THREAT ASSESSMENT BRIEF

Risks posed by reported increased circulation of human parvovirus B19 in the EU/EEA

05 June 2024

Summary

ECDC is following reports from several European Union and European Economic Area (EU/EEA) Member States of substantial increases in the detection of parvovirus B19 (B19V). A Threat Assessment is developed to raise awareness of public health and substances of human origin (SoHO) professionals and competent authorities about this event, particularly as regards population groups at high risk for severe complications and suggest actions that can be taken to address this situation.

Epidemiological situation

Since March 2024, nine EU/EEA countries have reported increased detections of B19V on EpiPulse from a number of monitoring systems, mostly during the end of 2023 and beginning 2024. As a response to an inquiry from ECDC to the National Focal Points (NFPs) in the ECDC-SoHO network blood group [1] on B19V infections, 10 countries reported an increase in reactive tests for B19V in blood donors or in donations of plasma for fractionation during the first months of 2024 compared to the same period in 2023.

Risk Assessment

Based on the unusually high numbers of B19V cases reported in 14 EU/EEA countries, the risk of infection is assessed in four population groups as follows:

- **Risk for the general population** is assessed as **low,** as most infections are in the form of a mild exanthematous disease of childhood, although some complications may occur.
- **Risk for pregnant women**, less than 20 weeks gestation is assessed as **low to moderate**, considering the uncertainties about the virus circulation, the fact that an estimated 30-40% of women of childbearing age are susceptible to the infection and severe outcomes occur in a small percent of infected pregnancies.
- **Risk for immunosuppressed persons** is assessed as **moderate**, as these patients cannot clear the infection and can suffer chronic anaemia, pancytopenia, graft loss or dysfunction and organ-invasive disease.
- **Risk for persons with chronic haematological diseases** (e.g. sickle cell disease, thalassaemia, etc) is assessed as **moderate,** as B19V infection can cause transient aplastic crisis.

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Recommendations

For public health authorities

ECDC recommends that public health authorities in the countries should:

- **Raise the awareness of clinicians** about the observed increase of B19V to assist in counselling and managing their patients appropriately.
- **Conduct risk communication to the risk groups**, including pregnant women, immunosuppressed and transplant recipients, and patients with chronic blood disorders, particularly haemolytic anaemias.
- **Review**, in a multidisciplinary collaboration, any available datasets collected on B19V infections going back to the years before the pandemic to establish trends and changes in patterns of transmission. Reporting these findings to EpiPulse will assist in improving the risk assessment and tailor the risk communication messages for all EU countries.

For SoHO professionals and competent authorities

- Additional systematic testing of blood donors for B19V infection is not required. However, if a B19V infection is suspected or confirmed for a donor, the B19V-positive blood or blood components should not be transfused to individuals susceptible to severe clinical outcomes of B19V infections, i.e. pregnant women, patients with chronic haemolytic diseases or hemoglobinopathies, or immunosuppressed people.

Epidemiological situation

On 22 March 2024, public health authorities in Denmark notified other EU/EEA Member States and the ECDC about a steep increase in pregnant women infected with parvovirus B19 (B19V) in the first quarter of 2024. Since then, an additional 14 EU/EEA Member States (Czechia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Slovakia and Spain) have reported increased detections of B19V infections through various surveillance systems (laboratory, hospital and primary care surveillance), screening of blood donors or screening of donations of plasma for fractionation.

B19V infection is not notifiable at the EU level and surveillance is not established in the majority of EU/EEA countries, therefore ECDC requested any available epidemiological information in order to assess the situation. The following Member States reported information through EpiPulse:

- **Czechia**: tenfold increase of erythema infectiosum diagnoses in 2024, compared to 2023;
- **Denmark:** increase in detections in pregnant women during the first quarter of 2024 with data comparable to the biggest surge previously noted in 2017. During 2024 and as of 10 April, 250 cases of B19V were recorded. Among these cases, 50 (20%) were pregnant women, of whom 10% required hospitalization; [2]
- **France:** since July 2023, an unusually high number of severe paediatric B19V cases, several infections in pregnant women and an unusually high number of miscarriages and abortions related to B19V infection. In the first quarter of 2024, five deaths were reported among children under one year of age, of which four were congenital B19V infections. Between 2015-19, 1.8 deaths per year were registered due to B19V, the majority of which (78%) were in children >15 years of age; [3]
- **Ireland:** increase in B19V detections during the first quarter of 2024. In this period, 102 PCR positive results were identified, which is significantly higher than the annual number of positive PCR results for the years 2020 to 2023 (ranging from 30 to 61 cases annually). There have been 51 positive B19V IgM samples detected in quarter 1 of 2024 compared to between 60 and 84 in the previous three years. The positivity rate of B19V IgM increased in the first quarter of 2024 to 3.5% which is higher than the average recorded positivity rates for 2019 to 2023;
- **Latvia**: 58 cases (positivity rate of 56% among the cases tested) for the season 2023-2024 compared to zero to six cases during the same period (December to March) in previous five years. Of the 58 B19V cases reported during the current season, 67% were children;
- **Lithuania:** increased detections of parvovirus B19V in the screening of blood donors in some counties;
- **The Netherlands:** increased detections since the end of 2023. This increase has continued in the first few months of 2024 and was observed in blood and plasma donors at the national blood bank, in national virological surveillance, and in reports from local health authorities stating an increase in erythema infectiosum in the paediatric population.
- **Norway:** increase in positive tests – mainly for IgM but also PCR – in the adult population (30–59 years of age). The positivity rate increased since late January 2024;
- **Spain:** a higher positivity rate for B19V in 2023 and in the first months of 2024 compared to pre-pandemic years.

Furthermore, a study published on 23 May 2024 from France reports similar increasing trends of B19V detection in more than 25 million blood donations in the country [4].

Following a report on this event in ECDC's Weekly Communicable Disease Threats Report (CDTR) of 5 April 2024 [5], the United Kingdom published a Health Protection Report [6] featuring an increase of cases of B19V in the UK at the end of 2023 and the beginning of 2024. However, the reported numbers did not reach those seen in 2017 and 2018, when previous peaks occurred.

In Israel, a study published in November 2023 [7], revealed a surge in B19V cases, which was the highest known to date in the country. More than 40% of total infections detected over the study period (January 2015 to September 2023) were recorded during the last nine months of the study. The adjusted incidence rate ratio (IRR) was 6.6 (95% CI 6.3–6. 9) when comparing 2023 detections to previous years. When comparing 2023 to peak COVID-19 years, the surge is even more pronounced, with a 9-fold increase in incidence rates. Unlike previous surges, the highest B19V incidence rates in 2023 extended into the autumn months. Children constituted over 80% of infections, and pregnant women also experienced a relative increase in infection rates.

On 22 April 2024, ECDC contacted the substances of human origin (SoHO)-Net National Focal Points (NFPs) for blood to inquire about B19V testing among blood donors and whether any increases in B19V infections have been observed in the donor population. A total of 18 countries responded to the request. Most countries do not routinely test blood donors for B19V. As of 6 May 2024, among the 10 countries (Finland, Hungary, Luxembourg, Lithuania, the Netherlands, Czechia, Denmark, France, Germany, and Slovakia) that reported data on blood donors or donations of plasma for fractionation, all reported an increase in reactive tests for B19V in their respective donor populations during the first months of 2024 compared to the same period in 2023. In addition, Italy has recently shared preliminary information indicating a significantly increased number of positive B19V units of plasma for fractionation from December 2023 onwards compared to the same period in the previous year.

ECDC risk assessment for the EU/EEA

This threat assessment is based on the data available at the time of publication and follows the ECDC rapid risk assessment methodology, where the overall risk is determined by a combination of the probability of infection and its impact [8].

What is the risk associated with the reported increase of parvovirus B19 in the EU/EEA?

Table 1. Assessment of the risk associated with parvovirus B19 infection in the EU/EEA, by population group

Risk group	Probability	Impact	Overall risk
General population	Low to moderate	Very low	**Low**
Pregnant women <20 weeks gestation	Low to moderate	Low	**Low to Moderate**
Immunosuppressed individuals, incl. transplant patients	Moderate	Moderate	**Moderate**
Patients with chronic haemopoietic diseases	Low to moderate	Moderate	**Moderate**

There is substantial uncertainty regarding the true levels of circulation of B19V in the EU, as diverse information is reported by 14 countries in the EU/EEA and good information from surveillance of this pathogen in other countries is lacking. However, the reporting countries have discovered significantly increased trends of B19V infections, either in laboratory testing databases, analysis of hospital records, or through screening of blood donors or donations of plasma for fractionation. A recent report from this latter group in France based on almost 26 million donations shows substantial increases of B19V in 2023-2024 compared to 2015-202, and potential changes in the seasonal pattern of the annual outbreaks [4]. The **probability of infection** after exposure **depends on prior 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 elderly persons; therefore, the probability of infection decreases with age [9]. The secondary transmission rate in a household can be as high as 50% [9].

Risk for the general population is assessed as **low**. Most of the illness from B19V infection happens in childhood and is mild, usually in the form of erythema infectiosum. Illness in adulthood may also present with rash in addition to transient joint pain and swelling, and myalgias, which are reported more frequently than in children [10]. Despite the reported complications, the general prognosis is quite good (see Technical Annex). We assess the impact in the general population as very low.

Risk for pregnant women less than 20 weeks gestation is assessed as **low-to-moderate**. Infection with B19V of a susceptible woman in the first part of pregnancy may result in foetal death and miscarriage in 5-9% of pregnancies, due to nonimmune hydrops fetalis caused by the infection of the erythrocyte precursor cells [11]. Probability of infection can be low to moderate depending on the circulation of the virus in the community or occupational exposure of the pregnant person (e.g. health professionals, teacher, kindergarten staff). Considering that an estimated 30-40% of women of childbearing age are susceptible to the infection and severe outcomes occur in a small percentage of infected pregnancies, we assess the impact as low at the population level, although a miscarriage has significant impact at the individual patient's level.

Risk for immunosuppressed persons is assessed as **moderate**. The probability of infection in this population group is assessed as moderate. Infection can be either through person-to-person transmission or through transfusion or transplantation of B19V-positive SoHO [12]. Nosocomial transmission of B19V has also been reported. The impact of B19V infection in immunosuppressed persons (e.g. under immunosuppressants, immunosuppression due to HIV infection, cancer, transplantation, etc.) is assessed as moderate due to the inability to produce neutralising antibodies. B19V can cause chronic infection, anaemia, pancytopenia, graft loss or dysfunction and organ-specific complications (e.g. myocarditis, hepatitis, etc.). Intravenous immunoglobulin (IVIG) has been used to treat chronic infection in immunocompromised hosts [13].

Risk for persons with chronic haematological diseases is also assessed as **moderate.** Infection in this risk group can happen by person-to-person transmission or due to exposure to a B19V-positive blood component, as they are frequently transfused (including patients with haemolytic anaemias, e.g. sickle cell disease (SCD), thalassaemia, hereditary spherocytosis etc.). B19V infection in this group can result in transient aplastic anaemia crisis (TAC), which can be life-threatening if not diagnosed early. Older studies in newly infected SCD patient cohorts report that roughly 60-80% develop B19V-associated TAC [14,15]. TAC can occur also in immunocompetent hosts, where it may affect other blood cell lineages as well, but it is a rare event [16]. Considering uncertainty around the testing of blood donors to ensure safe components for recipients at risk, we assess the impact as moderate in the currently increased circulation of B19V.

ECDC considerations for public health and SoHO authorities

For public health authorities and clinicians

Although there are limited surveillance data available, several national reports indicate significant increases of circulation of B19V in the season 2023-2024, which is expected to continue in the 2024 summer months. Overall, B19V infection is a mild childhood disease, but specific population groups can suffer severe complications. In response to this ongoing threat, ECDC recommends the following:

- In view of the current signs of increased circulation of B19V, there is a need for **raising awareness and appropriate risk communication to clinicians** (e.g. GPs, paediatricians, obstetricians, etc.), which can help counsel their patients. Clinicians should be reminded of the relevant complications of B19V infection in these groups and their management options.
- Appropriate **risk communication** is needed **for the risk groups** as described above (pregnant women, immunosuppressed and transplant recipients, frequently transfused patients).
- Pregnant women working in healthcare, education, and childcare settings in the context of local outbreaks, should be counselled and advised to check their antibody status in order to take appropriate precautions. . Exclusion from work is not advised in general, as a pregnant woman can become infected through family or other community contacts as well. In case of infection, close follow-up is recommended by specialists.
- For countries with existing surveillance systems, either laboratory based and/or syndromic, we recommend reviewing their data going back before the pandemic years and establishing trends and/or changes of patterns of circulation/transmission. For countries where laboratory testing is performed independently either in pregnant women or in the blood safety sector (including plasma for fractionation), we recommend reviewing existing information in a multidisciplinary collaboration, to establish again changes in trends and patterns of transmission.
  - **Reporting to EpiPulse these findings can help improve ECDC's risk assessment** and tailor risk communication messages towards all EU/EEA public health authorities and clinicians regarding this pathogen.

For SoHO professionals and competent authorities

Transmission of B19V through SoHO has been described in the literature via transfusion of red blood cells and platelets, treatment with plasma-derived medicinal products [17-22], and hematopoietic stem cells (HSC) [23] and solid organ transplantation [24]. However, clinically significant transfusion-transmitted B19V infection seems to be a rare or overlooked event, as indicated by data from different European countries. For instance, in the UK, only one case was reported between 1996 and 2022 [25] and in Germany, no transfusion-transmitted B19V infection

was reported between 1997 and 2017 [26], in the absence of routine testing for this virus in blood donors during this period.

Due to the limited number of transmission cases reported, the exact level of B19V titres that pose a risk of virus transmission through SoHO cannot be adequately assessed.

To reduce the risk of possible B19V transmission by plasma-derived products, the European Pharmacopoeia mandates testing plasma pools for fractionation for B19V using a validated nucleic acid amplification test (NAT). These plasma pools, used in manufacturing, can only contain B19V DNA loads below 10 000 international units (IU) per millilitre. Any final manufacturers' plasma pools exceeding this B19V DNA level must be discarded [27].

Systematic testing of blood donors for B19V infection, in addition to the screening of donations of plasma for fractionation, is not required. However, if a B19V infection is suspected or confirmed for a donor, the B19V-positive blood or blood components should not be transfused to individuals susceptible to severe clinical outcomes of B19V infections i.e. pregnant women, patients with chronic haemolytic diseases or hemoglobinopathies, and immunosuppressed persons [28]. Selective screening of donations with NAT to provide safe components for these recipients could be considered [29]. An alternative testing strategy in use in the Netherlands is the selective testing of donors for B19V antibodies to make B19V-tested blood components available for susceptible patients upon request. Donors with two positive B19V (IgG) antibody tests at an interval of at least six months are considered safe for B19V-susceptible recipients [30].

Even though B19V transmission cases through HSC transplantation are seldom reported, regarding the current epidemiological situation, the risk of B19V infections in HSC transplant recipients should be considered.

Limitations

- The above assessment and recommendations are based on limited data reported by Member States to ECDC. B19V is not under routine surveillance at the national level in many EU countries and not under EU surveillance. This prevents a full assessment of the situation in all the EU countries.
- ECDC is in the process of requesting more systematic data from relevant stakeholders and may revise this assessment and advice, as needed.

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Technical annex (max 2 000 words)

Human parvovirus B19

Pathogen

Human parvovirus B19 (B19V) belongs to genus *Erythrovirus*, of the *Parvoviridae* family. It is a small (~23 nm diameter), non-enveloped single-strand DNA virus. Three B19V clades have been identified, differing 5% to 20% in sequence. Within each clade, the viruses differ by less than 1% to 4% [31].

Transmission

The virus is primarily spread by respiratory droplets; however it can be also transmitted by blood, plasma-derived medicinal products as well as transplanted organs [32]. Parvoviruses replicate in dividing cells only; after entering via the respiratory tract, B19V establishes a systemic infection with significant viremia,~3 days after infection and lasting for~10 days. The virus is excreted during the viremia peak. B19V inhibits the formation of erythroid blast-forming colonies therefore affecting the erythroid lineage [33].

Clinical presentation

Clinical manifestations include nonspecific flulike symptoms, followed by a generalised erythematous rash with a "slapped cheek" appearance (erythema infectiosum or fifth disease), and a generalized inflammation of the joints [33]. Asymptomatic and subclinical, non-exanthematous, infection with B19V can occur, especially in children. In most of the cases, the acute infection lasts for fewer than 10 days. In adults, transient small joint arthropathy may be the main clinical presentation of parvovirus B19. Generally, joint symptoms coincide with the expected onset of rash in children. While arthritis usually improves within 1-3 weeks, it may persist for months [34]. Other manifestations include arthritis and arthralgia, intrauterine infection and hydrops fetalis, transient aplastic crisis (TAC) in patients with sickle cell disease and other hemoglobinopathies, and persistent infection with chronic anaemia, pancytopenia and graft dysfunction in patients with immunodeficiencies [13].

In pregnant women, B19V can cross the placenta and cause infection in the foetus and foetal hydrops due to severe anaemia, leading to cardiac failure, foetal death, and miscarriage [33]. Studies in cohorts of susceptible pregnant women exposed to B19V during pregnancy show that not all foetuses are infected and foetal demise is reported in 5-10% of pregnancies [35-37]. Maternal infection prior to 20 weeks of gestation has the higher risk of congenital infection [35].

Epidemiology

Outbreaks of B19V have been observed worldwide, though most reports originate from nontropical regions. Community epidemics are most prevalent in winter and spring, typically lasting 3 to 6 months. Annual peaks of B19V follow similar cycles to rubella, with which its exanthem is frequently confused. Incubation period for erythema infectiosum is reported between 4 and 14 days [33]. During epidemics, the attack rate is high, with transmission among household contacts reaching nearly 50% [38].

Diagnosis

IgM and IgG antibodies can be detected by enzyme immunoassay, haemo-adherence, radioimmunoassay, or immunofluorescence. Rising IgM titres indicate recent infection. The antigen can be detected by PCR, DNA hybridization, or electron microscopy [33]. PCR can remain positive for long periods of time.

Treatment

There is no specific treatment for B19V infection. Symptomatic therapy for erythema infectiosum is not often needed, especially in children. Arthralgia may be treated with analgesics. Patients with TAC should receive transfusions with packed erythrocytes, as needed.

If B19V infection is documented in early pregnancy careful frequent follow up is needed. Foetal hydrops has been reportedly with in utero transfusions, but the treatment is not free of complications.

Control measures

B19V spreads through oral and respiratory routes, with virus shedding starting already with non-specific symptoms, before the onset of rash. Patients with erythema infectiosum do not need isolation as they are no longer infectious. However, patients with TAC and all patients with chronic infection should be isolated with droplet precautions and considered infectious. For chronic infections, measures can be stopped after IVIG treatment and testing showing that they are non-viremic.

In the context of outbreaks, pregnant women and other risk groups should be counselled about potential risks and complications. Immunocompromised persons and patients with chronic blood diseases should avoid contact with sick people. Occupational exposure of pregnant women in healthcare, education and childcare setting increases their risk of exposure and they should be aware of their immunity status [33].