Report of the 1st Meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)

Copenhagen, 15 - 19 June 2009

Part 1: WHO List of Critically Important Antimicrobials

Part 2: Strategic Framework for WHO Activities on Integrated Surveillance of Antimicrobial Resistance

World Health Organization

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We would like to thank the AGISAR members as well as the resource advisers for their valuable technical input; we are particularly grateful to Frank Aarestrup, Scott McEwen and Fred Angulo for their outstanding chairmanship and to Ezra Barzilay for excellent rapporteuring.

Finally we wish to express our sincere gratitude to the Danish Technical University for generous financial support and for hosting the meeting.

1. Preamble

The World Health Organization (WHO) Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) was established in December 2008 to support WHO's effort to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animals. In particular, the Advisory Group will assist WHO on matters related to the integrated surveillance of antimicrobial resistance and the containment of food-related antimicrobial resistance. The Terms of Reference of WHO-AGISAR are as follows:

- Develop harmonized schemes for monitoring antimicrobial resistance in zoonotic and enteric bacteria. This should include appropriate sampling.
- Support WHO capacity-building activities in Member countries for antimicrobial resistance monitoring by developing Antimicrobial Resistance (AMR) training modules for Global Foodborne Infections Network (GFN) training courses.
- Promote information sharing on AMR.
- Provide expert advice to WHO on containment of antimicrobial resistance with a particular focus on Human Critically Important Antimicrobials (CIA).
- Support and advise WHO on the selection of sentinel sites and the design of pilot projects for conducting integrated surveillance of antimicrobial resistance.
- Support WHO capacity-building activities in Member countries for antimicrobial usage monitoring.

The WHO-AGISAR comprises of over 20 internationally-renowned experts in a broad range of disciplines relevant to antimicrobial resistance, appointed following a web-published call for advisers, and a transparent selection process. WHO-AGISAR holds quarterly telephone conferences and annual face-to-face meetings.

WHO convened the first meeting of the AGISAR in Copenhagen, Denmark, from 15 to 19 June 2009.

The first part of the meeting was organized to follow previous expert consultations on critically important antimicrobials for human health risk management strategies of non-human use (1st WHO Expert Meeting on Critically Important Antibacterial Agents for Human Health, Canberra, Australia, February 2005; 2nd WHO Expert Meeting on Critically Important Antimicrobial Agents for Human Health, Copenhagen, Denmark, May 2007; and Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials, Rome, Italy, November 2007). The advisers updated the first revision of the WHO list of CIA taking into account available scientific information as well as newly developed antimicrobial drugs for human medicine.

The second part of the meeting focused on integrated surveillance of antimicrobial resistance; the experts 1) provided expert advice to WHO on containment of food-related antimicrobial resistance, 2) evaluated existing surveillance programmes to determine the minimum efforts required for establishing a programme on integrated surveillance of antimicrobial resistance in countries with limited resources, 3) drafted a strategic framework for WHO activities on surveillance and containment of food-related antimicrobial resistance.

Following opening remarks delivered by Dr Awa Aidara-Kane, of the World Health Organization and Lead of WHO-AGISAR, Dr Frank Aarestrup of the Danish Technical University, and local organizer of the meeting, was elected as overall Chairperson. Dr Scott McEwen of Ontario Veterinary College, Ontario, Canada, and Dr Fred Angulo of the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America (USA), were respectively elected Chairpersons of Part I and Part II. Dr Ezra Barzilay of the Centers for Disease Control and Prevention, Atlanta, USA, was elected as Rapporteur.

2. Executive Summary

Antimicrobial resistance is a global public health concern that is impacted by both human and non-human antimicrobial use. It is therefore essential to prevent and control emerging antimicrobial resistance problems in a coordinated manner in agriculture, human and veterinary medicine. The consequences of antimicrobial resistance are particularly important when disease is caused by pathogens that are resistant to antimicrobials considered *critically important* in the treatment of human disease by the World Health Organization.

WHO convened the first meeting of the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) in Copenhagen, Denmark on 15-19 June 2009. At this meeting, participants reviewed the criteria.

During the first part of the consultation, the experts adapted the WHO list of CIA developed in Canberra in 2005 and reviewed in Copenhagen in 2007. The AGISAR participants felt the criteria were appropriate; minor changes were made for sake of clarity of the text describing the criteria and greater explanation were given in the text accompanying the list.

The participants reviewed the categorization of drugs already on the list as well as new drugs available since the time of the 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health (Copenhagen 2007) list.

The participants came to conclusions regarding the classification of drugs which were very similar to those of the previous meeting in 2007 with the exception of tetracyclines, fusidic acid and mupirocin which were re-categorized, and the addition of the new agents doripenem, ceftobiprole and retapamulin which were added to the tables.

The participants suggested that **tetracyclines** be placed on the list of critically important drugs due to their use as one of the sole therapies in human brucellosis and the ability of *Brucella* spp. to transmit from animals to humans. Participants suggested that **fusidic acid and mupirocin** be elevated from important to highly important based on the evidence of transmission of MRSA from animals to humans.

Three **new drugs** were added to the list:

- ceftobiprole (cephalosporins, critically important)
- doripenem (carbapenems, critically important)
- retapamulin (pleuromutilin, highly important)

The participants discussed other drugs (televancin, oritavancin, iclaprim, cethromycin and ceftaroline) but decisions on these drugs were deferred since they are still under evaluation and not yet available.

The prioritization of classes of antimicrobials to be addressed most urgently, in terms of risk management strategies for non-human use of antimicrobials, resulted in the selection of three groups of antimicrobial agents: **quinolones, 3rd/4th generation cephalosporins, and macrolides.**

In the second part of the meeting, participants presented examples of antimicrobial resistance programmes in their particular countries and regions in an effort to evaluate existing

surveillance programmes and determine the minimum efforts required to establish an integrated antimicrobial resistance surveillance programme in countries with limited resources.

The meeting concluded with the development of a strategic framework for WHO activities on surveillance and containment of food-related antimicrobial resistance.

NB: In this document the word **"list"** refers to the entire listing of all antimicrobial classes used in human medicine. The term **"category"** refers to the characterization of various antimicrobials into the groupings of *critically important*, *highly important*, or *important*. The term **"class"** of drugs as used here refers to agents with similar chemical structures that exert an effect on the same target in bacteria and may be affected by the same mechanisms of resistance.

3. Introductory Chapter

3.1. Public Health Impact of Use of Antimicrobials in Animal husbandry: General Considerations and Recent Developments

The introduction of antimicrobial agents in human clinical medicine and animal husbandry was one of the most significant achievements of the 20th century. Antimicrobial agents have literally changed our way of living. We can now successful treat infections that previously were almost always lethal (e.g. *Staphylococcus aureus* bacteraemia).

Unfortunately, after the introduction of antimicrobials, bacteria resistant to antimicrobial drugs began to emerge, sometimes rapidly. This problem has continued to follow the introduction of all new antimicrobial compounds. This antimicrobial resistance poses a major threat to the continued use of antimicrobial agents in both human and veterinary medicine; a problem made worse because new and effective antimicrobials are not being developed at a sufficient rate nor are likely to be so in the future.

Antimicrobial agents are important for the treatment of infectious diseases in food animals and thereby play an important role in ensuring animal welfare and global food production. In addition to therapeutic use, an even larger mass/volume of antimicrobial agents is used for other purposes such as prophylaxis and growth promotion in some countries/regions. Consequently, very large amounts of antimicrobial agents are used in modern food animal production. This provides favourable conditions for development, emergence, spread and persistence of antimicrobial-resistant bacteria capable of causing infections not only in animals, but also in people. The great adaptive ability of bacteria has meant that resistant bacteria can evolve quickly and then rapidly spread worldwide. Over time, and under continued selection pressure, any initial fitness disadvantages faced by these newly resistant bacteria will disappear, leading to increased prevalence of these strains relative to their susceptible counterparts.

The antimicrobial agents used for food animals are frequently the same or else belong to the same classes as those used in human medicine. In addition, bacteria may be resistant to several classes of antimicrobials (co-resistance); thereafter, use of one class of antimicrobial may select for resistance against another, unrelated class. Resistant bacteria that develop and are carried in food animals can spread to people (mainly via foods but also by environmental spread and via direct animal contact). Examples include *Escherichia coli*, *Salmonella*, *Enterococcus*, *Clostridium difficile* and *Staphylococcus aureus*. These bacteria (especially *E. coli* and enterococci) can be carried in the bowels of humans, although mostly often only transiently. However, on occasions some of these enteric bacteria can cause non-bowel infections in people (e.g. urinary tract infections). If these bacteria are resistant to commonly used antimicrobial agents, then this causes an added problem for those people with these infections. Importantly, the genes that encode this antimicrobial resistance in what are normally commensal bacteria can be transferred to other more pathogenic bacteria, and many of these latter bacteria may reside for longer periods in people's bowel or on their skin, or cause more severe clinical disease.

If individuals carrying these resistant bacteria are admitted to a hospital, not only their own recovery could be compromised, but potentially the recovery of other patients in the healthcare facility should these resistant bacteria spread. Patients admitted to hospitals often need to receive prophylactic antibiotics because of procedures being performed (e.g. bowel

surgery). When these patients harbour resistant bacteria (e.g. VRE, resistant *E coli,* etc.), then these resistant bacteria will dominate after those people receive antibiotics, not only because these bacteria have now been given a selective advantage, but also because their competitors have been diminished in numbers. When resistant bacteria are present in higher numbers, this makes it easier for them to cause infections - not only in the person initially carrying them, but also in others since the higher numbers of resistant bacteria makes it more likely for them to spread from patient to patient within the healthcare facility.

This is why it is important that we minimize the risk that resistant bacteria might spread to people from food animals and why we need to decrease their spread in both the community and hospitals. This is especially important for "critically important" antibiotics, because if resistance to these products is present in bacteria, then available alternatives for treating life-threatening infections (e.g. bloodstream infections) may be few or none. Examples of particular concern that are, or have been present, in food animals following the use of antimicrobial agents, include *E. coli* and *Salmonella* resistant to 3rd and 4th generation cephalosporins and fluoroquinolones, *Staphylococcus aureus* resistant to all beta-lactam type drugs (i.e. MRSA), *Enterococcus* resistant to vancomycin (VRE) and *C. difficile*.

In general, the amounts and classes of antimicrobials used in food animals is currently not sufficiently documented or controlled worldwide. There is now increasing awareness of the potential problems for human health caused by antimicrobial-resistant bacteria occurring among food animals. Food animals and foods of animal origin are traded world-wide which means that the occurrences of antimicrobial resistance in the food supply of one country is potentially a problem for all countries. This emphasizes the need for global initiatives to monitor and control antimicrobial resistance and antimicrobial usage. Previous working groups hosted by WHO, FAO an OIE have addressed these issues extensively and have also provided suggestions for management actions to be taken by national and international authorities.[1, 2, 3, 4]

3.2. Antimicrobial Resistance in Foodborne and Enteric Bacteria - Recent Developments

All uses of antimicrobial agents eventually lead to the development of antimicrobial resistance. The importance of food animal reservoirs for problems with antimicrobial resistance in humans is documented best for well known zoonotic bacteria such as *Salmonella* and *Campylobacter*. A large number of studies have shown that the use of antimicrobial agents in food animals favours antimicrobial resistance among non-typhoid *Salmonella* and *Campylobacter*; later, these can transmit to and cause infections in people. This can then result in failure of antimicrobial treatment in people with resistant infections. Recent studies also suggest that people taking antimicrobials for other diseases are at increased risk of

[1] WHO global principles for the containment of antimicrobial resistance in animals intended for food. Report of a WHO consultation, Geneva, Switzerland, 6-9 June 2000. (http://www.who.int/salmsurv/links/en/GSSGlobalPrinciples2000.pdf).

[2] Joint FAO/WHO/OIE expert workshop on non-human antimicrobial usage and antimicrobial resistance: scientific assessment, Geneva, Switzerland, 1-5 December 2003. (http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_ZFK_2004.7.pdf).

[3] Second joint FAO/WHO/OIE expert workshop on non-human antimicrobial usage and antimicrobial resistance: management options, Oslo, Norway, 15-18 March 2004. (http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_ZFK_2004.8.pdf).

[4] Joint expert meeting on critically important antimicrobials. Report of the FAO/WHO/OIE expert meeting, FAO, Rome, Italy, 26-30 November 2007. (http://www.who.int/foodborne_disease/resources/Report%20joint%20CIA%20Meeting.pdf)

acquiring new infections due to antimicrobial resistant bacteria such as *Salmonella*. The main route of transmission between food animals and people is via contaminated food products. This transmission occurs mainly in the community through inadequately cooked food, but can also occur in hospitalized patients via the same route.

Food of animal origin is traded worldwide resulting in the dissemination of resistant bacteria from one country to the other. This necessitates a global initiative to monitor and control the spread of resistant bacteria.

Until recently it was the general belief that methicillin-resistant *Staphylococcus aureus* (MRSA) was almost entirely a hospital-created problem. However, during the last 10 years MRSA have spread to the community and since 2003 it has become clear that a new variant of MRSA (CC398) has emerged and spreads among food animals, primarily swine, in many countries. The importance of this new farm-associated MRSA for human health is not yet fully quantified, but it is already a problem for the control of MRSA in some countries and the prevalence seems to be increasing. All the reasons for the spread of MRSA among food animals are not known nor what has been the contribution of antimicrobial volumes or classes used in food animals towards facilitating this emergence and spread.

C. difficile colonize many food animals and also causes disease in some food animals with an associated high mortality (e.g. piglets). *C. difficile* is found in foods produced from food animals, sometimes frequently (e.g. 20% of samples of ground beef). People can ingest *C. difficile* spores from foods. In the Netherlands since 2005, there has been an increase in infections in people caused by similar *C. difficile* strain types as those found in food animals (i.e. PCR ribotype 078). Clinical infections associated with these strains have occurred mainly in younger people and were typically community acquired. In people, *C. difficile* infections and carriage are greatly increased by their use of broad spectrum antibiotics, especially cephalosporins and fluoroquinolone. Thus it would not be surprising if similar factors drive *C. difficile* proliferation and spread in food animals, although this has not yet been shown. Increased exposure and subsequent community carriage of *C. difficile* in people could increase the risk of *C. difficile* disease, especially among those that enter healthcare facilities and are treated with antibiotics. It may also increase the chance of *C. difficile* spores contaminating the hospital environment and spreading from person to person.

Recently, increasing numbers of studies have indicated that a major component of the antimicrobial-resistant *E. coli* causing extra-bowel infections in humans, may have originated in food animals, especially poultry. On a global scale, *E. coli* is the most important human pathogen causing many more infections than *Salmonella* and *Campylobacter* combined. Thus the importance of this organism, typically considered a benign commensal, should not be underestimated if confirmed in future studies.

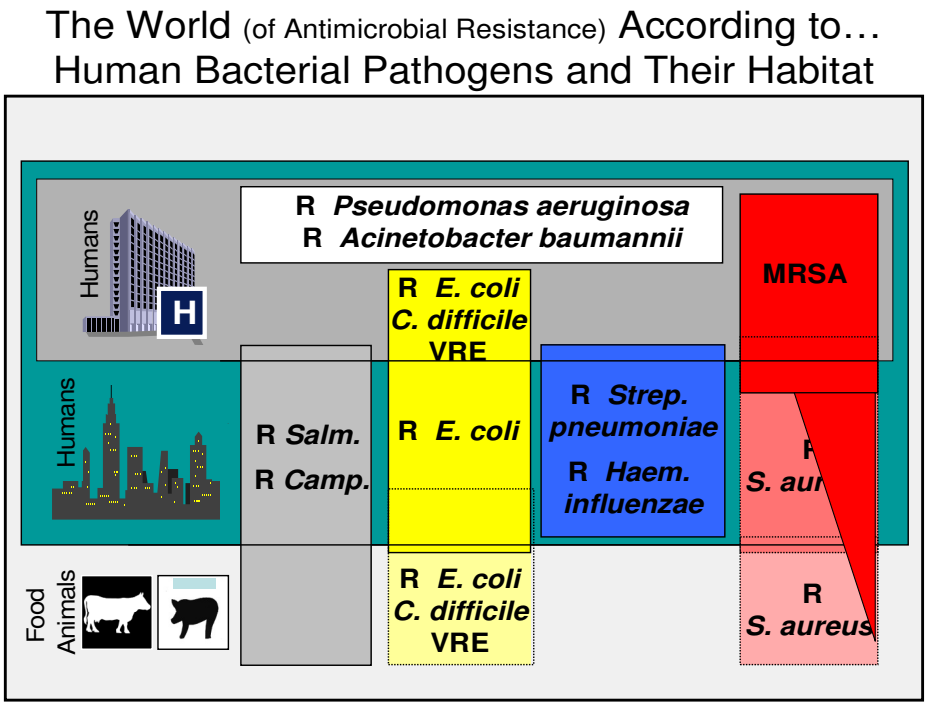

Fig 1. Schematic overview of some of the most important antimicrobial resistant pathogens and the over-lap between the different reservoirs. As indicated some pathogens are strictly confined within the human reservoir, whereas others have a mainly or partly animal reservoir.

In addition, to the transmission of resistant bacteria, the use of antimicrobial agents in food animals also selects for standalone and transferable resistance genes. These resistant genes can be transferred from animals to humans via non-pathogenic bacteria in food products and then be transferred to bacterial pathogens in the human gastrointestinal tract. The overall contribution of this mechanism has not been adequately documented. However, for example in the case of vancomycin and cephalosporin resistance it has been shown that the same types of resistance genes are present in both the humans and the animal reservoirs. Furthermore, in the case of streptothricin and apramycin it has also been documented that the introduction of these antimicrobial agents for food animals was followed by an emergence of resistance first in the food animal population and later in the human population, including in bacterial species such as *Shigella* and *Klebsiella.* These latter bacteria are not believed to transfer directly between food animals and humans and thereby represent strong evidence for horizontal transfer of the genes encoding for streptothricin and apramycin resistance.

Today global trade with food products is increasing. Thus, an increasing number of reports document that resistant bacteria can transfer from one country to another and then cause infections in the importing jurisdiction. Furthermore, people frequently travel internationally and it is also well-known that tourists can acquire resistant pathogenic and non-pathogenic bacteria in the countries they visit; later, these bacteria can then be taken home where they might cause further infections. This emphasizes the need for global control of antimicrobial resistance in the global food animal population.

3.3. Update on WHO initiatives in the area of Food-Related Antimicrobial Resistance

Three important initiatives are currently undertaken by WHO in the area of antimicrobial resistance.

3.3.1. Ad Hoc Codex Intergovernmental Task Force on Antimicrobial Resistance

Considering that antimicrobial resistance issues have implications for many disciplines, an that current risk assessment approaches for chemical and microbiological contamination are inadequate for risk assessment of antimicrobial resistance, the experts of the joint FAO/OIE/WHO meetings on Non -Human Antimicrobial Usage and Antimicrobial Resistance, recommended the establishment of a Codex Task Force to address this complex issue. The Codex Task Force on Antimicrobial Resistance was established in 2006 and held its first meeting in Seoul, Korea in 2007. The task force will develop a guideline document specific to AMR risk analysis taking into consideration the complexity and multidisciplinary aspects of AMR within the entire food production to consumption continuum, and the need to identify appropriate risk mitigation strategies. More specifically, these guidelines will provide a structured risk analysis framework to address the risks to human health associated with the presence in food and feed, and the transmission through food and feed, of antimicrobial resistant microorganisms or resistance determinants linked to non-human use of antimicrobial agents. The guidelines will describe the steps to be used by Codex or national/regional authorities in conducting risk analysis activities as they relate to AMR.

The initial phase of the framework consists of a group of tasks collectively referred to as preliminary risk management activities. A systematic preliminary risk management process brings the food safety issues into focus and provides a guide for further actions. The second phase of the framework is the conduct of a risk assessment that provides a transparent, science-based approach that characterizes the exposure pathways, the adverse health effects, and the human health impact associated with specific foodborne exposures to the antimicrobial resistant microorganisms of concern. The third phase of the framework includes identification, selection, and implementation of appropriate risk management actions to minimize and contain the identified human health risks. Good communication between risk assessors and managers as well as with other interested parties should be in place for a transparent and informed risk analysis. Furthermore these guidelines will emphasize the importance of integrated surveillance of antimicrobial use and antimicrobial resistance in this process.

3.3.2. Antimicrobial Resistance as Third Challenge of the WHO Patient Safety Programme

The Patient Safety Programme (PSP) delivers the patient safety programme of the WHO World Alliance for Patient Safety. As part of this programme, PSP includes an extensive action area developing strategic interventions in selected Patient Safety-relevant topics (Global Patient Safety Challenges). The 3rd Global Patient Safety Challenge is addressing the growing global threat of antimicrobial resistance. The programme is establishing a coalition of internal WHO programmes and external partners, including organizations representing civil society and patients. The programme is due to be launched in 2010. A Global AMR-work-plan is currently being developed. An additional document will summarize the Burden or AMR in a comprehensive way and will lead to ongoing AMR surveillance activities and future estimations of the Burden of AMR. Beginning 2010 a third Challenge intervention will be developed, pilot tested and distributed for implementation. Antimicrobial resistance related

to antimicrobial agents in animal husbandry is one of the topic areas to be addresses by this The 3rd Global Patient Safety Challenge

3.3.3. Establishment of an Advisory Group on integrated surveillance of antimicrobial resistance

The WHO Advisory Group on integrated surveillance of antimicrobial resistance was established in December 2008 to support WHO activities on integrated surveillance and containment of antimicrobials: Furthermore, the AGISAR will be asked to review and update the WHO list of Critically Important Antimicrobials for Human Health every two years.

PART I

WHO LIST OF CRITICALLY IMPORTANT ANTIMICROBIALS

CATEGORIZATION FOR THE DEVELOPMENT OF RISK MANAGEMENT STRATEGIES TO CONTAIN ANTIMICROBIAL RESISTANCE DUE TO NON-HUMAN ANTIMICROBIAL USE

2ND REVISION

4. Part I: WHO List of Critically Important Antimicrobials

4.1. Introduction

Use of antimicrobials in food animals can create an important source of antimicrobial resistant bacteria that can spread to humans through the food supply. Improved management of the use of antimicrobials in food animals, particularly reducing those "critically important" for human medicine, is an important step towards preserving the benefits of antimicrobials for people. The World Health Organization (WHO) has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine. Clinicians, regulatory agencies, policy-makers and other stakeholders can use this ranking when developing risk management strategies for the use of antimicrobials in food production animals. These lists will help regulators and stakeholders determine which types of antimicrobials could be used in food animal production and determine how these antibiotics might be managed (e.g. single animal therapy or mass medication via water, prohibiting off-label use, etc.). The use of these lists will help preserve the effectiveness of currently available antimicrobials. The ranking allows stakeholders to focus risk management efforts on drugs used in food animals that are the most important to human medicine and thus need to be addressed most urgently.

Effectiveness of critically important antimicrobials for human medicine should not be compromised by inappropriate over-use and/or misuse in the non-human sector. Agreeing on a list of antimicrobials whose use should be controlled/limited in the non-human sector is only one of many risk management strategies to contain the problem of antimicrobial resistance. There have been a number of recent different WHO initiatives and approaches to containing antimicrobial resistance in the human sector since the late 1990s. All these reports are available at: http://www.who.int/foodborne_disease/resistance/en/).

There is a need for internationally recognized principles for risk assessment (the probability of occurrence and the severity of adverse health outcomes) related to antimicrobial resistance owing to non-human use of antimicrobials. The purpose of these lists of antimicrobials is to function as part of, but not the sole part of risk assessments of non-human antimicrobial use and their potential impact on human health. This list focuses primarily on the consequences of the potential loss of effectiveness of various antimicrobials in the treatment of human disease. This list does not focus on other components of risk assessments such as the probability for development of resistant organisms in animals owing to animal use of antimicrobials (release assessment), and the probability of the risk of potential spread of resistant organisms from animals to humans (exposure assessment). An overall assessment of risk involves the release, exposure and consequence assessment integrated into an overall risk estimate. Prioritization among the classes of antimicrobials within the critically important category of the list should not be used to minimize the importance of other critically important antimicrobials in the same category.

At present the link between the potential spread of antimicrobial resistant pathogens appears most clear for bacteria, while the movement of resistance genes in bacteria from non-human sources to human bacteria is less evident. The list of antimicrobial agents considered *critically important* for human health (based on criteria defined below) is therefore confined to antibacterial agents for which there is potential that their utility in man might be threatened by bacterial resistance resulting from their non-human use. However, the criteria drawn up to select this list would be applicable to any antibacterial agents for which the mechanisms of bacterial resistance have not yet been elucidated.

History of the current document

The 1st WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Canberra, Australia, in 2005. Participants considered the list of all antimicrobial classes used in human medicine and categorized antimicrobials into three groups of *critically important*, *highly important*, and *important* based on criteria developed during the meeting.

Briefly (see explanation in section 4.4, page 19) the two criteria were: whether an antimicrobial is the sole or one of the few treatments available for serious human infection (**criterion 1**), and whether an antimicrobial agent treats diseases caused by pathogens that have the potential to transfer from animals to humans (**criterion 2**).

Participants developed these criteria to categorize all antimicrobial classes in human medicine and then applied those criteria to each drug or class of drugs. The term "class" of drugs as used here refers to agents with similar chemical structures that exert an effect on the same target in bacteria and may be affected by the same mechanisms of resistance (for example, ketolides are considered a variation on the macrolide class). In developing such criteria, participants took into account how certain antimicrobials are used in human medicine, the availability of data from randomized trials on the safety and effectiveness of various drugs in the treatment of particular diseases, the seriousness of the diseases treated with those agents and the availability of similarly effective therapies in the treatment of such diseases. Participants were then able to assess the potential consequences to human health of the potential loss of effectiveness of antibacterial agents due to bacterial resistance. Participants also took into consideration pathogenic and commensal bacteria (or their genes) that may transfer to people from animals, water, food products or the environment.

The 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Copenhagen, Denmark, in May 2007. Participants reviewed comments on the Canberra document received from various parties including the WHO Expert Committee the Selection and Use of Essential Medicines. Comments indicated that the title of the document should include an explanation regarding the purpose of this list, so participants modified the title accordingly to indicate that the purpose of this list is for consideration as part of developing risk management strategies for antimicrobial resistance owing to non-human antimicrobial use. The wording in the title was also modified from "**antibacterials**" to "**antimicrobials**" in order to be consistent with OIE listings and the concept that this list at present includes antibacterials but in the future may expand to include other agents. Participants also reviewed the two criteria used to classify human antimicrobials at the Canberra meeting and decided that these criteria remained valid. Participants then used those criteria to re-examine the categorization of all human antibacterial classes in light of new drug development and scientific information since 2005. On the basis of this re-examination, relatively few changes were needed to update the categorization of antimicrobials.

Participants were requested to prioritize agents within the *critically important* category in order to allow allocation of resources on the agents for which management of the risks from antimicrobial resistance are needed most urgently. For this, a more detailed application of the two original criteria was used than that employed to develop the original list developed during the 1st WHO Expert Meeting on Critically Important Antimicrobials for Human Health (Canberra, 2005). Participants considered drugs of greatest priority when **(i)** there are relatively large absolute numbers of people affected with diseases for which the drug is the sole or one of few alternative therapies, **(ii)** the overall frequency of use of the drugs in human

medicine for any use (whether appropriate or inappropriate) is relatively large, therefore increasing the threat to use of those drugs as sole therapy for serious diseases and **(iii)** the drug is used to treat disease owing to pathogens for which there is a greater degree of confidence in transmission of bacteria or their genes from non-human sources (animal, food, water and the environment) to humans (e.g. *S. aureus*, *Enterococcus* spp., *E. coli*, *Campylobacter* spp. and *Salmonella* spp.)

This prioritization resulted in the designation of the classes for which comprehensive risk management strategies are needed most urgently: quinolones, 3rd/4th generation cephalosporins and macrolides. Participants also emphasized that the prioritization of these three classes of drugs should not minimize the importance of other drugs categorized as *critically important* on the list.

Recommendations were provided to WHO on various aspects related to antimicrobial resistance in order to protect human health. It was pointed out that there are important gaps in our knowledge and that there is a need for better data to assess the various risk factors for the development of antimicrobial resistance due to non-human use as well as human use. There is a need for more and better information on burden of illness in relation to antimicrobial resistance attributable to non-human use of antimicrobials. There is also a need for data on antimicrobial utilization in both humans and animals, data on factors that lead to development and spread of antimicrobial resistance in various pathogens in animals and humans, and better data on the benefits of antimicrobials in both animals and humans in order to balance the benefits as well as the risks of antimicrobial use. In addition, there is a need to apply this document in different regions worldwide and give WHO appropriate feedback on its contribution to the containment of antimicrobial resistance due to non-human use.

The first part of this AGISAR meeting (Copenhagen, 2009) was a follow up of these two previous expert consultations. Experts were asked to review the Copenhagen 2007 list of CIA (1st revision of the CIA list) and come up with the 2nd revision of the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and new drugs.

What should the list be used for?

The list of CIA can be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance due to non-human antimicrobial use. Specific examples include:

- Prioritization of the antimicrobials characterized as *critically important* for most urgent development of risk management strategies in order to preserve their effectiveness in human medicine.
- Elevating the categorization of specific antimicrobials in regions/countries where it is warranted
- Designing antimicrobial susceptibility testing platforms for use in national programmes to monitor antimicrobial resistance
- Informing national policies related to antimicrobial resistance
- Developing appropriate new drugs and vaccines that will preserve critically important antimicrobial agents

What should the list NOT be used for?

- As the sole source of information for developing risk management strategies.
- As the sole source of treatment guidelines for either animals or humans.
- To minimize the importance of other *critically important* antimicrobials in the same category.

Geographical considerations

The availability of certain antimicrobials and the burden of disease may vary significantly in different regions of the world and as such may result in the need for countries to reclassify certain antimicrobials as *critically important.* For example, in many low-income countries, there is a lack of availability of quinolones and 3rd/4th generation cephalosporins to treat infections that are common and that often have serious consequences to human health (e.g. urinary tract infections, shigellosis, pneumonia, meningitis). These regions may therefore wish to reclassify an antimicrobial (e.g. trimethoprim-sulfamethoxazole) as a *critically important* antimicrobial if in that region the antimicrobial in question is the sole treatment available for serious infections (criterion 1). Another example is the combination of rifampicin and fusidic acid, which is frequently used in Australia as oral therapy for multidrug resistant *S. aureus* infections. Fusidic acid constitutes the sole or one of the few alternative therapies available for the treatment of multiresistant *S. aureus* (criterion 1). If fusidic acid was used in animals and resistance developed in animal staphylococcal strains (criterion 2), fusidic acid could be classified in Australia as *critically important.* Classes of antimicrobials that fall into this category have been highlighted in the tables with an asterisk.

It should be noted that the second criterion for categorizing antimicrobials is based on the likelihood of transmission of organisms from animals to humans. In some parts of the world, there are few alternatives to aminopenicillins for the outpatient management of common respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (criterion 1). Yet there is no evidence at present to suggest the transmission of *Streptococcus pneumoniae* and *Haemophilus influenzae* from animals to humans. For this reason, antimicrobials such as trimethoprim-sulfamethoxazole, which are widely used in developing countries to treat acute lower respiratory tract infections, are not categorized as *critically important* when considered to be alternative therapy for the treatment of bacteria such as *E. coli* (criterion 1) which are transmitted via the food-chain (criterion 2).

Comparison with WHO Essential Medicines List

It is important to note that the list of antimicrobials presented here differs from the WHO Model List of Essential Medicines. The purpose of this list of antimicrobial agents is for use as part of risk management strategies of non-human antibacterial use. The antimicrobial agents that appear on the WHO Model List of Essential Medicines comprise those that satisfy the priority health needs of the population; they were selected with regard to public health relevance, and evidence of efficacy, safety and comparative cost effectiveness. In contrast, cost was not a primary consideration in developing the list of antimicrobials for this current document as there is little choice regarding cost when an antimicrobial is the sole or one of few available alternatives to treat a disease. Most of the antimicrobials in the WHO's Model List of Essential Medicines also appear in this list. Those in the list of essential medicines that have not been listed as *critically important* in this document are chloramphenicol, clindamycin, cloxacillin, doxycycline, metronidazole, nitrofurantoin, spectinomycin and sulfonamides.

4.2. Updating the report of the 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health (Copenhagen 2007)

Participants updated *the report of the* 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health (Copenhagen 2007) taking into account recent developments in antimicrobial resistance and the comments received from WHO**.**

Recent developments in antimicrobial resistance relevant to the changes in the current list of Critically Important Antimicrobials

Bacteria producing Extended Spectrum Beta-lactamase (ESBL) producing enzymes or AmpC-like betalactamases

The prevalence of ESBL positive *Enterobacteriaceae,* including Salmonella and *E. coli,* from food animals that produce extended-spectrum beta-lactamases have continued to increase and has also emerged in more countries. More evidence that ESBL/AmpC-like-genes and ESBL/AmpC-like-harbouring clones spread through the food-chain has also become available.

Escherichia coli

Increasing numbers of studies suggest that a major part of the antimicrobial resistant *E. coli* causing infections in humans, have originated in food animals, mainly poultry. *E. coli* is the most important human pathogen on a global scale. It causes many more infections that *Salmonella* and *Campylobacter* combined. Thus the importance of this observation can not be underestimated if confirmed in future studies.

Salmonella enterica

Increasing number of reports, mainly from Africa, show that the importance of non-typhoidal *Salmonella enterica* as a cause of invasive infections in humans, primarily children. This suggests a more important role of *Salmonella enterica* as a major human pathogen in some regions than so far assumed.

Transferable low-level fluoroquinolone resistance in Enterobacteriaceae

Until recently, chromosomal mutations in different genes involved in DNA-transcription and replication were considered the main mechanisms of quinolone resistance in *Enterobacteriaceae*. New and transferable mechanisms have been described in the last decade. The new fluoroquinolone resistance mechanisms encoded by *qnr- and aac(6')I* genes are frequently located on plasmids that also carry other resistance genes (multiple resistances), notably resistance to higher generations of cephalosporins.

Emergence of pan resistant Gram-negative bacteria in human hospitals

Resistance to carbapenems, a class of drugs used for treatment of multidrug resistant Gram-negative bacteria (sometimes resistant to higher generation cephalosporins), is emerging in an increasing number of countries. In some settings, polymixins (e.g. colistin) are the only option for treatment of some patients. Additionally, outbreaks of hospital-acquired infections caused by pan-resistant bacteria have been reported. Although these specific problems are not linked

to antimicrobial resistance in food producing animals, it underlines the urgency to manage risks related to antimicrobial resistance.

Methicillin-resistant Staphylococcus aureus in animals

From being almost exclusively a health-care-associated pathogen, Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged during the last two decades into the community and has recently also caused infections in and colonized pets and production animals. Today MRSA should be considered a zoonosis. In countries with a low prevalence of MRSA in human medicine and a high prevalence in large animals, the transfer from animals can have a significant impact.

Clostridium difficile

Clostridium difficile has been identified among food animals in many countries and the same strain types have been found in animal and man. Thus, there are some indications that food animals may play a role in the epidemiology of this bacterium.

4.3. Changes in this document compared to the report of the 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health (Copenhagen 2007)

At the 1st WHO-AGISAR meeting in Copenhagen in June 2009 participants reviewed the criteria from the 1st and 2nd WHO Expert Meetings on Critically Important Antimicrobials for Human Health (Canberra 2005 and Copenhagen 2007, respectively) and considered that these remained valid, and provided clarification and greater explanation in the text accompanying the list. One instance of such clarification was reserving the use of the term "criterion" for primary categorization of antimicrobial agents. The qualifying terms used to prioritize the antimicrobial agents within the critically important category were changed from "Criterion" to "Application" to avoid confusion between the criteria themselves and the principles used to focus those criteria.

The participants also reviewed the categorization of drugs already on the list as well as new drugs available since the time of the 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health (Copenhagen 2007) list.

Changes in antimicrobial categorization

The modifications to the classification tables are listed below:

- Tetracyclines were re-categorized from *Highly Important* to *Critically Important*; this class represents antimicrobial agents that are among few alternatives for treatment of brucellosis – a zoonotic disease – thus meeting both criteria 1 and 2.
- Fusidic acid and mupirocin were re-categorized from *Important* to *Highly Important* based on the evidence of transmission of MRSA from animals to humans.
- Retapamulin, a pleuromutilin antimicrobial, was recently introduced in human medicine for topical treatment of MRSA infections. Although a new class in human medicine, pleuromutilins (valnemulin, tiamulin) have been used for more than 15 years in veterinary medicine. Thus, this class was not considered as new and pleuromutilins were classified as highly important.
- Two new substances, doripenem (a carbapenem, critically important) and ceftobiprole (a higher generation cephalosporins critically important) were added to Tables 1 and 2.

- Tables were modified to reflect the possibility of elevating the importance of antimicrobials according to regional considerations. Those highly important antimicrobials that would be considered one of the few alternatives to treat serious human disease in specific settings have an asterisk placed next to the "No" in the column for criterion 1. Each instance of a "No*" is followed by an explanation in the comment column.

4.4. The Criteria

4.4.1. Considerations in the development of criteria

The purpose of this list was to rank antimicrobial agents according to their importance to human health, to use as a tool for development of risk-management strategies for non-human use. This list would be one factor, but not the only factor, to consider in such risk management strategies. The categorization of specific drugs on the list may be customized by region or country to address their specific situation. The categorization may increase the importance on the list (e.g. increase from important to highly important or critical) but should not be used to decrease the importance of drugs on the list.

Participants did not consider such issues as the likelihood of resistance developing in non-human sources with non-human use of these drugs, or the likely exposure of humans to such organisms should such resistance develop. These may be important considerations in developing overall risk-management strategies but are not important considerations in the development of the criteria themselves, which relate to importance in human medicine.

The panel considered the issue of the time-course of the emergence of resistance. For instance, the history of the development of antimicrobial resistance shows that resistance may appear after long periods of usage (e.g. vancomycin resistance in *Enterococcus faecium* was first detected after the drug had been in use for over 40 years). Because resistance has not developed to date, this does not guarantee that it will not develop in the future.

The panel agreed that the list of *Critically Important* antibacterial agents should be updated regularly as new information became available, including data on resistance patterns, new and emerging diseases, and the development of new drugs.

In developing these classifications, participants considered that no antibacterial or class of antimicrobials used in human medicine could be considered unimportant. Participants therefore decided to address all antimicrobial drug classes used in human medicine to provide a comprehensive list divided into *Critically Important*, *Highly Important* and *Important* agents.

The criteria used by the panel for designating an antimicrobial agent (or class) as *critically important* are:

4.4.2. Criterion 1:

Antimicrobial agent is used as sole therapy or one of few alternatives to treat serious human disease.

Explanation: It is self-evident that antimicrobials that are the sole or one of few alternatives for treatment of serious infectious diseases in humans have an important place in human

medicine. Serious disease refers to those illnesses which, if left untreated, are likely to result in irreversible morbidity or mortality. Seriousness of disease may relate to the site of infection or the host (e.g. pneumonia, meningitis). Multidrug resistance alone may or may not influence patient outcomes. For instance, multidrug resistance in *S. aureus* limits options in the treatment of pneumonia, but incision and drainage alone appears effective without antimicrobials in the treatment of skin abscesses. Therefore drug resistance does not influence the treatment of patient outcomes in skin abscesses.

It is of prime importance that the utility of such antibacterial agents should be preserved, as loss of efficacy in these drugs due to emergence of resistance would have an important impact on human health. Participants included in the *Comments* section of the table examples of the diseases for which the given antibacterial (or class of selected agents within a class) was considered one of the sole or limited therapies for specific infection(s). This criterion does not consider the likelihood that such pathogens may transmit, or have been proven to transmit, from non-human sources to humans.

4.4.3. Criterion 2:

Antimicrobial agent is used to treat diseases caused by either: (1) organisms that may be transmitted via non-human sources or (2) diseases causes by organisms that may acquire resistance genes from non-human sources.

Explanation: Antimicrobial agents used to treat diseases caused by bacteria that may be transmitted to man from non-human sources are considered of higher importance, because these are most amenable to risk-management strategies related to non-human antimicrobial use. The organisms that cause disease need not be drug-resistant at the present time, but the potential for transmission shows the potential path for transmission of resistance now or in the future. The evidence for a link between non-human sources and the potential to cause human disease is greatest for certain bacteria (e.g. *S. aureus*, *Enterococcus* spp., *E. coli*, *Campylobacter* spp. and *Salmonella* spp.). Commensal organisms from non-human sources (animals, water, food, or the environment) also may transmit resistance determinants to human pathogens and the commensals may themselves be pathogenic in immunosuppressed hosts. The Comments section of the table includes examples of the bacterial genera or species of concern. It is important to note that transmission of such organisms or their genes need not be demonstrated, the potential for such transmission remains.

Interpretation:

Critically Important – those antimicrobials which meet both criteria 1 and 2.
Highly Important – those antimicrobials those which meet either criterion 1 or 2.
Important – those antimicrobials those which meet neither criteria 1 nor 2.

Other classes of antibacterial drugs not used in humans

Classes of drugs that are not used in humans and which are currently only used in animal medicine include arsenicals, bambermycins, ionophores, orthosomycins, quinoxalines, and others.

The list below is meant to show examples of members of each class of drugs, and is not meant to be inclusive of all drugs. Not all drugs listed in a given class have necessarily been proven safe and effective for the diseases listed.

4.5. Listing and categorization of antimicrobials used in human medicine.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	**Criterion 1**	**Criterion 2**	**Comments[1]**
Aminoglycosides amikacin arbekacin gentamicin netilmicin tobramycin streptomycin	Yes	Yes	(Criterion 1) Limited therapy as part of treatment of enterococcal endocarditis and MDR (Multi Drug Resistant) tuberculosis (Criterion 2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*), and *Mycobacterium* spp. from non-human sources
Ansamycins rifabutin rifampin rifaximin	Yes	Yes	(Criterion 1) Limited therapy as part of therapy of mycobacterial diseases including tuberculosis and single drug therapy may select for resistance (Criterion 2) May result from transmission of *Mycobacterium* spp. from non-human sources
Carbapenems and other penems doripenem ertapenem faropenem imipenem meropenem	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR *Enterobacteriaceae* (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
Cephalosporins (3rd and 4th generation) cefepime cefixime cefoperazone cefoperazone/sulbactam cefoselis cefotaxime cefpirome cefpodoxime ceftazidime ceftizoxime ceftobiprole ceftriaxone	Yes	Yes	(Criterion 1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources

(cont.)

[1] Comments were included in the list table when it was recognized that regional factors could affect the ranking, but these comments were not meant to be exhaustive and other regional factors could be relevant)

CRITICALLY IMPORTANT ANTIMICROBIALS (CONT.)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Glycopeptides teicoplanin vancomycin	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (Criterion 2) May result from transmission of *Enterococcus* spp. And MRSA from non-human sources
Glycylcyclines tigecycline	Yes	Yes	(Criterion 1) Limited therapy for infections due to MRSA (Criterion 2) May result from transmission of MRSA from non-human sources
Lipopeptides daptomycin	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources
Macrolides and ketolides azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin	Yes	Yes	(Criterion 1) Limited therapy for *Legionella*, *Campylobacter,* and MDR *Salmonella* infections (Criterion 2) May result from transmission of *Campylobacter* spp. and Salmonella from non-human sources
Oxazolidinones Linezolid	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources

(cont.)

CRITICALLY IMPORTANT ANTIMICROBIALS (CONT.)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin amoxicillin/clavulanate ampicillin ampicillin/sulbactam azlocillin carbenicillin mezlocillin penicillin G penicillin V piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanate	Yes	Yes	(Criterion 1) Limited therapy for syphilis (natural penicillins) *Listeria, Enterococcus spp.(aminopenicillins)* and MDR *Pseudomonas spp.(antipseudomonal)* (Criterion 2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* including *E. coli* as well as *Pseudomonas aeruginosa* from non-human sources
Quinolones cinoxacin ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin nalidixic acid norfloxacin ofloxacin pipemidic acid sparfloxacin	Yes	Yes	(Criterion 1) Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp. and MDR *Shigella* spp. infections (Criterion 2) May result from transmission of *Campylobacter* spp. and *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
Streptogramins quinupristin/dalfopristin, pristinamycin	Yes	Yes	(Criterion 1) Limited therapy for MDR *Enterococcus faecium* and MRSA infections (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources
Tetracyclines chlortetracycline doxycycline minocycline oxytetracycline tetracycline	Yes	Yes	(Criterion 1) Limited therapy for infections due to *Brucella, Chlamydia* spp. and *Rickettsia* spp. (Criterion 2) Transmission of *Brucella* spp. from non-human sources

(cont.)

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CRITICALLY IMPORTANT ANTIMICROBIALS (CONT.)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Drugs used solely to treat tuberculosis or other mycobacterial diseases cycloserine ethambutol ethionamide isoniazid para-aminosalicylic acid pyrazinamide	Yes	Yes	(Criterion 1) Limited therapy for tuberculosis and other *Mycobacterium* spp. disease and for many of these drugs, single drug therapy may select for resistance (Criterion 2) May result from transmission of *Mycobacterium* spp. from non-human sources

Comments on the classification of some specific antibacterial agents

Aminopenicillins and natural penicillins are among the few available therapies for invasive enterococcal and Listeria infections. *Enterococcus* spp. is transmitted to humans from food animals via the food-chain. Therefore, according to the criteria used to develop the list of Critically Important antibacterial agents, the natural penicillins and aminopenicillins have been classified as being critically important for human health.

Quinupristin/dalfopristin remains one of few available therapies for the treatment of infections due to multidrug resistant *Enterococcus faecium*, particularly given the emergence of Linezolid-resistant strains. A related streptogramin, virginiamycin, is known to select for quinupristin/dalfopristin resistance in *Enterococcus faecium* in food animals

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Amdinopenicillins mecillinam	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MDR *Shigella* spp. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Aminocyclitols spectinomycin	No	Yes	(Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Aminoglycosides (Other) kanamycin neomycin	No	Yes	(Criterion 2) May result from transmission of *Enterococcus* spp., and *Enterobacteriaceae* including *E. coli* and *Salmonella* from non-human sources.
Amphenicols chloramphenicol thiamphenicol	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for acute bacterial meningitis, typhoid and non-typhoid fever and respiratory infections (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* from non-human sources.
Cephalosporins (1st and 2nd generation) cefaclor cefamandole cefazolin cefuroxime cephalexin cephalothin cephradine loracarbef	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Cephamycins cefotetan cefoxitin	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources

(cont.)

HIGHLY IMPORTANT ANTIMICROBIALS (CONT.)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Fusidic acid	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MRSA (Criterion 2) May result from transmission of MRSA from non-human sources
Monobactams aztreonam	No	Yes	(Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Pseudomonic acids Mupirocin	No	Yes	(Criterion 2) May result from transmission of MRSA from non-human sources
Penicillins (Antistaphylococcal) cloxacilllin dicloxacillin flucloxacillin oxacillin nafcillin	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for staphylococcal infections (*S. aureus*) (Criterion 2) May result from transmission of *S. aureus* including MRSA from non-human sources
Pleuromutilins retapamulin	No	Yes	(Criterion 2) May result from transmission of *S. aureus* including MRSA from non-human sources
Polymyxins colistin polymyxin B	Yes	No	(Criterion 1) Limited therapy for infections with MDR *Enterobacteriaceae* (e.g. *Klebsiella* spp.*, E. coli, Acinetobacter, Pseudomonas* spp.)
Riminofenazines Clofazimine	Yes	No	(Criterion 1) Limited therapy for leprosy
Sulfonamides, DHFR inhibitors and combinations* para-aminobenzoic acid pyrimethamine sulfadiazine sulfamethoxazole sulfapyridine sulfisoxazole trimethoprim	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for acute bacterial meningitis, systemic non-typhoidal salmonella infections and other infections (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Sulfones dapsone	Yes	No	(Criterion 1) Limited therapy for leprosy

IMPORTANT ANTIMICROBIALS			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Cyclic polypeptides bacitracin	No	No	
Cyclic ethers fosfomycin	No*	No	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for Shiga-toxin producing *E. coli* O157
Lincosamides clindamycin lincomycin	No	No	
Nitrofurantoins furazolidone nitrofurantoin	No	No	
Nitroimidazoles metronidazole tinidazole	No*†	No	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for anaerobic infections including *C. difficile* †Evaluation based on its use as an antimicrobial agent

4.6. Prioritization within the critically important category

Given their mandate to prioritize agents within the *Critically Important* category, the Copenhagen panel (2007) focused on the two criteria developed by the Canberra panel to prioritize agents within the *critically important* category:

4.6.1. Focusing criterion 1:

Sole therapy or one of few alternatives to treat serious human disease

- *Application 1.1* – High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few alternatives to treat serious human disease.
- *Application 1.2* – High frequency of use of the antimicrobial for any indication in human medicine, since usage may favour selection of resistance.

Explanation: In order to apply criterion 1 in a focused manner, the panel developed two applications, both of which related to volume of antimicrobial usage. Increased volume of usage directly relates to development of resistance and therefore poses a greater threat to the utility as sole therapies. Furthermore, humans receiving antimicrobials for any indication have a greater susceptibility to acquiring infection by a foodborne pathogen resistant to those antimicrobial agents.

4.6.2. Focusing criterion 2:

Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources.

- *Application 2.1* – Greater degree of confidence that there are non-human sources that result in transmission of bacteria (*Campylobacter* spp.) or their resistance genes to humans (high for *Salmonella* spp., *Escherichia coli*, and *Enterococcus* spp*).*

Explanation: In order to apply criterion 2 in a focused manner, the panel developed one application. Risk-management strategies are most urgently needed in situations where evidence suggests that transmission from non-human sources is already occurring.

Table 2. Prioritization of antimicrobials categorized as *Critically Important* in human medicine

CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**Application 1.1**	**Application 1.2**	**Application 2.1**	**Comments**
Aminoglycosides amikacin arbekacin gentamicin netilmicin streptomycin tobramicina	No	No	Yes	(Application 2.1) Transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*), and *Mycobacterium* spp. from non-human sources
Ansamycins rifabutin rifampin Rifaximin	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance.
Carbapenems and other penems doripenem ertapenem faropenem imipenem meropenem	Yes	No	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources

(cont.)

CRITICALLY IMPORTANT ANTIBIOTICS (CONT.)				
Drug name	**Application 1.1**	**Application 1.2**	**Application 2.1**	**Comments**
Cephalosporins (3rd and 4th generation) cefepime cefixime cefoperazone cefoperazone/sulbactam cefoselis cefotaxime cefpirome cefpodoxime ceftazidime ceftizoxime ceftobiprole ceftriaxone	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
Glycopeptides teicoplanin vancomycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Glycylcyclines tigecycline	Yes	No	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* from non-human sources

(cont.)

CRITICALLY IMPORTANT ANTIBIOTICS (CONT.)				
Drug name	**Application 1.1**	**Application 1.2**	**Application 2.1**	**Comments**
Lipopeptides daptomycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Macrolides and ketolides azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Campylobacter* spp. from non-human sources
Oxazolidinones Linezolid	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available

(cont.)

CRITICALLY IMPORTANT ANTIBIOTICS (CONT.)				
Drug name	**Application 1.1**	**Application 1.2**	**Application 2.1**	**Comments**
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin amoxicillin/clavulanate ampicillin ampicillin/sulbactam azlocillin carbenicillin mezlocillin penicillin G penicillin V piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanate	No*	Yes	Yes	(Application 1.1*) In certain geographic settings, application 1.1 may be met: there may be a high absolute number of people affected by all disease for which the antimicrobial is the sole/one of few therapies available (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Enterobacteriaceae* from non-human sources
Quinolones cinoxacin nalidixic acid pipemidic acid ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin norfloxacin ofloxacin sparfloxacin	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Campylobacter* spp. and *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources

CRITICALLY IMPORTANT ANTIBIOTICS (CONT.)				
Drug name	**Application 1.1**	**Application 1.2**	**Application 2.1**	**Comments**
Streptogramins quinupristin/dalfopristin, pristinamycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Tetracyclines chlortetracycline doxycycline minocycline oxytetracycline tetracycline	No	Yes	Yes	(Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Drugs used solely to treat tuberculosis or other mycobacterial diseases cycloserine ethambutol ethionamide isoniazid para-aminosalicylic acid pyrazinamide	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance.

Those drugs categorized as highest priority met all three applications (1.1, 1.2 and 2.1): Cephalosporines, Quinolones and Macrolides.

4.6.3. "Highest" priority drugs

Macrolides are widely used in food animal production and are known to select for macrolide-resistant *Campylobacter* spp. in animals. At the same time, macrolides are one of few available therapies for serious campylobacter infections, particularly in children, in whom quinolones are not recommended for treatment. Given the high incidence of human disease due to *Campylobacter* spp., the absolute number of serious cases is substantial.

Quinolones are widely used in food animal production and are known to select for quinolone-resistant *Salmonella* spp. in animals. At the same time, quinolones are one of few available therapies for serious Salmonella infections, particularly in adults. Given the high incidence of human disease due to *Salmonella* spp., the absolute number of serious cases is substantial.

3rd and 4th generation cephalosporins are widely used in food animal production and are known to select for cephalosporin-resistant *Salmonella* spp. in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella infections, particularly in children. Given the high incidence of human disease due to *Salmonella* spp., the absolute number of serious cases is substantial.

NOTE: Amoxicillin is categorized as critically important but has not been ranked in this report as treating a large absolute number of people with serious disease based on the incidence of Listeria and enterococcal infections (application 1.1). However, in low-income countries, amoxicillin may be extensively used for many infections (application 1.2) and its main use may be for serious infections such as pneumonia which have a high disease burden. Such countries may wish to consider amoxicillin as having met application 1.1.

4.7. Conclusions

Participants reviewed all the agents used in human medicine previously categorized, during the 2nd WHO Expert Meeting on Critically Important Antimicrobial Agents for Human Health, (Copenhagen 2007) as well as several antimicrobial agents that have been approved for use since that time. The participants came to conclusions regarding the classification of drugs which were very similar to those of the previous meeting in 2007 with the exception of tetracyclines, fusidic acid and mupirocin which were re-categorized, and the addition of the new agents doripenem, ceftobiprole and retapamulin which were added to the tables.

The prioritization of classes of antimicrobials to be addressed most urgently, in terms of risk management strategies for non-human use of antimicrobials, resulted in the selection of three groups of antimicrobial agents: quinolones, 3rd/4th generation cephalosporins, and macrolides. These drugs meet both criteria 1 and 2 (being the sole or one of few alternatives to treat serious human diseases, and used to treat diseases that may result from transmission of bacteria or their resistance genes to humans from non-human sources). In addition, these drugs are used widely and the absolute numbers of people affected by the diseases for which they are the sole therapies are relatively common. These drugs also are used to treat diseases due to organisms where there is the greatest degree of confidence of a non-human source of bacteria or genes.

The antimicrobials listed as those of highest priority for risk management strategies is identical to those mentioned in the list developed at the Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials, held in Rome, Italy, in November 2007 (report available at: ftp://ftp.fao.org/docrep/fao/010/i0204e/i0204e00.pdf) and are to be included on any priority list. The evidence presented at that meeting indicated that the list of critically important classes of antimicrobials should include; quinolones and 3rd generation

cephalosporins for *Salmonella* and other *Enterobacteriaceae*, as well as quinolones and macrolides for *Campylobacter* spp. (see page 18 of the report: http://www.who.int/foodborne_disease/resistance/en/).

4.8. Recommendations to WHO on the use of the list of Critically Important Antimicrobials

Participants recommend the following activities by WHO to promote the use of the list of CIA:

- Develop educational material for prudent antimicrobial use guidelines in plain language and translated versions for all stakeholders
- Establish a working group to measure the impact of the guidance
- Partner with WHO Global Foodborne Infections Network (GFN) to include, in regional training, information on how the CIA list can be used appropriately; along with examples of other completed risk assessments
- Seek feedback from stakeholders
- Communicate to regulatory authorities, via INFOSAN or other partners, experience of use of the list in surveillance and risk management
- Continue collaborative work with other agencies such as OIE and FAO

PART II

STRATEGIC FRAMEWORK FOR WHO ACTIVITIES ON INTEGRATED ANTIMICROBIAL RESISTANCE SURVEILLANCE

5. Part II - Strategic Framework for WHO Activities on Integrated Antimicrobial Resistance Surveillance

5.1. Introduction

In the second part of the meeting, the objectives of the advisers were:

- To take note of existing integrated surveillance programmes and to determine the minimum requirements to establish an integrated antimicrobial resistance surveillance programmes in countries with limited resources.
- To draft a strategic framework for WHO activities on surveillance and containment of food-related antimicrobial resistance (building as much as possible on existing WHO initiatives, e.g. WHO Global Foodborne Infections Network (GFN), WHO initiative to estimate the Global Burden of Foodborne Diseases).

5.2. Integrated Antimicrobial Use Surveillance in resource-limited countries

This section outlines the participant's discussion on the minimal elements required for integrated antimicrobial resistance surveillance systems.

There are several resources in existence that address integrated surveillance of antimicrobial resistance in foodborne pathogens. The term **"integrated monitoring" or "integrated surveillance"** in this context refers to the ongoing testing of foodborne bacteria recovered from humans, food animals, and meats derived from food animals, plus data analysis and reporting.

Integrated monitoring requires a close collaboration between the medical, veterinary and food sectors. A selection of relevant resources of antimicrobial resistance surveillance is provided in ANNEX 3 of this report.

General public health prerequisites include the presence of sufficient infrastructure and understanding to:

- Recognize a public health burden due of enteric illness due to a specific foodborne etiologic agent
- Adequate health care infrastructure to properly collect clinical specimens and perform microbiological culture as part of routine patient care.
- Identify sites where laboratory facilities are in place, or where there is a plan in place for transporting isolates to a reference laboratory
- Capacity to capture, analyse and report surveillance data

5.2.1. Sampling

Because *Salmonella* it is a major foodborne pathogen around the globe, members of this genus are the first priority for testing. Expanded monitoring would add other common foodborne pathogens such as *Campylobacter, E. coli,* or other microorganisms. Initial monitoring would focus on human isolates from hospital and other public health laboratories, and include both hospitalized patients and outpatients. Expanded human sampling strategies can include select sub-populations (elderly, young, healthy carriers).

As programmes mature and move towards integrated sampling, it is recommend that monitoring of non-processed retail raw meats are added as the next element of testing. Testing of samples from food animal sources would be the third step in programme expansion.

5.2.2. Retail Meats Sampling and Testing

For integrating human and retail meat surveillance, countries must have the capacity to collect retail foods and culture relevant food matrices for the presence of *Salmonella*. Other WHO capacity building activities like GFN may help provide technical support and training in microbiology.

It is important to capture the source of the isolates and as much additional information as possible (e.g. date, sample type, animal species, location). After evaluating available laboratory strains for their relevance, they can be sent to the national reference laboratory for further testing.

Retail meats can include protein sources from beef, chicken, turkey, fish, pork, lamb, etc. The meat samples should be collected in a manner that reflects the purchasing habits of the consumer (i.e., open market vs. chain store). Selection of meats for surveillance should also reflect consumption preferences of the population, but may be varied year-to-year to capture multiple commodities. See FAO Statistical Database (FAOSTAT) for consumption data in different countries.

Retail meat isolates should be sent to reference laboratories where comparable testing schemes are used, and data must be made available for comparison with human isolates. The advisory group recommends tasking an individual or group with coordinating data collection and the generation of integrated analyses and reporting.

5.2.3. Animal Sampling and Testing

Slaughter houses are usually the most convenient point to collect animal samples for testing, and allows for the analysis of samples close to the consumer market. Animal species to be sampled should ideally correspond to the retail meats under surveillance. Specimens for culture should be collected from the intestinal contents of animals.

Several countries have already conducted pilot studies which demonstrate integration of all three areas described above. The data obtained by these studies may be used as reference material.

A sound monitoring programme has minimum laboratory testing capacity. Laboratories must be able to:

1) Isolate, on artificial growth medium, the target pathogen(s) from different specimen types.

2) Identify bacteria to the genus and species levels using accepted microbiological methods.

3) Determine serotypes of *Salmonella* or have access to a reference testing centre. Serotyping is a critical part of *Salmonella* surveillance. It is not expected that all laboratories would test for all possible serotypes of *Salmonella*. There should be understanding of the most common serotypes in a given region in order to ensure that an adequate supply of antisera is available.

4) Perform antimicrobial susceptibility testing using validated methods according to established standards (e.g. CLSI, ISO), including the use of appropriate quality control organisms. It is preferable to generate quantitative data. If disk testing is used, zone diameters (in millimetres) should be captured. Participation in quality assurance programmes is necessary. Established external programmes such as EQAS are recommended.

   Recommended antibiotics to test for *Salmonella* are:

   Cefotaxime or Ceftriaxone
   Nalidixic Acid
   Ciprofloxacin
   Ampicillin
   Tetracycline
   Chloramphenicol
   Gentamicin
   Streptomycin
   Trimethoprim
   Sulfonamide

   If possible all isolates should be tested for antimicrobial susceptibility. If this is not achievable, a representative subset of isolates should be tested. For determining the minimum sample size for testing, see Surveillance Standards for Antimicrobial Resistance, WHO 2001, Table 1. See also Report of the Task Force on Zoonoses Data Collection including a proposal for harmonized monitoring scheme of antimicrobial resistance in *Salmonella* in flow, turkeys, and pigs and *Campylobacter jejuni* and *C. coli* in broilers, EFSA Report, 2007, Appendix A.

5) Data should be captured electronically using data management software such as WHONET or other appropriate tools. Data should be captured and maintained by the reference laboratory. In a timely manner, aggregated summary data should be made available to the submitting laboratory, publicized in stakeholder reports, and transmitted to public health officials. Data can be captured locally and extracted in a manner to maintain patient confidentiality and sent to a coordinating body that can further aggregate data with other countries for summary reports. Another option would be to send isolate-level data files to a global server for subsequent aggregation and reporting. Merging antimicrobial susceptibility data with other available data sets such as PulseNet and GFN enhances the usefulness of the information. (See previous WHO consultations and references to EnterNet and PulseNet policy).

5.2.4. Data Management and Reporting

The WHONET software is available at no charge and is widely used in many countries. It is necessary that an individual or group be tasked with coordinating data collection and the generation of integrated analyses and reporting.

Facilitate WHONET training and customizing to regional needs.

Provide data template to allow expansion of GFN country databank to include susceptibility templates for data management and reporting.

5.2.5. Identified Gaps to be addressed

The group acknowledged that proficiency gaps exist in laboratories monitoring antimicrobial resistance in foodborne pathogens that should be addressed in revised training documents and included in future training courses. These include:

- Internal quality control deficiencies in laboratories
- Weaknesses in laboratory quality management including quality assurance protocols
- Epidemiology training in surveillance of resistance and interpretation of data
- A formalized outline for launching in-country pilot studies for surveillance of antimicrobial resistance in foodborne bacteria
- Tools to communicate and present summary data to different audiences
- Guidance on ways to identify and train a leading coordinating in country
- Provide WHONET training

Table 3: Surveillance and monitoring priorities.

Type	Venue for Sample Collection	Type of Test/ Screen	Resource Needs	National Reporting	Regional Data Sharing	International Data Sharing
Human	Level 1. Collect samples from Hospitals: Regional/ National Level 2. Collect samples from Public Health Laboratories Level 3. Collect samples from Sub-Populations, e.g. young, elderly, food workers	*Salmonella* 1. Serotyped 2. Susceptibility Testing for Surveillance 3. Target list of 10 Core AMA to analyse 4. Establish minimum number of isolates; randomize if needed 5. Generate quantitative susceptibility data (e.g. MIC, zone diameters)	1. Staffing to support sample collection in hospitals 2. Mechanism to capture and retain isolates 3. Laboratory Capacity (WHO designate National Reference Laboratory; Standardized methods, (e.g. CSLI, ISO) 4. Funding for transport of samples	1. Reporting infrastructure 2. Electronic data collection 3. Develop WHONet default for analysing the data 4. Reference Laboratory should capture data and report back as needed for patient management 5. Summary data to National Competent Authority, develop interpretation and trends 6. Sharing data with stakeholders (cleaned of personal identifiers) Utilize regional laboratories where available to assist in data analysis	1. Network of regional laboratories 2. Data submitted to regional integrator, e.g. PAHO	1. WHONET 2. Global Foodborne Infections Network (GFN) data server

Food	Level 1. Collect samples on Retail Meat commodity of choice. Level 2. Country should do an assessment of available isolates from for retail meats	Same as above Level 1. Need appropriate sample collection, as defined by WHO Level 2. WHO should assist countries in evaluating sample set to determine if representative of food consumed in country	Level 1. Collection capacity for retail foods at appropriate markets (proportional to where consumers commonly purchase their meat) Level 2. If useful, request to send all available samples to National Reference Laboratory	Same as above, unless nation has National Reference Food Laboratory If so, identify a central body to coordinate data collection and dissemination Utilize regional laboratories where available to assist in data analysis	Same as above	Same as above
Animal	Level 1. Collect samples from Slaughter Houses; sampling of same commodity as retail meat	Use OIE or other appropriate sample collection Testing of intestinal contents	Collection capacity should capture regional, seasonal and geographic differences if possible	A National Reference Laboratory should either coordinate with the Animal Reference Laboratory, if appropriate, or expand to accommodate these samples. Utilize regional laboratories where available to assist in data analysis.	Same as above	Same as above

5.2.6. Developing a Model

There are several resources in existence that discuss monitoring of antimicrobial use in animals. A selection of these resources includes:

- OIE Terrestrial Animal Health Code 2008 (Section 6, Chapter 6.6, available at http://www.oie.int/eng/normes/Mcode/en_chapitre_1.6.6.htm)
- Report of an *ad hoc* WHO expert consultation titled "Monitoring antimicrobial usage in food animals for the protection of human health" (available at http://whqlibdoc.who.int/hq/2002/WHO_CDS_CSR_EPH_2002.11.pdf)
- A review of studies focusing on "Medicines use in primary care in developing and transitional countries" (available at http://www.who.int/medicines/publications/primary_care_8April09.pdf)

The documents pertaining to use of antimicrobial agents in animals describe an approach to the monitoring of quantities of antimicrobial use in animal husbandry; they do not, however, provide sufficient technical guidance on how to establish such surveillance.

The review of the "Medicines use in primary care in developing and transitional countries", however, provides examples of what can be done, especially in limited-resource settings. Some of these models may be used as a starting point for the development of models for integrated surveillance of antimicrobial use and resistance.

There is consensus among reports of expert committees that the models for antimicrobial use data collection will vary from country to country; the participants approached this outcome using a stepwise approach as described below. This approach may be used for both animal and human drug use surveillance.

Steps:

1) Describe drug distribution system in the country and identify purchase venues outside of the mainstream regulatory system (e.g. internet sales, importation medicated animal feeds and movement of pharmaceuticals across open borders);

2) Identify which drugs are actually in commercial circulation;

3) Identify potential points of data collection;

4) Assess what each data source represents;

5) Set parameters for precision and completeness of the surveillance system; and

6) Establish priorities according to the needs and resources available.

Table 4: Options for antimicrobial agent use data collection

Type of Antimicrobial Agent Use Data (in order of priority / degree of refinement)	**Source / Method of Acquisition**	**Methods**
Situation Analysis / Description of Antimicrobial Distribution and Use Practices	• Competent authorities • Physicians / Veterinarians • Pharmaceutical industry • Hospitals • Farmers • Own-use import by internet purchase etc	Key informant interviews / surveys
National level consumption data	• Customs declarations • Pharmaceutical industry / wholesalers • Pharmacies • Physician / Veterinary records • Farmer records • Wholesalers & other intermediaries	Accessing data directly from the source Electronic or paper records Surveys, interviews Sentinel studies Targeted studies
National data aggregated to overall hospital and community population levels	• Hospital • Pharmacies • Physicians	Electronic or paper records Prescriptions Surveys
Data aggregated to species level	• Pharmacies • Wholesalers & other intermediaries • Veterinary records • Farmer records	Accessing data directly from the source Electronic or paper records Surveys, interviews Sentinel studies Targeted studies
Data aggregated to species and group or individual animal treatment – level	• Pharmacies • Wholesalers & other intermediaries • Veterinary records • Farmer records	Determined by formulation Veterinary records or bills, prescription data from pharmacies, farmer's records
Individual hospital / outpatient clinic / veterinary practice level	• Hospital • Clinic • Veterinary practice	Veterinary records or bills, prescription data from pharmacies, farmer's records
Farm / animal-level data	• Pharmacies • Wholesalers & other intermediaries • Veterinary records • Farmer records	Veterinary records or bills, prescription data from pharmacies, farmer's records

5.2.7. Developing training packages on integrated surveillance

(to be taught in WHO GFN advanced workshops)

A standard training programme should include guidance on how to establish quantitative drug-use surveillance, how to standardize data collected, how to perform quality assurance and how to effectively communicate the data collected in a report format.

This training programme should be modular in nature and easily adaptable to different settings. Regional needs can vary dramatically; for example in some settings national data may be available, while in other settings data sources may be limited to the results of pilot or sentinel surveys.

A starting point for developing a curriculum focusing on drug use surveillance may be the training courses offered by the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no) focusing on the Anatomical Therapeutic Chemical (ATC) Classification for surveillance of human drug use, which could also be adapted to surveillance of animal drug use, based on the ATC-VET system. Furthermore, the European Society for Clinical Microbiology and Infectious Diseases' Study Group on Antibiotic Policies (ESGAP, available at http://www.escmid.org/research_projects/study_groups/esgap) offers training on monitoring drug use, which could contribute to the development of a comprehensive, modular curriculum.

An important component of such a curriculum should also include training in basic epidemiological survey methods, population sampling strategies as well as a variety of analytic tools. Finally, a "train-the-trainer" programme would be an important adjunct to the curriculum and would likely increase the uptake of the training programme and its effectiveness.

5.2.8. Developing user-friendly standardized tools to generate and share reliable data on integrated Antimicrobial Use Surveillance in resource-limited countries

(to be used at country level)

A key component of a comprehensive, modular training programme for establishing an integrated antimicrobial use surveillance system is the development of common, flexible protocols that serve as templates for the development of national systems for collection of data on drug use. These protocols would serve as a common starting point that can be further modified and adapted to meet specific national/regional needs.

The development of a user-friendly "toolbox" should focus on practical, easy to use and inexpensive products such as:

- Data collection and analysis software (e.g. Epi-Info)
- Open source, productivity software available in many languages(e.g. OpenOffice)
- Drug-use calculators including a standardized unit of measurement of drug use
- A suite of communication, advocacy, education materials to raise awareness about prudent use of drugs and the consequences of imprudent use and resistance emergence.

5.3. WHO-AGISAR Strategic Framework

5.3.1. Immediate action item:

1) AGISAR should meet on a yearly basis and hold quarterly conference calls. Next meeting take place in Guelph in June 2010 and will be organized in conjunction with the 2nd ASM meeting on Antimicrobial Resistance in Foodborne and zoonotic bacteria to be held at Toronto, Canada.

5.3.2. Short term (2009) action items:

1) Develop a common flexible protocol on international harmonization that can serve as a template for the national systems for *collection, analysis* and *reporting* of data on antimicrobial drug usage. Form a subcommittee on "Integrated Surveillance of Antimicrobial Usage" will be chaired by Kari Grave.

2) Develop a common flexible protocol on international harmonization of *resistance surveillance activities* for collection, analysis and reporting of data on antimicrobial drug resistance starting for existing programmes. Form a sub committee on "International Harmonization of Antimicrobial Surveillance" will be co-chaired by Patrick McDermott and Frank Aarestrup.

3) Facilitate the enhancement of capacity building through GFN for the surveillance of AB drug usage and resistance, particularly in developing countries. The sub committee on "capacity building " will be co-chaired by Rene Hendricksen, Danilo Lo Fo Wong and Awa Aidara-Kane.

4) Ensure close collaboration with other WHO/FAO/OIE initiatives. This initiative will be led by Awa Aidara-Kane.

5) Work with the WHO collaborating centre for surveillance of AB resistance (WHONET):1) to identify software development needs to support integrated surveillance of AMR; 2) to develop strategy for dissemination and use of the software. The subcommittee on "Software Development and Dissemination" will be chaired by John Stelling.

6) Facilitate pilot studies focusing on integrated surveillance of Antimicrobial resistance, and antimicrobial drug use, with appropriate interventions in one or more developing countries. The subcommittee on "Pilot projects" will be co-chaired by Enrique Pérez-Gutiérrez and Rebecca Irwin.

5.3.3. Longer term action items:

1) Facilitate the identification of regional and national reference labs (veterinary, human and public health) to focus capacity building.

2) Facilitate the identification of competent authorities (veterinary, human and public health) in order to advance the communication capacity and surveillance.

3) Develop communication strategy and advocacy to promote integrated surveillance and to promote the use and interpretation of surveillance data at the national level for policy and local level to support therapeutic decisions.

5.4. Final Recommendations to WHO

1) Identify national/regional reference laboratory(s) for enteric pathogens that can characterize *Salmonella* isolates as to serotype and antimicrobial susceptibility.

2) Work with regional office, OIE and FAO to facilitate intersectoral collaborations.

3) Provide information to reference laboratories on sources of quality reagents.

4) WHO should facilitate acquisition of sufficient resources to allow susceptibility testing of the recommended antimicrobials.

5) Assist national laboratories to expand capacity for handling and processing samples from meat sources.

6) Encourage countries testing human isolates to expand surveillance to include retail meats.

7) Encourage countries to evaluate available culture collections within a country for existing isolates of *Salmonella*.

8) Encourage countries to conduct a pilot project to determine the prevalence and resistance of *Salmonella* in the most commonly consumed meat commodities within a region.

9) Provide guidance on developing sampling strategies suitable to a given region based on the results of the pilot study such that a representative sample set is collected.

10) Assist national laboratories to expand capacity for handling and processing samples from animal sources.

11) If a central testing facility does not exist, WHO should facilitate increasing the capacity of the national reference laboratory to culture animal samples for Salmonella and provide testing of isolates.

12) Identify countries that have the interest and resources to launch pilot surveillance efforts.

13) Encourage countries to sustain integrated surveillance efforts.

14) Provide GFN, OIE and other material already developed and expand the training.

15) The group also makes to following recommendations to WHO.

- Provide standard protocols for isolation, identification, serotyping, and susceptibility testing (ISO on web)

- Enhance External Quality Assurance System (EQAS) to include other countries
- Provide training materials in the form of fact sheet, briefing paper, PowerPoint files that can be downloaded
- Facilitate travel grants to member institutes to attend international meetings on AMR to facilitate data sharing and collaboration
- Prioritize international studies with participation from different countries

ANNEX 1: List of participants

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ANNEX 2: Agenda

Time	Monday, 15 June 2009	Speakers
09.00 – 09.15	**Session I: Opening** • Welcome and Opening Remarks • Election of Chairperson and Vice-Chairpersons • Appointment of Rapporteur • Adoption of the Agenda	Dr Awa AIDARA-KANE, WHO
09.15 – 10.30	**Session II - Critically Important Antimicrobials (CIA)** **Session II-A: Introductory Presentations** Antimicrobial resistance in foodborne pathogens: recent developments Update on WHO AMR initiatives	Frank AARESTRUP Awa AIDARA-KANE
10.30 – 11.00	Tea/Coffee break	
11.00 – 12.30	**Session II-B: Review of Previous WHO Consultations on CIA** Introduction Recommendations from joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials	Scott McEWEN
12.30 – 13.30	Lunch	
13.30 – 15.30	**Session II-C: Defining Criteria** Revisiting the Criteria for establishment of the Human CIA list Revisiting criteria for establishing priorities in the list of CIA	
15.30 – 16.00	Coffee break	
16.00 – 18.00	**Session II-D: Applying Criteria** Updated WHO list of Critically Important Antimicrobials for Human Medicine Categorization for development of Risk Management strategies to contain antimicrobial resistance due to non-human use of antimicrobials	

Time	Tuesday, 16 June 2009	
09.00 – 10.30	**Session II-E: Use of WHO list of CIAs** Use of the CIA list in the risk analysis framework What Should be done by WHO to increase awareness and commitment for use of the concept of CIA for priority setting at the national, regional and international level	
10.30 – 11.00	Coffee break	
11.00 – 11.30 11.30 – 13.00	**Session II F : Adoption Updated WHO list of CIA** Adoption of the Updated WHO list of CIA and recommendations to WHO on the way forward	
13.00 – 13.30	Lunch	
13.30 – 15.30	**Session III: Charting a WHO Strategy for Surveillance, Prevention and Control of Foodborne Antimicrobial Resistance** **Session III-A: Taking Stocks** **Country Experiences on Surveillance of Antimicrobial resistance and Antimicrobial Drug Use** -Canada -Denmark -Japan -Kenya -Mexico	 Richard REID-SMITH F. AARESTRUP Haruo WATANABE Sam KARIUKI, Eric MITEMA Mussaret ZAIDI
15.30 – 16.00	Coffee break	
16.00 – 18.00	**Session III-A(ccd): Taking Stocks** **Country Experiences on Surveillance of Antimicrobial resistance and Antimicrobial Drug Use** -Qatar -Sweden -USA	 Sittana S. ELSHAFIE Christina GREKO Ezra BARZILAY, Paula F. CRAY and Patrick Mc DERMOTT

Time	Wednesday, 17 June 2009	
0900 – 10.30	**Session III-A(ccd): Taking Stocks** **Regional Initiatives on Antimicrobial Resistance Surveillance and Antimicrobial Drug Use** -EFSA -ECDC -PAHO -Data on usage of AM agents from 9 European countries. Is the collection and presentation harmonized?	 Stef BRONZWAER Ole HEUER Enrique PEREZ, Pilar RAMON Kari GRAVE, Christina GREKO
10.30 – 11.00	Coffee break	
11.00 – 12.30	**Session III-B : Establishment of an AMR Integrated Surveillance Programme** Introduction Discussion: -What is the added value of an integrated surveillance programme? -Minimum requirements for an integrated surveillance programme? - How can WHO provide support to Member States?	 John STELLING
12.30 – 13.30	Lunch	
14.00 – 15.30	**Session III-B (ccd): Establishment of an AMR Integrated Surveillance Programme** Discussion (ccd) -What is the added value of an integrated surveillance programme? -Minimum requirements for an integrated surveillance programme? - How can WHO provide support to Member States?	
Expected output: *Developing models for integrated antimicrobial surveillance in resource limited countries - Assigning tasks -Setting timeframe*		
15.30 – 16.00	Coffee break	
16.00 – 18.00	**Session III-C: Capacity Building on AMR Surveillance** Introduction: Global Foodborne Infections Network AMR activities -Review of Existing AMR curricula in GFN -What are the identified gaps -How to address them?	 Rene S. HENDRIKSEN
Expected output*: Developing a training package on integrated surveillance of antimicrobial resistance to be taught in GFN advanced workshops - Assigning tasks -Setting timeframe*		

Time	Thursday, 18 June 2009	
09.00 – 10.30	**Session III-D : Pilot Studies at Country level** Introduction Discussion: -Rationale for country integrated antimicrobial resistance pilot studies -What are the criteria for selection of sentinel sites -What are the Challenges? How to address them?	Fred ANGULO
10.30 – 11.00	Coffee break	
11.00 – 12.30	Session III-D: Pilot Studies at Country level Discussion (ccd) -Rationale for pilot studies on integrated surveillance of antimicrobial resistance -What are the criteria for selection of sentinel sites -What are the Challenges? How to address them?	
Expected output : *Developing user-friendly standardized tools and protocols to be used at country level to generate and share reliable data on integrated AMR surveillance in resource limited countries - Assigning tasks -Setting timeframe*		
12.30 – 13.30	Lunch	
14.00 – 15.30	**Session IV-Report finalization** Working Group 1: Finalization of the report Session II Working Group 2: Finalization of the report Session III	
15.30 – 16.00	Coffee break	
16.00 – 18.00	Plenary: Restitution of Working Groups 1 and 2	

ANNEX 3: Examples of programmes on surveillance of antimicrobial resistance in animal, food and human

NARMS-USDA (animal) – United States of America
http://www.ars.usda.gov/Main/docs.htm?docid=6750&page=1

NARMS-FDA (food) – United States of America
http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem

NARMS-CDC (human) – United States of America
http://www.cdc.gov/NARMS

CIPARS (human, animal, food) - Canada
http://www.phac-aspc.gc.ca/cipars-picra/index-eng.php

MARAN (animal, food) - The Netherlands
http://www.cvi.wur.nl/UK/publications/otherpublications/maran/

DANMAP (human, animal, food) - Denmark
http://www.danmap.org

NORM-NORMVET (human, animal, food) - Norway
http://www.vetinst.no/eng/Research/Publications/Norm-Norm-Vet-Report

EARSS (human) - 33 European countries
http://www.rivm.nl/earss/

ESAC (human usage) - 34 countries (27 EU)
http://app.esac.ua.ac.be/public/

EFSA (animal, food, human) - EU
http://www.efsa.europa.eu/

SVARM (animal) - Sweden
http://www.sva.se/en/Target-navigation/Animal-health/Antibiotic-Resistance/Monitoring-of-antimicrobial-resistance/SVARM-reports/

ITAVARM (animal, human) - Italy (2003)
http://195.45.99.82:800/pdf/itavarm.pdf

MARAN (food, animal) - The Netherlands (2007)
http://www.cvi.wur.nl/NR/rdonlyres/DDA15856-1179-4CAB-BAC6-28C4728ACA03/83791/MARAN_2007_def2.pdf

FINRES-VET (animal, food) - Finland
http://www.evira.fi/uploads/WebShopFiles/1198141211941.pdf

ONERBA (animal, human) - France
http://www.onerba.org/rubrique.php3?id_rubrique=15

JVARM (animal) - Japan
http://www.maff.go.jp/nval/tyosa_kenkyu/taiseiki/monitor/e_index.html

DAFF - pilot surveillance program (animal) - Australia
http://www.daff.gov.au/agriculture-food/food/regulation-safety/antimicrobial-resistance/antimicrobial_resistance_in_bacteria_of_animal_origin

WHO AGISAR

The World Health Organization (WHO) Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was established in December 2008 to support WHO's effort to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animals. WHO-AGISAR comprises of over 20 internationally-renowned experts in a broad range of disciplines relevant to antimicrobial resistance and mainly functions to provided expert advice to WHO on containment of food-related antimicrobial resistance.

The main objective of this first WHO-AGISAR meeting was to review the WHO list of Critically Important Antimicrobials and chart a strategic framework for WHO activities on integrated surveillance and containment of food-related antimicrobial resistance.

The TOP 3 Critically Important Antimicrobials

Quinolones are widely used in food animal production and are known to select for quinolone-resistant *Salmonella* spp. in animals. At the same time, quinolones are one of few available therapies for serious Salmonella infections, particularly in adults.

3rd and 4th generation cephalosporins are widely used in food animal production and are known to select for cephalosporin-resistant *Salmonella* spp. in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella infections, particularly in children.

Macrolides are widely used in food animal production and are known to select for macrolide-resistant *Campylobacter* spp. in animals. At the same time, macrolides are one of few available therapies for serious campylobacter infections, particularly in children, in whom quinolones are not recommended for treatment.

Given the high incidence of human diseases due to *Salmonella* spp. and *Campylobacter* spp., the absolute number of serious cases is substantial.

http://www.who.int/foodsafety

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