Use of antibiotics in food animals
(not for circulation outside the CGD working group)

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I. Introduction

A variety of types of antibiotics are today used in agriculture, industry and livestock production. In agriculture, antibiotics are sprayed on crops (particularly fruit trees) to eliminate surface bacteria, and in industry, antibiotics are, for example, applied to the inside of oil pipelines to avoid bacterial growth. In livestock production, antibiotics are dispensed to animals for a number of different reasons: therapeutic treatment, disease prophylaxis and growth promotion. The administration of antibiotics to bacterial populations is a significant driving force for the selection of resistant forms of bacteria, and such forms of bacteria can spread from one organism to another. There is therefore an important question of whether the use of antibiotics in agriculture and livestock production poses a threat to human health. In particular, the worry is that resistant forms of bacteria spread from animals and/or the environment (ground-water/surface-water/soil) to humans and cause diseases in humans that are either troublesome or impossible to treat because available antibiotic therapies in human medicine are either expensive or impotent.

This paper focuses on the use of antibiotics in food animals. Section two seeks to give an overview of what is currently known about the impact of this use of antibiotics on human health. Section three contains information about the extent of use of antibiotics in food animals in developing countries. In the final section, two discussion-points are to be found together with two explicit recommendations.[1]

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[1] The decision about what literature to review as part of this study was influenced by a number of people. The organization *Keep Antibiotics Working: the Campaign to End Antibiotic Overuse* has an annotated bibliography of scientific literature on antibiotic resistance: http://www.keepantibioticsworking.com/new/indepth_keyevid.cfm. This

II. The effects of antibiotics in food animals on human health

1) Some examples of documented detrimental effect

There is broad scientific consensus that the use of antibiotics in food animals, on some occasions, has detrimental effects on human health. According to (Collignon 2003:78), the use of the antibiotic avoparcin as a growth promoter in food animals in Europe resulted in the development and amplification of vancomycin-resistant enterococci (VRE) and subsequent colonization of a significant percentage of the human population via the food chain (between 2 and 17%).[2] A subsequent ban on the use of avoparcin in food animals in the EU resulted in a marked reduction of the percentage of the general population carrying VRE in their bowel. Vancomycin-resistance is a cause for concern because vancomycin is used in Australia as a 'last-line' antibiotic for some hospital-acquired infections of enterococci and staphylococci that have become resistant to the more commonly used antibiotics.

(Collignon 2003:78) also mentions that the use of the antibiotic enrofloxacin has been approved for use in food production animals in many countries. The use of this antibiotic in food animals has resulted in the development of ciprofloxacin-resistant strains of Salmonella ssp and Campylobacter ssp. These resistant bacteria have subsequently caused human infections.

According to (Khachatourians 1998:1131), the use of animal feed supplemented with the antibiotic tylosin has led to the development of erythromycin-resistant streptococci and staphylococci not only in the animals but also in their caretakers.

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bibliography was consulted in the literature search due to the advice of Julie Hantman (Senior Program Officer for Public Health) from the Infectious Diseases Society of America (IDSA). Dr. Iruka Okeke (Haverford College) provided input by drawing attention to the works of Eric Mitema and Sam Kariuki. Dr. Rachel Nugent (CGD) drew attention to the work by Anderson et al. Lastly, a number of WHO reports on the use of antibiotics outside of human medicine were consulted, and from the associated bibliographies, a number of new titles were selected for review. I owe a great thanks to all those who have contributed with input about what literature to select for review.

[2] It should be noted that in private correspondence, Dr. Scott Weese (University of Guelph) has urged that one should be careful implicating food in specific percentages of human infections/colonizations since there were simultaneous changes in the epidemiology of hospital-associated VRE in humans with the concurrent spread to the community.

(WHO 2002b) estimates that the majority of the rising antimicrobial resistance problem in human medicine "is due to the overuse and misuse of antimicrobials by doctors, other health personnel and patients. However, some of the newly-emerging resistant bacteria in animals are transmitted to humans; mainly via meat and other food of animal origin or through direct contact with farm animals. The best-known examples are the food-borne pathogenic bacteria Salmonella and Campylobacter and the commensal (harmless in healthy persons and animals) bacteria Enterococcus. Research has shown that resistance of these bacteria to classic treatment in humans is often a consequence of the use of certain antimicrobials in agriculture".[3]

Unfortunately, the WHO report does not specify what research it is that shows the resistance of these bacteria to classic treatment. The following studies can, however, be used to support the conclusion of the WHO report.

Campylobacter:

(FDA 2001:I-2) states that since the approval of fluoroquinolones for use in food-producing animals, reports have identified a relationship between the approval of fluoroquinolones for therapeutic use in food producing animals and the development of fluoroquinolone resistance in campylobacter in animals and humans. The approval of these drugs in food-producing animals in the Netherlands, Spain and the United States preceded increases in resistance in campylobacter isolates from treated animals and ill humans. (Smith et al. 1999) is cited as one of the sources for this claim.

(Anderson et al. 2003:231) echoes the FDA report by saying that the emergence of fluoroquinolone resistance among campylobacter is an example of antimicrobial resistance resulting from the use of antimicrobial agents in food animals and the subsequent transfer via the

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[3] In private correspondence and as a comment to this passage in the WHO report, Scott Weese has stressed that enterococci are important opportunistic pathogens.

food supply of resistant bacteria to humans. The source of this claim is again (Smith et al. 1999) which reports a study showing that resistance of human Campylobacter jejuni infections to quinolones increased from 1% in 1992 to 10% in 1998. Resistant infections that were domestically acquired increased significantly from 1996 through 1998. This finding was temporally associated with the licensure of fluoroquinolones for use in poultry in 1995.

Salmonella:

(Anderson et al. 2003:236) claim that the emergence of multi-drug-resistant Salmonella typhimurium definitive type 104 (DT104) in the United States and the United Kingdom is an example of how a highly resistant clone of salmonella has the ability to effectively spread among animals and then to humans. DT 104 is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline.

(Fey et al. 2000) report a case of domestically acquired ceftriaxone-resistant salmonella in a 12-year old child from Nebraska. (Ceftriaxone is a third-generation antibiotic that is commonly used for treatment of salmonella infections in children). The child lived on a farm and his father was a veterinarian who before the child’s illness had been treating several cattle herds for outbreaks of (culture-confirmed) salmonella infection. (Fey et al. 2000) suggest that ceftriaxone-resistance emerged in the cattle-herds, probably following use of the antibiotic ceftiofur or other antibiotics that would have selected for and maintained the ceftriaxone-determinant within the intestinal flora of the involved herds, and then spread to the child via the father.

2) *The Danish ban on the use of antibiotics as growth-promoters and disagreement about its scientific foundation*

Driven by a concern for human health, Denmark initiated in 1995 a process to end the use of antibiotics as growth-promoters in livestock production.[4] This process involved both voluntary and legislative elements and led to the situation that virtually no antimicrobial growth-promoters have been used in Denmark since the end of 1999 (WHO 2002a:6).[5]

What were the effects of the ban on efficiency of food animal production, animal health, food-safety and consumer prices? This is an important question given that the kind of reasoning underlining the ban in Denmark (and underlining deliberations elsewhere about implementing a similar ban) is a cost-benefit analysis that weighs economic costs against improvements in animal and human health.

According to a WHO estimate, the ban has been a success at a number of different levels. The issues of efficiency of food animal production, animal health, food safety and consumer prices "have been addressed in the 'Danish experiment', and there have been no serious negative effects" (WHO 2002a:8). The WHO report goes on to say that the ban has been very beneficial in reducing antimicrobial resistance in important food animal reservoirs. This reduces the threat of resistance to public health, and from a precautionary point of view, the ban appears to have achieved its desired public health goal (WHO 2002a:8).

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[4] Importantly, ending this type of use of antibiotics did not end *therapeutic* or *prophylactic* uses of antibiotics. Sick animals continue to be treated with antibiotics and Ionophores are antimicrobials that are approved in Denmark and many other countries as coccidiostats (i.e. preventives of coccidiosis, a parasitic infection). Coccidiosis predisposes broilers to necrotic enteritis (NE). Since antimicrobial growth-promoter termination, Danish broiler producers believe that ionophores are the only effective means of NE prophylaxis, and continue to use them for this purpose (WHO 2002a:34).

[5] In December 1997, the EU banned the animal growth-promoter (AGP) avoparcin in all member states. In July in 1999, the EU banned another four AGPs (tylosin, spiramycin, bacitracin and virginiamycin) because they belonged to classes of anti-microbial drugs also used in human medicine. AGPs are still widely used in the United States. (Mellon, Benbrook, and Benbrook 2001) estimate that every year livestock producers in the United States use 12.5 million kilos of antimicrobials for non-therapeutic purposes. At least one bill has been introduced to the United States Congress with the aim of terminating this use: The Preservation of Antibiotics for Medical Treatment Act of 2007 (S. 549, H.R. 962). The bill was introduced by Senators Kennedy, Snowe, Brown and Reed.

(Collignon 2003) offers a similarly positive estimate of the impact of the Danish ban. Interestingly, he addresses an argument that therapeutic use of antibiotics would replace the discontinued use of antibiotics as growth-promoter. According to (Collignon 2003:76), the therapeutic use of antibiotics in Denmark remains much lower per kilogram of meat produced than in nearly all other countries in the EU.

Not everyone within the scientific community agrees with Collignon's and WHO's estimate of the effects of the ban on growth-promoting antibiotics. (Casewell et al. 2003:160) agree that published evidence suggests that the growth-promoter bans have reduced overall antibiotic use in animals. In their view, it is, however, increasingly clear that the use of growth-promoters was "accompanied by other, previously unrecognized, health-promotional or prophylactic effects. After the withdrawal of these antibiotics, animal welfare has suffered and despite efforts to improve other aspects of husbandry, the veterinary use of therapeutic antibiotics, which are identical to those used in human medicine, has increased, and this constitutes a theoretical hazard to human health in relation to resistance in salmonellae, campylobacters and zoonotic strains of *E. Coli*".

(Phillips et al. 2004:276) explicitly rejects the scientific foundation of the ban. "The banning of growth-promoting antibiotics in Europe required the application of the Precautionary Principle, which conceded that data were inadequate to support such a ban, and required that good data to be actively sought. In light of such data, it is our conclusion that the growth-promoter ban is still not supported by evidence that it protects human health." (Phillips et al. 2004:276) also claim that data which do *not* support the hypothesis that animal antibiotic use harms human health is often played down, or even ignored, by those who advise risk managers responsible for antibiotic regulation.

(Smith, Dushoff, and Morris 2005:0731) acknowledge that there is evidence linking bacterial antibiotic resistance on farms to resistance in humans. They are, however, of the opinion that the impact of agricultural antibiotic use remains controversial and poorly quantified. The controversy arises, at least partly, because of the complexity of population-level processes underlying the between-species (heterospecific) and within-species (horizontal) spread of antibiotic-resistant bacteria. To emerge as human pathogens, new strains of antibiotic-resistant bacteria must (1) evolve, originating from mutations or gene transfer; (2) spread, usually horizontally among humans or animals, but occasionally heterospecifically; and (3) cause disease. In the opinion of (Smith, Dushoff, and Morris 2005), all three of these steps are complex and imperfectly understood.

III. Use of antibiotics in food animals in developing countries

1) How widespread is the use of antibiotics in food animals in developing countries?

Reliable data on antibiotic consumption (for both animals and humans) is not widely available. (Mitema et al. 2001:386) give a few examples of academic papers (Bager 2000; Grecko 2000; Grave et al. 1999) that offer an estimate of overall consumption of antibiotics in selected geographical regions. According to (Mellon, Benbrook, and Benbrook 2001:18), the yearly, overall production of antibiotics in the United States is 17.5 million kilos. 12.5 million kilos are used for non-therapeutic purposes in livestock production and (only) 1.5 million kilos are used for human medical therapy.[6]

[6] The remaining amount of antibiotics is used in agriculture and industry and for animal therapy. It should be noted that Scott Weese sees the Mellon reference as a highly biased one that is not strongly supported. According to him, the key point is that nobody really has a good grasp of the overall use of antibiotics and that many reports/estimates on the matter are from highly biased sources. The organization *Keep Antibiotics Working* (KAW) cites the Mellon reference on their website under 'The Basics': http://www.keepantibioticsworking.com/new/basics.cfm

(WHO 1998:10) indicates that a number of quinolones are licensed for use in food animals in Asia, Latin America and South Africa. The report does not, however, specify the magnitude of use of these antibiotics in the different regions. The report does contain an estimate that annual quinolone consumption in animals in China is in the range of 470 tons (WHO 1998:1).

In an excerpt from a yet unpublished work, Samuel Kariuki from the Center for Microbiology Research (Kenya Medical Research Institute) says that fluoroquinolones are commonly used in poultry production in Asia and South America. (WHO 1998) is cited as a reference for this claim, but no page reference is given, and as mentioned above, the report in question does not involve any quantitative assessment of the use of antibiotics in African food animals.

(Mitema et al. 2001) contains reliable quantitative information about antimicrobial consumption in food animals in Kenya. In the five-year period from 1995 to 1999, the annual mean antimicrobial consumption was 14.6 tons. The study confirms that antimicrobials are not used for growth promotion in Kenya (Mitema et al. 2001:385).

(Collignon et al. 2005:1008) claim that the limited data available show that very large amounts of antibiotics are used in agriculture in nearly every country, mostly as feed additives to promote animal growth on intensive, industrial (landless) farms. No reference is, however, given to studies that indicate the magnitude of use of antibiotics as feed additives in developing countries. References are given to studies that document the use of antibiotics in Australia, Denmark and the United States, but it is not obvious how these studies can support the claim that very large amounts of antibiotics are used and agriculture ‘in nearly every country’.

(Collignon et al. 2005:1008) also assert that it is in developing countries "where the largest increases in industrialized meat production (especially poultry production) are occurring, where it is hard to successfully regulate the use of antibiotics, and where "critically important" human antibiotics (such as fluoroquinolones) are used in large quantities for nontherapeutic uses in healthy animals". 'Large quantities' is not further specified, and no reference is given to a study that supports this assertion about the non-therapeutic uses of antibiotics in healthy animals.

IV. Discussion

1) *Should Denmark's ban on use of antibiotics as animal growth-promoters (AGPs) be implemented in other countries?*

A well-founded answer to this question requires that it is clear what the effects were of Denmark's ban. This is, however, not clear. As is evident from section two, there are very substantial disagreements within the scientific community about what consequences Denmark's termination of AGPs had. More data on the effects of Denmark's ban, and more analysis of this data, is therefore needed before the above question can be answered with a satisfactory degree of certainty. As far as I can see, the crucial questions that need to be answered are: did the abandonment of antibiotics as growth-promoters lead to an increase in therapeutic uses of types of antibiotics commonly used in human medicine? If so, did the use of these 'new' types of antibiotics create a pool of resistant bacteria that from a public health perspective is more worrisome than the pool of resistant bacteria created by the 'old' antibiotics used as growth-promoters? I can offer no interesting insights on these empirical questions, and it might be worthwhile for the working group to have someone with veterinarian/epidemiological expertise weigh in on the dispute between (Collignon 2003) and (Casewell et al. 2003).

However, assume that (WHO 2002a) is correct in the estimate that there has been no serious negative effects of the ban. On this assumption, is there an uncontroversial case for supporting the implementation of a similar ban in other countries? The answer should be negative. There might be disanalogies between Denmark and other countries with respect to husbandry and the physical facilities in which livestock production takes place. Moreover, these disanalogies might be such that an implementation of Denmark's ban in these other countries leads to significant negative effects in terms of decreased animal welfare, reduced productivity and declining profits.[7] One possible explanation as to why there were no serious negative effects in Denmark of the ban on AGPs is, after all, that the kind of livestock production methods practiced there (e.g., All-In-All-Out), together with relatively high standards of hygiene and relatively well-educated farmers, promote the steady growth of healthy animals.[8] It is this consideration that presumably led to the WHO recommendation "that under conditions similar to those found in Denmark, the use of antimicrobials for the sole purpose of growth promotion can be discontinued" (WHO 2002a:8).

On the assumption that there are countries in which implementation of a ban, similar to the one introduced in Denmark, leads to serious costs in terms of worsening animal health, decreasing production-efficacy and declining profits in the livestock sector, there is an important question of whether the ban should be implemented in such countries. It should here be noted that some give an affirmative answer to this question (e.g., Rollin 2001). In my view, it is, however, difficult to give a well-founded answer. Again, the problem is one of not knowing

[7] (Collignon et al. 2005:1009) offer some data in support of the belief that there are no significant disanalogies between Denmark and other developed countries. The authors claim that routine in-feed antibiotic use does not decrease mortality among food animals in developed countries. They cite a study involving close to seven million chickens in the United States (Engster, Marvil, and Stewart-Brown 2002). This study showed no statistically significant effects on mortality (or weight gain) when the routine use of in-feed antibiotics in poultry was stopped.
[8] (Phillips et al. 2004:276) assert that the Danes have commendably introduced conditions of husbandry that have minimized, but not prevented, infections in food animals.

enough of what the consequences of AGPs are for human health. If AGPs *do* constitute a serious threat to human health, then this is certainly something that weighs in favor of banning their use. However, if AGPs do *not* constitute a serious threat to human health, then a ban on AGPs that has serious costs in terms of worsening animal health, decreasing production-efficacy and declining profits in the livestock sector should not be implemented.

It is important to note that the plausibility of this consequentialist way of reasoning depends crucially on what 'serious threat to human health' and 'serious costs in terms of worsening animal health, decreasing production-efficacy and declining profits in the livestock sector' exactly amount to.

2) *What would a United States ban on the use of antibiotics as AGPs mean for the pharmaceutical industry?*

Assume that (Mellon 2001) is correct in the estimate that, in the United States, 70% of total antibiotic production is devoted to non-therapeutic use in livestock production. On this assumption, a United States ban on non-therapeutic use of antibiotics in livestock production will lead to a very significant reduction in the market for antibiotics. Such a reduction in the market will influence the decision-makers in the pharmaceutical industry who determine what research and development resources should be spent on. Most likely, such decision-makers will allocate fewer resources to antibiotic research and development because earning possibilities are severely diminished. According to (Power 2006:26), economic considerations are now the most common reason for terminating drug development, ahead of efficacy and safety.

Predicting a negative influence of a ban on non-therapeutic use of antibiotics on antibiotic research and development is not warranted if the types of antibiotics used in livestock production cannot be used in human medicine. Put differently, if there were two completely separate markets (one for antibiotics used in food animals and one for antibiotics used in human medicine), the diminishing of one market would likely not affect attempts to introduce new products on the other market. However, such two distinct markets do not exist. Antibiotics that are used in human medicine can be (and often are) used in animals (Khachatourians 1998:1131; WHO 2002b). Quinolones used in livestock production are, for example, also used for the treatment of a broad range of infections in humans (WHO 1998:1).

3) Two recommendations

a. As mentioned in section three, there is a dearth of reliable data on human and non-human consumption of antibiotics. One way in which the Center for Global Development could make a useful contribution to the overall debate about drug resistance would be to highlight the need for (and push for) data collection programs for: i) human and non-human consumption of antibiotics in the United States, and ii) non-human consumption of antibiotics in developing countries. The reason ii) is important is that, as commonly mentioned in the academic literature on the subject, drug resistance does not respect national or regional borders. When this feature of drug resistance is coupled with the fact that the use of antibiotics in food animals, at least on some occasions, poses a threat to human health, there is a compelling case for an advancement of our knowledge about the magnitude of this use of antibiotics in developing countries.

b. (Collignon 2003:73) has proposed that antibiotics that are 'critical' or 'last-line' for serious human infections should not be used in food production animals or agriculture. This principle seems well-founded and is one that CGD should support.[9] The principle has, however, a somewhat limited relevance for a developing country setting. There are at least two reasons for this. First, in such a setting it is unlikely that there is a well-organized infrastructure in place to detect and penalize misuse. Second, it is unlikely that advanced/latest-generation antibiotics (which are often the ones that constitute 'last-line' clinical options) will be available in significant amounts outside hospitals in developing countries.[10]

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[9] This principle is consistent with a guideline, created by the Office International des Epizooties (IOE), on the responsible and prudent use of antimicrobials in animal husbandry. The guideline is published in (Anthony et al. 2001), and on page 833 of this paper, it is stressed that antimicrobials which are considered important in treating critical diseases in humans should only be used in animals when alternatives are either unavailable or inappropriate.

[10] I would like to thank Rachel Nugent and Scott Weese for very helpful comments on an earlier version of this paper.

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