Critically Important Antimicrobials for Human Medicine

3rd Revision 2011

World Health Organization

WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)

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1. History of the current document

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

The 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Copenhagen, Denmark, in May 2007. During the second meeting, participants reviewed the two criteria and re-examined the categorization of all human antibacterial classes in light of new drug development and scientific information since 2005. Participants were also requested to prioritize agents within the critically important category in order to allow allocation of resources towards the agents for which management of the risks from antimicrobial resistance are needed most urgently. These antimicrobial classes were fluoroquinolones, 3rd and 4th generation cephalosporins and macrolides.

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was formed in 2009, following a worldwide solicitation of experts from a variety of relevant fields, including human health and veterinary medicine, to serve as members. One agenda item of the 1st AGISAR meeting held in Copenhagen, 2009 was a follow-up of the two previous expert consultations on critically important antimicrobials. Experts at the 2009 meeting reviewed the Copenhagen 2007 list of CIA (the 1st revision of the CIA list) and produced the 2nd revision of the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and new drugs.

The 3rd AGISAR meeting was held in Oslo, Norway, in June 2011, and a further revision of the list included not only new drug developments and scientific information, but also focused on consolidating the suggestions on how the list might best be used to manage risks associated with antimicrobial use. Additional substances were added to the list according to their ATC codes (per the WHO Collaborating Centre for Drug Statistics), to ensure a more complete listing of products. Veterinary drugs falling in the same classes of antimicrobials as those in the human medicine list are now also listed in the tables to help risk managers more readily identify those drugs

and classes that are analogous to human medicines and with greater potential to impact resistance among the critically important antimicrobials for human medicine.

1.1 Contemporary context

Antimicrobials are used widely in agriculture. This includes non-therapeutic use such as for growth promotion. It also includes use as prophylaxis to try to prevent infections developing in food animals and therapeutic use to treat sick animals. However, this use also includes using agents defined by WHO as "critically important" for human medicine.

Bacteria (including those resistant to antimicrobials) that commonly transfer to people from food animals are *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp. More recently, emerging evidence has shown that *Staphylococcus aureus* (including MRSA) and *Clostridium difficile* also occur in food animals and can later be found in food products and environments shared with humans. More details and background information can be found in the previous edition of the 1st AGISAR report at www.agisar.org.

Resistant Gram negative bacteria (e.g., *E. coli*) have become a major and rapidly increasing problem. There are no new classes of antimicrobials in the pipeline and so it is unlikely that any new classes of effective antimicrobials will be available for 10 years or more to treat infections caused by resistant Gram negative bacteria.

Recently, we have seen the development and spread of bacteria carrying metallo-betalactamase genes that are resistant to carbapenems (and all beta-lactams). One of the most concerning aspects is the recent intercontinental spread of a multi-resistant strain of E.coli (New Delhi metallo- betalactamase or NDM strain) which are resistant to carbapenems and nearly all other antimicrobials (including non-betalactam classes). These types of multi-resistant bacteria have caused infections not only in hospitals, but also in the community. They have also spread within hospitals in Britain and elsewhere. The genes encoding for the metallo-betalactamases have been transferred to many other genera of bacteria (e.g., *Klebsiella*, *Vibrio* and *Providentia*). These increasingly commonly isolated bacterial isolates have necessitated using therapy with intravenous polymyxin; which, as an "old" antimicrobial had previously been discarded from systemic clinical use because of toxicity and other problems. In many cases it is now the only agent with proven

activity against many of these multi-resistant isolates. Notwithstanding this, some bacterial strains carrying the NDM gene are resistant to all antimicrobials, including the polymyxins. The end of the age of the miracle drug may indeed be upon us.

In The Netherlands the same genes encoding for ESBL (extended spectrum beta-lactamases) in *E. coli* isolates are found in both food animal isolates (especially poultry) and in those causing serious infections in people. On a global scale, *E. coli* is the most important human pathogen and causes substantially many more infections than *Salmonella* and *Campylobacter* combined. Thus, the importance of resistance in *E. coli*, typically considered a benign commensal, should not be underestimated.

2. Purpose

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that critically important antimicrobials are used prudently both in human and veterinary medicine.

Of special importance, risk managers should carefully consider that fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been categorized as being of highest priority for risk management among those antimicrobials.

Carbapenems, lipopeptides and oxazolidinones currently have no veterinary equivalent. WHO recommends that these classes as well as any new class of antimicrobial developed for human therapy should not be used in animals, plants, or in aquaculture.