Policy Brief and Recommendations #2
Misuse of Antibiotics in Food Animal Production

How Epidemics of Untreatable Infections Develop

APUA

POLICY BRIEF AND RECOMMENDATIONS #2
MISUSE OF ANTIBIOTICS IN FOOD ANIMAL PRODUCTION

DATE: SEPTEMBER 1, 2010

AUTHOR: THOMAS F. O'BRIEN, MD, VICE PRESIDENT, APUA; ASSOCIATE PROFESSOR OF
MEDICINE, HARVARD MEDICAL SCHOOL

HOW EPIDEMICS OF UNTREATABLE INFECTIONS DEVELOP

EXECUTIVE SUMMARY

The resistance genes that made infecting bacteria resistant to a new antibiotic after it was used had existed before. Some were mutants of infecting bacteria, unseen until the antibiotic selected for their overgrowth. More took years to first get from obscure to infecting bacteria somewhere and to then spread from there.

Antibiotics drive resistance by killing susceptible bacteria and letting a resistant one then multiply explosively to replace a billion dead susceptible ones overnight. After three billion years of evolution, few infecting bacteria had any resistant gene, but 70 years of antibiotic use has put many into more than a quarter of them.

A succession of irregular global epidemics has given us a growing global catalog of resistance genes and growing local inventories of them in any region that might diminish, but could be rapidly recalled. The examples cited herein glimpse the enormous resources of the world's bacterial populations for responding to introduced antibiotics and the negligible barriers to those responses of the species of the bacteria or the species of the hosts that carry them. This global web necessitates the need for a global surveillance system so that the medical community is never caught off-guard by emerging resistances. Most importantly, it is imperative that use of antibiotics in agriculture be restricted to therapeutic use only, and that antibiotic use for growth promotion and other non-therapeutic uses be terminated.

INTRODUCTION: HOW ANTIBIOTICS AND RESISTANCE GENES WORK

Antibiotics are small molecules that enter bacterial cells and bind to and block specific functional sites within them. Some antibiotic resistance mechanisms are alterations in a functional site that

make antibiotic binding impossible. Resistance can also emerge through bacterial enzymes or other proteins that destroy the antibiotic, nullify its effect, or eject it from the bacterial cell. Either type is expressed by what can be called a resistance gene, which susceptible cells do not have.

Naomi Datta found almost no resistance genes in infecting bacteria stored from the 1930s, and resistance to each new antibiotic was rarely seen, until after it had been widely used for years or even decades [1]. So the central questions are, how do resistance genes arise and spread and how can we delay it.

Some resistance genes emerge from mutation

Resistance genes can now be seen to emerge in two different ways. Resistance to some antibiotics, such as fluoroquinolones, may arise in a strain of bacteria from a mutation in a gene that is normally carried by strains of that species. This classic Darwinian model has been in our thinking about antibiotic resistance for much of its seventy years. Such mutations have been occurring in those strains at rates like once in a million cell divisions, but they are entirely unnoticed until the antibiotic is used. In a crowded bacterial world, a single resistant bacterial cell, with no other advantage, is condemned to obscurity, until the antibiotic arrives to kill its billion susceptible neighbors and give it some space - and let it then overgrow by such "selection".

More resistance genes emerge unpredictably from obscure recombinant events

It is increasingly recognized now that many of the most important resistance genes, including those for MRSA, vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococus pneumoniae* (PRSP), etc. differ too much from genes in their susceptible ancestors to have arisen by mutation from them.   Such resistance genes, moreover, can often be seen to have first emerged only after many years of use of the antibiotic (30 years for PRSP or VRE) and initially, in one or a few parts of the world - with gradual but eventual spread to other parts.   Finally, some of these same genes are now being found in more obscure kinds of bacteria.

Many, if not most, of the most damaging antibiotic resistance genes can thus be seen to have emerged not from simple, predictable mutation in the strains and species in which they are now widely infecting. The resistance genes appear, instead, to have emerged by one or a succession of rare mobilization and recombination events from some remote strain or species, which had the gene. The strain/species was obscure, because it was outside of the small subset of pathogens that clinical laboratories report. It may take years for such a resistance gene to first emerge somewhere in infecting bacteria that those laboratories would notice, and then more years for it to spread to other places.

Examples of the evolution and spread individual antibiotic resistance genes

An enzyme that destroys penicillin and ampicillin, TEM, spread widely among Gram-negative bacilli in humans and animals throughout the world. This enzyme accounted for most of the resistance to

ampicillin in the commonest infecting Gram-negative bacillus, *Escherichia coli*, when 15% of them were resistant to ampicillin 35 years ago. Now, more than twice that many are resistant and, consistent with what Naomi Datta found, that extrapolates back to zero when penicillin use began.

At about the midpoint of the era, penicillin could still treat all gonorrhea, and ampicillin could treat any kind of bacterial meningitis anywhere in the world. So both of these major diseases could be treated optimally immediately without a laboratory. This was a huge advantage anywhere but immense to the larger world, that has more of those diseases and fewer, or no, laboratories. Within a few years, however, *E. coli* carrying resistant enzymes had presumably become prevalent enough and contacted enough of these very different kinds of bacteria to engineer a genetic transfer of this resistance to a gonococcus and another to the commonest cause of meningitis, *Hemophilus influenzae.* Such "second generation" resistant strains then spread to cause untold numbers of treatment failures and deaths.

When entirely new cephalosporins were introduced around 1980, all Gram-negative enteric bacilli were susceptible. Within 5 years, however, mutations enabled TEM and the others to "open wider" and destroy these drugs too. Four decades of penicillin and ampicillin use had thus spread the resistance enzyme gene from somewhere to make resistance to both prevalent everywhere, but also to be available widely for "third generation" mutations to destroy the new drugs that were meant to fix the problem.

Vancomycin, an entirely different antibiotic for entirely different kinds of bacteria, Gram-positive cocci, was also used for many decades. Unlike penicillin or ampicillin., however, no one saw growing resistance to it during that time or any resistance at all. Then about 20 years ago, such resistance appeared first in enterococci of animals in Europe that had been given an analog of vancomycin and then by the same mechanism in patients in hospitals all over the United States [2]. This mechanism, too, has had a beginning "second generation" in 8 patients in whom it transferred vancomycin resistance to MRSA, although none have yet spread to additional patients - a truly catastrophic threat [3].

These "second" and "third generation" resistance examples tell us that resistance begets more resistance and that there is no going back. A succession of such irregular global epidemics has given us a growing global catalog of resistance genes and growing local inventories of them in any region that might diminish but could be rapidly recalled [4]. The examples also glimpse the enormous resources of the world's bacterial populations for responding to introduced antibiotics and, importantly, the negligible barriers to those responses of the species of the bacteria or the species of the hosts that carry them. This global web necessitates the need for a global surveillance system so that the medical community is never caught off-guard by emerging resistances.

The alarm has gone out

What can be done to slow the pace 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. 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* [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* [5]. *In addition, antibiotics should be administered to animals only on prescription by a veterinarian* [5].

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 [5]. *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* [5]. *Surveillance programs for antimicrobial resistance should be harmonized to permit integrated analysis of human and animal data* [5].

This policy brief is made possible with the support of The Pew Charitable Trusts.

References

1. Hughes, V.M. and N. Datta, *Conjugative plasmids in bacteria of the 'pre-antibiotic' era.* Nature, 1983. **302**(5910): p. 725-6.
2. Martone, W.J., *Spread of vancomycin-resistant enterococci: why did it happen in the United States?* Infect Control Hosp Epidemiol, 1998. **19**(8): p. 539-45.
3. Perichon, B. and P. Courvalin, *VanA-type vancomycin-resistant Staphylococcus aureus.* Antimicrob Agents Chemother, 2009. **53**(11): p. 4580-7.
4. Miller, G.H., et al., *The most frequent aminoglycoside resistance mechanisms--changes with time and geographic area: a reflection of aminoglycoside usage patterns? Aminoglycoside Resistance Study Groups.* Clin Infect Dis, 1997. **24 Suppl 1**: p. S46-62.
5. FAAIR, *Policy recommendations.* Clin Infect Dis, 2002. **34 Suppl 3**: p. S76-7.