Netherlands
The Journal of Medicine

REVIEW

# Blood products and parvovirus B19

**K. Groeneveld[1*], J. van der Noordaa[2]**

[1]Health Council of the Netherlands, PO Box 16052, 2500 BB The Hague, the Netherlands, tel.: +31 (0)70-340 56 88, fax: +31 (0)70-340 75 23, e-mail: k.groeneveld@gr.nl,
[2]Emeritus Professor of Virology, Weesp, the Netherlands, * corresponding author

## ABSTRACT

**A Committee of the Health Council of the Netherlands has expressed its opinion on introducing testing of blood products for parvovirus B19 (B19). Although infections with B19 generally run their course without any serious health problems, for some groups, such as pregnant women, patients with underlying haematological problems and patients with immunodeficiency, infections with B19 can result in serious complications. For cellular blood products, which are derived either from a single donor or a limited number of donors and are administered either to a single patient or to a limited number of patients, the Committee recommends that a risk-group approach be adopted and that 'B19-virus safe' blood products be administered to the risk groups mentioned above. The Committee defines as 'B19-virus safe' cellular blood products from a donor in which IgG antibodies against B19 have been detected in two separate blood samples, one taken at least six months after the other. Patients other than those in the risk groups should continue to receive cellular blood products that have been produced in accordance with current safety criteria. For plasma products, which are prepared from plasma pools and are administered to large numbers of patients, the measures must be aimed at cutting down the levels of B19 infectivity in such pools. For plasma pools, the Committee proposes a maximum permissible limit of $10^4$ genome copies of B19 per ml.**

## INTRODUCTION

Infections with parvovirus B19 (henceforth referred to as B19) are quite common, particularly in children.[1,2] The most widespread clinical picture caused by B19 is erythema infectiosum, which is also known as 'Fifth disease'. In otherwise healthy individuals, the infection generally runs its course without any problems. In some groups, however, such as pregnant women, patients with underlying haematological problems and patients with immunodeficiency, B19 infections can result in serious complications. Current attempts to maximise the safety of blood and blood products focus on entirely eliminating the risk of transmitting infectious agents. This has led to a wide range of screening tests. The general introduction of such tests for hepatitis B virus, hepatitis C virus and HIV has greatly reduced the risk for transmission.[3,4] It would also be possible, but expensive, to test all blood products for the presence of viruses such as B19 and cytomegalovirus, the transmission of which is a risk for only some of those using these products. A Committee of the Health Council of the Netherlands has expressed its opinion on the introduction of such tests for B19.[5]

In its deliberations, the Committee has drawn a distinction between cellular blood products, which are prescribed relatively frequently, and products derived from plasma such as coagulation factors, which are less frequently prescribed. Cellular blood products are derived either from a single donor or a limited number of donors. These products are administered to, at the most, a limited number of patients. Plasma products are prepared from plasma pools, which are sometimes derived from very large numbers of donors and are administered to large numbers of patients.

## PARVOVIRUS B19 INFECTIONS

B19 is one of the nonenveloped viruses. With a particle size of 20 to 30 nm, it is one of the smallest DNA viruses.[6] For the purpose of replication, B19 is dependent on erythroid precursor cells in the bone marrow. These cells are destroyed by the process of viral replication. B19 is usually transmitted by coughing, but it can also be acquired by blood transfusions or, if a pregnant woman becomes infected, it can be passed from mother to unborn child. Infections with parvovirus B19 are quite common. It is estimated that in the Western world 50% of all 15-year-olds have experienced an infection.[6] Even higher percentages can be seen in the elderly, possibly as high as 80 or 100%.[1]

The diagnosis of a B19 infection is traditionally based on serological screening tests. Such tests make use of the antibodies that are produced in response to a viral infection. More modern tests, based on the detection of viral DNA, are now available. Some examples are the dot-blot test and the nucleic acid amplification test (NAT). The result of the latter test is given in number of complete copies of viral DNA (genome copies).

After B19 infection, most individuals form anti-B19 antibodies and recover with few problems. The anti-B19 antibodies persist throughout life.[7] In some groups, however, B19 infections can result in serious complications or health problems. Infection during the second trimester of pregnancy results in an approximately 10% increase in prenatal mortality and in 3% of cases leads to hydrops foetalis.[8,9] Recently published data indicate that there is also an elevated risk during the last part of pregnancy.[10]

In patients with underlying haematological problems, such as patients with congenital haemolytic anaemia, infection by B19 can result in an aplastic crisis.[2,6] B19 can persist in patients with cellular immunodeficiency, for example resulting from a HIV infection, or from treatment with immunosuppressive drugs following organ transplantation. This can cause long-lasting bone marrow damage and aplasia, not only of red blood cells,[2] but also of other cell types.[11]

Recent publications on research into small, selected groups of patients suggest that B19 infections can persist for a protracted period of time in patients with an apparently intact immune system.[12,13] Persistence of B19 was also demonstrated in bone marrow[12] and synovial membrane,[14] but not in blood, of healthy individuals.

Chronically infected individuals are treated with immunoglobulin preparations, which are administered intravenously.[2] The action of these preparations is probably based on the presence of anti-B19 antibodies.

## PREVALENCE OF B19 IN BLOOD DONATIONS AND PLASMA POOLS

The reported prevalence of B19 in blood donations varies from 0.03% to 0.6%.[15-19] No data have been published concerning the prevalence of B19 in Dutch donors.

DNA of B19 can be detected in more than 60% of the plasma pools used for the production of plasma products, though usually in relatively small quantities.[20,21] The products derived from these pools also contain B19 DNA.[20] The higher viral titres found in some pools are probably caused by a small number of highly contaminated donations. The infectivity of plasma given to individual patients is dependent on the level of the viral titre.[22] This has led to the conclusion that the reduced infectivity of plasma with low titres of B19 DNA is caused by binding of anti-B19 antibodies to the viral particles.[20,23]

## RECOMMENDATIONS

The Committee has drawn a distinction between cellular blood products and plasma products.

In the case of cellular blood products, the Committee recommends a risk-group approach in which 'B19-virus safe' blood products are administered to risk groups. In this way, patients for whom infection with B19 could cause problems will be given maximum safety blood products. This approach is in keeping with measures previously used in blood transfusion medicine with respect to cytomegalovirus transmission. The Committee defines as 'B19-virus safe' cellular blood products from a donor in which IgG antibodies against B19 have been detected in two separate blood samples, one taken at least six months after the other. The Committee has opted for this double test since the virus can persist for some time after IgG antibody formation has started. After six months, the antibodies will have resulted in removal of B19 from the blood.

The Committee recommends that B19-virus safe cellular blood products be administered to pregnant women (except in the case of transfusions given during birth), patients with congenital or acquired haemolytic anaemia who have no detectable antibodies to B19 and patients with cellular immunodeficiency who have no detectable antibodies to B19. The Committee takes the view that anti-B19 antibody testing is not feasible in the case of pregnant women, since an emergency blood transfusion may be required in some cases. In such an event, there is no time to carry out tests for the presence of antibodies.

The Committee points out that it has not yet been established whether others, such as patients with other haematological problems who require transfusions, are categorically at high risk. There is probably a wide range of individual variation. The Committee urges that further

research be carried out in this area. Patients other than those in the risk groups should continue to receive cellular blood products that have been produced in accordance with current safety criteria. The Committee emphasises that the prescription of blood products to individual patients remains the responsibility of their attending physician. The risk-group approach that is recommended for cellular products cannot be used for plasma products, given their large-scale production and use. The measures used for plasma products must be aimed at cutting down the levels of infectivity in such pools. Highly infected donations should be identified and removed before the individual samples are pooled. For final pools, the Committee proposes a maximum permissible limit of $10^4$ genome copies of B19 per ml. Earlier, the American Food and Drug Administration (FDA) suggested a similar maximal load.[22]

## CONCLUDING REMARKS

Technical developments, such as the inactivation of micro-organisms[24] and the use of nanofiltration[25] to cut down the number of viral particles in the final product, can lead to other options for making blood products B19-virus safe. The Committee feels that its proposal should be reviewed when it becomes feasible to incorporate these techniques into standard blood bank procedures. However, no such development is expected for several years.
A recently published study in a small, selected group of patients with apparently intact immune systems indicates that B19 can persist in bone marrow.[12] The Committee considers this initial report to be quite remarkable, and it urges that further research be carried out. The Committee would like to draw attention to the possibility of B19 infection in recipients of bone marrow transplants.
Finally, the Committee would like to emphasise that in the Netherlands, although being treated with blood products always involves an element of risk, even the 'standard' blood products are extremely safe.

## REFERENCES

1. Elsacker-Niele AMW van, Kroes ACM. Human Parvovirus B19: relevance in internal medicine. Neth J Med 1999;54:221-30.
2. Cherry JD. Parvovirus Infections in children and adults. In: Advances in pediatrics. Mosby Inc: 1999:245-69.
3. AuBuchon JP, Birkmeyer JD, Busch MP. Safety of the blood supply in the United States: opportunities and controversies. Ann Intern Med 1997;127:904-9.
4. Kleinman SH, Glynn SA, Busch MP, Wright DJ, McMullen Q, Schreiber GB. Declining incidence rates and risks of transfusion-transmitted viral infections in US blood donors. Vox Sang 2002;83:106.
5. Health Council of the Netherlands. Blood products and Parvovirus B19. The Hague: Health Council of the Netherlands, 2002; publication no. 2002/07E, www.healthcouncil.nl.
6. Azzi A, Morfini M, Mannucci PM. The transfusion-associated transmission of Parvovirus B19. Trans Med Rev 1999;13:194-204.
7. Kurtzman GJ, Cohen BJ, Field AM, Oseas R, Blaese RM, Young NS. Immune response to B19 parvovirus and an antibody defect in persistent viral infection. J Clin Invest 1989;84:1114-23.
8. Public Health Laboratory Service working party on fifth disease. Prospective study of human parvovirus (B19) infection in pregnancy. BMJ 1990;300:1166-70.
9. Miller E, Fairley CK, Cohen BJ, Seng C. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. Br J Obstet Gynaecol 1998;105:174-8.
10. Tolfvenstam T, Papadogiannakis N, Norbeck O, Petersson K, Broliden K. Frequency of human parvovirus B19 in intrauterine fetal death. Lancet 2001;357:1494-7.
11. Luban NLC. Human parvoviruses: implications for transfusion medicine. Transfusion 1994;34:821-7.
12. Cassinotti P, Burtonboy G, Fopp M, Siegl G. Evidence for persistence of human parvovirus B19 DNA in bone marrow. J Med Virol 1997;53:229-32.
13. Lundqvist A, Tolfvenstam T, Bostic J, Söderlund M, Broliden K. Clinical and laboratory findings in immunocompetent patients with persistent parvovirus B19 DNA in bone marrow. Scand J Infect Dis 1999;31:11-6.
14. Söderlund M, Essen RV, Haapasaari J, Kiistala U, Kiviluoto O, Hedman K. Persistence of parvovirus B19 DNA in synovial membranes of young patients with and without chronic arthropathy. Lancet 1997;349:1063-5.
15. Cohen BJ, Field AM, Gudnadottir S, Beard S, Barbara JAJ. Blood donor screening for Parvovirus B19. J Virol Meth 1990;30:233-8.
16. Jordan J, Tiangco B, Kiss J, Koch W. Human Parvovirus B19: prevalence of viral DNA in volunteer blood donors and clinical outcomes of transfusion recipients. Vox Sang 1998;75:97-102.
17. McOmish F, Yap PL, Jordan A, Hart H, Cohen BJ, Simmonds P. Detection of parvovirus B19 in donated blood: a model system for screening by polymerase chain reaction. J Clin Microbiol 1993;31:323-8.
18. Tsujimura M, Matsushita K, Shiraki H, Sato H, Okochi K, Maede Y. Human parvovirus B19 infections in blood donors. Vox Sang 1995;69:206-12.
19. Yoto Y, Kudoh T, Haseyama K. Incidence of human parvovirus B19 DNA detection in blood donors. Br J Haematol 1995;91:1017-8.
20. Willkommen H, Schmidt I, Löwer J. Safety issues for plasma derivatives and benefit from NAT testing. Biologicals 1999;27:325-31.
21. Saldanha J, Minor P. Detection of human parvovirus B19 DNA in plasma pools and blood products from these pools: implications for efficiency and consistency of removal of B19 DNA during manufacture. Br J Haematol 1996;93:714-9.
22. Brown KE, Young NS, Barbosa LH. Parvovirus B19: implications for transfusion medicine. Summary of a workshop. Transfusion 2001;41:130-5.
23. Solheim BG, Rollag H, Svennevig JL, Arafa O, Fosse E, Bergerud U. Viral safety of solvent/detergent-treated plasma. Transfusion 2000;40:84-90.
24. Corash L. Inactivation of viruses, bacteria, protozoa and leukocytes in platelet and red cell concentrates. Vox Sang 2000;78:205-10.
25. Burnouf-Radosevich M, Appourchaux P, Huart JJ, Burnouf T. Nanofiltration, a new specific virus elimination method applied to high-purity factor IX and factor XI concentrates. Vox Sang 1994;67:132-8.