Parvovirus B19 causes "slapped cheek syndrome" or fifth disease, one of the 5 common childhood exanthems (measles, chicken pox, rubella, scarlet fever and fifth disease). The virus infects and destroys red blood cell precursors, causing inevitable anemia. Acute infection in non-immune pregnant women can lead to fetal hydrops. Methods: The data are based on a selective search of the literature and on the authors’ clinical experience. Results: In seronegative pregnant women acute parvovirus B19 infections can result in fetal death and/or hydrops fetalis. Since the majority of infections occur during childhood, the risk of complications is high in seronegative pregnant women working in contact with children, particularly in nursery and primary school teachers and in child health. Discussion: This article reviews current scientific knowledge and presents incidence data for fetal complications in Germany, to inform antenatal care and public health.

Key words: Parvovirus B19, erythema infectiosum, fetal hydrops, pregnancy, childcare

Parvovirus B19 causes "slapped cheek syndrome" or fifth disease, one of the 5 common childhood exanthems (measles, chicken pox, rubella, scarlet fever and fifth disease). The virus infects and destroys red blood cell precursors, causing inevitable anemia. Acute B19 infection in seronegative pregnant women can cause fetal death or hydrops (1). According to § 4 Section 2 No. 6 of the Antenatal Care Act, a pregnant women is not allowed to carry out any work "which puts her, by virtue of the pregnancy, at increased risk of occupational disease, or in which the risk of an occupational disease might endanger either mother or fetus". This legal requirement has led to an increasing tendency in recent years in Germany to declare seronegative pregnant women who work with children medically unfit to work for the duration of pregnancy. If the employer is unable to offer alternative work, the pregnant woman is relieved of her duties until the birth of the baby. This practice has unleashed heated debate. Against this background, it is essential to present the current state of knowledge in relation to the epidemiology and clinical course of Parvovirus B19 infection, based on personal experience and international publications, together with an evaluation of the current situation on Germany.

Transmission
Parvovirus B19 is transmitted via droplet infection, or via contact with saliva, blood or other body fluids. Acutely infected individuals have extremely high viral concentrations (10^11 to 10^13 particles/ml) in blood and other body fluids such as saliva or urine. Since parvoviruses have no lipid capsule, their infectivity is unaffected by solvents and detergents. A strong emphasis on hygiene is essential in pediatric practices, where a high level of infection is to be expected, but also in nursery schools, if viral transmission via contaminated objects is to be prevented. Since viremia proceeds symptoms and can be persistent, one in every 1000 to 2000 blood donations is affected by the virus, sometimes in high concentrations. The virus is stable in blood products (clotting factors VIII and IX, albumin, immunoglobulins) and remains infectious.

SUMMARY
Introduction: Parvovirus B19 is the causative agent of erythema infectiosum (fifth disease), a predominantly benign and self-limiting disease manifesting as rash with associated anemia. Occasionally, arthritis and arthralgia, hepatitis, encephalitis, meningitis and myocarditis can develop as complications. Acute infection in non-immune pregnant women can lead to fetal hydrops. Methods: The data are based on a selective search of the literature and on the authors’ clinical experience. Results: In seronegative pregnant women acute parvovirus B19 infections can result in fetal death and/or hydrops fetalis. Since the majority of infections occur during childhood, the risk of complications is high in seronegative pregnant women working in contact with children, particularly in nursery and primary school teachers and in child health. Discussion: This article reviews current scientific knowledge and presents incidence data for fetal complications in Germany, to inform antenatal care and public health.
Diagnosis

The virus is detected directly via polymerase chain reaction (PCR). B19 specific antibodies can be assayed using ELISA or immunoblot tests. The viremia begins around 4 to 5 days following exposure. 2 to 3 days later the blood viral load will have reached the level of $10^{11}$ to $10^{13}$ particles/ml. IgM antibodies, predominantly against VP2 capsid proteins, are detectable after around 10 days post contact, at around the same time as the onset of rash. At this phase of the illness and in the days following, blood and saliva levels of $10^4$ to $10^8$ genome equivalents of virus DNA/ml can be found. B19 specific IgM is frequently undetectable from 3 weeks following initial contact, although the patient is still viremic at this stage. Rising titers of anti VP1 and VP2 capsid protein IgG are measurable around 2 weeks after initial contact, and remain elevated for life (diagram 1a). IgM and IgG are partially neutralizing, and lower the viral load (diagram 2). In children, the pathogen has usually

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**DIAGRAM 1**

(a) Antibody production and blood virus concentration during acute infection

(b) Antibody production and blood virus concentration during infection with a prolonged viremic phase. A prolonged viremic phase is common in pregnant women with acute parvovirus B19 infection.
been eliminated by 3 to 4 weeks following infection, and undetectable in blood or saliva even with sensitive PCR methods. In adults, the viremic phase with blood levels of between $10^3$ and $10^7$ genome equivalents/ml of blood can last longer, sometimes several years. In addition to IgG antibodies against structural proteins, these patients also form immunoglobulins against the non structural protein NS1 (diagram 1b). Even after elimination from the blood, B19 DNA can persist in skin, synovial, bone marrow, myocardial and liver cells. This latent presence of viral genome occasionally poses a diagnostic problem in poorly defined illnesses with a possible B19 association.

Acute infected pregnant women are often viremic for months, often beyond delivery, despite IgG production (between $10^3$ and $10^4$ genome equivalents/ml). Similar viral loads are detectable in umbilical cord blood. Because IgM levels often fall rapidly in the presence of persistent viremia, pregnant women with questionable parvovirus B19 serology should undergo PCR to look for possible viral DNA, in addition to antibody assay, wherever there has been contact with fifth disease infected individually, and regardless of symptoms. The presence of B19 specific IgG antibodies in the absence of DNA and IgM assays is suggestive of old B19 infection with successful elimination of virus from the blood. These individuals can be treated as immune, and are protected against reinfection with B19.

**Clinical course**

The clinical picture associated with parvovirus B19 infection is variable (box) (2). Around 30% of infections are sub clinical in children, whereas adults tend to be more unwell. B19 commonly begins as erythema infectiosum, following with a non specific prodromal phase and flu like symptoms such as fever, headache, nausea and diarrhea. After 2 to 5 days, at around the same time as the first virus specific IgM antibody, the characteristic rash appears as a fiery red eruption on the cheeks (slapped cheek syndrome) (figure 1), extending over the following one to four days into a characteristic ring-shaped erythematous, maculopapular rash on the arms and legs (figure 2). All B19 infections, whether or not symptomatic, are accompanied by a transient fall in reticulocyte count and hemoglobin, marking viral destruction of erythrocyte precursors. Occasionally the acute symptoms are followed by severe arthralgia and arthritis. In addition to anemia, severe and occasionally persistent thrombocytopenia and neutropenia can occur, which can be life threatening (2).
Infection before the 20th week of pregnancy can have severe consequences for the fetus, where fetal mortality rates of around five percent greater than in the background population are quoted. The cause of death is probably infection related platelet damage in the placenta.

Infectable fetal erythrocyte precursors are formed from the 10th to 12th week of pregnancy. From this point on, the virus no longer reproduces within the fetus, even if it is transferred across the placenta. This type of viral transmission was found in 16% to 33% of acutely infected pregnant women. The fatality rate is however markedly lower, at 0% to 15%.

### Box

**Illness patterns associated with parvovirus B19 infections**

**Immunocompetent individuals**
- Common
- Non specific malaise
- Erythema infectiosum
- Transient anemia
- Transient mono or polyarthritis
- Transient arthralgia

**Rare**
- Thrombocytopenia
- Granulocytopenia
- Henoch-Schönlein Purpura
- Chronic arthritis
- Scleroderma
- Idiopathic thrombocytopenic purpura
- "papular purpuric gloves and socks syndrome" (PPGSS)
- Pancytopenia
- Virus associated hemophagocytic syndrome (VAHS)
- Acute liver failure/hepatitis
- Pseudoappendicitis/mesenteric lymphadenitis
- Myositis
- Myocarditis
- Glomerulonephritis
- Meningitis
- Encephalitis
- Guillian-Barré syndrome
- Cerebellar Ataxia

**Individuals with underlying hematologic disease**
- Severe anemia
- Aplastic crisis

**Fetuses**
- Miscarriage
- Fetal hydrops
- Intrauterine death

**Immunosuppressed individuals**
- Chronic anemia
- Erythroblastopenia ("pure red cell aplasia")
- Chronic thrombocytopenia
- Chronic granulocytopenia
- Chronic pancytopenia
- Myocarditis/pericarditis/acute heart failure
- Acute liver failure/hepatitis
- Meningitis/encephalitis
From the tenth to twelfth week of pregnancy the virus infects and reproduces within the pronormoblasts in the fetal liver. The destruction of erythrocyte precursors disrupts the formation of red blood cells, leading to severe anemia, edema, ascites, hydrothorax, and hydropericardium. This non immunological fetal hydrops develops between weeks 14 and 28 of pregnancy. It is estimated that parvovirus infection accounts for around 10% of these in total (4).

The onset of symptoms in the fetus are delayed, usually to around 3 to 6 weeks after the acute maternal infection, but occasionally up to 18 weeks later. Sometimes viral genome is found in the fetal lung and myocardium. Myocarditis can develop, accompanied by heart failure which exacerbates the hydropic symptoms. It is unclear whether other factors such as level and duration of viremia, maternal health and coinfection affect fetal illness. A twin pregnancy has been reported in which only one fetus developed hydrops.

Since B19 infection has been an established cause of fetal hydrops, fetal mortality has fallen markedly. Early studies quoted fetal demise in 9% of B19 infected pregnant women (5). A recent German study in 1 018 women with acute B19 infection showed that of 40 fetuses, (3.9%) with fetal hydrops, 12 died, corresponding to a mortality rate of 1.2%. The marked decrease in deaths is probably attributable to increased awareness and early diagnosis of fetal anemia using Doppler ultrasound. Swedish studies of intrauterine deaths in late pregnancy without hydrops suggested that 7.5% were associated with parvovirus B19 (10). Again, fetal symptoms can arise more than five months after the acute maternal infection. Possible causes include virally induced vasculitides in the placental lobes, or fetal myocarditis. There are no indications to date of fetal anomalies resulting from parvovirus B19 infection (8, 9). Occasionally, B19 induced fetal myocarditis can persist postnatally and require heart transplantation due to terminal heart failure.

**Prevention and treatment**

There is currently no vaccination against parvovirus B19. High dose immunoglobulin treatment may be used to treat persistent infection, particularly in immune suppressed patients. Single case reports suggest that this may also be used to treat fetal hydrops, but no studies have been carried out.

Immunoglobulin prophylaxis to prevent transplacental transmission in pregnant women is not indicated. However, close monitoring using Doppler sonography should be instituted, with a view to early detection of fetal anemia. Since fetal symptoms are delayed relative to the maternal infection, women must be followed up into late pregnancy. In the case of severe hydrops (Hb < 6–8 g/dl), intrauterine blood transfusion via the umbilical vein saves the lives of 80% of fetuses (3). Around two thirds die without treatment. In the remainder, hydrops is so mild as to be spontaneously resorbed.

**Epidemiology**

Most parvovirus B19 infections occur in childhood: 40% to 50% of children and adolescents between 10 and 15 years old have B19 specific IgG antibody as a sign of old B19 infection. Since adults are also infected, the rate of infection in the population rises to around 60 to 70% in 20 to 30 year olds, and 80% in 60 to 70 year olds. Studies in several countries have investigated how many women of reproductive age are immune to parvovirus B19 (table). Values of between 28% in the USA and 81% in Sweden were quoted (8, 11–21). Some studies explicitly report large fluctuations when groups are studied from different regions or at different times (15). No large scale serological studies of this type have been carried out in Germany. One study in healthy blood donors (average age 35 years) showed B19 specific IgG antibody in 68%.

Annual seroconversion rates in susceptible adults differ between endemic and epidemic periods. In endemic phases an incidence of between 0.65% and 1.5% in non immune individuals would be expected (11–14, 17, 20). Regionally circumscribed epidemics with incidence rates of 10% to 15%, and up to 30% at the height of the outbreak are observed between February and June (8, 12, 13, 22).

During an epidemic, the infection risk is independent of whether susceptible individuals are occupationally exposed to B19 infected or potentially infected patients – such as doctors, hospital staff, teachers, nursery nurses – or work in unrelated areas. A study from the USA compared hospital staff in contact with acutely infected patients suffering from aplastic anemia with unexposed staff: 3.1% of susceptible individuals in the groups with
patient contact became infected, whereas in the unexposed group 8.1% seroconverted (23).
During a B19 outbreak on the delivery unit of an American maternity hospital staff working
on the unit were examined, as well as staff from other areas of the hospital, staff from
another hospital, and registered blood donors in the same area. In all groups, independently
of exposure, new infection rates of 23% to 30% were found (24). In Mexico, clinical
medical students exposed to infected patients during a parvovirus B19 outbreak were
compared with preclinical students (22). The potentially exposed group showed a
seroconversion rate of 33.6%, the other group 42.6%. These examples show that during an
epidemic, the extremely stable parvoviruses are ubiquitous, leaving all susceptible
individuals with a similar exposure risk to affected individuals or contaminated objects.

A number of studies have attempted to clarify whether the risk of parvovirus B19
infection in non immune pregnant women is dependent on contact with children, as in the
case of teachers and nursery nurses. The largest of these studies examined more than 30,000
Danish pregnant women in respect of B19 specific IgM and IgG. Data were collected on
occupation, family circumstances and age (13). Women working with children under six
had a threefold increased risk of becoming infected with parvovirus B19 during pregnancy,
relative to other occupational groups (Odds-Ratio [OR] 3.97). Women with a child of their
own at home showed a similar risk (OR 3.17), whereas with two or three children at home
the odds ratio increased to 5.47 und 7.54. In teachers teaching 7 to 16 year olds, the risk of
infection was not significantly increased.
That children in the home environment pose the greatest parvovirus B19 risk during pregnancy is confirmed by other authors: Harger studied 618 pregnant women in contact with B19 infected individuals and found no significantly increased risk in teachers, nursery nurses or in women employed in the health system (8). Children in the home represented the greatest infection risk (factor 2.8). A Canadian study suggested that 50% of acute infections in pregnant women are attributable to contact with infected children and only 20% to 30% to occupational exposure. Similar data have been reported from Japan, where contact with own children was responsible for 60% of new infections in pregnant women, and only 20% due to occupational exposure. In a review article Mead et al. calculated a 6.3% increased risk of B19 associated complications of pregnancy arising in domestic contact with children, while the occupational risk was estimated to be 1.7% (25). A Canadian study examined seroprevalence rates in women employed in a variety of pre-school child care settings (17). The highest infection rate was found among individuals who had contact with children under 18 months. The seroprevalence increased with length of employment. Employees with five years' employment experience had an increased odds ratio of 1.7 (at age 20) and 1.4 (at age 30) relative to new employees of equivalent age. These results suggest that the greatest risk of an acute B19 infection in pregnant women arises from contact with a woman’s own children.

Estimation of annual numbers of cases in Germany

The population of adult women in Germany is around 42 161 000. Of these, around 19 000 000 are of reproductive age. According to current trends, reproductive age is between the ages of 15 and 50. 700 000 live births occur annually. Based on an estimated seroprevalence of 65% in the population at large, around 300 000 children annually are born to B19 seronegative women. An annual new infection rate of 1.5% gives an expected rate of acute parvovirus B19 infection in pregnant women of 3 000 to 4 000 (13). This figure would yield an expected 70 to 80 fetal deaths due to miscarriage and fatal hydrops, and

### Table

<table>
<thead>
<tr>
<th>Land</th>
<th>Untersuchte Bevölkerungsgruppe</th>
<th>Seroprävalenz (%)</th>
<th>Autor/Veröffentlichung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>pregnant women</td>
<td>58.6</td>
<td>Alanen et al., 2005 (14)</td>
</tr>
<tr>
<td>Mexico</td>
<td>medical students</td>
<td>45.9</td>
<td>Noyola et al., 2004 (22)</td>
</tr>
<tr>
<td>Canada</td>
<td>child carers</td>
<td>69.8</td>
<td>Gilbert et al., 2005 (17)</td>
</tr>
<tr>
<td>Iran</td>
<td>women</td>
<td>66.5</td>
<td>Ziyaeyan et al., 2005 (20)</td>
</tr>
<tr>
<td>Italy</td>
<td>blood donors</td>
<td>79.5</td>
<td>Manaresi et al., 2004 (e1)</td>
</tr>
<tr>
<td>Ireland</td>
<td>pregnant women</td>
<td>64.0</td>
<td>Knowles et al., 2004 (15)</td>
</tr>
<tr>
<td>Russia</td>
<td>pregnant women</td>
<td>75.3</td>
<td>O’dall et al., 2001 (e2)</td>
</tr>
<tr>
<td>Australia</td>
<td>pregnant women</td>
<td>64.0</td>
<td>Karunajeewa et al., 2001 (16)</td>
</tr>
<tr>
<td>Denmark</td>
<td>pregnant women</td>
<td>66.0</td>
<td>Jensen et al., 2000 (12)</td>
</tr>
<tr>
<td>USA</td>
<td>pregnant women</td>
<td>65.0</td>
<td>Valeur-Jensen et al., 1999 (13)</td>
</tr>
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<td>Sweden</td>
<td>pregnant women</td>
<td>49.7</td>
<td>Harger et al., 1998 (8)</td>
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<tr>
<td>USA</td>
<td>child carers</td>
<td>81.0</td>
<td>Skjoldbrand-Sparre et al., 1996 (11)</td>
</tr>
<tr>
<td>USA</td>
<td>women</td>
<td>58.0</td>
<td>Gillespie et al., 1990 (18)</td>
</tr>
</tbody>
</table>

Table: Daten zur Seroprävalenz von IgG-Antikörpern gegen Parvovirus B19 bei jungen Erwachsenen

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110 to 120 cases of fetal hydrops. The detailed figures will be published by the authors elsewhere along with an economic evaluation. No such data exist for other infectious diseases in pregnancy which are not preventable by immunization. Rubella, which is preventable by vaccination, causes embryopathies, where the infection is contracted before the 20th week of pregnancy. One to two cases are seen in Germany, annually.

**Conclusion**

Parvovirus B19 infection in a pregnant woman represents a risk to the unborn child. It therefore makes sense to establish a woman’s immunological status early in pregnancy. 5% of infections in the first twenty weeks of pregnancy will result in fetal death. These are often early miscarriages. 4% of infections contracted during the whole of pregnancy will result in fetal hydrops following transplacental transmission. Early diagnosis of fetal anemia via close sonographic monitoring allows treatment with intrauterine blood transfusion, which is usually successful.

In endemic periods, it is women who have contact with children at home who have the highest risk of a new infection during pregnancy. Pregnant women who are occupationally exposed to children under six have a slightly raised infection risk, especially in the first years of their career. During epidemics, the infection risk for all population and occupational groups is similar, and not dependent on direct exposure to infected individuals. Current evidence does not therefore support a general prohibition on working for seronegative pregnant women who have occupational contact with children.

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**Conflict of Interest Statement**

The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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**REFERENCES**

For e-references please refer to the additional references listed below.


ADDITIONAL REFERENCES


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