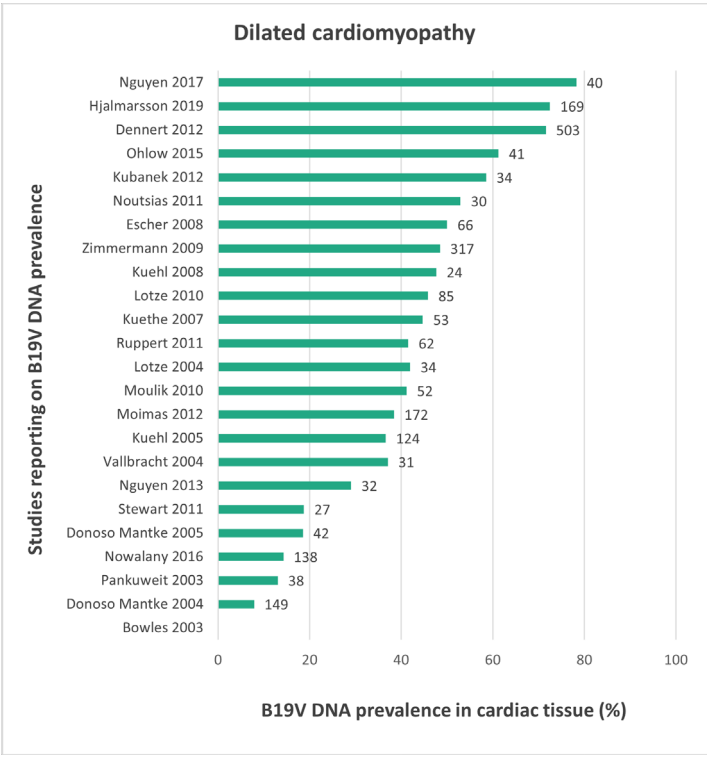
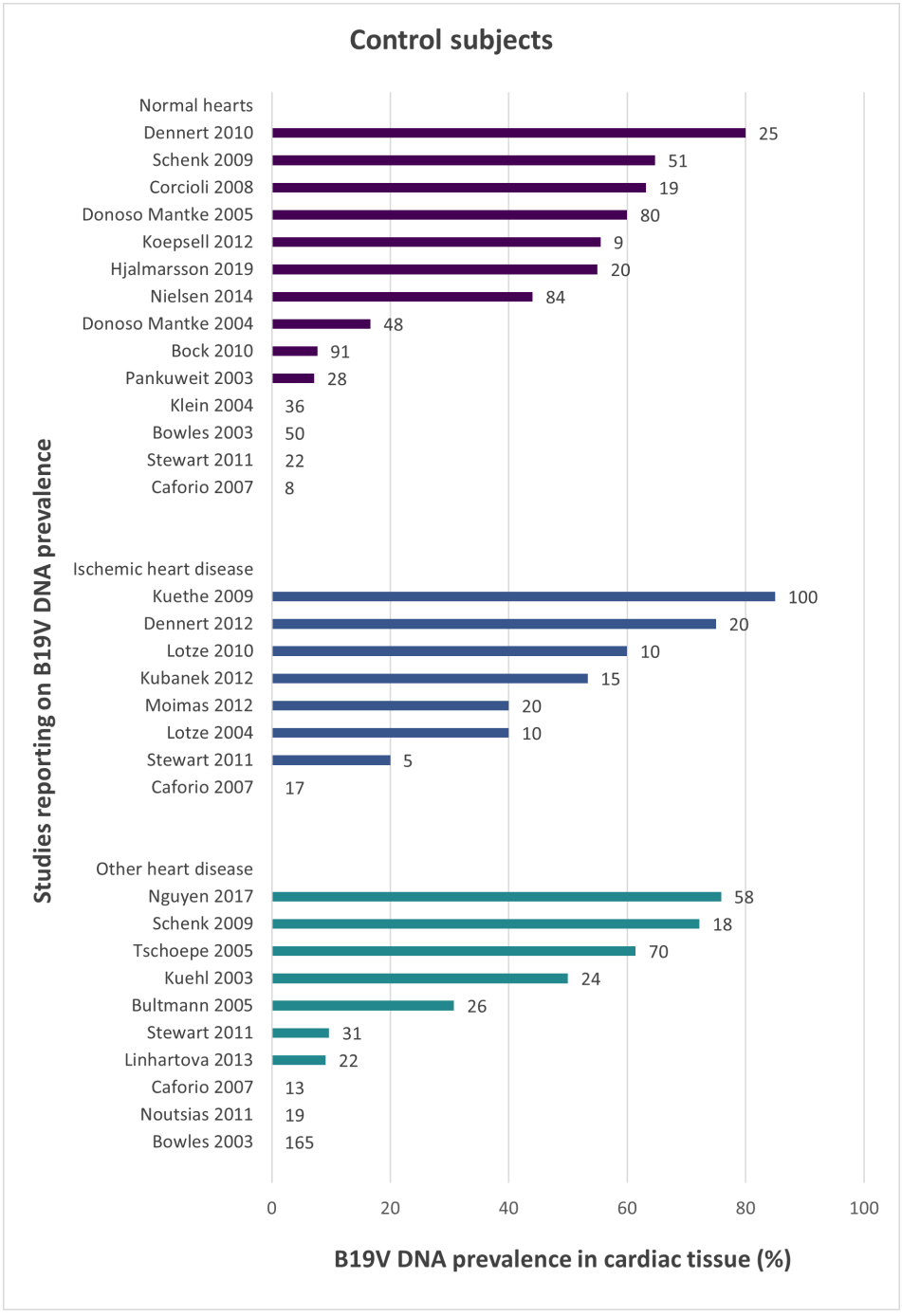


Figure 5: *Overview of prevalence of B19V DNA in cardiac tissue in various clinical conditions. End of border notes denominators. Studies are listed by first author and year of publication. Adapted from [183], supplemented with recent literature.*


Control subjects
Studies reporting on B19V DNA prevalence
Normal hearts
Dennert 2010 25
Schenk 2009 51
Corcioli 2008 19
Donoso Mantke 2005 80
Koepsell 2012 9
Hjalmarsson 2019 20
Nielsen 2014 84
Donoso Mantke 2004 48
Bock 2010 91
Pankuweit 2003 28
Klein 2004 36
Bowles 2003 50
Stewart 2011 22
Caforio 2007 8
Ischemic heart disease
Kuethe 2009 100
Dennert 2012 20
Lotze 2010 10
Kubanek 2012 15
Moimas 2012 20
Lotze 2004 10
Stewart 2011 5
Caforio 2007 17
Other heart disease
Nguyen 2017 58
Schenk 2009 18
Tschoepe 2005 70
Kuehl 2003 24
Bultmann 2005 26
Stewart 2011 31
Linhartova 2013 22
Caforio 2007 13
Noutsias 2011 19
Bowles 2003 165
0 20 40 60 80 100
B19V DNA prevalence in cardiac tissue (%)

TREATMENT

In persistent or relapsing B19V infection with clinically relevant anemia, mainly among immunocompromised patients, treatment with intravenous immunoglobulins is now standard practice [141, 190]. Treatment with IVIG reduces B19V viral load and leads to improvement of anemia [141]. However, relapse after IVIG is seen in about 30% of patients, and these patients require a second course or even multiple courses of IVIG [39, 40, 191, 192]. As relapsing infection after IVIG may occur, while B19V DNA can also be present in blood for months after infection without causing disease, it is essential to differentiate between active infection (and thus, the need for repeated treatment) and past infection.

IVIG has also been applied in other supposed manifestations of B19V disease. A randomized, double-blind, placebo-controlled trial using IVIG in idiopathic chronic cardiomyopathy with B19V persistence in cardiac tissue did not show a beneficial effect on left ventricular ejection fraction (LVEF) or other outcomes such as functional capacity, quality of life or cardiac B19V DNA load [193].

Currently, targeted antiviral treatment is not available for B19V infection. In the search for compounds inhibiting B19V replication, multiple compounds including known antiviral agents such as nucleotide analogues (e.g. cidofovir), foscarnet and the S-phase inhibitor hydroxyurea have been evaluated. At present, observed in-vitro effects and data from case reports or small case series have not yet shown convincing efficacy or clear directions for use in clinical care [194, 195]. The very limited availability of specific viral enzymatic targets obviously limits the development of targeted antiviral therapy.

AIMS AND OUTLINE OF THIS THESIS

The main aim of this thesis is to investigate new approaches and techniques to diagnose B19V infection and to determine the significance of detection of the infection in different patient populations. This would lead to a better understanding of the pathogenetic nature of B19V, its clinical impact and disease burden.

In **chapter 2**, epidemiological trends for B19V over the last 33 years are analyzed. The changes that occurred during and after the COVID-19 pandemic are described and their clinical impact is investigated by analyzing trends in intrauterine erythrocyte transfusions, performed for B19V-related fetal hydrops.

Chapter 3 investigates the clinical impact of the B19V epidemic in 2024, showing the increase in intrauterine erythrocyte transfusions during the epidemic and reporting on the outcome of pregnancies after intrauterine erythrocyte transfusion.

Chapter 4 investigates the persistence of B19V DNA in postnatal blood of newborns with intrauterine B19V infection. The suitability of postnatal blood samples as potential screening samples for intrauterine B19V is investigated, to improve insight in the real prevalence of this infection.

Chapter 5 describes the development and application of a new tool, an endonuclease-based assay, to differentiate between the presence of intact B19V viral particles and DNA remnants in blood. This could improve the interpretation of detection of B19V viral DNA in various clinical conditions, which is currently challenging, as described before.

In **chapter 6**, the application of the endonuclease-assay in a cohort of patients with presumed B19V-induced cardiomyopathy is evaluated.

Chapter 7 determines the prevalence of B19V DNAemia after kidney transplantation in a large Dutch teaching hospital and investigates the relevance of this finding, in relation to the presence of active replicative infection.

In **chapter 8**, mNGS is used to determine viral loads of 6 different DNA-viruses, including B19V. The relationship between viral load, clinical course of the disease and identification of clinically relevant cut-off points or thresholds for intervention is analyzed.

In **chapter 9**, intra-host viral evolution and potential humoral evasion are explored, analyzing longitudinal samples of relapsing B19V infections in immunocompromised patients by whole genome sequencing and protein modeling.

Chapter 10 contains the general discussion, in which the implications of the findings in this thesis are discussed and in which remaining areas for future research are identified.

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