Health Council of the Netherlands

Antibiotics in food animal production and resistant bacteria in humans

Gezondheidsraad
Health Council of the Netherlands

To
the Minister of Health, Welfare and Sport
the State Secretary of Economic Affairs, Agriculture and Innovation

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Dear Minister and Secretary of State,

I am please to present you with the advisory report *Antibiotics in food animal production and resistant bacteria in humans*. It was drafted in response to the request for advice by the Ministers of Health, Welfare and Sport and of Agriculture, Nature and Food Quality at the time, by a specially appointed committee chaired by myself.

The Committee approached the problem of antimicrobial resistance by focusing on a 'top three' of bacteria that currently pose the largest threat to public health, and for which the use of antibiotics in food animal production appears to (also) play a role. Using this foundation, the Committee assessed where measures already in place are sufficient and where additional policy is required. Regarding the latter, the Committee distinguishes between recommendations for measures to address existing problems, and recommended precautionary measures designed to prevent new problems that could affect the treatment of humans in future. Some of the measures proposed by the Committee can be taken in the short term and lead to relatively fast results, while others will take longer to produce eventual (final) results. The Committee recommends these measures also be implemented as swiftly as possible.

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The Netherlands has an excellent international reputation with regard to the use of antibiotics in humans. In my opinion, the goal must be to build an equivalent reputation for animal husbandry. As the understanding is growing in society – including within the sector itself (farmers and veterinarians) – that the use of antibiotics in food animal production must be reduced, I feel it is an opportune time to implement the proposals made by the Committee. In the opinion of the Committee, the ideal would be for the sector and the government to take joint responsibility for this reduction.

Yours sincerely,
(signed)
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to:

the Minister of Health, Welfare and Sport

the State Secretary of Economic Affairs, Agriculture and Innovation

No. 2011/16E, The Hague, August 13, 2011

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

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Contents

Executive summary

Bacteria are becoming increasingly more resistant to antibiotics. As a result, the number of usable drugs is decreasing, while no new drugs are expected in the short term. This complicates the treatment of certain infections in humans. The scope of the problem is so great that the World Health Organisation made ‘antimicrobial resistance’ the theme of its annual *World Health Day* in 2011.

The extensive use of antibiotics in food animal production, the sector that produces food of animal origin, plays an important role in the discussion around the development of resistance. Since resistant bacteria can be passed on from animals to humans, the use of antibiotics in the treatment of animals contributes to the problem. In 2010, the Ministers of Health, Welfare and Sport and of Agriculture, Nature and Food Quality of that day asked the Health Council of the Netherlands to examine what is known regarding the contribution of antibiotic use in food animal production to the presence of resistant bacteria in humans and what measures can be taken to reduce this contribution. The Health Council put together a Committee to answer this request for advice.

Top three resistant bacteria

According to this Committee, there are three groups of resistant bacteria that pose the largest threat to public health and for which there are concerns about a possible causal relationship with the use of antibiotics in food animal production. These three groups are the vancomycin-resistant enterococci (VRE), the methicillin-resistant *Staphylococcus aureus* (MRSA) and the bacteria that produce extended spectrum beta-lactamase (ESBL). VRE and MRSA are primarily an issue within hospitals and are kept in check by an intensive infectious disease control programme, which in the case of MRSA is referred to as a ‘search and destroy’ policy (which involves detecting carriers, isolating them and eliminating the bacteria from their system). The relationship between the use of antibiotics in food animal production and the occurrence of VRE in hospitals is not as clear as once thought years ago. The livestock-associated MRSA can be well contained in hospitals, but it now also seems to occur in the general population. The biggest problem is posed by the ESBL-producing bacteria. These bacteria spread quickly and are not confined to hospitals but also occur outside of them, particularly as the cause of poorly treatable urinary tract infections. Though it is not possible to determine precisely the extent to which food animal production contributes to the spread of resistance due to ESBL, the Committee thinks that the greatest microbial risk to public health arising from food animal production at the present and in the near future is posed by ESBL-producing bacteria.

Recommendations

The government and food animal production sector have made agreements to reduce the use of antibiotics in food animal production and in this way to rein in the risks of resistance development. The Committee applauds this development, but finds that additional measures are needed – in some cases to stop problems that have already arisen, such as the ESBL-producing bacteria, and in some cases as a precaution, to prevent new problems from impacting the treatment of people in the future. The Committee makes a distinction here between measures which can be taken in the short term and lead to relatively fast results and measures which will take longer to produce eventual results.

Additional measures against ESBL

The Committee recommends that the antibiotics now used as a last resort to treat infections caused by ESBL-producing bacteria be reserved for this treatment. For this reason, the Committee proposes barring tigecycline from the veterinary market and discouraging the veterinary use of carbapenem class antibiotics by tightening up the so-called ‘cascade system’. In the long term, an alternative must be found for the use of colistin in veterinary medicine. A ban is not feasible in the short term because colistin is the drug of first choice in the treatment of certain animal diseases.

The second recommendation with respect to the ESBL-producing bacteria pertains to prohibiting third and fourth generation cephalosporins in the group treatment of animals, also in the short term. The fact is, there are indications that the use of these antibiotics in group treatment has promoted the occurrence of ESBL-producing bacteria. In addition, the Committee recommends that third and fourth generation cephalosporins are banned for use in drying off dairy cows (i.e. stopping lactation). To ensure that resistance is actually reduced, the preventive and systematic use of all beta-lactam antibiotics in food animal production should be banned in the longer term. Therapeutic use for individual animals based on good diagnostics will need to remain available in exceptional cases. The regulations the profession is developing should then, however, be followed to the letter, as the Committee is of the opinion that a general ban is appropriate if this is not the case.

Limiting antibiotic use in food animal production

The risk of antibiotic resistance grows in proportion to the amount and frequency of antibiotic use in food animal production. Due to the public health risk and by way of precaution, the Committee therefore recommends in the short term to reserve all new antibiotics – as well as existing antibiotics not yet used or no longer used in veterinary medicine – for use on humans in the first place. In addition to tigecycline, which was already mentioned in connection with the ESBL-producing bacteria, these antibiotics include various glycopeptides (e.g. vancomycin), daptomycin, oxazolidinones (e.g. linezolid) and mupirocin.

Secondly, the Committee advises taking measures to ensure the discontinuation of fluoroquinolones and aminoglycosides (in addition to colistin and beta-lactam antibiotics already mentioned in connection with the ESBL-producing bacteria) in the long term, apart from therapeutic use in individual animals based on good diagnostics and according to professional guidelines. The Committee expects that banning these antibiotics will enable them to continue to be used on humans. The Committee finds a longer period of outphasing necessary so as not to endanger the treatment of animal infections. It does, however, recommend that these measures are implemented as soon as possible. The Committee expressly states that it feels a general ban is applicable if the professional guidelines are not closely followed in daily practice.

In limiting the use of antibiotics in food animal production, the Committee sees the enforcement of the agreements as crucial: it must be clear which agency will monitor compliance and is authorised to punish violations. Good and transparent registration of antibiotic use in food animal production is essential in this regard.

Research on resistance

Research is necessary for gaining more knowledge and insight into the development, mechanism of action and spread of antibiotic resistance. Resistance develops dynamically and it is currently unclear as to which sources and routes of transmission play what role in its occurrence and spread.

In conclusion

This advisory report has been drawn up from the perspective of public health and in line with the implemented policy to reduce the use of antibiotics in food animal production. The Committee makes recommendations that are intended to result in a reduction in the use of antibiotics in general and some classes of antibiotics in particular. Antibiotic resistance is an international problem; some of the Committee's recommendations would therefore have more effect if they were to be adopted in an international context. However, the Committee is of the opinion that measures only taken in the Netherlands could certainly also lead to a reduction of the problem. The Committee also realises that, if its recommendations are adopted, they will ultimately not be able to be carried out without restructuring that is sometimes drastic. The responsibility for bringing about this kind of restructuring goes further than just the food producers and pertains just as much to the market and the consumers. That issue, however, falls outside the scope of this advisory report.

Chapter 1

Introduction

In 2011, the World Health Organisation (WHO) made antimicrobial resistance the theme of its annual *World Health Day.*[1] The WHO rang the alarm because the growing problem of antimicrobial resistance results in ever-shrinking availability of effective antibiotics. Using the slogan 'no action today, no cure tomorrow', the WHO called on various groups within society to take responsibility and ensure the medication required to treat people with bacterial infections remains available in the future. The spectre of the pre-antibiotic age, when people died of relatively trivial infections, may rise again if nothing is done. The food animal production sector – which produces food of animal origin – was expressly addressed by the WHO.

1.1 A brief retrospective

The use of antibiotics has always been associated with the development of resistance. Following the introduction of penicillin in the 1940s, articles on resistance against this antibiotic appeared almost immediately in the scientific literature.[2] Later on, worries were also expressed regarding the use of antibiotics in food animal production.[3,4] Such use, it was said, would induce the development of resistant bacteria in animals and promote transmission of such bacteria to humans.[5-8] In our country, with its intensive food animal production sector and associated extensive use of antibiotics, the debate about these risks flares up regularly.

Expressed as tons of product, veterinary use of antibiotics amply exceeds human use.

The Health Council has previously examined the use of antibiotics in food animal production. In 1998, the Council recommended terminating the addition of antimicrobial growth promoters to animal feed.[9] Based on said advisory report and European regulations, this use of antibiotics in food animal production was halted in The Netherlands from 1 January 2006. However, this did not lead to a reduction in the use of antibiotics in the sector. On the contrary, until 2009, annual use hardly decreased, as the drop due to the ban on antimicrobial growth promoters went hand in hand with increased use of antibiotics registered for therapeutic use.[10] Furthermore, annual monitoring of antibiotics use in The Netherlands showed that both resistance and multiresistance (resistance against multiple groups of antibiotics at the same time) are on the rise.[11] Increased antibiotic resistance is associated with an increased risk of infections in humans and animals that are less easily treated.

1.2 Request for advice and the Committee

The global epidemic of so-called ESBL producing bacteria is cause for concern. ESBL (Extended Spectrum Beta-Lactamases) are enzymes that can break down most antibiotics with a β-lactam structure, thereby inactivating the antibiotic. This makes the bacteria resistant to this group of antibiotics, which includes penicillins and cephalosporins. The threat posed by this type of resistance is significant, not only because many antibiotics are unsuitable for treating infections with ESBL-producing bacteria, but also because this form of bacterial resistance can be transferred to other species of bacteria. The genetic material for ESBL is also present in bacteria found naturally in human and animal gastrointestinal tracts which, under normal circumstances, do not cause disease.

The developments relating to ESBL-producing bacteria in particular were why the Ministers of Health, Welfare and Sport and of Agriculture, Nature and Food Quality of that day asked the Health Council about the current state of knowledge on the contribution of food animal production-related resistance to antibiotics to the resistance problems in humans, and what measures can be taken to reduce this contribution. The full text of the request for advice is included as Annex A. A committee of experts was appointed to respond to this request for advice, the membership of which is included as Annex B.

1.3 Scope of the advisory report

In this advisory report, the Committee addresses the question about the risks of antibiotics use in food animal production from a public health perspective, in accordance with the question asked by the Ministers of Health, Welfare and Sport and of Agriculture, Nature and Food Quality. Its recommendations on measures to reduce risks dovetail into the already initiated government policy of reduced use of antibiotics in food animal production.[12]

The Committee notes that antimicrobial resistance is a global problem that cannot be solved by measures taken in The Netherlands alone. The Committee previously noted WHO interest in the issue. At the European level, a report by the *European Food Safety Authority* (EFSA) was published recently, in which said organisation made strategy recommendations for addressing resistance issues from within food animal production together with various member states.[13] However, the Committee is of the opinion that international attention does not mean measures taken in The Netherlands could not also contribute to reducing the problems.

The issue of resistance is not limited to antibiotics: earlier, the Health Council warned that the increased use of disinfectants also leads to resistance, not only against the disinfectants themselves, but possibly also to antibiotics.[14] However, the Committee will not address the use of disinfectants in this advisory report.

Finally, the Committee realises that, should its recommendations for long-term measures in particular be implemented, this will require significant efforts from the professional groups involved. Other parties, such as retailers, wholesalers and consumers, will need to be involved. Further elaboration of the effects falls outside the scope of the Council's mandate.

1.4 Committee methods and structure of the advisory report

Following a brief explanation of the phenomenon of resistance and the relationship between the occurrence of resistant bacteria in humans and animals (Chapter 2), the Committee will discuss the bacteria it believes pose the greatest public health problem in Chapter 3. It will address the question of the degree to which the use of antibiotics in food animal production is responsible for this. In Chapter 4, the Committee recommends measures to be taken. It distinguishes between measures that can be taken in the short term and can lead to relatively fast results and measures which will take longer to produce eventual (final) results. In the final Chapter, the Committee links its recommendations to questions from the request for advice.

Chapter 2

Resistance to antibiotics

In the Health Council advisory report on the use of antibiotics as growth promoters, the appointed Committee provided an extensive description of the resistance of bacteria to antibiotics and the development of resistance.[9] In this advisory report, the – current – Committee will limit itself to a brief description, providing the background important to this advisory report. It will conclude this Chapter with a paragraph on the role the use of antibiotics in food animal production plays in the development of resistance.

2.1 The resistance phenomenon

Bacteria resistant to antibiotics are found in humans, animals and the environment. Resistance occurs in bacteria that cause disease (so-called pathogenic bacteria), as well as in skin and intestinal bacteria, for example, that are found in humans and animals and under normal circumstances do not cause disease (commensal bacteria). Resistant bacteria may be transferred from animals to humans (as well as the reverse), but resistance may also be transferred between species of bacteria, from one to the other.

Resistance develops due to a change in bacterial chromosomal genetic material or via transmission of genetic material from one bacterium to another. This transfer is easiest when the information required for resistance lies on extrachromosomal genetic material. This is the case for the previously mentioned

ESBL-producing bacteria, for example: that genetic information may be found in plasmids, ring-shaped structures of extra-chromosomal genetic material.

An important factor in the development of resistance is the selective pressure caused by the presence of the antibiotic. Bacterial populations with resistance to an antibiotic are able to reproduce in the presence of that antibiotic, while sensitive bacterial populations are unable to do so; their growth is inhibited or they die. This leaves a population of bacteria that is not sensitive to antibiotics and can continue to grow.

2.2 Dissemination

Much remains unclear about the epidemiology of resistance. What is clear is that plasmid-mediated resistance (like in ESBL-producing bacteria) has become a growing problem over the past decade, not only in hospitals, but also among the general population.[15-20]

The transmission of resistant bacteria from human to human may occur directly, for example in hospitals and nursing homes, as well as indirectly, for example via food or contaminated surface water. Travellers also bring resistant bacteria with them from foreign countries[21,22], which is why hospital patients from other countries are always quarantined in Dutch hospitals. However, there is no clear picture of the much larger population of travellers who are not ill – including people who have received treatment in foreign hospitals – while they may also be carrying such bacteria.

2.3 Use of antibiotics in food animal production and the development of resistance

There is extensive use of antibiotics in food animal production in The Netherlands. More antibiotics are used per kilogram of meat produced in our country than in many other European nations.[23] Although all categories of animals are treated with antibiotics, both therapeutically and preventively, there are clear differences between the amounts of antibiotics used per animal species or per product category. Sometimes animals may be treated individually, for example cows, but in other situations there is no avoiding treating the entire group in the event of disease (so-called mass treatment). This is required not only because other (still healthy) animals have likely already been contaminated, but also because individual treatment is impossible, for example in poultry farms. The antibiotic is then administered via feed or drinking water (mass oral treatment). In many cases, treatment takes place without first identifying the causal agent or its antimicrobial susceptibility.

These differences in treatment approach are associated with variation in the incidence of resistance. Where mass treatment is employed, the repeated presence of an antibiotic in large numbers of animals leads to a high risk of resistance developing. After all, there is continuous selective pressure on the populations of (commensal) bacteria present in all animals. Therefore, the sectors which frequently employ mass treatments face greater resistance problems than sectors where animals are treated individually. Antibiotics are administered relatively frequently to poultry (broilers), pigs (young piglets and fattening pigs) and veal calves.[11]

There are multiple examples of resistant bacteria that cause problems in humans and originate (in part) in food animal production. For example, the introduction of fluoroquinolones in poultry farming led to the development of fluoroquinolone resistant bacteria (Campylobacter species) in chickens in the 1980s. Shortly thereafter, this resistant Campylobacter was found in humans with gastrointestinal infections.[24] Two more recent examples are livestock-associated methicillin resistant *Staphylococcus aureus* and ESBL-producing (β-lactam resistant) bacteria. The Committee will address this in more detail in the next Chapter.

Chapter **3**

A top three of resistant bacteria

Based in part on recently published reports [25,26], the Committee selected bacteria it believes are the largest problem in the treatment of hospitalised patients, and for which there are worries about a potential causal link with the use of antibiotics in food animal production.* There are currently three: vancomycin-resistant enterococci, methicillin resistant *Staphylococcus aureus* (MRSA) and ESBL-producing (β-lactam resistant) bacteria. In this Chapter, the Committee will examine what conclusions current evidence allows to be drawn on the plausibility or strength of this association.

3.1 Vancomycin-resistant enterococci

3.1.1 Description

Infections caused by enterococci, such as *Enterococcus faecalis* (*E. faecalis*) and *E. faecium* are among the most significant hospital infections. Resistance of enterococci to vancomycin is a global, major problem, as this medicine is considered a last resort antibiotic. The prevalence of vancomycin-resistant enterococci (VRE) within Europe varies from less than one to more than forty per-

* The WHO also periodically publishes a list of *Critically Important Antimicrobials for Human Medicine.*[27] The WHO chooses a different approach than the Committee has done in this advisory report.

cent.[28] Despite a few outbreaks, the prevalence of VRE in The Netherlands is currently extremely low – less than one percent – thanks to an intensive infectious disease control programme, similar to the *search and destroy* policy put in place for MRSA. This policy encompasses early identification of carriers of the bacteria, patient quarantine and extermination of carrier status.[29] However, there is one worrying development, namely the rise of ampicillin resistant *Enterococcus faecium* (AREfm) in Dutch hospitals.[30,31] The past has shown that this may herald the swift rise of VRE.

3.1.2 Relationship with antibiotic use in food animal production

For years, avoparcine was used as an antimicrobial growth promoter in animal feed in numerous countries. Cross-resistance occurs between avoparcine and vancomycin as both medicines belong to the same chemical group. The occurrence of VRE in hospitals and the suspected transfer of resistance from enterococci from food animal production to humans resulted in banning avoparcine as an animal feed additive in the late 1990s, in accordance with the Health Council advisory report.

Subsequent research found that vancomycin resistance in human bacteria demonstrates a complex dynamic, and that the relationship with avoparcine use in food animal production is not as strong as believed at the time.[32-36] For example, banning the use of avoparcine in animal feed in some cases did, and in others did not lead to the disappearance of VRE from hospitals.

3.2 Methicillin resistant Staphylococcus aureus

3.2.1 Description

Methicillin resistant *Staphylococcus* aureus (MRSA) is a bacterium that has become resistant to methicillin, and thereby also to a number of other commonly used antibiotics. Healthy people may carry MRSA, but only rarely become ill. In hospitals, *Staphylococcus aureus* (*S. aureus*) is an important pathogen. An MRSA bacterium can, like non-resistant *S. aureus*, cause infections in people undergoing surgery or who receive venous drips and urinary catheters. The Netherlands has strict policies in place to prevent the spread of the bacteria, with the aim of keeping MRSA prevalence low. High-risk groups are screened and patients are isolated.

3.2.2 *Relationship with antibiotic use in food animal production*

The appearance of a hitherto unknown MRSA strain (then designated 'non-typeable MRSA') caused a great deal of commotion a few years ago. Standard quarantine and hygiene measures against MRSA and the search and destroy policy were quickly adjusted. The strain was found to originate in food animal production, and is now referred to as livestock associated MRSA (LA-MRSA) or sequence type 398 (ST398). Dutch research shows a connection between treating calves with antibiotics and carrier status for MRSA ST398: carrier status in calves, but also among involved cattle farmers.[37] Identifying this LA-MRSA resulted in all individuals with intensive contact with pigs or calves for meat production being classified as a high-risk population for MRSA carrier status and treated as such. Previously, this group was limited to patients who had been admitted to a foreign hospital. These measures create major pressures on hospital logistics in areas with intensive food animal production in the form of high costs and additional efforts required from employees.

In the meantime, more information has become available regarding the clinical picture associated with LA-MRSA, with or without comparison to HA-MRSA (*hospital-acquired* MRSA). LA-MRSA was found not to spread easily to other patients in the hospital.[38-41] The total number of patients with sepsis caused by LA-MRSA is small, likely about 5 per year, within a total of 30 cases of sepsis caused by MRSA per year. In recent years, however, patients with LA-MRSA infections have been found that cannot be related to contact with food animal production.[42]

3.3 Extended Spectrum Beta-Lactamase-producing bacteria

3.3.1 *Description*

There appears to be a global epidemic of plasmid-mediated resistance against β-lactam antibiotics. In the past five to ten years, the number of patients in hospitals with (β-lactam resistant) ESBL-producing bacteria has increased ten to twentyfold.[15-20,20,43] The problems are not limited to hospitals, however; infections with ESBL-producing bacteria among the general population – particularly urinary tract infections – are increasingly common. ESBL-producing strains are commonly brought into the country by travellers from India and the Far East.[22,44]

ESBL-producing bacteria are currently a growing threat to public health. This is true for hospital patients, but also – to an unknown degree – for nursing home patients and even the general population. The problem is currently being compounded by the lack of methods for swift diagnosis and typing of ESBL-producing bacteria.[13] A further rise in the incidence of these bacteria will require patients with sepsis to initially be treated empirically using an antibiotic from the carbapenem group. These medicines are generally one of the few types of antibiotics still effective against ESBL-producing bacteria. They are therefore considered last resort antibiotics.[45] This is a valid choice for clinicians, but extensive empirical use of carbapenems may lead to large-scale resistance to these medicines as well. The first carbapenem-resistant strains of bacteria have already been identified in Europe (including The Netherlands).[21,46]

3.3.2 Relationship with antibiotic use in food animal production

Where does resistance by ESBL-producing bacteria come from, and to what degree does transfer of resistance from food animal production contribute to the total circulation of these bacteria? No complete answer can currently be given to this question. It is known that ESBL-producing bacteria occur worldwide, in humans, animals and the environment.[19,47-49]. What are unknown are the causes for the sudden increase in prevalence. Much also remains unclear about the epidemiology of the plasmids that code for ESBL. Of the roughly 700 described genes that code for enzymatic resistance to β-lactam antibiotics, some are found globally, while others are more regional.

Various studies support the theory that transfer of ESBL from food animal production to humans is taking place.[50-54] For example, genetic similarities between ESBL-producing *E.coli* bacteria in patients and in poultry were found to be very large in some cases: in 11% of cases, the *E.coli* bacteria, the ESBL-carrying plasmid and the ESBL gene were all identical.[53] An association between the use of antibiotics in poultry and the development of ESBL was also suggested by a Canadian study.[55] The authors conclude that the use of ceftiofur has led to resistance in chickens and humans, and that resistance decreased again after reducing its use. Other research also suggests exchange of plasmids with genes for ESBL occurs between various micro-organisms and various ecosystems, and that transfer from animal to human (and from human to animal) is likely.[50]

Although the search for the source of ESBL-producing bacteria among intensive food animal production is in itself logical, given the extensive use of antibiotics, the Committee notes that these bacteria are also found among pets (including horses) and in wild animals.[56,57] The total use of antibiotics by pets is negligible compared to use in food animal production, but contacts between humans and pets is far closer. This makes identification of ESBL-producing bacteria in pets a real concern.[51,57] ESBL-producing bacteria in wild animals are likely an indicator for the incidence of these bacteria in the environment.

3.4 Conclusion

With regard to the three micro-organisms it has selected, the Committee concludes that VRE and MRSA are typical intramural health care problems, causing increased morbidity and mortality in hospitals and nursing homes. An intensive infectious disease control programme (search and destroy) is in place to combat VRE and MRSA. Currently, the problems with VRE in The Netherlands are not very large, although the increase in AREfm is worrying. Livestock associated MRSA, by definition related to food animal production, is primarily a risk for people who work in food animal production. Regarding morbidity and mortality, there are currently significantly fewer problems than with 'human' MRSA strains. Of the top three of bacteria that pose the largest threat to public health, the ESBL-producing bacteria are currently the greatest worry. The scientific literature on these bacteria shows the problem is not limited to intramural health care, but that resistance genes also circulate in the general population and cause problems there, mainly in the form of difficult to treat urinary tract infections. In the opinion of the Committee, the degree to which ESBL-producing bacteria currently occur demands other control measures in addition to an intensive infectious disease control programme.

Chapter **4**

Recommendations

In 2010, the Minister of Agriculture, Nature and Food Quality announced that the use of antibiotics in food animal production must drop significantly in the coming years.[12] The sector itself (farmers and veterinarians) is acutely aware of the risks of using antibiotics and is working to find solutions. The Committee applauds this. However, it is of the opinion that, from a public health perspective, additional measures are possible and necessary to further reduce the problem of resistant bacteria. An overview is provided in this Chapter. In making its recommendations, the Committee distinguishes between specific measures targeting the 'top three', general measures aimed at reduction and restriction of the use of antibiotics, and measures focusing on increasing knowledge and insight. Policy already in place will be described briefly per category, followed by the additional measures the Committee believes are needed.

The Committee makes recommendations that may yield an effect in the short term as well as recommendations for measures for the longer term. Some measures are so radical as to require more time. However, the Committee is of the opinion that measures that may only yield results in the longer term should be implemented as swiftly as possible.

Some of the Committee's recommendations are precautionary measures, designed to prevent the current use of antibiotics in food animal production from causing new problems with resistant bacteria in the future.

4.1 Measures targeting the 'top three'

4.1.1 *Current policy and adjustment agreed upon*

The search and destroy policy has resulted in VRE and LA-MRSA currently being controlled in Dutch hospitals. The Committee feels continuous monitoring remains necessary.

The recently obtained data that show that LA-MRSA, compared with HA-MRSA, may lead to less disease and spreads less quickly within the hospital, are important. However, it is still too early to adjust search and destroy policies based on these findings; the Committee believes more information is required. It therefore advises the recommendations outlined in the Health Council advisory report *MRSA Policy in the Netherlands* be followed.[58]

Of the selected 'top three', the Committee's greatest worries relate to the ESBL-producing bacteria. The presence of these bacteria in chicken meat has led to additional checks for the use of antibiotics in food animal production; this has resulted in, for example, the reduction of (illegitimate) use of ceftiofur in poultry farming. However, no specific measures are currently in place to address the problem posed by these types of bacteria.

4.1.2 *Additional measures with effects in the short term*

The Committee concludes that current policies regarding VRE and LA-MRSA require no additional measures. Careful monitoring of developments is sufficient. This is not the case for ESBL-producing bacteria; after all, this group is the biggest problem for health care. Furthermore, (Dutch) research has found that at least part of the ESBL that causes disease in humans in our country is identical to ESBL from food animal production.[53,59] This suggests transmission from animal to human. The Committee therefore recommends a number of measures be taken in the short term.

Patients infected with ESBL-producing bacteria can only be treated with certain antibiotics, so-called last resort antibiotics. For ESBL-producing bacteria, this means carbapenems, and in certain cases colistin and tigecycline. Some of these medicines are also used in veterinary medicine as part of the so-called cascade regulation. This regulation dictates that in the event of veterinary need, treatment with medicines that are not authorised for veterinary use may be initiated. The Committee recommends this cascade regulation be tightened in order to discourage use of carbapenems as soon as possible. It also recommends not permitting the use of tigecycline in the veterinary market. The Committee would also like to terminate the use of colistin in the veterinary market as quickly as possible, but is aware that this could lead to significant problems in the treatment of animals; it is currently the treatment of first choice in a number of situations. Therefore, the Committee feels a limiting measure for the longer term is more appropriate for this antibiotic (see paragraph 4.1.3).

There are signs that mass treatment of poultry with third and fourth generation cephalosporins has promoted the development of ESBL-producing bacteria.[55] The Committee therefore recommends banning these medicines for all mass treatments. Additionally, it recommends banning the use of third and fourth generation cephalosporins for 'drying' cows (stopping milk production). The EFSA also outlines stopping the use of third and fourth generation cephalosporins as a possibility for controlling the risks of ESBL-producing bacteria.[13]

4.1.3 Additional measures with effects in the long term

Regarding the top three, the Committee will limit itself to the ESBL-producing bacteria for measures with effects in the longer term.

The Committee advises expanding its recommendation to ban the use of third and fourth generation cephalosporins for mass treatment to a general ban on the use of all β-lactam antibiotics for preventive and systematic use in food animal production. The reason for this is that other classes of β-lactam antibiotics also promote the development of ESBL-mediated resistance in populations of bacteria. Therapeutic use for individual animals based on good diagnostic testing will have to remain possible in exceptional cases. The guidelines developed by the profession will have to be adhered to closely in such cases. Should it become apparent that these guidelines are not being followed sufficiently, the Committee's vision of a general ban may apply.

Previously, the Committee stated that colistin has become a last resort antibiotic in the treatment of infections caused by ESBL-producing bacteria in humans. At the same time, it is the treatment of first choice in a number of veterinary situations. Therefore, immediate termination of this medicine is impossible. Resistance against colistin is uncommon, but has been observed – to a limited degree – in both humans and food animal production.[7,60] As a precaution, the Committee recommends looking for alternatives to colistin in food animal production in order to allow stopping its use in the longer term.

4.2 General measure to reduce and restrict the use of antibiotics

4.2.1 Current policy

Until recently, agreements regarding reducing the use of antibiotics in food animal production were made in consultation between the agricultural sector, the veterinary profession and the government. An example is the convenant on antimicrobial resistance in food animal production ('antibioticaresitentie dierhouderij') agreed on in 2008.[61] In recent years, the ministry of Economic Affairs, Agriculture and Innovation (previously the ministry of Agriculture, Nature and Food Quality) has been placing greater pressure on the sector to reduce the use of antibiotics. For example, in 2010, the Minister announced that the use of antibiotics in 2011 (expressed as so-called animal daily dosages) must be reduced by twenty percent compared to 2009, and by fifty percent by 2013.[12] The new Food and Consumer Product Safety Authority will be enforcing adherence to legislation and regulations more stringently.[62]

4.2.2 Additional measures with effects in the short term

In order to ensure sufficient means remain to treat infections in humans, the Committee recommends reserving all newly authorised antibiotics with a new mechanism of action or expansion of microbial spectrum initially be reserved for human use, as well as existing antibiotics that are not yet or no longer used in veterinary medicine. In essence, this is an expansion of the recommendation to reserve last resort medicines for the treatment of ESBL-producing bacteria, such as tigecycline, for human use. In the opinion of the Committee, this expansion should include various glycopeptides (such as vancomycin), daptomycin, oxazolidinones (linezolid) and mupirocin.

Adherence to agreements is crucial for the measures designed to reduce the use of antibiotics in food animal production, starting with following the rules for proper veterinary use of antibiotics and correct use of pharmacopoeia. In order to achieve the stated goals of deployed initiatives, the Committee believes there is a need for clear final responsibility and an institution with the authority to monitor adherence to rules and measures. Good and transparent registration of all antibiotics use in food animal production is an essential part of this.

4.2.3 Additional measures with effects in the long term

A number of (groups of) antibiotics is currently still useful for the treatment of humans and is of great importance to public health. At the same time, the development of resistance due to the use of antibiotics in food animal production and the transmission of resistance to humans is highly possible. The Committee includes previously mentioned cephalosporins and fluoroquinolone in this group, as well as aminoglycosides.[24,63] Stopping the veterinary use of these medicines will help safeguard their efficacy for human use.

However, the Committee realises it is impossible to ban the use of multiple groups of antibiotics for veterinary use at the same time. After all, treatment for sick animals must remain available. Concurrent and short-term banning of all listed antibiotics might also have a negative effect, as second or third choice medication might be selected in food animal production. This development might potentiate rather than reduce the development of resistance. Therefore, the Committee recommends, as in the case of beta-lactam antibiotics (see paragraph 4.1.3), only permitting the use of fluoroquinolones and aminoglycosides for therapeutic use in individual animals based on good diagnostic testing. Here, too, the Committee wishes to emphasize that in its opinion, a general ban must be considered if professional guidelines are not sufficiently adhered to in daily practice.

4.3 Measures to increase knowledge and insight

4.3.1 Current policy

Insight into the use of antibiotics, the development of resistance to antibiotics and the relationship between the two is obtained in various ways in our country. For quite some time, surveillance of antibiotics usage and resistance in humans and animals has been handled by the Dutch Working Party on Antibiotic Policy (SWAB, for humans) and the Veterinary Antibiotic Usage and Resistance Surveillance working party (VANTURES, for animals).[64] Since 2002, VANTURES has been responsible for the so-called MARAN reports (Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in The Netherlands) on antibiotic usage in farm animals and the occurrence of resistance.[11]

Per 1 January 2011, the Veterinary Medicines Authority (SDa) became active.[65] The SDa will analyse antibiotics usage and propose detailed measures to reduce usage based on results. The SDa will use a central registry of antibiotics usage. Data for this registry is provided via veterinary information systems that veterinary practices use to record their data. An example of such a system is VetCIS, which has been in use since 2010.

The Committee emphasizes the importance of (mandatory) registration of antibiotics usage. The Committee considers this an important precondition for monitoring the effects of measures that have already been and have yet to be implemented as well as an aid in regulation.

4.3.2 Additional measures with effects in the short term

Central registration of the use of antibiotics may contribute to increasing knowledge and insight. The Committee recommends setting up the registry in a way that allows analysis per animal sector, so the treatment and antibiotic used can be included in analyses of the bacteria involved. This registration and analysis will allow careful monitoring of the development and spread of antimicrobial resistance.

The Committee recommends combining veterinary resistance monitoring with human monitoring, as already occurs at the European level.[66]

4.3.3 Additional measures with effects in the long term

In order to improve knowledge and insight, the Committee recommends research into development, mechanisms of action and spreading of resistance.

In addition to the spread of resistance, insight into the exact transmission routes is essential, including knowledge of critical and high-risk moments for resistance transmission. Research should also be conducted into import of meat and livestock and the contribution of these imports to the total resistance reservoir, and the possibility for reducing this route for resistance transmission.

Furthermore, the Committee recommends surveillance and monitoring in order to test the effects of implemented measures.

It also recommends research into alternatives for the current food animal production system and into the motivations for the use of antibiotics in food animal production, in order to help achieve healthy business practices that are less or perhaps even not at all dependent on said use.

4.4 Marginal notes

The Committee wishes to place the following marginal notes on its recommendations. As shown in Chapter 3, food animal production certainly does not bear sole responsibility for the problems caused by resistant bacteria in hospitals. However, the Committee is of the opinion there are sufficient indications that resistant bacteria from food animal production are part of the problem. Therefore, measures targeting the development of resistant bacteria in food animal production are certainly relevant.

Second of all, the Committee wishes to note that even if all proposed measures are implemented swiftly in food animal production, the problem of antimicrobial resistance will be reduced but not solved. This is because resistant bacteria do not only originate in food animal production, and because the precise effect of certain measures is difficult to predict. However, the Committee is of the opinion that measures are required, not only to prevent existing problems from worsening, but also to prevent future problems.

Chapter **5**

The request for advice answered

In this final Chapter, the Committee reviews its considerations, conclusions and recommendations in a cohesive fashion. In doing so, it responds to the questions in the request for advice (see Annex A). Finally, there are a number of comments regarding the broader context within which the issue of food animal production-related resistance to antibiotics may be placed and on possible or desirable paths towards solutions.

5.1 Risks

First, the Ministers asked about new insights obtained since the Health Council advisory report published in 1998. In order to obtain a full picture, the Committee feels it is useful to outline the insights from that report. A fundamental conclusion was that the use of antibiotics in food animal production contributes to the problem of resistance in humans, because resistant bacteria can be transferred from animals to humans. This was supported by both laboratory and epidemiological studies. At the time, data on VRE prevalence were particularly worrying. As the Committee outlined in paragraph 3.2, the link between avoparcine use in food animal production and the occurrence of VRE in hospitals is now less evident than believed at the time. On the other hand, new worries have arisen instead. For example, we currently face livestock associated MRSA, which is currently well controlled thanks to strict quarantine and hygiene measures in hospitals, but also occasionally pops up in the general population (see paragraph

3.3). And ESBL-producing bacteria have introduced a new villain to the stage (paragraph 3.4). In recent years, the prevalence of infections with these bacteria has been rising sharply both in hospitals and among the general population. According to the Committee, it is now highly likely that transmission from food animal production is in part responsible. Based on current evidence, the Committee concludes that these ESBL-producing bacteria are currently the biggest threat to public health coming from food animal production. At the same time, the Committee would like to note that experience gathered since 1998 has shown that the issue of resistance is extremely dynamic. Over time, problems may turn out to be less serious than expected, but new and unexpected surprises may also present themselves. The risk of the latter increases in step with veterinary antibiotics usage. Now that all parties are acutely aware of the risks, the time has come to actually drastically reduce said usage.

5.2 Transmission

The Committee has already pointed out the dynamic nature of resistance development. Chapters 2 and 3 addressed the issue in greater detail. There are various sources and associated transmission routes involved: therapeutic use of antibiotics for the treatment of patients in and outside of the hospital, travellers taking along resistant bacteria from travels abroad, environmental sources, foods, and food animal production. The relative contribution of these sources and routes of transmission is difficult to determine based on current evidence. Furthermore, indirect processes also play a role, such as dissemination of resistant bacteria from food animal production to the environment. In Chapter 4, the Committee outlined a number of areas for further research required to address knowledge gaps in this area. The current The Netherlands Organisation for Health Research and Development programme *Priority medicines antimicrobial resistance* may make a significant contribution.[67] Furthermore, it is important to emphasize the importance of reducing the use of antibiotics and adequate implementation of hygiene measures in order to decrease the odds of transmission.

5.3 Veterinary source

In the opinion of the Committee, there are signs that the odds of resistance to antibiotics increase with increased extent and frequency of antibiotics usage. That is why mass treatments are particularly risky and reduction should be made a priority. Because of this, the Committee recommended banning the use of third and fourth generation cephalosporins for mass treatment in the short term in paragraph 4.1. From the perspective of the risk to public health and in part based on the precautionary principle, the Committee recommends the following two-stage procedure (see Chapter 4).

- The Committee recommends starting by reserving all new antibiotics, as well as existing antibiotics that are not yet or no longer used in veterinary medicine, for human use. This includes tigecycline, various glycopeptides (such as vancomycin), daptomycin, oxazolidinones (linezolid) and mupirocin. The Committee also recommends prohibiting the use of third and fourth generation cephalosporins when 'drying' cows and tightening the cascade regulation in order to discourage the use of carbapenems (last resort antibiotics for humans).
- Secondly, the Committee makes a number of recommendations that should yield effects in years to come. The Committee recommends measures be taken as quickly as possible to stop the use of colistin (last resort antibiotic for humans) in food animal production in the longer term. It also recommends prohibiting the use of all β-lactam antibiotics for preventive and systematic use in food animal production. Therapeutic use for individual animals based on good diagnostic testing will have to remain possible in exceptional cases. Analogously to this, the Committee feels fluoroquinolones and aminoglycosides use should be limited to therapeutic use in individual animals. All cases of individual treatment must occur in strict adherence to guidelines developed by the profession. Should these guidelines not be followed sufficiently in daily practice, the Committee is of the opinion a general ban on the use of the antibiotics in question should be considered.

5.4 In closing

The Committee began its advisory report with the comment that the public health perspective holds a central position. Its recommendations are therefore substantiated and motivated from within said context. At the same time, there are veterinary health considerations to be examined and weighed. As the Committee outlined in Chapter 4, this may create a conflict of interests. In part because of this fact, the Committee feels it would be wise to introduce recommended measures in a phased manner. It also feels phased introduction of measures has a good chance of succeeding, as the sector has indicated an understanding of the need for changes. As mentioned previously, far-reaching reduction of antibiotics usage in food animal production is impossible in the long run without – likely major – restructuring of operations. Furthermore, the responsibility for achieving such a restructuring extends beyond food producers and also affects wholesalers, retailers and consumers. However, this topic falls outside the scope of this advisory report.

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A Request for advice

B The Committee

Annexes

Annex

A

The request for advice

On 14 July 2010, the President of the Health Council of the Netherlands received a request from the Minister of Health, Welfare and Sport and the Minister of Agriculture, Nature and Food Quality for advice on livestock production-related antimicrobial resistance. The Ministers wrote (letter PG/CI-3009915):

The National Institute for Public Health and the Environment conducted an expert consultation relating to the increase in 'Extended Spectrum Beta-Lactamase' (ESBL)-producing bacteria in the Netherlands. On 9 April of this year we informed the Dutch House of Representatives of the resulting recommendations and our position in this regard. One of the recommendations generated by the consultation was to appoint a multi-sector Health Council Committee. We drafted this request for advice based on this recommendation. This request is focused on antimicrobial resistance originating in livestock production, part of the overall resistance issues in humans.

Treatment of infections caused by resistant bacteria is complex, and often requires the use of alternative antibiotics that can have severe side effects. These infections therefore also lead to a greater disease burden for patients, as well as to uncertainty regarding treatment outcome. The prevention, treatment and combating of these infections can result in a higher workload and higher health care costs.

We ask that the Health Council advise us on the public health risks of antibiotics use in livestock production. The Health Council advisory report from 1998 on antimicrobial growth promoters is a suitable starting point. We ask that you take the fact that antimicrobial resistance is an issue that is not limited to the Netherlands into account.

We ask you to give particular attention to the following aspects:

Risks
- What new insights have been gained since 1998 regarding the contribution of livestock production-related antimicrobial resistance to the overall human resistance issue?
- Can a ranking be made of the risks livestock production-related antimicrobial resistance pose to public health? If so, based on scientific evidence, what are the greatest risks?

Transmission
- Via which routes do resistant bacteria originating in animals reach humans, and what are the relative contributions of these routes of transmission?
- How can these routes of transmission be interrupted in order to prevent resistant infections in humans?

Veterinary source
- What type of treatments or methods of administration (such as mass treatments) contribute most to the development of antimicrobial resistance in livestock production, and what public health risks do these create?
- Which antibiotics or groups of antibiotics present the greatest risk to public health within this context?
- Is it useful to reserve certain antibiotics for human use?

Should available knowledge not be sufficient to answer these questions, we ask that you indicate research priorities in order to fill these gaps.

We would like to receive your advisory report by the end of 2010 at the latest.

Sincerely,
the Minister of Public Health, Welfare and Sport
(signed)
Dr A. Klink

The Minister of Agriculture, Nature and Food Quality
(signed)
G. Verburg

Annex **B**

The Committee

- Prof. L.J. Gunning-Schepers, *Chairperson*
  President of the Health Council of the Netherlands, The Hague
- E.J. de Boer, *observer*
  Ministry of Health, Welfare and Sport, The Hague
- Prof. M.J.M. Bonten
  Professor of Molecular Epidemiology of Infectious Diseases, Utrecht University Medical Centre
- Prof. J.E. Degener
  Professor of Medical Microbiology, Groningen University Medical Centre
- Prof. J.T. van Dissel
  Professor of Internal Medicine, with a special interest in infectious diseases, Leiden University Medical Centre
- Prof. J. Fink-Gremmels (until 7 June 2011)
  Professor of veterinary pharmacology and toxicology, Faculty of Veterinary Medicine, Utrecht University
- Prof. L.O. Fresco
  University Research Professor in Sustainable Development from an international perspective, University of Amsterdam
- Prof. R.B.M. Huirne
  Professor of Agricultural Business Economics, Wageningen University and Research Centre

- Prof. J.A.J.W. Kluytmans
  Professor of Medical Microbiology and Infectious Disease Prevention, VU University Medical Centre, Amsterdam
- Prof. F. van Knapen
  Professor of Veterinary Public Health, Faculty of Veterinary Medicine, Utrecht University
- Dr W. van Pelt, *adviser*
  National Institute for Public Health and the Environment, Bilthoven
- E.L.J.M. Pierey, *observer*
  Ministry of Economic Affairs, Agriculture and Innovation, The Hague
- Prof. J.M. Prins
  Professor of Internal Medicine, with a special interest in the treatment of infectious diseases, Academic Medical Centre, Amsterdam
- Prof. J.A. Stegeman
  Professor of farm animal health, Faculty of Veterinary Medicine, Utrecht University
- Prof. H. Vaarkamp
  Professor of Veterinary Pharmacy, Faculty of Veterinary Medicine, Utrecht University
- Prof. J.A. Wagenaar
  Professor of Clinical Infectiology, Faculty of Veterinary Medicine, Utrecht University
- Dr. K. Groeneveld, *scientific secretary*
  Health Council of the Netherlands, The Hague
- Dr. M.F.M. Langelaar, *scientific secretary*
  Health Council of the Netherlands, The Hague
- E.J. Schoten, *scientific secretary*
  Health Council of the Netherlands, 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 inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.