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World Health Organization Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies for the Use of Antimicrobials in Food Production Animals

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The use of antimicrobials in food animals creates 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 the usage of those that are "critically important" for human medicine, is an important step toward preserving the benefits of antimicrobials for people. The World Health Organization 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. 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, such as fluoroquinolones, macrolides, and third- and fourth-generation cephalosporins.

Antimicrobials decrease morbidity and mortality associated with serious and life-threatening infections. Antimicrobial resistance decreases the effectiveness of these drugs, increasing the risk of morbidity and mortality in serious diseases and, thus, compromising human health [1–6].

Antimicrobial resistance is an inevitable consequence of antimicrobial use. Poverty; suboptimal control of the sale, quality, and use of antimicrobials; and poor sewage and water systems are factors that contribute to the emergence and spread of antimicrobial resistance. High rates of resistance have been reported, even in *Escherichia coli*, one of the most common causes of bacterial infection in people [7, 8]. Increasing levels of resistance complicate the selection of empirical and definitive antimicrobial therapy for serious bacterial infection. Some authors have recommended broad-spectrum agents, such as carbapenems, as empirical therapy [9], but the collateral damage to commensal and colonizing organisms is likely to accelerate the development of multidrug resistance through the selection and spread of bacteria that produce metallo-β-lactamases.

Food animals (e.g., chickens, cattle, turkeys, and pigs) are a source for bacterial species that cause human infections, including *Campylobacter* and *Salmonella* species. Commensal bacteria, such as *E. coli* and *Enterococcus*, and the resistance genes they carry, are transmitted to people via the food chain or by direct exposure to animals [10–14]. The administration of antimicrobials occurs in higher volumes among food animals, compared with people [14, 15]. The amount of antimicrobial-resistant bacteria that develop are proportionate to

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the total volume of antimicrobials used, and the development of resistance is affected by the ways in which the drugs are used. In many countries, antimicrobial use in food animals occurs in situations with little or no associated economic or health benefits (e.g., growth promotion) while contributing to the risk of antimicrobial resistance [16].

Antibiotic usage in food animals leads to the development and spread of organisms that are resistant to fluoroquinolones, third- and fourth-generation cephalosporins, and vancomycin, among others. The relative contribution of foodborne transmission to antimicrobial resistance in humans remains unknown, but it is not zero and is likely more substantial than is currently appreciated [10–14]. Humans are exposed to antimicrobial-resistant bacteria and resistance genes that are present in the food chain. Some studies have suggested that the majority of antibiotic-resistant *E. coli* carried by people may have originated in food animals, especially chickens [12].

Mitigating the risks of antimicrobial resistance to human health requires risk management strategies for the use of antimicrobials in animals. To decrease the development and spread of antimicrobial-resistant foodborne bacteria, we must reduce the use of antibiotics in food animals and decrease the injudicious use of antimicrobials in human medicine. These issues are of great importance for drugs that are critical to human medicine.

The World Health Organization (WHO) has developed criteria to rank antimicrobials according to their importance in human medicine [17, 18]. These lists will be a component of risk management strategies to mitigate the human health risks associated with antimicrobial use in food animals. The WHO lists help to prioritize resources that address the use in food animals of the most critical antibiotics for humans. 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 treatment via water, prohibiting extra-label use, etc.). The use of these lists will help preserve the effectiveness of currently available antimicrobials. We present the development, criteria, and content of these lists in this paper.

WHAT ARE THE BACTERIA AND ANTIMICROBIAL-RESISTANCE TRAITS OF MOST CONCERN FROM FOOD ANIMALS?

Campylobacter *and* Salmonella. *Campylobacter* and non-typhoid *Salmonella* species spread from animals to people via food and water, particularly in developed countries. When antimicrobials are indicated for treatment of *Salmonella* infection (e.g., bloodstream infections), clinicians often treat with fluoroquinolones and third-generation cephalosporins [19]. However, these same classes of antimicrobial agents are also administered to food animals, which leads to the inevitable development of resistant bacteria [20–26].

An increasing prevalence of *Campylobacter* that are resistant to fluoroquinolones is associated with the use of this class of drugs in food animals [20–26]. In countries where fluoroquinolones are banned or used sparingly in food animals (e.g., Sweden, Norway, and Australia), studies demonstrate a low prevalence of fluoroquinolone-resistant *Campylobacter* [21, 25], despite the use of fluoroquinolones in human medicine for >20 years. In countries where fluoroquinolones are or were frequently used in food animals (e.g., Spain, China, and the United States), higher rates of resistance are observed among isolates from both food animals and humans [20–26]. In these latter countries, high resistance rates developed very rapidly, but did so only after the introduction of fluoroquinolones in food animals.

Staphylococcus aureus. *S. aureus* causes infections in many animals, including poultry, pigs, and cattle. In Europe, the United States, and Canada, methicillin-resistant *S. aureus* isolates have spread from food animals [27–30] and companion animals to people [31, 32]. Although it currently represents a low proportion of the total methicillin-resistant *S. aureus* infections that occur in people, there are an increasing number of reports of animal-derived methicillin-resistant *S. aureus,* especially from pigs, causing community-onset infection in people.

E. coli. Antimicrobial resistance in *E. coli* is an increasing problem [7, 8, 33–42], particularly in developing countries (e.g., China and Mexico) [7, 33] where strains that cause blood stream infections are frequently multidrug resistant. The main reservoir for *E. coli* is the gastrointestinal tract, where there is a large turnover of *E. coli* each day [41]. Food is an important vector for these organisms [10, 12, 13, 38, 39]. Food animals likely contribute a substantial proportion of the *E. coli* in the human gastrointestinal tract, including drug-resistant strains. Although most strains of *E. coli* are relatively host specific, various studies have demonstrated that drug-resistant strains of animal origin (e.g., fluoroquinolone-resistant *E. coli* from chickens) can either colonize or cause infection in humans [12, 13, 36, 38]. Human infections with bacteria that are resistant to third-generation cephalosporins, fluoroquinolones, and/or aminoglycosides are now widespread, and the number of such infections is rapidly increasing in many countries [3].

Studies report an increasing frequency of community-acquired infections due to extended-spectrum β-lactamase–producing *E. coli* strains, despite the relatively infrequent use of third- and fourth-generation injectable cephalosporins for treating people in the community [33, 34, 37, 38]. Increasing numbers of community-acquired, extended-spectrum β-lactamase–producing *E. coli* are carried in the population. Researchers have reported increasing frequencies of drug-resistant

isolates in foods around the world. In Spain [38], studies found similar bacteria in humans, food, animal farms, and sewage. The use of third- and fourth-generation cephalosporins in food animals select for undesired drug-resistance phenotypes in animal bacteria, including selection of extended-spectrum β-lactamase–producing strains [40–43]. Worldwide spread of these highly drug-resistant bacteria and their genes (genes that encode CTX-M and CMY β-lactamases are transferable among bacteria) is occurring.

Enterococcus. *Enterococcus* species, in particular *Enterococcus faecium,* are intrinsically resistant to a number of antimicrobials, which limits treatment options for infection due to these pathogens. The emergence of genetic determinants that confer resistance to vancomycin can limit treatment options still further [43].

WHO CLASSIFICATION ON THE CRITICAL IMPORTANCE OF ANTIMICROBIALS USED IN HUMAN MEDICINE

The Canberra meeting, 2005. In 2005, the WHO organized a consultation in Canberra, Australia, to develop a list of critically important antimicrobial agents in human medicine [17]. This list was generated in an effort to provide a tool for developing risk-management strategies and focusing resources to address antimicrobial use in agriculture and veterinary medicine. Until that time, there had been no international consensus on the classification of different groups of antibiotics in relation to their importance to human medicine [3, 14, 15, 25, 26].

In developing the list, the consultants did not consider any antimicrobial or class of antimicrobials used in human medicine to be unimportant. Therefore, to categorize the relative importance of these drugs in human medicine, they defined 3 categories of antimicrobials: *critically important* (table 1), *highly important* (table 2), and *important* (table 3). The consultants included comments in the tables in recognition of regional factors that might affect the rankings, but these comments were not meant to be exhaustive, and other regional factors may be relevant. The purpose of the comments was to increase, not decrease, the importance of drugs on the list on the basis of these regional factors. An antimicrobial class is defined as a group of agents with a similar mechanism of action, regardless of chemical structure.

Each antimicrobial agent (or class) was assigned to 1 of the 3 categories of importance on the basis of 2 criteria: (1) the agent or class is the sole therapy or one of few alternatives to treat serious human disease; and (2) the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via nonhuman sources or diseases caused by organisms that may acquire resistance genes from nonhuman sources. *Critically important* antimicrobials are those that meet both criteria. *Highly important* antimicrobials are those that meet 1 of 2 criteria. *Important* antimicrobials are those that do not meet either criteria.

The consultants considered it important to set ranking criteria first to categorize drugs in a fair and impartial manner. The consultants arrived at these criteria through discussion and consensus. These criteria are based on sound scientific reasoning. For criterion 1, it is obvious that antimicrobials that are one of few alternatives for treatment of serious diseases have a critical place in human medicine. Criterion 2 grants greater importance to antimicrobial agents that are used to treat diseases caused by bacteria that can be transmitted from nonhuman sources to humans. The panel did not suggest that the transmission of such organisms or their genes must be proven, but only that there is the potential for such transmission to occur.

Tables 1, 2, and 3 outline the rankings of antimicrobials. The tables list only the generic drug names of antimicrobials used in humans. The tables show examples of members in each class, but the list is not inclusive of all drugs. In most groups, similar drugs are used in animals, for example, both enrofloxacin (a fluoroquinolone) and tylosin (a macrolide) are used in food animals (table 4). If resistance develops to 1 member of a class, generally, all other members of that group are affected because of cross-resistance. The WHO classification should be considered to be a core list of the most critical antimicrobial agents globally [17, 18]. However, considerations such as cost and availability of antimicrobials in various geographic areas and local resistance rates could increase the ranking of some drugs. For instance, an antimicrobial agent that is ranked *highly important* may become *critically important* in a particular region, because that agent may be the sole agent available in that area.

The Copenhagen meeting, 2007. The WHO convened a second meeting in Copenhagen, Denmark, in 2007 to re-evaluate the classification of antimicrobials and update the list on the basis of recent developments [18]. Relatively few changes were needed. The panel recommended the following changes:

- 1. Tigecycline (a new tetracycline-derivative with activity against multidrug-resistant *S. aureus* and gram-negative bacteria) became available in 2005 and was categorized as *critically important.*
- 2. All penicillins (except for penicillins active against staphylococcal organisms) were grouped together as a single class and remained *critically important.*
- 3. The penicillins active against staphylococcal organisms were moved from the *important* to the *highly important* category, because there is now more evidence of the potential transfer of *S. aureus,* including methicillin-resistant *S. aureus,* from animals to humans.
- 4. Because of the evidence of transfer of *flo* genes and chloramphenicol-resistant *Salmonella* species from animals to hu-

Table 1. ***Critically important*** **antimicrobials that are used in human medicine.**

Antimicrobial class	Antimicrobial(s)	Criterion 1[a]	Criterion 2[b]	Comment(s)
Aminoglycosides	Amikacin and arbekacin; gentamicin, netilmicin, and tobramycin; and streptomycin	Yes	Yes	Limited therapy as part of treatment of enterococcal endocarditis and MDR tuberculosis Potential transmission of *Enterococcus* species, Enterobacteriaceae (including *Escherichia coli*), and *Mycobacterium* species from nonhuman sources.
Ansamycins	Rifabutin, rifampin, and rifaximin	Yes	Yes	Limited therapy as part of therapy of mycobacterial diseases including tuberculosis and single drug therapy may select for resistance Potential transmission of *Mycobacterium* species from nonhuman sources
Carbapenems and other penems	Ertapenem, faropenem, imipenem, and meropenem	Yes	Yes	Limited therapy as part of treatment of disease due to MDR gram-negative bacteria Potential transmission of Enterobacteriaceae, including *E. coli* and *Salmonella* sprecies, from nonhuman sources
Cephalosporins, third and fourth generation	Cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftizoxime, cefoperazone, cefoperazone-sulbactam, and ceftriaxone; cefepime, cefpirome, and cefoselis	Yes	Yes	Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children Fourth-generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever Potential transmission of Enterobacteriaceae, including *E. coli* and *Salmonella* species, from nonhuman sources
Glycopeptides	Teicoplanin and vancomycin	Yes	Yes	Limited therapy for infection due to MDR *Staphylococcus aureus* and *Enterococcus* species Potential transmission of *Enterococcus* species and MDR *S. aureus* from nonhuman sources
Lipopeptides	Daptomycin	Yes	Yes	Limited therapy for infection due to MDR *S. aureus* Potential transmission of *Enterococcus* species and MDR *S. aureus* from nonhuman sources
Macrolides, including 14-, 15-, and 16-membered compounds, and ketolides	Azithromycin, clarithromycin, erythromycin, midecamycin, roxithromycin, spiramycin, and telithromycin	Yes	Yes	Limited therapy for infection due to *Legionella, Campylobacter,* and MDR *Salmonella* species Potential transmission of *Campylobacter* species from nonhuman sources
Oxazolidinones	Linezolid	Yes	Yes	Limited therapy for infection due to MDR *S. aureus* and *Enterococcus* species Potential transmission of *Enterococcus* species and MDR *S. aureus* from nonhuman sources
Penicillins, including natural penicillins, aminopenicillins, and antipseudomonals	Penicillin G, penicillin V, ampicillin, ampicillin-sulbactam, amoxicillin, amoxicillin-clavulanate, piperacillin, piperacillin-tazobactam, azlocillin, carbenicillin, mezlocillin, ticarcillin, and ticarcillin-clavulanate	Yes	Yes	Limited therapy for syphilis (natural penicillins), *Listeria* and *Enterococcus* species (aminopenicillins), and MDR *Pseudomonas* species (antipseudomonals) Potential transmission of *Enterococcus* species, Enterobacteriaceae (including *E. coli*), and *Pseudomonas aeruginosa* from nonhuman sources
Quinolones	Cinoxacin, nalidixic acid, and pipemidic acid; ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, and sparfloxacin	Yes	Yes	Limited therapy for *Campylobacter* species, invasive disease due to *Salmonella* species, and MDR *Shigella* species infection Potential transmission of *Campylobacter* species and Enterobacteriaceae, including *E. coli* and *Salmonella* species, from nonhuman sources
Streptogramins	quinupristin-dalfopristin and pristinamycin	Yes	Yes	Limited therapy for MDR *Enterococcus faecium* and *S. aureus* infection Potential transmission of *Enterococcus* species and MDR *S. aureus* from nonhuman sources
Tetracyclines and glycylcyclines	Tigecycline	Yes	Yes	Limited therapy for infection due to MDR *S. aureus*

Table 1. ***(Continued.)***

Antimicrobial class	Antimicrobial(s)	Criterion 1[a]	Criterion 2[b]	Comment(s)
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Cycloserine, ethambutol, ethionamide, isoniazid, para-aminosalicylic acid, and pyrazinamide	Yes	Yes	Limited therapy for tuberculosis and other disease due to *Mycobacterium* species For many of these drugs, single drug therapy may select for resistance Potential transmission of *Mycobacterium* species from nonhuman sources

NOTE. From the World Health Organization meeting in Copenhagen, Denmark [18]. Both of the 2 criteria were met for classification as a *highly important* antimicrobial. MDR, multidrug-resistant.

[a] Criterion 1: the agent or class is the sole therapy or one of few alternatives to treat serious human disease.

[b] Criterion 2: the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via nonhuman sources or diseases causes by organisms that may acquire resistance genes from nonhuman sources.

mans, the amphenicols were moved from the *important* to the *highly important* category.

- 5. Because of differing resistance mechanisms, the aminoglycosides were divided into 2 groups. As a result, 2 aminoglycosides (kanamycin and neomycin) were moved from the *critically important* to the *highly important* category.
- 6. Third- and fourth-generation cephalosporins were combined in the tables, because the mechanisms of action and antimicrobial resistance are similar.. The first- and second-generation cephalosporins were also combined.

PRIORITIZATION WITHIN THE *CRITICALLY IMPORTANT* CATEGORY

The WHO asked the consultants in Copenhagen to prioritize agents within the *critically important* category, to assist the allocation of resources toward agents for which risk management of antimicrobial resistance is needed most urgently. The consultants considered drugs to be of greatest priority if: (1) there are relatively large absolute numbers of people affected by diseases for which the drug is the sole alternative or one of few alternative therapies; (2) the overall frequency of use of the drugs in human medicine for any reason (whether appropriate or inappropriate) is relatively large; and (3) the drug is used to treat disease due to pathogens for which there is evidence regarding transmission of bacteria or their genes from nonhuman sources to humans (i.e., *E. coli, Campylobacter* species, and *Salmonella* species).

This prioritization resulted in the designation of quinolones, third- and fourth-generation cephalosporins, and macrolides as the classes for which risk-management strategies are needed most urgently. In the future, the WHO might consider convening a meeting of stakeholders to discuss the progress of various government agencies in addressing risk-management strategies for the use of these antimicrobials. In addition, there should be reliable, unbiased measures of the impact on resistance of any prudent-use guidelines or principles that are adopted by veterinary medical associations or animal production groups.

The expert panel emphasized that prioritization of these 3 classes of drugs should not minimize the importance of other drugs that are categorized as *critically important* on the list. Furthermore, any use of the ranking should consider regional differences, as noted above. Therefore, drugs that are not considered to be *critically important* in the list might be *critically important* in some developing countries (e.g., the importance of chloramphenicol might be increased because of a lack of access to cephalosporins).

Comments on the WHO classification of antimicrobial agents. The WHO criteria were developed with regard only to the importance of these antimicrobials in human medicine. Drug classes that are not used in humans and that are currently used only in animal medicine include arsenicals, bambermycins, ionophores, orthosomycins, quinoxalines, and others. The Office International des Épizooties (now known as the World Organisation for Animal Health) has undertaken a similar initiative to define critically important antimicrobial agents in veterinary medicine.

The classification in 2005 by the WHO was the first international attempt to classify antimicrobial agents on the basis of their importance in human medicine. The conclusions by the WHO panel in 2005 were unanimous on all drug classifications, with 1 exception [17]. There was significant discussion regarding the classification of natural penicillins and aminopenicillins. After thorough discussion, the consensus was that clinicians use both types of drugs as therapy when there are few other options for serious human disease, such as in the case of invasive enterococcal infection. This view was reinforced at the second WHO meeting in Copenhagen [18].

The purpose of the WHO classification is to serve as a factor in guiding decisions regarding risk management strategies for antimicrobial use in food animals and agriculture. Cost was not a primary consideration in developing the list of *critically important* antimicrobial agents, because there is little choice regarding cost when an antimicrobial agent is the sole alternative or one of few available alternatives to treat a disease.

The list will need to be updated regularly as new information becomes available, including data on resistance patterns, new and emerging diseases, and new drug development. It is also

Table 2. *Highly important* antimicrobials that are used in human medicine.

Antimicrobial class	Antimicrobial(s)	Criterion 1[a]	Criterion 2[b]	Comment(s)
Amidinopenicillins	Mecillinam	No[c]	Yes	Potential transmission of Enterobacteriaceae, including *Escherichia coli,* from nonhuman sources MDR *Shigella* species infections may be a regional problem
Aminoglycosides, other	Kanamycin, neomycin, and spectinomycin	No	Yes	Potential transmission of gram-negative bacteria that are cross-resistant to streptomycin from nonhuman sources
Amphenicols	Chloramphenicol and thiamphenicol	No[c]	Yes	May be 1 of limited therapies for acute bacterial meningitis, typhoid fever, and respiratory infections in certain geographic areas
Cephalosporins, first and second generation	Cefazolin, cephalexin, cephalothin, and cephradine	No	Yes	Potential transmission of Enterobacteriaceae, including *E. coli,* from nonhuman sources
Cephalosporins, second generation	Cefaclor, cefamandole, cefuroxime, and loracarbef	No	Yes	Potential transmission of Enterobacteriaceae, including *E. coli,* from non-human sources
Cephamycins	Cefotetan and cefoxitin	No	Yes	Potential transmission of Enterobacteriaceae, including *E. coli,* from nonhuman sources
Clofazimine	Clofazimine	Yes	No	Limited therapy for leprosy
Monobactams	Aztreonam	No	Yes	Potential transmission of Enterobacteriaceae, including *E. coli,* from nonhuman sources
Penicillins, antistaphylococcals	Cloxacillin, dicloxacillin, flucloxacillin, oxacillin, and nafcillin	No	Yes	*Staphylococcus aureus,* including methicillin-resistant *S. aureus,* has been transferred to humans from animals
Polymyxins	Colistin and polymyxin B	Yes	No	Polymyxins may be the only available therapy for some infections due to gram-negative bacteria (e.g., infection due to *Acinetobacter* species and *Pseudomonas aeruginosa*)
Sulfonamides, dihydrofolate reductase inhibitors, and combinations	Para-aminobenzoic acid, pyrimethamine, sulfadiazine, sulfamethoxazole, sulfapyridine, sulfisoxazole, and trimethoprim	No[c]	Yes	Potential transmission of Enterobacteriaceae, including *E. coli,* from nonhuman sources May be 1 of limited therapies for acute bacterial meningitis and other infections in certain geographic areas
Sulfones	Dapsone	Yes	No	Limited therapy for leprosy
Tetracyclines	Chlortetracycline, doxycycline, minocycline, oxytetracycline, and tetracycline	Yes	No	Limited therapy for infection due to *Chlamydia* species and *Rickettsia* species

NOTE. From the World Health Organization meeting in Copenhagen, Denmark [18]. One of the 2 following criteria were met for classification as a *highly important* antimicrobial: (1) the agent or class is the sole therapy or one of few alternatives to treat serious human disease; and (2) the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via nonhuman sources or diseases causes by organisms that may acquire resistance genes from nonhuman sources. MDR, multidrug-resistant.

[a] Criterion 1: the agent or class is the sole therapy or one of few alternatives to treat serious human disease.

[b] Criterion 2: the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via nonhuman sources or diseases causes by organisms that may acquire resistance genes from nonhuman sources.

[c] The importance of the class or antimicrobial may change on the basis of regional differences.

Table 3. *Important* antimicrobials that are used in human medicine.

Antimicrobial class	Antimicrobial(s)	Criterion 1[a]	Criterion 2[b]	Comment(s)
Cyclic polypeptides	Bacitracin	No	No	…
Fosfomycin	Fosfomycin	No[c]	No	May be 1 of limited therapies for Shiga toxin–producing *Escherichia coli* O157 in certain geographic areas
Fusidic acid	Fusidic acid	No[c]	No	May be 1 of limited therapies to treat multidrug-resistant *Staphylococcus aureus* infection in certain geographic areas
Lincosamides	Clindamycin and lincomycin	No	No	…
Mupirocin	Mupirocin	No	No	…
Nitrofurantoins	Furazolidone and nitrofurantoin	No	No	…
Nitroimidazoles	Metronidazole and tinidazole	No[c]	No	Criterion 1 was evaluated on the basis of antibacterial properties only May be 1 of limited therapies for some anaerobic infections, including *Clostridum difficile* infection, in certain geographic areas

NOTE. From the World Health Organization meeting in Copenhagen, Denmark [18]. Neither of the 2 following criteria were met for classification as an *important* antimicrobial: (1) the agent or class is the sole therapy or one of few alternatives to treat serious human disease; and (2) the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via nonhuman sources or diseases causes by organisms that may acquire resistance genes from nonhuman sources.

[a] Criterion 1: the agent or class is the sole therapy or one of few alternatives to treat serious human disease.

[b] Criterion 2: the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via nonhuman sources or diseases causes by organisms that may acquire resistance genes from nonhuman sources.

[c] The importance of the class or antimicrobial may change on the basis of regional differences.

important to take into account that antimicrobial resistance may also develop slowly after a long period of usage. As an example, investigators first detected vancomycin resistance in *Enterococcus* after >40 years of vancomycin usage. Thus, even if resistance has not yet developed among particular groups of bacteria, it does not mean that it will not develop in the future.

CONCLUSION

The WHO lists are the first attempt to develop an international consensus on the relative importance of classes of antibacterial agents to human medicine to help guide risk management strategies for use of similar agents in food animal production and agriculture. Reducing the use of *critically important* antimicrobials in food animals will reduce the amount of resistant bacteria that can develop and spread. This will help mitigate a threat to human health and decrease morbidity and mortality in humans, by preserving effective treatments for use in the case of serious disease caused by these bacteria. We should strive to reduce the use of antimicrobials everywhere (and thus reduce resistance everywhere), including reduction of inappropriate use in humans for treatment of viral and fungal diseases, as well as for treatment of diseases in which the benefit of antibacterials is unclear (e.g., sinusitis and bronchitis). However, these lists allow us to focus initially on those agents that are *critically important* to human medicine.

The US Food and Drug Administration (FDA) has been particularly concerned about the extra-label use of cephalosporins (e.g., ceftiofur) in food animals, especially poultry [46]. The extra-label use of cephalosporins in food animals has contributed to emerging cephalosporin-resistant zoonotic foodborne bacteria. The FDA determined that extra-label use in animals presents a risk to the public health and, therefore, proposed a rule to prohibit the extra-label use of cephalosporins in food animals [46]. The rule was scheduled to take effect in November 2008, but the FDA has delayed implementation of the final rule to review comments by various stakeholders. However, there does not appear to be new scientific data to alter the risks and benefits to human health with respect to the use of cephalosporins in food-producing animals.

The same principles that were used in deriving this WHO antibacterial ranking apply for other pathogens and the drugs used to treat them, such as fungal diseases and antifungal agents. It is also critical to acknowledge that most research has involved organisms that directly cause disease, focusing less on important contributions by commensal bacteria, which carry antimicrobial resistance genes. Although these organisms generally do not cause disease in immunocompetent people, they can transfer resistance genes to other bacteria. It is possible that this phenomenon has occurred with some pathogenic bacteria, including *S. aureus*. The gene encoding methicillin resistance *(mecA)* may have originated from less-virulent coagulase-negative staphylococci. Horizontal transfer may occur relatively infrequently, but once the gene is established in a successful virulent clone, the clone and the carried gene can spread in individual countries and worldwide, such as in the case of multidrug-resistant *S. aureus* and pneumococci.

Table 4. Antimicrobial agents approved for use in human and veterinary medicine.

Category, antimicrobial class	Example(s) of antimicrobials used in human medicine	Example(s) of antimicrobials used in veterinary medicine or as growth promoters
Critically important		
Aminoglycosides	Amikacin, arbekacin, gentamicin, kanamycin, netilmicin, neomycin, tobramycin, and streptomycin	Amikacin, apramycin, gentamicin, neomycin, streptomycin, dihydrostreptomycin, kanamycin, framycetin, and paromomycin (aminosidine)
Ansamycins	Rifabutin, rifampin, and rifaximin	Rifampicin
Carbapenems and other penems	Ertapenem, faropenem, imipenem, meropenem, and doripenem	None approved or known to be used
Cephalosporins, third generation	Cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftizoxime, cefoperazone, cefoperazone-sulbactam, and ceftriaxone	Cefpodoxime, ceftiofur, cefoperazone, and cefovecin
Cephalosporins, fourth generation	Cefipime, cefpirome, and cefoselis	Cefquinome
Lipopeptides	Daptomycin	None approved or known to be used
Glycopeptides	Teicoplanin and vancomycin	Avoparcin[a]
Macrolides, including 14-, 15-, and 16-membered compounds, and ketolides	Azithromycin, clarithromycin, erythromycin, midecamycin, roxithromycin, spiramycin, and telithromycin	Erythromycin, pirlimycin, spiramycin, tylosin, tulathromycin, kitasamycin, oleandomycin, tilmicosin, and jasamycin
Oxazolidinones	Linezolid	None approved or known to be used
Penicillins, aminopenicillins	Ampicillin-amoxicillin, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin, and piperacillin-tazobactam	Ampicillin-amoxicillin, ampicillin-sulbactam, and amoxicillin-clavulanate
Penicillins, natural	Penicillin G and penicillin V	Penicillin G and penicillin V
Quinolones	Cinoxacin, nalidixic acid, pipedemic acid, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, and sparfloxacin	Nalidixic acid, oxolinic acid, flumequin, pipemidic acid, danofloxacin, difloxacin, enrofloxacin, Ibafloxacin, marbofloxacin, sarafloxacin, orbifloxacin, and moxifloxacin
Streptogramins	Quinupristin-dalfopristin and pristinamycin	Virginiamycin[b]
Drugs used solely to treat tuberculosis or other mycobacterial disease	Cycloserine, ethambutol, ethionamide, isoniazid, para-aminosalicylic acid, and pyrazinamide	None approved or known to be used
Highly important		
Cephalosporins, first generation	Cefazolin, cephalexin, cephalothin, and cephradine	Cephalothin, cephalonium, cephalexin, cefadroxil, and cefazolin
Cephalosporins, second generation	Cefaclor, cefamandole, cefuroxime, and loracarbef	Cefuroxime
Cephamycins	Cefotetan and cefoxitin	None approved or known to be used
Clofazimine	Clofazimine	None approved or known to be used
Monobactams	Aztreonam	None approved or known to be used
Penicillins, aminopenicillins	Mecillinam	None approved or known to be used
Penicillins, antipseudomonals[a]	Azlocillin, carbenicillin, mezlocillin, ticarcillin, and ticarcillin-clavulanate	None approved or known to be used
Polymyxins	Polymyxin B and colistin	Polymyxin B and colistin
Spectinomycin	Spectinomycin	Spectinomycin
Sulfonamides, dihydrofolate reductase inhibitors, and combinations	Para-aminobenzoic acid, pyrimethamine, sulfadiazine, sulfamethoxazole, sulfapyridine, sulfisoxazole, and trimethoprim	Sulfadiazine, sulfadimidime, sulfadimethoxine, trimethoprim, and baquiloprim
Sulfones	dapsone (for treatment of leprosy)	None approved or known to be used
Tetracyclines	Chlortetracycline, doxycycline, minocycline, oxytetracycline, and tetracycline	Chlortetracycline, doxycycline, oxytetracycline, and tetracycline
Important		
Amphenicols	Chloramphenicol and thiophenicol	Chloramphenicol, florfenicol, and thiamphenicol
Cyclic polypeptides	Bacitracin	Bacitracin
Fosfomycin	Fosfomycin	Fosfomycin
Fusidic acid	Fusidic acid	Fusidic acid
Lincosamides	Clindamycin and lincomycin	Clindamycin and lincomycin
Mupirocin	Mupirocin	Mupirosin
Nitrofurans	Furazolidone, nitrofurantoin, and nitrofurazone	Furazolidone, nitrofurantoin, and nitrofurazone
Nitroimidazoles	Metronidazole and tinidazole	Metronidazole and dimetridazole
Penicillins, antistaphylococcals	Cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin, and oxacillin	Cloxacillin, nafcillin, methicillin, oxacillin, and dicloxacillin
Classes not used for human treatment		
Bambermycin	None approved or known to be used	Flavomycin

Table 4. ***(Continued.)***

Category, antimicrobial class	Example(s) of antimicrobials used in human medicine	Example(s) of antimicrobials used in veterinary medicine or as growth promoters
Novobiocin	Might be some use for humans in some countries	Novobiocin
Orthosomycins	None approved or known to be used	Avilamycin
Quinoxaline	None approved or known to be used	Olaquindox and carbadox
Pleuromutilins	None approved or known to be used	Tiamulin and valnemulin
Polyethers	None approved or known to be used	Monensin, salinomycin, lasalocid, and narasin[c]

NOTE. This table mainly includes antimicrobials approved for veterinary use in Australia, Europe, and the United States [14, 44, 45]; thus, it is not a complete list of antimicrobials used in all countries. Extra-label use of human drugs in food animal production is also a possibility. This table was reproduced from [13] with permission from the publisher.

[a] Until 2000, avoparcin was extensively used around the world (except in North America) as a growth promoter.

[b] Until 2000, virginiamycin was extensively used as a growth promoter in Europe. It is still used extensively in North America, Australia, and many other parts of the world.

[c] Extensively used for growth promotion and/or control of coccidiosis around the world.

Antimicrobial resistance, whether attributable to animal or human use, poses a threat to human health. The food animal reservoir is an important source of antimicrobial resistance, even though it might be difficult to quantify the exact burden, compared with human use. However, to ensure the future effectiveness of antimicrobials in therapy for human disease, the time to act is now. Protecting human health requires immediate development and implementation of risk-management strategies by government authorities for the use of fluoroquinolones, third- and fourth-generation cephalosporins, and macrolides in food-producing animals. The rankings provided by the WHO can assist the risk management process so that stakeholders can take appropriate actions that are urgently needed.

LIST OF WHO MEETING PARTICIPANTS

Canberra, Australia, 2005: Suleiman Mohamed Al-Bussaidy, Tom Chiller, Peter Collignon, Patrice Courvalin, Mohammad Iqbal Issack, John Powers, Jin Shaohong, Kurien Thomas, John Turnidge, Haruo Watanabe, Mair Powell, Awa Aïdara-Kane, Jaques Acar, Phillip Jenkins, Fiona J. Brooke, and Angelo A. Valois.

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