Health Council of the Netherlands

Q fever: risk of transmission via blood or other body material
Dear Minister,

I am pleased to present you the advisory report *Q fever: risk of transmission via blood or other body material*. The advisory report is the third and final report in response to your questions relating to Q fever. In the first two advisory reports, the specially appointed Committee examined the added value of human vaccination against Q fever; in this report, it advises on possible measures for blood and other body material in relation to Q fever. A draft of the advisory report was assessed by the Standing Committees on Medicine and on Infection and Immunity.

In this advisory report, the Committee provides a brief overview of the course of the Q fever outbreak in The Netherlands. The situation looks promising with regard to acute Q fever: the number of new patients was lower in 2010 than in the two previous years, and to date, this trend has continued for 2011. The Committee is less reassured about chronic Q fever. The number of patients with chronic Q fever is significantly lower than the number of patients with acute Q fever, but the Committee cannot rule out that *Coxiella burnetii* (the bacterium responsible for Q fever) is also present in blood or body material from patients who will developed chronic Q fever but currently have no health complaints or in whom the infection follows a sub-clinical course. If these groups become donors, the Committee cannot rule out transmission of Q fever via blood or other body materials.

With regard to blood transfusion, the Committee recommends conducting a model-based analysis of the expected costs and effects of serological testing of blood donors for Q fever. For other body materials, the Committee differentiates between body materials with a very low risk of transmission and materials with a higher risk.
For material with a higher risk, the Committee recommends testing donors for contamination with *C. burnetii*. The Committee can easily imagine that the nature of the material may dictate whether infection will also lead to rejection. For example, body material that has the potential for significantly improving the recipient’s quality of life or even be life-saving, it may still be used despite a positive test result for Q fever in the donor. I agree with the Committee’s conclusions and recommendations.

I also offered this advisory report to the Minister of Economic Affairs, Agriculture and Innovation today.

Yours sincerely,

(signed)
Professor L.J. Gunning-Schepers
President
Q fever: risk of transmission via blood or other body material

to:

the Minister of Health, Welfare and Sport

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 and health (services) research…” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. 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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Q fever is a zoonosis – an infectious disease that can be transmitted from animals to humans – caused by the bacterium *Coxiella burnetii* (*C. burnetii*). Until 2006, Q fever was a rare disease in The Netherlands, with an average of around twenty reported patients per year. In 2007, the first major outbreak of Q fever occurred in our country, concentrated around the village of Herpen, Brabant. A total of 168 patients were reported. In 2008 and 2009, the outbreak of Q fever spread further, with 1,000 and 2,354 reported cases, respectively. Outside these high-risk areas, there were reports of cases in Gelderland and Utrecht. In 2009, the Dutch government took various measures in the veterinary field (measures ‘at the source’). In early 2010, it was still unclear whether, and if so when said measures would positively affect the incidence of Q fever in humans. The Minister of Health, Welfare and Sport subsequently questioned whether new research data and recent insights might lead to reassessment of previous advisory reports and decisions on additional measures in humans. The Minister requested particular attention for vaccination and blood transfusion measures. Given the greater urgency surrounding vaccination issues, the Committee published two previous reports on the subject, on 1 July and 14 December 2010, respectively. The Committee addresses Q fever and blood transfusion in this advisory report. On the Ministry’s request, the Committee also examines Q fever and body materials, for example organs for transplantation. As will become clear, this advisory report primarily examines chronic Q fever, while the previous advisory reports focused more on acute Q fever.
Recent patient data

In 2010, the number of new patients with Q fever was lower than in the previous two years. It is likely that various measures taken ‘at the source’ have had a positive impact, but it is currently impossible to state with certainty whether the positive developments in terms of the number of disease cases mean that the Q fever epidemic in The Netherlands is actually nearing its end. That assessment can likely be made with greater certainty later in 2011. To date, however, developments this year are positive: once again, there are fewer new patients with acute Q fever and no risk area can be defined.

The decrease in the number of new patients with Q fever does not mean that the problem of Q fever for the health care system is automatically reduced. The focus now shifts from patients with acute Q fever to patients with chronic Q fever, about which far less is known. The number of patients with chronic Q fever is much lower than that of patients with acute Q fever: an estimated 1.5 to 2 percent of patients with acute Q fever develops chronic Q fever. Patients with chronic Q fever may carry the bacterium for a long time. It cannot be ruled out that the bacterium is also located in the blood or body material of patients who will develop chronic Q fever, but currently have no health complaints or in whom the infection follows a sub-clinical course. If these groups become donors, the Committee cannot rule out transmission of *C. burnetii* via blood transfusion or body material.

Measures in the area of blood transfusion

In discussing possible measures in the area of blood transfusion, the Committee will limit itself to blood products with a short shelf-life: red blood cells, platelets and (non-inactivated) plasma.

There is only a single report of Q fever transmission via blood transfusion in the scientific literature, from 1977. In recent years, data on contamination of Dutch donors with *C. burnetii* have become available thanks to serological research and research into the micro-organism’s genetic material. In 2010, the Sanquin Blood Supply Foundation (Sanquin), responsible for the blood supply in The Netherlands, screened donors from those regions in The Netherlands with the highest infection burden of *C. burnetii* for the presence of said micro-organism’s DNA. Sanquin stopped testing on 1 November 2010 due to the lack of positive samples. The so-called look-back study also provides information. This is research among receivers of blood products, whose donors reported health com-
plaints caused by – in this case – infection with *C. burnetii* after donation. Based on the results of these different types of research, the Committee determined that a relatively high percentage of donors from the studied high-risk area (twelve percent) is or has been infected with *C. burnetii*. In 2009 and 2010, two receivers of short shelf-life blood products were found to be infected with *C. burnetii*. As both recipients live in Noord-Brabant, infection may also have occurred via the environment. The Committee concludes that the risk of Q fever transmission via blood transfusion in The Netherlands, even during a major Q fever outbreak, may not be zero, but is very likely to be limited. The Committee notes that it was forced to draw its conclusions on transmissibility of Q fever via blood transfusion based on a relatively limited amount of research data.

Even in the event of a persistently lower number of patients with acute Q fever, given this lack of data and the potential transmission of *C. burnetii* by infected donors without health complaints, the Committee recommends that a model-based analysis be performed of the expected costs and effects of serological testing of blood donors for Q fever on a regional or national scale. Because the Committee cannot currently state with certainty whether the Q fever epidemic is actually nearing its end, it recommends that this cost-effectiveness analysis include the possibility of a renewed outbreak of acute Q fever. While awaiting the outcome of this analysis, the Committee suggests that the Minister ask Sanquin to prepare for the possible development of donor testing on a regional or national scale.

In the event of a Q fever outbreak, the outcome of the cost-effectiveness analysis could guide the decision on whether or not to take measures. If an outbreak of acute Q fever occurs before the cost-effectiveness analysis has been conducted, the Committee recommends restarting screening for *C. burnetii*. The Committee recommends that expert opinion be consulted should restarting screening be considered, for example the Outbreak Management Team.

**Measures in the area of body material**

Given the outbreak of Q fever in The Netherlands, and based on available research data, the Committee believes it is possible *C. burnetii* could be transmitted via body materials. The Committee differentiates between body materials with a very low risk of transmission and materials with a greater risk.
The Committee expects the risk of transmission of Q fever to be very low for body material collected and stored prior to 2007—i.e., prior to the Q fever outbreak—for example, bone, heart valves or cord blood, and for material very unlikely to carry C. burnetii (for example cornea), and for material for which preparation methods greatly reduce the risk of contamination (for example, long shelf-life blood products such as clotting factors and immunoglobulins). The Committee feels no measures are needed for these body materials. For materials collected and stored prior to 2007, however, the Committee feels that separate storage from material collected later, and therefore potentially high-risk, or storage in such a manner that transmission of C. burnetii is extremely unlikely, is a requirement.

In the event of a persistently lower number of patients with acute Q fever, the Committee recommends serological testing of donors of body materials with a higher risk of Q fever transmission for infection with C. burnetii. Although Q fever has mainly manifested itself in certain parts of The Netherlands, the Committee recommends—given the international exchange of body material—that donor testing be implemented nationally. Whether potential contamination of said material will also lead to rejection is likely to depend on the nature of the material. For example, the Committee can imagine that for organ or stem cell transplant, the body material may still be used despite a positive test result for Q fever in the donor. After all, receiving organs or stem cells represents a major quality of life improvement for the receiver, and can sometimes be life-saving. Information about the potential contamination of the transplanted material is still valuable in such cases; the attending doctor may consider prescribing prophylactic antibiotics after transplantation. The Committee notes however, that it is unknown whether such prophylaxis in receivers of transplants is effective, and how long such prophylaxis should be given. For other body materials with a higher risk of Q fever transmission, the Committee recommends that serological test results determine whether the material can be used. The Committee makes this recommendation because infection with C. burnetii can lead to serious problems in the receiver (for example, for heart valves or blood vessels), or because use of material obtained from another donor is, in principle, possible. The Committee makes an exception to testing on a national scale in the case of sperm donation for intra-uterine insemination. In the case of donation by an individual other than the partner of the woman involved, or in the case of donation by the partner followed by sperm storage, the Committee recommends that the donor be tested if he is from the former high-risk area for Q fever. In the case of direct processing and use of the partner’s sperm, the Committee does not feel testing is
needed. Potential contamination is likely to have already occurred at a previous point in time.

In the event of a new outbreak of Q fever, the Committee recommends that donors of body materials with a higher risk be screened for the presence of *C. burnetii* DNA. The Committee also recommends that screening be conducted on a national scale, and feels that expert opinion should be consulted when making the decision on whether to initiate screening.

**Research recommendations**

At various points in this advisory report, the Committee notes there is a (relative) lack of data, not only on the potential transmission of Q fever via blood transfusion or body materials, but also regarding more basic questions. With regard to the latter, the Committee refers to the diagnosis and treatment of (primarily chronic) Q fever and the results of the already initiated vaccination campaign for Q fever. In closing, the Committee therefore makes recommendations for further research.
Introduction

1.1 Background

On 18 January 2010, the Health Council received a request for advice from the Minister of Health, Welfare and Sport regarding measures that could counteract Q fever in The Netherlands (see Annex A). The Minister is particularly interested in the role human vaccination might play and measures relating to blood transfusion.

The request for advice was drafted due to the increased scope of the problem Q fever poses in The Netherlands. Q fever is a zoonosis – an infectious disease that can be transmitted from animals to humans – caused by the bacterium *Coxiella burnetii* (*C. burnetii*). Until 2006, Q fever was a rare disease in The Netherlands, with an average of about twenty reported patients per year. In 2007, the first major outbreak of Q fever occurred in our country, concentrated around the village of Herpen, Brabant. A total of 168 patients were reported. In 2008 and 2009, the Q fever epidemic expanded to eastern Noord-Brabant as well as Zuid-Limburg (respectively with 1,000 and 2,345 reported cases in those years).* Out-

* At the time of the initial advisory report by the Committee, the number of patients for 2009 was reported to be 2,361. The National Institute for Public Health and the Environment (RIVM) later revised this figure to 2,354.
side of these high-risk areas, there were reports of cases in Gelderland and Utrecht.

In 2009, the Dutch government took various measures in the veterinary field (measures 'at the source'). Among other things, milk goats were vaccinated against \textit{C. burnetii}, and pregnant goats were culled at contaminated farms.

### 1.2 Request for advice and recommendations

In the period between 2007 and 2009, the number of patients increased each year. In early 2010, it was still unclear whether, and if so when measures ‘at the source’ would positively affect the incidence of Q fever in humans. The Minister of Health, Welfare and Sport subsequently questioned whether new research data and recent insights might lead to reassessment of previous advisory reports and decisions on additional measures in humans. The Minister requested particular attention for vaccination and blood transfusion measures. Given the greater urgency surrounding vaccination issues, the Committee published two previous reports on this subject, on 1 July and 14 December 2010, respectively.\textsuperscript{1,2}

In this advisory report, the Committee addresses the possible measures for blood transfusion. On the Minister's request, the Committee expanded its recommendations to cover possible measures relating to the use of body material, such as organ and tissue transplants.

### 1.3 Structure of this advisory report

In the first advisory report, the Committee provided an overview of the disease Q fever and of the outbreak of Q fever in our country. In its second report, the Committee provided a brief overview of the developments in 2010 and up to publication of the advisory report. The Committee also examines the course of the Q fever outbreak in Chapter 2 of this report. It will pay particular attention to the areas most relevant to blood transfusion and body materials. In Chapter 3, the Committee will address the question relating to Q fever and blood transfusion, and the final Chapter (Chapter 4) will examine Q fever and body material. Both Chapters conclude with recommendations.
The Q fever outbreak in The Netherlands

Until 2006, Q fever was a rare disease in The Netherlands, with an average of about twenty reported patients per year. In the years 2007 through 2009, the number of patients rose from 168 to 1,000 and 2,354, respectively. In 2009, various veterinary and agricultural measures were taken to combat Q fever. At the time the first advisory report was drafted, it was still too early to tell what influence these measures would have on the number of patients in 2010. It has since become clear that the number of new patients with Q fever in 2010 was lower than in the two previous years, and that developments for 2011 to date are also promising. The Committee provides an overview of these developments and outlines potential consequences below.

2.1 Number of patients

Compared to 2008 and 2009, the number of new reports of Q fever dropped in 2010. In 2010, the National Institute for Public Health and the Environment (RIVM) received 504 reports of acute Q fever. This is significantly less than in 2008 and 2009, but still more than in 2007 and earlier. In 2008 and 2009, there was a clear, fairly sudden increase in the number of patients, a peak that did not materialise in 2010. The Committee notes that despite this promising development, The Netherlands has remained, for the past three years, the country with the highest number of new Q fever patients.
It is likely that various measures taken ‘at the source’ have had a positive impact, but it is currently impossible for the Committee to state with any certainty whether the positive developments in terms of number of disease cases means the Q fever epidemic in The Netherlands is actually nearing its end. Greater certainty in this regard will likely only be possible later in 2011, but developments to date this year remain promising. For example, the number of new patients has decreased further (on 15 June 2011, 37 new patients with acute Q fever had been reported), once again there was no new peak in the number of patients, and as in 2010, no high-risk area for Q fever can be defined. Some of the measures have now been withdrawn.

2.2 Acute versus chronic Q fever

The decrease in the number of new patients with Q fever does not mean the problem Q fever poses for the health care system is automatically reduced. The focus now shifts from patients with acute Q fever to patients with chronic Q fever, about which far less is known. This is due in part to the fact testing for chronic Q fever (in particular) is difficult. Over the past year, a Dutch group of experts has developed algorithms for diagnosing acute and chronic Q fever. Experts differentiate between proven, probable and possible chronic Q fever. The presence of antibodies against Q fever (serology) is a criterion for each of these three categories. For ‘proven Q fever’, clinical data and tests for C. burnetii genetic material using so-called polymerase chain reaction (PCR) are also involved.

Chronic Q fever, particularly expressing as endocarditis, poses a serious health problem. The number of patients with chronic Q fever is, however, much lower than the number of patients with acute Q fever: an estimated 1.5 to 2 percent of patients with acute Q fever develops chronic Q fever. A recent publication on Dutch patients found that after one year of follow-up, chronic Q fever – diagnosed using the algorithm mentioned above – had occurred in eleven of the 686 patients with acute Q fever (1.6 percent). However, it is conceivable that this number will grow in the coming years. This is because chronic Q fever can also present later than one year after acute infection, and patients may develop chronic Q fever without (recognised) acute Q fever.

Patients with chronic Q fever may host the bacterium for a long time. It cannot be ruled out that the bacteria is also located in the blood or body materials of patients who will develop chronic Q fever, but currently have no health complaints or in whom the infection follows a sub-clinical course. If these
groups act as donors, the Committee cannot rule out transmission of *C. burnetii* via blood transfusion or body materials.
In this Chapter, the Committee first discusses data obtained from Dutch research among donors and recipients of blood products with a short shelf-life: red blood cells, platelets and (non-inactivated) plasma. Subsequently, it provides an overview of various approaches that may be used when dealing with risks during medical interventions. Such an overview is relevant, as far more stringent requirements apply to blood transfusion medicine than to other medical interventions. The Committee concludes this chapter with recommendations for potential measures.

In discussing possible measures regarding blood transfusion, the Committee will limit itself to the previously mentioned blood products with a short shelf-life. The Committee expects that various steps taken in preparing blood products with a long shelf-life, such as clotting factors, will lead to a significant reduction in the number of any *C. burnetii* bacteria present. The Committee will examine these long shelf-life blood products in more detail in Chapter 4.

### 3.1 Data

There is only a single report of Q fever transmission via blood transfusion in the scientific literature, from 1977.\(^\text{12}\) This is a well-documented case from the United States, where Q fever was extremely rare at the time. Almost 20 years earlier, there was a report of isolation of *C. burnetii* from the blood of a patient with chronic Q fever.\(^\text{13}\) In 2008, the Health Council stated that existing safety meas-
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Measures meant the odds of Q fever transmission via blood transfusion were negligibly small.14 The transmission in 1977 occurred via a full blood donation, a form of blood transfusion that no longer takes place. Currently, so-called leukodepletion is used in blood transfusion to remove white blood cells, and it is possible *C. burnetii* resides in these cells in particular.

Until recently, no reliable screening test existed for Q fever.14 This has changed: in recent years, data on infection of Dutch donors with *C. burnetii* have become available thanks to serological research and research into the micro-organism’s genetic material. Using existing serological tests (detecting antibodies, often using a so-called ELISA technique), it can be determined whether a donor is or has been infected with this micro-organism or not.7 Serology is not suitable for screening in the first two to three weeks from the moment of infection.7 In order to allow testing in that phase, a PCR test for *C. burnetii* genetic material was developed in recent years.15 The Sanquin Blood Supply Foundation (Sanquin), responsible for the blood supply in The Netherlands, has used this test to study blood donations.16 Finally, so-called look-back studies also yield information. This is research among receivers of blood products, the donor of which reported health complaints caused by – in this case – infection with *C. burnetii* after donation.

### 3.1.1 Research into *C. burnetii* genetic material

Research into *C. burnetii* genetic material in donor blood used a PCR test which identifies the presence of DNA fragments of this bacterium.15 A positive test means that the bacterium’s DNA was found in the donor’s blood. This does not mean the blood contains actual (infectious) bacteria.

Perforce, the test has not been validated in the manner blood transfusion tests normally are. This was impossible, as there are no reference positive or negative test samples or so-called conversion series available that can be used to determine whether a test is sufficiently sensitive. To date, the test could only be performed manually, and automation is not feasible in the short-term. This means a maximum of 94 donations can be screened per day.16 Sanquin used the PCR test for research in 200917 and for screening in 2010.18

In 2009, blood samples from about 40,000 donations were stored. At the end of that year, samples from donors from parts of The Netherlands with the highest infectious burden for *C. burnetii* were selected.17 These areas were defined by the National Institute for Public Health and the Environment (RIVM) by postal
code. Six of 1,004 donations tested – from different donors – were found to be positive. The test result for each of these donors could be checked by performing a serological test on a second blood sample. In three of them, infection with \textit{C. burnetii} was confirmed serologically; it was not for the three others. The conclusion was that the PCR test had yielded a false-positive for the latter three. For the three actually positive donations, recipient testing was only possible for one. One recipient was found to have had a \textit{C. burnetii} infection. As this recipient resided in Noord-Brabant, however, it is unclear whether the infection was transfusion related or had environmental origins.

In 2010, Sanquin used the PCR test to screen for infection with \textit{C. burnetii}, again in areas with the highest infectious burden.\textsuperscript{18} A total of 6,380 donations were tested. Four samples were positive, but infection was not confirmed serologically in any of these four. Due to the low number of positive samples, combined with the low number of new reported cases of Q fever, Sanquin decided to cease testing donor blood for \textit{C. burnetii} per 1 November 2010.\textsuperscript{19}

### 3.1.2 Serological research

The 1,004 blood samples used to study the PCR method in 2009 were also used for serological testing. By testing two consecutive donations from the same blood donor, it could be determined whether infection had occurred during the study period or before then. If the first sample is negative for \textit{C. burnetii} antibodies and the second positive, the donor was infected during the study period, and has undergone a so-called seroconversion.

A second donation was available for 543 of the 1,004 original donors by late 2009. Signs of infection were found in a total of 66 of these 542 donors (12 percent).\textsuperscript{20} Another study into Q fever among pregnant women yielded a very similar percentage: fourteen percent of pregnant women from high-risk areas for Q fever were found to be infected or have been infected.\textsuperscript{21,22}

In 56 of the 66 infected donors, infection had occurred before the start of the study, the other 10 were infected during the study. Extrapolating to the number of new disease cases or infections in one year (the incidence), these results imply that over the course of a single year, 5.7 percent of donors in the areas examined would have been infected with \textit{C. burnetii}.\textsuperscript{20} This percentage is significantly higher than the incidence in the area as calculated based on reports of new cases of Q fever (0.7 percent).\textsuperscript{23} This kind of difference is often seen for infectious diseases and is certainly imaginable for Q fever, as a significant proportion of infections has an asymptomatic course\textsuperscript{1}. 

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3.1.3 Look-back studies

In 2010, twelve look-back studies were performed because the donor reported disease symptoms that were found to be related to Q fever after donation. Testing was possible in six recipients of blood products from these donors. Based on serological testing, two recipients were found to be positive for Q fever; one was already positive before the blood product from the donor who had fallen ill was administered. As both recipients live in North Brabant, it is again unclear whether the infection was caused by the blood transfusion.

3.2 Conclusion

The results of the serological research performed in 2009 show that twelve percent of the studied group of donors from high-risk areas is or has been infected with *C. burnetii*. However, these data cannot be translated directly into the percentage of donors who can actually transmit the infection for a number of reasons. For example, donors who have suffered an acute infection and subsequently clear the bacteria – and therefore no longer carry it with them – remain seropositive. Also, donors who are already infected but not yet sick may transmit the infection.

In 2009 and 2010, two receivers of short shelf-life blood products were found to be infected with *C. burnetii*. As both recipients live in North Brabant, infection may also have occurred via the environment.

The Committee feels the results of the *C. burnetii* screening performed in 2010 – which found no actual positive donations – reflect the drop in new reports of patients with acute Q fever.

The Committee draws attention to the difference in incidence shown by serological data and reported cases. According to the Committee, this difference may indicate a higher number of asymptomatic cases of Q fever than previously estimated. It notes that under-reporting of new patients cannot be ruled out. The Committee believes that in future, these asymptomatic but – potentially chronically – infected donors will play a greater role.

The Committee notes that in the high-risk area studied, a proportion of donors is or has been infected with *C. burnetii*, the bacteria responsible for Q fever. Nonetheless, the Committee concludes that the risk of Q fever transmission via blood transfusion in The Netherlands, even during a major Q fever outbreak, may not be zero, but is very likely to be limited. The Committee notes that it was forced
to draw its conclusions on transmissibility of Q fever via blood transfusion based on a relatively limited amount of research data.

The European Centre for Disease Prevention and Control (ECDC) published a report on Q fever in May 2010. The ECDC estimated the risk of receiving a blood donation contaminated with C. burnetii from a donor without symptoms of Q fever, under current conditions in The Netherlands, to lie between 0.32 and 0.70 per 10,000 donations, depending on underlying assumptions. The ECDC also indicated that risk estimates regarding Q fever are complicated by a lack of data. The ECDC concluded that, even should a contaminated donation result in infection, the risk of developing Q fever via transfusion in our country is lower than the risk of infection via environmental exposure. The Committee underwrites this conclusion, but this does not release it from advising on measures that could reduce this risk further.

3.3 Dealing with risks during medical interventions

3.3.1 Maximal or optimal safety

Previously, the Health Council stated that receiving blood and blood products is not free of risk, and will likely remain so in future. In this regard, a blood transfusion is no different from other medical interventions. However, measures taken in blood transfusion medicine – more so than for other interventions – are often based on maximal safety. Even measures with a relatively poor cost-effectiveness balance are introduced or maintained. An example of this is testing all blood donations for the extremely rare – in The Netherlands – human T-lymphotropic virus (HTLV). Other medical interventions, such as vaccination, pay more attention to the balance between cost and effectiveness. In 2002, the then Minister of Health, Welfare and Sports expressed the desire to move towards optimal rather than maximal safety for blood transfusion. According to the Minister, this meant that not all available safety measures may be introduced, particularly if the benefits are marginal in relation to the costs.

3.3.2 Risk group approach

An alternative to testing all donated blood (maximal safety) is a risk group-based approach: only testing donations destined for certain categories of recipient. In The Netherlands, blood transfusion medicine has selected this approach for measures countering Cytomegalovirus and Parvovirus B19. For Q fever, this approach could be used to mirror past Committee recommendations on vaccin-
tion: the vaccine must only be offered to certain groups of patients that have an increased vulnerability for Q fever. In the opinion of the Committee, this includes various categories of patients with cardiovascular disease.

### 3.4 Recommendations in case of a permanently lower number of patients with acute Q fever

The Committee concluded that the risk of Q fever transmission via blood transfusion in The Netherlands under the current circumstances – with a dropping number of new cases of acute Q fever, and chronic Q fever being the greatest problem – may not be zero, but is very likely to be limited. However, it was forced to base this conclusion on a limited amount of research data, and without knowledge about whether a blood donor infected with *C. burnetii* who does not have any health complaints (yet) can transmit this microorganism via blood transfusion.

Due to the lack of data, the Committee recommends conducting a model-based analysis of the expected costs and effects of serological testing of blood donors for Q fever on a regional or national scale.

Currently, it is not technically feasible for Sanquin to test all roughly 900,000 donations collected each year. This capacity cannot be realised overnight, and can only be made possible with extensive investments. While awaiting the outcome of the cost-effectiveness analysis, the Committee suggests the Minister may ask Sanquin to prepare for the possible development of donor testing on a regional or national scale.

The Committee has also discussed other options for testing donors for Q fever.

If the principle of maximal security is followed in preventing (potential) transmission of Q fever via blood transfusion, all donated blood would have to be tested serologically for (past) infection. The Committee feels such a measure is currently too far-reaching, irrespective of the technical feasibility at this time. It recommends waiting for the results of the proposed cost-effectiveness analysis.

The second option discussed by the Committee is testing donations destined for certain groups of patients for Q fever (the previously mentioned risk group approach). The Committee would at the very least include the groups of patients defined in the previous advisory report on vaccination for Q fever. However, there are also signs that individuals with poorly functioning immune systems must be considered at risk for Q fever. Based on Dutch data, the Committee estimates that a total of at least 35 percent of blood transfusion recipients belong to this risk group. In the Committee’s opinion, this makes a risk group
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3.5 Recommendations in the event of a renewed outbreak of Q fever

In 2010, Sanquin screened donors from the regions in The Netherlands with the highest infection burden of *C. burnetii* for the presence of said micro-organism’s DNA. The organisation ceased testing on 1 November 2010 due to the lack of positive samples, which – in the Committee’s opinion – is related to the low number of new disease cases reported in 2010. Under the current conditions – without an outbreak – the Committee can agree with the decision to suspend screening. However, the Committee recommends including a scenario for a renewed outbreak of acute Q fever in the recommended cost-effectiveness analysis. In the event of a Q fever outbreak, the outcome of the cost-effectiveness analysis could guide the decision on whether or not to take measures.

Should the Minister take on the Committee’s recommendations and if an outbreak of acute Q fever occurs before the cost-effectiveness analysis has been conducted, the Committee recommends restarting screening of donor blood. The Committee recommends expert opinion be consulted should restarting screening be considered, for example the Outbreak Management Team.

The Committee sees screening as important not only for the quality of tested donations, but also as the first step in an intervention model. Screening may provide (additional) information about the extent of the outbreak. Should the outbreak prove too large, more stringent measures may be required. The Committee recommends the Minister ask Sanquin to take suitable measures under such circumstances, for example ceasing blood collection in the high-risk area. This approach was chosen during an outbreak of Q fever in Chamonix, France, in a clearly delineated area with a relatively limited number of involved individuals. Maximising blood collection in the rest of the country could just about compensate for the loss of a large area (for example the province of Noord-Brabant).

For completeness’ sake, the Committee notes that in the event of a risk area larger than a province, excluding donors from that area would no longer be a suitable solution, as the blood supply as a whole would be endangered. However, the Committee expects this situation – blood deficits – will not occur. After all,
goat farms are concentrated in certain parts of the country, and various measures already taken ‘at the source’ appear to be successful.⁴
Chapter 4

Measures in the area of body material

Tissues and organs that become available for transplantation are screened for a number of infectious diseases. Screening for *C. burnetii* is currently not part of this screening. Given the course of the outbreak of Q fever in The Netherlands, it is possible that transplantation here could lead to the transmission of Q fever. The transmission of *C. burnetii* via body material has been demonstrated in animal studies.34

On the instructions of the European Commission, the ECDC also issued an advisory report on body material and Q fever.35 The ECDC recommends considering setting up screening for donors of body material in affected areas, as well as active surveillance of recipients of said material. The ECDC does not distinguish between various types of body material.

4.1 Data

The research conducted to date into the transmission of Q fever via body material or the presence of *C. burnetii* in said material has primarily been conducted in bone marrow, heart valves and sperm. Less is known about other material, such as stem cells, bone, ear bones, cartilage, skin, organs, egg cells and embryos. Some research was conducted a long time ago, some as far back as the 1950s.
4.1.1 Presence of C. burnetii in body material

Most research conducted into the presence of C. burnetii was conducted using the previously described PCR techniques, or using techniques that can be used to identify parts of the bacteria. The disadvantage of both techniques is that while information can be obtained about the presence of parts or remains of the bacteria, nothing can be said about the potential for infection. This is possible based on experiments in which C. burnetii is cultured from tissues or organs. Such research has been conducted on a fairly small scale.

It was demonstrated some time ago that C. burnetii can be isolated from various tissues. Q fever was successfully cultured from bone marrow and aortic valves of patients with chronic Q fever. C. burnetii was present to a higher degree in the aortic valve than in other tissues, such as spleen and lung.

In patients with chronic Q fever, genetic material from C. burnetii or parts of the bacteria have been found, among other things, in heart valves, blood vessels, serum, lungs, sperm, bone marrow and liver. The heart valves of five patients with endocarditis in whom Q fever was diagnosed were found to contain C. burnetii genetic material.

4.1.2 Transmission of Q fever via body material

There are seven cases in the literature of suspected sexual transmission of Q fever via sperm. Person-to-person transmission has also likely occurred during autopsy. There is one reported case of Q fever after bone marrow transplantation. However, it is unclear whether infection was actually related to transmission via bone marrow.

4.2 Conclusion

The Committee is of the opinion that transmission of Q fever via body material is possible. Particularly in patients with chronic Q fever, C. burnetii is demonstrable in and can be cultured from bone marrow and heart valves. Q fever transmission has also been described for other body materials – but not all of them.

Whether transmission will result in Q fever in the recipient, with all this would entail, depends on a variety of factors. The Committee feels transmission is most likely where donation of infected heart valves, bone marrow, blood vessels and sperm is involved. Given the highly contagious nature of the bacteria, transmission of even a small number of bacteria, therefore also possible with other body...
materials, may potentially lead to disease. The Committee feels the odds of infection will further increase in case of suppression of the immune system, as is often needed in, for example, recipients of organ donations to prevent rejection of the organ.

4.3 Variation in transmission risk for Q fever

For body material, there is great variation in the risk of transmission for *C. burnetii*. In discussing various possible measures for preventing transmission, the Committee therefore chooses an approach based on the material in question rather than the recipient. Before discussing potential measures, the Committee first provides an overview of various types of material. The Committee does not aim to provide a complete overview; however, it does expect that materials not discussed can be fit into the overview provided. Unfortunately, only a limited amount of research data were available for this purpose.

4.3.1 Body material with a very low risk of transmission

The Committee expects the risk of Q fever transmission to be very low for some body materials. This is the case for body materials collected and stored prior to 2007 (for example bone, heart valves or cord blood). After all, there was no Q fever epidemic in The Netherlands at the time.

A second group with a very low risk is material that is extremely unlikely to be carrying *C. burnetii*. The Committee includes the – non-vascularised – cornea in this group.

A final group with a very low risk is material for which preparation greatly reduces the risk of contamination. For example, the Committee expects that various steps required for preparing blood products with a long shelf-life (such as clotting factors and immunoglobulin products) will lead to a significant reduction in the number of any *C. burnetii* bacteria present. The Committee notes that it is not certain that processing leads to the complete removal or inactivation of *C. burnetii*.

The Committee feels no measures are needed for body material with a very low risk of transmission. Material collected and stored prior to 2007 must be stored separately from material collected later – and therefore potentially high-risk – or in such a manner that transmission of *C. burnetii* is extremely unlikely.
4.3.2 **Body material with a higher risk of transmission**

The transmission of *C. burnetii* via various body materials has been described. The Committee feels transmission is possible for certain others. The Committee recommends testing donors of these materials for *C. burnetii*. Whether contamination of material will also lead to rejection likely depends on the nature of the material. For some material, contamination will be of secondary importance, while for others it will be unacceptable.

**Body material for which potential contamination is of secondary importance**

The Committee can imagine that for organ or stem cell transplantation, the body material may still be used despite a positive test result for Q fever in the donor. After all, receiving organs or stem cells represents a major quality of life improvement for the receiver, and can sometimes be life-saving. The Committee would like to emphasize that Q fever remains a serious condition, perhaps doubly so for transplant recipients. Information about the potential contamination of the transplanted material is still valuable in such cases; the treating doctor may consider prescribing prophylactic antibiotics after transplantation.

**Body material for which contamination is unacceptable or that can be replaced**

For other body material with a higher risk of Q fever transmission, the Committee recommends serological test results determine whether the material can be used. The Committee makes this recommendation because infection of these body materials with *C. burnetii* could lead to serious problems in the recipient given the nature of the material (for example for heart valves or blood vessels), or because use of material obtained from another donor is possible in principle (for example – in case of donation by a person other than the partner – sperm).

4.4 **Recommendations in case of a permanently lower number of patients with acute Q fever**

The Committee previously stated no measures are needed for body material with a very low risk of transmission. For body material with a higher risk of transmission, the Committee recommends testing for infection with *C. burnetii* is neces-
Measures in the area of body material

sary in principle, in part because the transmission of the bacteria via body materials would occur as a result of medical intervention. The Committee recommends serological screening for Q fever for donors of all body material with a higher risk.8 Although to date, Q fever has primarily manifested in certain parts of the country, the Committee recommends donor testing be introduced on a national scale, given the international exchangeability of body material. Whether a positive test result will lead to rejection likely depends on the nature of the material. Information about contamination of the transplanted material is still valuable in cases where it is of secondary importance; the treating doctor may consider prescribing prophylactic antibiotics after transplantation. The Committee notes that it is unknown whether such prophylaxis in receivers of transplants is effective, and how long such prophylaxis should be given.

The Committee makes an exception to testing on a national scale for sperm donation for intra-uterine insemination. The Semen working group of the Netherlands Association for Clinical Chemistry and the Association for Clinical Embryology came to the same conclusions.47 The Committee identifies three options.

If the sperm belonging to the involved woman’s partner is processed and used directly for insemination, the Committee feels donor (in this case the partner) testing is unnecessary. Potential contamination has likely already occurred at a previous point in time.

If the partner’s sperm is stored prior to insemination, the Committee recommends partner testing if he is from the previous high-risk area for Q fever. The Committee recommends defining the high-risk area in the same way as for vaccination of people against Q fever. By storing sperm from donors with a positive test result separately from that from donors with a negative test result, or storing it in such a way that transmission of C. burnetii is extremely unlikely, cross-contamination of donated sperm during storage can be prevented.

If the sperm of anyone other than the partner is used for insemination, the Committee recommends testing the donor if he is from the previous high-risk area for Q fever. In the Committee’s opinion, this should also occur if the donor is an acquaintance of the woman in question. The Committee recommends excluding sperm from donors with positive test results from further use.

The Committee realises that sperm donated in 2008 and 2009 is stored frozen. It recommends conducting additional tests to determine potential contamination of this sperm with C. burnetii.
4.5 Recommendations in the event of a renewed outbreak of Q fever

In the event of a new outbreak of Q fever, the Committee recommends donors of body materials with a higher risk also be screened for the presence of *C. burnetii* DNA. In this situation, the Committee recommends screening be limited to donors of body material with a higher risk of *C. burnetii* transmission, as described in paragraph 4.3.2. Given the international exchangeability of body materials, the Committee recommends screening be introduced on a national scale in the event of a Q fever outbreak. Finally, as for blood transfusion, the Committee recommends expert opinion be consulted should restarting screening be considered, for example the *Outbreak Management Team*. 
At various points throughout this advisory report, the Committee notes there is a (relative) lack of data. Not only on the potential transmission of Q fever via blood transfusion or body material, but also regarding more basic questions of diagnostic testing and treatment of (primarily chronic) Q fever and the results of the Q fever vaccination campaign currently underway. In this Chapter, the Committee therefore makes recommendations for further research. This includes both human and animal studies.

5.1 **Research into Q fever in general**

The Committee recommends continuing to carefully track the Q fever outbreak in The Netherlands, preferably through active surveillance. Previously, the Committee mentioned the drop in the number of new patients in 2010 and the resulting shifting of the problem from acute Q fever to chronic Q fever.

There are a number of reasons why it is extremely important to stay abreast of developments. In the eyes of the Committee, this is necessary first and foremost because it recommends screening donors from regions in The Netherlands with the highest infection burden of *C. burnetii* for the presence of said microorganism’s DNA in the event of a renewed outbreak. Secondly, greater knowledge of Q fever and its treatment will be developed. For example, should people with poorly functioning immune systems be considered a high-risk group for Q fever? Thirdly, closely tracking the outbreak will also allow data to be col-
lected on the transmission of Q fever via blood transfusion or body material. The ECDC also recommends involving recipients of blood or body material in surveillance in affected areas.\textsuperscript{6,35}

The Committee expects the increased knowledge will not only benefit individuals in our country who will develop Q fever in future, but also Q fever patients abroad. After all, the number of Q fever outbreaks in Europe is on the rise.\textsuperscript{48}

5.2 Research into Q fever and blood transfusion or body material

The Committee recommends the potential for Q fever transmission via blood transfusion be studied using patient-control research, which should show how many patients with Q fever underwent blood transfusion before contracting the disease.

The Committee feels animal testing to determine transmissibility of Q fever via blood transfusion and the role of leukodepletion is desirable. The Committee feels that such research, for example in goats, could easily be conducted given the level of knowledge and research facilities available in our country, and in the Committee’s opinion may help clarify questions relating to transmissibility of Q fever through blood transfusion.

The BISLIFE foundation, which mediates collection and release of human tissue for transplantation purposes in The Netherlands, is conducting research into the seroprevalence of Q fever among tissue donors. The Committee already touched on research into contamination of frozen sperm with \textit{C. burnetii} in paragraph 4.4. The Committee applauds such research.
Literatuur


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Literatuur 36
A Request for advice

B The Committee

Annexes
On 18 January 2010, the Health Council received the following request for advice from the Minister of Health, Welfare and Sport regarding Q fever:

A group of experts, led by the National Institute for Public Health and the Environment (RIVM), advised the Minister of Agriculture, Nature and Food Quality and me on 4 December 2009 on combating Q fever. One of the recommendations was to ask the Health Council for advice on the added value of human vaccination for the prevention of Q fever. The matter has already been discussed between yourself and my staff on numerous occasions. With this letter, I formally request that you answer this question. Additionally, I ask that you once again advise me on measures relating to blood donations.

Vaccine
At this time, a human vaccine is only authorised in Australia. There, the vaccine is used to protect professionals in the veterinary sector. As the vaccine has serious side-effects in humans who are or have previously been infected with Coxiella burnetii at the time of vaccination, people are first tested for seropositivity for Coxiella burnetii before being vaccinated.

In 2007, based on a recommendation from the National Institute for Public Health and the Environment (RIVM), I made the decision not to vaccinate people, given the potential side-effects of the vaccine. In part given the course of the Q fever epidemic since 2007, the question of whether new research data has become available that might lead to re-evaluation of this decision has become rele-
vant. For example, an article published in early 2009 in the journal Vaccine presents results from Australia.

I request that you answer the following questions:

1. What role can human vaccination play in preventing Q fever in addition to the measures already taken?
2. Can target groups be identified for whom vaccination may be important in preventing Q fever? This may include groups with increased vulnerability or exposure.
3. Is the existing Q-VAX vaccine by CSL Limited Australia sufficiently effective?
4. Is the existing Q-VAX vaccine by CSL Limited Australia sufficiently safe? I ask that you also consider the requirement for serological testing prior to vaccination.

The Australian government has indicated it will cooperate in obtaining an export license for the vaccine, should it be desirable.

I assume you will involve the National Institute for Public Health and the Environment (RIVM) and the Medicines Evaluation Board (MEB) in answering these questions.

Blood donation
In 2008, you advised me that temporarily excluding blood donors from the area contaminated with Q fever at that time was not a suitable measure. In 2008, you indicated that no reliable screening test for Q fever existed. A number of hospitals and Sanquin have since been working on a test for screening blood donors for Q fever. The test may prevent all donors from high-risk areas from being excluded perforce in the event of new Q fever outbreaks; exclusion could significantly impact the availability of donated blood. I ask that you advise on the introduction of above-mentioned test.

I look forward to receiving your written advisory report as swiftly as possible, at the latest within six months.

Sincerely,

(signed)
Dr A. Klink
Annex B

The Committee

- Prof. E.J. Ruitenber, *chairman*
  Emeritus Professor of Immunology, Utrecht University; Professor of International Public Health, VU University, Amsterdam
- Prof. J.G. Aarnoudse
  Professor of Obstetrics and Gynaecology, University Medical Centre, Groningen
- M. Augustijn, MSc, *observer*
  Ministry of Economic Affairs, Agriculture and Innovation, The Hague
- Prof. C. Boog
  Professor of Infectious Diseases and Immunology, Utrecht University, Netherlands Vaccine Institute, Bilthoven
- Prof. W.J.H.M. van den Bosch
  Professor of Health Care Innovation, University Medical Centre St. Radboud, Nijmegen
- Prof. A. Brand
  Professor of Transfusion Medicine, Leiden University Medical Centre
- Prof. E. Hak
  Professor of Clinical Pharmacology, Groningen University
- Prof. J.A.P. Heesterbeek
  Professor of Theoretical Epidemiology, Utrecht University
The Netherlands consensus group on Q fever diagnostics (Nederlandse consensusgroep diagnostiek Q-koorts) at the National Institute for Public Health and the Environment (RIVM) has drafted guidelines on diagnostic testing for acute and chronic Q fever. The consensus group has also been consulted by various parties in the field for advice on Q fever and body materials. These questions reached the Committee via Dr H.A. Bijlmer of the consensus group. The Committee has integrated the responses to these questions in this advisory report.
The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee’s work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other’s possible interests.