



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

Subject : Advisory letter *Tightening up on antibiotic use in animals*
Your reference : 750179-135172-PG
Our reference : U-882908/ES/KG/msj/044-B Publication no. 2015/31E
Enclosure(s) : 1
Date : December 16, 2015

Dear Minister and State Secretary,

In 2011, at your request, the Health Council of the Netherlands issued an advisory report entitled “Antibiotics in food animal production and resistant bacteria in humans”.¹ This was prompted by growing concern about the extensive use of antibiotics in our food animal production sector and its potentially adverse impact on the development of resistance to the antibiotics used to treat human patients. In compliance with the advisory report, animal keepers, veterinarians and the government have taken steps to reduce the veterinary use of antibiotics in recent years. While major successes have been achieved, a number of problems still remain. In a letter to the Dutch House of Representatives dated 24 June 2015², you and your colleagues stated that the government aspired to a further reduction of antibiotic resistance across the board. This is also one of the themes to be addressed during the Netherlands’ presidency of the EU in the first half of 2016. In this connection, on 23 April you asked me for an update of the 2011 advisory report (reference 750179-135172-PG, see Annex A). In response to your request for advice, I installed a committee, the composition of which is given in Annex B. This letter contains details of the Committee’s deliberations on the current level of knowledge, together with its conclusions and recommendations.

Structure of this advisory letter

The request for advice revisits all of the issues raised in the previous advisory report. It includes an assessment of risks to public health, where possible broken down by bacterium, antibiotic, animal sector, and the route of transmission used by resistant bacteria. It also addresses the priorities in terms of reducing those risks. In this advisory letter, the Committee first presents the core message of the 2011 advisory report. It then assesses what has been achieved to date, partly on the basis of that advisory report. The Committee then determines whether any information that has become



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available in the meantime is sufficiently compelling to warrant modifying or supplementing the original conclusions and recommendations. If for no other reason, this is necessary because the previous advisory report contained both short-term and long-term recommendations, and the short term has now passed.

Two additional points require attention. Firstly, the public health perspective was a pivotal consideration in the previous advisory report. However, it was noted that there are also veterinary health considerations to be examined and weighed, and that this can occasionally result in conflicting demands. Secondly, the recommendations were based, in part, on the precautionary principle.³ The current Committee uses the same assessment framework. However, in accordance with the request for advice, it will evaluate the extent to which new data have reduced past uncertainties, and the implications this has for the scope of the precautionary principle. The Committee is aware that the Council on Animal Affairs has been asked to issue an advisory report from the perspective of animal health and welfare.⁴

The 2011 advisory report

Risks

At your request, the 2011 advisory report focused on those resistant bacteria that pose the largest threat to public health and that are linked to concerns about a possible causal relationship with the use of antibiotics in food animal production. A ‘top three’ was identified: VRE (vancomycin-resistant enterococci), livestock-associated MRSA (LA-MRSA, methicillin-resistant *Staphylococcus aureus*) and bacteria that produce extended spectrum beta-lactamase (ESBL).^a

At that time, and in what was then the foreseeable future, ESBL-producing bacteria were considered to pose the greatest problems. Only a few antibiotics – the so-called “drugs of last resort” – are available to treat patients who are infected with these bacteria.¹ These are antibiotics of the carbapenem group and, in certain cases, colistin and tigecycline.

^aThe Committee considers the term ‘ESBL-producing bacteria’ to include both Extended Spectrum Beta-lactamase-producing bacteria and plasmid-mediated AmpC beta-lactamase-producing bacteria.



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Recommendations

In the cases of VRE and LA-MRSA, it was thought that no additional measures were required, and that it would be sufficient to monitor developments carefully. With regard to ESBL-producing bacteria, however, the Health Council made a number of additional recommendations. In the short term, the use of carbapenems in veterinary medicine should be discouraged and tigecycline should not be authorised for the veterinary market. The Council also recommended banning the use of third and fourth generation cephalosporins for mass treatment and for ‘drying off’ dairy cows (i.e. stopping lactation). In the longer term there should be a general ban on the preventive and systematic use of all beta-lactam antibiotics. In addition, efforts should be made to find alternatives to colistin in food animal production, so that its use for that purpose could be terminated in the longer term.

Furthermore, the Health Council made recommendations concerning general measures to reduce the use of antibiotics in food animal production. As a precaution, all new antibiotics – as well as existing antibiotics not yet used or no longer used in veterinary medicine – should, in the short term, primarily be reserved for use on humans. In addition to tigecycline, the Council considers these to include various glycopeptides, daptomycin, oxazolidinones and mupirocin. In general, terminating the veterinary use of these medicines will help safeguard their efficacy for human use. In the short term, however, it is impossible to concurrently ban the veterinary use of several groups of antibiotics. However, the Council would permit the therapeutic use of fluoroquinolones and aminoglycosides in individual animals. Otherwise, it would still be necessary to consider a general ban.

What has been achieved?

Since the Health Council issued its advisory report in 2011, measures have been taken at various levels or ongoing initiatives have been continued in an augmented form. Here the Committee addresses broad changes in legislation, in the actual use of antibiotics (and resistance to them), and in assessment systems for food animal production facilities and for the veterinarians involved. For further details, it refers to the relevant reports in this field.^{5,6}



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Sharp fall followed by stagnation

The Royal Dutch Society for Veterinary Medicine's Working Group on Veterinary Antibiotic Policy (WVAB) issues guidelines in which the antimicrobial agents used in veterinary medicine are classified (by active ingredient) into drugs of first, second and third choice. These guidelines take precedence when drawing up formularies, the animal-species-specific regimens that serve as a mandatory guiding principle for the treatment plan to be set up by each individual farm. In response to the Health Council's 2011 advisory report, the formularies have been revised. In some sectors, the use of antibiotics may be more rigorously regulated by stricter guidelines drawn up on the basis of chain quality systems (e.g. IKB Varken), or by private parties, e.g. a guideline for the treatment of dairy cows issued by a milk buyer.

Partly in response to these stricter regulations, there was a sharp fall in antibiotic use that continued into 2013.^{5,6} In 2014, this decline in total use stagnated.^{5,6} From 2009 to 2014, the total volume of antibiotics sold fell by no less than 60 percent.⁶ The picture for 2014 varied from one sector to another: there was another sharp decline in the cattle sector while other sectors (pigs, calves) showed a smaller reduction. In others (broilers), there was actually an increase. For individual antibiotics (or groups of antibiotics), the picture is as follows. In the four sectors being monitored (poultry, cattle, pigs and veal calves), the use of third and fourth generation cephalosporins has been reduced to a very low level indeed.⁵ In the remaining sectors^a (i.e. those that were not being monitored), the situation was quite different. An analysis of sales figures showed that, in 2014, the use of third and fourth generation cephalosporins had actually increased. In that same year, 97 percent of all cephalosporins (i.e. the first generation through to the fourth) were used in the unmonitored sectors. The Netherlands Veterinary Medicines Authority (SDa) notes that there is no accurate information concerning the general use of antibiotics in the unmonitored sectors. In some sectors, such use is expected to be limited (laying hens, sheep), in others little or no information is available (goats, horses, pets).

While the use of polymyxins (the group to which colistin belongs) has declined in pigs, cattle and calves, it has increased in poultry.⁵ The WVAB has proposed several measures to limit (or further reduce) the use of colistin.⁷ Those proposals will be taken into account in the ongoing

^aIn the report, the Netherlands Veterinary Medicines Authority (SDa) cites the following unmonitored sectors, in order: laying hens, ducks, sheep, rabbits, goats, pets, horses, fish, mink, and pigeons.⁵ More generally, the Netherlands Veterinary Medicines Authority (SDa) also includes categories of more limited size that potentially involve regular human contact, such as petting zoos and zoo animals.



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revision of the formularies for the various animal species involved. At European level, the range of indications for colistin preparations has been reduced to just one.⁸

Finally, according to the WVAB, carbapenems and tigecycline should never be used in animals, not even in the context of the cascade system. Instead, they should be reserved for use in humans.⁹

Importantly, the reduced use of antibiotics in the period up to 2013 was associated with a decline in bacterial resistance.⁶ This is consistent with findings in other countries. In Denmark, for example, the termination of cephalosporin use in pigs was associated with a reduced incidence of ESBL-producing bacteria in those animals.¹⁰ In 2014, the decline in overall antibiotic use levelled off, and the incidence of resistant bacteria stabilised.⁶ According to the Committee, both of these findings indicate a causal relationship between antibiotic use and the development of resistance.

Benchmarking

Food animal production facilities are subjected to ‘benchmarking’, which categorises them either as target zones (green), signalling zones (orange) or action zones (red), depending on the quantities of antibiotics used. Up until 2014, the proportion of ‘action zone’ farms in the food animal production sector fell from 25 percent to around 10 percent. The situation differs from one sector to another. A relatively large percentage of farms in the veal-calf sector are in the signalling zone. The Committee notes that some of these categories are rather loosely defined. In the veal-calf sector, in particular, farms where substantial quantities of antibiotics are used may still fall within the target zone.

There is a similar assessment system for veterinarians who work in the food animal production sector. This is part of the private quality system used by the Approved Veterinarians Foundation. Approximately 60 percent of them fall within the target zone, 37 percent within the signalling zone, and just over three percent in the action zone.⁶ Any veterinarian who exceeds the standard must put forward an improvement plan. Here too, the categories are rather loosely defined. The Netherlands Veterinary Medicines Authority’s (SDa) expert panel concluded that the current limit value is not a particularly reliable indicator of elevated prescribing patterns.⁶ Here too, we see the above-mentioned differences between sectors. The veal-calf sector has the highest percentage of veterinarians in the action zone.

Farms in the unmonitored sectors and the associated veterinarians do not fall under the assessment system described here.



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The risks reviewed

The Committee has explored the picture that emerges from the post-2011 scientific literature.

LA-MRSA and ESBL-producing bacteria

There is still a relatively substantial focus on LA-MRSA and ESBL-producing bacteria. In 2011, the Health Council stated that, in hospitals, LA-MRSA does not spread readily from one patient to another. Also, compared to 'ordinary' MRSA, it caused fewer serious infections.¹ This picture was confirmed in a recently published Dutch study.^{11,12}

In the Committee's view, the 2011 situation with ESBL-producing bacteria has also been confirmed. For instance, a Danish study revealed that ESBL-producing bacteria occur more often in pigs on farms where cephalosporins had been used (in the past) than on farms where that was not the case.¹³ The study also showed that these bacteria (or their genetic material) had been transferred between the farmers and their pigs. In addition, it is still the case that ESBL-producing bacteria are not confined to hospital patients alone, they are also found in the general population.¹⁴ At the time, the Health Council drew attention to the fact that these bacteria are also found in horses, pets, and wildlife.¹⁵⁻¹⁹ Recent research reinforces this picture, for the Netherlands as well. In this regard, the Committee is particularly concerned about the situation in pets. For example, a longitudinal study of ESBL-producing bacteria in dogs found that, throughout the study period, 84 percent of the animals tested positive on at least one occasion.²⁰ In humans, contact with pets appears to be a risk factor for becoming a carrier of ESBL-producing bacteria.²¹

Carbapenem-resistant bacteria

A point of concern, which was touched on in the 2011 advisory report, was carbapenem-resistant strains of bacteria.^{22,23} This has since become a growing problem throughout the world. Of all European countries, resistant bacteria are most frequently encountered in Greece and Italy.^{24,25} A joint report by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) demonstrated the existence of a relationship between carbapenem use and the emergence of resistance to this drug.²⁶ In retrospect, the Committee finds that descriptions of the first three Dutch patients to be infected with carbapenem-resistant bacteria were published in 2010.²⁷ These individuals probably acquired



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the bacteria during a stay abroad (Greece and India). To date, carbapenem-resistant bacteria have only been encountered sporadically in the Netherlands, having caused outbreaks in a hospital and in a nursing home.^{28,29} In the above-mentioned study, which detected ESBL-producing bacteria in the general population, the investigators found no carbapenem-resistant bacteria.¹⁴

Sporadic cases of carbapenem-resistant bacteria in animals have been reported outside the Netherlands.^{30,31} These micro-organisms were encountered in the food animal production sector^{32,33}, in pets³⁴, and in wildlife.³⁵ The Committee is not aware of any reports of carbapenem-resistant bacteria in animals in the Netherlands. As the Committee has already pointed out (in the previous subsection), the WVAB has banned the use of carbapenems in veterinary medicine. Thus, the food animal production sector does not seem to be the primary basis for the public health risk in question. However, these bacteria could be imported from abroad, by people or animals, or in food.^a If they are then transferred to animals, this can create an animal reservoir of carbapenem-resistant bacteria, posing a new risk to public health.²⁹

Colistin-resistant bacteria

In 2011, the Health Council concluded that there was only a low incidence of resistance to colistin in the food animal production sector.¹ That is still the case: in 2014 no colistin-resistant *Escherichia coli* were found in the faeces of the animal species that were being monitored.⁶ However, they were detected in meat products on sale in Dutch shops. The import of infected meat products from abroad may be to blame for this.⁶ According to the Committee, if resistance to colistin were to develop in the food animal production sector, the possibility that this might be transferred to people could not be excluded.³⁶ That could pose a risk to public health.^{37,38}

In this context, the Committee feels that a recently published finding from China is a cause for concern. Worryingly, the first occurrences of colistin-resistant bacteria in animals and humans have been reported, in which the gene for such resistance was found to be located on a plasmid (a ring-shaped structure of extrachromosomal genetic material).³⁹ ^b This gene's location on a plasmid facilitates the spread of resistance, by means of horizontal transfer.

^a The Ministry of Health, Welfare and Sport and the Ministry of Economic Affairs have drawn up an action plan and a research agenda to reduce incidences of contaminated animal feed. This topic falls outside the scope of this advisory report.

^b Very recently, that same gene for colistin resistance was also found in a bacterium isolated from the blood of a Danish patient.⁴⁰



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Methylase-producing bacteria

Methylase-producing bacteria are capable of breaking down antibiotics belonging to the aminoglycoside group. While these bacteria only occur sporadically, they have now been described in patients in various parts of the world, including Europe.⁴¹⁻⁴⁴ They are equally rare in animals.⁴⁴ According to the Committee, if these bacteria were to be introduced to the Dutch food animal production sector, there would be a risk that this country might develop an animal reservoir too. Of particular concern in this connection is the combination of methylase production and carbapenem resistance.⁴⁴

Transmission

In its previous advisory report, the Health Council indicated that various sources and routes are involved in the transmission of resistance: the therapeutic use of antibiotics for the treatment of patients in and outside of hospital, travellers carrying resistant bacteria from their travels abroad, environmental sources, foods, and the food animal production sector.¹ According to the Council, little was known about the relative contribution of these sources and routes of transmission.

In the Committee's view, that picture is still largely true. However, it notes in LA-MRSA it is only clonal propagation that is important (the spread of the resistant bacteria as a whole), while in ESBL-producing bacteria, the horizontal transfer of genetic material is also a possibility. Such transfers are possible because the genes which encode for resistance in ESBL are also located on plasmids. Clonal propagation is the dominant factor in human to human transmission.⁴⁵ In cases of transfer from sources of animal origin, it is particularly likely that horizontal transfer will be involved.⁴⁶⁻⁴⁸ As there are numerous variants of the ESBL genes and a variety of sources of ESBL-producing bacteria (infected animals or their products, manure, surface water), this is a complex process.

As the Committee previously noted, we now have a better understanding of the levels of contamination from animal sources.⁶ However, nothing is known about the relative contribution made by these sources to the creation of carriers in the open human population of the Netherlands and to infections in primary care and in hospitals. For this reason, surveillance and testing will continue to be necessary. According to the Committee, this also applies in the case of LA-MRSA. It would then be possible to detect any adaptation to humans and increase in pathogenicity in good time.



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In 2011, reference was also made to the Netherlands Organisation for Health Research and Development's "Priority Medicines antimicrobial resistance" programme.⁴⁹ The Committee anticipates that this programme, which is scheduled to continue until 2018, will add to our knowledge of issues relating to the development and transmission of resistance.

Risk reduction: how to proceed?

It is gratifying to note that the veterinary use of antibiotics has been substantially reduced. The various sectors involved, together with the veterinarians, have conscientiously taken up this challenge. At the same time, any remaining issues have been spotlighted. According to the Committee, this offers a focus for potential measures to reduce the risks in question still further. The Committee still considers it important for the precautionary principle to be used in this connection. After all, the continued use of antibiotics could plausibly lead to new problems with resistant bacteria, though how soon this might happen and on what scale is still uncertain. In addition, according to the Committee, the measures to be taken need not necessarily be detrimental to animal health nor need they have economically adverse implications for the sectors (something that is always a consideration when taking precautionary measures). As in the previous advisory report, the Committee feels that it would make sense to distinguish between short- and longer-term measures.

Short term

As the Committee has already pointed out, in 2014, after several years of decline, this trend in the use of antibiotics levelled off in some sectors (pigs, calves) or actually started rising again (broilers). As a first step, it recommends focusing primarily on those farms that, according to the assessment system, are in the action zone. In such cases, robust measures must be taken to cut the use of antibiotics. The agreed sanctions must be imposed in the event of a failure to achieve adequate results. However, there are still substantial differences between farms in the signalling zone and target zone in terms of antibiotic use. Here too, efforts should be made to achieve a reduction in antibiotic use on farms that make relatively extensive use of these drugs. In this context, the Committee supports the Netherlands Veterinary Medicines Authority's (SDa) stated intention of adjusting the assessment system's limit values (the benchmark values) on a sector by sector basis, if this is necessary or desired.⁵ More specifically, the Committee recommends that the



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WVAB's proposals on reducing the use of colistin in the formularies be adopted, especially in view of the recently published finding of plasmid-mediated resistance to this antibiotic.³⁹

With regard to pets and those sectors that are (as yet) unmonitored, the Committee feels that it is of the utmost importance that the use of antibiotics be made transparent, and that here too a system should be drawn up and implemented. More specifically, for these areas too, it recommends cuts in the use of antibiotics that can promote the emergence of ESBL-producing bacteria. Furthermore, in the unmonitored sectors and in pets, the drugs of third choice (fluoroquinolones and third and fourth generation cephalosporins) may only be used on an individual basis and after proper diagnosis.

The request for advice also makes reference to a new European Regulation on the production, marketing and use of medicated feed. The aim is to achieve harmonisation in the prescription and use of medicated feed, while maintaining a high level of safety. In 2012, the NEVEDI (Dutch Feed Industry Association) took the decision to terminate production of these feeds. While it welcomes this development, the Committee feels that the use of medicated feeds should be terminated in all animal species.

In parallel to greater constraints on farms, the Committee feels that the prescribing behaviour of veterinarians in the action zone should also be subjected to sharper scrutiny. In this connection, it is important to remember that veterinarians are dependent on their customers. The sanctions that have been incorporated into the quality system must be imposed in the event of a failure to achieve adequate results. There are also gains to be made with regard to veterinarians in the signalling zone. In the Committee's view, it is also high time that veterinarians working in the unmonitored sectors or with pets were included in the assessment system.

To be sure that we are on course, we can not do without the effective monitoring of antibiotic use nor without the occurrence of resistant bacteria. The Committee, therefore, recommends that current monitoring activities be extended to include pets and those sectors in the area of food animal production that are (as yet) unmonitored.

Longer term

Over the longer term, in the unmonitored sectors and in pets, all beta-lactam antibiotics should only be used on an individual basis and after proper diagnosis. Other than this, the approach mainly involves additional measures to add to our knowledge and understanding. In this



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connection, the 2011 advisory report highlighted two themes: [1] research into the development, the mechanism of action and the spread of resistance, and [2] research into alternative forms of animal husbandry that involve only a very limited use of antibiotics. The Committee considers these lines of research to be of undiminished importance. It anticipates that the results of ongoing research into the transmission routes used by resistant micro-organisms may be helpful in further refining measures to counter resistance (and the transfer of resistance). The initial results of studies outside the Netherlands indicate that cutting the use of antibiotics in food animal production need not have an adverse economic impact on the sector.^{50,51} Further research should show whether this also applies to Dutch farms.

In conclusion

Antibiotic resistance is a problem that does not respect national borders. In this advisory letter, the Committee has made repeated reference to resistant micro-organisms that occur in other countries but not (or not yet) in the Netherlands, or that cause greater (or much greater) problems there than they do here. Thus, according to the Committee, it is of crucial importance that steps be taken, not just at national level but at international level as well. Various initiatives have already been launched to this end. One example is the joint report by the ECDC, EFSA and EMA, to which the Committee has referred.²⁶ In addition, selective monitoring for carbapenem resistance in cattle, which has been in effect in the Netherlands since 2012, became compulsory for all EU member states in 2015.²⁹ However, European cooperation is needed in more areas if further reductions in antibiotic use in animals are to be achieved. In the Committee's view, the upcoming Dutch Presidency of the EU provides an ideal opportunity to bring this about.

Having consulted the Standing Committee on Public Health, I endorse the Committee's conclusions and recommendations.

Yours sincerely,
(signed)
Professor W.A. van Gool
President



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The request for advice

On 24 April 2015, the President of the Health Council received a request from the Minister of Health, Welfare and Sport and the State Secretary of Economic Affairs for an advisory report on antibiotic resistance. The Minister wrote (letter reference 75179-135172-PG):

In August 2011, the Health Council of the Netherlands issued an advisory report entitled “Antibiotics in food animal production and resistant bacteria in humans”. In September 2011, in its response to the report, the government indicated that it endorsed the Health Council’s recommendations. In response to the advisory report, the sectors, the veterinarians and the government adopted a series of measures to boost the prudent use of antibiotics in the livestock industry. From 2011 onwards there were substantial reductions in the use of veterinary antibiotics and, more especially, in the use of antibiotics that are of critical importance to public health. In a letter to the Dutch House of Representatives (Parliamentary Document, 2013 - 2014, 29 683, No. 189), which was based on the 2013 Netherlands Veterinary Medicines Authority (SDa) report on antibiotic use in the livestock industry, the Minister of Health, Welfare and Sport and the State Secretary of Economic Affairs presented a summary of current antibiotic use. (<http://www.autoriteitdiergeenmiddelen.nl/nl/publicaties>)

Request

Consideration is currently being given to the follow-up policy needed to tackle antibiotic resistance in animals. Before the summer of 2016, we intend to inform the House of the follow-up policy needed to achieve further reductions of resistance in animals (and in resistance that spreads from them). In preparation for this,

we are asking the Health Council of the Netherlands to advise us on the public health risks of current antibiotic use in animals.

We would ask you to give particular attention to the following issues:

Risks

- What new insights have been gained since 2011 regarding the risks to public health posed by the use of antibiotics/groups of antibiotics in animals (including pets)?
- Do these new insights necessitate a review of the conclusions and recommendations contained in the Health Council's 2011 advisory report?
- If so, in the light of current scientific knowledge, what are the public health risks posed by animal-related antibiotic resistance? Are these risks related to the area of food animal production as a whole or are they restricted to specific sectors and/or animal species? Given the importance of this issue in terms of public health, which risks should be tackled as a matter of priority?
- Does the threat posed by antibiotic resistance to human health justify the use of measures based on the precautionary principle?

When responding to these questions, please include any relevant recent studies and advisory reports from bodies such as the EFSA, ECDC and EMA in your assessment, as well as the European Commission's proposals for the new regulations on veterinary medicines and medicated feed.

Transmission:

- What new insights have been gained since 2011 regarding the routes by which animal-related antibiotic-resistant bacteria are transmitted to humans (and to animals, via direct contact, via food, via the environment, etc.)?
- Do these new insights necessitate a tightening up/modification of the conclusions and recommendations contained in the 2011 advisory report? If so, which ones?

With a view to the process of drawing up the follow-up policy for tackling antibiotic resistance in the food animal production sector, please submit the advisory report to us before the end of 2015.

Yours sincerely,
the Minister of Health, Welfare and Sport,
(signed)
Ms. E.I. Schippers
the State Secretary of Economic Affairs
(signed)
Ms. S.A.M. Dijkma