MRSA policy in the Netherlands

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : MRSA report
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Mr Minister,

Please find enclosed the Health Council's report on MRSA policy in the Netherlands. On 29 January 2004, you asked the Council to advise you as to the public health implications of, on the one hand, retaining the current policy on MRSA and, on the other, abandoning it. More particularly, you asked that, in its response, the Council should address the relevant financial considerations, the prevalence of MRSA and policy in other countries. The committee that I formed to prepare the Council's response has now completed its work, in the context of which both the Medical Standing Committee and the Infection and Immunity Standing Committee were consulted.

The committee advises retention of the existing policy. The primary reason being that abandonment of the policy may be expected to result in a sharp rise in MRSA, leading to increased disease burden and mortality. The committee concludes that MRSA has become more common in the Netherlands since 2002. The committee would also recommends research to increase scientific knowledge concerning the prevalence of MRSA in various population groups and concerning the communication and spread of MRSA, both between hospitals and nursing or care homes and within the general population. Such knowledge would also provide a basis for the formulation of proposals regarding the adjustment of MRSA policy as and when necessary, so that MRSA remains a manageable problem. I fully endorse this recommendation.

Yours sincerely,

(signed)
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No. 2006/17E, The Hague, October 16, 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 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, and Agriculture, Nature & Food Quality. 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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This report can be downloaded from www.healthcouncil.nl.

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Contents

Executive summary

Background

MRSA is the abbreviation for Meticillin-Resistant *Staphylococcus aureus (S. aureus),* a bacterium that has become resistant to the commonly used antibiotics. Healthy people can carry MRSA but rarely become ill from it. Just like the non-resistant *S. Aureus*, an MRSA bacterium can cause infections in the blood, heart and bones of people with reduced immunity or during the use of drips and catheters. Research indicates that MRSA infections lead to excess mortality.

The Netherlands has a strict MRSA policy to prevent the spread of the bacterium and thus minimise its prevalence. High-risk groups are screened and patients are nursed in isolation. If a patient is diagnosed with an MRSA infection, this has to be treated with antibiotics that still work. A disadvantage of these drugs is that they are less effective and less safe. Further, these have to be administered via a drip and in some cases this can lead to an extended hospital stay.

Request for an advisory report

The Minister of Health, Welfare and Sport has requested the Health Council of the Netherlands to issue an advisory report about the MRSA policy in the Netherlands. This had to include the consequences for public health of both retaining and discarding the current policy, as well as the costs involved, the prevalence of MRSA and the policy in other countries.

The Committee observed that scientific knowledge about various aspects of MRSA is sparse. For example, little is known about the prevalence in different groups of the population, such as in nursing homes and care homes, or about the transmission of MRSA. In addition, the scientific basis for the efficacy of the MRSA policy is insufficient. Finally, the full costs of implementing the MRSA policy are also not sufficiently known. Despite these limitations, the Committee has managed to formulate several conclusions and recommendations based on the data available.

Improve epidemiological insights

On the basis of international data analysed by the National Institute for Public Health and the Environment (RIVM), the Committee concludes that MRSA infections in the bloodstream occur far less frequently in the Netherlands than in most other countries. The Committee also concludes that there appears to have been an increase in the incidence of MRSA since 2002.

MRSA surveillance performed by RIVM provides insights into the number of MRSA isolates in the Netherlands. Whether this concerns carriership of MRSA or an infection with MRSA is not clear from these data. It is also not clear how frequently MRSA carriers and infections occur in different groups of the Dutch population, such as in nursing homes and care homes. There is a concern that reservoirs of MRSA can particularly occur in nursing homes and care homes. If appropriate measures are not taken in such cases, for example screening of nursing home patients prior to hospital admission, this can result in a strong and unmanageable increase of MRSA.

In the Committee's opinion, greater insight into the prevalence of MRSA in different population groups in the Netherlands and into the transmission and distribution of MRSA is necessary, so that the causes behind the increase of MRSA since 2002 can be determined and changes to the MRSA policy can be proposed in time. Such policy changes will help to ensure that MRSA continues to be a manageable problem in the future. In particular, insights into transmission between hospitals and nursing homes or care homes, and in the general population are necessary so that high-risk groups can be detected. It is important that the data collected include a good description of the population concerned and that it is clear whether it concerns an MRSA infection or carriership.

Abandoning the current MRSA policy is probably more expensive

The Committee considers it very likely that the costs of the present policy are considerably lower than the costs of MRSA treatment and the longer stay in hospital arising from this if the policy were to be rescinded. This rise in costs will be further exacerbated by the fact that a strong increase in MRSA is expected if the policy is rescinded.

Additional research is needed to produce a balanced overview of the costs and effects of different options in MRSA policy, such as the effects on mortality and quality of life. A dynamic Dutch MRSA model is available and the Committee expects that the cost aspects can be added to this with relatively little effort. This model predicts the prevalence of MRSA in hospitals and the general population under various MRSA-policy scenarios, varying from the complete strict Dutch policy to separate components such as isolation of MRSA carriers or screening of high-risk groups on hospital admission. A cost saving could be made with respect to the current policy, if a new rapid screening test for MRSA were to be used. Dutch research into this test is currently in progress.

Maintaining current MRSA policy

The Committee recommends retaining the current strict policy to counteract the spread of MRSA. The most important argument for this is that rescinding the policy will lead to a much higher prevalence of MRSA and the associated increase in disease burden and mortality. British research has shown that rescinding a strict policy results in a marked increase in MRSA infections. This would then be in addition to the *S. aureus* infections that already occur in the Netherlands. Another important argument is that rescinding the policy would result in further development of resistance of MRSA against vancomycin and other antibiotics, as a result of which the chance of effectively treating MRSA infections would be reduced. Moreover, if the policy were to be rescinded, the costs incurred by MRSA infections would strongly increase and would probably be much higher than in the current situation with the strict MRSA policy.

Chapter 1

Introduction

1.1 What is MRSA?

MRSA stands for methicillin-resistant *Staphylococcus aureus*, a bacterium that has developed resistance to widely used antibiotics. Healthy people can carry MRSA without becoming ill. The number of MRSA carriers is small, certainly a lot smaller than the number of people who carry non-resistant *Staphylococcus aureus* (*S. aureus*). Roughly 20 per cent of the Dutch population carry the non-resistant bacterium.[1,2] MRSA is found mainly on the hair and skin and on the mucus membranes of the nose, throat and digestive system. People with skin conditions such as eczema are more likely to carry MRSA. In a care institution, the bacterium can under certain circumstances spread very quickly. In patients with wounds, infusions, catheters and those in poor health, exposure to MRSA can relatively easily lead to sepsis or wound infections. It has also been reported that MRSA infection is associated with increased mortality risk and disease burden.

1.2 Ministerial commission

Considerable international differences exist in terms of the approach taken to prevent the spread of MRSA and the associated infections. In some countries, control is left to individual hospitals, while in the Netherlands a strict policy is

applied, based on explicit national guidelines. Application of this strict policy requires considerable commitment from the hospitals and their personnel and has major cost implications. Against this background, the Minister of Health, Welfare and Sport asked the Health Council to report on MRSA policy in the Netherlands. Specifically, the Council was asked to consider the public health implications both of continuing to pursue the existing policy and of abandoning it, and to look at the associated costs, the prevalence of MRSA and the policies pursued by other countries. The full text of the minister's request is reproduced in Annex A.

On 30 June 2005, the Vice-President of the Health Council accordingly appointed an expert committee to prepare a report. The members of the committee are listed in Annex B. The committee has surveyed and reviewed the relevant scientific literature.

1.3 Structure of this report

Chapter 2 describes the disease burden and mortality attributable to *S. aureus* in general and MRSA in particular. In chapter 3, consideration is given to the prevalence of MRSA within medical institutions and the wider community; relevant gaps in knowledge are also identified. Chapter 4 summarises present MRSA policy in the Netherlands and other countries. The opportunities and threats present within the MRSA policy domain are highlighted in chapter 5; the threats in question are those associated with abandoning the present MRSA policy and with the rise of MRSA in the general population. Chapter 6 examines the cost of MRSA policy. The committee's conclusions and recommendations are presented in chapter 7.

Chapter 2

Morbidity and mortality associated with MRSA

2.1 *Staphylococcus aureus* infections sometimes have serious consequences

Although *S. aureus* is rarely problematic for a healthy carrier, it can cause serious infections in people whose resistance is impaired or upon whom invasive techniques, such as intravenous infusion or catheter insertion, are used. Infections of the bloodstream (bacteraemia) are common, but inflammation of the heart and the bones also occur with some regularity. The findings of international research suggest that the annual incidence of bacteraemia caused by *S. aureus* infection is roughly 25 cases per 100 000 of the population.[3] Hence, across the Netherlands, there are about four thousand *S. aureus* infections of the bloodstream each year.

Research at three Dutch hospitals has indicated that the hospital mortality rate for *S. aureus* bacteraemia is roughly 20 per cent and that overall mortality among patients with *S. aureus* infections is 32 per cent.[4] Another study found that, following a diagnosis of infusion-related bacteraemia, 50 per cent of patients developed complications, such as sepsis or the inflammation of another part of the body; 55 per cent of these patients died.[5] A third Dutch study put mortality due to *S. aureus* bacteraemia at 13 per cent and overall mortality among patients with *S. aureus* bacteraemia at 23 per cent.[6] In various international studies, it has been calculated that overall mortality among patients with *S. aureus* bacteraemia is about 35 per cent.[7-9]

These findings illustrate how serious an *S. aureus* infection can be. The incidence of *S. aureus* bacteraemia and the associated levels of mortality and morbidity are such that *S. aureus* infection constitutes a significant health problem.

2.2 A bacterium that is resistant to methicillin

MRSA was first reported shortly after the introduction of methicillin – an antibiotic specifically for controlling staphylococci – in 1959.[10] Methicillin resistance is derived from the acquisition of the so-called mecA gene, which imparts reduced affinity for various types of penicillin and related antibiotics. Because of this reduced affinity, the effectiveness of the standard treatments is diminished and it is necessary to treat any infection with less safe and less effective antibiotics.[11,12] MRSA's pathogenic capacity and ability to spread are determined largely by a range of virulence factors. Research has shown that the problems that have occurred are attributable to a small number of MRSA clones. This implies that MRSA is primarily being spread by contact; it is not the case that non-resistant strains of *S. aureus* are regularly acquiring the mecA gene.

MRSA is able to spread comparatively easily in hospitals, because of the intensive contact between patients, nursing staff, doctors and other personnel and the relatively high levels of antibiotic use. In hospital intensive care units, there is a great deal of close contact between medical personnel and patients; it is consequently on such units that the risk of transmission is greatest. The bacterium may be transmitted by direct contact, through the air or via the environment. However, in practice, direct contact is the main means of transmission. The use of antibiotics changes the microflora of, for example, the recipient's skin and digestive system. Thus, any antibiotic-resistant bacteria already present, or to which the patient is exposed, are able to multiply freely in an environment where sensitive bacteria are suppressed. It is clear, however, that other mechanisms influence the scope for colonisation by micro-organisms, such as the seriousness of the underlying condition.

2.3 Premature patient death is more likely

In 2003, an analysis of thirty-one studies was published, which showed that mortality among patients with MRSA infections was more than 40 per cent higher than mortality among those infected with a sensitive strain of *S. aureus*.[11] The analysis looked at mortality due to bacteraemia among 3 963 hospital patients, of whom 2 603 had been infected with non-resistant *S. aureus* and 1 360 with MRSA. Interpretation of the findings is complicated by the observation that less

healthy people may be at greater risk of contracting MRSA infections. The higher mortality rate might therefore be attributable to more serious underlying medical conditions, and this possibility needs to be taken into account in any analysis. Where eleven of the studies were concerned, it was possible to correct for distorting factors, such as the seriousness of the underlying condition, age, sex and duration of hospitalisation prior to infection. Even after such correction, the rate of mortality associated with MRSA infection was distinctly higher than that associated with non-resistant *S. aureus* infection; indeed the difference remained roughly as great as before. When mortality rates in various subgroups (patients with hospital infections; patients contaminated and infected during outbreaks; patients with infections acquired by particular mechanisms, e.g. intravenous infusion lines) were analysed, the rate of mortality associated with MRSA was higher in all cases. The committee has also taken account of research published since the appearance of this meta-analysis. Many of the more recent studies have confirmed the picture described above, although it was not possible to correct for distorting variables in all cases.[13-18] However, a small number of studies failed to discern any difference in mortality rates.[19-22]

From the evidence outlined above, the committee has concluded that there is strong evidence that the rate of mortality associated with MRSA infection is higher than that associated with non-resistant *S. aureus* infection.

2.4 The importance of prompt treatment

Researchers have also sought to explain the frequently reported difference between the rates of mortality associated with MRSA infection and non-resistant *S. aureus* infection.[23] From the studies undertaken, it appears that prompt, effective treatment is a key determinant.

Where MRSA is not particularly prevalent, treatment of an *S. aureus* infection tends to start with a standard therapy, on the assumption that a non-resistant strain is involved. Where MRSA is more prevalent, the first response is more likely to be treatment with an antibiotic that is effective against MRSA, such as vancomycin. With either approach, a small group of patients is likely to be disadvantaged. However, this is readily defensible, since the majority benefit from optimal treatment. In the Netherlands, where MRSA is not very prevalent, a patient infected with MRSA is unlikely to receive the most appropriate treatment for several days, since the cultivation of MRSA samples takes at least forty-eight hours. If the patient is weak, the delay in providing appropriate treatment is likely to increase the risk of death or prolong the recovery period.

2.5 Other consequences of resistance

Various studies have shown that, on average, patients with MRSA infections remain hospitalised for longer than patients with non-resistant *S. aureus* infections.[20-22] Those with MRSA require vancomycin by intravenous infusion, which necessitates a prolonged stay in hospital. There is also evidence to suggest that vancomycin, which tends to be the treatment of first recourse in countries where MRSA is much more prevalent, is less effective against non-resistant strains than standard antibiotics.[11,12]

One potential problem is that prolonged or frequent use of vancomycin increases the risk that MRSA develops resistance to this antibiotic as well, as observed in numerous US studies.[24] Such a development would further reduce the treatment options, and the development of new antibiotics is a slow process. Ultimately, therefore, a situation could arise where there is no effective means of treating people infected with MRSA. This would result in still higher rates of mortality due to MRSA, and the effect would be amplified if such vancomycin-resistant clones were able to spread easily.

Furthermore, a high level of MRSA prevalence would make it necessary to switch to the use of agents that were effective against MRSA, such as vancomycin, for the antibiotic prophylaxis necessary in the context of many surgical procedures. Any such move could be expected to aggravate the risk of further resistance acquisition.

Chapter 3

How prevalent is MRSA?

3.1 Methods for estimating the prevalence of MRSA

Before attempting to estimate the prevalence of MRSA, it is necessary to define one's inclusion criteria. This is important not only for the accuracy of the estimate, but also for the interpretation of and comparison with international data. In this context, it is important to distinguish between colonisation by MRSA (carrying the bacterium) and infection with MRSA. Colonisation involves a newly introduced micro-organism multiplying and becoming established on or in a host. Only if the host develops an immune response, together with the associated phenomena, is there said to be an infection.

In the international literature, reference is often made to MRSA infections as a percentage of all *S. aureus* infections. However, this figure gives no indication of the prevalence of MRSA in a (hospital) population. A study in the UK found that, between 1993 and 2002, the absolute number of bacteraemia cases attributable to non-resistant *S. aureus* rose only slightly.[25] By contrast, the number of MRSA-related bacteraemia cases rapidly increased in the same period, from 210 to more than 5 300. It would appear, therefore, that MRSA does not replace non-resistant *S. aureus*, but occurs in addition to it. By reporting the occurrence of MRSA merely as a percentage of all *S. aureus* infections, a great deal of relevant information is lost. The normal manner of expressing prevalence is as the number of cases per 100 000 patients or per 100 000 members of the general popula-

tion. Where MRSA is concerned, however, this approach too has disadvantages. The reason being that there is considerable case-to-case variation in terms of medical status and duration of hospitalisation: factors that probably influence the risk of developing MRSA. Such differences are not reflected in prevalence data expressed in terms of cases per 100 000 people.

3.2 MRSA in hospitals and nursing homes

Since 1989, RIVM has been recording the numbers of MRSA colonisations and infections and collecting other related data. The number of infections is a fraction of the number of colonisations. When someone is found to be carrying or infected with MRSA, a sample of the bacterium strain is sent to RIVM for classification. Since RIVM guidelines specify that only one sample should be submitted for any one patient, the committee considers it reasonable to assume that the number of samples submitted reflects the number of new MRSA cases (the incidence). Over the last year (from 1 June 2005 to 31 May 2006), more than 1 500 MRSA isolates have been received and classified, equating to an incidence of 9.6 per 100 000 people.[26] The corresponding denominator for the number of isolates cannot be determined, which is why this expression was chosen. Because the incidence figure includes colonisations (which far outnumber infections), it is relatively high. The split between colonisations and infections cannot be determined from the data presently available. Furthermore, there is reason to believe that, in colonisation cases, isolates are not always submitted to RIVM. Nor is it possible to ascertain how many cases involve MRSA acquired in hospital, in the community or in a nursing home.

A Dutch study of nearly two thousand residents at thirty-six nursing homes found that, in the early 1990s, MRSA accounted for a mere 0.15 per cent of *S. aureus* cases in such institutions.[27] By the end of that decade, following a number of MRSA outbreaks in nursing homes, data from eight local laboratories put the figure at 4.2 per cent.[28,29] This would appear to indicate a very sharp rise. However, the study was confined to nursing homes selected precisely because of their high MRSA statistics, and is therefore likely to have overestimated the prevalence of MRSA. To shed further light on the prevalence question, additional research was conducted between 2000 and 2002, involving roughly 1 200 residents at sixteen nursing homes.[30] Some 0.7 per cent of the residents examined were found to be carrying MRSA. The DNA profile of the MRSA bacterium concerned was consistent with one of the strains frequently found in nearby hospitals. This may indicate the transfer of MRSA from hospital to nursing home, or in the opposite direction. The researchers concluded that spread of MRSA within

the nursing homes remained very slow, because people could carry the bacterium for years without a problem.

In order to build up a picture of the way MRSA contamination occurs and spreads, it is important to know whether patients have acquired the bacterium in a hospital or nursing home, or in the community. Information about acquisition routes is likely to be helpful when formulating strategies for minimising the bacterium's prevalence in the Netherlands. The data presently available from RIVM do not shed any light on this particular matter.

3.3 MRSA is also found outside hospitals

Over the last few years, MRSA has attracted considerable public and media attention in the Netherlands, not only as a result of outbreaks in hospitals, but also because of reports concerning the presence of MRSA in the general population. No national data are available concerning the prevalence of MRSA in the population. A Dutch study established that 0.03 per cent of patients were carrying MRSA in their noses at the time of admission to hospital; this equates to a prevalence of 30 cases per 100 000 people.[2] In Limburg, a survey of more than 2 300 people in the community at large also sought to establish the prevalence of MRSA colonisation. Just two individuals (0.09 per cent or 90 per 100 000) were found to be carrying MRSA.[1] These findings support the belief that MRSA remains uncommon. Nevertheless, the survey data suggest a much higher prevalence of MRSA than RIVM's data. This is because RIVM's figures relate only to people who happen to have been found to be carrying or infected with MRSA in the context of MRSA control policy, whereas a survey will identify everyone in a study population who is carrying or infected with MRSA.

The discovery of MRSA in pigs has featured in the news recently. Several pig farmers and their immediate family members were found to be carrying an MRSA bacterium and some developed infections. The MRSA strain involved could not be classified, but was also detected in one of the pigs. Since this incident, the prevalence of MRSA among twenty-six pig farmers has been studied. It was found that a relatively high percentage of the pig farmers (23 per cent) were indeed carrying an MRSA bacterium.[31] The type of MRSA involved had previously been encountered in people only once, in a small study of pigs and pig farmers in France.[32] Clearly, this new variant must originate from a non-human reservoir. The Dutch Working Party on Infection Prevention (WIP) has accordingly revised MRSA policy in line with present scientific knowledge, so that people who work with pigs and calves are now required to take special precautions.[33] Data analysis has also revealed that the number of MRSA isolates sub-

mitted by care institutions in livestock farming regions did rise sharply in the course of 2006 (personal communication, JAJW Kluytmans). If this MRSA variant should also prove capable of spreading easily through livestock workers' families and other contacts, it could lead to a rise in MRSA in the general population, with possible consequences for future MRSA policy. The transfer of this MRSA strain from animals to humans emphasises the importance of MRSA origin tracking and classification in the Netherlands, with a view to promptly identifying new risk groups and revising MRSA policy as necessary.

3.4 Has MRSA become more prevalent in recent years?

In order to discern the trend seen over the last few years, the committee has made particular reference to comparative data collected for the European Antimicrobial Resistance Surveillance System (EARSS). The value of EARSS in this context is that the project has involved the methodologically consistent collection of data on *S. aureus* infections of the bloodstream over a period of years. From these data, it emerges that, in the Netherlands between 1999 and 2004, the proportion of blood infections accounted for by MRSA rose from 0.3 per cent in 1999 to 1.1 per cent in 2004.[34] However, in 2004, the Dutch Working Party on Antibiotic Policy (SWAB) reported that MRSA infections were running at a rate of 1.5 per cent.[35] The explanation for the difference between the EARSS and SWAB figures for 2004 is that EARSS does not cover all hospitals in the Netherlands, but SWAB does.

RIVM data on the absolute number of MRSA isolates received between 1998 and 2004 show an upward trend since 2002.[36] Up to and including 2001, roughly 500 isolates a year were submitted, but since 2002 the figure has been between 1,200 and 1 600.[36] The as yet unpublished figure for 2005 is consistent with this pattern (personal communication, HJ Grundmann). Various explanations for the rise are possible. First, the rise has coincided with the introduction of a new MRSA cultivation medium, what may have resulted in more positive test results.[37] Another possibility is that medical institutions have become more diligent about checking for MRSA and submitting isolates to RIVM. This would be understandable, in view of the increased levels of MRSA awareness generated by the Rotterdam and Rijnmond epidemic, which began in 2001 and continued until late 2004.[38] Hence, it could be that MRSA is no more commonplace than it was prior to 2002, but that detection has improved. Equally, there may have been a real rise in the prevalence of MRSA, due perhaps to more frequent transfer from hospital to nursing home, or – more significantly – to the arrival of MRSA strains from other countries, or to the emergence of new strains that are capable

of spreading more easily. The committee concludes that MRSA appears to be on the increase and considers it important that the causes are investigated, since increasing prevalence may have implications for MRSA policy in the Netherlands.

3.5 MRSA is much less common in the Netherlands than in many other countries

Little research has been done to compare the prevalence of MRSA in different countries. As indicated above, comparison is possible only if similar principles are applied in the collection of data in the various countries. One exception to the general picture is the European Antimicrobial Resistance Surveillance System (EARSS), which does support proper international comparison. Nevertheless, the EARSS database does have the drawback that it relates only to invasive infections, in the context of which *S. aureus* has been cultivated from blood samples. The most recent data are from 2004, when more than 27 000 samples of *S. aureus* from infected blood were analysed.[34,39] The analysis found that, in 2004, the percentage of the infections attributable to MRSA varied from 0.5 per cent in Iceland to 56.4 per cent in Malta. In the Netherlands, the figure for 2004 was 1.1 per cent. The other countries with MRSA rates below 2 per cent were Denmark, Sweden and Norway. Those where MRSA accounted for more than 40 per cent of *S. aureus* blood infections in 2004 were the UK, Malta, Greece, Portugal, Romania and Ireland. Although bacteraemia is the tip of the iceberg, the figures do show that MRSA is much less of a problem in the Netherlands than in most other countries.

Even in our neighbours Germany and Belgium, MRSA rates are much higher than in the Netherlands, at 19.4 and 33.3 per cent, respectively. In view of the substantial differences in MRSA prevalence between the Netherlands and neighbouring countries, research has started with a view to classifying MRSA strains and monitoring their spread in border areas.[40]

In almost all cases, MRSA prevalence data collected in other countries relate only to infections. This often reflects the absence of a (national) policy or any central system for the collection of MRSA data. In countries where the detection of an MRSA infection does not automatically trigger an active attempt to trace the source, the prevalence figures are lower, since many carriers are never recognised as such. Nevertheless, it is probable that there is a relationship between the number of infections and the number of MRSA colonisations. The precise nature of this relationship is not understood, but clearly the number of colonisations must be much higher. Proper international comparison of MRSA prevalence

rates requires the inclusion of colonisation data. The only published data the committee was able to find came from Sweden and gave an incidence figure that included colonisations.[41] Apparently, between 2000 and 2003, the incidence increased from 3.7 cases per 100 000 of the population, to 6.1 cases. As indicated earlier, the estimated incidence in the Netherlands during 2005 and 2006 was 9.6 per 100 000 of the population.[26]

3.6 Prevalence of MRSA in the Netherlands is uncertain

The RIVM data show the prevalence of MRSA in the Netherlands, particularly in hospitals. The data relate to cases where either an infection has been detected in a patient or where screening of a high-risk patient or staff member has led to the detection of MRSA. The data presently available do not permit distinction to be made between infections and colonisations. Furthermore, it is not possible to tell from the data whether new high-risk groups are emerging.

Problems also exist with many other sources of data concerning the prevalence of MRSA. The Dutch data collected for the international EARSS project relate only to infections of the bloodstream, which are merely the tip of the iceberg. The data from nursing homes are now some years old and date mainly from periods when MRSA outbreaks occurred in nearby hospitals. Data on MRSA prevalence in the general population are available, but come from just two studies. Furthermore, little is known about the dynamics of MRSA; in other words, it is by no means clear to whom MRSA is liable to spread or how quickly.

Chapter 4

What is the policy on MRSA?

4.1 Dutch MRSA policy

In the Netherlands, MRSA policy for hospitals and nursing homes is set out in national guidelines produced by the Dutch Working Party on Infection Prevention (WIP).[42,43] The prevention of MRSA infections is also dealt with in the WIP guidelines on the prevention of infection in the ambulance services, the home care sector and general medical practice. The Dutch Working Party on Infection Prevention includes experts in infectious disease, medical microbiology and hygiene and infection prevention. The WIP guidelines focus primarily on clinical care, while the National Centre for Infectious Disease Control (LCI) supervises infection prevention in the community. The LCI has recently drawn up guidelines on MRSA prevention in public health care.[44]

In addition to the various guidelines for use in the health care sector, there are guidelines on the detection of MRSA in the laboratory, produced by the Dutch Association for Medical Microbiology. The latter guidelines are intended to ensure optimal detection and reporting of MRSA that is consistent with national policy.[37]

4.1.1 *Policy in hospitals*

MRSA policy in hospitals may be divided into a number of key subdomains.[43] First, there is screening and isolation policy, also known as search and destroy policy. This policy is concerned with people at elevated risk of MRSA colonisation or infection. Under this heading come people who have recently been hospitalised outside the Netherlands, those who have previously been hospitalised in an institution with an MRSA problem in the Netherlands, and those who have previously been infected or colonised by MRSA. Recently, people who work with pigs and calves are also considered to be at elevated risk of MRSA colonisation or infection. Such patients are screened for MRSA on the basis of strict criteria and, where necessary, cared for in isolation until it is clear that they have not been colonised or infected by MRSA. Cultures are produced using samples from the throat, nose, perineum and, where relevant, wounds. This approach minimises the risk of MRSA being introduced to the hospital environment by high-risk patients. If an MRSA case nevertheless occurs, additional screening is instigated. In addition to isolation of the patient, the other patients and medical personnel with whom he or she has had contact are checked for MRSA and monitored for a time, in order to ascertain whether they are carrying the bacterium.

The second subdomain of MRSA policy is the treatment of MRSA carriers. With a view to restricting the spread of MRSA as quickly as possible, MRSA carriers are required to disinfect their skin, hair and nasal passages. Colonised medical personnel are allowed to work with MRSA-free patients only once culture tests have shown them no longer to be carrying the bacterium. However, personnel with skin abnormalities are sometimes difficult to treat and cannot be completely rid of MRSA. In some cases, alternative employment consequently has to be sought. An infectious disease specialist should be consulted regarding the treatment of patients with MRSA infections and those in whom colonisation persists after nasal disinfection.

The guidelines also describe the action that should be taken if there is an ‘outbreak’ of MRSA (technically, the detection of MRSA in two or more patients). In addition to screening medical personnel and patients and isolating those with the bacterium, a policy team has to be formed with special responsibility for managing the outbreak. For full details, please refer to the guidelines, which are available from the Internet, and which are regularly updated in line with policy refinements.[43]

When a patient who is carrying MRSA is discharged from hospital, communication is very important as well. The patient's GP and other carers should be informed about the situation, so that appropriate measures can be put in place. Communication is also critical if such a patient is transferred to another institution, such as a nursing home or psychiatric institution. Explicit guidance on this issue is included in the LCI's guidelines.[44] The Health Care Inspectorate's 2002 circular also draws attention to the exchange of MRSA status information when patients are transferred to other hospitals and other care institutions.[45]

4.1.2 *Policy in nursing homes and residential care centres*

Nursing home residents fall into two groups. Data from 2003 show that roughly 40 per cent of residents are there to recover following discharge from hospital.[46] Such people tend to remain at the nursing home for short periods only (a few days or weeks) resulting in a considerable flow of patients between nursing home and hospital. The remaining 60 per cent of clients are resident permanently until their death; the average stay of such a patient has been estimated at 1.5 to two years. Because the prevalence of MRSA within the latter group is believed to be low, it has thus far been deemed appropriate to pursue one policy for the two resident populations.

In nursing homes and residential care centres, the MRSA control measures are less stringent than those taken in hospitals. There are various reasons for this. First, the use of invasive procedures and antibiotics is much lower than in a hospital. Also, because the nursing home is 'home' to most residents, greater emphasis is placed on quality-of-life considerations. Furthermore, recovering residents often share facilities and locations with permanent residents, making the pursuit of separate MRSA policies impractical.

Nursing home and residential care centre residents who have been colonised by MRSA have to be cared for in a separate room, but are allowed to participate in social activities. When treating such residents, the staff are required to wear protective clothing, cloves, masks and hats. If MRSA infection is suspected, the person has to be treated as if the infection were confirmed, pending receipt of culture test findings. If an unexpected case of MRSA is detected, an investigation has to be carried out to establish whether the bacterium has spread, and the case has to be reported to the municipal health council.[42,44]

4.1.3 *MRSA guidelines for the public health care sector*

In 2005, an MRSA response plan for the public health care sector was published.[44] Within this sector, MRSA policy is designed to prevent MRSA being spread from public health care establishments to hospitals or vice versa by high-risk patients and medical personnel. As with the guidelines described above, the prescribed measures are geared to the risk of an individual carrying or being infected with MRSA. The measures range from steps to trace the source of MRSA infections originating outside the hospital setting, to informing care providers about MRSA colonisation.

Outside hospitals, there is often a lack of awareness of MRSA and the related test procedures. If MRSA is detected in a non-hospital setting, it is very important that the care provider involved enlists the help of appropriate experts, such as medical microbiologists or infection specialists.

4.2 Scientific basis for the guidelines

Ideally, guidelines should be based on good-quality research of practical relevance. However, guidance cannot be based solely upon such research. Account should also be taken of the practicability, cost, legal context and implications for occupational health and safety. There is a paucity of information about MRSA that derives from methodologically sound research. In the past, lack of awareness of scientific methodological principles meant that control measures were often introduced before their efficacy had been demonstrated under controlled conditions. The guidelines for the prevention and treatment of MRSA are based upon practical experience – as, indeed, are many of the guidelines used in the health care sector. No scientific research has been reported, in which the effect of a comprehensive package of measures has been compared with the effect of a less comprehensive package or with the effect of pursuing no coherent MRSA policy. The committee believes that Dutch policy should be based upon evaluation of measures collectively and in relation to one another, since it is suspected that the success of the policy pursued to date is attributable to the entire body of measures in place.

Despite the methodological shortcomings of much of the published research, the committee has sought to identify any scientific evidence that might support or question the validity of the present policy or any element of it. Cooper *et al*. undertook a systematic review to determine the effect of isolation (care in separate rooms or wards) on the incidence of MRSA,[47] as established from MRSA

culture test findings. The conclusion was that many of the reviewed studies exhibited methodological shortcomings and were poorly reported, as a result of which the possibility that the observed effects were attributable to other causes could not be excluded. No scientific evidence was available to support the hypothesis that isolation was effective in its own right. However, evidence was found to suggest that a package of measures including isolation was effective. The strongest evidence came from six studies, of which four showed that a body of intensive measures – including isolation – was effective as a means of controlling MRSA.[48-52] The other two studies related to situations where an epidemic was not successfully brought under control.[53,54] In the studies that provided evidence of that isolation had a positive influence on the incidence of MRSA, other control measures were also in use. These included other elements of Dutch policy, such as culture testing, the use of nasal cream by carriers, contact screening, barrier nursing and the encouragement of hand-washing.[48-52]

The committee concludes that there is no strong scientific basis for the policy presently pursued in hospitals. This conclusion is endorsed by a very recent British review.[55] The research by Cooper *et al*. supports the view that Dutch policy is capable of minimising the prevalence of MRSA. A recent model-based Dutch analysis indicates that a causal relationship very probably exists between the strict Dutch policy and the low prevalence of MRSA in the hospitals and the general population.[56]

4.3 The value of model analyses for decision support in the MRSA policy domain

Models have been used to analyse the implications of various scenarios for the prevalence of MRSA in the Netherlands, both in hospitals and in the general population.[56] In the context of this report, it is of particular interest to see what impact the relaxation of certain aspects of the national MRSA policy might have on prevalence levels. The models indicate, for example, that not screening people in high-risk groups would result in barely any change in the prevalence of MRSA after ten years. This prediction assumes that, in the event of a patient being found to have MRSA after admission, all the control measures prescribed by the existing guidelines would be implemented. What the model does not predict in any detail is the increase in the number of MRSA outbreaks that are liable to occur as a result of the cessation of screening. Such outbreaks tend to create commotion, additional work and extra costs in a hospital.

The model analyses also suggest that both the screening and isolation of high-risk patients and the identification of unexpected index patients can each

keep the MRSA rate below 1 per cent in the long term. However, it also appears that the combination of the two strategies is an even better means of maintaining a low prevalence. Another conclusion to come out of the analysis is that the screening of nursing staff and doctors, the temporary closure of wards and the treatment of all known carriers are unlikely to further reduce the prevalence of MRSA.

The committee believes that the findings of the model analyses do not presently justify revision of the present policy. There are various reasons for taking this view. First, any model is inevitably a simplified representation of reality. The model used for this particular analysis, for example, assumed that all hospitals were the same and pursued the same policies; in practice, this is not of course the case. Furthermore, the committee believes that further analysis is required in order to establish the prevalence implications of certain assumptions made in the context of the model. The committee is also concerned that, if certain aspects of the national policy were relaxed, a strong rise in the prevalence of MRSA might follow. The potential consequences of such a rise are sufficiently serious (see subchapter 5.1) that the committee considers it irresponsible to take the risk.

The findings of the model analysis indicate that a strict control policy can reduce the prevalence of MRSA to less than 1 per cent, even if introduced in circumstances where the prevailing prevalence is high and subsequently maintained. However, the dynamics of infectious disease are such that it may be expected to take roughly ten years to achieve this level. This finding is presently of interest mainly in relation to countries where the prevalence of MRSA is high.

4.4 Considerable international differences in MRSA policy

As indicated in subchapter 3.5, the percentage of *S. aureus* infections of the bloodstream accounted for by MRSA differs considerably from country to country.[57] Similar variety exists in terms of MRSA policy.[58] In the USA, where the prevalence of MRSA is high, the value of screening is disputed and only 30 per cent of hospitals screen for the bacterium as a matter of course.[59] Furthermore, there is no uniform national approach to MRSA control. MRSA is also very common in Japan, accounting for 70 per cent of all *S. aureus* blood isolates. A Japanese patient may attend any hospital without appointment, there is no screening for MRSA and little is known about the bacterium among care providers, the public or the media.[58] In Turkey, the high MRSA percentage is attributed to the absence of infection control measures and the widespread use of antibiotics where they are not indicated.[58]

The main features that distinguish Dutch MRSA policy from the policies pursued in many other countries are screening and the national application of guidelines on infection prevention. In the Netherlands, both patients and staff at increased MRSA risk are screened and, if warranted by the level of risk, cared for in isolation or suspended from care duties until their status is known. This strategy is one of the keys to preventing the introduction of MRSA to the hospital environment. High-prevalence and low-prevalence countries also tend to differ in terms of their approach to the use of antibiotics. Setting aside the specific issue of MRSA control, it is of great general importance for the prevention of resistance development in bacteria that antibiotics are used only where strictly necessary and that the antibiotic prescribed is always that which is most effective against the particular bacterium to be tackled.

Significantly, the UK and the USA have in recent years been showing increasing interest in the Netherlands' approach to MRSA control. The relationship between differences in policy and the prevalence of MRSA is often discussed at international congresses and the Netherlands plays an important role in this debate.

Chapter 5

Opportunities and threats in the MRSA policy domain

5.1 Policy relaxation would lead to increased MRSA prevalence

As explained above, MRSA is much more prevalent in most other countries than it is in the Netherlands. One of the countries with a high MRSA rate is the UK, where the situation was once similar to that in the Netherlands. The committee believes that what has happened in the UK serves as an important lesson for the Netherlands. If the Dutch policy of screening people in high-risk groups or the control measures implemented as a matter of course in the event of an MRSA outbreak were relaxed, we could find ourselves in the sort of situation that now prevails in the UK.

As recently as the late 1980s, the UK's MRSA status was similar to the Netherlands' present status. There was a strict control policy, many elements of which mirrored current Dutch policy.[60] However, financial pressures and uncertainty regarding the real value of MRSA control policy led to relaxation. In the fifteen years since, the UK has witnessed a major rise in MRSA prevalence, from less than 2 per cent to 40 per cent of all *S. aureus* blood isolates.[61] Furthermore, it has become apparent that the extra MRSA infections are occurring in addition to, rather than instead of, infections with non-resistant *S. aureus* strains.[25] Public and political disquiet at these developments has been such that the UK is now fighting a difficult and expensive battle to bring MRSA under control again. The fact that a certain proportion of people admitted to hospital are actually being made

more ill there, instead of being cured, is regarded as unacceptable. There is, moreover, a real possibility that MRSA will become increasingly insensitive to antibiotics. In the USA, strains have already been encountered that exhibit reduced sensitivity to vancomycin.[62,63] If this trend continues, the scope for effective therapy may be seriously reduced. The need to avoid resistance development in MRSA is one of the main reasons for controlling the spread of MRSA.

Researchers have established that MRSA is an increasingly common contributory or primary cause of death in the UK.[25] Of all cases where *S. aureus* was mentioned on the death certificate, 66 per cent involved MRSA in 2002, compared with just 12 per cent in 1993. Analysis of later data indicates that the trend continued into 2003 and 2004.[64] No comparable research has been carried out in the Netherlands. If the UK statistics are projected onto the Dutch population, the number of deaths in which MRSA was a contributory or primary cause of death in 2003 works out at more than two hundred.

The extent to which MRSA contributed to the deaths of the patients concerned – most of whom were in any case seriously ill – cannot be determined from these data. However, MRSA's contribution to mortality rates may be calculated by comparing data on patient populations of similar health status, which differ only in terms of the resistance of the *S. aureus* strains afflicting them. As observed in chapter 2, it appears that mortality among those who contract an MRSA infection is 40 per cent higher than among those infected by non-resistant *S. aureus*.

The committee believes that relaxation of Dutch MRSA policy would lead to a rise in the bacterium's prevalence. This belief is supported by Dutch model analyses, which suggest that prevalence would in due course rise to 15 per cent in the hospitals, i.e. that fifteen out of every hundred patients who contract an *S. aureus* infection would be affected by MRSA.[56]

5.2 Cautious antibiotic use as a means of controlling MRSA

It is generally accepted that cautious use of antimicrobial agents is very important as a means of containing the development of resistance.[65] In this context, 'cautious use' implies using antibiotics only where medically indicated and, whenever practicable, using an antibiotic that is intended for the specific pathogenic bacterium to be tackled. Research has shown that countries that apply a strict MRSA prevention and treatment policy combined with a strict antibiotic policy tend to have low MRSA prevalence levels.[57] By contrast, MRSA is very prevalent in countries with a more relaxed approach. One of the clearest examples of resistance development is the way that MRSA has responded to the intro-

duction of fluoroquinolones; within ten years of these drugs entering use, 95 to 100 per cent of MRSA strains had become resistant.[66]

Observational Dutch research has shown that outbreaks can be brought under control by an active search and destroy strategy, albeit sometimes with considerable trouble and at considerable expense.[38,67,68] Experts are divided as to the extent to which success in managing MRSA prevalence may be attributed to, respectively, cautious antibiotic use and control measures of the kind described earlier in this report. The committee takes the view that it is known that antibiotic use leads to the selection of resistant organisms. Hence both control measures and cautious antibiotic use are prerequisites for low MRSA prevalence.

5.3 Increasing prevalence of MRSA in the wider community

It is pertinent to consider the potential impact of growing numbers of MRSA carriers in the community for communication of the bacterium and for hospital outbreaks. MRSA can be brought into the hospital environment by newly admitted patients, outpatients and people visiting in-patients. As the number of people in the community who carry the bacterium increases, so too does the likelihood of hospital patients coming into contact with it.

The findings of a US study of the prevalence of *S. aureus* and MRSA in the wider community have recently been published.[69] It appears that roughly 32 per cent of Americans carry *S. aureus* bacteria in their nasal passages and that 0.84 per cent carry MRSA. The corresponding figures for MRSA are between 0.03 per cent and 0.09 per cent in the Netherlands.[1,2] An increase in the prevalence of MRSA in the population could justify screening all patients for MRSA prior to or upon admission to hospital. Such a move is being considered in various countries and universal screening is already the norm on certain high-risk wards in the UK.[70-72] It is in high-risk departments, such as intensive care units, that MRSA can most readily spread among vulnerable patients.

Another problem is so-called community-acquired MRSA, i.e. MRSA with which a patient has been infected prior to any contact with a hospital. A type of MRSA has been identified, which carries the Panton-Valentine virulence gene and causes infections in previously healthy people. This MRSA variant has been found both abroad and in the Netherlands, where it even caused the death of a fifteen-year-old.[73] Studies have established that the gene that characterises this type of MRSA is present in 15 per cent of all MRSA isolates.[74] Patients carrying or infected by the bacteria in question are on average younger than those carrying or infected by other MRSA variants. The reason for the high rate of mortality associated with the strain is not known. In the USA, 8 to 20 per cent of all MRSA iso-

lates have been found to involve this form of MRSA. In most cases, the bacterium had caused skin infection, while in a quarter of cases hospitalisation was necessary. From studies of two populations, the community incidence of this pathogenic MRSA variant has been put at between 18.0 and 25.7 per 100 000 people.[75]

US and Australian researchers have also shown that strains that were originally found in the community have subsequently caused hospital outbreaks among new mothers and neonates.[76,77] Of particular concern is that the infections in question were unusually serious (life-threatening), which implies that the spread of the strains in question could cause significant mortality.

On the basis of the observations reported above, it is probable that MRSA can be introduced to hospitals from the general population. Furthermore, community-acquired MRSA appears capable of causing serious problems for the hospital population. It is therefore very important to build up a better picture of the prevalence of the various types of MRSA in the community. This can be achieved by extending surveillance, by improving the molecular classification of MRSA and by gathering more information about the communication and spread of MRSA. These measures would facilitate the development of policy in response to the emergence of new high-risk groups.

5.4 Reservoir formation in nursing homes and care homes

The committee regards nursing homes as potential 'MRSA havens', where the bacterium can establish itself and from which it can readily spread. Many nursing home residents are weak and exhibit co-morbidity, necessitating intensive nursing and general care. Furthermore, because such people tend to have various ailments, they are relatively frequent hospital clients. If a nursing home resident is colonised by MRSA, it is reasonable to suppose that the bacterium will find it relatively easy to spread to other residents and to any hospital where they are treated. Nursing homes operate on much smaller budgets than hospitals and are less able to absorb the costs associated with MRSA. A national subsidisation scheme does exist, but a threshold system is operated, which may sometimes lead to delays in the treatment of MRSA patients. To complicate matters further, the treatment of a nursing home resident colonised by MRSA will normally entail more trouble and explanation. Most are elderly people whose families need to be consulted about treatment, and it can be difficult to persuade a family that a 'healthy' older relative should be treated for the protection of others. Under such circumstances, the WIP protocols are difficult to fully adhere to, despite adaptation to the particular circumstances.

One way of addressing the problems outlined above would be to screen nursing home and care home residents before they are accepted for hospital treatment or subsequently returned to their homes. Where screening detected MRSA, the patient could be temporarily transferred to a nursing home with a unit specially equipped for the nursing and treatment of MRSA patients. Once the colonisation or infection was resolved, the patient could be returned to the home or admitted to hospital for medical treatment.

A nationwide study in Belgium recently discovered a very high prevalence of MRSA (nearly 20 per cent) in rest and care homes.[78] The figure represents a three or four-fold increase in a five year period. The committee believes that there is a danger of MRSA reservoirs developing largely unnoticed in the Netherlands as well; hence, awareness of MRSA and its implications for residents and the general population needs to be promoted in nursing homes. Furthermore, more information is required regarding the prevalence of MRSA in nursing homes and MRSA policy should be reviewed to ensure that it takes proper account of the situation in such establishments.

5.5 Impact of MRSA policy on quality of life

One consequence of the present policy is that high-risk patients, e.g. those transferred from hospitals abroad, are cared for in isolation until the results of their MRSA culture tests are known. Such patients are looked after in conjunction with other patients and the number of contact moments is kept to the minimum, since repeated changes of protective clothing is time-consuming and more frequent contact increases the risk of MRSA being spread. The committee expects that isolation care reduces quality of life for the patients concerned, but has no scientific evidence to support this supposition. One study has shown, however, that patients cared for in isolation were more likely to report avoidable incidents, perceived that they received less care and were less satisfied with the care that they did receive.[79] The study in question found no evidence that the health status of the patients was adversely affected.

Furthermore, carrying MRSA can have far-reaching implications for nursing and medical staff. In a small proportion of cases, the MRSA cannot be eradicated; such persistent colonisation mainly tends to occur among personnel with chronic skin conditions such as eczema and psoriasis, who can rarely be entirely rid of the bacterium. While waiting to be cleared of MRSA, personnel are unable to work. Some find this difficult to accept, because it is not clear how long eradication will take and/or because they feel that the bacterium has been discovered

by accident, although they have carried it for some time without it giving rise to problems.

5.6 New MRSA test methods

To determine whether a sample contains MRSA, a culture has to be incubated for two to five days. While the test results are awaited, the patient either has to be cared for in isolation or has to wait at home to be admitted to hospital. Nursing and medical staff who are suspected of carrying the bacterium are not able to work until it has been eradicated. In all cases where it ultimately proves that the person is not carrying MRSA (roughly 95 per cent of the patient cases[80]), isolation or suspension from work will have been to no avail. From the viewpoint of the patient, the care staff and the hospital, it is desirable that the period between taking a sample and receiving the analysis results should be kept as short as possible. The possibility of using more rapid test techniques, which do not rely on traditional culture incubation, is therefore being investigated. To be attractive, an alternative test method would need to have similar properties while providing considerable time savings. Dutch models have shown that the number of isolation days could be reduced by about 90 per cent if a rapid test method were available.[56] A study was recently published, describing a promising test technique that was capable of providing a result within an hour.[81] The value of using such a technique is presently being investigated in the Netherlands in a study involving several hospitals.[82]

Chapter 6

The costs associated with MRSA policy

6.1 The factors that determine present costs

The MRSA policy pursued in the Netherlands costs money. Some of the costs are ongoing and unrelated to any particular outbreak of MRSA, such as the cost of screening patients arriving from abroad and other high-risk groups. In addition, there are various one-off costs that arise out of the particular circumstances surrounding an outbreak of MRSA. So far, these costs have been borne by the hospitals themselves.

The ongoing costs associated with the present policy derive mainly from culture testing and the provision of isolation care. The unit cost of a test is not high, but the volumes involved in screening are considerable. Isolation care involves the use of protective gear and makes nursing procedures time-consuming. Furthermore, the need to isolate patients sometimes leads to beds being left unoccupied.

In the event of an MRSA outbreak, the volume of testing increases still further because of the need to check the patients and personnel who have been in contact with those known to be infected or colonised. In addition, the number of patients in need of isolation increases. Meanwhile, the hospital often loses income, because wards have to be closed until the epidemic is brought under control. Furthermore, MRSA treatment involves the use of vancomycin, which is not only more expensive than the antibiotics used under normal circumstances,

but also less effective, meaning that patients spend longer in (costly) isolation. Vancomycin also has to be administered by intravenous infusion. New anti-MRSA drugs, such as linezolid and daptomycin, are even more expensive. Finally, as indicated earlier, the rate of mortality associated with MRSA is higher than that associated with non-resistant *S. aureus.*

6.2 Cost-effectiveness

Cost-effect analysis can facilitate the process of weighing up different policy options. Where MRSA is concerned, such an analysis should involve determining the total cost of pursuing the present strict policy (capacity and resources deployed) and all the mortality and morbidity benefits of the policy, then comparing them against the costs and benefits of other policy options. By also including quality-of-life effects, a thorough analysis of the cost-health benefit balance associated with each option can be made. Policy-makers may then make an informed decision as to how best to proceed.

MRSA cost data collected in other countries are available, but have various shortcomings. In most cases, the circumstances elsewhere are only partially comparable with those that prevail in the Netherlands. The prevalence of MRSA is liable to be different, and the policies pursued in other countries are liable to differ in ways that make comparison difficult.[83-88] Furthermore, none of the published analyses seeks to quantify mortality effects; in all cases, the emphasis is on cost. Nevertheless, all the studies conclude that, at low prevalences, the cost of screening for MRSA or the isolation of MRSA patients outweighs the cost of dealing with MRSA outbreaks. Even at higher prevalences, which imply the isolation of more patients in the event of an outbreak, a screening and isolation policy proves to be cost-effective. Considerable costs are bound up with prolonged hospitalisation.

No cost-effect analyses of Dutch policy have been performed. However, two analyses have been made of the cost of MRSA policy in the Netherlands. The one study sought to determine the overall cost of MRSA policy at Utrecht University Medical Centre.[68] The other looked at the cost of an outbreak at a general hospital.[67]

6.3 The estimated cost of Dutch MRSA policy

As indicated above, two studies have been published, which sought to quantify the cost of the Netherlands' MRSA policy.[67,68] The committee has used the article by Vriens as the starting point for its own cost estimates.[68] This study has

been preferred because it looked at costs over an extended period, in which there were several outbreaks, and because it took account of the cost of screening high-risk patients and of the associated isolation. In addition, the committee has received information concerning several hospital outbreaks of MRSA, and has compared this information with Vriens' findings.

Vriens estimated the cost of implementing MRSA policy within Utrecht University Medical Centre at 280 000 euros a year in the period 1991 to 2000. Data from other hospitals suggest that Vriens' estimate of lost income resulting from ward closures is relatively low. Furthermore, an estimate of the present cost needs to take account of inflation in the years since 2000. On the other hand, costs at university hospitals are generally higher than the corresponding costs at general hospitals. On balance, the committee is inclined to regard Vriens' estimates as conservative.

Analysis of data from a number of hospitals that experienced major MRSA outbreaks involving between seven and thirty-one people puts the average cost per outbreak at more than a million euros. In other words, a major outbreak can be a serious drain on a hospital's finances.[67] Because major outbreaks are – at least for the time being – unusual in the Netherlands, the largest cost items are presently the screening of high-risk patients, the provision of isolation care and tackling minor outbreaks that involve only a handful of people.

6.4 Relaxation of MRSA policy likely to result in increased costs

Vriens' research sought not only to cost existing MRSA policy, but also to determine how the cost pattern could be expected to change if that policy were abandoned. Vriens assumed that such a change would lead to a sharp rise in MRSA, to the point where it accounted for 50 per cent of all *S. aureus* infections. The committee considers this assumption to be probably correct. The result of such a rise would be corresponding growth in antibiotics consumption, due to the use of vancomycin and other agents to treat the additional MRSA cases. Even after setting off the costs associated with the present MRSA policy and existing expenditure on antibiotics, the cost of moving away from the existing policy works out considerably higher. As indicated earlier, this conclusion is supported by cost projections made in other countries.[83,85,88]

The committee considers it probable that, if the present MRSA policy were abandoned, as many as four thousand blood stream infections a year would occur, over and above the *S. aureus* infections to be expected if the present policy is continued. This projection is consistent with actual developments in the UK, as described in subchapter 5.1. The additional infections would generate consider-

able extra costs, since the patients concerned would remain hospitalised for longer and would require expensive treatment. More important, a move away from existing MRSA policy would also mean a sharp rise in disease burden and probably a rise in mortality.

6.5 Further research needed to gauge the cost-effectiveness of MRSA policy

Since little research has been carried out in the Netherlands into the cost of MRSA policy, it is difficult to draw conclusions regarding the cost-effectiveness of that policy. A cost-effect analysis should, in the committee's view, quantify the costs associated with all policy elements, as well as the health benefits (impact on mortality and quality of life) associated with the various policy options. Furthermore, the committee would like to see use made of a model that takes account of the dynamic nature of the spread of MRSA. The assumptions made in the modelling process should also be varied. The model output would then be of real value in the context of policy development, in a manner analogous to what was seen with the introduction of the breast cancer screening.

One possible way of reducing the costs associated with MRSA policy, which is already being investigated, would be to identify and introduce a faster method of testing for the bacterium. The availability of such a test would remove the need to isolate patients pending the outcome of a culture test. This could reduce costs considerably, provided that the unit cost of testing were not unreasonable and the test properties were acceptable.

Chapter 7

Conclusions and recommendations

In various domains, scientific understanding of MRSA is far from complete. Significant gaps in knowledge exist, for example, with regard to the bacterium's prevalence in various population groups, such as nursing and care home residents; furthermore, much remains unclear about the spread of MRSA. Scientific knowledge pertaining to the effectiveness of MRSA policy is patchy, and questions remain unanswered with regard to the cost of MRSA policy. Nevertheless, the available data are sufficient to permit the committee to draw certain conclusions and make a number of recommendations. The committee also wishes to make various research recommendations, with a view to addressing the gaps in knowledge that exist where some pertinent matters are concerned.

7.1 Understanding of the epidemiology of MRSA should be improved

RIVM's MRSA surveillance activities provide information regarding the number of MRSA isolates in the Netherlands. However, the RIVM data do not distinguish between MRSA colonisation and infection. Nor do they shed light on the prevalence of colonisation and infection in various groups within the Dutch population, such as nursing home and care home residents.

On the basis of international data provided by RIVM, the committee concludes that MRSA infections of the bloodstream are considerably less common

in the Netherlands than in many other countries, and that MRSA appears to have been increasing since 2002.

If MRSA is to be kept under control in the future, it is very important to have information regarding developments in the prevalence of MRSA in the Netherlands. At present, data regarding the bacterium's prevalence in nursing and care homes and in the general population are particularly sparse. The possibility that nursing and care homes might become MRSA reservoirs is a source of concern. If that were to happen, a sharp and uncontrollable rise in MRSA might result unless appropriate measures were implemented in response, such as the screening of nursing home residents prior to hospitalisation. Greater understanding of the mechanisms by which MRSA is communicated and spread is also desirable. Such understanding is necessary if the reasons for the increase in MRSA seen since 2002 are to be identified and MRSA policy adapted promptly. When gathering data on MRSA, particular attention should be given to the representativeness and definition of the population and to distinguishing between infection and colonisation.

7.2 Abandonment of existing MRSA policy probably more expensive

Neither the precise cost of applying the existing MRSA policy (in terms of manpower and resources), nor its precise effect (the prevention of morbidity and mortality) are known. Improved understanding of these matters would also provide a sound scientific basis for any future policy revisions that might be warranted.

In view of the data currently available, the committee considers it very likely that the cost of the present policy comfortably outweighs the costs that would arise if the policy were abandoned. Such a move would lead to higher MRSA treatment costs and the associated costs of prolonged hospitalisation. These costs would escalate as the prevalence of MRSA increased, as may reasonably be expected.

In order to make a detailed comparison of the costs and effects associated with various MRSA policy options, further research is needed with a view to more accurately determining both the costs and the effects on mortality and on quality of life. A dynamic Dutch MRSA model is available, which the committee expects could be modified relatively easily to take account of the associated costs as well.[56] The model presently predicts the prevalence of MRSA in hospitals and the wider community, as associated with various policy scenarios, ranging from continuation of the existing strict national policy in full, to the separate application of elements of the policy, such as the isolation of MRSA carriers and the

screening of high-risk groups on admission. One way in which the cost of the present policy might be reduced would be to introduce a faster MRSA screening test; the scope for such a change is currently under investigation.

Meaningful comparison of the costs of different MRSA policy options depends upon the availability of cost data that meet certain criteria. When costing the various components it is important to distinguish between MRSA colonisations and infections, and between the costs associated with addressing outbreaks and the ongoing costs of MRSA management.

7.3 Current MRSA policy should be retained

The committee recommends retention of the present strict policy for controlling the spread of MRSA. The primary reason being that abandonment of the policy may be expected to lead to MRSA becoming much more prevalent and thus to considerably greater disease burden and mortality. From the findings of British research, it is clear that that country's move away from a strict containment policy resulted in major growth in the number of MRSA infections. Furthermore, such infections have apparently occurred in addition to the *S. aureus* infections that might otherwise have been expected. The committee's recommendation is also motivated by the belief that policy relaxation is liable to promote further resistance development in MRSA, leading to the emergence of strains that are insensitive to vancomycin and other antibiotics, thus reducing the medical profession's ability to treat MRSA infections effectively. Furthermore, the costs associated with MRSA may be expected to rise, perhaps very considerably, if the present strict MRSA policy is abandoned.

Finally, the committee wishes to see special attention paid to the treatment of MRSA carriers, particularly those working at hospitals. It is clear that it is not always possible to rid a carrier of the bacterium using the present treatment methods. This can have significant implications for the individuals concerned, including the need to seek alternative employment. Not enough is yet known about appropriate follow-up treatment methods.

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A Request for advice

B The committee

Annexes

Annex **A**

Request for advice

On 29 January 2004, the Minister of Health, Welfare and Sport wrote as follows to the President of the Health Council, under reference POG/ZP 2.445.254:

Introduction

Since the introduction of antibiotics in the middle of the last century, the medical profession has been able to cure infectious diseases that had previously been untreatable. However, the use of antibiotics brings with it the risk of resistance development in the pathogens against which the drugs are deployed. Where resistance develops, the antibiotics concerned cease to be effective for the treatment of certain conditions. This at least implies additional cost, since alternative and typically more expensive medicines have to be used. Potentially, however, the development of resistant pathogens could result in people dying from conditions that we are presently able to treat with relative ease. The latter scenario is certainly not unrealistic where very weak people, such as patients in intensive care, are concerned.

Prevention of resistance development in health care

Resistance development is problematic mainly in the livestock industry and the human health care sector. Health carers make relatively frequent use of antibiotics, leading to considerable selection pressures in care establishments. Furthermore, in such establishments there is a high concentration of patients, some of whom tend to be very weak. Consequently, if good hygienic precautions are not taken, a resistant bacterium can readily spread, sustain itself and cause considerable damage within the vulnerable patient or resident population.

One of the most notorious resistant bacteria in health care institutions is *methicillin-resistant Staphylococcus aureus* (MRSA). MRSA has not so far become very prevalent in the Netherlands. Nevertheless, there has been a slight increase in MRSA cases in recent years, partly because of changes in the demographics of the patient population and partly as a result of importation from other countries. While it has fortunately been possible to ensure that the prevalence of MRSA remains low in the Netherlands, the maintenance of this state of affairs entails considerable effort. Active measures are required at all points in the care chain in order to prevent the development and spread of MRSA.

The measures in place are:

- Prevention by means of the cautious prescription of antibiotics and the application of a strict hygiene policy
- The monitoring of MRSA and other resistant micro-organisms in hospitals
- In the event of an outbreak, the isolation of contaminated patients and, where necessary, the closure of hospital wards

This policy appears to be effective, but is also vulnerable. Its implementation requires considerable commitment and cooperation from everyone involved in the care process. Acute MRSA outbreaks place a particularly severe burden on already hard-pressed hospital personnel. It is occasionally necessary to shut down entire wards or to keep contaminated personnel away from work. Such responses have major organisational and financial implications. Some establishments have expressed doubt as to whether the health benefits secured by the present containment policy are sufficient to justify the cost and operational implications. Continuation of the present policy is therefore under threat, and there is a possibility that certain hospitals will cease to apply it.

Commission

In view of the situation outlined above, I would like you to advise me regarding present scientific thinking on the MRSA issue and regarding the possible public health implications of abandoning or relaxing the present policy. Please indicate the costs likely to arise both from retention of the present policy and its abandonment, and advise me accordingly on the most appropriate way of addressing MRSA in the Netherlands.

In your advice, please give specific attention to the following questions:

1 How prevalent is MRSA in the Netherlands? Have there been changes in the prevalence pattern in recent years?
2 What policies on MRSA are pursued in other countries and what impact have such policies had on public health?

I shall be grateful to receive your report by the end of 2004. Finally, I would ask that you permit Ms M.A.J. Bilkert-Mooiman of the Health Care Inspectorate to attend the meetings at which your Council's response is considered (IGZ).

Yours sincerely,
(signed)
H. Hoogervorst
Minister of Health, Welfare and Sport

Annex **B**

The committee

- Professor JE Degener, *chairman*
  professor of medical microbiology; Groningen University Medical Centre
- MAJ Bilkert-Mooiman, *adviser*
  hygiene inspector; Health Care Inspectorate, The Hague
- Professor PJ van den Broek
  professor of infectious diseases; Leiden University Medical Centre
- Professor HJM Cools
  professor of nursing home care; Leiden University Medical Centre
- Professor HJ Grundmann
  medical microbiologist/infectious disease epidemiologist; National Institute of Public Health and the Environment, Bilthoven, and Groningen University Medical Centre
- PBG ten Ham
  physician specialising in infectious disease control; Central Holland Municipal Health Service, Gouda
- Professor JAJW Kluytmans
  professor of hospital infection epidemiology; VU University Medical Centre, Amsterdam
- Dr M Koopmanschap
  health economist; Erasmus Medical Centre, Rotterdam
- R Simons
  nursing manager; Amsterdam University Medical Centre

- Professor CMJE Vandenbroucke-Grauls
  professor of medical microbiology; Amsterdam University Medical Centre and VU University Medical Centre, Amsterdam
- Professor HA Verbrugh
  professor of medical microbiology; Erasmus Medical Centre, Rotterdam
- Dr PMM Beemsterboer, *secretary*
  Health Council, The Hague

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 establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.