



Assessment of the risks of emergence of antimicrobial resistance associated with modes of antibiotic use in the field of animal health

ANSES Opinion
Extracts from the Working Group's report:
Chapters 4 and 5 and maps

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Scientific publication



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The Director General

Maisons-Alfort, 11 April 2014

OPINION
**of the French Agency for Food, Environmental
and Occupational Health & Safety**

relating to

**Risks of emergence of antimicrobial resistance associated with modes
of antibiotic use in the field of animal health**

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 11 April 2014 shall prevail.

On 11 March 2011, ANSES issued an internal request to carry out the following expert appraisal: assessment of the risks of emergence of antimicrobial resistance associated with modes of antibiotic use in the field of animal health.

1. BACKGROUND AND PURPOSE OF THE REQUEST

In the past decade, the development of antimicrobial resistance has become a major concern in terms of human and animal health, both in Europe and internationally. This trend calls into question the efficacy of medicinal products and can worsen the prognosis for some infectious diseases, with significant social and economic consequences.

AFSSA, which became ANSES on 1 July 2010, has been working on the issue of antimicrobial resistance for the past ten years or so. In 2006, it wrote a report entitled "*Veterinary uses of antibiotics, antimicrobial resistance and consequences on human health*". This report describes the mechanisms of antimicrobial resistance which can develop further to antibiotic use in animals, and the mechanisms by which this resistance spreads to bacteria of interest in human medicine. The conclusions and recommendations of this report focus on improving information tools (data on antibiotic use and antimicrobial resistance) and methods for the production, analysis and interpretation of this information. These tools are an essential pre-requisite for the implementation of measures to ensure controlled antibiotic use on farms and assess the consequences on human health.

All countries currently need to take up the challenge of making the essential control of antimicrobial resistance compatible with the need to treat humans and animals suffering from bacterial diseases. The control of these infectious diseases, both in humans and in animals, is indeed a central public health issue.

After many exchanges with various stakeholders and scientists in 2011, the French Ministry of Agriculture launched a national plan for the reduction of antimicrobial resistance risks in veterinary medicine for the 2012-2017 period. This plan, referred to as Ecoantibio 2017, is intended to coordinate and optimise the efforts of all stakeholders involved in this issue. This plan is consistent with the 2011-2016 national antibiotic alert plan undertaken by the French Ministry of Health, and with the European Union action plan against the rising threats from antimicrobial resistance.

In this context, ANSES decided to mobilise its resources to set out, on a scientific basis, the most appropriate measures to be implemented in the field of animal health, for an effective antimicrobial resistance control policy. The Agency thus issued an internal request to assess the risks of emergence of antimicrobial resistance associated with modes of preventive, metaphylactic or curative antibiotic use in the field of animal health in the various animal production sectors (ruminants, pigs, poultry, rabbits and fish), as well as in horses and pets.

This Opinion, accompanied by the collective expert appraisal report, provides scientific data and recommendations for each animal sector or species, in a context in which work is actively being undertaken to control antimicrobial resistance at national and European levels. It supplements the actions currently provided for in the French bill on the future of agriculture.

The internal request pointed out some limitations to the scope of the expert appraisal. These are as follows:

- Coccidiostats used as additives are not included in the scope of the request;
- The proposed expert appraisal does not take into account the environment as a reservoir for resistant bacteria and resistance genes;
- The risk of human exposure to bacteria of animal origin carrying antimicrobial resistance genes, irrespective of the route of exposure, has not been specifically assessed in the context of this internal request. In particular, the following have not been taken into account:
 - The risk of exposure to infection with such bacteria in certain professional categories (farmers, veterinary practitioners, manufacturers of medicated feedstuffs);
 - The risk related to the consumption of foodstuffs of animal origin contaminated by resistant bacteria, regardless of the origin of these foodstuffs (France or third countries).

2. ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003)".

It falls within the sphere of competence of the Expert Committees (CESs) on Animal health (SANT), Animal feed (ALAN) and Veterinary medicinal products (MV). The SANT CES was appointed the leader for this internal request.

ANSES entrusted the expert appraisal to the Working Group (WG) on Antimicrobial resistance, which was selected after a call for applications. Created on 11 October 2011, the Working Group was made up of 27 experts from the areas of research, risk assessment and veterinary medicine.

The methodological and scientific aspects of this group's work were presented to the Expert Committees in various meetings between 2012 and 2014 (ALAN CES: 15 May 2012, 9 July, 12 November and 10 December 2013 / MV CES (formerly the CNMV): 14 February and 26 June

2012, 21 January 2014 / SANT CES: 4 July 2012, 18 September, 20 November and 18 December 2013).

The final collective expert appraisal report was validated on 5 February 2014 by the SANT CES after rereading by the ALAN and MV CESs. The Expert Committees adopted the conclusions and recommendations that appear in this Opinion.

The following three stages were necessary to achieve the objective set by the internal request:

- A first survey stage, targeting:
 - Antibiotic uses in various animal production sectors and in horses and pets (canines and felines), with a primarily qualitative focus;
 - Tools (measurement methods, indicators) and systems (networks, surveillance plans) for monitoring antibiotic use and antimicrobial resistance for bacteria isolated from animals;
 - The main forms of resistance encountered in 2012 in the field of animal health.
- A second assessment stage:
 - Assessment of tools and systems for monitoring antibiotic use and antimicrobial resistance in bacteria isolated from animals;
 - Assessment of the risk of antimicrobial resistance selection in the various animal sectors and species, based on the surveys undertaken and knowledge of the mechanisms underlying antimicrobial resistance;
 - Assessment of the risks associated with practices in veterinary medicine for production livestock and pets.
- A third stage on proposals and recommendations intended to reduce, avoid or abandon at-risk practices in veterinary medicine.

Nine plenary meetings, 15 sub-group meetings (Ruminants [dairy cows, suckler cows, veal calves, milk sheep, meat sheep, goats]; Pigs/Poultry, rabbits; Fish/Equines/Dogs and cats; Surveillance tools) and 22 hearings with various stakeholders in the sectors of animal feed and animal production were required to handle this request in order to collect relevant data on modes of antibiotic use.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public on ANSES's website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE WORKING GROUP, VALIDATED BY THE EXPERT COMMITTEES

3.1. Relationship between antibiotic exposure and antimicrobial resistance

Many different factors (biological, environmental, pharmacological and epidemiological) influence the emergence, selection and spread of antimicrobial resistance. Resistance mechanisms depend on each bacterium, the bacterial population in which it is found and each antibiotic compound. To understand these mechanisms, it is necessary to consider various levels of life and investigate each of its elements, from genes to bacterial populations. Since the discovery, in the 1970s and 1980s, of mobile genetic elements of resistance likely to promote the spread of antimicrobial resistance genes in bacterial populations, levels of investigation have been refined. Now, the molecular characterisation of bacterial resistance plays a decisive role in the analysis of observed and monitored phenomena.

The following key points have emerged from this knowledge:

- Any antibiotic use can lead to the selection and then maintenance and spread of resistance genes in bacteria;
- An animal can acquire resistant bacteria and permanently host them even if it has not received any antibiotics, i.e. in the absence of selective pressure;
- Once resistance to an antibiotic has been acquired and selected, its frequency can be reduced but it cannot be eliminated. It will remain discreet in the bacterial population and may re-emerge in the presence of selective pressure;
- Use of an antibiotic can select resistance to this antibiotic and to compounds in the same class (cross resistance). Whenever a bacterium hosts genes of resistance to other antibiotic classes (multi-resistance), use of an antibiotic in one of those classes will also select all of the bacterium's resistance genes (co-selection). Thus, discontinuing use of an antibiotic class will not necessarily result in a decrease in resistance for that class;
- Selective pressure is a significant factor to be taken into account in the development of resistance, but the spread of resistant bacteria and/or genetic determinants of resistance is just as significant and depends on other factors such as hygiene measures, biosafety and the control of various zootechnical parameters;
- The percentage of bacteria resistant to a class of antibiotics depends both on antibiotic use and on the nature of bacterial clones and genetic elements in this resistance (competitiveness of the bacterium, spread, etc.);
- Various bacterial species will not necessarily respond the same way to selective pressure from an antibiotic (genetic characteristics) or to dissemination factors (ecology of the bacterium);
- The administration of an antibiotic in an animal or human affects the pathogenic bacterium targeted by the treatment but also exposes other bacterial populations to this antibiotic, and particularly the bacteria in the commensal flora, which are also subject to selective pressure. These largely contribute to the spread of resistance genes in their reservoir;
- Favouring the use of narrow-spectrum antibiotics helps reduce the selective pressure exerted on the various bacteria exposed to the antibiotic. However, this means that the targeting of bacterial species responsible for the disease should be improved.

To assess the risks of emergence of antimicrobial resistance associated with modes of antibiotic use in the field of animal health, it was necessary to identify and define the various modes of animal treatment. Three treatment modes were defined:

Preventive: treatment applied to healthy animals exposed to a risk factor for the infectious disease. Preventive treatment can be individual or collective;

Metaphylactic: treatment of clinically sick animals and other animals in the same group that are still clinically healthy but likely to be infected due to close contact with the sick animals;

Curative: individual or collective treatment only of animals showing symptoms of a disease.

The types of antibiotic treatments can influence the risk of antimicrobial resistance developing. With preventive treatment, there is risk associated with the selective pressure exerted on the bacteria in the commensal flora in all of the treated animals, while the therapeutic benefit depends on the actual presence of the pathogenic bacterium, which is only suspected. The benefit-risk ratio for preventive treatments therefore appears unfavourable in terms of the risk of antimicrobial resistance. The experts consider that metaphylactic treatment is an appropriate mode, insofar as it can improve the benefit-risk ratio compared to preventive treatment. Moreover, it should be noted that in veterinary medicine, treatments can only be applied to whole groups of animals in some species.

Many factors come into play in the selection and spread of antimicrobial resistance. They show the complexity of the relationship between antibiotic use and resistance. Thus, reducing this use is one

significant driver for action but should not be the only one to control the risk associated with antimicrobial resistance in animals.

3.2. Monitoring antibiotic use and antimicrobial resistance

• Monitoring the resistance of pathogenic bacteria

France has had a system for monitoring the antimicrobial resistance of pathogenic bacteria in animals (RESAPATH network) for over 30 years. The analysis laboratories participating in the network pool the results of antibiograms requested by veterinary practitioners (in 2012, 31,211 antibiograms from 64 laboratories were collected).

Resistance to latest-generation antibiotics is particularly monitored.

- Resistance to 3rd and 4th generation cephalosporins (3GC/4GC) essentially involves the *E. coli* species. This resistance is decreasing in hens and chickens but is continuing to increase in calves, dogs and horses. However, it still remains highest in hens and chickens compared to other animal groups. The proportion of 3GC/4GC-resistant *E. coli* is twice as high in broiler chickens than in laying hens; in cattle, resistance to 3GC/4GC is primarily found in veal calves; in domestic carnivores, 3GC/4GC-resistant strains often have strong similarities to human strains.
- As for fluoroquinolone resistance, a downward trend has been observed for most animal species (stabilisation for cattle).
- Multi-resistance is common in most sectors, particularly for 3GC/4GC-resistant strains. This phenomenon is more pronounced in cattle, horses and dogs.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is rarely isolated from samples of infectious origin in production livestock. In fact, it is almost non-existent in cattle and very marginal in hens and chickens. In pigs, the proportion of MRSA cannot be quantified in the framework of RESAPATH due to the low frequency of *S. aureus* infections. However, this resistance has previously been described in France in pigs (carriage). In dogs, it is also low and most of the identified MRSA strains have been human clones. The highest proportions of *S. aureus* strains resistant to ceftiofur (a marker of resistance to methicillin) have been measured in horses and further analyses are being undertaken to confirm these data from a molecular perspective.

• Monitoring the resistance of commensal and zoonotic bacteria

Monitoring plans at the slaughterhouse, developed to monitor antimicrobial resistance in zoonotic (*Salmonella enterica*, *Campylobacter jejuni* and *coli*) and commensal (*E. coli*, *Enterococcus faecium* and *faecalis*) bacteria, have been harmonised for the main animal sectors at European Union (EU) level since 2004.

Implemented in France for over ten years for broiler chickens and pigs, these monitoring plans have observed a gradual decrease in resistance in *Enterococcus faecium* to the main antimicrobial growth promoters used before 2002.

Since 2006, they have also observed an increase in resistance to quinolones and beta-lactams in *E. coli* isolates collected in broiler chickens and a relative decrease in most of the main forms of antimicrobial resistance in *E. coli* isolates in pig production.

These plans are being updated in 2014 to better understand the development of cephalosporin resistance in Enterobacteriaceae (*Salmonella* sp. and *E. coli*) and monitor more animal species (calves, turkeys).

Targeted prevalence studies have also been initiated in France and the EU to estimate the prevalence of certain resistance phenotypes (vancomycin-resistant Enterococci, methicillin-resistant *Staphylococcus aureus*, cephalosporin-resistant *E. coli*).

These monitoring systems help detect emerging resistance and determine trends in terms of resistance percentages. Firstly, they are essential instruments for informing decision-makers who adopt policies for prudent antibiotic use; secondly, they contribute to the understanding of biological phenomena underlying the development of resistance. They are supplemented by surveys to study emergence and identify routes and modes of transmission. New molecular typing tools have helped improve the capacity to characterise bacterial clones and the mechanisms and media of resistance and also improve risk assessment capacities in the fields of animal and human health.

- **Monitoring uses**

Since 1999, France has had a national monitoring tool for antibiotic use in veterinary medicine (sales survey) developed by the French Agency for Veterinary Medicinal Products.

This monitoring tool is used to determine trends in antibiotic therapy practices for various animal species. However, sales volumes for antibiotics do not accurately reflect their use. Indeed, recent antibiotics are more potent and require the administration of a smaller amount. Thus, a decrease in sales volume does not necessarily mean a decrease in the rate of use. That is why it is necessary to calculate¹ antimicrobial exposure in animals to better reflect reality.

Between 2011 and 2012, exposure to antibiotics decreased by 19.9% for rabbits, 10.1% for pigs, 8.4% for domestic carnivores, 5.6% for poultry and 0.6% for cattle.

In 2012, all animal species combined, exposure in animals to veterinary medicinal products containing antibiotics returned to a level similar to that of 1999, the year when the monitoring plan was launched (+1.1%) and the ban on antimicrobial growth promoter additives was introduced. Since 2007, there has been a continuous decline, with a 10.9% overall decrease in exposure in the last five years.

Compared to 1999, volumes of antibiotic sales have dropped nearly 41.2%. They fell 14% between 2011 and 2012. But the overall decrease observed is partly due to an increase in the use of more recent and more potent compounds including fluoroquinolones and 3rd and 4th generation cephalosporins. For example, compared to 1999, fluoroquinolone exposure in animals has virtually doubled and cephalosporin exposure has nearly tripled, although exposure has stabilised for the past three to five years depending on the compound.

In addition to this monitoring tool, surveys on the prescribing practices of veterinary practitioners and conditions of use on farms have made it possible to better characterise exposure periods, study changes in practices and highlight the wide range of usage profiles.

These various monitoring systems are complementary and have helped raise prescriber and user awareness of the need to modify practices to reduce antibiotic use.

Henceforth, in order to preserve the effectiveness of the available therapeutic arsenal and optimise its use, it is advisable to develop sustainable and upgradable tools for monitoring antibiotic use and antimicrobial resistance by animal species, sector and production type and refine knowledge down to farm level. The aim is to adapt and improve veterinary prescriptions and preventive and protective health measures to optimise the therapeutic use of antibiotics.

¹ The calculation of exposure takes into account the dosage and administration period as well as changes in the corresponding animal population over time.

Thus, current tools need to be updated to support the efforts of professionals aiming to use antibiotics less but more effectively:

- Regarding the monitoring of antibiotic use: antibiotic use can be factually analysed by developing sustainable monitoring tools for a farming system combined with the monitoring of veterinary prescriptions. In combination with statistical analysis tools, these systems can contribute to the development of responsible, sustainable behaviour regarding use. Thus, it is advisable to develop a traceability tool for all prescribing and dispensing of anti-infective medicinal products, in all animal sectors. The data analysis programme linked to this traceability tool should enable the establishment of a dashboard of antibiotic use on each farm, thus giving farmers and veterinarians a basis for evaluation and the implementation of corrective measures when necessary. In addition, such a system should make it possible to strengthen the routine veterinary monitoring of farms with high antibiotic use with the aim of introducing preventive measures.

Furthermore, the experts point out the risk of seeing parallel and illegal sales channels develop that will also require monitoring;

- Regarding the monitoring of resistance in pathogenic bacteria: these tools need to be broadened to animal species for which there is currently no information (fish in particular) and to bacteria for which few studies have been undertaken (mycoplasmas). It is also advisable to refine the collection of information within production systems and regions. The development of such a tool should be encouraged at EU level;
- Regarding antibiograms, they need to be adapted to veterinary medicine: resistance data based on an analysis of antibiogram results for animal bacteria can be used to monitor trends in various production sectors and provide an indication of effectiveness for measures taken in terms of use. However, there is ample room for improving the prognostic clinical value of veterinary antibiograms, considering the wide range of animal species and antibiotics used. As part of a PK/PD approach, it is advisable to provide the necessary tools to better adapt dosages and therapeutic indications for each compound in order to grant higher positive predictive value to veterinary antibiograms.
- Monitoring the resistance of commensal bacteria is just as important as monitoring that of pathogenic bacteria in veterinary medicine. The experts recommend taking into account bacteria representative of the intestinal microbiota and risks of gene transmission. It is also advisable to improve this system's sensitivity to emerging resistance. The importance of having information on the development of resistance in stages of production other than the final slaughtering stage is also underlined. Lastly, the experts note the importance of exploring new approaches to monitoring at genome level to improve molecular information;
- It seems relevant to assess the role of the food chain in the transmission of resistance genes to humans and particularly to develop the targeted surveillance of products of animal origin, for both EU products and imported products, given the high level of international trade in foodstuffs.

3.3. Inventory of antibiotic uses and at-risk practices and recommendations

The inventory of antibiotic therapy practices was carried out by the Working Group, firstly based on the results of field studies undertaken by ANSES in various animal sectors and secondly based on expert knowledge in this area and hearings with a large number of veterinary representatives specialising in the various animal species, the list of which can be found in the collective expert appraisal report.

This inventory covers a given reference period (2010-2011) and largely relied on information collected about known practices. Indeed, other than antibiotic sales survey reports and the results of the pharmaco-epidemiological studies published by the French Agency for Veterinary Medicinal

Products (ANMV) and the ANSES laboratories, very few bibliographic data are available on modes of antibiotic use in veterinary medicine.

For want of quantitative studies on modes of antibiotic use for all of the animal species targeted by the request, the data in this identification stage are essentially qualitative.

Considering the conditions in which it was undertaken, this inventory could therefore not claim to be completely exhaustive.

This stage provided the WG with a working tool it was able to use throughout the handling of the internal request. It was compared in particular to the ten-year results of tools for monitoring antibiotic sales and bacterial resistance for each sector. It was then used for the assessment of 'at-risk' modes of antibiotic use by sector. The collective expert appraisal report covers these points in detail in Section 4.

This identification stage showed a wide variety of veterinary practices depending on the sector and animal species. This was due to the variety of farming methods and the physiological and pathological particularities of each species.

As indicated above, antibiotic use always poses the risk of selecting, amplifying or disseminating bacterial resistance. However, some practices have a higher risk. The objective of the Working Group was to identify these at-risk practices, which can be defined as practices for a given animal species resulting in the significant selection of resistant bacteria (or resistance determinants) likely to pose a risk to health in general (human, animal or environmental). For the Working Group, the identification of 'at-risk' modes of antibiotic use, referred to as 'at-risk practices', therefore needed to rely on a comparison between modes of antibiotic use on the one hand and the development of antimicrobial resistance on the other hand, in various sectors. That said, it is not always possible to establish a causal link between these two factors, considering the complexity of the relationship between antibiotic use and resistance, as pointed out above. Thus, the few available results in this area call for caution when it comes to associating the development of antimicrobial resistance with modes of antibiotic use.

These difficulties in interpretation and the resulting inability to directly assess 'at-risk practices' according to data on the resistance of both pathogenic and commensal bacteria led the Working Group to adopt a pragmatic, multi-stage risk assessment approach to highlight 'at-risk' modes of use. This approach is summarised below and presented in full in the collective expert appraisal report.

The methodology developed was modelled on the following:

- the risk analysis process of the World Organisation for Animal Health (OIE);
- the methods used in ranking exercises, by assigning scores to the criteria taken into account for the risk assessment;
- methods for eliciting expert knowledge to set an acceptability threshold for the various practices of antibiotic use.

▪ **Two stages were used to establish a list of at-risk practices**

- 1st stage: this consisted in establishing a classification of antibiotic modes of use as 'antibiotic – route of administration – treatment type' triads and determining a general acceptability threshold for these practices, independently of the species and production stage.

During this stage, criteria for indirectly assessing the 'consequences' dimension of risk (OIE) were established in terms of significance for humans and animals, taking into account the lists of antibiotics (highest priority, critical, highly important and important) provided by the World Health Organization (WHO) for humans and by the OIE for animals. For the 'exposure' dimension, the criteria taken into account were the route of administration and type of treatment (preventive, metaphylactic, curative).

Acceptability thresholds for practices were established using a questionnaire sent to the experts in the Working Group. Practices whose score was above the group's acceptability threshold were considered at-risk practices.

- 2nd stage: this consisted in assessing, for each animal species and production stage, all of the identified practices. During this stage, modulating factors were applied in order to take into account additional factors when applicable (frequency of use, data on the development of resistance, co-selection, treatment of specific animal populations, etc.) or else factors that would cause a practice recognised as at-risk in the first stage to be downgraded.

These two successive stages resulted in a list of the 'most at-risk practices' for each animal species and production stage.

▪ **Assessment and classification of at-risk practices**

The essential need to use each practice and the existence of recognised alternatives were examined by the experts. This stage was important since some practices may be considered at-risk but cannot be avoided for want of other solutions.

At the end of this exercise, each at-risk practice was classified into one of the following categories:

- *'Practice with no further control'*;
- *'Practice to be controlled'* (with regulation recommendations) in order to precisely target the situations when this antibiotic use can be considered;
- *'At-risk practice that should be abandoned over time'*, by developing replacement measures, since this practice is considered still essential for want of alternative means developed by the sector in question;
- *'At-risk practice to be abandoned without delay'*: this at-risk practice must be abandoned immediately, because it is either considered unnecessary, a poor practice requiring correction or an avoidable practice given that alternative solutions are available.

The results of this assessment are presented in full, for each sector and animal species, in the collective expert appraisal report.

▪ **Conclusions**

- **Consideration for human health:** During this assessment, risks to human and/or animal health were taken into account in their various aspects, including the existence of common antibiotics to treat both humans and animals. This led the Working Group in particular to recommend reserving the use of latest-generation cephalosporins and fluoroquinolones for specific situations, which should be clearly identified by sector and strictly controlled.
- **Preventive practices:** In this survey of 'at-risk practices', there was a common recommendation to abandon preventive practices of antibiotic use, immediately or over time.

The treatment of pets (dogs and cats) was no exception, except for specific uses for non-convenience surgery.

For other species, the experts point out some situations for which preventive antibiotic use cannot immediately be abandoned, even though this is an 'at-risk practice'. Their abandonment will require some time, so that professionals may develop and adopt alternative measures, but the experts stress the need to seek out such replacement solutions without delay. Each sector has its particularities in terms of 'at-risk practices'. Therefore, the Working Group recommends that these specific situations be listed in collaboration with professionals. A first inventory was drawn up by the Working Group for the various species. These lists should be revised on a regular basis to take into account available and validated alternative solutions and the health context. In this framework,

action plans and timetables for the implementation of alternative measures and means could be defined.

- **Metaphylaxis:** In general, all sectors combined, for the treatment of animal batches by metaphylaxis, sick animals should be identified as early as possible and veterinary regulation should be strengthened. The experts recommend:
 - defining appropriate indicators of metaphylaxis (nature and threshold number of indicators);
 - collectively defining decision-making criteria for such prescriptions, based on indicator values;
 - encouraging the development of early detectors of animal disease so as to ultimately improve the available indicators.
- **Practices to be controlled** In addition, common principles for practices 'to be controlled' should be defined and adapted by sector:
 - no systematic use;
 - use in the established presence of the targeted etiological agent (no first-line² prescription);
 - documented justification of the use of these practices (traceability of the criteria that resulted in these practices being adopted);
 - request for alternative supporting measures to gradually reduce these practices (corrective and alternative measures);
 - prescriptions of limited duration.
- **Promoting factors:** While this assessment stage made it possible to identify and survey 'at-risk practices' in terms of antimicrobial resistance, the experts stressed the major relevance of the following:
 - factors that promote the introduction and/or development of bacteria on farms, thus increasing antibiotic use. These were grouped under the concept of 'risk factors in the occurrence of diseases';
 - technical, economic, sociological and regulatory constraints that result in poor practices in terms of antibiotic use.

The experts underline the significance of taking into account all of these promoting factors, which need to be reduced just as much as the 'at-risk' practices themselves.

These points are described in detail in the collective expert appraisal report and are covered by recommendations. Note the following key points:

- The critical significance of both internal and external biosafety measures;
- The importance of acting at sector level on critical production stages, in which antibiotics are very frequently used for prevention or metaphylaxis (clustering of animals of different origins, management of weaning in industrial farming, etc.) ;
- The need to develop rapid diagnostic tools facilitating differential diagnoses;
- The European regulatory barrier to the revision of dosages from older Marketing Authorisations (MAs) which needs to be removed, in keeping with the European Union's position on reducing risks of antimicrobial resistance.

It should be noted that the collective expert appraisal report and its conclusions were validated by all of the Working Group's members, except for Dr Denis Fric, who wished to make diverging comments, which can be found in the annexes of the report.

² First line: choice of treatment relying on epidemiological and clinical data

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the Working Group's findings and recommendations.

Considering the scope of this report, which contains a great deal of scientific data relating to antibiotic use and antimicrobial resistance, ANSES would like to highlight several points underlined by the experts, which it considers essential in the current context of general mobilisation around the control of antimicrobial resistance, particularly in the framework of the Ecoantibio 2017 plan and the French bill on the future of agriculture.

4.1. Monitoring tools

- **Complementary monitoring tools**

France has had tools for monitoring antibiotic use and antimicrobial resistance for 15 and 30 years respectively. These tools have improved, growing in scope and becoming more precise, and now make it possible to study changes in these indicators over a period of more than ten years.

- The 15-year analyses from the antibiotic sales survey show that real efforts have been made by the various sectors in the past years to reduce antibiotic exposure in animals, and also highlight the significant development of certain at-risk practices in the use of latest-generation compounds (fluoroquinolones and 3rd and 4th generation cephalosporins). The level of exposure to these classes of antibiotics remains high, particularly in certain animal species, and is a concern of highest priority.

Moreover, a correlation has been observed between the arrival of generic medicinal products for latest-generation compounds on the market of veterinary antibiotics and the increase in their sales volume.

- The resistance of pathogenic bacteria has been monitored by the RESAPATH network for nearly 30 years. In this network, resistance to latest-generation antibiotics is monitored especially closely. It has increased steadily over the past 15 years, becoming a subject of concern for most species. However, in the last few years, there has been a decrease in resistance to fluoroquinolones. The recent trend in resistance to 3rd and 4th generation cephalosporins has been more contrasted, ranging from a decrease in resistance to continued growth depending on the animal species.
- Antimicrobial resistance surveillance plans for zoonotic and commensal bacteria have been harmonised for the main animal sectors at European level since 2004. These plans are being updated in 2014 to better understand the development of cephalosporin resistance in Enterobacteriaceae (*Salmonella* and *E. coli*) and monitor more animal categories (calves, turkeys). It is important to underline the significance of sector-specific monitoring, insofar as surveillance data regularly show that a level of resistance in a bacterium detected in one animal species cannot in any circumstances be generalised to other species.

- **Monitoring better to control better**

Monitoring of antibiotic use and antimicrobial resistance is now effectively implemented in France. The monitoring tools have provided the health authorities with decision-making information to adopt management measures, and the means to monitor their effects.

In a context of growing awareness in animal sectors with a will to commit to prudent antibiotic use, recommendations are now being made to develop sustainable tools for monitoring practices on the basis of antibiotic administration on farms, by animal species, sector and production type. The computer recording of farm data and systematic reporting

of these data combined with the recording of veterinary prescriptions in a suitable information system would facilitate the development of various studies, particularly pharmaco-epidemiological studies, required to better analyse practices in relation to other production data.

The results of these studies could be used by sectors to develop responsible and sustainable behaviour:

- For farmers, these monitoring data would allow them to position their farms in a cohort of equivalent producers, by using benchmarks, and also analyse them in relation to other permanent information about their farms;
- For veterinarians, this data analysis would help them position their prescribing practices in relation to *ad hoc* indicators and would provide them with an additional indicator of the health status of each farm;
- The analysis of these data should also make it possible to issue recommendations for good practices of antibiotic use.

France is well-positioned in terms of the age of its monitoring tools. It developed a sales monitoring system ten years before the European tool and it monitors resistance not only in commensal and zoonotic bacteria, as required by Europe, but also in bacteria that are pathogenic to animals (30 years of surveillance). It thus has a satisfactory control tool.

However, controlling requires closely taking into account the particularities of each animal species or sector.

ANSES recommends that this tool remain upgradable and capable of adapting to the needs of each sector and changes in scientific knowledge (increasingly detailed surveillance, sector by sector, taking into account the molecular characterisation of resistance, monitoring the circulation of resistance genes in the environment).

Furthermore, the Agency stresses the significance of including live animals and products of animal origin from other countries in surveillance plans for antimicrobial resistance.

4.2. Better managing at-risk practices in veterinary antibiotic therapy

The management of various risk factors in the occurrence of bacterial diseases on farms plays a decisive role in reducing antibiotic use in veterinary medicine: the aims are to reduce infective pressure in the animals' environment and place these animals in physiological conditions that allow them to best express their natural defences. The achievement of these objectives is dependent on compliance with biosafety measures (internal and external to the farm), building quality, diet, farming practices found in more resilient production systems³ (weaning age, batch management of animals, etc.) and the characteristics of the animals themselves (genetics/immune responses of animals, robustness, etc.).

The collective expert appraisal report underlined several times the complex relationship between antibiotic use and resistance. Reducing this use is one relevant driver for action: it is currently necessary to reduce the selective pressure of all antibiotics and all stakeholders need to be involved in this effort. However, reducing use should not be the only method undertaken to control the risk associated with antimicrobial resistance in animals.

The precise and systematic work undertaken by the experts to identify 'at-risk practices' in antibiotic use led to the following converging conclusions and recommendations for all animal species:

³ A system capable of resisting even though it has been affected by one or more disturbances.

- Abandon preventive antibiotic use. The Working Group's analysis clearly shows that the benefit-risk ratio of preventive treatments is unfavourable in terms of the risk of antimicrobial resistance. Depending on the sector, context and antibiotic class, this practice should be abandoned either immediately or after a certain period. Indeed, in some farming and production situations, at-risk practices cannot be abruptly abandoned for want of available alternatives;
- Reserve the use of latest-generation cephalosporins and fluoroquinolones as a last resort, for specific situations that should be clearly identified by sector and strictly regulated. Monitoring tools have been quick to highlight an increase in the use of these compounds in veterinary medicine, in tandem with a rapid increase in bacterial resistance to these latest-generation antibiotics. It is therefore necessary to implement corrective measures without delay, which some sectors have already begun to do;
- The use of antibiotics authorised in human medicine only should be reserved for very specific and regulated situations;
- The use of routes of administration other than those provided for in the MA should also remain exceptional. This is particularly the case for the administration of medicinal products through the environment (spraying, nebulisation, nest powder);
- Favour the use of narrow-spectrum antibiotics. This recommendation raises three comments:
 - more precisely targeting the bacterium involved means identifying it better;
 - it is advisable to use combinations of antibiotics to achieve synergistic activities on the targeted bacterium and reduce the risk of resistant mutants emerging;
 - it is advisable to reduce the use of antibiotic combinations for spectrum broadening purposes.

In the rest of these recommendations, ANSES underlines the need to assess the impact of the measures put into place to control antimicrobial resistance. Many means are being implemented at once to reduce the impact of practices on antimicrobial resistance. It is important to acquire analytical and research capacities to not only assess the overall impact of these measures but also evaluate the effectiveness of each one. This should make it possible to optimise the selection of actions to be undertaken.

Lastly, with the experts, ANSES would like to point out that the control of antimicrobial resistance also requires the provision of tools to better target antibiotic treatments and the development of alternatives to the use of these compounds. Thus, the Agency recommends the following:

- encouraging the development of accessible rapid diagnostic tools and regulating their validation before they are placed on the market;
- continuing efforts to develop vaccines;
- in general, developing a specific framework for the development of alternatives to antibiotic therapy, in order to ensure the marketing of products that have been validated according to the regulations.

4.3. Understanding better to act better

The work involved in this internal request also highlighted a need to improve knowledge of a number of phenomena and mechanisms.

- Regarding mechanisms involved in the development and spread of antimicrobial resistance:

- significant work remains necessary to better assess the relationship between use and resistance, and particularly multi-resistance;
 - work needs to be developed aiming to improve the positive clinical predictive value of veterinary antibiograms, taking into account the variety of animal species, therapeutic indications and dosing regimens, and the corresponding pharmacokinetic/pharmacodynamic data;
 - monitoring the circulation of resistance genes in the environment and in animal and human populations requires integrative molecular approaches (characterisation of the resistome⁴ in the various compartments), which are not yet directly available for widespread field monitoring. The benefits of such approaches may be assessed in relation to expectations and management needs, in combination with the tools that are already available.
- Regarding modes of antibiotic use and their impact on antimicrobial resistance: depending on the context, sociological, zootechnical, economic and microbiological (etc.) factors can have varying impacts on antibiotic use and the development of resistance. It is essential, for each situation of interest, to develop studies enabling their identification and classification, with the aim of more precisely adapting management options on a case-by-case basis.
 - Regarding treatment modes, it should be noted that the abandonment of preventive practices of antibiotic use requires a clear definition of metaphylaxis, the challenge being the rapid detection of sick animals. Some of the Working Group's recommendations in this area involve research, which should be encouraged, to:
 - define appropriate indicators of metaphylaxis (nature and threshold number of indicators);
 - develop early indicators of changes in the health status of an animal or group of animals.

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KEYWORDS

Antibiotic, antimicrobial resistance, at-risk practices, cat, curative, dog, farm, fish, horse, metaphylaxis, pig, poultry, preventive, rabbit, ruminant, veterinarian.

⁴ The resistome is defined in bacteriology as all of the resistance genes to one or more given antibiotics in a given environment.



Assessment of the risks of emergence of antimicrobial resistance associated with modes of antibiotic use in the field of animal health

Extracts from the Working Group's report: Chapters 4 and 5 and maps.

April 2014

Scientific publication

This document is a translated extract from the original report published in French on the Agency's website. In the event of a discrepancy or ambiguity, the French language text dated April 2014 shall prevail.

4 Inventory of antibiotic therapy practices in the various animal sectors

4.1 Methodology

4.1.1 A sociological take on the expert appraisal protocol

A scientific and technical expert appraisal is generally based on an extensive corpus of data giving experts an objective overview of the risks they are supposed to assess. The expert appraisal protocol thus depends on the type of data available and, of course, a number of constraints more or less faced by the experts such as the composition of the working group, the content of the formal request, the state of available knowledge and know-how, the political and institutional context, etc. In this respect, this expert appraisal on antimicrobial resistance risks has several fairly singular characteristics that it may be worth underlining in order to highlight its significance and originality, all while drawing attention to some limitations that should also be taken into consideration to clearly define the scope of its results.

There is currently a fairly wide range of monitoring tools for measuring antimicrobial resistance phenomena in the animal world. These tools are part of a complex and heterogeneous set of systems for producing data on antibiotic use in veterinary medicine and trends in antimicrobial resistance. Scientists and experts regularly refer to all of these data to assess antimicrobial resistance risks so that political and administrative decision-makers and stakeholders may adopt measures to control these risks. However, ANSES decided to use a risk assessment method also relying on expert 'practitioners', i.e. field veterinarians with perfect knowledge of practices of antibiotic use in the various sectors they specialise in. Indeed, since the data produced by monitoring tools are neither infallible nor exhaustive, the experts considered that to fully answer the request they had received, it was necessary to combine a traditional scientific and technical expert appraisal with a 'practical' (or 'professional') expert appraisal, i.e. in-depth, accurate knowledge of concrete practices of antibiotic use that monitoring tools do not always take into account. It is therefore relevant to discuss this unique method in order to understand to what extent the state of available data and therefore knowledge impacts the protocol that a group of experts is likely to implement in its risk assessment work and therefore the results of this expert appraisal. Therefore, this section first presents the challenges encountered by the expert group and the approaches used to try to overcome them. It then shares some lines of thought intended to generally rethink expert appraisal work for an issue that is as complex – and sensitive – as the assessment of antimicrobial resistance risks in the animal world. However, the political and institutional context in which this expert appraisal was undertaken will not be discussed, even though, from a sociological standpoint, it played a significant role, especially at a time when the issues of antimicrobial resistance and the regulation of antibiotic uses (human and veterinary) are particularly salient public health matters.

4.1.1.1 The challenge of assessing practices of antibiotic use

Ignorance-producing systems...

It is first worthwhile to consider to what extent certain aspects of antibiotic use on farms are missed by monitoring tools and why only the practical experience of field veterinarians made it possible to make these aspects 'visible' or, to put it in other terms, 'put them in data form' and make them comprehensible to the experts (Jouzel and Dedieu, 2013). In reality, the fact that various data production systems are unable to objectively specify all risks and at-risk practices is not specific to antibiotic monitoring or the surveillance of resistant bacteria in veterinary medicine. Rather, this truth is inherent in most tools for the assessment of health and environmental risks (Frickel and Edwards, 2014). Indeed, science & technology studies (STS) have shown that such systems do not only produce knowledge of a given risk but also produce 'ignorance' (Kleinman and Suryanarayanan, 2013) or, to put it otherwise, risk 'invisibilisation' phenomena (Décosse, 2013; Torny, 2013). This means that in spite of extremely sophisticated techniques, indicators and measuring instruments, monitoring and surveillance systems cannot appreciate the full social, economic and even technical complexity that causes a risk (or at-risk practice) to exist. Moreover, sometimes it is the way in which such tools are designed that causes ignorance to be produced

instead of, or at the same time as, knowledge (Frickel S. and Vincent, 2007). In the case of antimicrobial resistance risks, a number of biases and limitations have already been pointed out: the multiplication of systems, at national and European levels, whose measuring instruments are not always the same; the indicators used, which create data based on certain criteria and which are not always compatible with one another (problem of non-cumulative data); difficulties accessing private data (those of farmers, veterinarians and industry) which would improve representativeness and exhaustiveness; practices that are not recorded, such as off-label and illegal uses; the over-representation of certain bacteria that are sampled more systematically than others; a lack of background data that would provide information about the health context and allow 'sampled' data to be compared to a set of related practices; a lack of attention granted to commensal bacteria and the molecular characteristics of resistant bacteria, which are essential for an accurate risk assessment; failure to take into account the economic and social factors that surround antibiotic use, etc.

...and an expert appraisal protocol that is intended to enlighten

It was to overcome this ignorance, if only in part, that the Working Group was put together in such a way as to reflect a variety of expertise and fill in these gaps insofar as possible. The protocol that was implemented was thus intended to draw up a new inventory of practices of antibiotic use, making it possible to supplement the available data and then identify which of these practices could be described as 'at-risk' based on the available knowledge of antimicrobial resistance phenomena. The following two sections present the results of this unique methodology (Section 4 on the inventory and Section 5 on at-risk practices). It is similar to a semi-quantitative methodology aiming to objectify and link the practical knowledge of expert 'practitioners' and professionals to that of 'scientific and technical' experts and the available data. The advantages and disadvantages of this methodology described below will not be addressed, but it should be noted that its effectiveness largely relied on the operating mode of the expert group and the 'formal' challenges it had to face: representativeness and legitimacy of various viewpoints; division of scientific and editorial work; ways of mobilising knowledge and expertise; management of controversy and consensus-reaching; organisation of 'collegiality' and 'multiplexity'; time management and more or less implicit consideration of the political and institutional context, etc. (Granjou and Barbier, 2010). Even though such a protocol clearly cannot claim to overcome all of the biases mentioned, it nonetheless offers a major advantage in relation to the many available data. Indeed, by using the notion of 'at-risk practices', the concrete forms in which medicinal products are used in animal health can be described more clearly, by comparing the knowledge provided by monitoring tools with the 'field' experience of expert 'practitioners'. Lastly, in the notion of 'at-risk practices', focus is placed more on 'practices' (than on 'risks') to offer a more accurate view of 'real' antibiotic uses in veterinary medicine.

We would also like to insist on two latent issues that, while outside of the scope of this request, could be examined more closely in the coming years considering how fundamental they appear for the management and assessment of antimicrobial resistance risks. The first involves taking into account the economic and social factors that govern practices of antibiotic use; the second refers to the operational modes and purposes of monitoring and surveillance tools for antimicrobial resistance.

4.1.1.2 Taking into account socio-economic and professional challenges in expert appraisal work

Difficulties taking into account economic and social factors

Aside from some one-off, localised studies, the various knowledge production systems available (monitoring of antibiotic use and surveillance of resistant bacteria) are not suited to measuring the economic and social factors that govern antibiotic use. And yet it seems clear that these factors play a role not only in the existence (or not) of antimicrobial resistance risks but also in the effectiveness of the measures and recommendations that decision-makers may issue. Whether it is the economic structure of agri-food sectors and markets, the production system itself, the socio-economic relations between medicine stakeholders or the whole set of regulatory, technical and professional constraints influencing the decisions of antibiotic users, all of these factors impact what could be called the 'social organisation of veterinary medicinal products' and therefore the at-risk practices that stakeholders sometimes adopt. While these factors are not essential in a quantitative risk assessment, they are so when undertaking a qualitative assessment, seeking to understand the reasons for misuse and identify tools for changing practices. Furthermore, while outside of the scope of this request, some of these economic and social factors sometimes 'emerged' during the expert appraisal, particularly thanks to the field knowledge of the expert 'practitioners'; this raises the issue of a risk assessment that does not explicitly incorporate a socio-economic analysis and refers to implicit rather than disciplinary professional knowledge. It can therefore be reasonably assumed that in the future, taking into account the social sciences when examining an issue as complex as antibiotic use will enable a more cross-cutting approach to risk assessment.

Improving knowledge production systems

Regarding the control of practices of antibiotic use and support with changing practices considered 'at-risk', consideration could be given to monitoring and surveillance tools. We touched on the forms of ignorance that these systems can produce insofar as some information (particularly socio-economic) about the inventoried practices has not been 'put into data form'. And yet this 'fortuitous organisation of ignorance' (Frickel S. and Vincent, 2007) largely stems from the fact that these systems, first and foremost designed for public health purposes (risk assessment), actually rely on a set of professional practices whose purposes are mainly clinical, i.e. preventing and treating animal diseases. This finding is not specific to the issue of antimicrobial resistance. Rather, it is inherent in any surveillance activity for example in the case of BSE (Barbier, 2006), bovine brucellosis (Bronner, 2013) and systems involving plant health (Prete, 2008) and human health, particularly occupational health (Jouzel and Dedieu, 2013). This brings up the relevance of rethinking the purpose of surveillance tools in such a way that they provide a better link between risk management and assessment and a better match between the practical/clinical objectives they rely on and the public health objectives they are assigned. In the future, granting attention to the way in which such knowledge is produced and disseminated could not only help reduce the areas of ignorance and uncertainty that still characterise the issue of antimicrobial resistance but could also benefit the technico-economic and health management of farms, the management of antibiotic use in sectors and territories and ultimately the assessment of public health risks.

4.1.2 Inventory method

The inventory of antibiotic therapy practices was carried out by the Working Group, firstly based on the results of field studies undertaken by ANSES in various animal sectors and secondly based on expert knowledge in this area and hearings with a large number of veterinary representatives specialising in the various animal species, the list of which can be found at the beginning of this report.

This inventory was undertaken over a given reference period (2010-2011) and largely relied on information collected about known practices. Indeed, other than antibiotic sales survey reports and the results of the pharmaco-epidemiological studies published by ANMV and the ANSES laboratories, very few bibliographic data are available on modes of antibiotic use in veterinary medicine.

For want of quantitative studies on modes of antibiotic use for all of the animal species targeted by the request, the data in this inventory are essentially qualitative.

Considering the conditions in which it was undertaken, this inventory can therefore not claim to be completely exhaustive.

4.1.2.1 Inventory tables: a working tool for the WG

This inventory was first presented as tables (Table) broken down by animal species containing the following information:

- ✓ Animal species;
- ✓ Production stage;
- ✓ System targeted by the practice (respiratory, digestive, systemic, etc.);
- ✓ Treatment type (preventive, metaphylactic, curative);
- ✓ Motivation for the choice of antibiotic: first-line¹ (or empiric) or second-line² treatment
- ✓ Route of administration (oral, parenteral, local, intra-mammary, other);
- ✓ Antibiotic classes or sub-classes;
- ✓ Duration of treatment;
- ✓ Frequency of use.

These inventory tables were intended to provide the WG with a working tool throughout the handling of the request. They were used in particular for the assessment of at-risk practices by sector (see Section 5).

¹ Choice of treatment relying on epidemiological and clinical data

² Choice of treatment relying on analytical data such as detection of the causal agent and establishment of an antibiogram

Table 4: Header of inventory tables on modes of antibiotic use in veterinary medicine

Production stage	Names of compounds	USE										Frequency of use	Decision-making criteria	Alternatives	Open comments
		Indication / Disease	Route of administration	Preventive	Metaphylaxis	Curative	1st or 2nd line (1 or 2)	After clinical examination (rarely, often, always)	Use of an antibiogram (rarely, often, etc.)	Dosage	Years of use in the sector				

These tables were systematically filled in for all of the animal species covered by the internal request, by production type, production stage and disease. Seven hundred and fifty modes of antibiotic use (table rows) were identified, all species and all compounds included.

- As stated in Section 2 of the Report (untranslated), **treatment types** were defined by the Working Group as follows:

Preventive: prophylactic treatment applied to healthy animals exposed to a risk factor for the infectious disease. Preventive treatment can be individual or collective;

Metaphylactic: treatment of clinically sick animals and other animals in the same group that are still clinically healthy but likely to be infected due to close contact with the sick animals (EMEA, 2013);

Curative: individual or collective treatment only of animals showing symptoms of a disease.
- Routes of administration** were defined as follows:
 - Medicated premix: administration of the antibiotic through food (MP);
 - Non-premix oral route: administration of the antibiotic through the mouth *via* drinking water, *bolus*³, top feeding⁴;
 - Local route: intra-mammary, cutaneous (ointments, sprays, etc.), *in utero*;
 - Parenteral route: injection;
 - Other routes: antibiotic administration *via* the immediate environment of animals (spraying, nebulisation, nest powder, footbath, dipping, etc.). When necessary, the maps specify the nature of the route(s).
- Antibiotic compounds were grouped together by class**, with some sub-classes being distinguished due to different antimicrobial resistance mechanisms or trends (Table):

Table 5: Classification of compounds by class or sub-class

Antibiotic class or sub-class	Compounds listed in the inventory (not exhaustive)
Aminoglycosides 1	Streptomycin, spectinomycin, dihydrostreptomycin
Aminoglycosides 2	Gentamicin, apramycin, neomycin, kanamycin
Beta-lactams 1	Penicillins, amoxicillin, ampicillin cloxacillin, nafcillin
Beta-lactams 2	1 st -2 nd generation cephalosporins
Beta-lactams 3	3 rd -4 nd generation cephalosporins
Quinolones	Flumequine, oxolinic acid
2 nd and 3 rd generation quinolones	Fluoroquinolones
Lincosamides	
Macrolides 1	Spiramycin, tylosin, erythromycin
Macrolides 2	Tulathromycin, tilmicosin, gamithromycin, tylvalosin, tildipirosin
Other sulfonamides	Sulfonamides
Polypeptides	Bacitracin, colistin
Phenicols	
Pleuromutilins	Tiamulin
Rifampicin	
Tetracyclines	Tetracycline, chlortetracycline, doxycycline, oxytetracycline
Trimethoprim sulfonamide (or sulfonamide-TMP)	
Furans	
Human antibiotics	miscellaneous (nitroimidazoles, etc.)

³ Large pill administered to an animal orally using a balling gun

⁴ Sprinkling medicated premix onto food

- **Treatment duration:** the Working Group agreed to use 'long treatment' to refer to a period of administration of more than 14 days. The aim was to identify long-acting treatments or long treatment periods, while distinguishing them from treatments with medicated feedstuffs (generally two weeks in duration, corresponding to the time taken to empty a feed silo in farms); these treatments with medicated feedstuffs were also identified (route of administration).

This definition adopted by the Working Group for the needs of the assessment is different from a more conventional definition: indeed, in MAs, standard short treatments are around five days long and no more than one week long. Thus, in contrast, a conventional long treatment is one that lasts one week or more.

- **Frequency of use:** the experts were asked to qualitatively estimate frequency of use according to the following scale:
 - 'exceptional' → +
 - 'rare' → ++
 - 'occasional' → +++
 - 'frequent' → ++++
 - 'very frequent' → +++++

This estimation was undertaken by expert consensus in sub-groups of species.

4.1.2.2 Mapping: an overview of uses by sector

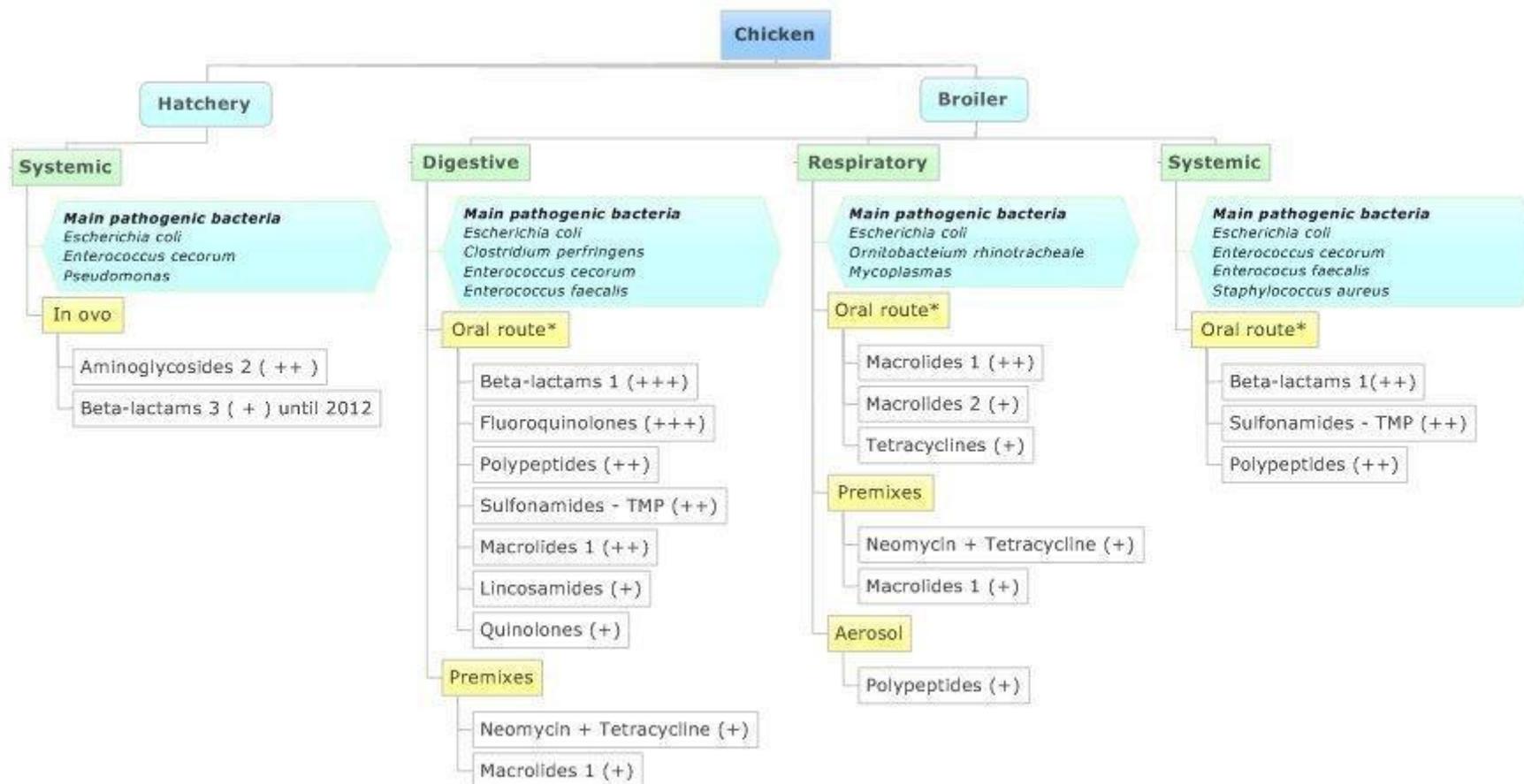
In addition to the 'working tool' objective, the inventory undertaken when handling this request was also depicted in graphic form as maps providing an overview of the main uses identified in the various sectors (see below).

These maps do not claim to be exhaustive. More occasional practices that are still of interest given the risk of antimicrobial resistance developing have been analysed and taken into account in the descriptive texts accompanying the maps.

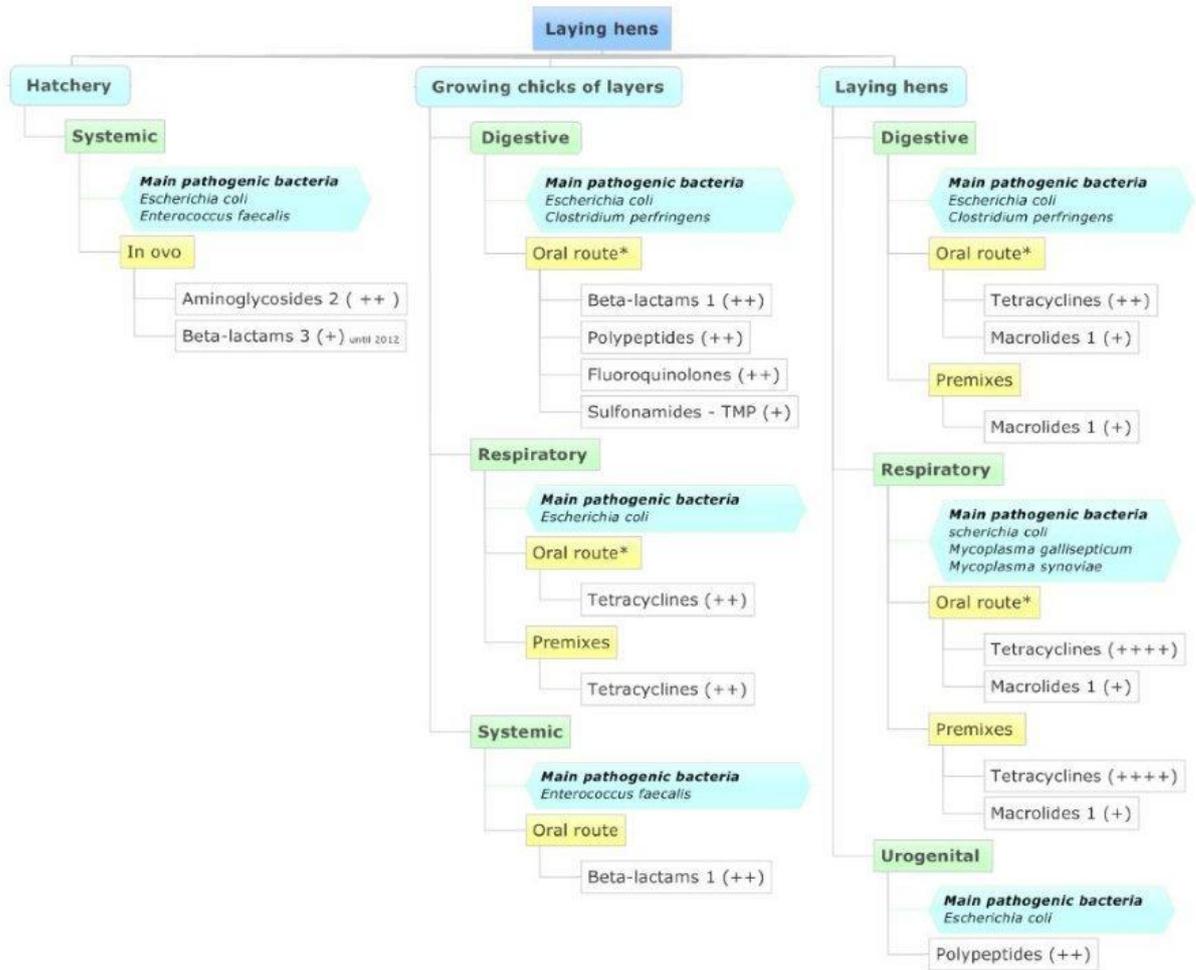
Furthermore, these maps do not show all of the information collected during the inventory for each mode of use, for readability reasons. In particular, the treatment type (preventive, metaphylactic, curative) is not specified. This mode was analysed thoroughly in the assessment of at-risk modes of use in Section 5 of the Report.

These concise overviews were then intended to be compared with the ten-year results of monitoring tools for antibiotic sales and the resistance of pathogens and commensal flora when such information was available. The following presentations illustrate this information for each sector (or animal type).

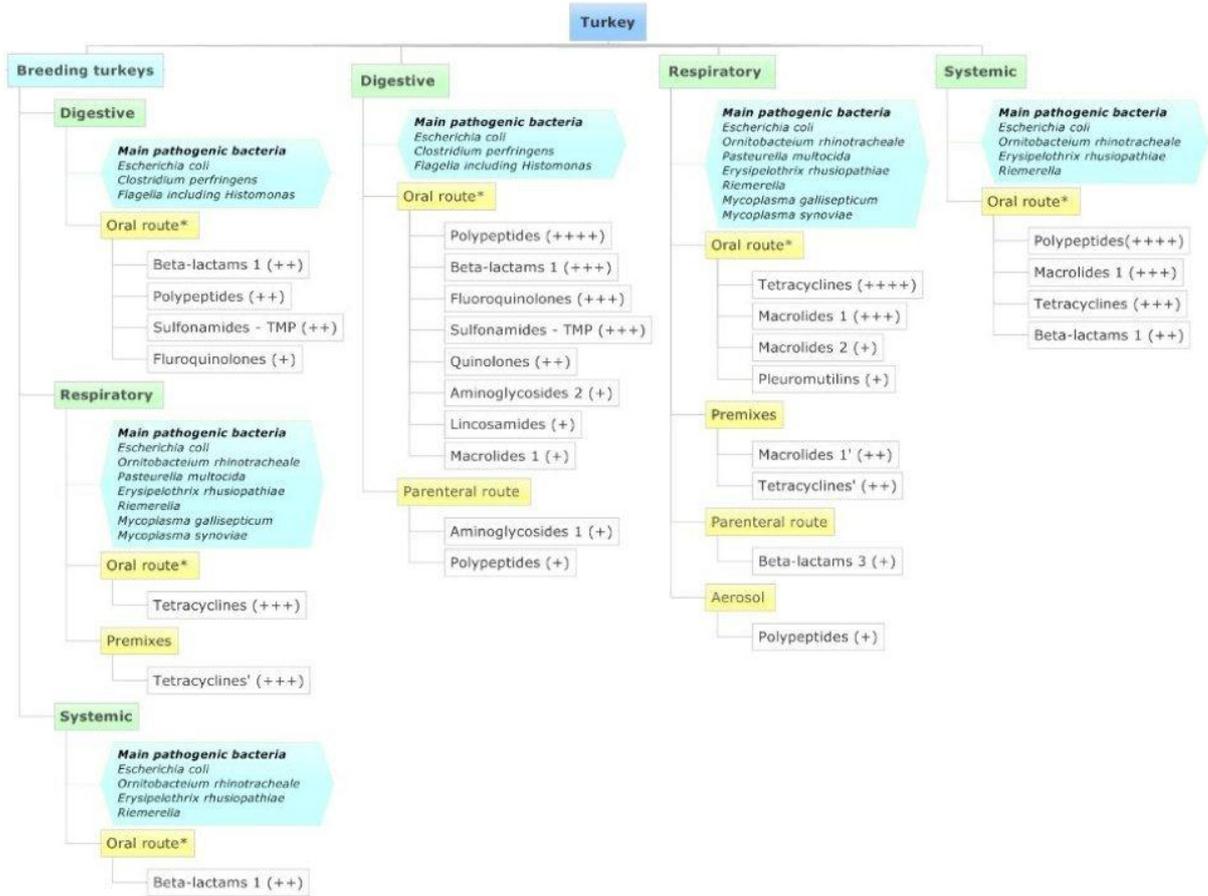
Map 1: Chickens



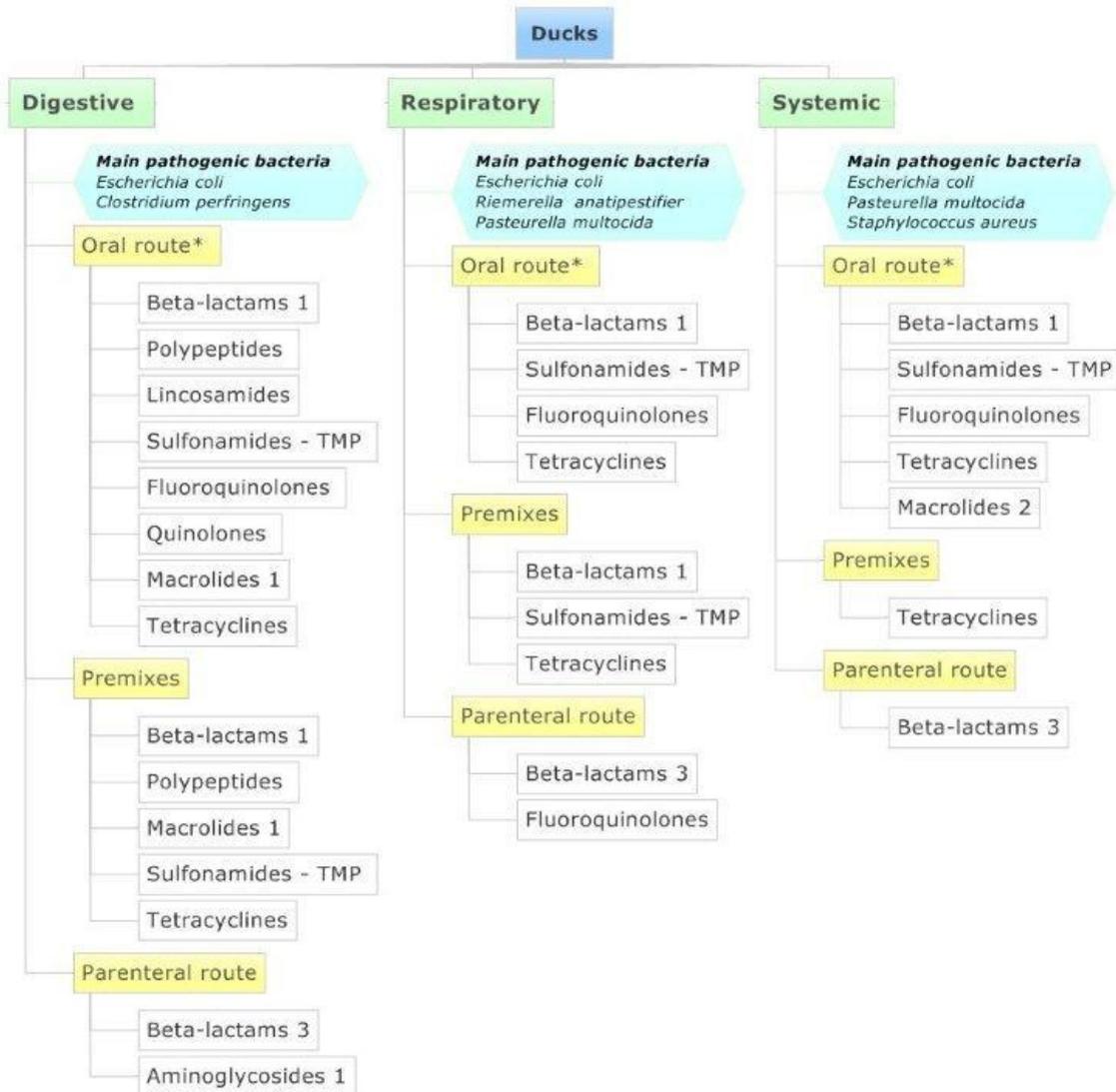
Map 2: Laying hens, all types of production and table eggs



Map 3: Turkey

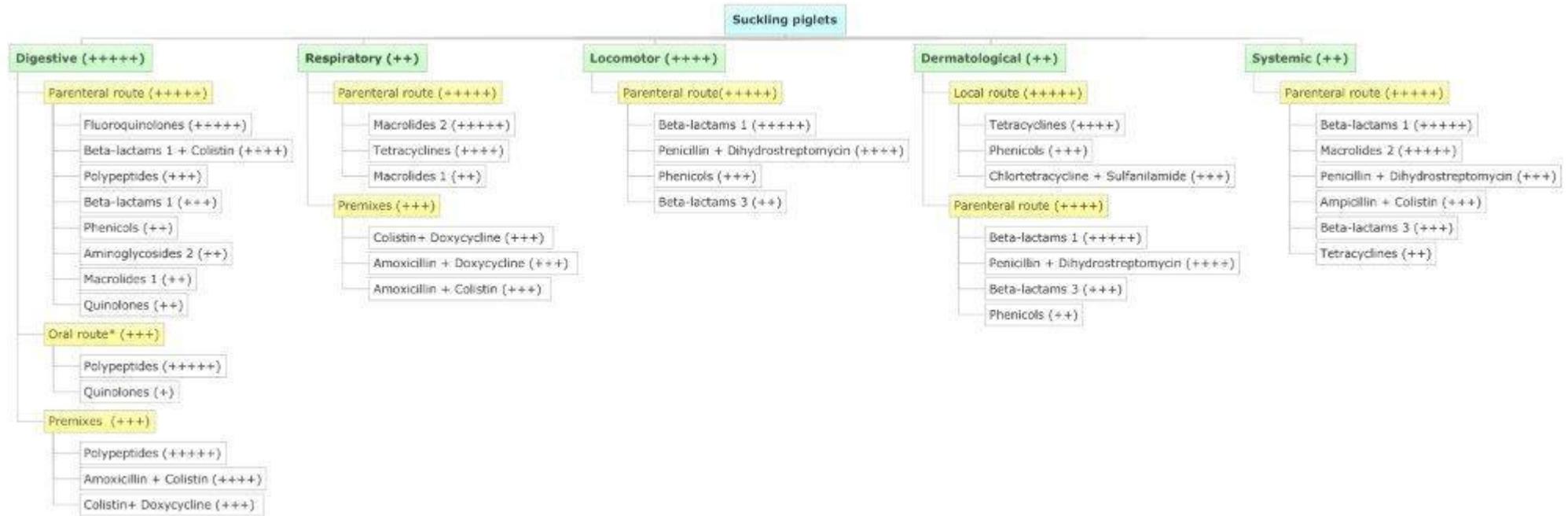


Map 4: Duck species*

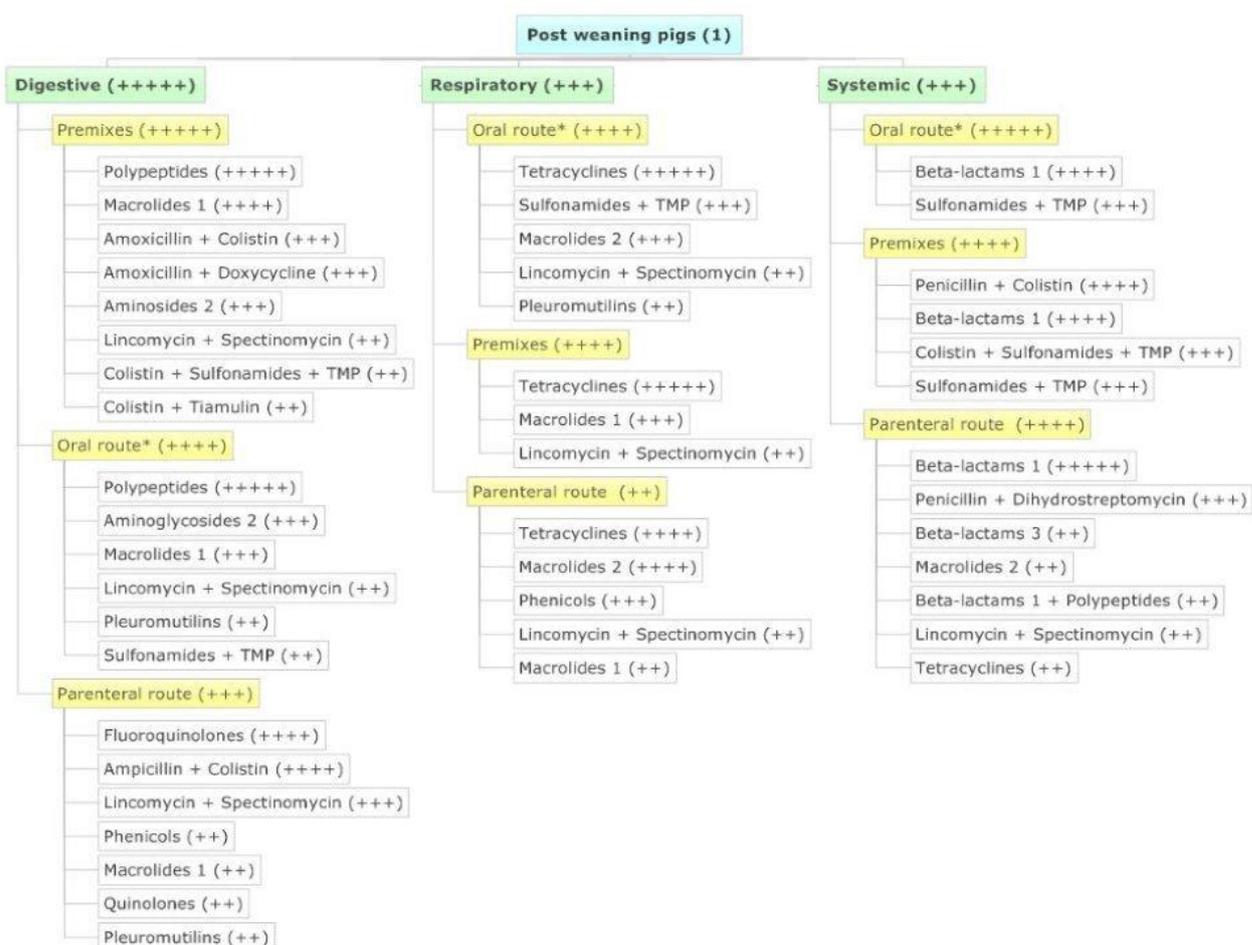


*The Expert Group had limited competence on fattened duck farms. They could not be more accurate on this sector that could be the subject of a more in-depth study taking into account the recommendations of this report.

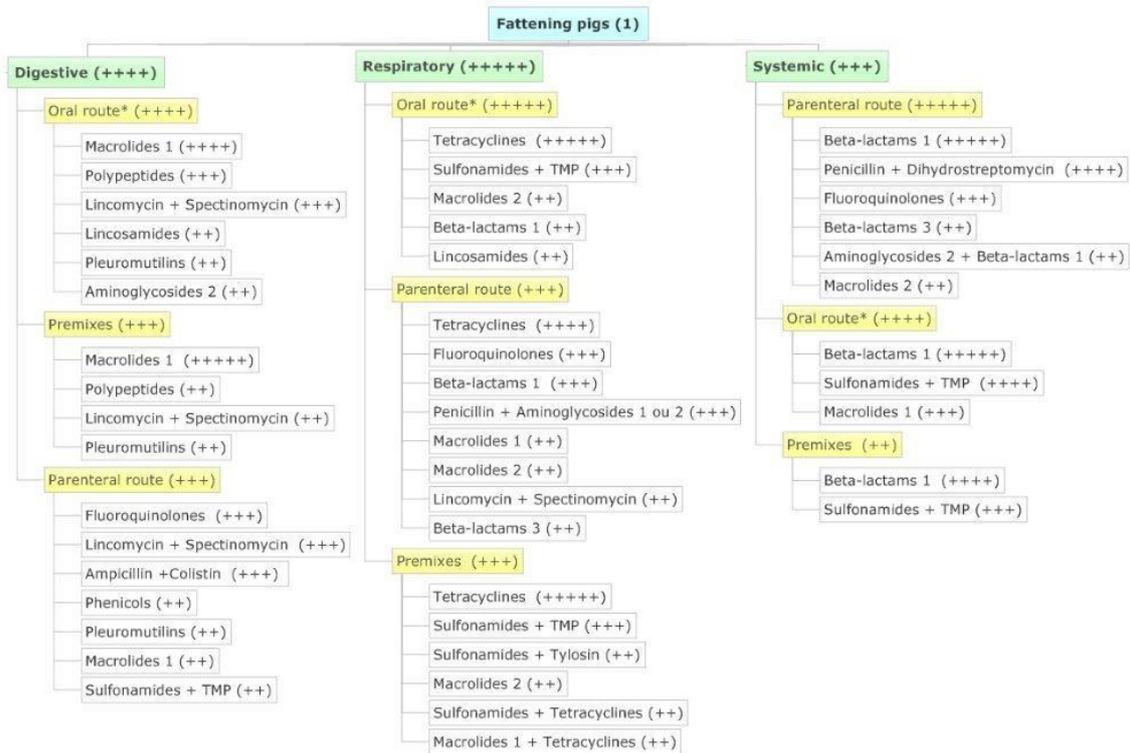
Map 5: Suckling piglets



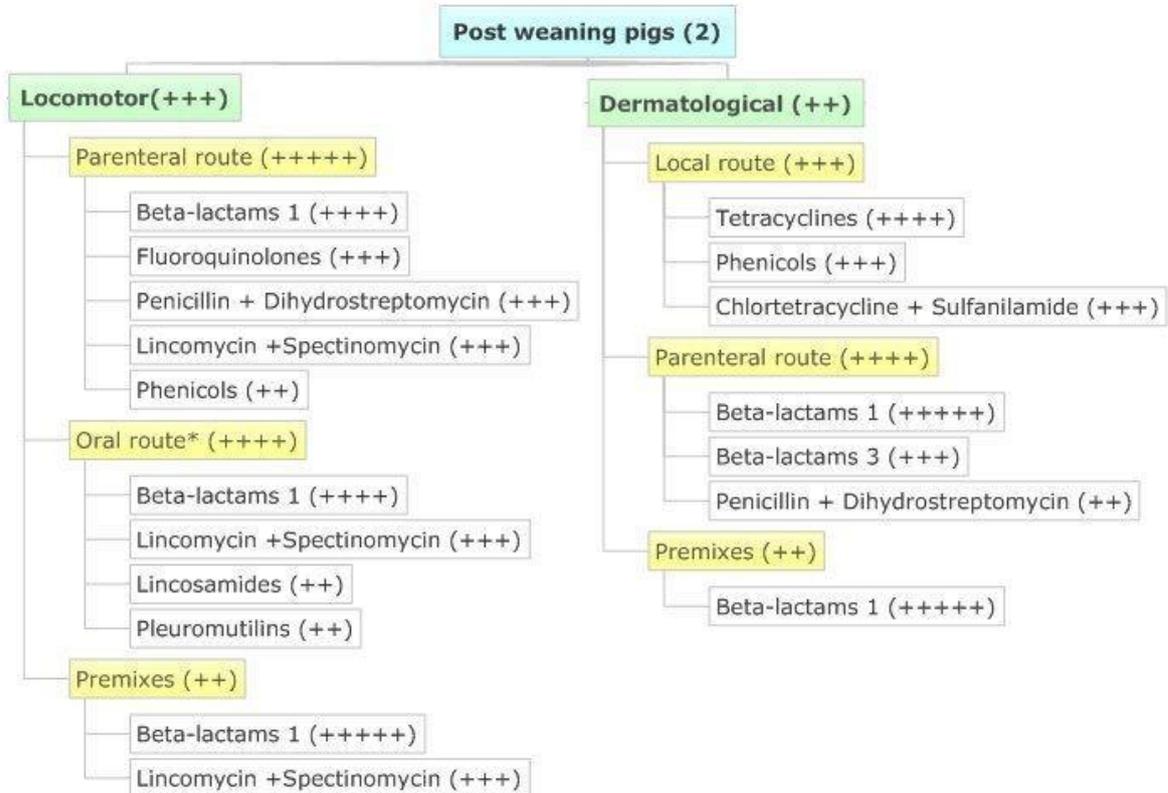
Map 6: Post-weaning pigs – Digestive, respiratory, systemic



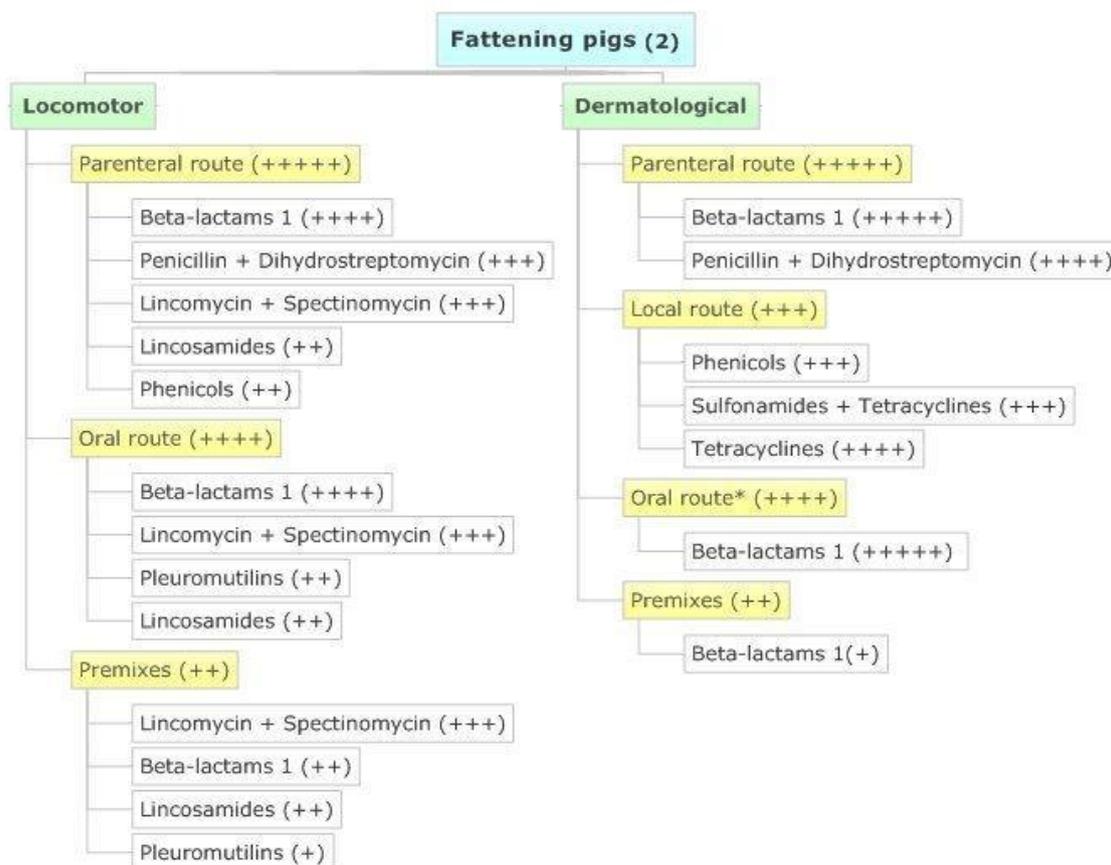
Map 7: Post-weaning pigs – Locomotor, dermatological



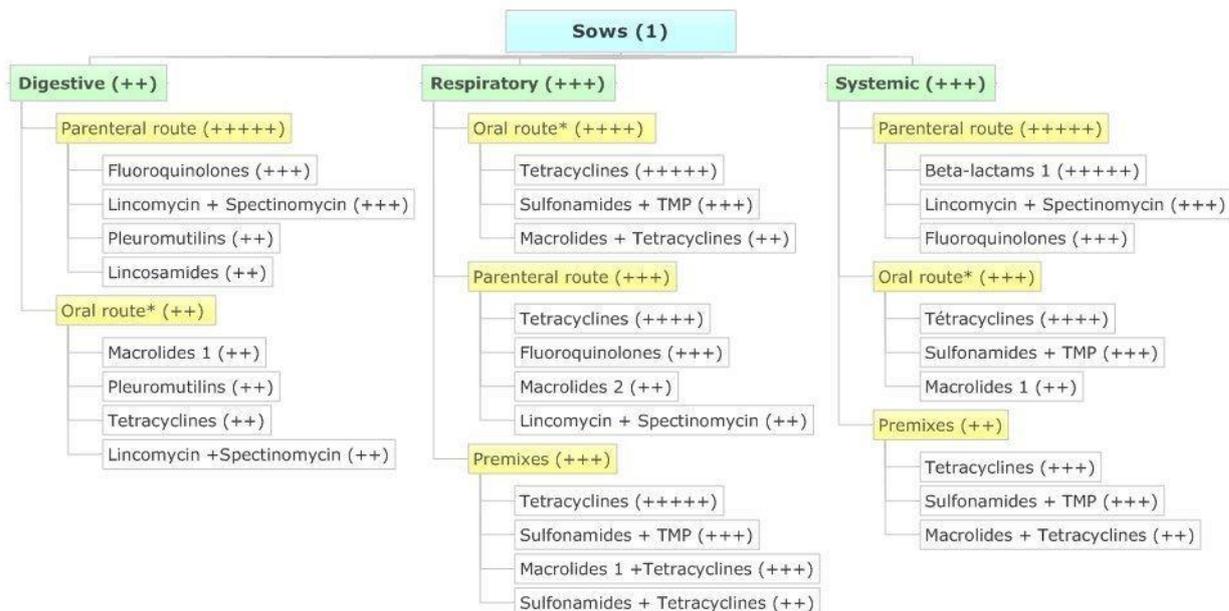
Map 8: Weaning pigs - Digestive, respiratory, systemic



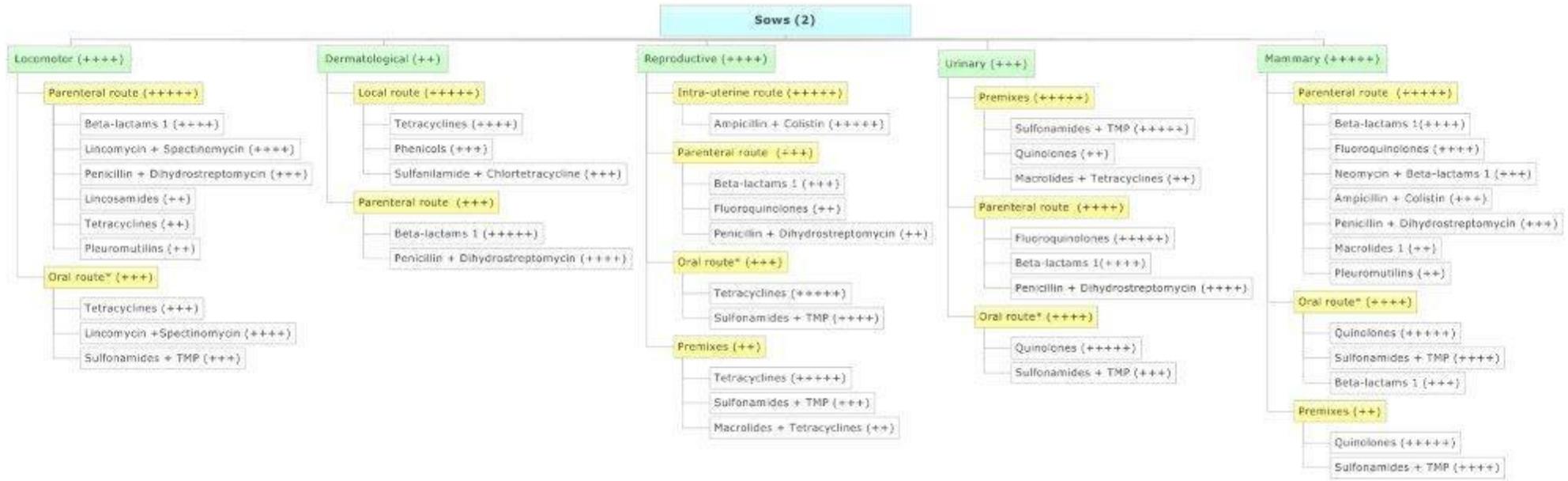
Map 9: Fattening pigs - Locomotor, dermatological



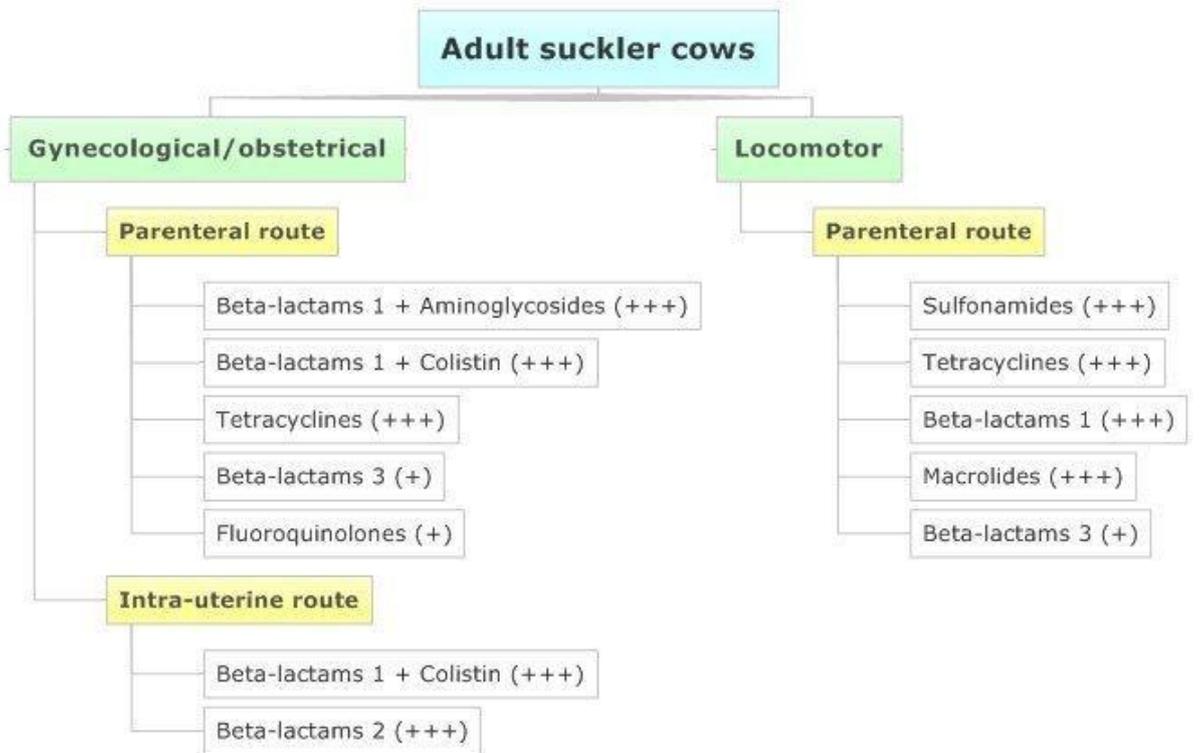
Map 10: Breeding pigs - Respiratory, systemic



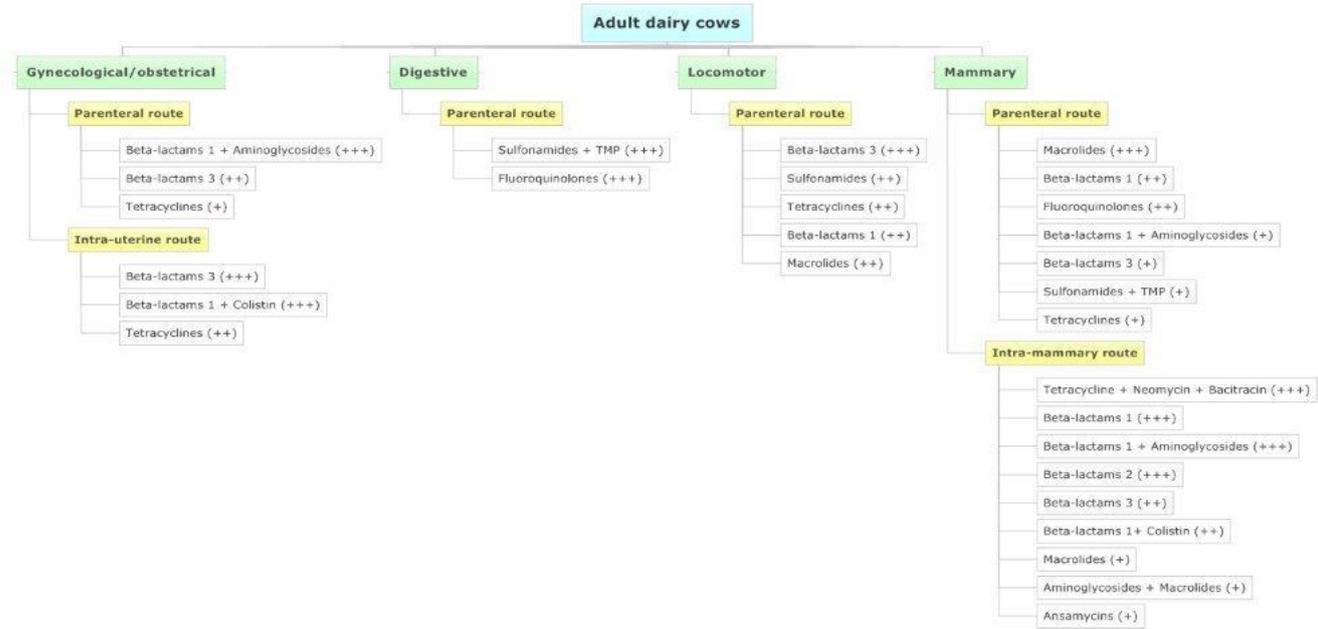
Map 11: Breeding pigs - Locomotor, uro-genital, dermatological



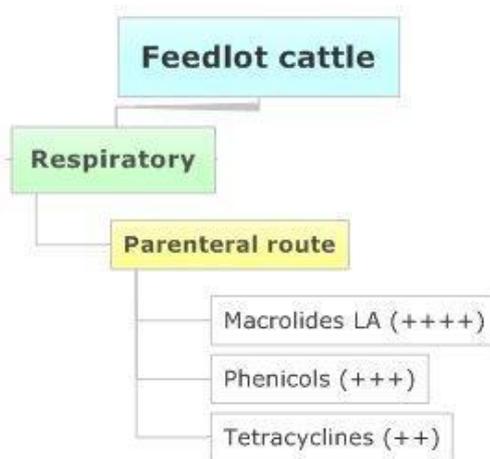
Map 12: Adult suckler cows



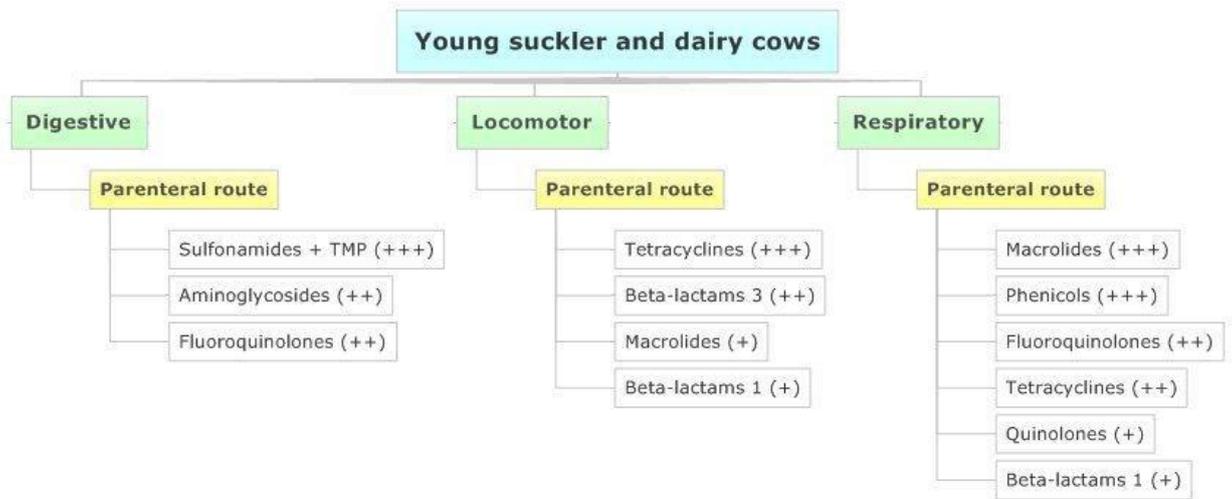
Map 13: Adult dairy cows



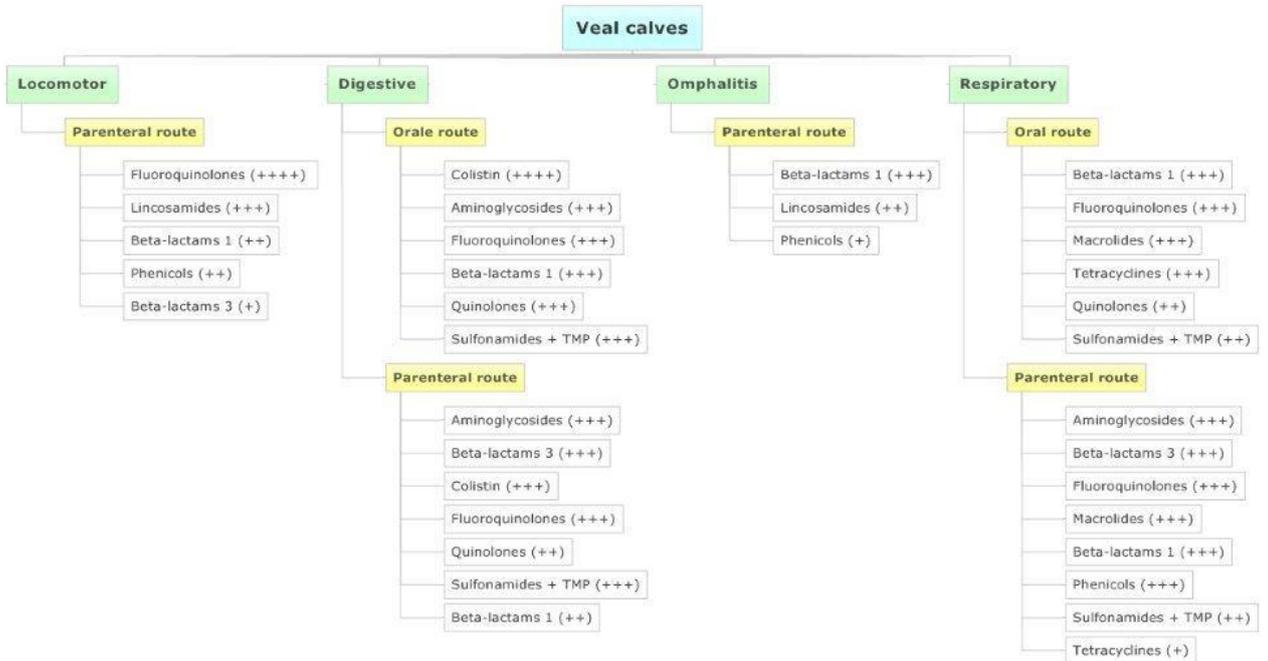
Map 14: Feedlot cattle



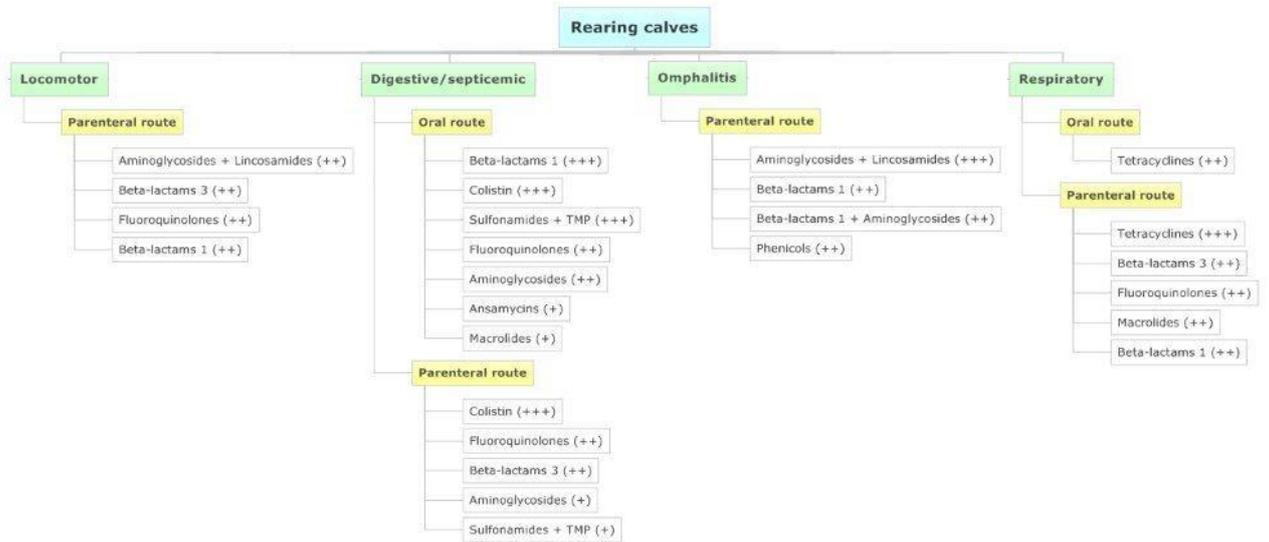
Map 15: Young suckler and dairy cows



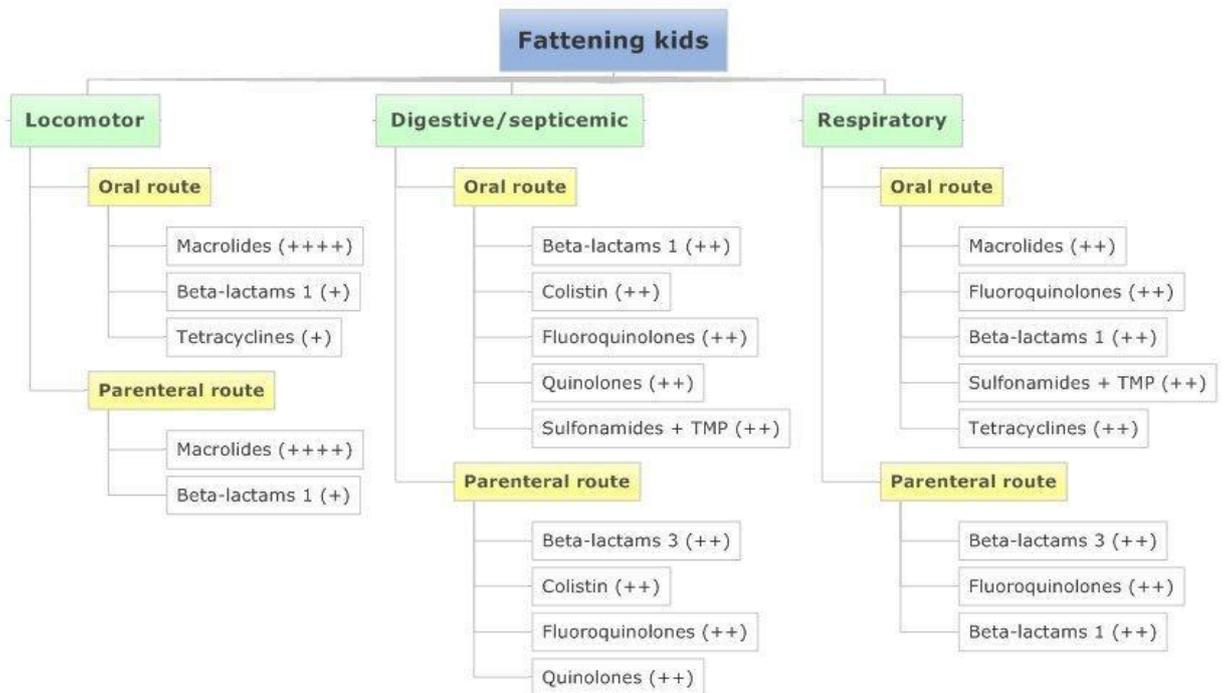
Map 16: Veal calves



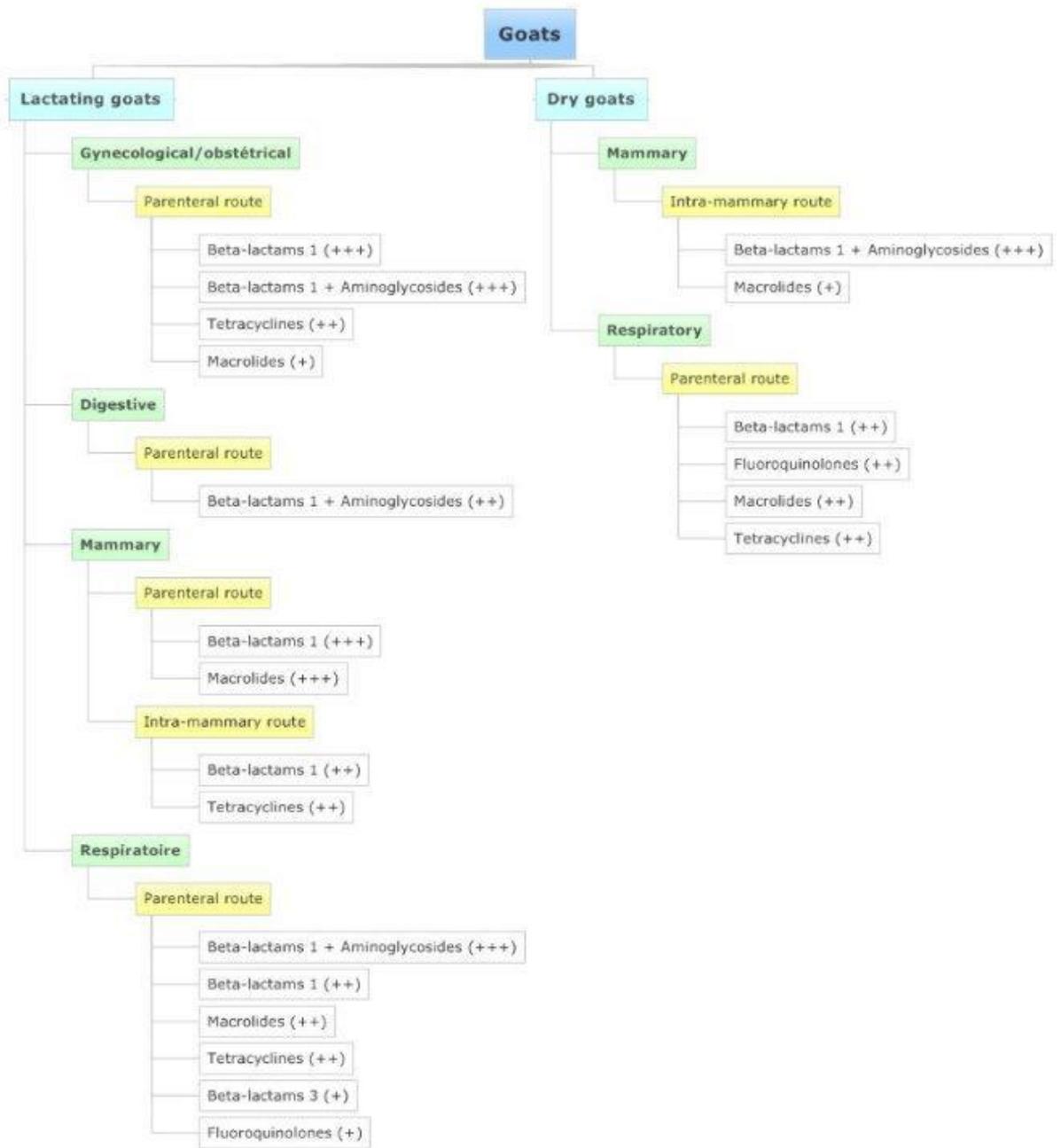
Map 17: Rearing calves



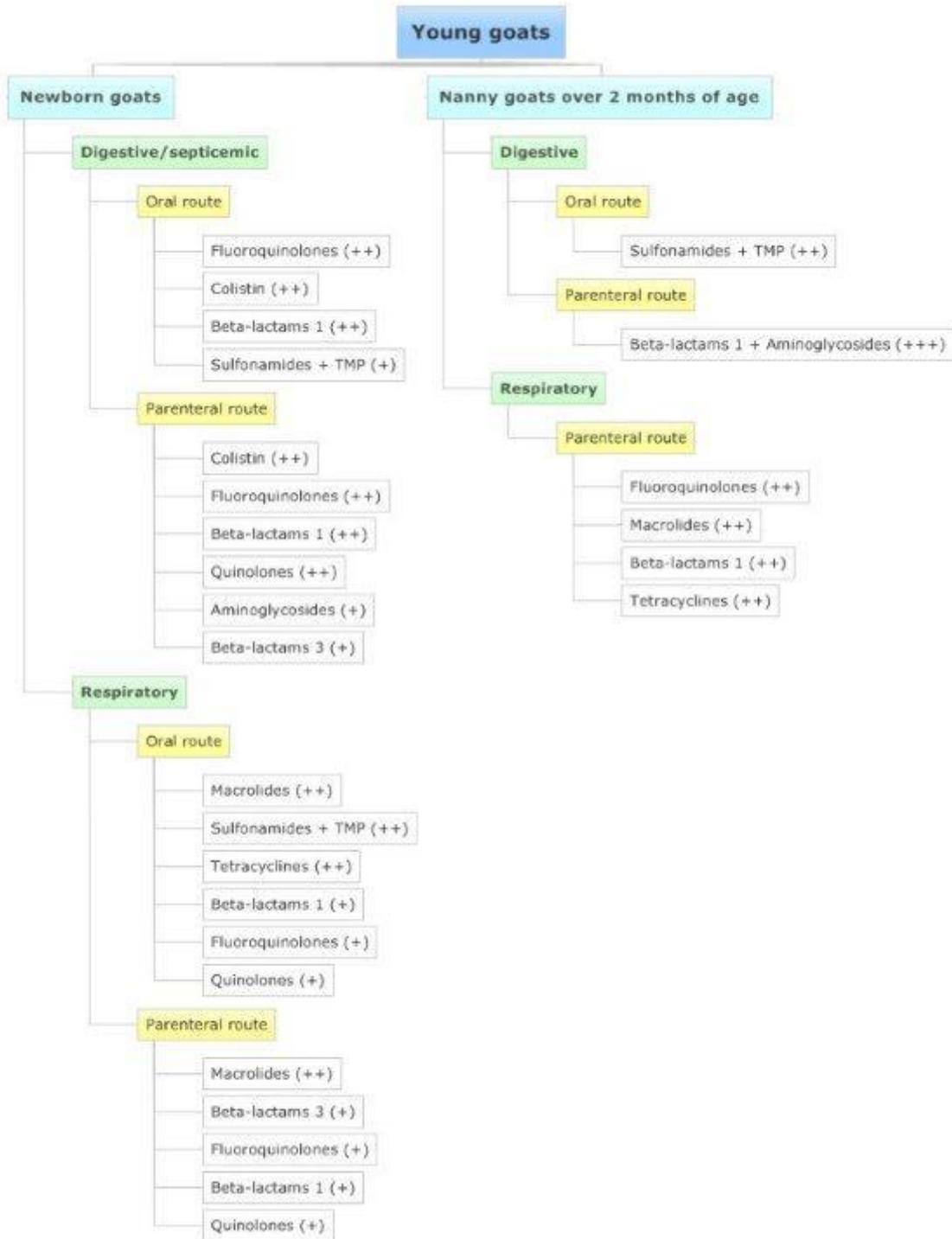
Map 18: Fattening kids



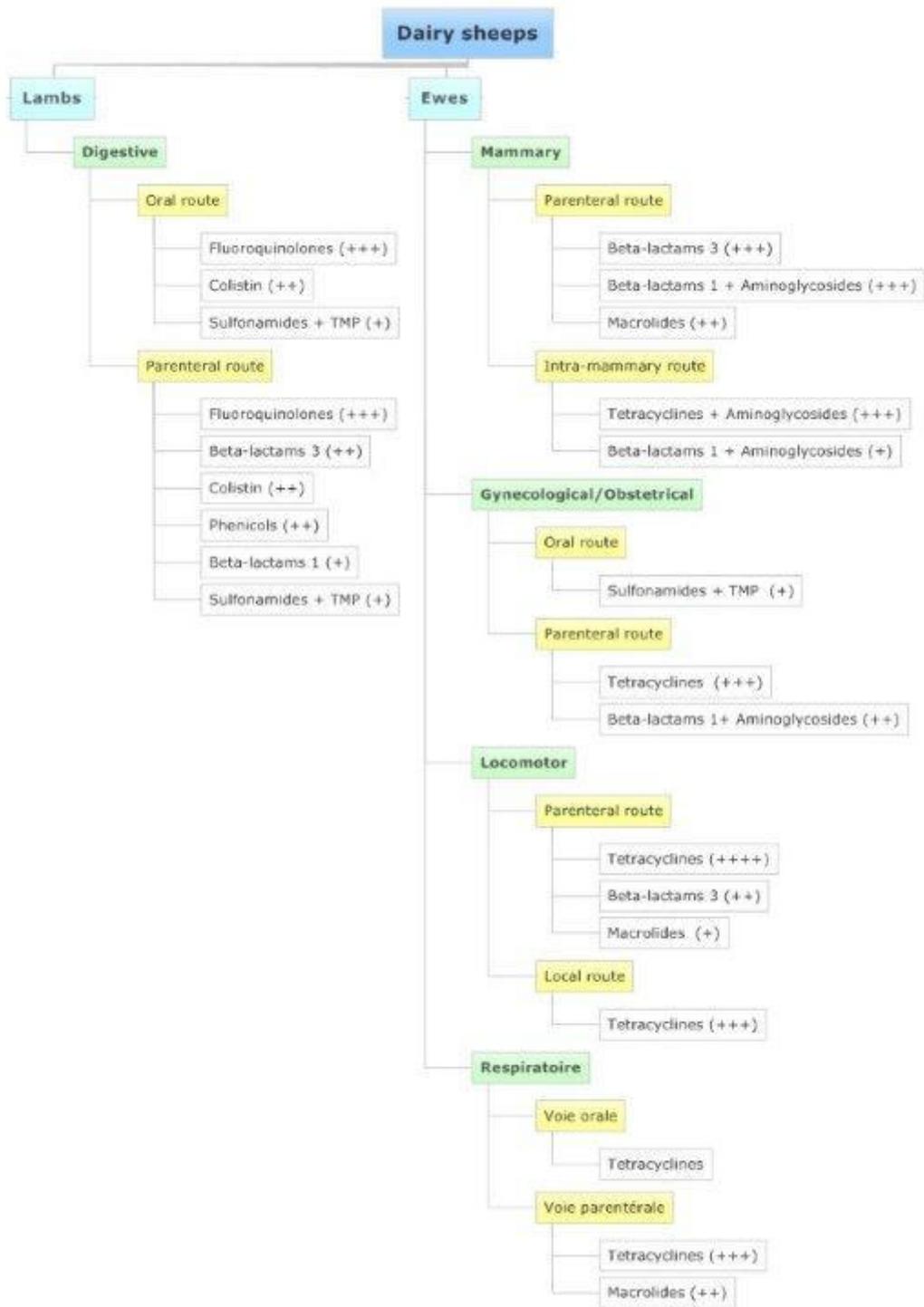
Map 19: Goats



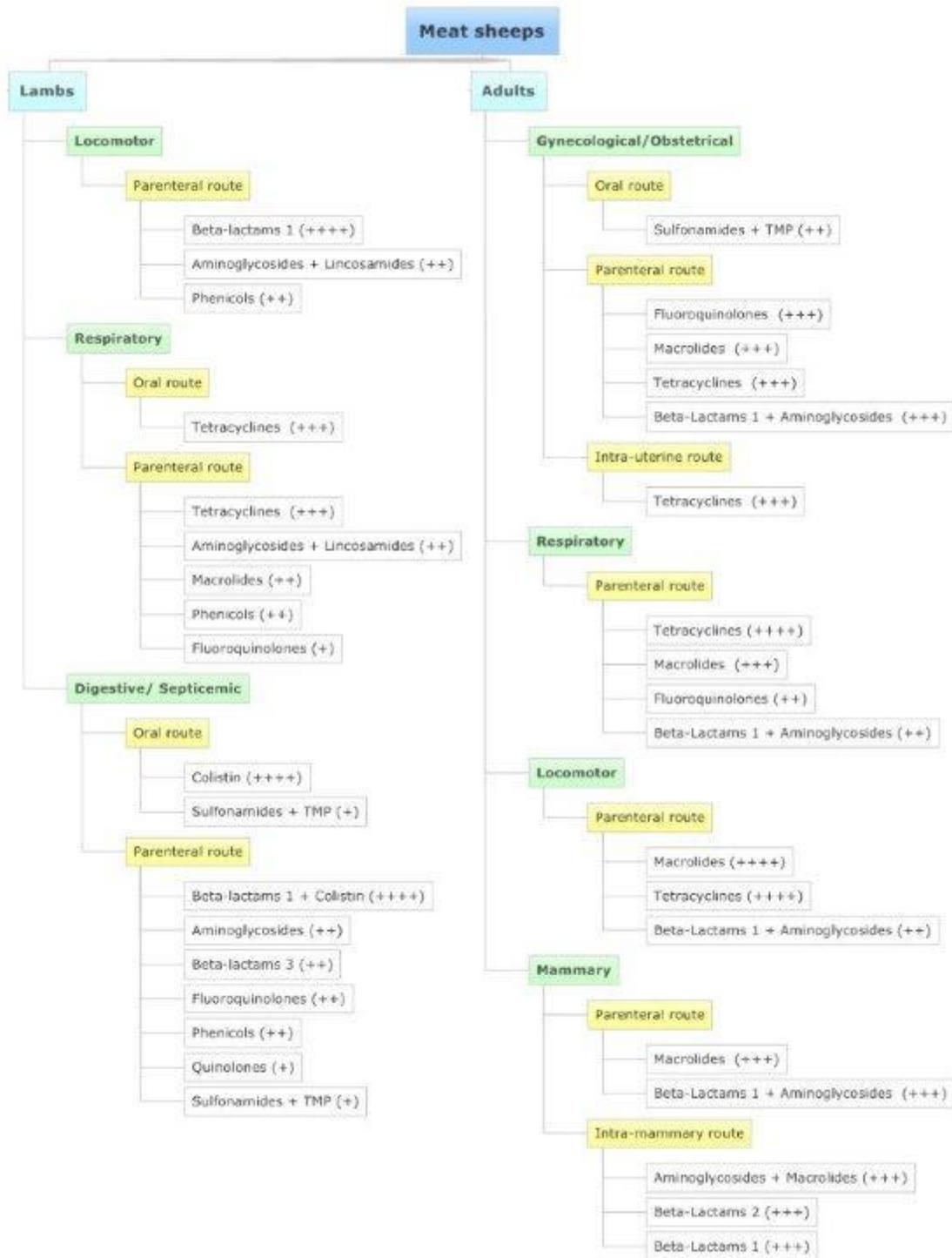
Map 20: Newborn and nanny goats over 2 months of age



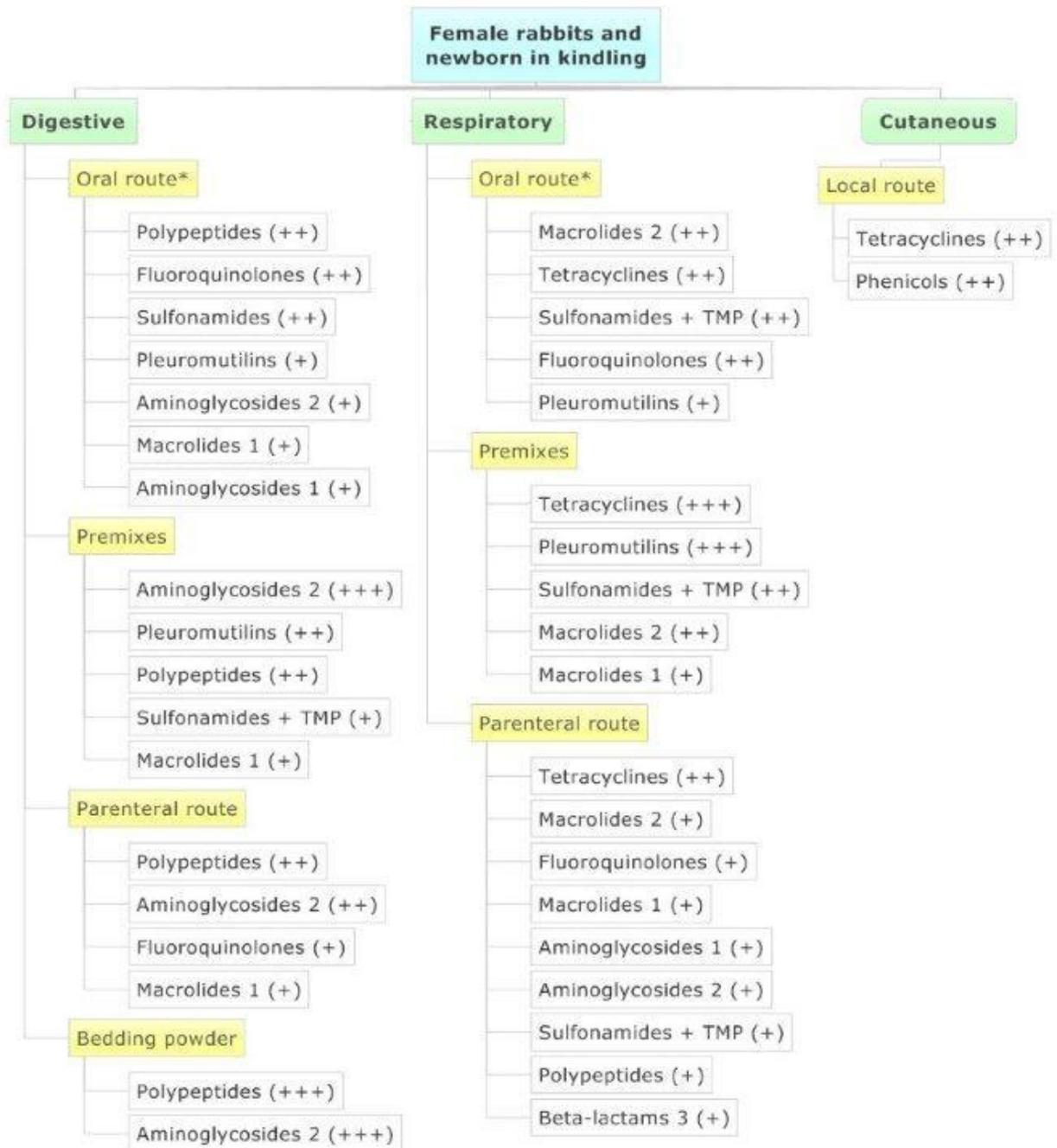
Map 21: Dairy sheep



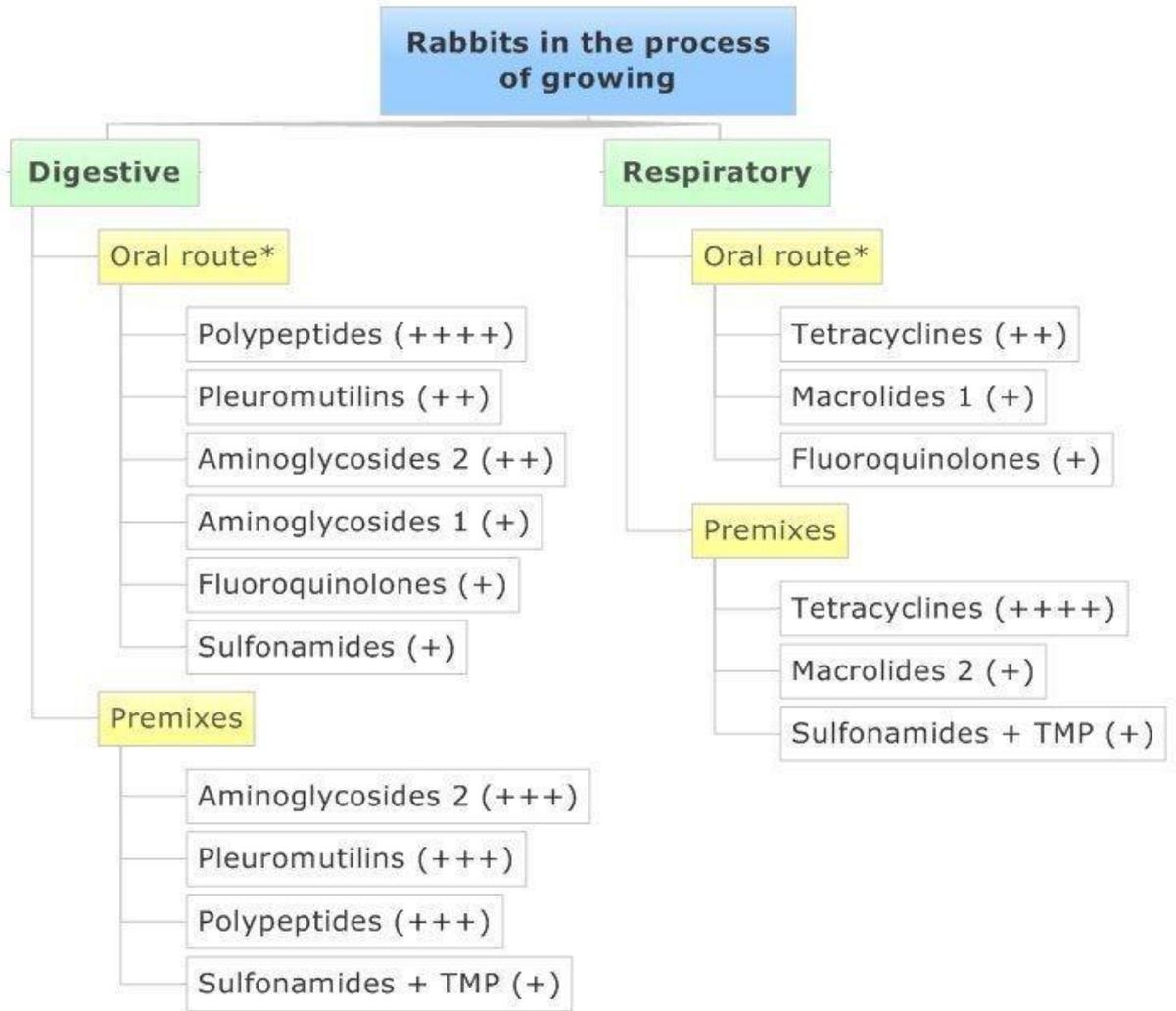
Map 22: Meat sheep



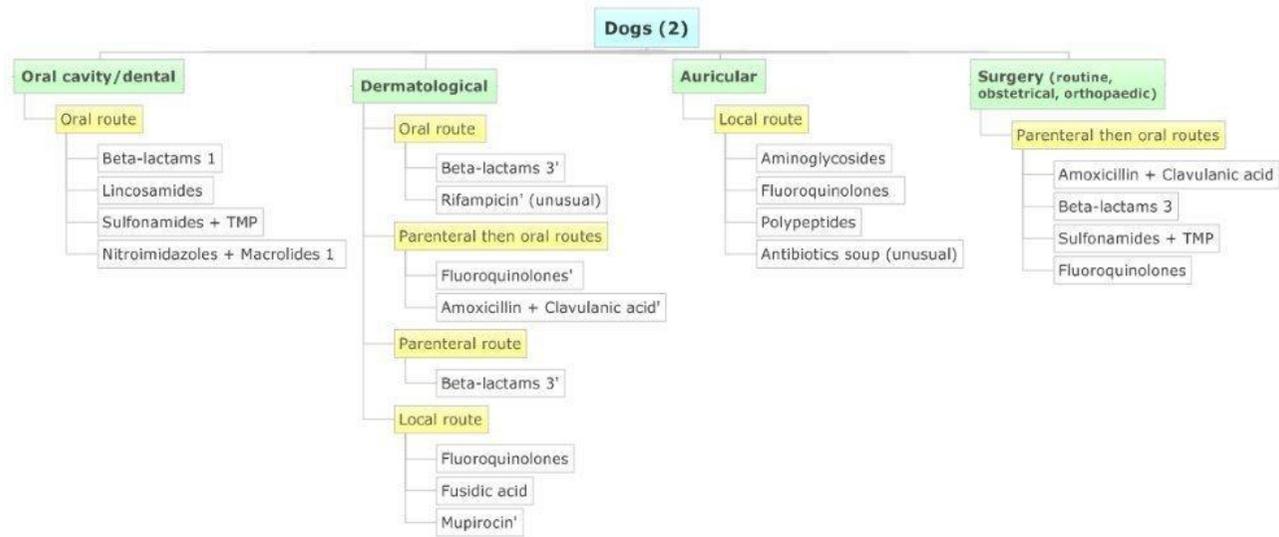
Map 23: Female rabbits in kindling



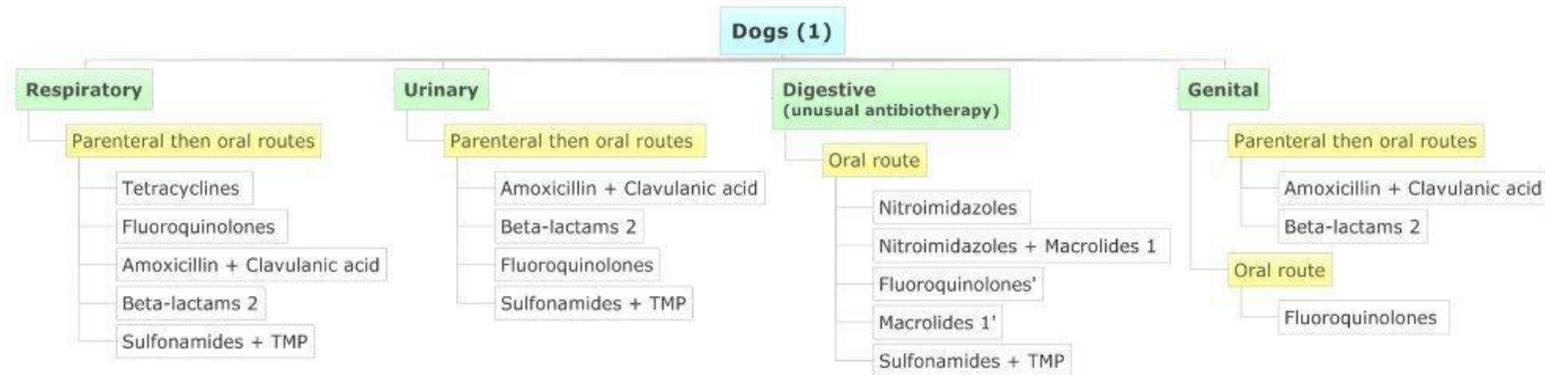
Map 24: Rabbits in the process of growing



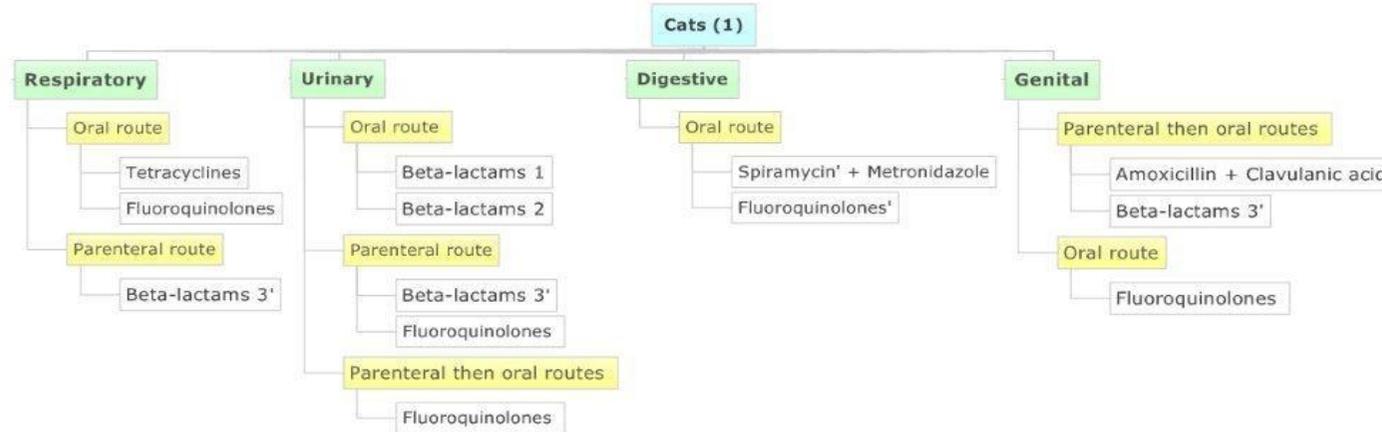
Map 25: Dogs - Digestive, respiratory, urinary, genital



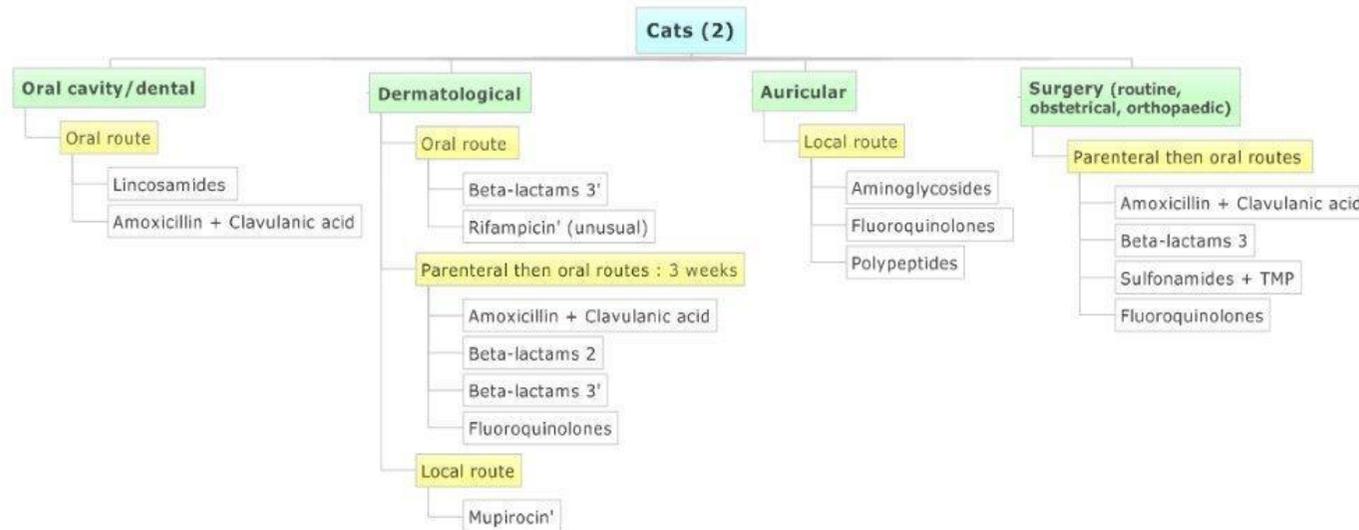
Map 26: Dogs – Oral cavity/dental, dermatological, auricular, surgery (2)



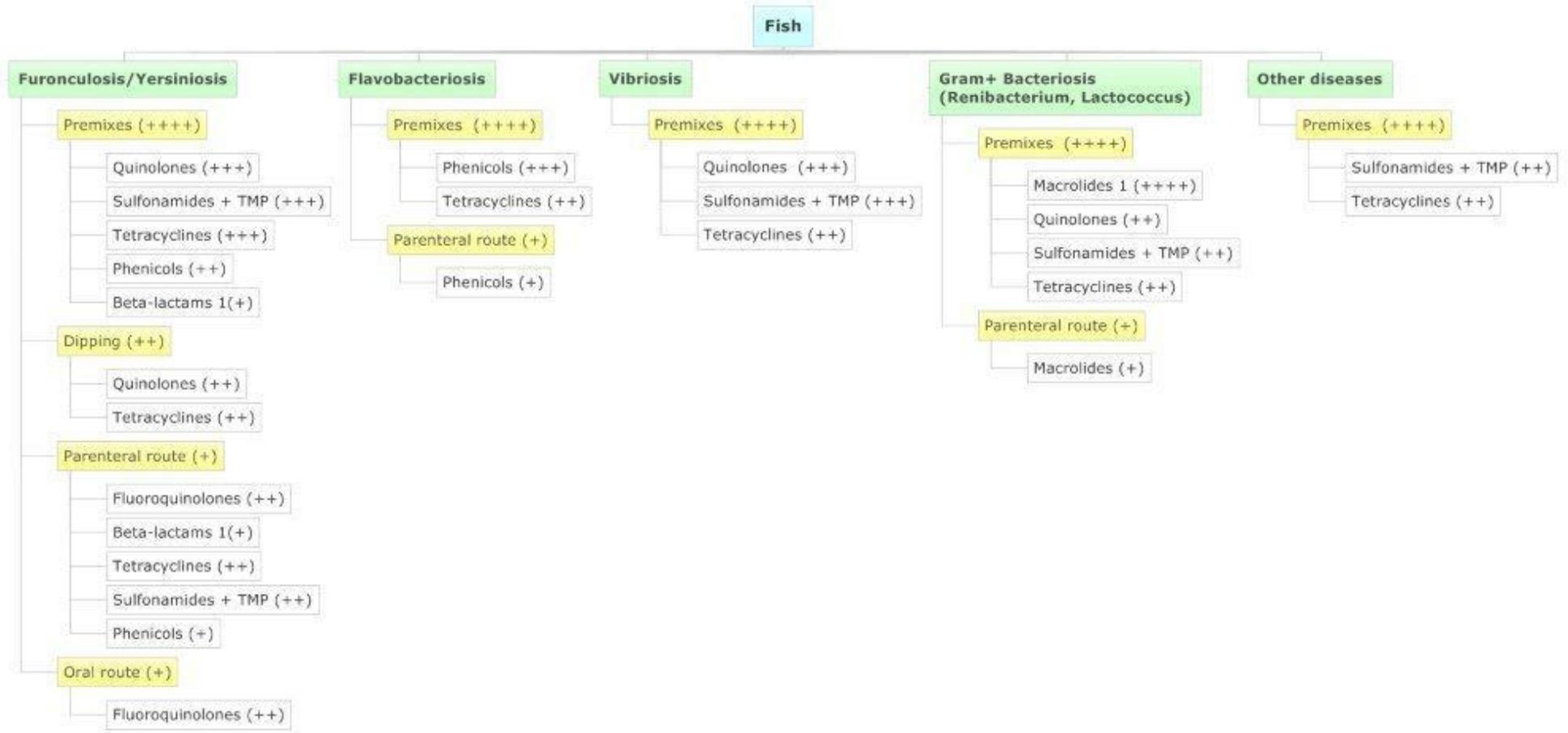
Map 27: Cats - Digestive, respiratory, urinary (1)



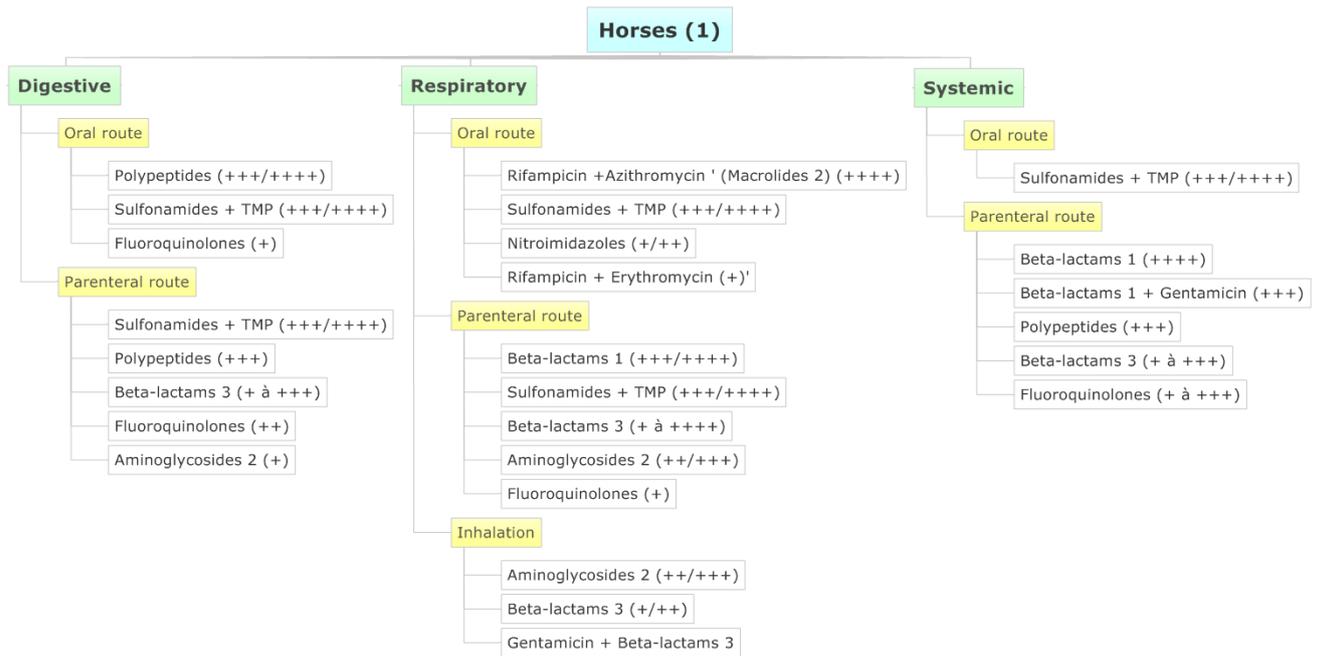
Map 28: Cats – Genital, oral cavity, dermatological, auricular, surgery (2)



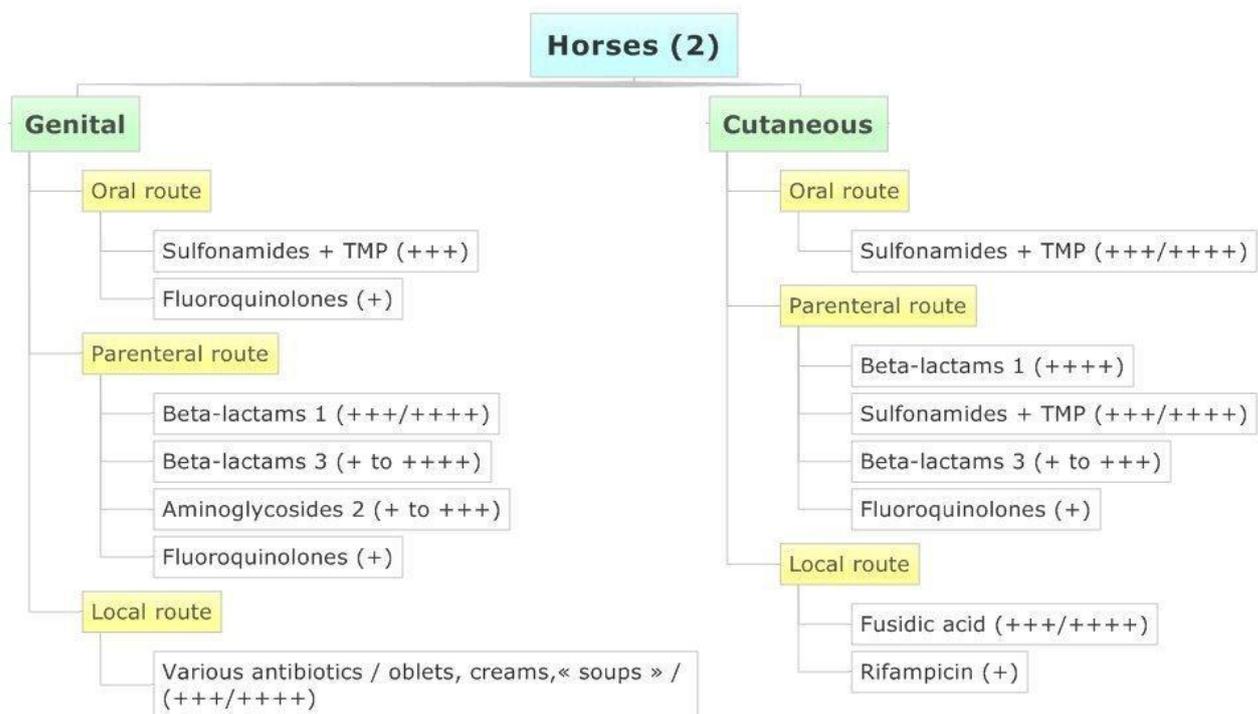
Map 29: Fish



Map 30: Horses (1) - Digestive, respiratory, systemic



Map 31: Horses (2) – Genital, cutaneous



5 Assessment of at-risk practices

This section assesses the risk of antimicrobial resistance emerging and developing in relation to modes of antibiotic use in veterinary medicine.

For the purposes of this risk assessment, the hazard is the resistance determinant that emerges as a result of the use of a specific antimicrobial in animals. This definition reflects the development of resistance in a species of pathogenic micro-organisms, as well as the development of a resistance determinant in non-pathogenic commensal bacteria that may be passed to other species of micro-organisms.

The conditions under which this hazard might produce adverse consequences include any scenarios through which humans or animals could become exposed to a pathogen which contains that resistant determinant, fall ill and then be treated with an antimicrobial that is no longer effective because of the resistance (OIE, 2013).

Thus, the unfavourable consequences of antibiotic use in veterinary medicine can be divided into the following four areas:

- ✓ Human health: decrease in the efficacy of certain classes of antibiotics required to treat infectious diseases in humans, selection of multi-resistant zoonotic bacteria, spread of resistance mechanisms;
- ✓ Animal health: increase in the resistance of certain bacterial species to certain classes of antibiotics, thus reducing the available therapeutic arsenal;
- ✓ Commensal flora: imbalance in the digestive, cutaneous and urogenital flora benefiting bacterial species that are naturally resistant or have acquired resistance and spread of resistant bacterial species in the exterior environment;
- ✓ Environment: the environmental release of antibiotics or metabolites in active form can be a factor in the imbalance of the bacterial ecosystem of soils, plants and the aquatic environment. That said, the internal request did not specifically take into account this hazard, insofar as knowledge of this issue still primarily falls within the sphere of scientific research.

The risk assessment methodology adopted by the Working Group took into account these various points (see Section 4.2.1).

While this assessment stage made it possible to identify and survey 'at-risk practices' in terms of antimicrobial resistance among the various modes of antibiotic use in veterinary medicine, the Working Group would like to stress the particular relevance of factors that either promote the introduction and/or development of bacteria on farms, thus increasing antibiotic use, or else result in 'poor practices' in antibiotic use. The former can be grouped under the concept of 'risk factors in the occurrence of diseases' and the latter can be considered constraints (technical, economic, sociological or regulatory) leading to poor practices. The experts underline the relevance of taking into account all of these promoting factors, which need to be reduced just as much as the 'at-risk' practices themselves.

5.1 Identification of risk factors in the occurrence of diseases

The general, zootechnical and environmental conditions of farms have a major impact on health. Many diverse factors contribute to the occurrence of bacterial diseases in a production unit and their significance varies considerably in terms of risk. The frequency at which antibiotics are used is inseparable from these risk factors. These risk factors are synergetic and determine a farm's degree of vulnerability to bacterial (and viral) infections.

Risk factors have been consolidated into six points:

- farm management;

- microbial contamination of animals at the 'top of the pyramid'⁵;
- at-risk phases (stages) of production;
- clustering of animals;
- transport of animals;
- level of hygiene and biosafety measures.

5.1.1 Farm management

5.1.1.1 Types of farms

Regardless of the sector, the type of farm influences the course of infections and therefore potentially the frequency at which antibiotics are used. For example:

- On pig farms, having all representative physiological stages of production (farrow-to-finish) on the same site is a health risk factor. However, batch management and all-in/all-out production, which have become essential, limit this risk factor.
- Conversely with poultry, due to the pyramid structure of the sector, there are almost no multi-age and/or multi-species sites and all-in/all-out systems are predominant, reducing this health risk.
- For rabbits, there are three types of farms in France in which management of the environment and microbism is more or less easy:
 - The kindling cage + fattening type: the females are constantly kept in the kindling cage. At weaning, the kittens are transferred for fattening to confined, free-range (steel) or semi-free-range (covered or not, latticed or steel cages in a shed with static ventilation) facilities. These buildings were often designed before the advent of artificial insemination and single-batch management. Environmental management in free-range and semi-free-range buildings is not easy. Keeping females in kindling cages makes a real fallow period impossible and limits cleaning-disinfection operations. In the worst of cases, cleaning operations can be a triggering factor in respiratory disease, particularly in cold periods by introducing excess moisture in the animals' environment.
 - The 'mixed' single compartment type: breeding does and bucks are kept in the same building either with separate sectors for kindling and fattening or with multi-purpose cages (all-in/all-out system). In this system, the animals are better protected from the exterior environment but the same challenges as for the previous type are encountered where it is not possible to have a real fallow period.
 - The all-in/all-out type: there are two rooms or two buildings, often identical, in which breeding does and fattening rabbits are farmed alternatively since the cages are multi-purpose and can accommodate either a doe with her nest or young fattening rabbits from weaning to slaughter (single-batch management). At weaning, all of the breeding does are moved to the other room (or building) and the fattening rabbits remain in the room where they were born. Under this system, which is more recent, there can be a real fallow period after each breeding cycle.
- In general, farm size and animal density can also influence the course of infections (see Section 2.1). The management of large farms, with high animal densities, requires specific human and technical resources to control risk factors for infection.
- Some animal sectors use fewer antibiotics than others (Pavie *et al.*, 2012). These sectors, in which antibiotic therapy is limited by production specifications, could be studied from a pharmaco-epidemiological standpoint in order to provide lines of thinking on preventive measures with the aim of reducing antibiotic use in veterinary medicine;

⁵ The top of the pyramid in a sector is the nucleus breeding herds.

5.1.1.2 Water and Diet

Diet is often a key factor in controlling the general health of animals. Poorly managed diets can have consequences on the occurrence of diseases on farms. For example:

- ✓ In the pig sector, the dietary management of breeding stock should optimise reproduction, a key factor in farm management, and enable trouble-free birthing and the postpartum period and lactation. An appropriate diet for breeding pigs can ensure grouped births and therefore a small range of weaning ages, limit gynaecological procedures and reduce mastitis-metritis-agalactia (MMA) syndrome and arthritis in suckling piglets (competition for the teat). In this context, over the past few years, many farms have begun monitoring the fat-cover of breeding pigs by measuring back-fat and muscle thickness. This monitoring enables the feeding programme to be better tailored to the animals' needs.
The diet of piglets and fattening pigs has an undeniable impact on digestive diseases. Nutritionists currently recommend developing specially formulated feedstuffs that can be broken down more easily by the digestive flora of animals with recurring digestive problems.
- ✓ Dairy cows are exposed to metabolic diseases if dietary intake is insufficient. Metabolic disorders result in a cascade reaction of gynaecological and locomotor diseases, and consequently calf diseases.
- ✓ In the rabbit sector, feeding and nutritional programmes for breeding rabbits should be optimised in order to prevent muscle loss during reproduction cycles and keep from having a herd that is 'too fat'. For example, a diet that does not provide enough energy risks impacting post-weaning viability while one that provides too much energy can be a factor in the onset of mastitis or reduced fertility. Higher energy feeding programmes may promote the clinical expression of pathogenic *E. coli*.
In fattening rabbits, the practice of limiting food intake (quantity-controlled meals) is widespread since it improves control of epizootic rabbit enteropathy (ERE). At the same time, compliance with the nutritional recommendations and more specifically minimum fibre intakes helps reduce the risk of digestive problems.

Water and food can also be vehicles for bacteria on farms if their sanitary quality is not controlled.

5.1.1.3 Buildings – Equipment – Environment

The type of farm building and its design, age, technical capacities for environmental management and convenience with regard to the application of biosafety measures also influence the course of infections and therefore potentially the frequency at which antibiotics are used, irrespective of the sector.

For example, risk factors for respiratory diseases such as building design defects and bad environmental management are common to all production types.

The environment has a significant impact, not only on respiratory diseases but also on digestive diseases.

Another example: specific risk factors for mammary infections depend on the type of housing and litter (e.g. straw bedding – risk / *Streptococcus uberis*), the type of milking parlour and the proper functioning of the milking machine.

In the rabbit sector, equipment investments have limited the expression of certain diseases and therefore antibiotic use. For example, sitting boards have limited the expression of pododermatitis.

These various factors are highly dependent on another factor, described below, which is the economic context of a specific farm or the sector in general.

5.1.2 Microbial contamination of top-of-pyramid animals

Animal health is highly dependent on the health of breeding stock, since in pig farming for instance, most pathogens are transmitted asymptotically from sows to piglets in the first days of life. Many epidemiological studies have been undertaken to determine at what age contamination occurs. Indeed, it varies depending on the pathogen. It is therefore known, for pigs, that it is necessary to wean before the age of 14 days to prevent the transmission of *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Mycoplasma hyopneumoniae* (Amass and Baysinger, 2006). With *Streptococcus suis*, contamination is particularly early. This bacterium is in fact transmitted to piglets during parturition (Amass *et al.*, 1996; Amass *et al.*, 1995). In birds, contamination of eggs during incubation is well-known and poses a significant risk of infections spreading and persisting, especially for mycoplasmas and salmonellae (Humbert and Salvat, 1997).

Carriage of small quantities of pathogenic bacteria is asymptomatic in herds at the top of the genetic pyramid (nucleus and even multiplication), but in pig production for example, on conventional farrow-to-finish farms, it can evolve into a clinical form at any time (Fittipaldi *et al.*, 2003). It is therefore essential to carry out eradication in nucleus herds so as to be able to depopulate and repopulate production herds. Partial depopulation is a satisfactory and less expensive way of controlling disease (Stärk *et al.*, 2007) but in light of the epidemiological data, the ideal solution is total depopulation followed by repopulation with perfectly healthy animals born by caesarean section to guarantee the top-of-pyramid status in genetic schemes: Specific-Pathogen-Free (SPF) animals (Akkermans, 1991). This measure, which has been highly effective on pig farms, is at the basis of the Danish and Swiss eradication programmes. On production farms, it is expensive, but return-on-investment is possible within 18 months when supporting biosafety conditions are strictly applied (Guyomarc'h *et al.*, 2003; Marchand and Remigereau, 2009; Menard, 2009). Antibiotic use is then reduced to the bare minimum. On nucleus farms, this measure is essential to then be able to populate livestock with healthy animals in complete safety.

To guarantee the success of these operations, it is important that genetic schemes use strict, validated methods to monitor the situation of nucleus and multiplier herds to specify what guarantees they are providing to buyers (Laval, 2010; Laval, 2013).

5.1.3 At-risk production stages

Each sector has identified and is aware of at-risk phases (stages) of production in terms of the development of infections.

- ✓ In the poultry sector, these include:
 - start-up, all species;
 - finishing for broiler poultry;
 - clostridial diseases associated with the coccidiosis cycle: 4th or 5th week (*Gallus*, turkeys);
 - period of susceptibility to histomoniasis in young turkeys;
 - transfer to rangeland;
 - arrival for gavage.
- ✓ In the pig sector, weaning is an at-risk stage. Weaning age influences the significance of this risk factor. Weaning is one of the greatest stresses suffered by piglets and a piglet's immune status varies depending on its age at weaning (which ranges from three to four weeks). Differences in weaning age result in the creation of sub-populations with heterogeneous immune statuses, which can generate various disease dynamics.
- ✓ In the rabbit sector, the pre-weaning period remains difficult because the mother and kitten have different nutritional requirements but share the same feed: a nutritional compromise is necessary. Likewise, the two weeks after weaning are often considered a period with high digestive risks.

- ✓ Milk production is itself a context with an inherent risk of mammary infections. The risk of mastitis remains high and automatic milking, which occurs at least twice a day, can be a factor of physical aggression and contamination for teats.

The dry period is also an at-risk time, with two particularly susceptible periods: stoppage of milking and the pre-partum period.

5.1.4 Clustering and transport of animals

Regardless of the sector or animal species, clustering animals with different origins that are therefore carriers of different microbes is a risk factor that fosters exchanges of pathogens against which some individuals are 'naive', causing infections to develop. Certain modes of production increase this risk. For example:

- Veal calf production in fattening units with groups of young animals, all with different origins, that have undergone one or more transport phases.
Batching occurs at a sensitive age, when the calves are 'immunodeficient': passive immunity is not suited to the new environment and active immunity is still being acquired.
Each calf is a potential carrier of pathogens from its farm of origin.
There are 260 calves per farm on average.
The new farming standards arising from the 1997 welfare directive have improved the welfare of calves (social contact, travel, comfort, intake of fibrous foods) but promoted contamination due to direct contact between animals.
- The fattening of young cattle: this type of animal husbandry has many similarities with the farming of veal calves in fattening units: clustering of animals with various origins, multiple contacts and proximity during transport and then housing, and transport and batching stress.
- Fattening activity in pig production with the purchasing of piglets of multiple origins and frequent changes in suppliers of gilts on farrow-to-finish farms.

The transport of animals increases contact and induces stress. These two factors promote the development of infections and the clinical expression of diseases.

5.1.5 Level of biosafety measures

- ✓ Internal biosafety measures applied on farms, such as cleaning-disinfection operations, wearing specific clothing, adhering to the forward-flow principle so as to protect the least contaminated animals, etc. have an impact on the spread of microbism and its level of clinical expression.
- ✓ External biosafety measures involve both 'intruders' that need to be controlled (pest control) and 'animal inputs' (e.g. purchases of breeding stock) likely to disrupt the stability of the panel of pathogens on the destination farm. In this context, quarantine management should be optimised (mainly the duration) based on the pathogens found on the receiving farms in order to prevent microbial and viral resurgences. Furthermore, special attention should be paid to sanitary precautions relating to visitors, external parties and lorries (origin, inputs, outputs, transported products, etc.).

These points are relevant no matter what the sector.

The following specific points apply to aquaculture:

- Quality of farming water: whether in fresh water (waterways) or coastal zones (sea cages), it is often not possible to control the quality of farming water and thus the presence in this water of antimicrobial resistant bacteria (environmental, of human or animal origin) likely to be selected during treatments.
- Farming basins are seldom de-watered and disinfected due to the loss of earnings that these practices generate. This can promote the persistence of pathogenic bacteria in basins and therefore the occurrence of recurring infections requiring antibiotic treatments.

5.2 Constraints resulting in poor practices

Professionals in charge of controlling animal diseases face technical, regulatory, economic and sociological constraints and challenges that can negatively influence modes of antibiotic use, thus resulting in poor practices.

5.2.1 Regulatory challenges

A number of regulatory provisions, insofar as they were developed and introduced in a context other than antimicrobial resistance, may be risk factors in this area. These include:

✓ Withdrawal periods

Most antibiotics do not have marketing authorisations for certain 'minor' species, leading prescribers to commonly enter into a 'prescribing cascade'. It is then necessary to comply with a set withdrawal period that can be incompatible with certain farming times or certain sectors and activities. It can then be difficult to adapt practices. Some poultry sectors, fish sectors, small ruminants (namely goats) and horses are highly affected.

Moreover, when there is a choice, it is tempting, for practical reasons, to opt for more recent compounds with shorter withdrawal periods. This is particularly significant in milk production with latest-generation compounds that have zero withdrawal periods in milk unlike older MAs that have withdrawal periods of several milkings.

✓ Anti-doping rules: in horses, it should be noted that there are many different concerns and constraints related to the nature of the treated equine and the type of caregiver, beginning with veterinarians (specialising in equine only or mixed activity) but also including owners and trainers. For example, sport horses participating in gallop and trot races, competitions (show jumping, eventing, dressage) or endurance riding are potentially subject to anti-doping checks, which can lead to therapeutic decisions that prioritise a short or even zero withdrawal period potentially at the expense of antimicrobial resistance risks. Indeed, some antibiotics contain procaine, a doping substance, thus limiting their possibilities for use in sport horses.

✓ The failure to review older MAs: some older antibiotic compounds have MAs whose dosages are now inappropriate. Their use according to the MA's indications leads to under-dosing which is a known risk factor in antimicrobial resistance. Recommendations for the careful, moderate use of new antibiotic compounds may only be issued if the older therapeutic arsenal is updated, particularly in terms of dosing.

Under the current European regulations transposed into national law, it is difficult to update certain parts of the dossiers for older MAs, which means that new studies need to be provided, particularly in the field of ecotoxicology, to revise the old dosages for example. In addition, these procedures will sometimes need to be managed at European level. This raises the issue of the required financial investment and the returns that pharmaceutical laboratories can expect from older compounds, since the periods of protection for the data and contracts have expired. It is therefore necessary to consider upgrading this system at European level.

✓ Administrative rules can be a barrier to the upgrading and renovation of buildings.

5.2.2 Technical constraints

A number of technical challenges that have not yet been resolved cause antibiotics to be used inappropriately. These include:

- ✓ The lack of rapid diagnostic tools: it is currently essential to provide veterinarians with rapid diagnostic and decision-support tools. These may be kits helping to distinguish between infections likely to require antibiotic treatment and others. Such tools have been developed for human health and should also be made available in veterinary medicine. It is also important to have indicators of infection as early as possible, particularly for the optimisation of metaphylactic treatments (e.g. automated systems for taking body temperature).
- ✓ The relative lack of predictive value for antibiograms performed in veterinary medicine (see untranslated Section 3.3.1 of the Report).
- ✓ The lack of routinely available and updated information on changes in the predominant infectious diseases and the resistance of the main pathogens in certain species.
- ✓ The little knowledge available to prescribers on antibiotic bioavailability, not enabling them to take into account this criterion which would help limit the volumes of antibiotics used.
- ✓ The unsuitability of sales units: a number of antibiotics are only available as sales units not tailored to their use. This can either lead to under-dosing if the volume is insufficient for the number of treatments to be administered, or to self-medication using the remainder of the medicinal product if the volume is greater than that corresponding to the number of treatments to be administered.
- ✓ Difficulties estimating the weight of certain animals (horses, cattle) can lead to improper dosing.
- ✓ Administration difficulties: restraining animals is a systematic prerequisite for the individual administration of an antibiotic, whether in pets or in animal production. This constraint is a barrier to prescription compliance with repeated administration. 'Long-acting' formulations are an effective response to these challenges, in terms of convenience and compliance. However, they have the following disadvantages:
 - the slow elimination of the antibiotic: the property responsible for its 'long-acting' nature means it also persists longer after the time required for its curative action, with a potentially unfavourable impact on bacterial flora in terms of antimicrobial resistance (see Section 2.5.2)
 - with a single administration of the 'long-acting' formulation, the exposure time of the body is frozen. This type of formulation is not suited to re-assessment of the treatment period by the prescriber (see Section 2.5.2 of the Report).

5.2.3 Economic, sociological constraints and/or opportunities

The experts also identified a number of economic and sociological constraints and opportunities influencing the prescription of antibiotics, but were unable to scientifically assess them in the framework of this Working Group, which did not have expertise in these areas. They have been listed in this report to help identify avenues for investigation and research:

- ✓ The arrival of generics in veterinary medicine: generics have helped lower the cost of antibiotics, which seems to be a factor that has promoted use of these products.
- ✓ Cost of labour: with injectable medicines, treatment must include the cost of labour, which is far from negligible in most sectors. It can be a barrier to the use of this route of administration where the commensal (digestive) bacteria are less exposed to antibiotics than with the oral route, or on the contrary encourage the use of long-acting presentations (see Section 5.2.2).
- ✓ Consideration for productivity in genetic schemes: in dairy cows, for example, genetic selection has taken into account productivity but until recently, has only rarely considered 'resistance' to mammary infections. For example, milking speed has been subject to selection. The selected animals then have greater susceptibility to mammary infections.
- ✓ The economy of the farm and/or sector heavily determines the required investment capacity to improve buildings and equipment with the aim of placing the animals in an environment where infections can be controlled more effectively. Current economic constraints often force farmers to increase the size and even density of animal groups,

which is a risk factor for the emergence of diseases and therefore antibiotic use (see Section 2.1). This increase in size and density should be accompanied by better control means which necessarily require additional investments on the farm.

✓ The farmer-owner factor:

- Irrespective of the sector, farmers are farm managers. Through their decisions, choices, rigour, consistency, expertise and objectives, they have a major influence on the management of diseases on their farms. They are responsible for compliance with biosafety measures and animal surveillance; they also manage feeding, environmental parameters, animal surveillance and sorting, the eradication of diseases and the quality of diets.

Treatment compliance by farmers is essential in the control of antimicrobial resistance.

Veterinary practitioners prescribe in one of the following two ways:

- during visits to farms and the clinical examination of animals
- with no clinical examination of animals, in accordance with a treatment protocol they have defined. This second method currently makes up the vast majority of antibiotic prescriptions. It is then farmers who administer medicinal products as nurses.

The ability of farmers and their staff to recognise diseases (diagnose), refer to and comply with the treatment protocol and prescription for medicinal products (timeliness of treating, choice of anti-infective agent, evaluation of animal weight, administration method and period, etc.) and assess treatment efficacy is essential.

- ✓ Cat and dog owners are a unique category of stakeholders insofar as they are not farming professionals. Even so, they often directly impact modes of administering antibiotic treatment. The increase in the sterilisation of dogs (+6%) and cats (+2%) from 2006 to 2009 is an indicator of the growing medicalisation of dogs and cats, both in towns and in the countryside.

Seeking treatment in this way has been accompanied by an increase in prescriptions and the establishment of short- and medium-term treatments. These various aspects of medicine for these carnivores mean that the prescription of antibiotic treatments for a bacterial infection (recognised or presumed) is common practice for veterinary practitioners, and use of these treatments by owners varies in quality: although it cannot be characterised, it is known that there is some self-medication and reuse of old prescriptions for dogs and cats (in the event of recurring pyoderma for example); furthermore, non-compliance by not adhering to prescriptions, and particularly prematurely stopping a treatment due to clinical improvement and difficulties administering a treatment, is commonly encountered for these pets.

5.3 Assessment of at-risk practices

5.3.1 Methodology

Antibiotic use always poses the risk of selecting, amplifying or disseminating bacterial resistance. However, some practices can have a higher risk. The Working Group developed a methodology to assess these 'at-risk' modes of use.

These 'at-risk' practices could be defined as ways of using a class (or sub-class) of antibiotics, for a given animal species, resulting in the significant selection of resistant bacteria (or resistance determinants) likely to pose a risk to health in general (human, animal) and to the environment.

As stated in the conclusion of Section 3, it is not currently possible to assess 'at-risk' practices based on relationships identified between use and resistance, due to the complexity of antimicrobial resistance phenomena, the wide range of bacteria involved (pathogenic and commensal), co-resistance and therefore co-selection phenomena and also the current level of precision offered by monitoring tools.

These difficulties in interpretation and the resulting inability to directly assess modes of antibiotic use according to data on the resistance of both pathogenic and commensal bacteria led the Working Group to adopt a more indirect risk assessment approach to highlight at-risk practices in terms of antimicrobial resistance.

A small sub-group of experts developed the methodology, which was modelled on the following:

- the OIE risk analysis process (OIE 2013);
- methods used in ranking exercises, by assigning scores to the criteria taken into account for the risk assessment;
- methods for eliciting expert knowledge to set an acceptability threshold for the various practices of antibiotic use.

It can be broken down as follows (Figure):

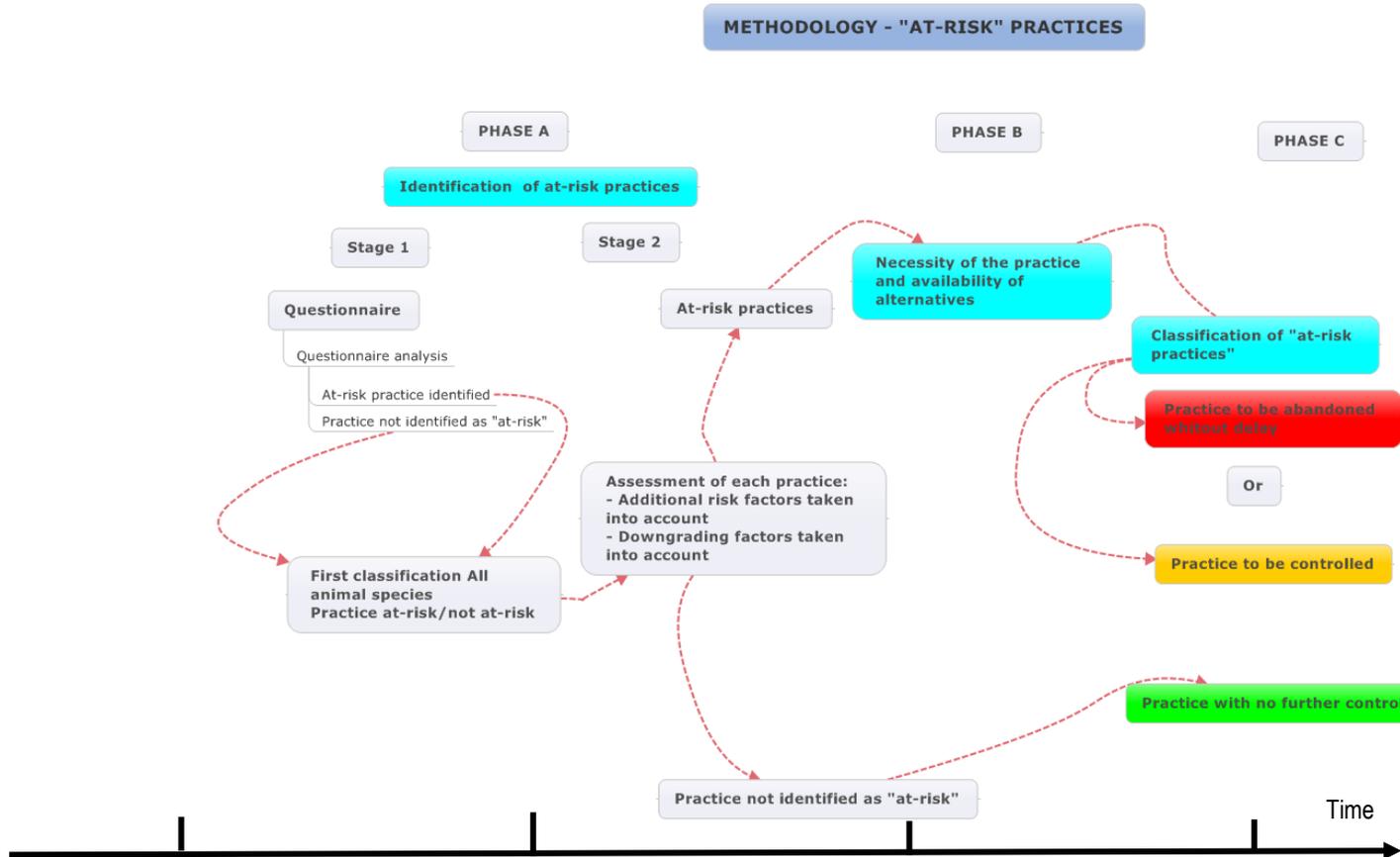
- ✓ Phase A: Identify 'at-risk' modes of use.
 - 1st stage: all sectors combined.

The first stage consisted in establishing a classification of 'antibiotic – route of administration – treatment type' triads and determining a general acceptability threshold for these practices, independently of the species and production stage. Practices whose score was above the group's acceptability threshold were considered at-risk practices, all sectors combined.
 - 2nd stage: taking into account each sector's particularities.

The second stage involved examining each of the practices identified in stage 1, for each species and each production stage. In this stage, modulation factors (additional risk factors or conversely downgrading factors) were applied in order to take into account some sector-specific particularities.
- ✓ Phase B: Assess the necessity of each 'at-risk' mode of use and whether there are alternatives.
- ✓ Phase C: Classify each 'at-risk' mode of use accordingly.

In phases B and C, each 'at-risk' practice in each sector was examined and recommendations were issued for its elimination or control depending on its context of use (essential or unessential nature of the practice).

Figure 25: Methodology for the assessment of at-risk practices



5.3.1.1 Phase A, stage 1: list of 'at-risk' practices and acceptability threshold

Stage 1 of phase A was made up of three successive operations:

- a) Identification of risk assessment criteria for antimicrobial resistance (according to the OIE principles: release/exposure/consequences);
- b) Establishment of a risk ranking table;
- c) Blind questionnaire for all of the WG experts, in order to determine a threshold of acceptability or non-acceptability for each class of antibiotics, based on its mode of use.

Modes of antibiotic use were described using the 'class (or sub-class) of antibiotic / route of administration / treatment type' triad. The information in this triad had been broken down in the inventory of modes of antibiotic use in the various sectors (see Section 3.1.2).

a) Identification of risk assessment criteria for antimicrobial resistance

The assessment of risk related to modes of antibiotic use in veterinary medicine took into account the conventional OIE risk assessment criteria which are release, exposure and consequences.

- ✓ For exposure, the criteria taken into account were the route of administration (oral, parenteral, local, etc.) and type of treatment (preventive, metaphylactic, curative) since these can qualitatively and quantitatively impact antibiotic exposure in the microbiota.
- ✓ The release criterion was only partially taken into account in this methodology stage. Indeed, the assessment of release partly depends on the route of administration and type of antibiotic treatment; but it also depends on the transferable or non-transferable nature of the acquired resistance determinant. And yet the non-transferable nature varies greatly depending on the bacterium and antibiotic compound and is not expressed the same way in all sectors. This criterion was therefore taken into account in each sector when there was adequate knowledge.
- ✓ The criteria taken into account to assess the 'consequences' aspect could only be indirect in the current state of knowledge. Indeed, the consequences for humans, animals and the environment of a bacterium acquiring antimicrobial resistance in animals (whether this is a pathogenic bacterium or a commensal bacterium) are not always known and no such indicators are available. The Working Group therefore chose to indirectly express the 'consequences' criterion with the lists of Critically Important Antimicrobials established by the WHO for humans and by the OIE for animals. The classes of antibiotics included in these lists can in a way be considered the antimicrobials that remain available to treat certain diseases, while other antibiotics have become ineffective on account of resistance. This was therefore an indirect assessment of the 'consequences' criterion.

In this stage of the assessment, the following criteria were taken into account:

- ✓ Importance of the antibiotic for human health according to the WHO (4 classes)
 - Important (IA)
 - Highly important (HIA)
 - Critically important (CIA)
 - Highest priority critically important (highest priority CIA)
- ✓ Importance of the antibiotic for animal health according to the OIE (4 classes)
 - Important (VIA)
 - Highly important (VHIA)
 - Critically important (VCIA)
 - Highest priority critically important (highest priority VCIA)
- ✓ Route of antibiotic administration (4 routes)
 - Local
 - Parenteral
 - Oral
 - Other routes: antibiotic administration *via* the immediate environment of animals (spraying, nebulisation, nest powder, footbath, dipping, etc.).

- ✓ Treatment type (3 types)
 - Curative
 - Metaphylactic
 - Preventive

b) Establishment of a risk ranking table

A value was given to each criterion in this risk analysis, using a scale to express the effects of the various classes of antibiotics and the ways in which the microbiota are exposed to these antibiotics. The values given take into account the available scientific knowledge of how these criteria impact the risk of antimicrobial resistance developing and spreading.

- ✓ Importance of the antibiotic for human health according to the WHO (4 classes): N_1 value
 - Important: $N_1 = 1$
 - Highly important: $N_1 = 2$
 - Critically important: $N_1 = 3$
 - Highest priority critically important: $N_1 = 4$
- ✓ Importance of the antibiotic for animal health according to the OIE (4 classes): N_2 value
 - Important: $N_2 = 1$
 - Highly important: $N_2 = 2$
 - Critically important: $N_2 = 3$
 - Highest priority critically important: $N_2 = 4$
- ✓ Route of antibiotic administration: N_3 value
 - Local: $N_3 = 1$
 - Parenteral: $N_3 = 2$
 - Oral: $N_3 = 3$
 - Other routes: $N_3 = 4$
- ✓ Treatment type: N_4 value
 - Curative: $N_4 = 1$
 - Metaphylactic: $N_4 = 2$
 - Preventive: $N_4 = 3$

The simple unweighted product of these values expresses how these criteria were taken into account, since the Working Group decided to grant equal importance to each criterion (Table 14).

Each antibiotic / route of administration / treatment type triad is classified as such in the risk ranking table

The product of the values (referred to as 'score' hereinafter) for each triad appears in the right-hand column of the table.

Table 14: Risk assessment criteria

Antibiotic class	Consequences				Exposure				Aggregation of criteria
	Humans	N ₁	Animals	N ₂	Route of administration	N ₃	Treatment type	N ₄	
See Table 5	IA	1	VIA	1	Local	1	Curative	1	N ₁ x N ₂ x N ₃ x N ₄
	HIA	2	VHIA	2	Parenteral	2	Metaphylactic	2	
	CIA	3	VCIA	3	Oral	3	Preventive	3	
	Other				Other	4			
	Highest priority CIA	4	Highest priority VCIA	4					

Table 15: Risk assessment table (example* for 3 antibiotics or classes of antibiotics)

Antibiotic or Antibiotic class	Consequences				Exposure				Aggregation of criteria		
	Humans		Animals		Route of administration		Treatment type				
Beta-lactams 3	Highest priority CIA	4	Highest priority VCIA	4	16	Local	1	Curative	1	1	16
	Highest priority CIA	4	Highest priority VCIA	4	16	Local	1	Metaphylactic	2	2	32
	Highest priority CIA	4	Highest priority VCIA	4	16	Local	1	Preventive	3	3	48
	Highest priority CIA	4	Highest priority VCIA	4	16	Parenteral	2	Curative	1	2	32
	Highest priority CIA	4	Highest priority VCIA	4	16	Parenteral	2	Metaphylactic	2	4	64
	Highest priority CIA	4	Highest priority VCIA	4	16	Parenteral	2	Preventive	3	6	96
	Highest priority CIA	4	Highest priority VCIA	4	16	Oral	3	Curative	1	3	48
	Highest priority CIA	4	Highest priority VCIA	4	16	Oral	3	Metaphylactic	2	6	96
	Highest priority CIA	4	Highest priority VCIA	4	16	Oral	3	Preventive	3	9	144
	Highest priority CIA	4	Highest priority VCIA	4	16	Other routes	4	Curative	1	4	64
	Highest priority CIA	4	Highest priority VCIA	4	16	Other routes	4	Metaphylactic	2	8	128
	Highest priority CIA	4	Highest priority VCIA	4	16	Other routes	4	Preventive	3	12	192
Oxytetracycline	HIA	2	Highest priority VCIA	3	6	Local	1	Curative	1	1	6
	HIA	2	Highest priority VCIA	3	6	Local	1	Metaphylactic	2	2	12
	HIA	2	Highest priority VCIA	3	6	Local	1	Preventive	3	3	18
	HIA	2	Highest priority VCIA	3	6	Parenteral	2	Curative	1	2	12
	HIA	2	Highest priority VCIA	3	6	Parenteral	2	Metaphylactic	2	4	24
	HIA	2	Highest priority VCIA	3	6	Parenteral	2	Preventive	3	6	36
	HIA	2	Highest priority VCIA	3	6	Oral	3	Curative	1	3	18
	HIA	2	Highest priority VCIA	3	6	Oral	3	Metaphylactic	2	6	36
	HIA	2	Highest priority VCIA	3	6	Oral	3	Preventive	3	9	54
	HIA	2	Highest priority VCIA	3	6	Other routes	4	Curative	1	4	24
	HIA	2	Highest priority VCIA	3	6	Other routes	4	Metaphylactic	2	8	48
	HIA	2	Highest priority VCIA	3	6	Other routes	4	Preventive	3	12	72
Colistin	Highest priority CIA	3	Highest priority VCIA	3	9	Local	1	Curative	1	1	9
	Highest priority CIA	3	Highest priority VCIA	3	9	Local	1	Metaphylactic	2	2	18
	Highest priority CIA	3	Highest priority VCIA	3	9	Local	1	Preventive	3	3	27
	Highest priority CIA	3	Highest priority VCIA	3	9	Parenteral	2	Curative	1	2	18
	Highest priority CIA	3	Highest priority VCIA	3	9	Parenteral	2	Metaphylactic	2	4	36
	Highest priority CIA	3	Highest priority VCIA	3	9	Parenteral	2	Preventive	3	6	54
	Highest priority CIA	3	Highest priority VCIA	3	9	Oral	3	Curative	1	3	27
	Highest priority CIA	3	Highest priority VCIA	3	9	Oral	3	Metaphylactic	2	6	54
	Highest priority CIA	3	Highest priority VCIA	3	9	Oral	3	Preventive	3	9	81
	Highest priority CIA	3	Highest priority VCIA	3	9	Other routes	4	Curative	1	4	36
	Highest priority CIA	3	Highest priority VCIA	3	9	Other routes	4	Metaphylactic	2	8	72
	Highest priority CIA	3	Highest priority VCIA	3	9	Other routes	4	Preventive	3	12	108

*This process was applied for all classes of antibiotics

c) Questionnaire and acceptability threshold

Acceptability thresholds for practices were established by eliciting knowledge from the Working Group's experts in relation to which of the triads in question they considered to be 'at-risk' modes of antibiotic use. All of the group's experts, regardless of their speciality vis-à-vis antibiotic use and antimicrobial resistance, received a questionnaire asking them individually to evaluate each antibiotic / route of administration / treatment type triad: "In your opinion, is this mode of use for this antibiotic acceptable or not in terms of the risk of antimicrobial resistance?" (Table). Twenty-one experts participated.

The experts' answers to the questionnaire were 'blind', meaning that in this stage of the expert appraisal, they did not have knowledge of the previous identification of risk analysis criteria or the establishment of the risk analysis table (developed by the 'methodology' sub-group).

Table 16: Questionnaire sent to the experts (extract)

In your opinion, what is acceptable in terms of antimicrobial resistance?

Tick Yes (acceptable) or No (not acceptable). No other possible answers!

Antibiotic or antibiotic class	Route of administration	Treatment type	Acceptability	
			Yes	No
Aminoglycosides 1	Local	Curative		
	Local	Metaphylactic		
	Local	Preventive		
	Parenteral	Curative		
	Parenteral	Metaphylactic		
	Parenteral	Preventive		
	Oral	Curative		
	Oral	Metaphylactic		
	Oral	Preventive		
	Other routes	Curative		
	Other routes	Metaphylactic		
	Other routes	Preventive		
Aminoglycosides 2	Local	Curative		
	Local	Metaphylactic		
	Local	Preventive		
	Parenteral	Curative		
	Parenteral	Metaphylactic		
	Parenteral	Preventive		
	Oral	Curative		
	Oral	Metaphylactic		
	Oral	Preventive		
	Other routes	Curative		
	Other routes	Metaphylactic		
	Other routes	Preventive		

Analysis of the questionnaire's results

A first 'horizontal' analysis of the questionnaire was undertaken in order to verify the consistency of the results. The details of this analysis appear in Annex 3.

d) Determination of the acceptability threshold

Once the consistency of the results had been verified, a 'vertical' analysis of the questionnaire was undertaken (excluding the local route and furans) and the experts' responses (acceptable/not acceptable) were compared with the scores in the risk analysis table in order to:

- ✓ determine a minimum threshold of acceptability and non-acceptability for each expert
 - taking the minimum score for the 'yes' answers (acceptability threshold)
 - taking the maximum score for the 'no' answers (non-acceptability threshold)
- ✓ determine the threshold of acceptability or non-acceptability for the group
 - averaging the acceptability or non-acceptability thresholds for all of the experts
- ✓ compare the score for each antibiotic / route of administration / treatment type triad with the average threshold determined through this process. If the score was greater than the average acceptability threshold, then the mode of antibiotic use corresponding to this triad was considered an 'at-risk' practice.

For the sake of clarity, an example has been provided for just two classes of antibiotics and three expert answers in Table . However, this methodology was applied to all classes of antibiotics, with the answers of all of the experts who had completed the questionnaire.

The acceptability threshold was calculated for the following scenarios:

- ✓ All valid answers: 40.23
- ✓ Answers without the local route: 40.65
- ✓ Answers without furans: 41.92
- ✓ Answers without the local route or furans: 43.57

The aggregation of criteria for the development of the risk classification table resulted in irregularly staggered values (varying intervals of 1, 2, 3, 4, 6, 8, 9, 12, 16, 18, 24, 27, 32, **36, 48**, 54, etc.). At the same time, the values calculated for the acceptability threshold all ranged from 36 to 48, irrespective of the scenario. The choice of either scenario therefore had no impact on the identification of 'at-risk' practices: below the score of 36, practices were considered acceptable; above the threshold of 48, practices were considered 'at-risk'.

Table 17: Establishment of the acceptability threshold and determination of at-risk practices. Example for 2 antibiotic classes and 3 expert answers

Antibiotic or Antibiotic class	Route of administration	Treatment type	Risk prioritisation table										Questionnaire: determination of the acceptability threshold												Determination of at-risk practices		
			Consequences					Exposure					Aggregation of criteria	Expert 1				Expert 2				Expert 3				Acceptability threshold and at-risk practices (ARP)	
			Humans		Animals			Route of administration		Treatment type				Yes	Score	No	Score	Yes	Score	No	Score	Yes	Score	No	Score		
Aminoglycosides 1	Local	Curative	IA	1	VCIA	3	3	Local	1	Curative	1	1	3	X	3			X	3			X	3			< threshold	-
	Local	Metaphylactic	IA	1	VCIA	3	3	Local	1	Metaphylactic	2	2	6			X	6			X	6	X	6			< threshold	-
	Local	Preventive	IA	1	VCIA	3	3	Local	1	Preventive	3	3	9			X	9			X	9			X	9	< threshold	-
	Parenteral	Curative	IA	1	VCIA	3	3	Parenteral	2	Curative	1	2	6	X	6			X	6			X	6			< threshold	-
	Parenteral	Metaphylactic	IA	1	VCIA	3	3	Parenteral	2	Metaphylactic	2	4	12	X	12					X	12	X	12			< threshold	-
	Parenteral	Preventive	IA	1	VCIA	3	3	Parenteral	2	Preventive	3	6	18			X	18			X	18			X	18	< threshold	-
	Oral	Curative	IA	1	VCIA	3	3	Oral	3	Curative	1	3	9	X	9			X	9			X	9			< threshold	-
	Oral	Metaphylactic	IA	1	VCIA	3	3	Oral	3	Metaphylactic	2	6	18			X	18			X	18			X	18	< threshold	-
	Oral	Preventive	IA	1	VCIA	3	3	Oral	3	Preventive	3	9	27			X	27			X	27			X	27	> threshold	ARP
	Other routes	Curative	IA	1	VCIA	3	3	Other routes	4	Curative	1	4	12	X	12					X	12			X	12	< threshold	-
	Other routes	Metaphylactic	IA	1	VCIA	3	3	Other routes	4	Metaphylactic	2	8	24			X	24			X	24			X	24	> threshold	ARP
Other routes	Preventive	IA	1	VCIA	3	3	Other routes	4	Preventive	3	12	36			X	36			X	36			X	36	> threshold	ARP	
Aminoglycosides 2	Local	Curative	CIA	3	VCIA	3	9	Local	1	Curative	1	1	9	X	9			X	9			X	9			< threshold	-
	Local	Metaphylactic	CIA	3	VCIA	3	9	Local	1	Metaphylactic	2	2	18			X	18			X	18			X	18	< threshold	-
	Local	Preventive	CIA	3	VCIA	3	9	Local	1	Preventive	3	3	27			X	27			X	27			X	27	> threshold	ARP
	Parenteral	Curative	CIA	3	VCIA	3	9	Parenteral	2	Curative	1	2	18	X	18			X	18			X	18			< threshold	-
	Parenteral	Metaphylactic	CIA	3	VCIA	3	9	Parenteral	2	Metaphylactic	2	4	36	X	36					X	36	X	36			> threshold	ARP
	Parenteral	Preventive	CIA	3	VCIA	3	9	Parenteral	2	Preventive	3	6	54			X	54			X	54			X	54	> threshold	ARP
	Oral	Curative	CIA	3	VCIA	3	9	Oral	3	Curative	1	3	27	X	27			X	27			X	27			> threshold	ARP
	Oral	Metaphylactic	CIA	3	VCIA	3	9	Oral	3	Metaphylactic	2	6	54			X	54			X	54	X	54			> threshold	ARP
	Oral	Preventive	CIA	3	VCIA	3	9	Oral	3	Preventive	3	9	81			X	81			X	81			X	81	> threshold	ARP
	Other routes	Curative	CIA	3	VCIA	3	9	Other routes	4	Curative	1	4	36	X	36					X	36			X	36	> threshold	ARP
	Other routes	Metaphylactic	CIA	3	VCIA	3	9	Other routes	4	Metaphylactic	2	8	72			X	72			X	72			X	72	> threshold	ARP
Other routes	Preventive	CIA	3	VCIA	3	9	Other routes	4	Preventive	3	12	108			X	108			X	108			X	108	> threshold	ARP	
													36		6		27		6		54		9	23	acceptability		
													max		min		max		min		max		min	average	threshold		

At the end of this stage 1 of phase A, the Working Group thus drew up a list of 'at-risk practices', all sectors combined, corresponding to certain antibiotic class (or sub-class) / route of administration / treatment type triads.

5.3.1.2 Phase A, stage 2: Taking into account each sector's particularities

During this second stage of phase A, the list of 'at-risk practices' obtained in the previous stage was applied to the summary table of modes of antibiotic use in each sector (see Table 4) in order to visualise the various at-risk practices for each species.

The experts considered each identified mode of use and assessed whether the particularities of the sector in question required taking into account modulating factors (other than the criteria used in stage 1) that would classify as 'at-risk' a practice that had not been identified as such or conversely downgrade a practice recognised as at-risk in the first stage.

The Working Group first defined modulating factors so as to have a standardised approach applicable to all species. The following additional factors were taken into account:

- ✓ pyramid treatment;
- ✓ duration of treatment;
- ✓ development of resistance;
- ✓ co-selection;
- ✓ frequency of use.

It was primarily in this stage of the risk assessment that the available data on the development of resistance to the antibiotic classes in question were taken into account.

5.3.1.3 Phase B: Necessity of each 'at-risk' mode of use; existence of alternatives

An 'at-risk practice' must be assessed to determine if it should be considered unnecessary, avoidable, useful or essential for want of alternatives.

The necessity of each practice and the existence of recognised alternatives were examined. This stage was important since some practices may be considered 'at-risk' but cannot be avoided for want of other solutions.

This phase therefore drew upon the knowledge of the experts for each sector with the aim of incorporating a benefit/risk notion for each of the practices identified in phase A.

5.3.1.4 Phase C: Classification of each 'at-risk' mode of use

At the end of this risk assessment, each mode of antibiotic use in each sector was classified into one of the following four categories:

- ✓ Practice with no further control;
- ✓ Practice to be controlled (with control recommendations) in order to precisely target situations when this antibiotic use can be considered;
- ✓ 'At-risk' practice that should be abandoned over time by developing replacement measures, since this practice is considered essential today for want of alternative means developed by the sector in question;
- ✓ Practice to be abandoned without delay: this 'at-risk' practice should be abandoned immediately, because it is either considered unnecessary, a poor practice requiring correction or an avoidable practice given that alternative solutions are available.

5.3.2 Results of the assessment of 'at-risk practices' by sector

The results obtained through this assessment are presented below for each sector in table form with the classification of the various modes of antibiotic use and as text explaining the control recommendations and some particularities for the sector.

The following colour code has been used:

	Practice to be abandoned without delay		Practice to be regulated		Practice not surveyed
	Measures taken to abandon the practice over time		Practice with no further regulation		
	Practice to be abandoned without delay <u>except</u> for infections related to the bacteria mentioned in <u>specific situations in the text</u> , for which the practice is to be abandoned over time and research into alternatives to this preventive treatment is to be rapidly undertaken				

Lastly, all of the tables were analysed in a plenary working group. Experts in each sector presented their findings, which were discussed collectively to seek consensus among the whole Working Group, with conclusions that would be as harmonised as possible between the sectors.

5.3.2.1 At-risk practices in the poultry sector

Poultry production is characterised by the flock management of hundreds to thousands of birds of the same species and same age farmed in a shared space. It is rarely possible to isolate and treat sick animals only. For certain bacteria, contagion is unavoidable and more or less rapid. At flock level, metaphylaxis is the most appropriate mode of curative treatment.

Autopsy, bacteriology and antibiograms are practised routinely. The most common route of administration is the oral route, primarily through drinking water and more rarely through feed.

In this context, the conclusions of the Working Group for at-risk practices in the poultry sector are summarised in Table.

Note: the expert group had limited expertise for the fattened duck sector. It was unable to provide more details for this sector which could be studied more thoroughly taking into account the recommendations of this report.

• At-risk practices to be abandoned without delay

- ✓ Injection of ceftiofur at the hatchery: since several publications have shown an increase in resistance to latest-generation cephalosporins in Enterobacteriaceae and the spread of resistance elements, these practices have already been abandoned in France for the French market since the Working Group was created.
- ✓ All uses of 3rd and 4th generation cephalosporins, since they are not indicated for poultry.
 - The occasional use of 3rd and 4th generation cephalosporins for metaphylaxis in the duck sector can be replaced with penicillins.
 - The use of 3rd and 4th generation cephalosporins as curative treatment in breeding stock in the turkey sector can be replaced with beta-lactams+injectable polypeptides.
- ✓ The sometimes systematic oral administration of fluoroquinolones in broiler chicks from the first day of life is concomitant with an increase in the antimicrobial resistance of Enterobacteriaceae in broiler chicken production. This preventive practice should be abandoned in favour of reasoned metaphylaxis with other antibiotics as a priority.
- ✓ The systematic use of other antibiotics for prevention should also be abandoned with the aim of reducing overall selective pressure. However, in some situations these preventive practices remain essential for want of alternatives as indicated below.

• Measures taken to abandon the practice over time

Some at-risk practices remain essential and the experts recommend immediately developing measures so they may eventually be abandoned.

- ✓ For the poultry sector, these measures are primarily preventive treatments in infected environments. Some pathogens, by their very presence on a farm, can cause serious and recurring diseases, and therefore early treatments are justified at certain critical moments even before the first symptoms appear.

Below are some examples:

- Pathogenic *Escherichia coli* for all species;
- *Mycoplasma* and *Enterococcus* for production chickens and laying hens;
- *Ornithobacterium* for turkeys;
- *Pasteurella* and *Riemerella* for ducks.

This non-exhaustive list may change depending on the pathogenicity of the bacteria in question and the farming systems used. The current use of colistin, macrolides and beta-lactams 1 (penicillins) in the poultry sector does not appear to have a negative impact on the susceptibility of the target bacteria. For tetracyclines, the susceptibility of mycoplasmas remains very good. It can be altered locally for pasteurellae, *Ornithobacterium* and *Riemerella*. It is highly altered for Enterobacteriaceae, which are not the bacteria targeted by the treatment. However, these treatments have an impact on the commensal flora. That is why it is essential to seek out alternative solutions, including disease control solutions, with the aim of ultimately abandoning these practices.

- ✓ While strictly metaphylactic, alternatives should be sought to the occasional use of aerosolised colistin for the treatment of respiratory colibacillosis, since its impact has not been studied.

The impact of these infections for the sector is such that these practices cannot be abandoned over the short term without having serious consequences on the economy and animal welfare. However, decreasing overall selective pressure and risks of co-selection should motivate the sector to research alternatives.

- ✓ **Export:** Like for other sectors that export breeding stock, the requirements of importing countries can impose some preventive modes of antibiotic use that cannot be abandoned immediately unless the regulations in these countries change. One example is the injection of ceftiofur at the hatchery.

• Practices to be controlled

Precise knowledge of fluoroquinolone uses should be taken into account to reserve them for the most relevant needs defined by a benefit/risk assessment in terms of health, animal welfare and antimicrobial resistance. Regulatory measures should be proportional to the risk level. Their effectiveness will be partially assessed by monitoring the development of antimicrobial resistance.

Regulating the use of first-generation quinolones is also recommended. Indeed, used repeatedly, they can end up reducing the efficacy of second- and third-generation quinolones. Their repeated use should therefore be avoided. This mainly applies to quinolone-based metaphylactic treatments in broiler poultry.

Early treatments containing aminoglycosides that have replaced cephalosporins *in ovo* and in one-day-old chicks should also be controlled.

For the poultry sector, in which laboratory use is already highly widespread, practices can be further controlled by ensuring the traceability of treatments and justifying them with laboratory tests or epidemiological data specific to each batch.

• Practices with no further control

These include all practices not listed above that are already subject to rules for the prescribing and dispensing of medicinal products by veterinarians further to a clinical examination or as part of a treatment protocol. They remain subject to the general objective of reducing the antibiotic exposure of animal, human and environmental microbiota.

In this context, it is nonetheless necessary to insist on treatment compliance. Research should focus on implementing new treatment regimens taking into account the risk of antimicrobial resistance development.

Table18: At-risk practices in the poultry sector

	Parenteral route			Oral route (excl. premix)			Oral route-medicated premix			Local route			Other routes		
	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative
Aminoglycosides 1							E coli								
Aminoglycosides 2				E coli											
Beta-lactams 1				Enteroc., Pasteur. Riemerella											
Beta-lactams 2															
Beta-lactams 3															
Quinolones				E coli											
2nd and 3rd G quinolones															
Lincosamides															
Macrolides 1				My coplasma			My coplasma								
Macrolides 2				My coplasma											
Other sulfonamides															
Poly peptide colistin				E coli										E coli	
Other poly peptides															
Phenolics															
Pleuromutilin															
Rifampicin															
Tetracycline				My copl., Pasteur., Riemerella			My coplasma								
Trimethoprim sulfonamide				E coli											
Furans															
Human antibiotics															
Extemporaneous preparation															

Individual curative almost non-existent almost not used ?

Individual curative almost non-existent almost not used ?

	Practice to be abandoned without delay		Practice to be regulated		Practice not surveyed
	Measures taken to abandon the practice over time		Practice with no further regulation		
	Practice to be abandoned without delay <u>except</u> for infections related to the bacteria mentioned in <u>specific situations in the text</u> , for which the practice is to be abandoned over time and research into alternatives to this preventive treatment is to be rapidly undertaken				

This table does not take into account practices related to exports

5.3.2.2 At-risk practices in the pig sector

The conclusions of the Working Group for at-risk practices in the pig sector are summarised in Table 19.

• **At-risk practices to be abandoned without delay**

The practices to be abandoned for the pig sector are mainly as follows:

- ✓ Any preventive use of 3rd and 4th generation cephalosporins and fluoroquinolones;
- ✓ The distribution of medicated feedstuffs for suckling piglets (major justification: under-dosing);
- ✓ Preventive treatments in the form of oral pastes for suckling piglets (major justification: non-compliance);
- ✓ Local metaphylactic or preventive treatments with antibiotics in the form of aerosol sprays (major justification: non-compliance);
- ✓ Local metaphylactic or preventive treatment: intra-uterine treatment of metritis in sows (major justification: non-compliance);
- ✓ Preventive, curative or metaphylactic treatments administered to lactating sows aiming to treat or prevent digestive problems in suckling piglets through milk supply (major justification: under-dosing and non-'compliance' in sows);
- ✓ 'Preventive' treatments for neonatal diarrhoea containing pleuromutilins or macrolides 1 by injection in sows (the concentration of antibiotics in the colostrum and milk is then insufficient, resulting in under-dosing).
- ✓ The systematic use of other antibiotics for prevention should also be abandoned with the aim of reducing overall selective pressure. However, in some situations these preventive practices still remain essential for want of alternatives as indicated below.

• **Measures taken to abandon the practice over time**

Some at-risk practices remain essential and the experts recommend immediately developing measures so they may be abandoned.

- ✓ The preventive use of certain antibiotics still remains essential, until alternatives become available to control serious diseases on farms caused by certain bacteria, in specific circumstances. These are limited to:
 - *Escherichia coli* (pathogenic strains) post-weaning: the weaning of piglets is an at-risk context described in this report, requiring that the sector find alternative solutions, including zootechnical and disease control solutions, to preventive antibiotic use to control post-weaning diarrhoea. Until such solutions are implemented, the preventive use of polypeptides in particular and aminoglycosides 2 may be essential today on some farms;
 - *Mycoplasma hyopneumoniae*: for disease control in nucleus and multiplier herds, *Mycoplasma hyopneumoniae* eradication plans are implemented on nucleus farms that want to create a pyramid free of this bacterium. These disease control protocols use all required dosage forms combined with the strengthening of biosafety measures with a time-limited calendar. Various antibiotic classes can be involved: macrolides 1 and 2; tetracyclines; pleuromutilins; lincosamides. Oral and injectable administration;
 - *Actinobacillus pleuropneumoniae*: same as for *Mycoplasma hyopneumoniae* in nucleus and multiplier herds (use of trimethoprim sulfonamide, beta-lactams 1, macrolides 2, tetracyclines);
 - *Brachyspira hyodysenteriae*: for disease control on farms clinically infected with swine dysentery. The programme uses antibiotics (macrolides, pleuromutilins, lincosamides) in feed in addition to a hygiene programme. This type of treatment can only be considered if there has been a formal diagnosis of swine dysentery, by laboratory analyses with antibiograms, a formalised eradication protocol and regular farm follow-up at least every three months for a maximum period of one year.
- ✓ **Export:** Like for other sectors that export breeding stock, the requirements of importing countries can impose some preventive modes of antibiotic use that cannot be abandoned

immediately unless the regulations in these countries change. This is the case in particular for aminoglycosides 2 combined with a beta-lactam 1 against leptospirosis and for macrolides and tetracyclines against *Mycoplasma hyopneumoniae*.

• Practices to be controlled

Some practices should be controlled so that they are only used when strictly necessary. These are primarily the use of 3rd and 4th generation cephalosporins and fluoroquinolones, which should be reserved for specific situations that should be clearly identified by the sector and strictly controlled.

The same is true for first-generation quinolones which, when used repeatedly, can end up reducing the efficacy of 2nd and 3rd generation quinolones. Their repeated use should therefore be avoided.

Furthermore, combinations of antibiotics should be limited and respond to clearly defined indications. Indeed, some combinations have MAs as is and their use does not require further control. However, combinations not covered by MAs need to be controlled. This is the case in particular of combinations of medicated premixes (off-label injectable combinations in aqueous solutions are rare on account of frequent incompatibilities between excipients).

The experts' recommendations for practices to be controlled are as follows:

- avoid all first-line use;
- use all possible means to justify the necessity of this mode of use;
- avoid all systematic use;
- request alternative supporting measures to gradually reduce these modes of use;
- prescriptions should be limited to a maximum period of three months.

• Practices with no further control

These include all practices not listed above that are already subject to rules for the prescribing and dispensing of medicinal products by veterinarians further to a clinical examination or as part of a treatment protocol. They remain subject to the general objective of reducing the antibiotic exposure of animal, human and environmental microbiota.

Treatment protocols need to be improved. It is important to insist on methods for preventing infections and proper treatment compliance and precisely define appropriate thresholds of intervention for metaphylactic treatment.

Table 19: High risk practices in pig farming

	Parenteral route			Oral route (excl. premix)			Oral route - medicated premix			Local route			Oral route - suckling piglets			Other routes		
	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative
Aminoglycosides 1																		
Aminoglycosides 2				E. coli			E. coli											
Beta-lactams 1	Actinobacillus			Actinobacillus			Actinobacillus											
Beta-lactams 2																		
Beta-lactams 3																		
Quinolones																		
2nd and 3rd G quinolones																		
Lincosamide	Mycoplasma			Mycopl., Brachys.			Mycopl., Brachys.											
Macrolides 1	Mycoplasma, Actinobacillus			Mycopl., Actinob., Brachyspira			Mycopl., Actinob., Brachyspira											
Macrolides 2	Mycoplasma, Actinobacillus						Mycoplasma											
Other sulfonamides																		
Poly peptide colistin				E. coli			E. coli											
Other poly peptides																		
Phenicol																		
Pleuromutilin	Mycoplasma			Mycopl., Brachys.			Mycopl., Brachys.											
Rifampicin																		
Tetracycline	Mycoplasma, Actinobacillus			Mycoplasma, Actinobacillus			Mycoplasma, Actinobacillus											
Trimethoprim sulfonamide	Actinobacillus			Actinobacillus			Actinobacillus											
Furans																		
Human antibiotics																		
Extemporaneous preparation																		

	Practice to be abandoned without delay		Practice to be controlled		Practice not inventoried
	Measures taken to abandon the practice over time		Practice with no further control		
	Practice to be abandoned without delay <u>except</u> for infections related to the bacteria mentioned in <u>specific situations in the text</u> , for which the practice is to be abandoned over time and research into alternatives to this preventive treatment is to be rapidly undertaken				

This table does not take into account practices related to exports

5.3.2.3 At-risk practices in the ruminant sector

The conclusions of the Working Group for at-risk practices in the ruminant sector are summarised in Table and Table . Given the differences between farming systems, fattening farms of batched animals were distinguished (Table 21) from other ruminant production sectors (Table 20).

• At-risk practices to be abandoned without delay

- ✓ Practices not justified due to a lack of MAs in France (e.g. paromomycin) or the abusive use of the cascade approach for compounds such as rifaximin used in neonatal diarrhoea and lincosamides in footbaths.
- ✓ Oral treatments for polygastric ruminants (weaned ruminants), with the exception of the salmonellosis treatment described below as a practice to be controlled. Indeed, oral antibiotics in polygastric animals have an unfavourable impact on the ruminal flora that can cause serious bloat and exert selective pressure on the microbiota.
- ✓ All preventive treatments containing fluoroquinolones and 3rd and 4th generation cephalosporins.
- ✓ The systematic use of other antibiotics for prevention should also be abandoned with the aim of reducing overall selective pressure. However, in some specific situations these preventive practices remain essential for want of alternatives as indicated below.
- ✓ Injectable metaphylactic treatments with latest-generation cephalosporins, since other compounds can be used.
- ✓ Oral curative treatments with fluoroquinolones (*bolus* or liquid) given the risk of antimicrobial resistance induced by the use of these compounds, when other antibiotic treatments are possible.

• At-risk practices to be abandoned over time

Some at-risk practices remain essential and the experts recommend immediately developing measures so they may eventually be abandoned.

- ✓ Preventive treatments with antibiotics other than fluoroquinolones and 3rd and 4th generation cephalosporins for the following situations:
 - For batched animals (oral or injectable powders), against *E. coli* and *Salmonella* infections for neonatal diarrhoea and *pasteurellaceae* and mycoplasmas for respiratory infections. These uses should eventually be abandoned, as soon as vaccination, sanitary and environmental measures make it possible to control the risk of infection and do without antibiotic prevention.
 - Preventive intra-mammary treatment at dry-off. 'Treatment' at dry-off has two objectives: to treat infected animals and prevent new infections when milking is stopped and during the dry period.
Prevention should be ensured by plugs when the epidemiological status of the herd and the individual infectious status of the cow allow it.
- ✓ Metaphylactic treatments:
 - Orally in monogastric ruminants, through medicated premixes, since these treatments expose the commensal flora more than the other routes;
 - Orally with quinolones and fluoroquinolones, regardless of the type or stage of production, given the risks of resistance related to the use of these compounds, particularly by the oral route which exposes the commensal flora more;
 - By injection with fluoroquinolones, as a last resort, when other compounds (such as macrolides) cannot be used.

These practices should be controlled more closely until they have been abandoned.

Furthermore, the experts would like to point out a practice not listed in the inventory, since it is not used on a prescription basis but is rather a farming practice: the milk of cows treated for mastitis is usually distributed to calves during the withdrawal period. The Working Group stresses that this is an at-risk practice that should be abandoned as soon as possible. That said, no other solutions for discarding this milk are currently available to farmers.

• Practices to be controlled

- ✓ Metaphylactic treatments, except when these practices are classified as at-risk. Metaphylaxis should be prescribed after a veterinarian has visited the farm, assessed the treatment's timeliness and analysed risk factors promoting the spread of the disease in the batch. Prescriptions without a clinical examination for the same illness should be of limited duration (three months).
- ✓ The antibiotic treatment of mastitis in cattle is the main form of antibiotic use on dairy farms. It should be subject to a global approach specific to each farm that is periodically re-assessed in accordance with a professional standard. This work should be recorded in the farm's treatment protocol.
 - Herd diagnosis is firstly epidemiological and undertaken based on information on individual cell concentrations and cases of clinical mastitis as well as an assessment of risk factors.
 - Treatments should be prescribed at dry-off after the results from the previous dry period have been assessed.
 - Bacteriological analyses should be recommended for cases of clinical mastitis.
- ✓ Curative treatments with 3rd and 4th generation cephalosporins or fluoroquinolones. These antibiotics should be reserved for specific situations, which should be clearly identified by the sector and strictly controlled. In particular:
 - They cannot be prescribed as part of a treatment protocol.
 - They can only be prescribed after a visit to the farm and a clinical examination.
 - Additional examinations of the clinical symptoms are recommended whenever possible.
- ✓ The treatment of salmonellosis in polygastric ruminants, given the potential public health risk, which may include a narrow-spectrum antibiotic (colistin) administered orally. This treatment can only be prescribed after a visit and clinical examination of the animal(s) and after isolation of the strain.

Moreover, the experts are issuing the following general recommendations for practices to be controlled:

- ✓ The obligation to prescribe according to a treatment regimen that is as short as possible and is validated by the MA: when there is no MA (minor species), refer to a validated regimen (standard).
- ✓ Alternatives to antibiotics should be sought out, preferring vaccination whenever possible.

• Practices with no further control

These include all practices not listed above that are already subject to rules for the prescribing and dispensing of medicinal products by veterinarians further to a clinical examination or as part of a treatment protocol. They remain subject to the general objective of reducing the antibiotic exposure of animal, human and environmental microbiota.

In this context, it is nonetheless necessary to insist on treatment compliance. Research should focus on implementing new treatment regimens taking into account the risk of antimicrobial resistance development.

Table 20: At-risk practices in the ruminant sector (not including batched ruminants)

	Parenteral route			Oral route (excl. premix)			Oral route - medicated premix			Local route			Other route (footbath)		
	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative*	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative
Aminoglycosides 1	Red	Yellow	Green	Red	Yellow	Green									
Aminoglycosides 2		Yellow	Green	Red	Yellow	Green				Red	Yellow	Yellow			
Beta-lactams 1	Red	Yellow	Green							Red	Yellow	Yellow			
Beta-lactams 2		Yellow	Green							Red	Yellow	Yellow			
Beta-lactams 3		Red	Yellow								Yellow	Yellow			
Quinolones	Red	Yellow	Green		Red										
2nd and 3rd G quinolones	Red	Red	Yellow	Red	Red	Red									
Lincosamide														Red	
Macrolides 1	Red	Yellow	Green		Yellow	Green				Red	Yellow	Yellow			
Macrolides 2	Red	Yellow	Green							Red	Yellow	Yellow			
Other sulfonamides															
Polypeptide colistin	Red	Yellow	Green	Red	Yellow	Salm.						Yellow			
Other polypeptides															
Phenicol	Red	Yellow	Green												
Pleuromutilin															
Rifampicin											Yellow	Yellow			
Tetracyclines	Red	Yellow	Green	Red	Yellow	Green	Red	Red			Yellow	Yellow			
Trimethoprim sulfonamides		Yellow	Green	Red	Yellow	Green									
Furans															
Human antibiotics															
Extemporaneous preparation															

	Practice to be abandoned without delay		Practice to be regulated		Practice not surveyed
	Measures taken to abandon the practice over time		Practice with no further regulation		

* no oral antibiotic treatment of polygastric ruminants except for salmonellosis in specific conditions

Salm: oral administration of colistin for salmonellosis in polygastric ruminants

Table 21: At-risk practices in the ruminant sector (fattening-batched)

	Parenteral route			Oral route (excl. premix)			Oral route-medicated premix			Local route			Other routes		
	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative*	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative
Aminoglycosides 1	<i>E. coli, Past., Mycopl.</i>														
Aminoglycosides 2															
Beta-lactams 1	<i>E. coli, Past., Mycopl.</i>			<i>E. coli, Past., Mycopl.</i>											
Beta-lactams 2															
Beta-lactams 3															
Quinolones	<i>E. coli, Past., Mycopl.</i>														
2nd and 3rd G quinolones															
Lincosamide															
Macrolides 1	<i>E. coli, Past., Mycopl.</i>														
Macrolides 2	<i>E. coli, Past., Mycopl.</i>														
Other sulfonamides															
Polypeptide colistin				<i>E. coli, Past., Mycopl.</i>		<i>Salm.</i>									
Other polypeptides															
Phenicol	<i>E. coli, Past., Mycopl.</i>														
Pleuromutilin															
Rifampicin															
Tetracyclines	<i>E. coli, Past., Mycopl.</i>														
Trimethoprim sulfonamides				<i>E. coli, Past., Mycopl.</i>											
Furans															
Human antibiotics															
Extemporaneous preparation															

	Practice to be abandoned without delay		Practice to be controlled		Practice not inventoried
	Measures taken to abandon the practice over time		Practice with no further control		
	Practice to be abandoned without delay except for infections related to the bacteria mentioned in specific situations in the text , for which the practice is to be abandoned over time and research into alternatives to this preventive treatment is to be rapidly undertaken				

5.3.2.4 At-risk practices in the rabbit sector

The conclusions of the Working Group for at-risk practices in the rabbit sector are summarised in Table.

• At-risk practices to be abandoned without delay

- ✓ The practices to be abandoned for the rabbit sector are mainly preventive antibiotic uses. However, for certain infections (see below), they remain irreplaceable and the experts recommend immediately developing measures so they may be rapidly abandoned.
- ✓ The use of dihydrostreptomycin (aminoglycoside 1) for metaphylaxis for the treatment of caecal paresis is a practice that should be abandoned since magnesium chloride is a recognised alternative.

• Measures taken to abandon the practice over time

Some at-risk practices remain essential and the experts recommend immediately developing measures so they may eventually be abandoned.

- ✓ The following serious diseases jeopardise farm survival and therefore preventive antibiotics cannot be abruptly abandoned:
 - *Escherichia coli*: highly pathogenic serotypes;
 - High-virulence *Staphylococcus aureus*;
 - *Salmonella*;
 - *Pasteurella and Bordetella*⁶.

Note that in some exceptionally serious cases of farms infected with major salmonellosis or colibacillosis, the preventive use⁷ of injectable fluoroquinolones is combined with the addition of antibiotics in the nest powder ('other route'). Considering the serious consequences of these diseases, all means should be implemented to contain contagion.

This type of treatment can only be considered if the responsible serotypes have been formally diagnosed by laboratory analyses with an antibiogram. The antibiotic chosen then depends on the result of the antibiogram.

This practice, recognised by professionals, has not been scientifically assessed. But at this point in time, it is impossible to overlook the sharp contrast between how attached the sector's professionals are to this practice and the scientific questions it raises.

- ✓ Although strictly metaphylactic or curative, alternatives should be sought to the use of antibiotics in nest powder for want of impact studies.
- ✓ The prevention of respiratory complications on a farm affected by an immunosuppressant disease such as myxomatosis requires preventive respiratory antibiotic therapy. This mode is one part of the action plan that should be implemented, on the same level as immunisation (which is almost exclusively practised in breeding stock and is not 100% effective), the strengthening of hygiene measures and nutritional support. Oral administration (drinking water and medicated feedstuffs) is preferred, since the parenteral route is an aggravating factor in contagion. Oxytetracycline is the most commonly used antibiotic in this case. This control plan is implemented at the onset of myxomatosis on a farm and is generally applied in three to six successive batches.
- ✓ **Export:** Like for other sectors that export breeding stock, the requirements of importing countries can impose some preventive modes of antibiotic use that cannot be abandoned immediately unless the regulations in these countries change. The preventive individual use of long-acting antibiotics is necessary in particular to prevent the development of respiratory infections (pasteurellosis and staphylococcal infections).

⁶ *Bordetella* is a co-factor of *Pasteurella*. Eradicating *Pasteurella* eliminates the risk of *Bordetella*. However, when both types of bacteria occur concomitantly, the choice of antibiotic is different and more difficult since these two bacteria do not have the same antimicrobial resistance profile.

⁷ Use in the event of declared diseases in previous batches

• Practices to be controlled

Latest-generation cephalosporins and fluoroquinolones should be reserved for specific situations which should be clearly identified and strictly controlled.

The experts' recommendations for practices to be controlled are as follows:

- ✓ avoid all first-line use;
- ✓ use all possible means to justify the necessity of this mode of use;
- ✓ avoid all systematic use;
- ✓ request alternative supporting measures to gradually reduce these modes of use;
- ✓ prescriptions should be limited to a maximum period of three months.

• Practices with no further control

These include all practices not listed above that are already subject to rules for the prescribing and dispensing of medicinal products by veterinarians further to a clinical examination or as part of a treatment protocol. They remain subject to the general objective of reducing the antibiotic exposure of animal, human and environmental microbiota.

In this context, it is nonetheless necessary to insist on treatment compliance. Research should focus on implementing new treatment regimens taking into account the risk of antimicrobial resistance development.

Table 22: At-risk practices in the rabbit sector

	Parenteral route			Oral route (excl. premix)			Oral route-medicated premix			Local route			Other routes		
	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention*	Metaphylaxis	Curative
Aminoglycosides 1	E. coli, Salm			E. coli, Salm									E. coli, Salm		
Aminoglycosides 2	E. coli, Salm., Past., Bordetel.			E. coli, Salm.			E. coli, Salm.						E. coli, Salm		
Beta-lactams 1															
Beta-lactams 2															
Beta-lactams 3															
Quinolones				E. coli, Salm.											
2nd and 3rd G quinolones	Staphylo., Salm., Bordetel*.			E. coli, Salm.											
Lincosamides															
Macrolides 1	Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.								
Macrolides 2	Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.								
Other sulfonamides	Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.											
Polypeptide colistin	E. coli, Salm			E. coli, Salm			E. coli, Salm						E. coli, Salm		
Other polypeptides (bacitracin)				Clostridium											
Phenicols															
Pleuromutilin	Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.								
Rifampicin															
Tetracyclines	Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.								
Trimethoprim sulfonamides	Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.			Staphylo., Past., Bordetel.								
Furans															
Extemporaneous preparation															
Human antibiotics															

Individual curative treatment almost non-existent/ almost not used ?

Individual curative treatment almost non-existent/ almost not used ?

* Use in the event of a declared disease in previous batches

	Practice to be abandoned without delay		Practice to be controlled		Practice not inventoried
	Measures taken to abandon the practice over time		Practice with no further control		
bacteriu	Practice to be abandoned without delay except for infections related to the bacteria mentioned in specific situations in the text , for which the practice is to be abandoned over time and research into alternatives to this preventive treatment is to be rapidly undertaken				

5.3.2.5 At-risk practices in dogs and cats

The experts stress the difficulty inherent in the individual treatment of dogs and cats in terms of dosages and treatment compliance (non-compliance by prematurely stopping treatment, compliance difficulties leading practitioners to focus on the dosage form rather than the compound, self-medication after dispensing by a pharmacist upon presentation of an old prescription or even without a prescription).

They recommend raising pet owners' awareness of these issues in terms of antimicrobial resistance.

The conclusions of the Working Group for at-risk practices in dogs and cats are summarised in Table .

• **At-risk practices to be abandoned without delay**

- ✓ The use of 3rd and 4th generation cephalosporins and fluoroquinolones with no veterinary MA should be prohibited.
- ✓ The preventive use of any antibiotic for convenience surgery, whether administered by parental route or oral route post-surgery, should be abandoned immediately.
- ✓ The use of fluoroquinolones and 3rd and 4th generation cephalosporins outside of a curative context (i.e. based on a clinical assumption of infection with no verification of its bacterial nature) should be classified as an at-risk practice to be prohibited.
- ✓ The use of antibiotics by oral route for bacterial infections whose treatment can be local (eyes) or strictly surgical (contained abscess) should be prohibited.
- ✓ While intermittent or 'pulse' antibiotic therapy was used a few years ago (for economic reasons), this practice should be completely prohibited in the current context in which multi-resistant bacteria are emerging.
- ✓ The use of human antibiotics (when the class does not exist in veterinary medicine) should be prohibited unless justified by clinical and bacteriological examinations and in curative situations.

• **Measures taken to abandon the practice over time**

- ✓ The oral and/or parenteral use of fluoroquinolones and 3rd and 4th generation cephalosporins for non-convenience surgery is an at-risk practice that should eventually be abandoned. In some cases, it may still be used if epidemiologically, clinically and bacteriologically justified.

• **Practices to be controlled**

With any route of antibiotic administration other than the parenteral and oral routes, careful consideration should be given to the choice of compound.

The experts' recommendations are as follows:

- ✓ Avoid all first-line use of broad-spectrum antibiotics.
- ✓ Use all possible means to justify the necessity of this mode of use (e.g. nebulisation).
- ✓ Avoid all systematic use.
- ✓ Request alternative supporting measures to gradually reduce these modes of use.
- ✓ For specific cases requiring long treatments (e.g. osteomyelitis and prosthetic infections), prescriptions should be limited to a maximum period of three months.
- ✓ The use of off-label compounds should be accompanied by an antibiogram.

The use of 3rd and 4th generation cephalosporins and fluoroquinolones as first-line curative treatment (empiric therapy) should be controlled and remain exceptional. The experts recommend only prescribing these compounds after systematically undertaking bacteriological sampling and an antibiogram (to be controlled in a guide to good practices).

- **Practices with no further control**

These include all practices not listed above that are already subject to rules for the prescribing and dispensing of medicinal products by veterinarians further to a clinical examination or as part of a treatment protocol. They remain subject to the general objective of reducing the antibiotic exposure of animal, human and environmental microbiota.

In this context, it is nonetheless necessary to insist on treatment compliance. Research should focus on implementing new treatment regimens taking into account the risk of antimicrobial resistance development.

Table 23: At-risk practices in dogs and cats

	Parenteral route				Oral route				Local route			Other routes (nebulisation, etc.)		
	Prevention convenience surgery	Prevention non-convenience surgery	Metaphylaxis (farm)	Curative	Prevention convenience surgery	Prevention non-convenience surgery	Metaphylaxis (farm)	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative
Aminoglycosides 1														
Aminoglycosides 2														
Beta-lactams 1														
Beta-lactams 2														
Beta-lactams 3														
Quinolones														
2nd and 3rd G quinolones														
Lincosamides														
Macrolides 1														
Macrolides 2														
Other sulfonamides														
colistin / polymyxin														
Other polypeptides														
Phenolics														
Pleuromutilin														
Rifampicin														
Tetracycline														
Trimethoprim sulfonamide														
Furans														
Human antibiotics														
Fusidic acid														
Mupirocin														
Extemporaneous preparation														

	Practice to be abandoned without delay		Practice to be controlled		Practice not inventoried
	Measures taken to abandon the practice over time		Practice with no further control		

5.3.2.6 At-risk practices in the aquaculture sector

In this sector, given the high volumes of water and discharges containing residues of antibiotics and bacteria from treated growing ponds, the main antimicrobial resistance risk is environmental. Even though the assessment of this environmental risk was not included in the request, the experts underline the importance of taking into account avenues for improving aquaculture effluents in future studies in order to better characterise and control this risk of antimicrobial resistance through the environment.

The conclusions of the Working Group for at-risk practices in the aquaculture sector are summarised in Table .

• **At-risk practices to be abandoned without delay**

The preventive use of antibiotics in fish, while highly marginal since it is limited to antibioprophyllaxis with parenteral vaccination, should be abandoned. To avoid opportunistic infections at the point of injection, alternative methods such as dipping in disinfectant solutions should be preferred.

• **Practices to be controlled**

In farmed fish, the majority of antibiotics are used as metaphylactic treatments. This practice, based on the distribution of medicated feedstuffs in water to whole batches of fish, only some of which have clinical signs, is clearly 'at-risk' in terms of the selection and spread of resistance. It cannot currently be abandoned due to the lack of realistic alternatives and its control is recommended. It would be advisable in particular to specify decision-making criteria for the implementation of treatments.

Curative antibiotic use by dipping should be subject to effluent management.

Fluoroquinolones should be reserved for specific situations, which should be clearly identified and strictly controlled.

Regarding shellfish farming, there is a lack of recent research in this area and the use of antibiotics in this type of animal production raises questions in terms of good practices (appropriate treatment regimens, respect for consumers and the environment).

• **Practices with no further control**

Curative antibiotic use, which is also rare since it is limited to large fish with high economic value, does not require further control.

Table 24: At-risk practices in the aquaculture sector

	Parenteral route			Oral route (medicated premix)			Local route			Other routes (dipping, etc.)		
	Prevention (1)	Metaphylaxis	Curative	Prevention (1)	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative	Prevention	Metaphylaxis	Curative
Aminoglycosides 1												
Aminoglycosides 2												
Beta-lactams 1		Yellow			Yellow							
Beta-lactams 2												
Beta-lactams 3												
Quinolones					Yellow	Green						Yellow
2nd and 3rd G quinolones		(2)			(2)							
Lincosamides												
Macrolides 1		Yellow			Yellow							
Macrolides 2												
Other sulfonamides												
Poly peptide colistin												
Other poly peptides												
Phenicol	Red	Yellow	Green	Red	Yellow	Green						
Pleuromutilin												
Rifampicin												
Tetracyclines	Red	Yellow	Green	Red	Yellow	Green						Yellow
Trimethoprim sulfonamide	Red	Yellow	Green	Red	Yellow	Green						
Furans												
Human antibiotics												

(1) Preventive antibiotic use limited to certain parenteral vaccines

(2) Rare use, only in young fish (oral route) or adults with high added value (parenteral route in turbot, sturgeons)

Practice to be abandoned without delay	Yellow	Practice to be regulated
Practice not surveyed	Green with diagonal lines	Practice with no further regulation

5.3.2.7 At-risk practices in the equine sector

The conclusions of the Working Group for at-risk practices in the equine sector are summarised in Table.

• At-risk practices to be abandoned without delay

- ✓ The use of rifampicin is not scientifically justified except for the treatment of *Rhodococcus equi* infection;
- ✓ The preventive use of any antibiotic and particularly fluoroquinolones, 3rd and 4th generation cephalosporins and rifampicin should be abandoned without delay;
- ✓ Considering the insufficient scientific justification for antibiotic inhalation, aggravated by the tendency to self-medicate without veterinary advice, this practice should be abandoned.

• Measures taken to abandon the practice over time

Some at-risk practices remain essential and the experts recommend immediately developing measures so they may eventually be abandoned.

- ✓ Due to the issue of doping in horses, some practices of antibiotic use, while considered at-risk, cannot be abandoned. For example, the metaphylactic use of 3rd and 4th generation cephalosporins (justified by the MA and/or scientific publications) cannot always be avoided (no MA for penicillins G in 'crystalline' form; veterinary procaine penicillins posing a doping problem).
- ✓ The use of antibiotics by local cutaneous route is generally not justified. However, with severe exfoliative dermatitis caused by *Dermatophilus congolensis* and with epithelialisation problems, the *in situ* administration of antibiotics may be justified.

• Practices to be controlled

Some practices should be controlled so they are only used when strictly necessary. In particular, it is necessary to strictly regulate the use of latest-generation cephalosporins and fluoroquinolones, which should be reserved for specific situations that should be clearly identified by the sector.

The experts' recommendations for practices to be controlled are as follows:

- ✓ avoid all first-line use;
- ✓ use all possible means to justify the necessity of this mode of use;
- ✓ avoid all systematic use;
- ✓ request alternative supporting measures to gradually reduce these modes of use;
- ✓ prescriptions should be limited to a maximum period of three months.

Rifampicin should only be used in combination with at least one antibiotic from another class (see good practices) in order to limit the risk of resistance emerging.

• Practices with no further control

These include all practices not listed above that are already subject to rules for the prescribing and dispensing of medicinal products by veterinarians further to a clinical examination or as part of a treatment protocol. They remain subject to the general objective of reducing the antibiotic exposure of animal, human and environmental microbiota.

In this context, it is nonetheless necessary to insist on treatment compliance. Research should focus on implementing new treatment regimens taking into account the risk of antimicrobial resistance development.

Table 25: At-risk practices in the equine sector

	Voie parentérale			Voie orale			Voie locale génitale			Voie locale cutanée			Autres voies (nébulisation,...)		
	Prévention	Métaphylaxie	Curatif	Prévention	Métaphylaxie	Curatif	Prévention	Métaphylaxie	Curatif	Prévention	Métaphylaxie	Curatif	Prévention	Métaphylaxie	Curatif
Aminoglycosides 1	Red checkered	Green diagonal	Green diagonal						Green diagonal			*			
Amionoglycosides 2	Red checkered	Green diagonal	Green diagonal						Green diagonal						Red vertical
Bétalactamines 1	Red checkered	Green diagonal	Green diagonal						Green diagonal			*			
Bétalactamines 2									Green diagonal						
Bétalactamines 3	Red checkered	Red solid	Yellow solid						Yellow solid						Red vertical
Quinolones															
Quinolones 2 et 3ème G	Red checkered	Red solid	Yellow solid	Red checkered	Red solid	Yellow solid			Yellow solid						Red vertical
Lincosamides									Green diagonal						
Macrolides 1				Red checkered	Yellow solid	Yellow solid			Green diagonal						
Macrolides 2									Green diagonal						
Autres sulfamides															
Polypeptide colistine	Red checkered	Green diagonal	Green diagonal						Green diagonal			Red solid			
Autres polypeptides															
Phénicolés									Green diagonal			Red solid			
Pleuromutiline												Red solid			
Rifampicine				Red checkered	Yellow solid	Yellow solid						Red solid			
Tétracyclines	Red checkered	Green diagonal	Green diagonal						Green diagonal						
Triméthoprime sulfamide	Red checkered	Green diagonal	Green diagonal	Red checkered	Yellow solid	Green diagonal			Green diagonal			*			
Furanes															
Spécialités humaines	Red checkered	Red solid	Red solid	Red checkered	pour association avec rifampicine							Red solid			
Préparation extemporanée				Red checkered	Red solid	Red solid			Yellow solid			Red solid			Red vertical

Practice to be abandoned without delay	Yellow solid	Practice to be regulated	Grey solid	Practice not surveyed
Measures taken to abandon the practice over time	Green diagonal	Practice with no further regulation		

*Possible use for the treatment of dermatophilosis in some resistant cases

Conclusions of Section 5

- During this assessment, risks to human and/or animal health were taken into account in their various aspects, including the use of the same antibiotics to treat both humans and animals. This led the Working Group in particular to recommend reserving the use of latest-generation cephalosporins and fluoroquinolones for specific situations that should be clearly identified by sector and strictly controlled.
- In this assessment of at-risk practices, there was a common recommendation to abandon preventive practices of antibiotic use, immediately or over time. The treatment of domestic animals (dogs and cats) was no exception, aside for specific uses for non-convenience surgery. For other species, the experts point out some situations for which preventive antibiotic use cannot immediately be abandoned, even though this is an at-risk practice. Their abandonment will require some time, so that professionals may develop and adopt alternative measures, but the experts stress the need to seek out such replacement solutions without delay.

Each sector has its particularities in terms of at-risk practices. Therefore, the Working Group recommends that these specific situations be listed in collaboration with professionals. A first inventory was drawn up by the Working Group for various species. These lists should be revised on a regular basis to take into account available and validated alternative solutions and the health context. In this framework, action plans and timetables for the implementation of alternative measures and means could be defined.

- Regarding the poultry sector, the Working Group underlines that necessary changes to reduce at-risk practices should be adopted taking into account the globalised market, both in terms of the selection and circulation of end products. The sector has some strengths, including the current control of practices (many autopsies and antibiograms) and a high level of responsiveness to adapt practices on the basis of surveillance data. Efforts are already being made to research alternative solutions. They should focus on the main bacteria for which antibiotics are used (*E coli*, *Mycoplasma*, *Pasteurella*, *Riemerella*, *Enterococcus*, *Clostridium*) in order to abandon, as quickly as possible, preventive practices that are still necessary in some cases. Alternatives are not only general but also specific to each pathogen. They include eradication (*Mycoplasma*), the development of vaccines or autogenous vaccines (*Ornithobacterium*, *Riemerella*), animal genetics, phytotherapy and the use of competitive flora. Regarding the pig sector, the experts note that efforts have been made to improve farming conditions, making it possible to reduce infectious pressure and therefore antibiotic use: disease control in nucleus and multiplier herds, building renovation, compliance with batch management, with the use of all-in/all-out rooms, application of biosafety measures, etc. These efforts should be encouraged and extended to the majority of farms.

Research into alternatives to antibiotic therapy is also underway and should be continued. Such alternatives include the quantitative and qualitative improvement of food rations to better control digestive diseases, flora regulation using organic acids, enzymes, pro- and pre-biotics and vaccination.

- Regarding the rabbit sector, in which an inter-professional policy to reduce antibiotic use has been in place for several years, the challenge now is to gradually continue this reduction policy, so that the sector may adapt its practices to the new recommendations. The Working Group recommends continuing the limitation of medication in feedstuffs, which does not facilitate the treatment of batch fractions. Lastly, the experts underline the need to improve zootechnical parameters such as nutrition and farming conditions to further limit risks of infections.
- Regarding ruminants, the experts recommend researching and implementing alternatives to avoid the negative effects of critical production stages such as the batching of animals of various origins. The Working Group stresses that individual treatment, for a good percentage of ruminant farms, is a feasible practice in many

situations. This type of treatment should therefore be preferred, thus limiting risks of antimicrobial resistance. The treatment of mastitis is a significant challenge considering that it is the main indication for antibiotic use in the dairy sector. It should be subject to a global approach specific to each farm that is periodically reassessed in accordance with a professional standard. This work should be recorded in the farm's treatment protocol.

- Regarding cats and dogs, the Working Group recommends abandoning preventive antibiotic use for convenience surgery, regardless of the route of administration. The experts underline the significance of raising pet owners' awareness of the risk of antimicrobial resistance related to self-medication and illegal procurement. The use of human antibiotics should be limited to exceptional situations and the conditions of use should be strictly controlled.
- Regarding the aquaculture sector, the Working Group recommends researching alternatives to metaphylaxis, particularly through zootechnical innovations. Moreover, the experts underline the particularity of this sector in terms of the risk of antimicrobial resistance spreading in the environment due to the animals' living environment. Although the assessment of this environmental risk was not included in the request, the Working Group points out the significant issue of effluent management and recommends developing knowledge and resources in order to improve this management, to limit the spread of resistant bacteria and/or resistance genes.
- Regarding the equine sector, the Working Group stresses that the use of rifampicin should be exclusively reserved for the treatment of confirmed *Rhodococcus equi* infection and only in combination with other antibiotics. Moreover, the experts recommend abandoning the local cutaneous use of all antibiotics. They also recommend developing studies justifying antibiotic use by nebulisation. Lastly, they underline the significance of raising animal owners' awareness of the risk in terms of antimicrobial resistance related to self-medication.
- In general, all sectors combined, for the treatment of animal batches by metaphylaxis, sick animals should be identified as early as possible and veterinary supervision should be strengthened.
- In addition, common principles for practices 'to be controlled' should be defined and adapted by sector:
 - ✓ no systematic use;
 - ✓ avoid first-line use⁸;
 - ✓ documented justification of the use of these practices;
 - ✓ request for alternative supporting measures to gradually reduce these practices (corrective and alternative measures);
 - ✓ prescriptions of limited duration.
- Lastly, the experts recommend making as many efforts to reduce risk factors in the occurrence of diseases and the technical, economic and regulatory constraints as to eliminate at-risk prescribing practices in terms of antimicrobial resistance.

They stress the following points:

- ✓ The critical significance of biosafety measures, compliance with which requires good farm organisation, and building quality, whose renovation should be encouraged.
- ✓ The significance of acting at sector level on the organisation of critical production stages, in which antibiotics are very frequently used for prevention or metaphylaxis (clustering of animals of different origins, management of weaning in industrial farming, etc.).
- ✓ The importance, for certain sectors such as the pig sector, of creating perfectly

⁸ Choice of treatment relying on epidemiological and clinical data

healthy 'nucleus' herds born by caesarean section to guarantee the top-of-pyramid status in genetic schemes: Specific-Pathogen-Free (SPF) animals. If it is not possible to have SPF subjects, require more transparency from genetic organisations on the nature of guarantees provided to buyers of breeding animals.

- ✓ Since farm size and animal density can influence the course of infections, it is necessary to take these factors into account when determining the human and technical resources to be devoted to farms to control their health situation.
- ✓ The need to develop rapid diagnostic tools facilitating differential diagnoses.
- ✓ The European regulatory barrier to the revision of dosages from older MAs which needs to be removed, in keeping with the European Union's position on reducing risks of antimicrobial resistance.



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