Policy Brief and Recommendations #1
Misuse of Antibiotics in Food Animal Production

Preserve Antibiotics for the Future

APUA

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MISUSE OF ANTIBIOTICS IN FOOD ANIMAL PRODUCTION

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PRESERVE ANTIBIOTICS FOR THE FUTURE

EXECUTIVE SUMMARY

Bacteria have been evolving for three billion years into countless kinds totaling a billion trillion trillion with more mass than all animals. A few kinds, pathogens, can invade and infect tissues of animals, but few of them are infecting at any time. Yet those infecting bacteria have shortened human life more than all other causes.

Discovery of antibiotics that diffuse through human tissues, kill bacteria infecting them and cure the infections was the greatest medical advance ever. After each new antibiotic was widely used, however, bacteria increasingly became resistant to it and a new antibiotic was needed to cure the infections they caused.

Killing infecting but fewer non-infecting bacteria by treating truly infected patients while needed has been hard to attain case-by-case in a complex world. Ending antibiotic use for animal growth promotion is a cost-effective way to slow the progression of resistance before it outruns drug discovery.

THE 70-YEAR HISTORY OF ANTIBIOTIC RESISTANCE

INTRODUCTION

Trouble was identified soon after the discovery of penicillin in 1942. Some early penicillin workers noted strains of bacteria that were not killed by it, and within a few years such strains were shown to produce an enzyme that actually destroyed penicillin. The significance of this may have been overshadowed over the next decade because a large number of new classes of antibiotics; aminoglycosides, tetracyclines, chloramphenicol and macrolides, were discovered and brought to market, and it seemed like there would be no end to them.

But early in the following decade an end became apparent, and it was of two kinds. No further classes of antibiotics had come to market, and in fact only a few more would in the following half century. Worse was the realization that a particular strain, one of the most dangerous pathogens, *Staphylococcus aureus,* was spreading through the world infecting and killing people regardless of which of the new antibiotics were used to treat its infections. It had become resistant to all of them and rampaged for a decade until semi-synthetic penicillins and cephalosporins came to market in 1960. Strains resistant to those, methicillin-resistant *Staphylococcus aureus* (*MRSA*), also emerged soon in some parts of the world but not in others, including the US, for another 15 years. Treatment for those now ubiquitous *MRSA* has depended on the difficult-to-use vancomycin and two recent drugs, with resistance to each now being reported.

At the same time, multiple species of a different category of pathogen, Gram-negative bacilli, were also becoming resistant to more antibiotics and many to all of them becoming untreatable. The semi-synthetic penicillins and cephalosporins were of limited help for this problem and so it continued to grow until the introduction of gentamicin in 1970. Gentamicin was effective for virtually all such strains, but only a short reprieve. In 1975, enzymes inactivated the newly introduced gentamicin. It became apparent that this, as well as earlier types of resistance, was spreading in global epidemics, not just of resistant strains of bacteria but of the smaller and more portable plasmids. These latter mobile genetic elements could carry genes expressing resistance from one strain of bacteria to a different strain, or even one of a different species, so that this new and previous susceptible strain and all its progeny were, thereafter, resistant [1].

Finally, around 1980 there was a triple rescue from the growing menace of multiple-resistant Gram negative bacilli, from modifications of older classes, giving us newer generations of cephalosporins, fluoroquinolones and carbapenems. Unfortunately, due to natural bacterial mutations and to human misuse, resistance to the first two has been building steadily and merging, and in recent years to the third also, so that untreatable strains are again spreading and killing with no definite rescuing agent in sight [2].

As antibiotic resistance increases, it is likely to be more devastating, especially for the larger part of the world that lacks access to laboratories to identify what antibiotic would still cure which infection. These infections will have to be treated blindly and more often ineffectively from a limited stock of locally available antibiotics.

THE ANTIBIOTIC ERA --- MORE OF A MIRACLE THAN WE REALIZED

In retrospect now, it appears that when each new antibiotic was developed and marketed, the resistance genes that would limit or end its usefulness already existed. Its useful life was predestined by the time it took for one or more of those genes to either arise in pathogens in multiple places by local antibiotic usage selecting mutant resistant genes, or for existing resistance genes to be mobilized eventually from obscure bacteria somewhere and then spread widely from that place or those places.

THE LOST ERA

Antibiotics were introduced at varying intervals and resistance to each emerged at irregular intervals thereafter. Sometimes a new rescuing antibiotic arrived before the wide spread of infecting strains

that were resistant to all earlier antibiotics - and thus untreatable even in the affluent world - or of strains resistant just to antibiotics commonly available in the rest of the world - and thus virtually untreatable by the blind therapy there [3]. And sometimes a rescuing antibiotic for either part of the world did not arrive in time.

The antibiotic era can be seen now as a double miracle. It seemed like a miracle when it began that there could be such things as antibiotics – and, indeed, they were commonly referred to then as "miracle drugs". And we might now consider it wondrously fortunate that it took the immensely resourceful microbial world a decade or more to come up with and distribute ways to nullify each one. Stringing together a series of such intervals of delayed response, with occasional lethal gaps, was how the antibiotic era has survived. Having an effective antibiotic came to seem an entitlement, but was really just luck –and luck is running out.

What can be done to slow the progression of antibiotic resistance?

Only by employing a multi-pronged approach to this serious public health problem can one hope to make an impact on preserving this precious resource to both safeguard and extend human and animal life. Part of the solution lies in reducing antibiotic use in circumstances that do not require them. Inappropriate/over use of antibiotics in food animal production is a case in point. *It is essential that use of antibiotics in agriculture be limited to the treatment of diseased animals and should not be used for non therapeutic purposes: growth promotion, feed efficiency, or to compensate for stress of transport and on-farm conditions of crowding and poor hygiene* [4, 5]. Use of alternative infection prevention measures is encouraged, where possible. *Fluoroquinolones and third generation cephalosporins, antibiotics critical to treating human diseases, should be restricted to treating refractory infections in individual animals* [4]. *In addition, antibiotics should be administered to animals only on prescription by a veterinarian* [4].

To assess the human health risk and inform public health policy, quantitative data on antimicrobial use in agriculture should be made available by pharmaceutical manufacturers, importers and end users [4]. *Regulatory agencies should consider the ecology of antimicrobial resistance –the processes of spread and complex interactions between bacteria – both pathogens (disease causing) and non-pathogens (commensals), food animals, humans, and their environments* [4]. *Surveillance programs for antimicrobial resistance should be harmonized to permit integrated analysis of human and animal data* [4].

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References

1. Watanabe, T., *Infective heredity of multiple drug resistance in bacteria.* Bacteriol Rev, 1963. **27**: p. 87-115.
2. Pournaras, S., et al., *Clonal spread of KPC-2 carbapenemase-producing Klebsiella pneumoniae strains in Greece.* J Antimicrob Chemother, 2009. **64**(2): p. 348-52.
3. Archibald, L.K. and L.B. Reller, *Clinical microbiology in developing countries.* Emerg Infect Dis, 2001. **7**(2): p. 302-5.
4. FAAIR, *Policy recommendations.* Clin Infect Dis, 2002. **34 Suppl 3**: p. S76-7.
5. Institute of Medicine. in *Microbial Threats to Health: Emergence, Detection, and Response.* 2003: National Academy Press.