Human vaccination against Q fever

First advisory report
Subject: presentation of advisory report *Human vaccination against Q fever*

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Dear Minister,

I am happy to present you with the Advisory Report on Human Vaccination against Q Fever, which was drawn up by a specially appointed Committee in response to your question regarding the added value of human vaccination against Q fever. A draft version of the report has been assessed by the Standing Committee on Infection and Immunity.

In discussing the vaccine the Committee distinguishes between vaccination against infectious diseases within the framework of public vaccination programmes, such as the National Immunisation Programme, and the use of vaccines in individual health care. The Health Council of the Netherlands has drawn up a protocol for the inclusion of vaccines in public programmes that comprises seven criteria. Based on assessment of these criteria, the Committee holds that vaccination of the entire population of the Netherlands as part of a public programme is not warranted. The Committee also advises against the vaccination of regional or local populations as part of a public programme, and against the vaccination of those working in the livestock industry. An important factor in the deliberations of the Committee was the fact that there is currently only one available human vaccine against Q fever, namely Q-VAX, which was developed and licensed in Australia. This vaccine has not been licensed for use in the Netherlands and the data concerning its efficacy and its safety were obtained from a very select group (mainly abattoir workers).

The Committee does conceive a role for vaccination in the framework of individual health care as part of extended patient care. The Committee advises you to make the vaccine available to specific categories – as defined by the Committee – of patients with cardiovascular disease, who have a heightened risk of complications on contracting Q fever. For these groups, after weighing up the danger of possible complications as a result of Q fever...
and the comparative paucity of data on the vaccine, the Committee comes down in favour of vaccination. I endorse this conclusion and concur with the advice of the Committee.

The Committee had to work under considerable time constraints. It has not yet been able to address your second question concerning the advisability of measures against Q fever with regard to blood transfusions. The Committee will give recommendations on this matter in a separate advisory report that has yet to be drawn up.

I have also presented the Minister of Agriculture, Nature and Food Quality with this advisory report today.

Yours sincerely
(signed)
Prof. D. Kromhout
Acting President
Human vaccination against Q fever

First advisory report

to:

the Minister of Health, Welfare and Sport

No. 2010/08E, The Hague, July 1, 2010
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, Housing, Spatial Planning & the Environment, Social Affairs & Employment, Agriculture, Nature & Food Quality, 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.

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Contents

Executive summary 8

1 Introduction 12
  1.1 Background 12
  1.2 The request for an advisory report 13
  1.3 The Advisory Report 13

2 Q fever 15
  2.1 The bacterium 15
  2.2 Coxiella burnetii in animals 16
  2.3 Q-fever in humans 16
  2.4 Diagnosis 17
  2.5 Treatment 18
  2.6 Conclusion 18

3 Measures to tackle the source 19
  3.1 Veterinary measures 19
  3.2 Hygiene measures 20
  3.3 Conclusion 20

4 The vaccine 22
  4.1 Efficacy 23
Executive summary

Q fever is a zoonotic disease (i.e. a disease that can be transmitted from animals to humans) caused by the *Coxiella burnetii* bacterium (*C. burnetii*).

For humans infected by *C. burnetii*, more than 60 percent of the cases are asymptomatic. A distinction is made, in the case of those that do fall ill, between acute Q fever, most commonly manifested as flu-like symptoms, sometimes accompanied by pneumonia and hepatitis, and the far less common chronic Q fever, which predominantly manifests itself as endocarditis (inflammation of the tissue lining the inner layer of the heart chambers and the heart valves). Generally speaking, acute Q fever is a self-limiting disease, but research shows that forty percent of patients still experience health problems and/or impairments a year after first contracting the disease. Chronic Q fever occurs more frequently in individuals with underlying conditions, such as (hidden) heart valve defects.

Q fever cannot be diagnosed on purely clinical grounds. Diagnostic tests are used to confirm suspected cases. It is far from easy to interpret the results of such tests, or to do so on objective grounds. It is also hard to distinguish between acute and chronic Q fever on the basis of these tests.

Q fever in the Netherlands

Prior to 2007, when the first large-scale outbreak of Q fever occurred (concentrated around the village of Herpen in Brabant), Q fever was a rare disease in the Netherlands, with around twenty reported cases each year. The number of cases
increased annually between 2007 and 2009. In 2009 the Dutch government decided to tackle the source, by taking various veterinary measures. Dairy goats are now routinely vaccinated against *C. burnetii* and pregnant goats from infected farms have been culled. Although less cases of Q fever were reported in the first half of 2010 compared to the same period in 2009, it is too early to be sure that these measures would help to reduce the incidence of Q fever in humans. This prompted the Minister of Health, Welfare and Sport to question whether new research data and recent insights could lead to a reconsideration of earlier recommendations and decisions concerning supplementary measures aimed at humans. The Minister has urged for close consideration to be given to vaccination and for measures to be taken to eliminate the risk of the disease being transferred through blood transfusions.

Given the urgent nature of the problem currently caused by Q fever in the Netherlands, the Committee has decided to first give its advice on the possible role of vaccination.

**The vaccine**

Currently there is only one available human vaccine against Q fever, namely Q-VAX, which was developed and licensed in Australia. This vaccine has not been licensed for use in the Netherlands, and on the basis of the current data and the current criteria, the Committee deems it unlikely that this situation will change. Without a license, Q-VAX can only be administered after the patient’s physician has signed a doctor’s statement and the patient has signed a form of informed consent.

While the data concerning the effectiveness and the safety of Q-VAX do not give rise to concern, they were obtained from selected groups (mainly abattoir workers). The producers of Q-VAX therefore advise against the vaccination of pregnant women. The Australian National Health and Medical Research Council also advises against the vaccination of children under the age of 15. The Committee has adopted these recommendations. The limited data regarding the efficacy of the vaccine make it difficult to draw conclusions regarding the situation in the Netherlands. It is important that vaccination with Q-VAX is only authorised for individuals who have not previously come into contact with *C. burnetii*. Vaccinating an individual who has already come into contact with the bacterium can lead to serious adverse reactions in the form of inflammation, both systemic and local. A serological test and a skin test must therefore be performed prior to vaccination. There is no standard laboratory diagnostic test for Q fever and performing and interpreting the skin test is not straightforward.
Vaccination

In discussing the vaccine the Committee distinguishes between vaccination against infectious diseases within the framework of public vaccination programmes such as the National Immunisation Programme and the use of vaccines in individual health care.

The Health Council of the Netherlands has drawn up a protocol for the inclusion of vaccines in public programmes that comprises seven criteria. Based on assessment of these criteria, the Committee holds that vaccination of the entire population of the Netherlands as part of a public programme is not warranted. The Committee also advises against the vaccination of regional or local populations as part of a public programme, and against the vaccination of those working in the livestock industry.

The Committee does conceive a role for vaccination in the framework of individual health care as part of extended patient care. It advises the Minister of Health, Welfare and Sport to make the vaccine available to the following categories of patient:

- patients who have had endocarditis
- patients who have an artificial heart valve (including bioprosthetic valves, allografts and conduits)
- patients known to have certain congenital defects, specifically:
  - untreated cyanotic heart defects (pulmonary atresia, tetralogy of Fallot, tricuspid atresia, univentricular heart)
  - cyanotic heart defects palliated by shunts or conduits
  - patients with fully corrected congenital heart defects using prosthetic material (ASD, VSD, open ductus)
  - patients with treated congenital heart defects with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device (which inhibit endothelialisation) (residual VSD, residual ductus)
- patients known to have a structural defect of the aortic valve or mitral valve (excluding a mitral valve prolapse)
- patients known to have an aortic aneurism or – if a heightened risk of complications is thought to exist on the basis of the known clinical information – an aneurism of the other major vessels
- patients known to have severe peripheral vascular disease (such as Buerger’s disease)
- patients with a vascular prosthesis (including PTFE shunts). The Committee does not include patients with stents resulting from balloon angioplasty of coronary vessels in this definition. The Committee does not have data regard-
ing these patients and their risk of complications on contracting Q fever, but it estimates that this risk is low.

For the groups defined above, after weighing up the danger of possible complications as a result of Q fever and the comparative paucity of data on the vaccine, the Committee comes down in favour of vaccination. The Committee regards vaccination against Q fever as part of extended patient care in the framework of individual health care, and the decision to vaccinate as the responsibility of individual doctors in consultation with their patients. Part of that responsibility, in the view of the Committee, lies in actively approaching patients known to the practice as eligible for vaccination. The Committee recommends the vaccination of the above categories of high risk patient, at least in the high risk areas of Noord-Brabant and Zuid-Limburg. Yet infected farms are not confined to these areas and here, too, the Committee sees an important role for the doctor in attendance. The Committee wishes to stress that it does not advise an active campaign to trace patients in these categories in the Netherlands: the issue at stake is individual care for high risk patients.

**Conclusion**

From a logistical point of view vaccination against Q fever is not straightforward. Though only a single injection is needed, two tests need to be performed prior to a possible vaccination. It is the opinion of the Committee, therefore, that there is much to be gained by having a single central body coordinate the implementation of the laboratory test, the skin test and the vaccination. In the view of the Committee, this would also facilitate the necessary standardisation of the programme and registration of the vaccination, including identification of target groups and possible adverse events.

The Committee has had to base its recommendations on the current situation regarding the outbreak of Q fever and current knowledge on the Q-VAX vaccine. As stated above, it is currently unclear how the outbreak of Q fever will develop in 2010, and knowledge of the vaccine is still limited. The Health Council previously postulated that the outbreak of Q fever in the Netherlands provides an excellent opportunity to carry out research aimed at a more reliable method of diagnosing Q fever, improving treatment, charting the long-term effects of infection and examining scope for prevention through human or animal vaccination. The present Committee endorses this aim.
On 18 January 2010 the Health Council received a request for an advisory report from the Minister of Health, Welfare and Sport regarding measures that could be taken to combat Q fever in the Netherlands (see Annex A). The Minister especially requested recommendations on the role of human vaccination and on measures to eliminate the risk of the disease being transferred through blood transfusions.

1.1 Background

The request for advice is a result of the increasing problem formed by Q fever in the Netherlands. Q fever is a zoonotic disease (i.e. an infectious disease that can be transmitted from animals to humans) caused by the Coxiella burnetii bacterium (C. burnetii). Prior to 2007, Q fever was a rare disease in the Netherlands, with around twenty reported cases each year. In 2007 the first large-scale outbreak of Q fever occurred, concentrated around the village of Herpen in Brabant. The total number of patients reported was 168. In 2008 and 2009 the outbreak of Q fever spread further within Noord-Brabant and also reached Zuid-Limburg (with, in those years, reported cases being 1,000 and 2,361 respectively). Outside these high risk areas cases were reported in Gelderland and Utrecht.

In 2009 the Dutch government decided to tackle the source, by taking various veterinary measures. Dairy goats are now routinely vaccinated against C. burnetii and pregnant goats from infected farms have been culled.
1.2 The request for an advisory report

The number of cases has increased annually between 2007 and 2009. At the start of 2010 it was not yet clear whether, and if so when, the above veterinary measures would help to reduce the incidence of Q fever in humans. This prompted the Minister of Health, Welfare and Sport to question whether new research data and recent insights could lead to a reconsideration of earlier recommendations and decisions concerning supplementary measures aimed at humans. The Minister has urged for close consideration to be given to vaccination and for measures to be taken to eliminate the risk of the disease being transferred through blood transfusions (see Annex A).

In Australia, professionals in the agricultural and veterinary sectors who are routinely exposed to *C. burnetii* (mainly abattoir workers) can have themselves vaccinated against this bacterium with a vaccine that was developed and licensed in Australia, namely Q-VAX. In 2007 the Minister of Health, Welfare and Sport decided not to instigate a nation-wide vaccination programme, based on recommendations by the National Institute for Public Health and the Environment (RIVM) concerning the possible adverse reactions of this vaccine (see Chapter 4).

In 2008 the Minister asked the Health Council for recommendations on Q fever, including possible measures to eliminate the risk of the disease being transferred through blood transfusions. During a one-day international meeting organised by the Health Council and the RIVM’s Centre for Infectious Disease Control, the participating experts decided that such measures were not warranted at that time. The Sanquin Blood Supply Foundation (hereafter: Sanquin), which is responsible for blood supply in the Netherlands recently cooperated with a number of hospitals in developing a method to indicate when blood donors are, or have been, infected with *C. burnetii*.

1.3 The Advisory Report

In order to provide the requested advisory report, on 22 March 2010 the President of the Health Council set up a Committee, which has since met three times. The composition of the Committee is given in Annex B. Given the urgent nature of the problem currently caused by Q fever in the Netherlands, the Committee has decided to first give its advice on the possible role of vaccination.

In the following chapter the Committee will give a brief overview of what is known about Q fever. In Chapter 3 the Committee will describe the agricultural and veterinary measures that have been taken so far. In Chapter 4 the Committee
will examine the data on the Q-VAX vaccine and in Chapter 5 it will give its opinion on the possible role of human vaccination. In the final chapter (Chapter 6) the Committee will qualify its recommendations and discuss the follow-up report that has yet to be published.
Chapter 2

Q fever

2.1 The bacterium

Q fever is a zoonotic disease (i.e. an infectious disease that can be transmitted from animals to humans) caused by the Coxiella burnetii bacterium (C. burnetii). C. burnetii is a small obligate intracellular Gram-negative bacterium, which is capable of surviving for a long time outside a host due to the fact that it exists in different forms. The cells that C. burnetii targets are monocytes or macrophages, as it requires the pH level within the phagosome of those cells to survive and to reproduce.

The pool of animals in which C. burnetii reproduces and propagates itself is very diverse. In the Netherlands people are primarily infected by dairy goats and dairy sheep. The bacterium is excreted in the milk, faeces and urine of these animals and it is present in extremely high concentrations in their amniotic fluid and placental tissue. Humans can be infected with C. burnetii via these substances, but the most common route of infection is the inhalation of aerosols or dust particles contaminated with the bacterium. Other domesticated animals such as cattle, rodents, cats and dogs can also be infected. However, the role that these animals play in the spread of C. burnetii is not yet clear; the same applies to wild animals and ticks.
2.2 *Coxiella burnetii* in animals

Dairy goats and dairy sheep appear to be the primary source of new human infections in the Netherlands. In 2008 the seroprevalence of *C. burnetii* in the Netherlands was 7.8 per cent for dairy goats and 2.4 per cent for dairy sheep. For goats and sheep infected by *C. burnetii* most of the cases are asymptomatic. However, infection of pregnant animals does lead to an increase in premature births, during which large amounts of bacteria are released that can spread far beyond the pen via aerosols. Such dispersion is facilitated by the fact that, in the Netherlands, the majority of dairy goat farms use a deep litter housing system, in which the animals are free to move around.

Though more than half of the cattle herds in the Netherlands contain at least one animal that produces antibodies against *C. burnetii*, the infection of humans by cattle is far less common. This is possibly connected to the fact that the types of *C. burnetii* found in cattle are different to those found in goats. Premature births resulting from an infection with *C. burnetii* are almost never seen in cattle. The differences between dairy cattle farms and dairy goat farms in terms of animal housing and farm management are probably also significant. A comparable prevalence in cattle is reported in other European countries, such as Great Britain and Spain.

2.3 Q-fever in humans

Prior to 2006 Q fever was a rare disease in the Netherlands, with around twenty reported cases each year. In 2007, 168 cases were reported; in 2008 this figure increased to 1,000 and in 2009 to 2,361. In that same year various veterinary and agricultural measures were taken to reduce the incidence of Q fever (see Chapter 3), but at this stage it is too early to say how these measures will affect the number of cases in 2010. In 2008 and 2009 there was a clear, relatively sudden increase in the number of cases and at the present moment that is not the case in 2010. However, in comparison to the two previous years, the number of newly reported cases is higher and relatively more constant. On 16 June of this year the RIVM had received 376 reports of Q fever so far. At this moment in time the Committee cannot yet pronounce on the estimated incidence for 2010. The number of new cases might still peak, but that number could equally stay at the current, relatively constant level or eventually decrease.
Infection via aerosols is held to be the main cause of Q fever in the Netherlands. In a much smaller proportion of cases the infected person had been in direct contact with animals, professionally or otherwise.

For humans infected by *C. burnetii*, more than 60 per cent of the cases are asymptomatic. A distinction is made, in the case of those that do fall ill, between acute Q fever, most commonly manifested as flu-like symptoms, sometimes accompanied by pneumonia and hepatitis, and the far less common chronic Q fever, which predominantly manifests itself as endocarditis (inflammation of the inner lining of the heart chambers and the heart valves).

Generally speaking, acute Q fever is a self-limiting disease, but research done by the municipal health services in Brabant shows that forty per cent of patients still experience health problems and/or impairments a year after first contracting the disease. These health problems and impairments lead to an increase in sickness absenteeism. Around 2 per cent of people who contract Q fever have the chronic form. It is possible that this form is more common in pregnant women and it is certainly more prevalent in individuals with underlying conditions, such as (hidden) heart valve defects. Since 2008 the Radboud University Nijmegen Medical Centre has diagnosed Q fever in ten to twenty per cent of patients with endocarditis. Previously this percentage was virtually zero. Chronic disease can occur without acute disease being previously identified. In recent years there have been reports of the onset of chronic fatigue syndrome following acute Q fever.

The scientific literature contains indications that contracting Q fever during pregnancy can lead to premature birth, abortion and neonatal death. This can even apply to pregnant woman who have become infected without themselves falling ill. However, in its earlier advisory report on Q fever the Health Council concluded that the research on the risks associated with Q fever during pregnancy is limited and that the results of this study are possibly distorted. Indeed, results from the first Dutch (retrospective) study do not indicate a connection between infection with *C. burnetii* during pregnancy and an increased risk of death, premature birth, low birth weight or congenital defects. A prospective study on this matter has recently been set up in the Netherlands. Its findings are not yet available.

### 2.4 Diagnosis

Q fever cannot be diagnosed on purely clinical grounds. For suspected cases the diagnosis is confirmed by serological tests or molecular diagnostic tests (PCR).
Diverse serological methods are used, such as the complement binding test, the immunofluorescent antibody test and the enzyme immunoassay. It is far from easy to interpret the results of such tests, or to do so on objective grounds. It is also difficult to distinguish between acute and chronic Q fever using these methods. Though the Netherlands Society for Medical Microbiology is working to achieve standardisation, there is currently no standard laboratory diagnostic test for Q fever in the Netherlands. The Committee incidentally deems it unlikely that this lack of standardisation has led to the underdiagnosis of Q fever.

The Committee notes that serological tests are also part of the tests needed to decide whether individuals who are eligible for vaccination do indeed receive the vaccine. Aside from serological tests, a skin test is also required to make this decision. The Committee will discuss this matter further in section 4.2.

### 2.5 Treatment

Q fever is treated with antibiotics, preferably with doxycycline.\textsuperscript{20} For the chronic form of the disease this drug – sometimes in combination with chloroquine – must be taken for a very extended period, occasionally for life.\textsuperscript{21} Moxifloxacin is the drug of second choice for treating the disease. Pregnant women with Q fever are advised to take co-trimoxazol.\textsuperscript{2,12}

### 2.6 Conclusion

In the past couple of years Q fever has developed into a serious health problem in the Netherlands. Even acute Q fever can give rise to long-term health problems, impairments and sickness absenteeism. There is no standard diagnostic test for Q fever. The extent of the effect of the veterinary measures taken in 2009 to reduce the incidence of Q fever in humans has yet to be established.
Chapter 3

Measures to tackle the source

The increase in the number of patients with Q fever in the period between 2007 and 2009 led to various measures being taken to tackle the source of infection. Most of these measures were veterinary in nature, but steps were also taken with regard to on-farm hygiene.

3.1 Veterinary measures

Q fever was classified as an infectious animal disease with effect from June 2008. Livestock farmers and vets are obliged to report any clinical symptoms of Q fever in dairy goats or dairy sheep. Moreover, since October 2009 it has been compulsory for dairy goat and dairy sheep farms with more than 50 animals to take part in a monitoring programme, based on the testing of tank milk samples. Farms that test positive are classified as infected.

In December 2009, following advice by an expert panel chaired by the RIVM, the Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV) decided to cull all pregnant goats and sheep on infected farms as a preventative measure. The remaining goats and sheep on these farms are subject to a lifelong breeding ban. A movement ban was also declared for dairy goat and dairy farms.

To prevent *C. burnetii* from spreading further, a vaccination programme was set up in 2008 to vaccinate all dairy goats and sheep with the French vaccine Coxevac. Vaccination not only protects animals from becoming infected with
C. burnetii, it also reduces the risk of abortion as a consequence of C. burnetii and concomitantly the release of bacteria. In 2008 around 40,000 dairy goats and dairy sheep in Noord-Brabant were vaccinated against Q fever. In 2009 more widespread vaccination was carried out in the south of the Netherlands. Vaccination is currently obligatory for professional dairy goat and dairy sheep farms with more than 50 animals and for farms with a public function such as social care farms (farms that offer services to individuals with care needs), petting farms, rearing farms, sheep and goats in nature reserves and roaming sheep herds. As a precautionary measure, the vaccination of breeding sheep on farms where sheep are reared for consumption has also been made compulsory.

Finally, a breeding ban was declared as of December 2009 for all dairy goat and dairy sheep farms with more than 50 animals, including rearing farms. This ban will apply at least until the end of June 2010. In addition, these farms are subject to a ban on expansion.

3.2 Hygiene measures

Since February 2009 measures have also been taken with regard to on-farm hygiene. These relate to pest control and the storage, transportation and application of manure. On farms with more than 50 dairy goats or sheep, manure may not be removed from pens during the lambing and kidding period and for a month afterwards. Furthermore, the manure must be kept in covered storage for three months prior to application. Infected farms are banned from cleaning out animal housing until 30 days after the last cull and must keep manure in covered storage for five months prior to application. There is also a ban on visiting infected farms: only people visiting the farm for professional purposes may enter animal housing on infected farms. Protective measures are called for regarding persons in this category.23

3.3 Conclusion

Various veterinary and agricultural measures have been in place since the publication of the Health Council’s first advisory report on Q fever. It is to be expected that these measures result in a decrease in the amount of bacteria released. However, at the start of 2010 it was not yet clear what effect these measures would have on the number of newly reported cases of Q fever in humans. This uncertainty prompted the Minister of Health, Welfare and Sport to again request the Health Council for an advisory report on possible supplementary measures aimed at humans. In Chapter 5 the Committee will discuss one of
these measures, i.e. the vaccination of humans against Q fever. First the Commit-
tee will examine the only available human vaccine against Q fever in Chapter 4.
Currently there is only one available human vaccine against Q fever, namely Q-VAX, which was developed and licensed in Australia. The Committee currently does not know of a vaccine being developed elsewhere that would be available for use in the Netherlands within the foreseeable future. Q-VAX, which is produced by the Australian company CSL Limited, consists of *C. burnetii* bacteria that have been inactivated using formaline. Q-VAX was developed to protect abattoir workers against Q fever. In Australia a review took place of a government programme aimed at protecting professionals active in the agricultural and veterinarian sector (such as abattoir workers, farmers and vets) against Q fever. The review showed a significant drop in the number of reported cases of Q fever among those working in the veterinary sector. Q-VAX is currently still in use in Australia to protect professionals in the agricultural and veterinary sectors.

Q-VAX has not been licensed for use in the Netherlands, and on the basis of the current data and the current criteria, the Committee deems it unlikely that this situation will change. An important aspect in this matter is the fact that the research on Q-VAX was performed using select groups of subjects (the Committee will discuss this matter further in the next section). As a consequence, it is difficult to license Q-VAX for use among other groups. The Committee notes that even if a comprehensive research dossier were available, licensing the vaccine would most likely take a year at least. Without a licence, Q-VAX can only be administered after the patient’s physician has signed a doctor’s statement and the individual receiving the vaccine has signed a form of informed consent.
4.1 Efficacy

By far the majority of research on the efficacy of the Q-VAX vaccine is based on studies of abattoir workers. This research indicates an efficacy of more than 90 per cent.26-30 Analysis carried out as part of this advisory report indicates an efficacy of 97 per cent according to the criteria employed by the Cochrane Collaboration (95% confidence interval [95% CI] 93-99 per cent; see Annex C). If this analysis is corrected for the cases of Q fever in the vaccinated group for which vaccination possibly took place within the incubation period of C. burnetii, the efficacy is even higher: 99.7% (95% CI: 96-100 per cent). Nevertheless, the way in which the different studies were set out was sometimes questionable. For example, the clinical case definition is often vague or even absent and in some cases there are differences between the treatment group and the control group. The Committee deems it likely that these factors led to an overestimation of the efficacy of Q-VAX. The use of a select sample population (i.e. Australian abattoir workers likely to be under a high infection pressure by C. burnetii) means that the experimental results cannot simply be extrapolated to different groups of people.

4.2 Necessary tests prior to vaccination

It is important that vaccination with Q-VAX is only authorised for individuals who have not previously come into contact with C. burnetii. Vaccinating an individual who has already come into contact with the bacterium can lead to serious adverse reactions in the form of inflammation, both systemic and local. Local inflammation reactions can manifest themselves in the form of sterile abscesses. Two screening tests are required to exclude the possibility of prior infection with C. burnetii, namely a serological test and a skin test. The skin test involves the intracutaneous administration of a dilution of the Q-VAX vaccine (similar to the Mantoux test used to detect tuberculosis).

The aforementioned screening tests are not ideal, however, and do not provide maximum safety. The current serological tests are not designed to screen large groups and there is presently no standard laboratory diagnostic test for Q fever (see also section 2.4). In any case, performing and interpreting these types of skin test is not straightforward.31 In addition to this, the skin test for C. burnetii does not always give a positive result when someone has already experienced an infection.24
4.3 Safety

For those who have not previously come into contact with *C. burnetii*, the risk of serious adverse reactions following vaccination is small. However, less serious adverse reactions commonly occur. A study performed by Marmion et al. in the 1980s monitored 464 subjects for a period of one to three days after they had been vaccinated and reported the following adverse reactions: sensitivity at the site of injection (48 per cent of subjects), erythema around the site of injection (33 per cent) and a headache (9 per cent). During the aforementioned vaccination programme carried out by the Australian government, 48,986 people were vaccinated in the period between 2002 and 2006. Of the 86 people that reported known adverse reactions as a consequence of being vaccinated (0.18 per cent), the majority (69 out of 86 or 80 per cent) had complaints as described above. Eight subjects suffered serious adverse reactions and were hospitalised as a result of being vaccinated. One patient experienced dyspnea, pruritus and a skin rash that was held to be life-threatening. There have been no reports of death as a result of vaccination with Q-VAX.

The fact that in Australia the vaccine was primarily given to abattoir workers – generally young, healthy, adult men – restricts its usefulness. As far as the Committee is aware, there are no data (or only casuistic data) concerning the safety of the use of Q-VAX in other groups, such as high risk patient groups, pregnant women or children. The manufacturers of Q-VAX advise that the screening and vaccination of pregnant women be postponed until after childbirth. Due to lack of data, they refrain from comment on other patient groups. The Australian National Health and Medical Research Council has set 15 as the minimum age for vaccination with Q-VAX. The Committee endorses these recommendations.

4.4 Efficiency

Research into the efficiency of human vaccination against Q fever is also extremely limited.

In the above-mentioned study by Marmion et al. (section 4.3) an average of 10 cases of Q fever a year occurred in the non-vaccinated control group, which comprised 2,012 people in total. Assuming that the vaccine is 100 per cent effective, 5 clinical cases of Q fever per 1,000 abattoir workers could thus be prevented each year.
As has already been stated, information on Q-VAX was obtained from select sample groups. This makes it difficult to determine and to interpret the efficiency of vaccinating other groups that possibly qualify for vaccination. This is particularly unfortunate, since it is precisely the group of non-professionals coming into contact with *C. burnetii* that have an increased risk of contracting Q fever in the Netherlands (see section 2.3).

### 4.5 Conclusion

There is currently only one available human vaccine against Q fever, namely Q-VAX, which was developed and licensed in Australia. This vaccine has not been licensed for use in the Netherlands. While the data concerning the efficacy and the safety of Q-VAX do not give rise to concern, they were obtained from selected groups. Given these limitations it is crucial that the pros and cons of using the vaccine are given careful consideration. Due to the fact that Q-VAX should only be given to individuals that have not previously come into contact with *C. burnetii*, a serological test and a skin test must be performed prior to vaccination. There is no standard laboratory diagnostic test for Q fever in the Netherlands and performing and interpreting the skin test is not straightforward. The limited data regarding the efficiency of vaccination make it difficult to draw conclusions regarding the situation in the Netherlands.
In this chapter the Committee will discuss human vaccination against Q fever. The Minister of Health, Welfare and Sport has asked the Council for its recommendations on the possibility of human vaccination being used as a supplementary measure to combat Q fever and whether any target groups can be defined based on increased risk or exposure.

The Minister’s question relates to the role of the government with regard to human vaccination against Q fever. The Committee distinguishes here between 1) vaccination against infectious diseases within the framework of public vaccination programmes like the National Immunisation Programme and 2) the use of vaccines in individual health care. The Committee will first elaborate on this distinction, after which it will discuss the deployment of the vaccine within each of these frameworks.

5.1 Public programme versus individual health care

Protecting against infectious diseases by way of public vaccination is pre-eminently a task for the government. In 2007 the Health Council outlined an assessment framework for this issue in its advisory report ‘The future of the National Immunisation Programme: towards a programme for all age groups’. This framework comprises seven criteria for the inclusion of a vaccination in a public programme. In the first part of this chapter the Committee will assess human vaccination against Q fever based on this framework and the seven criteria.
Public vaccination programmes are a service provided by the government. Naturally this does not apply if the vaccine against Q fever is deployed as part of individual health care. For this reason the Committee uses a different set of criteria when discussing this eventuality. In the second part of this chapter the Committee will discuss the utility and advisability of vaccinating specific groups of patients. The commission regards vaccination against Q fever within the framework of individual health care as the responsibility of individual doctors in consultation with their patients.

5.2 Vaccination within the framework of a public programme

In its advisory report ‘The future of the National Immunisation Programme: towards a programme for all age groups’ the Health Council stated the following general objective with regard to public vaccination:

To protect the people and society of the Netherlands against serious infectious disease by means of vaccination.33

Public vaccination programmes may target the population as a whole, but if a disease is not evenly distributed throughout the population, it can be more efficient to focus on the vaccination of one or more specific target groups or subpopulations.

5.2.1 The seven criteria

To address questions on human vaccination in the framework of a public programme such as the National Immunisation Programme (NIP), the Health Council has formulated a set of seven criteria.33 The Committee will provide a brief clarification of these criteria in the first section. This will be followed by a discussion on which target groups might qualify for vaccination.

The seven criteria for the inclusion of a vaccine in a public programme have been formulated so as to determine the desirability of including a particular vaccination in the programme, aimed at a particular target group.33 Identification of the appropriate target group – the entire population, all infants and young children, or one or more specific groups or subpopulations – is critical to any assessment of the effectiveness, acceptability and efficiency of a vaccination. In practice, assessment will sometimes involve examining and comparing several options at a time, using the seven criteria for guidance. A multi-option assessment should not only focus on the merits of vaccinating various possible target
groups, but also on various possible vaccination schedules. The criteria are based on two ethical principles: 1) that the best possible protection should be afforded to the population as a whole and 2) an equitable distribution among groups within the population, whereby protection is offered to the groups that most urgently require it. The seven criteria and their underlying principles provide a framework for the systematic examination of arguments for and against the inclusion (and prioritisation) of specific vaccines in the NIP. Each question is formulated on the assumption that the previous question has been answered in the affirmative. There is nothing to be gained, for example, from considering the effectiveness of a vaccine if the disease that it protects against is rare or not very serious. Furthermore, cost-effectiveness only becomes part of the equation when it is clear that the vaccine will be safe and effective when given to the relevant target group. The criteria should not, however, be regarded as a sort of checklist for generating instant answers to the NIP inclusion questions. Careful consideration must be given to the available scientific information in assessing the criteria and arriving at a conclusion. Furthermore, judgements on the desirability of inclusion are always qualified: almost no vaccine is 100 per cent effective or entirely without side-effects. The situation will be even more complex when multiple options are under consideration, each with its own pros and cons. The seven criteria are set out below, grouped under five thematic headings.

Seriousness and extent of the disease burden

1 The infectious disease causes considerable disease burden within the population
   • The infectious disease is serious for individuals, and:
   • The infectious disease affects or has the potential to affect a large number of people.

Effectiveness of the vaccination

2 Vaccination may be expected to considerably reduce the disease burden within the population.
   • The vaccine is effective for the prevention of disease or the reduction of symptoms.
   • The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought).
3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4 The inconvenience or discomfort that an individual may be expected to experience in connection with his/her personal vaccination is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

5 The inconvenience or discomfort that an individual may be expected to experience in connection with the vaccination programme as a whole is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

In previous years the Health Council has used these criteria to formulate recommendations on various types of vaccination. The criteria are evaluated and updated in the light of such past experiences.

5.2.2 Vaccination of the population of the Netherlands

The Committee first gave consideration to the question whether vaccinating the population of the Netherlands against Q fever would fit within the framework of a public vaccination programme such as the NIP.

In the period between 2007 and 2009 cases of Q fever in the Netherlands increased and in 2009 Q fever was diagnosed in 2361 individuals. In the majority of cases, Q fever is not a serious disease, but in some patients it can lead to long-term health problems. Q fever patients in the Netherlands predominantly originate
Vaccination from certain areas of the country. It is currently too early to say how the number of cases will develop in 2010 (criterion 1). The data show that, in Australia, the vaccination of professionals in the veterinary sector led to a considerable reduction of the disease burden; however, there is little or no information pertaining to other groups (criterion 2). Vaccination is only authorised for individuals who have not previously come into contact with *C. burnetii*. Vaccinating an individual who has already been infected with the bacterium can lead to serious adverse reactions. The tests required to exclude the possibility of infection are not standardised and do not ensure maximal safety on vaccination (criterion 3).

Given that Q fever is only prevalent in certain areas of the country and that information on the effectiveness and safety of the vaccine is limited, the Committee holds that vaccination of the entire population of the Netherlands is not warranted.

### 5.2.3 Vaccination of individuals at a higher risk of exposure

Regional or local population

So far, Q fever cases predominate in certain areas, especially in Noord-Brabant and Limburg. It is likely that this is due to the local population being relatively highly exposed to *C. burnetii*. However, even within these areas, clear differences exist. For example, a study done in the Netherlands indicates that there is a correlation between the incidence of Q fever in those living near an infected farm and the distance to the farm in question: the shorter the distance, the higher the risk of contracting Q fever.\(^39\) This research, which was carried out around a single infected goat farm, revealed that people living within a two-kilometer radius of the farm had a 376 in 100,000 chance of contracting Q fever. This risk is considerably higher than that for people living more than five kilometres from the farm: the relative risk is 31\% (95\% CI: 16-59).

These statistics indicate that the severity and the magnitude of the disease burden can increase on a local scale (criterion 1). The Committee’s earlier decision on the effectiveness of vaccination (criterion 2) and the possible adverse reactions (criterion 3) remains unchanged. On the other hand, it is the opinion of the Committee that when the severity and the magnitude of the disease burden are locally increased, vaccination on a local scale becomes more acceptable (criterion 4). The Committee incidentally deems it likely that the measures taken to tackle the source of infection (see Chapter 3) brought about a decrease in the number of premature births (in livestock), preventing the release of extremely large numbers of bacteria. Data are lacking on the efficiency of vaccinating...
regional or local populations (criterion 6). The Committee holds that, due to this lack of information on safety and effectiveness, vaccination of regional or local populations as part of a public programme is not warranted.

Professionals coming into contact with livestock

Persons who come into contact with goats and sheep as part of their profession are also at higher risk of infection. The professionals that the Committee has in mind are dairy goat and sheep farmers (including any family members living on the farm), sheep shearers, labourers and vets. Serological research revealed that some eighty per cent of Dutch dairy goat farmers and vets are, or have been infected with \textit{C. burnetii}.\textsuperscript{18}

The Committee concludes from these data that, for current professionals, the severity and the magnitude of the disease burden will probably remain limited in future (criterion 1). Based on the Australian data, the balance between the effectiveness of the vaccine (criterion 2) and the possible adverse reactions (criterion 3) is favourable in the case of these professionals. It is the opinion of the Committee that an increase in the severity and the magnitude of the disease burden would make the vaccination of professionals more acceptable (criterion 4). There is a lack of information on the efficiency of vaccinating (criterion 6) professionals in the Netherlands, but the Committee holds that the vaccination of this group is unlikely to be efficient, given that the majority has already been exposed to \textit{C. burnetii}. It is the opinion of the Committee that, due to the limited disease burden so far and, consequently, the limited efficiency of vaccination, vaccination of current professionals within the framework of a public programme is not warranted. The Committee will discuss the possible vaccination of future professionals (such as trainee vets and farmers) in a subsequent advisory report.

Various organisations have formulated guidelines aimed at preventing Q fever in the veterinarian and agricultural sector.\textsuperscript{7,23} The Committee stresses the importance of adhering to these guidelines.

5.3 Vaccination of particularly vulnerable individuals

The Committee advises the Dutch authorities not to vaccinate against Q fever within the framework of a public vaccination programme. This does not mean that the Committee is entirely opposed to vaccination. In this section the Committee will look in more detail at the vaccination of particularly vulnerable individuals, which it sees as falling under individual health care, as part of extended patient care. Because the measure under discussion does not relate to vaccination
within the framework of a public programme, the Committee does not base its decision on an assessment of the criteria laid out in section 5.2.1.

Several groups of cardiovascular patients have an increased risk of complications – endocarditis in particular – as a consequence of infection with *C. burnetii*. Based on a retrospective study, French researchers estimate that in patients with heart valve defects, Q fever leads to endocarditis in around 40% of cases. If endocarditis is left untreated, or if it is treated with the wrong antibiotics, this can have serious, sometimes fatal consequences. In Brabant and Gelderland, some 50 to 75 patients with serious cardiovascular complaints are momentarily being treated with antibiotics to combat the effects of chronic Q fever.

For these groups, vaccination against Q fever could serve a useful purpose. The aim of vaccination in this context is to tackle complications that result from an infection with *C. burnetii*. The Committee therefore advises the Minister of Health, Welfare and Sport to make the Q-VAX vaccine available to the following categories of patient:

- patients who have had endocarditis;
- patients who have an artificial heart valve (including bioprosthetic valves, allografts and conduits);
- patients known to have certain congenital defects, specifically:
  - untreated cyanotic heart defects (pulmonary atresia, tetralogy of Fallot, tricuspid atresia, univentricular heart)
  - cyanotic heart defects palliated by shunts or conduits
  - patients with fully corrected congenital heart defects using prosthetic material (ASD, VSD, open ductus)
  - patients with treated congenital heart defects with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device (which inhibit endothelialisation) (residual VSD, residual ductus)
- Patients known to have a structural defect of the aortic valve or mitral valve (excluding a mitral valve prolapse)
- Patients known to have an aortic aneurism or – if a heightened risk of complications is thought to exist on the basis of the known clinical information – an aneurism of the other major vessels.
- Patients known to have severe peripheral vascular disease (such as Buerger’s disease)
- Patients with a vascular prosthesis (including PTFE shunts). The Committee does not include patients with stents resulting from balloon angioplasty of coronary vessels in this definition. The Committee does not have data regard-
ing these patients and their risk of complications on contracting Q fever, but it estimates that this risk is low.

Patients in the first three categories are quoted by the Dutch Heart Foundation as being at high risk of bacterial endocarditis, patients in the remaining categories are included here by the Committee in connection with the specific risks associated with Q fever.

Having made these recommendations, the Committee wishes to add a few qualifying remarks.

Firstly, the Committee emphasises that the vaccine in question has not been licensed for use in the Netherlands and that it is aimed at a disease which is mostly prevalent in certain regions. The commission regards vaccination against Q fever as part of extended patient care in the framework of individual health care, and the decision to vaccinate as the responsibility of individual doctors in consultation with their patients. Part of that responsibility, in the view of the Committee, lies in actively approaching patients known to the practice as eligible for vaccination. The Committee wishes to stress that it does not advise an active campaign to trace patients in these categories in the Netherlands: the issue at stake is individual care for high risk patients.

The Committee recommends the vaccination of the aforementioned categories of high risk patients in at least the high risk areas of Noord-Brabant and Zuid-Limburg. Yet infected farms are not confined to these areas and here, too, the Committee sees an important role for the doctor in attendance, as described in the previous section. Up-to-date information on the epidemiological situation concerning risk areas can be obtained from the RIVM’s Centre for Infectious Disease Control and the municipal health service (GGD).

The Committee advises against the vaccination of pregnant women and children under the age of 15, even if they belong to the aforementioned high risk categories. The Committee realises that this may pose a difficult choice for patients, especially those with congenital heart defects, but there is insufficient information on the vaccination of young children to recommend vaccination (see also section 4.3). In advising against the vaccination of pregnant women, the Committee adopts the recommendations of the producers of Q-VAX.

The Committee notes that the aforementioned lack of knowledge of and experience with Q-VAX also applies to the groups of patients mentioned above and that these patients, too, must be tested for previous infection with C. burnetii prior to vaccination. The Committee has no reason to believe, however, that these groups of patients have an increased risk of complications resulting from
vaccination against Q fever in its own right (as opposed to the risks associated with infection).

The Committee advises that vaccination only be considered for these groups. Conversely, given the limited data on the vaccine, the Committee recommends against the vaccination of other groups of patients, such as those with immune system defects.

5.4 Conclusion

The Committee holds that vaccination of the entire population of the Netherlands as part of a public programme such as the NIP is not warranted. The Committee also advises against the vaccination of regional or local populations as part of a public programme, and against the vaccination of those working in the livestock industry.

The Committee does recommend that the Q-VAX vaccine be made available to certain specific categories of patients. For these groups, after weighing up the danger of possible complications as a result of Q fever and the comparative paucity of data on the vaccine, the Committee comes down in favour of vaccination. The Committee regards vaccination against Q fever as part of extended patient care in the framework of individual health care, and the decision to vaccinate as the responsibility of individual doctors in consultation with their patients. The Committee does not advise an active campaign to trace patients in these categories in the Netherlands.
In this chapter the Committee will comment in more detail on its recommendations with regard to human vaccination against Q fever. The chapter will end with a brief anticipation of a subsequent advisory report.

6.1 Additional comments

6.1.1 Expertise and research

The Committee was compelled to base its recommendations on the current state of affairs regarding the outbreak of Q fever and present information on the Q-VAX vaccine. As stated above, it is currently unclear how the outbreak of Q fever will develop in 2010, and knowledge of the vaccine is still limited. In the advisory report drawn up in 2008, the Health Council postulated that the outbreak of Q fever in the Netherlands provides an excellent opportunity to carry out research aimed at a more reliable method of diagnosing Q fever, improving treatment, charting the long-term effects of infection and examining scope for prevention through human or animal vaccination.\(^1\)

The present Committee endorses this aim.
In developing a strategy for diagnostic testing, it is of utmost importance to prevent the vaccination of individuals that have already been infected with *C. burnetii*. The Committee therefore regards sensitive and standardised tests as essential, along with quality controls of the labs where these tests are performed. It applauds the efforts of the Netherlands Society for Medical Microbiology to standardise the serological tests and at the same time urges this task to be completed with the utmost despatch. The Committee has already touched on the difficulties of performing and interpreting the necessary skin test.

From a logistical point of view vaccination against Q fever is not straightforward. Though only a single injection is needed, two tests need to be performed prior to a potential vaccination. To prevent people from being unnecessarily subjected to a skin test, it may be advisable to only perform the skin test after the laboratory test results are known, so that individuals with a positive laboratory test score are directly excluded. This procedure has the drawback that vaccination can only take place on the third visit to the GP or lab.

It is the opinion of the Committee, therefore, that there is much to be gained by having a single central body coordinate the implementation of the laboratory test, the skin test and the vaccination. In the view of the Committee, this would also facilitate the necessary standardisation of the programme and registration of the vaccination, including identification of target groups and possible adverse reactions. The data collected in this manner can be used to add to expertise on vaccination against Q fever.

### 6.2 Further recommendations

The Committee will give its recommendations on measures to prevent Q fever from being contracted through blood transfusion in a separate advisory report that has yet to be drawn up. Possible measures pertaining to organ and tissue donation will be included in this discussion.

In the preceding sections, the Committee advises for vaccination against Q fever to be carried out in such a way that a maximum amount of knowledge is obtained on test procedures and vaccination. The Committee can then draw on this knowledge – in addition to the latest epidemiological data – in formulating any subsequent recommendations on vaccination (for instance on the advisability of vaccinating future professionals).
References


33 Health Council of the Netherlands. The future of the National Immunisation Programme: towards a programme for all age groups. The Hague: Health Council of the Netherlands, 2007; publication no. 2007/02E.
39 Schimme B, Ter Schegget R, Wegdam M, Zuchner L, De Bruin A, Schneeberger PM et al. The use of a geographic information system to identify a dairy goat farm as the most likely source of an urban Q-fever outbreak. BMC Infect Dis 2010; 10: 69.
A Request for advice

B The Committee

C Effectiveness of the Q-fever vaccine: a meta-analysis

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

On 4 December 2009 the Minister of Agriculture, Nature and Food Quality and I received a number of recommendations on measures to combat Q fever from a group of experts led by the RIVM. One of these recommendations was to ask the Health Council for advice on the added value of human vaccination against Q fever. My staff have discussed this matter with you on several previous occasions. This letter constitutes a formal request for an advisory report on human vaccination against Q fever. I also request you to advise me again on measures to prevent Q fever from being contracted through blood transfusions.

Vaccine
There is currently only one available vaccine, which is licensed in Australia. There, the vaccine is used to protect professionals in the veterinary sector. Due to the serious side effects that the vaccine can cause in individuals that are, or have been infected with Coxiella burnetii, serological tests for this bacterium must be performed prior to vaccination.

Based on the RIVM’s advice, I decided in 2007 that, given the possible side effects of the vaccine, a vaccination programme was not warranted. The situation regarding Q fever has progressed since 2007 and the question arises whether new research data and recent insights could lead to a reconsid-
eration of earlier recommendations and decisions. For example, at the start of 2009 the journal *Vaccine* published new Australian data on Q fever.

I request your advice on the following questions:

1. What role can human vaccination play as a supplementary measure to combat Q fever?
2. Can target groups be defined for which vaccination could be important in preventing Q fever?
   The groups I have in mind are those that are particularly vulnerable and those that are at a higher risk of exposure.
3. Is the existing vaccine Q-VAX, produced by CSL Limited Australia, sufficiently effective?
4. Is the existing vaccine Q-VAX, produced by CSL Limited Australia, safe? Please keep in mind the fact that a serological test must be performed prior to vaccination.

The Australian government has meanwhile indicated its willingness to cooperate in providing an export licence if required.

I assume that you will consult with the RIVM and the Medicines Evaluation Board in answering these questions.

**Blood donation**

In 2008 you advised me that the temporary exclusion of blood donors originating from areas affected by Q fever was not warranted at the time. In 2008 you also indicated the lack of a reliable screening test for Q fever. Since then, Sanquin has worked with a number of hospitals to develop a screening test for Q fever, aimed at blood donors. This test could prevent the automatic exclusion of all donors from high risk areas in case of new outbreaks of Q fever; exclusion on such a large scale would greatly reduce the available supply of donated blood. I request your advice regarding the introduction of the aforementioned test.

I look forward to receiving your advisory report as soon as possible, in any case within six months.

Yours sincerely,
The Minister of Health, Welfare and Sport,
Signed,
Dr A. Klink
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The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – 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 establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other’s possible interests.
Effectiveness of the Q-fever vaccine: a meta-analysis

G. Gefenaite, J. Munster, R. van Houdt, E. Hak

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Introduction

The number of notified human Q-fever cases in the Netherlands showed a steep increase over the last years three years, with a peak incidence of 69 per 100,000 inhabitants in 2009 (1). Despite many measures being taken to prevent further transmission, it can be expected that Q-fever cases will occur in the next few years (1). Risk groups can be defined according to risk of exposure (e.g. goat farmer) or medical risk (e.g. immune compromised patients, patients with pre-existing valve defects and pregnant women) (2) (3) (4). Currently, only one Q-fever vaccine (Q-vax) is available that is registered in Australia only for preventive use in humans. Since, vaccination with Q-vax might be an option for certain risk groups to prevent Q-fever, evidence is needed about its effectiveness. We therefore conducted a meta-analysis to determine the evidence base for effectiveness for Q-fever vaccination in human populations.

Methods

A review of the literature was done by searching Pubmed and references. Only studies that included a control population, used the Q-fever vaccine and clinical outcome and reported raw data were included in the analysis. The design and possible limitations of the studies were assessed using criteria for randomized control trials (5) and longitudinal non-randomized observational studies (6). As the main possible limitations we considered bias because of information, selection or confounding. The Mantel Haenzel risk ratio was calculated using Episheet by K. Rothman (7;8). Vaccine efficacy was calculated by the following formula: \((1 - RR) \times 100\).

Results

Five studies containing the raw data about the effectiveness of the vaccine against Q-fever were included in our review (9-13). Two of them concerned a retrospective cohort study and one a prospective cohort study, one randomised controlled trial and one experimental study. The study populations were in all studies abattoir workers, except for the experimental study in which healthy men were included. Subjects were excluded from receiving Q-fever vaccination when they had a positive antibody titre (CF titre \(\geq 2.5\)) and/or positive skin test; however there were exceptions in some of them. All of the studies showed that there is a protective effect of the vaccine against Q-fever with an overall effecti-
Effectiveness of 97% (95% confidence interval 93% to 99%). After excluding Q-fever cases that occurred within 15 days after the vaccination (the time needed to induce complete immunisation) the vaccine effectiveness increased to 99.7% (95% confidence interval 96.3% to 100%) (9-13).

Discussion

Individual studies showed that the efficacy of the vaccine against Q-fever is very high, with no exception. The same high vaccine efficacy was found after pooling the raw data. However, the reported designs of the included studies had some potential flaws. The case definitions were usually rather vague or even absent. Furthermore, in some studies selection of subjects to vaccinees or nonvaccinees was not described at all or described insufficiently. Also no information about the baseline characteristics of vaccinees and nonvaccinees was available in most of the studies. A major problem with the reviewed literature was the selected study sample; four of the five studies focused on abattoir workers, the population which is relatively healthy and young and particularly at risk to attract Q-fever. How these results apply to populations at high risk of complications or in persons who are not at constant exposure remains uncertain. In all, the vaccine effectiveness may be overestimated and needs confirmation in controlled research settings, but is likely to be rather impressive for high-risk groups.

Reference List

4. RIVM. Q-koort. 2010.
Effectiveness of the Q-fever vaccine: a meta-analysis


