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Public Health Impacts of the Use of Antimicrobials in Food Animals

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Introduction

The first resistant bacteria were detected shortly after the first penicillin antimicrobials had been put into clinical use. With time, we have come to realize that every time a new antimicrobial is placed on the market, the bacteria quickly respond by becoming resistant. The rate of resistance emergence is usually proportional to the extent of usage of the new drugs, so it is fair to conclude that for antimicrobials the following rule of thumb applies; “the more we use them the faster we loose them”.

Antimicrobial resistant bacteria do not respond, or respond less well, to antimicrobial therapy. This in turn leads to treatment failures and increased duration of illness and risk of death in the patient. Overcoming the problem of antimicrobial resistance is one of the major challenges of public health systems globally as recently stressed by the World Health Organization[1].

There are two key responses to the problem of antimicrobial resistance: 1) to develop new drugs faster than the bacteria become resistant to the old drugs, and 2) to extend the effective lifespan of the available drugs, by using them wisely (avoid overuse and misuse). Unfortunately, most countries have relied more heavily on the “drugs race” and less on the “prudent use”.

Recently the use of antimicrobials in food animals has attracted renewed attention, because it has been shown (again) that pathogenic bacteria resistant to antimicrobials critical for the treatment of infections in humans can transmit from animal to humans, and furthermore, that resistance emerge because of indiscriminate antimicrobial use in food animals.

This paper provides an overview of some of the current issues in relation to antimicrobial use in food animals and emergence of resistant human infections.

Antimicrobial use in food animals

There are three modes of antimicrobial usage in animals: 1) therapy- the treatment of disorders or disease, 2) prophylaxis - administration of antibiotics in advance of symptomatic disease, for example medicated early weaning, and 3) growth promotion - antibiotics used as feed additives with the purpose to increases feed efficiency or growth rate.

Therapeutic use is non-controversial, assuming that disease could not have been prevented by simple preventive measures. Prophylactic use, in some of its forms, is justified, whereas chronic use in animal production systems, which are totally dependent on prophylactic

antimicrobials, such as medicated early weaning systems of pigs, is not appropriate. Most controversial is the use of antimicrobials as feed additives for growth promotion. Antimicrobials in feed tend to make animals grow slightly faster and/or reduce the need for feed marginally. The exact mechanism has never been elucidated, and the actual effect may well be one of prophylaxis. Growth promoters are used for the entire duration of the animal's life. The doses of antimicrobial growth promoters are referred to as "sub-therapeutic" because the concentrations in feed are lower than for therapeutic use. However, the concentrations are not "sub-inhibitory" to bacteria. Consequently, growth promoter use selects resistant bacteria.

There exist a close, but complex, relationship between the volumes of antimicrobials used and the rate of bacterial resistance development. Unfortunately, there are only few accurate and reliable data available on the volumes of antimicrobials used in animals and in humans. This is because pharmaceutical industry regards this information as proprietary. Estimates from the USA, suggest that approximately 85% of all antimicrobials, are used for non-therapeutic purposes in animals (systematic prophylaxis and growth promotion) [2]. Estimates from Europe suggest that animals only consume 35% of all antimicrobials, and that only a minor fraction of this is used specifically for growth promotion[3]. There is an acute need for accurate and reliable data.

Major differences exist between the European countries in relation to how much antimicrobials are used to produce a kilogram of meat. Differences in animal health and animal production systems may explain some of this difference, but other factors such as differences in veterinarians' incentives to prescribe drugs and presence of actively enforced veterinary antibiotic policies probably also play a significant part. In the Nordic countries, where there is a tradition for prudent antimicrobial use, and where veterinarians do not profit from the sale of drugs, the use is markedly lower than in countries where antibiotic policies are not formulated and enforced and where veterinarians traditionally generate a large fraction of their income from the sale of drugs.

Transmission of resistance from animals to humans

The list of bacterial species that can transmit from animals to humans is long. A survey of infectious diseases found that nearly half of all infectious microbial agents of humans have an animal reservoir. Furthermore, nearly 3 out of 4 newly recognized or emerging infections are zoonotic[4]. Some of the zoonotic infections are foodborne whereas others are spread by vectors, or by direct animal-to-man contact.

An area of particular concern is resistance emerging to standard empiric therapies for acute gastro intestinal tract infections in humans (diarrhoea) caused by foodborne zoonotic agents such as *Salmonella* and *Campylobacter*. Fluoroquinolones and 3rd generation cephalosporins are drugs of choice for treatment of *Salmonella* and fluoroquinolones and macrolides for *Campylobacter*. These drugs are widely used in agriculture, and the use is increasing

In every country where quinolones have been licensed for use in food animals, resistance to quinolones has emerged in *Salmonella* and *Campylobacter* shortly thereafter. This emergence has been followed by a concomitant emergence of resistance in human isolates[5].

Quinolone resistance in *Salmonella* may lead to treatment failures and death in humans[6]. In a recent study showed markedly higher mortality rate for infections with quinolone-resistant

Salmonella when compared to infections with sensitive strains[7]. There is a need for further detailed studies of the short and long term effects of *Salmonella* infections, especially the effects of infections caused by quinolone resistant *Salmonella*.

Campylobacter are the most common cause of foodborne infections world wide, causing millions of cases of diarrheal disease in developed and developing countries every year. Nearly all species of warm-blooded animals harbor *Campylobacter* in the gut, but poultry is probably the main reservoir of human infections. The increasing prophylactic and therapeutic use of fluoroquinolones in poultry production is believed to be the main driving force behind the increased levels of resistance observed in human infections worldwide. In developing countries, the vast majority of *Campylobacter* infections occur in children under the age of two. In Thailand, 90% of *Campylobacter* isolated from children with symptoms of dysentery are resistant to quinolones, which means that these drugs can no longer be used for empiric treatment of dysentery[8].

An area of recent concern is the detection, in animals, of enterococci resistant to important last resort antimicrobials for treatment of hospital-acquired infections in humans, notably vancomycin and Synercid®. *Enterococcus faecium* in animals have developed resistance to vancomycin and to Synercid® due to the use of two closely related drugs, avoparcin and virginiamycin, as growth promoters. Transmission of the resistant enterococci between animals and humans has been documented. Enterococci are among the commonest causes of severe infections in hospitalised patients worldwide. Resistance to vancomycin and Synercid® in enterococci increase morbidity and mortality in the infected patients[9].

Due to the large body of scientific evidence documenting that the use of avoparcin and virginiamycin as growth promoters had led to the creation of a large animal reservoir of resistant enterococci with potential for spread to humans, these drugs were banned by the European Union in 1997 and 1999 along with a number of other antimicrobial growth promoters belonging to classes of drugs used in humans (macrolides and bacitracin). Unfortunately, several of these drugs, including virginiamycin and tylosin, are still being used in other parts of the world for growth promotion and routine prophylaxis.

Containing the growing threat of animal-related resistance

Recently World Health Organization (WHO) published Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food[10]. Some of the main recommendations were:

- Pre-licensing evaluation of antimicrobials for animals should include consideration for resistance
- Obligatory prescription for all antimicrobials used for disease control
- Establish national systems to monitor antimicrobial usage in food animals
- Monitoring of resistance and timely corrective actions
- Develop guidelines for veterinarians to reduce overuse and misuse
- Termination or rapid phasing out of antimicrobial growth promoters

In Denmark, all antimicrobials for disease control in animals are on veterinary prescription. The use of fluoroquinolones is severely restricted, and furthermore, food animal producers have voluntarily discontinued all uses of antimicrobials for growth promotion since January 2000. What have been the consequences of these changes?

Denmark is the worlds' largest exporter of pork, and 70% of the broilers produced are exported. The Danish food animal production is modern, intense, non-subsidized and export oriented which means it competes favorably in the international market place. Thus antibiotic policies implemented in Denmark could probably be implemented in other countries with similar types of intense production systems for poultry and pigs.

Recently the WHO conducted a review of the consequences of the discontinuation of the use of antimicrobial growth promoters in Denmark[11]. The conclusions were that the discontinuation had resulted in a marked reduction in the total antimicrobial usage in food animals (< 50%), and furthermore that a significant reduction in the prevalence of resistance to antimicrobial growth promoters and their medicinal analogues had occurred in bacteria from pigs and broilers.

Importantly, the effects of the discontinuation on health and productivity of broilers and chickens were very minor. The only measurable problem has been an increase in treatments of pigs in the period after weaning in some herds. The Danish pig producers consider the problem among weaned pigs as temporary and that the problems with post weaning diarrhea can be solved with improvement of feed and management.

The Danish Integrated Antimicrobial Resistance Monitoring Programme (DANMAP) monitors the prevalence of antimicrobial resistance among animal pathogenic bacteria, human pathogenic bacteria and indicator bacteria isolated from food animals, food and humans in Denmark and furthermore the usage of antimicrobials in humans and animals. The system has been invaluable for the development of national risk management strategies[12].

Conclusion

Modern food animal production systems favor the establishment and spread of the modern foodborne zoonoses, and rely heavily on antibiotics to produce healthy animals. As a consequence increasing problems with antimicrobial resistant food borne infections have emerged. There is a need to modernize animal production systems so they rely less on antimicrobials and more on hygiene, feeding and management for the prevention of disease. A first important step would be for every country to implement and adhere to the WHO global principles.

Abstract in French

Les antibiotiques sont utilisés pour le traitement et la prophylaxie des maladies chez les animaux producteurs. Ils sont également utilisés pour la promotion de leur croissance. Cette utilisation mène au développement de bactéries résistantes, dont certaines sont pathogéniques chez les humains. La vitesse du développement de la résistance dépend de l'étendue de l'utilisation de ces antibiotiques. Il y a un besoin urgent de mettre en oeuvre le « WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food» pour contenir le développement et l'expansion de la résistance aux antibiotiques.

References

1. WHO Global strategy for containment of antimicrobial resistance. World Health Organization, Geneva, Switzerland. 2001; WHO/CDS/CSR/DSR/2001.2.
2. Mellon M, Benbrook C. and Benbrook KL. Hogging It - Estimates of Antimicrobial Abuse in Livestock. Report from the Union of Concerned Scientists, Cambridge, MA. 2001. (available from: www.ucsusa.org).
3. EMEA. 1999. Antibiotic resistance in the European Union associated with therapeutic use of veterinary medicines. Report and qualitative risk assessment by the committee for veterinary medicinal products. The European Agency for the Evaluation of Medicinal Products. London, UK. http://www.emea.eu.int/index/indexv1.htm.
4. Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. Philos Trans R Soc Lond B Biol Sci. 2001; 356:983-9.
5. Stöhr K, Wegener HC. Animal use of antimicrobials: impact on resistance. Drug Resist Update. 2000; 3:207-209.
6. Molbak K, Baggesen DL, Aarestrup FM, Ebbesen JM, Engberg J, Frydendahl K, Gerner-Smidt P, Petersen AM, Wegener HC. An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype typhimurium DT104. N Engl J Med 1999; 341:1420-5
7. Helms M, Vastrup P, Gerner-Smidt P, Molbak K. Excess mortality associated with antimicrobial drug-resistant Salmonella Typhimurium. Emerg Infect Dis. 2002; 8:490-5.
8. Bodhidatta L, Vithayasai N, Eimpokalarp B, Pitarangsi C, Serichantalergs O, Isenbarger DW. Bacterial enteric pathogens in children with acute dysentery in Thailand: increasing importance of quinolone-resistant Campylobacter. Southeast Asian J Trop Med Public Health. 2002; 33:752-7.
9. Wegener HC, Aarestrup FM, Jensen LB, Hammerum AM, Bager F. Use of antimicrobial growth promoters in food animals and *Enterococcus faecium* resistance to therapeutic antimicrobial drugs in Europe. Emerg Infect Dis. 1999; 5:329-35. Review.
10. WHO Global principles for the containment of antimicrobial resistance in animals intended for food. Report of a WHO consultation 5-9 June 2000. World Health Organization, Geneva, Switzerland 2000; WHO/CDS/CSR/APH/2000.4.
11. WHO. The effects of discontinuing the use of AGP's in Denmark – report of an international expert review. World Health Organization, Geneva, Switzerland, 2003; WHO/CDS/CPE/ZFK/2003.1.
12. DANMAP 2002. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. ISSN 1600-2032. http://www.dfvf.dk.