

Comments about Critically Important Antibiotic Proposal

This proposal addresses the issue of antibiotic use in agriculture and its potential for generating antimicrobial resistant strains of pathogenic bacteria that then cause infections in people that are resistant to the antibiotic that was given to the animals. The recommendation is that three lists of antibiotic drugs be developed and periodically revised. The lists are antibiotics that are “critically important”, “highly important” and “important”. A few antibiotics that are on the Model List were not considered critically important or highly important by the committee that drew up this proposal.

Under ideal circumstances for human medicine, there should be no use of those antibiotics in agriculture that are useful for humans when their use can potentially cause resistance to develop in bacteria that can infect humans. This proposal is to develop a compromise between this position and the expressed need for antibiotic use in agriculture. Conceptually, the activities outlined in the proposal are sound. How the actual specific compromises are developed and which specific drugs are proscribed for agricultural use will determine the value of this approach in delaying resistance development in pathogens that will impact on public health. (Parenthetically, one should add that the use of antibiotics in agriculture is only one aspect of the overall problem of the development of antimicrobial resistance. At this time, irrational use of antibiotics in humans appears to be a more important cause of antibiotic resistance development by pathogenic bacteria.)

The idea that one can classify antibiotics into several classes with different priorities for preventing resistance is a reasonable compromise for addressing the conflict between human need and agricultural use. The criteria for critically important antibiotics state that these are drugs used to treat serious disease for which no or very few alternatives exist and the diseases are caused by organisms that may be transmitted to humans from non-human sources or commensal bacteria containing resistance genes from non-human sources can colonize humans and transfer the resistance genes into pathogenic bacteria in or on the host. Drugs that meet these criteria are certainly critical for therapy and agricultural use of any drugs that lead to this risk of resistance should be proscribed from agricultural use. What the regulatory situation will be with drugs that don't meet all of these criteria is the key issue.

Essential medicines are those that are needed to meet the health care needs of the majority of the population. Some presently on the Model List do not meet the proposal's criteria for critically important. This is based solely on the proposal's criteria that no or few alternatives exist for therapy and the definite risk that the use of the antibiotic in agriculture can lead to resistant

pathogens that infect people. Conceptually, an antibiotic can meet the “essential” definition without meeting the criteria set out for “critically important”. Examples are:

The essential antibiotic may be one choice of several that are effective for a particular infection.

It may be for bacteria that are unrelated to non-human hosts.

Thus, antibiotics can be essential but not critically important as defined in the proposal. To ensure proper understanding of this major difference in concept, the terms “critically important”, “highly important”, and “important” should be changed to antibiotics causing high risk of resistance with few alternatives, antibiotics causing high risk of resistance or having few alternatives if resistance develops, and antibiotics that have less risk of causing medically important resistance. The word “important” is misleading in the proposal since it implies that antibiotics in the third category are not important when what is meant is that the risk of medically significant resistance developing from their use in agriculture is not very high.

The next question is how to proceed to make the compromises of the need for agriculture with the ideal for medicine. One can consider the principle of cost and efficacy analysis in developing a way to address this issue. While quantitative precision and accuracy will not exist, the concept of evaluating the risks and the benefits and then making a judgment about what action is best can be used to make these compromises. I assume there is some information about the need and value of use of these specific antibiotics in agriculture. This proposal classifies antibiotics in a medically meaningful way. One now needs an group of mature people, knowledgeable in medicine and agriculture and with good judgment, to look at the data, as limited as it might be, and determine the best actions to take for the overall good of mankind. Such a group of people should meet at intervals to re-evaluate the “data” and revise the recommended actions as appropriate.

In my opinion, there is no conflict between antibiotics being essential and not having much risk of agricultural use causing resistant pathogens for humans. The entire problem, in my opinion, is using the label “important” not to mean “of much significance or consequence” but rather to mean “risk that agricultural use will cause antibiotic resistance in pathogens”. Titles of the three classifications that correctly describe what they are should ameliorate any misconception about the meaning of “essential” and “not big risk of resistant pathogens”.

What action should this Expert Committee take at this meeting? I doubt that there is sufficient knowledge about agricultural practices for this committee to make the best judgments about what agricultural practices should be. The committee should make a very strong recommendation that the names of the three classes of antibiotics in the proposal be changed to reflect what they really mean and not mislead readers by using the word "important" when that is not what is meant. The committee can also recommend that the process of developing the advice for WHO to give to those interested be as described above.

And finally, a personal technical note: I question the placing of metronidazole on the lowest priority list. It is excellent therapy for anaerobic infection (often peritonitis due to perforated viscus) and the standard treatment for *C. difficile* colitis. Only oral vancomycin is the alternative for *C. dif* and that is very expensive. If *C. difficile* is part of the flora of farm animals' intestines, then I fear that metronidazole will cause resistance to this drug when used in agriculture and that could be catastrophic for human medicine. A more knowledgeable microbiologist than I can determine the likelihood of this scary scenario.