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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 to Control Antimicrobial Resistance From Food Animal Production

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Antimicrobial use in food animals selects for antimicrobial resistance in bacteria, which can spread to people. Reducing use of antimicrobials—particularly those deemed to be critically important for human medicine—in food production animals continues to be an important step for preserving the benefits of these antimicrobials for people. The World Health Organization ranking of antimicrobials according to their relative importance in human medicine was recently updated. Antimicrobials considered the highest priority among the critically important antimicrobials were quinolones, third- and fourth-generation cephalosporins, macrolides and ketolides, and glycopeptides. The updated ranking allows stakeholders in the agriculture sector and regulatory agencies to focus risk management efforts on drugs used in food animals that are the most important to human medicine. In particular, the current large-scale use of fluoroquinolones, macrolides, and third-generation cephalosporins and any potential use of glycopeptides and carbapenems need to be addressed urgently.

Keywords. antimicrobials; risk management; animals; antimicrobial resistance; food production.

Antimicrobials are life-saving drugs, but their effectiveness is seriously compromised by increasing resistance levels in nearly all bacteria causing infections in people. Infections from resistant organisms result in increased morbidity and mortality [1–3].

The World Health Organization (WHO) has developed criteria to rank antimicrobials according to their importance in human medicine [4–8]. The WHO list of critically important antimicrobials was developed for use in developing risk management strategies related to antimicrobial use in food production animals. The list was first developed in Canberra in 2005 and then revised in Copenhagen in 2007 and 2009, in Oslo in 2011, and, most recently, in Bogotá in 2013. The history and processes used to develop the definitions, criteria, and list of critically important antimicrobial agents have been outlined in detail previously [8]. The purpose of this document is to describe the updated WHO list reflecting the most recent changes since the description given in 2009 [8], and outline the antimicrobial classes for which there should be prioritizations.

The list supports strategies to mitigate the human health risks associated with antimicrobial use in food animals and has been used by both public-sector [9] and private-sector organizations, including some major national and international food supply corporations (eg, McDonald's Corporation) [10]. It does so by helping regulators and stakeholders know which types of antimicrobials used in animals present potentially higher risks to human populations and help inform how this use might be better managed (eg, restriction to single-animal therapy or prohibition of mass treatment and extralabel use) to minimize the risk of transmission of resistance to the human population. The use of this list should help preserve the effectiveness of currently available antimicrobials.

ANTIMICROBIAL RESISTANCE IS RAPIDLY RISING

Common gram-positive pathogens such as *Staphylococcus aureus* and *Enterococcus* species are often resistant to certain β-lactams and glycopeptides, respectively [3, 11]. More worrying, however, is increasing resistance in gram-negative enteric bacilli. In India, a significant proportion of *Escherichia coli*

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[a]See Notes section for full list of WHO-AGISAR members.

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causing urinary infections in the community are resistant to carbapenems and most other drugs [12, 13], making the infections they cause very difficult and sometimes impossible to treat; this is particularly concerning as *E. coli* strains are the most common bacteria causing bloodstream and urinary tract infections [1, 2, 13, 14]. The recent description from China and elsewhere of plasmid-mediated colistin resistance in Enterobacteriaceae creates a disturbing scenario whereby the polymyxins, one of the last-resort classes of antimicrobials, are no longer effective against multiply resistant carbapenem-resistant *E. coli* [15]. These findings, together with evidence of large quantities of colistin use in food animals [15], suggest links between agricultural use of colistin, colistin resistance in *E. coli* in food animals, and colistin resistance in bacteria from humans [16].

CONTROLLING ANTIMICROBIAL RESISTANCE

Overall, there are arguably just 2 major, but modifiable, factors that drive increasing levels of antimicrobial resistance. Both can be controlled. These factors are (1) the types, quantities, and ways antimicrobials are used and (2) the spread of resistant microorganisms and the genes encoding for that resistance.

At the recent World Health Assembly in May 2015 in Geneva, Switzerland, the WHO, in conjunction with all of its member countries, adopted a global action plan to combat antimicrobial resistance [17]. There are many things we can do better to control antimicrobial resistance. Most importantly, we need to decrease overall antimicrobial use [11, 17]. This includes usage in human medicine and in agriculture, aquaculture, and pets [11, 18–20]. Antimicrobials should never be used, particularly prophylactically, as replacements for proper infection control practices and good hygiene. Nationally, there are correlations between antimicrobial usage volumes in people and animals and prevalence of resistance in human and animal sectors, respectively [21, 22]. Importantly, we also know that stopping or severely curtailing use is often accompanied by reduction in antimicrobial resistance rates. There are many examples in both the agriculture and medical sectors [18, 19, 23–26].

While antimicrobial use drives resistance, many other factors contribute to the problem [27]. Spread of resistant microorganisms is facilitated by poor sanitation, overcrowding, poor animal husbandry, poor infection control practices, and the movement of foods, animals, and people [11, 19]. Spread occurs within various sectors (eg, person to person) and across different sectors (eg, agriculture to the human sector) [28]. Other factors include travel, the quality of food and drinking water [29–34], and the incidence of infection (whether resistant or not, as this drives antibiotic use) and the carriage of bacteria that can transmit resistance genetic elements.

We need to prevent both the acquisition of multiply resistant bacteria in human populations and prevent the infections caused by these microbes. In human medicine we can do this through improved hygiene and sanitation, improved education, better infection control practices (including higher rates of hand hygiene practices), robust immunization programs, and the supply of safe food and water [11]. We need to have better surveillance that includes up-to-date data on antimicrobial utilization and resistance patterns [17]. These data need to be available across all sectors, including the human and agricultural settings, locally and internationally. We must act on these results when we see either inappropriate antimicrobial usage or resistance levels rising in bacteria that are of concern for animal or human populations [11, 19]. We need to ensure that food and water do not spread multiply resistant microorganisms or resistance genes. The human sector, the agricultural sector, and the environment are all parts of "One Health" [9]. Because use of antimicrobials in any one sector can select for antimicrobial resistance in the other sectors, it is important that we adopt this One Health approach if want to better understand and control antimicrobial resistance [9, 29].

RATIONALE AND DEVELOPMENT OF RISK MANAGEMENT STRATEGIES FOR ANTIMICROBIAL CONTROLS IN FOOD PRODUCTION ANIMALS

In developed countries, most *Campylobacter* species and nontyphoidal salmonellae are acquired by humans from food animals, predominantly via foods. Humans can also acquire common commensal bacteria (eg, *E. coli* and *Enterococcus*) from food animals and foods of animal origin, and these bacteria may then cause infections in humans. More importantly, bacteria carrying resistance genes that originated from or were significantly amplified in food animals may also spread to humans through contaminated food, water, or direct contact, and these resistance genes can spread to bacteria carried by humans [19, 21, 28].

Antimicrobial resistance is related to the levels of antimicrobials used. Internationally, the largest volumes of antimicrobials appear to be used in food animals. In countries such as the United States, it may be as high as 80% of total volumes of antimicrobials used [35, 36]. Although not all of these antimicrobials are medically important (eg, ionophores), the unpredictable nature of co-selection means that many antimicrobial uses have the potential to select for resistance to other antimicrobial classes [37]. Similar percentages are seen in other developed countries; however, estimates from developing countries are more difficult to obtain. Recent data from China suggest that more than half of all antimicrobials are used in food animals [38, 39], and overall the antimicrobial usage volumes appear to be much higher than in developed countries. Similar usage patterns are likely to exist in other rapidly developing countries with large populations [38, 39]. In much of the world, only fragmentary data are available on antimicrobial consumption and antimicrobial resistance [15, 38]. The WHO, through its Advisory Group on Integrated Surveillance of

Table 1. Criteria Used to Categorize and Prioritize Antimicrobials of Importance to Human Health

Criteria Used to Categorize Antimicrobials of Importance to Human Health	Explanation
Criterion 1 (C1): The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.	It is evident that antimicrobials that are the sole or one of few alternatives for the treatment of serious bacterial infections in humans; therefore, they occupy an important place in human medicine. Serious infections are likely to result in significant morbidity or mortality if left untreated. Seriousness of disease may relate to the site of infection (eg, pneumonia, meningitis) or the host (eg, infants, immunosuppression). Even though multidrug resistance alone may or may not always influence patient outcomes, in general it is associated with poorer outcomes. It is of prime importance, then, that the use of such antibacterial agents be preserved, as loss of efficacy in these drugs due to the emergence of resistance would have a significant impact on human health, especially for people with life-threatening infections. The comments sections of the tables include examples of the diseases for which the given antibacterial agent or class was considered the sole or one of limited therapies. This criterion does not consider the likelihood that these pathogens may be transmitted, or have been transmitted, from nonhuman sources to humans.
Criterion 2 (C2): The antimicrobial class is used to treat infections in people caused by either (1) bacteria that may be transmitted to humans from nonhuman sources, or (2) bacteria that may acquire resistance genes from nonhuman sources.	Antimicrobial agents used to treat diseases caused by bacteria that may be transmitted to humans from nonhuman sources are considered of higher importance because these are most amenable to risk-management strategies related to nonhuman antimicrobial usage. The organisms that cause disease need not be drug resistant at the present time. However, the potential for transmission shows the path for acquisition of resistance now or in the future. The evidence for a link between nonhuman sources and the potential to cause human disease is greatest for certain bacteria (eg, nontyphoidal *Salmonella*, *Campylobacter* spp, *Escherichia coli*, *Enterococcus* spp, and *Staphylococcus aureus*). Commensal organisms from nonhuman sources (animals, water, food, or the environment) may also transmit resistance determinants to human pathogens; the commensals themselves may also be pathogenic in immunosuppressed hosts. The comments sections of the tables include examples of the bacterial genera or species of concern. It is important to note that the transmission of such organisms or their genes need not be demonstrated; rather, it is considered sufficient that the potential for such transmission exists.
Prioritization criteria	
Prioritization criterion 1 (P1): High absolute number of people affected by diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans.	The first 2 prioritization criteria relate to the antimicrobial use volume in humans. Increased volume of use directly relates to the development of resistance and, therefore, poses a greater threat to their use as sole therapies.
Prioritization criterion 2 (P2): High frequency of use of the antimicrobial class for any indication in human medicine, since use may favor selection of resistance.	Furthermore, humans receiving antimicrobials for any indication have a greater susceptibility to acquiring infection by a foodborne pathogen resistant to those antimicrobial agents.
Prioritization criterion 3 (P3): The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria (eg, nontyphoidal *Salmonella* and *Campylobacter* spp) or resistance genes (high for *E. coli* and *Enterococcus* spp) from nonhuman sources.	Risk management strategies are most urgently needed in situations where evidence suggests that the transmission of resistant bacteria or resistance genes from nonhuman sources is already occurring, or has occurred previously.

Adapted from [6, 7].

Antimicrobial Resistance (WHO-AGISAR), promotes integrated surveillance of consumption and resistance in both human and animal sectors, to support antimicrobial stewardship and public health [40].

To decrease the development and spread of antimicrobial-resistant foodborne bacteria, we must reduce the injudicious use of antimicrobials in veterinary and human medicine. This is of greatest importance for drugs that are "critically important" to human medicine, and the WHO list of critically important antimicrobials is an important tool at the country level for member states to use in development and implementation of risk management strategies in food production animals. At the international level, the WHO has previously recommended that "antimicrobials judged to be essential for human medicine should be restricted and their use in food animals should be justified by culture and susceptibility results" [41] and that antimicrobials which currently have no veterinary equivalent (eg, carbapenems) "as well as any new class of antimicrobial developed for human therapy should not be used in animals, plants, or in aquaculture" [6].

Strategies that control the use of critically important antimicrobials in food animals have been shown to be associated with lower resistance rates, not only in bacteria from animals but also in bacteria carried by humans [19, 24]. A dramatic example illustrating the effects of a reduction in antibiotic use was the withdrawal of the use of a third-generation cephalosporin (ceftiofur) in chicken hatcheries in Quebec, Canada. This was associated with reduction in resistance rates in *Salmonella enterica* serovar Heidelberg from human infections and retail chicken and *E. coli* from retail chicken [42]. In the Netherlands, increasing levels of bloodstream infections caused by extended-spectrum β-lactamase (ESBL)–producing *E. coli*

Table 2. Use of Criteria for Categorization and Prioritization of Antimicrobials of Importance to Human Health

Category	Definition
Critically important	Antimicrobial classes that meet both C1 and C2 are termed critically important for human medicine.
Highly important	Antimicrobial classes that meet either C1 or C2 are termed highly important for human medicine.
Important	Antimicrobial classes used in humans that meet neither C1 nor C2 are termed important for human medicine.
Highest-priority critically important antimicrobials	Antimicrobial classes that meet all 3 prioritization criteria (P1, P2, and P3) are considered the highest-priority critically important antimicrobials.

Adapted from [6, 7].

Table 3. List and Classification of Antimicrobials Important for Human Medicine

Antimicrobial Class	Example
Critically important	
Aminoglycosides	Gentamicin
Ansamycins	Rifampin
Carbapenems and other penems	Meropenem
Cephalosporins (third and fourth generation)	Ceftriaxone
Phosphonic acid derivatives	Fosfomycin
Glycopeptides	Vancomycin
Glycylcyclines	Tigecycline
Lipopeptides	Daptomycin
Macrolides and ketolides	Erythromycin, telithromycin
Monobactams	Aztreonam
Oxazolidinones	Linezolid
Penicillins (natural, aminopenicillins, and antipseudomonal)	Ampicillin
Polymyxins	Colistin
Quinolones	Ciprofloxacin
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Isoniazid
Highly important	
Amidinopenicillins	Mecillinam
Amphenicols	Chloramphenicol
Cephalosporins (first and second generation) and cephamycins	Cefazolin
Lincosamides	Clindamycin
Penicillins (antistaphylococcal)	Oxacillin
Pleuromutilins	Retapamulin
Pseudomonic acids	Mupirocin
Riminofenazines	Clofazimine
Steroid antibacterials	Fusidic acid
Streptogramins	Quinupristin/dalfopristin
Sulfonamides, dihydrofolate reductase inhibitors, and combinations	Sulfamethoxazole, trimethoprim
Tetracyclines	Chlortetracycline
Important	
Aminocyclitols	Spectinomycin
Cyclic polypeptides	Bacitracin
Nitrofurantoins	Nitrofurantoin
Nitroimidazoles	Metronidazole

Adapted from [6, 7]. See Supplementary Tables 1–3 for the full list of antimicrobials important for human medicine. Some antimicrobials are used in both people and animals (eg, erythromycin, ampicillin, colistin), and some other antimicrobials are used only in animals (drugs for veterinary use only; these are listed at the end for each class and in each different Supplementary Table). These Supplementary Tables also give a rationale for the classification of each individual drug class.

have been occurring. A relative decrease from 44% to 25% in human carriage of CTX-M-1–like ESBL genes was recently observed over a 5-year period, coincident with a >60% decrease in antimicrobial use in food animals in that country [43]. Curtailment of use will also keep resistance rates lower. In Australia, where fluoroquinolones are banned in food animals, there are few or no fluoroquinolone-resistant strains in food animals or foods, and much lower resistance rates in general populations compared with other countries with similar usage of fluoroquinolones in humans [18]. Unfortunately, fluoroquinolones are still widely used in food animals in many countries, as are many other members of the "critically important" category, such as aminoglycosides, third-generation cephalosporins, macrolides, penicillins, and polymyxins. Some of these classes were approved for veterinary use decades ago, before consideration of antimicrobial resistance was incorporated into the veterinary drug approval processes.

There are now more major food producers, purchasers, and suppliers that are requiring significant changes in which the types of antimicrobials that are being used and the manner in which they are used during production of meats that they purchase or distribute. These producers include large corporations [10, 44–46], and the WHO list of critically important antimicrobials is used as part of their global guidelines.

WHO CRITICALLY IMPORTANT ANTIMICROBIALS FOR HUMAN MEDICINE

The criteria used to categorize antimicrobials important to human health and the prioritization criteria are shown in Tables 1 and 2. These are derived from the third and fourth revisions [6, 7]. Since the 2009 publication in *Clinical Infectious Diseases* [8], several changes have been made to the list. The updated list of "critically important," "highly important," and "important" antimicrobials [4–7] is shown in Table 3, and full information listing all antimicrobials plus the criteria used to classify each individual antimicrobial class is given in Supplementary Tables 1–3. Additions to the "critically important" category (Table 3 and Supplementary Table 1) include phosphonic acid derivatives, monobactams, and polymyxins, reflecting the greater importance of these classes for treatment of multidrug-resistant gram-negative infections. Streptogramins, previously classified as critically important, are now classified as highly important because more-effective antimicrobials with fewer side effects are now available to treat

gram-positive infections. However, glycopeptides are still one of the few available therapies for serious enterococcal infections and thus are classified to the highest-priority category in light of the relatively high number of enterococcal infections, documented transmission of Vancomycin Resistant *Enterococcus* to people from food animals, and serious consequences of treatment failure. Previously, tetracyclines were placed in the "critically important" category, in part because they are the main treatment for *Brucella* infections transmitted from animals, but these infections have become less important with eradication of the animal reservoir in many countries. All aminoglycosides are now classified as critically important (previously, kanamycin and neomycin were considered highly important) to address cross-resistance concerns. Lincosamides (eg, clindamycin and lincomycin) were moved to "highly important" from "important" because of their greater importance for treating *S. aureus* (including methicillin-resistant *S. aureus* from animals). In the fourth edition, changes in prioritization classification based on criterion 2 (P2) were made for aminoglycosides and polymyxins because of increased frequency of use in humans (Supplementary Table 4).

HIGHEST-PRIORITY CRITICALLY IMPORTANT ANTIMICROBIALS

Antimicrobial classes that meet all 3 prioritization criteria (P1, P2, and P3) are considered the highest-priority critically important antimicrobials. The classes that met all 3 criteria were quinolones, third- and fourth-generation cephalosporins, macrolides and ketolides, and glycopeptides (see Supplementary Table 5 for more detailed information).

Application of the criteria for categorization and prioritization for the original list and revisions 1–4 was based on expert opinion. The WHO is currently in the process of developing a guideline based on the critically important antimicrobials list using a rigorous evidence-based approach with GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence profiles [47], which will inform recommendations on what and how antimicrobials should be used in food animals, including the use of critically important antimicrobial agents for human medicine.

CONCLUSIONS

Antimicrobial resistance remains a threat to human health, and drivers of resistance act in all sectors: humans, animals, and the environment. Thus far, it has not been possible to dissect the exact contribution of any one sector to the levels of resistant bacteria seen in other sectors. What is more important is to accept that antimicrobial resistance will develop in whichever sector antimicrobials are used and that these resistant microbes, and the genes that encode this resistance, can spread. It is essential that we do all we can to reduce the development of further antimicrobial resistance by reducing antimicrobial use in all sectors and then preventing any spread of the resistance. This embodies the One Health concept.

Prioritizing the antimicrobials that are critically important for humans is a valuable and strategic risk management tool and will be improved with the evidence-based approach that is currently underway. This risk management strategy focuses attention and resources on the highest-priority agents when decisions are made about control of their use in animals. The highest-priority classes of drugs are the quinolones, the third-/fourth-generation cephalosporins, macrolides/ ketolides, and glycopeptides. Although carbapenems did not meet one criterion when the list was last revised [7], this could change as evidence continues to accrue on the potential transmission of carbapenem-resistant Enterobacteriaceae, especially for *E. coli* and *Salmonella*, from animals [42]. Great prudence is required with carbapenems as, in many settings, they represent the last-line agent for serious infections. Colistin is now also of increased concern [14, 15].

Controlling antimicrobial resistance to preserve human health is a formidable challenge. The rankings provided by this WHO list can be of major assistance in risk management processes for the use of antimicrobials in food production animals and in agriculture.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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