An assessment of the risk, cost-effectiveness, and perceived benefits of anti-parvovirus B19 tested blood products

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BACKGROUND: Parvovirus B19 (B19V) can cause severe anemia, hydrops foetalis, and even death in vulnerable patients. To prevent transfusion-transmitted B19V infection of at-risk patients, B19V antibody screening of blood donors was implemented. The cost-effectiveness of this intervention is unclear, as the likelihood of transmission through blood and subsequent complications for recipients are unknown. This study estimates the cost-effectiveness of anti-B19V donor screening in the Netherlands.

STUDY DESIGN AND METHODS: The estimates needed for the cost-effectiveness model were: the occurrence of B19V in Dutch blood donors, the number of anti-B19V tested products required by hospitals, the likelihood of morbidity and mortality given B19V infection, treatment costs, and screening costs. These estimates were obtained from literature and observational data. When data were unavailable, structured expert judgment elicitation and statistical modeling were applied.

RESULTS: The costs of preventing one transfusion transmitted B19V infection are estimated at €68,942 (€42,045 – €102,080). On average, 1.25 cases of morbidity and 0.12 cases of mortality are prevented annually. Although the perceived risk of transfusion transmitted B19V infection was low, half of the treating physicians favored anti-B19V screening.

CONCLUSION: The estimated mortality and morbidity caused by B19V infection was low in the risk groups. The cost-effectiveness ratio is similar to other blood safety screening measures. No guidance exists to evaluate the acceptability of this ratio. The explicit overview of costs and effects may further guide the discussion of the desirability of B19V safe blood products.

Infection with parvovirus B19 (B19V) can have detrimental effects for specific patient groups like patients with hemolytic anemia or an immune-compromised condition, patients undergoing allogenic bone marrow or stem cell transplantation, and for pregnant women. Since these patients generally have problems with generating red blood cells or antibodies, an infection with B19V—which temporarily stops production of red blood cells—can cause severe anemia and/or an aplastic crisis. In addition, B19V can cause hydrops foetalis in the fetus. The main route of transmission is through the air (aerosols), but transmission through blood products does occur as well. Transfusion-transmitted B19V infections have only been reported through donations containing a viral load above 10^4–10^5 international units per milliliter (IU/mL).[1–4]

Currently, the Netherlands is the only country that has "anti-B19V tested" cellular products in stock to have "B19V

ABBREVIATIONS: Anti-B19V tested products = red blood cell and platelet products testing positive for B19V antibodies; B19V = parvovirus B19; CER = cost-effectiveness ratio; CI = confidence interval; RBC = red blood cell products; IgG = immunoglobulin G; IgM = immunoglobulin M; IUT = intra-uterine transfusion; IU/ml = international unit per milliliter; IVIG = immunoglobulin therapy (intravenous immunoglobulin); NAT = nucleic acid testing; PI = prediction interval; SCT = stem cell transplant; SD = standard deviation; PLT = platelet products.

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safe" blood available for specific risk groups. Anti-B19V tested products are obtained from donors who are screened and tested positive for B19V antibodies (IgG) twice, with at least 6 months between both IgG tests. These anti-B19V tested cellular products were advised in 2002 by the Dutch Medical Advisory Board for intra-uterine transfusions (IUT) of the unborn, premature babies (<32 weeks and/or <1500 gram), neonates after IUT (until 6 months after à terme date), pregnant women, patients with hemolytic anemia without B19V antibodies, patients with cellular immune deficiency without B19V antibodies, and patients undergoing allogenic bone marrow or stem cell transplantation.[5] The discussion about anti-B19V tested products started when the European committee introduced the obligatory B19V DNA test (NAT) for plasma-derived medicine products. The Dutch Health Council considered it unacceptable to release products for blood transfusion while it was (retrospectively) known that some donations were viremic for B19V, and hence anti-B19V screening was implemented for blood products.[5]

Yet very little is known about the likelihood of B19V infection through a highly viremic blood product, the size of the patient groups at risk, and the probability of morbidity and mortality given a B19V infection. This gap in knowledge exists because some of these factors are difficult (unethical or unfeasible) to study. The primary objective of the research described in this paper is to estimate the cost-effectiveness of donor B19V antibody screening. Secondary, we assessed the risk perception of treating physicians regarding B19V infection through blood transfusion in the Netherlands and their perception of the importance of the availability of anti-B19V tested blood products. The combined quantitative and qualitative results provide an interesting perspective for policy makers, showing an estimate of the risk as well as how it is perceived by practitioners. For each of the risk groups, the cost-effectiveness model allows estimation of how many cases of B19V transmission, morbidity and mortality are prevented by current screening, and what the costs are per case prevented.

METHODS

Cost-effectiveness model

Cost-effectiveness was modeled from a healthcare perspective: the outcomes were restricted to healthcare costs and health outcomes. The absolute number of cases prevented was chosen as outcome measure (as opposed to, for example, QALYs) as it is most relevant and easy to interpret. Moreover, as the prognosis of patients at risk for receiving B19V-tested products is not known—and in many cases relatively poor—it was not feasible to infer the effect of B19V-tested products in terms of changes in QALYs. Model parameters were estimated by literature review, data collection, expert judgment elicitation, and statistical modeling. Parameters comprised the number of B19V infections in blood donors, transmission probability of B19V through blood transfusion, number of anti-B19V tested blood products required per risk group, likelihood of treatment, morbidity and mortality caused by B19V infection, costs of treatment, and costs of current donor B19V antibody screening. Ultimately, the number of patients at risk is multiplied by the probability that a product is infected, the transmission probability, and the patient group specific probabilities of treatment, comorbidity, and mortality. Analyses were performed using R Version 3.5.0.

Number of B19V infections among donors

Data from the plasma screening department on the number of plasma pools with high-level B19 viremia (B19V DNA > 10^6 IU/mL) between 2013 and 2017 were collected. This screening was performed for manufacturing of plasma and plasma-derived medicines.* From these data, the number of infected whole blood donations and derived red blood cell (RBC) products and platelet (PLT) products were calculated, and expressed as a proportion of the total number of RBC and PLT products issued annually.

Literature search

Search terms combining "blood transfusion" and/or "parvo B19" with each of the individual patient groups were entered in PubMed (Appendix 1, available as supporting information in the online version of this paper). Of the publications found, the references and "cited by" lists were checked for additional relevant publications until the information on the parameters required were found. If a parameter could not be extracted from literature, it was estimated by structured expert judgment elicitation (see below). If results from the literature search contained multiple (different) estimates for one parameter, the parameter to be used in the model was selected based on similarity of the study settings to the Dutch population, time of publication, and policy. The uncertainty as a result of variability in the estimates found in the literature was expressed by means of minimum and maximum credibility values around the parameter estimate.

Blood use in the patient risk groups

Data were collected on the requested number of anti-B19V tested RBC and PLT products in 1 year (either 2016 or 2017). Eleven hospitals were included (3 academic, 4 teaching, and 4 smaller general hospitals). These data were extrapolated to all 87 Dutch hospitals using a quasi-Poisson regression model with the number of irradiated products as a predictor for the number of anti-B19V tested products requested per hospital. An association between these variables was expected a priori because many of the patients with an indication to receive irradiated blood also require anti-B19V tested blood. The prediction interval (PI) for the estimated number of blood

*Plasma pool screening is performed for plasma-derived medicine products, but is not a release criterion for blood products because test results are available with a delay and the sensitivity is not high enough for this purpose.

products per hospital was inferred using the standard error of the model predictions. The distribution of the anti-B19V tested products over the patient groups was based on the "transfusion advice" and was linearly extrapolated for academic and general hospitals separately.

Expert judgment elicitation

Structured expert judgment elicitation is a technique to obtain expert estimates on values that are unavailable from the literature.[7,8] Our experts were physicians specialized in hematology (adult or pediatrics), neonatology, and immunology, who treat patients with an indication for anti-B19V tested blood products. Through an online questionnaire, experts were asked to imagine the following scenario: "Suppose that a patient of yours becomes infected with the parvovirus B19. What proportion of patients will develop aplastic crisis or severe anemia due to the infection? What proportion will be treated for this infection and how (blood transfusion, immunoglobulin therapy [IVIG], or other)? What proportion of patients will develop other long-term morbidities as a result of the infection (myocarditis, viral hemophagocytic syndrome, arthritis, or other)? What proportion of infected patients will die due to (complications of) the infection?" Experts were asked to provide their "best guess" and an estimate of what the value would be "at least" and "at most." Finally, experts were asked: "Suppose that anti-B19V tested blood is no longer available, how severe would be the consequences for patients?" and "Do you consider it medically acceptable to abolish anti-B19V tested blood?" The answers of all experts were pooled into one distribution per question, used to calculate the median and the 95% confidence interval (CI).[9] A detailed description of the analysis and the elicitation process is provided in Appendix 2, available as supporting information in the online version of this paper.

Model assumptions

The following assumptions were made:

- Costs and effects of current practice as opposed to perfect adherence to current guidelines is evaluated.
- Seroprevalence of B19V for the risk groups is similar to that in the general population, including neonates and fetuses who will be passively immunized with antibodies from the mother for at least 6 months after birth.
- The consequences of fetal infection via vertical transmission and via IUT are similar.[10]
- The consequences of B19V infection in pediatric and adult hematological patients are similar in terms of probability of morbidity, mortality, and treatment.
- The consequences of B19V infection in allogenic SCT and autologous SCT patients are similar.

Sensitivity analysis

To quantify the impact of uncertain model parameters, a univariate sensitivity analysis was performed for various cost-effectiveness ratios. For each model parameter, credible lower and upper limits were established. By recalculating model outcomes for these alternative values, the impact of each individual parameter is shown.[11] For parameters found in literature, the credibility intervals were based on high and low values found in literature. For the estimated blood use in the risk groups, the credibility interval was based on the prediction intervals for the estimated model outcomes. For the expert judgment elicitation parameters, the credibility interval was based on the 95% CI from the pooled expert judgments.

RESULTS

Epidemiology in donors

In the period 2013-2017, on average 18.2 B19V infected whole blood donations were detected annually. This equates to 0.004% (18 of 423,673 issued) of RBC products and 0.03% (18 of 55,897 issued) of PLT products issued. In an outbreak year the average number of infected donations was 22, and 12 was the average number in a non-outbreak year (Fig. 1).

Model parameters found in literature

Transfusion-transmitted infections reported

Cases of transfusion-transmitted B19V infection that are reported show that B19V transmission does not occur with a viral load below 10^4 IU/mL and that transmissibility also depends on the immune status of the donor and the immune status of the recipient.[4,12–23] In the current model, a transmissibility of 100% was assumed for donations with a high viral load (B19V DNA $>10^4$ IU/mL) if the donor is both immunoglobulin M (IgM) and IgG negative, or IgM positive and IgG negative. If a highly viremic donor is both IgM and IgG positive, a transmissibility of 0% was assumed.[20] The proportion of highly viremic donors that is IgM and IgG positive was estimated from a dataset of 67 viremic donors with 4 cases of both IgM and IgG positivity at 6%.[6] Consequently, the current model assumes that 6% (CI 2%-15%) of highly viremic donations cannot transmit the B19V infection.

Pregnant women and intra-uterine transfusion

Annually, approximately 180,000 pregnancies occur in the Netherlands, resulting in approximately 170,000 live births in 2015.[24] Assuming a transfusion rate of 0.035% in pregnant women, as found in Denmark and Sweden,[25] we expect that 144 pregnant women will receive blood in the first and second trimester. This is when B19V transmission has the most severe consequences for the fetus. Assuming an average of 1.5 products per woman, 216 products are transfused annually. Of these, 207 are RBCs and 9 PLTs based on a ratio RBC:PLT of 96%:4% as found in Canada.[26] As 70% of pregnant women are expected to be seropositive, only 30% are at risk for infection. An additional risk is the transfusion of fetuses with IUTs. From 2014 to 2017, on average 70 IUTs were performed per year, based on the number of products for IUT issued by the blood bank. Parameters on the likelihood of

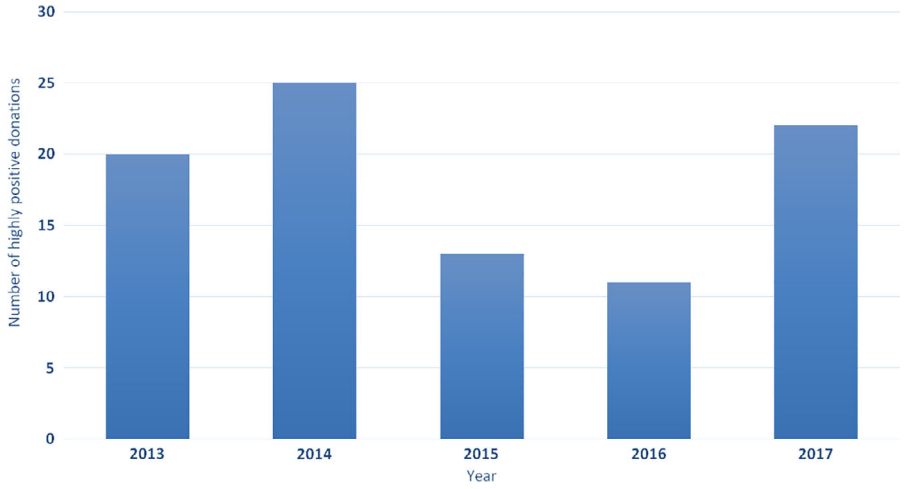


Fig. 1. Number of highly positive parvovirus B19 donations per year. [Color figure can be viewed at wileyonlinelibrary.com]

morbidity, mortality, and treatment were based on existing literature (Table 1; complete results of the literature search are provided in Appendix 3, available as supporting information in the online version of this paper). If parameters were not available in literature, they were inferred from other model parameters (Fig. 2, calculations shown in Table 1).

Anti-B19V tested products requested by hospitals

The prediction model estimates a national demand of 23,425 (PI 14,767–38,563) anti-B19V tested RBC and 16,742 (PI 7,775–39,303) PLT per year (excluding products for pregnancy or IUT). The estimated national distribution of anti-B19V tested products over the patient groups is shown in Fig. 3. Most anti-B19V tested RBC and PLT products were given to patients receiving an allogenic SCT.

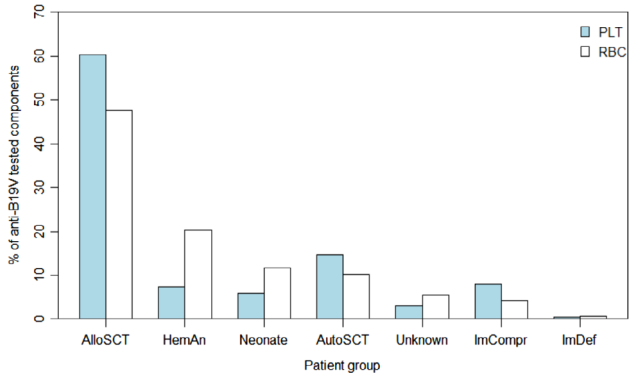


Fig. 2. Distribution of parvo anti-B19V tested (A) RBC (B) PLT use over different patient groups. AlloSCT = allogeneic stem cell transplant recipients; HemAn= haemolytic anaemia patients; Neonate = neonates; AutoSCT = autologous stem cell transplant recipients; Unknown = indication unknown or other; ImCompr = immune compromised patients; ImDef = immune deficiency patients; RBC = red blood cell products; PLT = platelet products. [Color figure can be viewed at wileyonlinelibrary.com]

Model parameters elicited from experts

In total, 25 experts of whom 16 hematologists (12 adult, 4 pediatric), 8 neonatologists, and 1 immunologist responded out of approximately 48 experts invited (excluding an unknown number of experts asked through snowball effect). Experts had on average 15.3 (SD = 8.7) years of experience in their field. For each question, the pooled estimates of the experts and 95% CI are presented in Table 2. Large variation between experts was found regarding the estimated probability of severe anemia and treatment with IVIG and blood transfusion, both between and within specialties. The experts were more in line with respect to the estimated probability of morbidity and mortality. Individual expert responses are reported in Appendix 4, available as supporting information in the online version of this paper.

Costs

Screening costs

In November 2017, 123,137 donors in the Netherlands were labeled "anti-B19V tested," which equals 37% of the total Dutch donor population. In the two most recent years 39,331 tests on average were performed annually. The price per test is estimated at €9.36 including costs for reagents, personnel, and equipment. Combined, the estimated costs of screening are €368,139 annually. The costs of having a double inventory of anti-B19V tested versus non-anti-B19V tested blood were neglected because these costs are very small relative to the testing costs, as no separate storage infrastructure is needed (the anti-B19V tested products are simply labeled accordingly). Implementation costs were also not considered as these are only incurred once and do not impact future decision making.

Treatment costs

Treatment costs prevented by screening were divided into costs of blood transfusion and costs of IVIG therapy. The costs of a transfusion with an irradiated RBC were €220 per

TABLE 1. Literature parameters selected for pregnant women and intra-uterine transfusions (minimum and maximum credibility values between brackets). Risks apply to the situation of infection of the fetus except when explicitly stated otherwise

Outcome parameter	Pregnant women	IUT recipients
Seroprevalence parvovirus B19	70%	70%
Vertical transmission rate	40%	-
% hydrops foetalis	5% (3-13) given infection of the mother	5%/40% = 12.5% (7.5-32.5)
% fetuses with developmental delay	8.7% (0-18.7) *0.15 = 1.3% (0-2.8)	1.3% (0-2.8)
% treated with intra-uterine transfusions	15% (1.2-30) given infection of the mother	15%/40% = 37.5% (0.3-75)
Average number of IUTs with RBCs	1 (1-1.04)	1 (1-1.04)
Average number of IUTs with PLTs	0.25 (0-0.25)	0.25 (0-0.25)
% fetal death	9% (5-11) given infection of the mother	9%/40% = 22.5% (12.5-27.5)

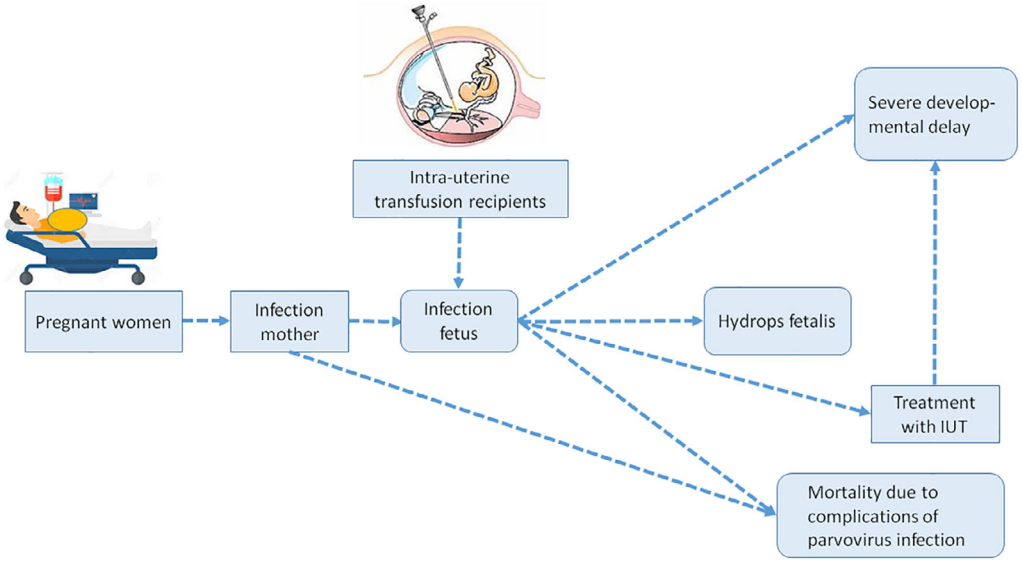


Fig. 3. Schematic model parameters for pregnancy and IUTs. Dotted arrows represent risks. [Color figure can be viewed at wileyonlinelibrary.com]

product (which was the purchase price for hospitals in the Netherlands) and €342 for IUTs. Similarly, the costs for IVIG therapy were €5,527 for an adult of 70 kilograms, whereas for a neonate the costs were €103.

Cost-effectiveness of anti-B19V screening

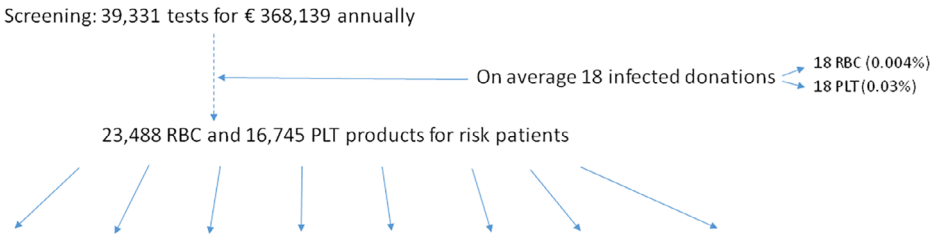
Combining the findings from the data collection, literature search, and expert judgment elicitation, it is estimated that the current implementation of B19V screening prevents 5.33 infections caused by blood transfusion on average annually. Of these infections, 1.25 would cause severe morbidity and 0.12 would cause mortality (Fig. 4). The costs (discounted with the costs of treatment of B19V infection) were €68,942 for preventing one infection in a vulnerable patient, €294,470 for preventing a case of severe morbidity, and €3,096,102 for preventing a fatal case.

Sensitivity analysis

The uncertainty in the estimated morbidity and mortality rates has the highest impact on the cost-effectiveness ratio

TABLE 2. Median and 95% CI results for the expert elicitation questions for neonates, hemolytic anemia patients, SCT patients, and immune deficiency patients

Patient group	Severe anemia	IVIG treat-ment	Blood transfusion	Myocarditis	Hemofagocytic syndrome	Arthritis	Mortality
Neonates	2% (0-76)	2% (0-51)	20% (2-96)	5% (1-22)	2% (1-11)	1% (1-11)	2% (0-32)
Hemolytic anemia	46% (1-90)	1% (0-79)	54% (4-99)	2% (0-11)	2% (0-8)	5% (0-48)	2% (0-14)
SCT	10% (2-99)	5% (0-98)	53% (4-100)	3% (0-12)	2% (0-11)	4% (0-15)	2% (0-29)
Immune deficiency	5% (3-7)	100% (100-100)	100% (100-100)	0% (0-1)	0% (0-0)	20% (16-24)	0% (0-1)



	SCT	Hemolytic anaemia	Neonates	Immune compromised	Immune deficiency	Pregnant women	IUT	Other/ Unknown	**Total**
Products transfused	13,532 RBC 12,558 PLT	4,751 RBC 1,242 PLT	2,748 RBC 1,000 PLT	975 RBC 1,341 PLT	143 RBC 89 PLT	63 RBC 3 PLT	21 RBC	1,277 RBC 513 PLT	**23,488 RBC 16,745 PLT**
Infections prevented	4.05	0.53	0.12	0.41	0.030	0.001 2	0.0007 9	0.19	**5.33**
Morbidity prevented	0.80	0.29	0.012	0.082	0.0078	0.00017	0.0001 2	0.050	**1.25**
Mortality prevented	0.094	0.081	0.0027	0.0096	0.00020	0.00028	0.0001 8	0.0041	**0.12**
Treatment costs prev.	€280	€71	€1	€29	€18	€1	€1	€1	**€398**

Fig. 4 Effectiveness of anti-B19V screening. Estimated number of transfusions and cases of B19V infection, morbidity and mortality prevented by anti-B19V screening per patient group annually. The estimated costs of anti-B19V screening are shown as well as the estimated treatment costs prevented. RBC = red blood cell products; PLT = platelet products; SCT = stem cell transplant reciepients; IUT = intra-uterine transfusion. [Color figure can be viewed at wileyonlinelibrary.com]

(Table 3). Especially the number of fatal cases significantly increases when a high parameter value for the mortality rate is assumed: from 0.12 to 1.41 fatal cases with a cost-effectiveness ratio of €260,851 per fatality prevented. Reversely, the lower bound credible value for the mortality rate would implicate that 0.01 fatal cases are prevented at €31,236,184 per case. As morbidities were combined and may occur in the same patient, the estimated number of morbidities can exceed the number of infections. The number of products transfused has a moderate impact, and the transmissibility rate and probability of treatment have a low impact on the cost-effectiveness ratio.

Risk perception by treating physicians

More than two-thirds of the medical specialists perceived the risk of receiving B19V through blood transfusion as low. Still half of these specialists did not consider it justified to abolish anti-B19V tested blood (Table 4). Two types of responses can be distinguished: (1) the risk was perceived as low which makes it acceptable to abolish parvo screening (n = 9), or (2) the risk was perceived as low but abolishing parvo screening is considered unacceptable because of the serious consequences that may occur in case of infection transmission (n = 7). Exposing patients to an additional disease was especially perceived as unethical.

TABLE 3. Univariate sensitivity analysis for number of cases prevented and the cost-effectiveness ratio between brackets. The lower and upper credibility values for the changed parameters are specified in the Results section. CER = cost-effectiveness ratio per case prevented. *differs per patient group, see Table 2 for the low and high parameter values

Changed parameter	Low vs. high parameter values	Number of infections prevented (CER)	Number of cases of morbidity prevented (CER)	Number of fatal cases prevented (CER)
Number of products transfused	low (22,758)	3.60 (€102,080)	0.9 (€422,414)	0.080 (€4,618,382)
	high (78,082)	8.74 (€42,045)	1.99 (€185,004)	0.20 (€1,878,722)
Transmissibility	low (0.85)	4.82 (€76,249)	1.13 (€325,742)	0.12 (€3,423,189)
	high (0.98)	5.56 (€66,125)	1.30 (€282,453)	0.12 (€2,968,620)
Risk of morbidities	low*	5.33 (€68,942)	0.16 (€2,325,974)	0.12 (€3,096,102)
	high*	5.33 (€68,942)	7.10 (€51,785)	0.12 (€3,096,102)
Likelihood of treatment	low*	5.33 (€69,010)	1.25 (€294,764)	0.12 (€3,099,194)
(blood transfusion, IVIG)	high*	5.33 (€67,752)	1.25 (€289,390)	0.12 (€3,042,694)
Risk of mortality	low*	5.33 (€68,942)	1.25 (€294,470)	0.012 (€31,236,184)
	high*	5.33 (€68,942)	1.25 (€294,470)	1.41 (€260,851)

TABLE 4. Risk perception of 24 experts

Abolishing medically responsible? → / Size of the risk ↓	Yes	No / for subgroup	Unknown	*Total*
Low	9	7	1	*17 (71%)*
Moderate	0	2	0	*2 (8%)*
Unknown	0	3	2	*5 (21%)*
Total	*9 (38%)*	*12 (50%)*	*3 (12%)*	*24 (100%)*

DISCUSSION

This study investigated the costs and effects of donor B19V antibody screening as a blood safety measure to prevent transfusion-transmitted parvovirus B19 infection. Unique estimates are presented for each patient group at risk by evaluating their use of anti-B19V tested products, the expected consequences of B19V infection, and the incremental cost-effectiveness of screening compared to no screening. The transparent overview of these outcomes may guide the discussion on the desirability and prioritization of anti-B19V screening.

In the Netherlands, transfusion of anti-B19V tested products prevents on average 5.3 cases of B19V infection, 1.2 cases of morbidity, and 0.1 cases of mortality in risk groups annually. The risk of transmission mostly originates from PLTs, as approximately 30% of these are given to patients in risk groups (in contrast to 5.5% of RBCs). The cost-effectiveness ratio is €68,942 per case of B19V infection prevented, €294,470 per case of morbidity prevented, and €3,096,102 per fatal case prevented. The rather unfavorable cost-effectiveness ratio is primarily the result of the low occurrence of B19V in blood donors of 0.005% per year. In comparison, the incidence of parvovirus infection in Dutch seronegative pregnant women is 2.4% per year.[27] Compared to this incidence, an additional 0.005% seems negligible. When the risk of B19V infection by transfusion is put into perspective with other risks, such as the common respiratory route of infection (contact with children, coughing) and other non-parvo B19V related problems that the risk patients face, the risk of infection by blood products is low. This poses the question whether it might be more cost-effective to target these competing risks. However, other aspects need to be considered in the decision-making process in addition to an (objective) consideration of risks. Factors that are (perhaps equally) important are the perception of the risk, the uncertainty in the estimated effects, the context of the decision, and the available alternatives.

Although the perception of the risk posed by transfusion-transmitted B19V infection was low, half of the treating physicians responding to the questionnaire did not find it acceptable to abolish the current screening. The severity of potential complications of B19V infection weighed heavily in their judgment. Arguments from those who find it acceptable to abolish screening are practical: the very small risk of infection through blood transfusion is outweighed by the higher risks of other problems (e.g., the risk of airborne transmission and other non-blood-borne infections), whereas those who find it unacceptable to stop anti-B19V screening consider it unethical to accept illness through medical intervention that can be prevented. In general, the physicians found it difficult to estimate the actual risk and impact of B19V infection because of the rarity of blood transfusion incidents and because it is context-dependent. For example, the risk of B19V infection-related morbidity for patients with autoimmune hemolytic anemia is associated with the availability of matched blood to bridge the period of B19V infection.

The uncertainty in the outcomes in the present study is caused for a large part by the assumptions made and the nature of the analysis methods used. By using the number of anti-B19V tested products requested by hospitals, we analyzed current practice in hospitals instead of the theoretical case of perfect adherence to guidelines. In some ways, this approach overestimates the number of products required according to guidelines because hospitals in fact use more anti-B19-tested products than necessary (e.g., patients may not be tested for B19V seropositivity). Also, for pragmatic reasons, hospitals often request anti-B19V tested blood for auto-SCT patients, which is not consistent with current guidelines. Another finding that leads to an increased demand of anti-B19V tested blood use is that the indications for the risk groups seem to be shifting: we found "new" indications that are not included in the actual guideline such as patients with immune-compromised conditions caused by medication. On the other hand, anti-B19V tested blood is sometimes not given to risk patients, either because the physicians miss the indication for anti-B19V tested blood, or because anti-B19V tested blood is not available in combination with other requirements such as extensively matched blood (especially for pooled PLTs). Although this produces a distorted image of the number of patients who need anti-B19V tested blood according to the guideline, the analysis accurately reflects the cost-effectiveness of current practice. The size of the group of patients with thalassemia and sickle cell disease might be overestimated because the patient population is not distributed homogeneously across the country. Another source of uncertainty concerns the parameters elicited from experts. While the expert judgment elicitation technique does fill a gap in knowledge by providing informed estimates of unknown parameters, a limitation of this technique is that no accuracy measure exists to evaluate experts' judgments. To facilitate the interpretation of these uncertain outcomes, confidence intervals around the estimates provide a credible range of outcomes. Finally, by assuming a 100% transmissibility of highly viremic donations without IgG antibodies we took a conservative, worst-case scenario in favor of patient safety.

Whether a cost-effectiveness ratio is considered appropriate is highly dependent on the context, such as the cost-effectiveness ratios found for other blood safety screening measures. Currently in the Netherlands, NAT screening is performed for HIV, hepatitis B virus, and hepatitis C virus.

The costs for these tests combined are €2.5 million per case prevented (and €5.2 million per QALY).[28] A more recent example is hepatitis E virus screening, which has a much higher incidence (0.188% of blood donations) and costs of €8,099 per transmission prevented and €3.0 million per incurable case averted from 2009–2011.[11] In comparison, the €68,894 per case prevented for the B19V does not seem out of line, however a framework for evaluating the cost-effectiveness is lacking.[29] Countries in Europe and across the world differ substantially in their policy from no B19V screening to testing on request. This may be due to differences in incidence and seroprevalence,[30,31] lack of evidence of actual transmission, or because the disease burden and the cost-effectiveness of screening are poorly understood. Recently, a study on the B19V blood safety risk in Australia concluded that TT-B19V is a tolerable risk to blood safety, given the small contribution of transfusion to the burden of B19V disease, and the significant costs that would be incurred by any strategy to reduce it.

There are various alternatives for the current serological screening. The first alternative would be to apply B19V NAT screening as used for plasma-derived medicinal products. This test will most likely be too costly because costs for daily, molecular screening of blood products are much higher than costs for serologic testing. Another alternative would be to restrict availability of anti-B19V tested products to a smaller selection of patients. For example, only provide anti-B19V tested products for pregnant women and IUTs, as the highest gain of QALYs is expected for unborns and the consequences of a B19V infection have been established with high certainty. This would imply abolishing screening for the other risk groups including SCT recipients, despite the fact that this is by far the largest groups that—as a result—carries the largest absolute risk. In addition, restricting product availability does not automatically lead to a substantially more favorable cost-effectiveness ratio. Estimating the screening costs for a smaller risk group is difficult as the number of donors to be tested does not change proportionally to the number of anti-B19V tested products required. Further alternatives for B19V antibody screening were mentioned by the treating physicians, such as performing lookback after notification of a positive NAT in the plasma pool screening. This would allow the monitoring of patients who received a potentially infected blood product and the direct measurement of effects of a B19V infection. According to a recent review, transfusion-transmitted B19V infections do occur but are overlooked by treating physicians because they do not have clinical relevance.[3] Finally, current blood screening could be replaced by standard testing and monitoring of the vulnerable patients at risk for transfusion-transmitted B19V infection, to be able to intervene quickly if necessary. This could be done by generating awareness among clinicians for the possibility of transfusion transmitted B19V infections and looking for symptoms of a B19V infection after transfusion.[3] All scenarios that involve a restriction of risk groups should account for difficulties associated with de-implementation of existing safety interventions.[32]

In conclusion, the cost-effectiveness of anti-B19V screening is similar to that of other blood safety interventions. Additional considerations play a role: the perception of the risk, the uncertainty in the effects, and the alternatives available. Further research on the (cost-) effectiveness of potential alternatives is recommended, but considering the possibility of clinical interventions and scarcity of known cases of transmission (also in other countries) we recommend considering abolition. It is encouraged to set up an international clinical registry of cases of transfusion-transmitted B19V infection for countries that are considering implementing B19V antibody screening of donors.

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CONFLICT OF INTEREST

The authors have disclosed no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Search terms used in literature search.
Appendix S2. Expert judgment elicitation process and analysis.
Appendix S3. Results of literature search for pregnancy and IUT.
Appendix S4. Expert judgment elicitation questionnaire responses.