Blood products and Parvovirus B19

Health Council of the Netherlands

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health,
Welfare and Sports

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Dear minister,

In addition to publishing advisory reports in response to requests from ministers, it is also the Health Council's legal duty to take the initiative in sounding the alert with regard to issues and trends that have important implications for government policy. The Health Council endeavours to meet the requirements of this activity by producing individual publications of an 'alerting' nature. It is in this context that I submit to you the 'alerting' advisory report entitled 'Blood products and Parvovirus B19'. The Blood Working Group and the Standing Committee on Immunology and Infectious Diseases formed a joint committee for the purpose of drawing up this advisory report. The document was checked by the Standing Committee on Medicine.

Parvovirus B19 infections are very common, but in most infected individuals they do not give rise to serious problems. Accordingly, in this advisory report, the Health Council proposes that a high-risk-group approach be adopted when testing blood products for infection with this virus. This means that 'B19-virus safe' blood products would only be given to those patients for whom infection with Parvovirus B19 would pose a serious health risk. Adoption of this differentiated approach would obviate the need to test all blood products for infection with Parvovirus B19. Nevertheless, if such a measure were to be introduced it would have repercussions for the manufacturers of blood products in particular.

Yours sincerely,
(signed)
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Blood products and Parvovirus B19

to:

the Minister of Health, Welfare and Sport

Nr 2002/07E, The Hague, 30 May 2002

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature management & Fisheries. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Executive summary

Infections with Parvovirus B19 (henceforth referred to as B19) are quite common, particularly in children. 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 serious 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 or health problems.

Due to the general introduction of screening tests for hepatitis B virus, hepatitis C virus and HIV, there has been a sharp fall in the risk of these viruses being transmitted via blood products. It would also be possible, but expensive, to test all blood products for the presence of micro-organisms such as B19 and Cytomegalovirus, the transmission of which is a risk to only a part of those using these products. A less expensive option is the risk-group approach, in which only selected groups of patients receive tested blood products. In this recommendation, a Health Council committee presents its verdict on the introduction of screening tests for B19.

In its deliberations, the Committee has drawn a distinction between cellular blood products and products derived from pooled plasma, such as coagulation factors.

In the case of cellular blood products, the Committee recommends that a risk-group approach be adopted and that ‘B19-virus safe’ blood products be administered to risk groups. 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 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 points out that it has not 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. Plasma products are prepared using pooled donations from what can be very large numbers of donors. These pooled donations are known as plasma pools. 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 millilitre.

Technical developments, such as the inactivation of micro-organisms and the use of nanofiltration 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.

Some recently published studies in small, selected groups of patients with apparently intact immune systems indicate that B19 can persist in bone marrow. The Committee considers these initial reports to be quite remarkable, and it urges that further research be carried out. The Committee would like to draw the 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.

Chapter 1

Introduction

Infections with Parvovirus B19 (henceforth simply referred to as B19) are quite common, particularly in children. 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 or health problems.

The Health Council’s Blood Working Group and the Council’s Standing Committee on Immunology and Infectious Diseases jointly functioned as the Committee in the present advisory report on screening tests for B19 in blood and blood products. The composition of the Blood Working Group and of the Standing Committee on Immunology and Infectious Diseases is given in appendix A.

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 either to a single patient or to 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.

1.1 Structure of the advisory document

In the following section, the Committee summarises information on B19 and on the prevalence of this virus in blood products. In section three, the Committee presents the standpoint of the Sanquin Blood Supply Foundation (which is responsible for the supply of blood in the Netherlands) with regard to testing for B19. In section four, the Committee presents its own verdict. In the final section it places its views in a wider context.

Chapter 2

Parvovirus B19

2.1 Characteristics

Parvovirus B19 is one of the non-enveloped viruses. With a particle size of twenty to thirty nanometres, it is one of the smallest DNA viruses (1). 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.

2.2 Infections

B19 infections are very common, particularly in children. It is estimated that, in the western world, fifty percent of all 15-year-olds have experienced an infection (1). Still higher percentages can be seen in the elderly, possibly as high as 80 or 100 percent (2).

The most widespread clinical picture caused by B19 is erythema infectiosum, which is also known as ‘Fifth disease’. The course of the infection is often relatively mild. In otherwise healthy individuals, the pathological effect of B19 on the erythroid precursor cells usually passes unnoticed. (2;3). Most infected individuals recover with relatively few problems, after forming anti-B19 antibodies (4). However, some individuals may experience joint problems, and these can be particularly persistent in adult women (5).

In some groups, however, B19 infections can give rise to serious complications or health problems. The major high-risk groups are pregnant women, patients with

underlying haematological problems and immunodeficient patients. Infection during the second trimester of pregnancy results in an approximately ten percent increase in prenatal mortality and, in three percent of cases, to hydrops fetalis (6;7). The high risk associated with the second trimester is probably due to the fact that there is a pronounced development of erythropoiesis during this period (1). Recently published data indicates that there is also an elevated risk during the last part of pregnancy (8). In patients with underlying haematological problems, such as patients with congenital haemolytic anaemia, infection by B19 can result in an aplastic crisis (1;3). B19 infections can persist in patients with cellular immunodeficiency, for example resulting from an HIV infection, or from treatment with immunosuppressive drugs following organ transplantation. This can cause long-lasting bone marrow damage, as well as aplasia of red blood cells (3) and other cell types (9).

B19 infection has also been described in various other groups of patients (2;3). In most of these cases it was unclear whether or not there was a causal relationship between this infection and the observed symptoms (2;3).

2.3 Diagnosis

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. In otherwise healthy patients, IgM class antibodies are produced shortly after the virus invades the body. Several days after producing IgM antibodies, the immune system generates IgG antibodies, which persist throughout life.

Serological tests suffer from a number of drawbacks, however. One of these is that a period of time usually elapses between the moment that the virus enters the body and the point at which the relevant antibodies can be detected. In the case of B19, this window phase lasts for only five to seven days (3). In immunodeficient patients, antibody formation is often disrupted. As a result, infection does not necessarily lead to the production of antibodies.

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). There is considerable variation in the sensitivity of these tests. The dot-blot test, which is relatively cheap and easy to perform, has a detection limit of around 10^4 viral particles. Using the more expensive and technically more demanding NAT, a sensitivity of 1 to 100 complete copies of viral DNA can be achieved (1;10).

2.4 Persistence

In patients with impaired immunity, B19 infections can persist for a protracted period of time (1;11). Older case reports indicate that persistence can also occur in patients whose immune system is apparently intact. This suspicion has been confirmed by recent research into small, selected groups of patients. It was shown that, after a lengthy period of time, B19 DNA could still be detected in the bone marrow of some of the patients studied. These either had symptoms ascribed to this virus (11) or inexplicable fever, joint problems or a reduced number of white blood cells (12).

In recent years, a number of papers have been published on studies into the persistence of B19 in healthy individuals. Cassinotti et al reported that, in donors with IgG antibodies to B19 (as a sign of a past infection), no B19 DNA could be detected in the blood, although – in a minority of cases – it was found in the bone marrow (11). Studies into the role of B19 in children with juvenile arthritis showed that detectable amounts of B19 DNA were present in these patients' articular cartilage (synovial membrane). Moreover, detectable amounts were also found in the synovial membranes of 13 of the 27 controls (anti-B19 IgG-positive) who had no symptoms associated with the joints (13). In this second study, no B19 DNA was detected in the blood or bone marrow.

This data confirms that B19 infections in healthy individuals lead to the production of antibodies, which clear the virus from the blood. Accordingly, individuals who have previously had an infection of this type would certainly appear to be suitable blood donors. The persistence of B19 in the bone marrow of healthy individuals with IgG antibodies raises questions about their suitability as bone marrow donors (see 5).

2.5 Treatment

The vast majority of individuals infected with B19 recover spontaneously (see 2.2). Chronically infected individuals are treated with immunoglobulin preparations, which are administered intravenously (3). The action of these preparations is probably based on the presence of anti-B19 antibodies.

2.6 Prevalence in donations

Research has been carried out to determine the incidence of B19 in blood donations (14-18). In these studies the prevalence varies from 0.03 percent (16) to 0.6 percent (18). The reported variation in prevalence could be a reflection of genuine differences. These could be caused by differences in the backgrounds of the research groups involved or by

seasonal variation in the prevalence of B19 (3). However, they could also be due (either partly or entirely) to differences in the detection methods used. No data have been published concerning the prevalence of B19 in Dutch donors.

Individuals receiving a B19-positive transfusion seldom develop a manifest infection. Research involving a limited number of patients has shown that one of ten patients who were administered a product derived from a B19-positive donation subsequently developed symptoms of B19 infection (15). The latter patient received red blood cells from the only donation that tested positive for B19 DNA and negative for anti-B19 antibodies.

2.7 Prevalence in plasma pools

The preparation of plasma products involves the pooling of donations from large numbers of donors. The pharmaceutical industry often tends to use plasma pools (henceforth referred to as 'pools') consisting of more than one thousand litres of plasma. Such pools are sometimes equivalent to more than four thousand donations (19). Research has shown that B19 DNA can be detected in more than sixty percent of such pools, though it is usually present in relatively small quantities (19;20). The products derived from these pools also contain B19 DNA (19-21). The higher viral titres found in some pools are probably caused by a small number of highly contaminated donations. B19 infections can result in viraemias with a titre of 10^{14} viral particles per millilitre (2).

The infectivity of plasma is dependent on the level of the viral titre. Thus, 18 of the 19 individuals who received plasma with a high viral titre ($10^{7.5}$ to $10^{8.5}$ genome copies per millilitre) (see 2.3) developed anti-B19 antibodies (22). The virus replicated in 14 of these individuals. The 58 individuals who received low-titre plasma ($10^{0.5}$ to $10^{3.5}$ genome copies per millilitre) did not produce any antibodies, and the virus did not replicate (22). Some authors conclude from these results that, in low-titre pools, the B19 viral particles are bound to anti-B19 antibodies (19;23). Such binding could explain the reduced infectivity of these pools.

On the basis of the above results, the American Food and Drug Administration (FDA) has suggested that, for approval for further processing, plasma pools should not exceed a limit of 10^4 genome copies per millilitre (22). In Europe, no official standpoints have been published concerning the maximum permitted number of genome copies per millilitre.

Chapter 3

Policy plan of the Sanquin Blood Supply Foundation

The previously described characteristics of B19, such as the lack of an envelope (see 2.1), imply that the virus is only partially inactivated, if at all, by the techniques that are currently used to keep blood products free of viral pathogens. In order to counteract the transmission of B19 via plasma products, the Sanquin Blood Supply Foundation advocates that donations intended for such use be tested by means of a NAT. Sanquin has not expressed an official standpoint with regard to cellular blood products.

Chapter 4

The Committee's standpoint

Current attempts to maximise the safety of blood and blood products focus on entirely eliminating the risk of transmitting infectious agents. This has produced 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 that these viruses will be transmitted in this way (24). It would also be possible, but expensive, to test all blood products for the presence of microorganisms such as B19 and Cytomegalovirus, the transmission of which is a risk for only part of those using these products. A less expensive option is the high-risk-group approach, in which only selected groups of patients receive tested blood products.

With regard to the testing of cellular blood products for infection by B19, the Committee has opted for a high-risk-group approach. 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 sheer scale of production and use makes it impossible to adopt a high-risk-group approach for plasma products (see 1). The Committee therefore proposes an alternative method of reducing the infectivity of the plasma pool used for production (see 2.7). This involves identifying and removing highly infected donations in advance.

4.1 Cellular blood products

In the case of cellular blood products, the Committee recommends that a high-risk-group approach be adopted. In most patients, a B19 infection generally causes relatively few problems. However, in those patients that belong to high-risk groups, it can lead to serious complications or health problems (see 2.2). Others have also suggested that this approach be used (25). This Committee is cognisant of the fact that a high-risk approach will have certain repercussions, both for the prescribing physicians and for the blood banks (the producers).

4.1.1 Repercussions for the prescribing physician

Physicians should distinguish between patients for whom a B19 infection represents a health risk and patients for whom such infections pose no serious problems. Here the Committee lists those groups of patients which, in its view, belong to high-risk groups. However, this is no way detracts from the fact that the prescription of blood products to individual patients is the ultimate responsibility of the attending physician. The latter is also responsible for providing his patients with adequate information.

The Committee recommends that 'B19-virus safe' blood products (see 4.1.2) 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
- patients with cellular immunodeficiency who have no detectable antibodies to B19

The Committee proposes that patients with haemolytic anaemia or cellular immunodeficiency should, as a matter of standard procedure, first be tested for anti-B19 antibodies. The Committee takes the view that this is not possible 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. Patients with haemolytic anaemia or cellular immunodeficiency receive frequent and regular blood transfusions. In such cases, treatment policy can be adjusted to allow for the presence of antibodies. The Committee anticipates that only a minority of such patients will have no detectable anti-B19 antibodies.

The Committee points out that it has not 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

advocates that further research be carried out into the risks posed to these groups of patients. The Committee feels that this topic should be given appropriate consideration in the so-called haemovigilance programme. This programme, which has yet to start in the Netherlands, will record the entire chain of events that take place during a blood transfusion (26).

Patients other than those in the high-risk groups should continue to receive blood products that have been produced in accordance with current safety criteria.

4.1.2 Repercussions for the producer

The Committee's recommendation implies that the producer must be able to supply 'B19-virus safe' blood products. The Committee proposes that this be accomplished by testing (some) of the donors for IgG antibodies to B19. The Committee considers donors to be B19-virus safe if IgG antibodies to B19 are detected in two successive blood samples taken from them with an intervening period of at least six months. The Committee has opted for this double test since the virus can persist for some time after the first IgG antibodies begin to be produced. After six months, the antibodies will have removed B19 from the blood (see 2.4).

The Committee has opted for these donors in spite of indications that B19 can persist in the bone marrow of healthy individuals (11;13). In this context, they point out that the research in question involved small groups of subjects and that B19 was not detectable in the blood (see 2.4). Furthermore, the Committee anticipates that if B19 were to be found in the blood of individuals with anti-B19 IgG antibodies, then the viral particles would be bound to these antibodies. This binding also explains why plasma pools with a low viral titre have such limited infectivity (see 2.7).

The Committee does not recommend the use of donors who have not previously been infected with B19. The reason for this is that, given the prevalence of these infections (see 2.2), it would be almost impossible to recruit a sufficiently large group of donors. Furthermore, when using such donors, there is a risk (admittedly a small one in the case of B19) that they will be in the window phase of an infection (see 2.3).

4.2 Plasma products

Measures for preventing the transmission of B19 via plasma products should be aimed at cutting the number of viral particles in the plasma pool used for production. The Committee feels that highly infected donations should be identified and removed before the final pool is created. Approaches of this kind, albeit on a limited scale, have been used successfully elsewhere (16).

For final pools, the Committee proposes a maximum permissible limit of 10^4 genome copies of B19 per millilitre. This (chosen) limit is based on the results of studies on the recipients of plasma (22) (see 2.7). The same recommendation has previously been made by the FDA (22).

Using a limit of this kind means that the majority of pools will still be weakly positive for B19. On the basis of the initial results, the presence of such small quantities of B19 DNA will not lead to infectivity of the final product (see 2.7).

In the Netherlands, the majority of donations are used in the preparation of both cellular blood products and plasma products. Testing for B19 can lead to a situation where a donation is identified as being infected with B19 on the basis of tests conducted on the plasma when the cellular blood products are already administered to a patient. The committee imagines that, in this case, the producer informs the physician who prescribed the cellular blood product. In this context, the Committee points out that use of the high-risk group approach would have meant that the patient receiving the infected cellular blood product would not have been in any of the high-risk groups. Any subsequent infection by B19 would not be expected to have serious effects on this patient's health (see 2.2).

Chapter 5

In closing

The measures proposed here are based on currently available screening tests for blood and blood products. Technical developments may produce more direct methods for rendering blood products B19-virus safe, such as the inactivation of microorganisms (27) and the use of nanofiltration to cut down the number of viral particles in the final product (28). It seems likely that the latter development could only be of use in the production of small-scale plasma products, such as coagulation factor IX. The Committee feels that its proposal should be reviewed when it becomes feasible to incorporate such techniques into standard blood bank procedures. However, this is expected to take several years.

The Committee considers it remarkable that, according to initial reports, B19 should be able to persist in bone marrow, despite the development of IgG antibodies. It feels that further research of this phenomenon is required. On the basis of currently available data, the Committee certainly does not advocate that bone marrow donors be excluded on the basis that they have previously been infected by B19. However, they would like to draw the attention of all therapists to the possibility of B19 infections in the recipients of bone marrow transplants.

Finally, the Committee would like to emphasise that, although there is always some risk attached to being administered with blood products, the ‘standard’ blood products in the Netherlands are extremely safe.

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A The committee

Annex

Annex **A**

The committee

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