LINKING ANTIBIOTIC USE IN LIVESTOCK & POULTRY TO INCREASING RESISTANCE IN HUMANS

A solid scientific consensus exists that antibiotic overuse in animal agriculture contributes to antimicrobial resistance transmitted to humans. Key additions to the consensus include:

- *National Academy of Science's Institute of Medicine (2003):* "Clearly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse of antimicrobials in animals and agriculture as well."
- *World Health Organization/FAO/OIE (2003):* "There is clear evidence of the human health consequences [from agricultural use of antimicrobials, including] infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections".
- *Clinical Infectious Diseases (2002):* "The elimination of non-therapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance…. with consequent benefits to human and animal health."

Sources: (1) National Academy of Science. 2003. Institute of Medicine, Board on Global Health (2003). Microbial Threats to Health: Emergence, Detection, and Response. National Academy of Sciences Press, Washington, DC. Available at: http://books.nap.edu/books/030908864X/html/R1.html#pagetop;
(2) WHO/FAO/OIE Expert Workshop on Non-human Antimicrobial Usage and Antimicrobial Resistance, Geneva, 1 – 5 December 2003, Executive Summary. Available at: http://www.who.int/foodsafety/micro/meetings/en/report.pdf . Accessed Jan. 30, 2004 (explanatory material available at http://www.who.int/foodsafety/micro/meetings/nov2003/en/ . Accessed Jan. 30, 2004.);
(3) Alliance for Prudent Use of Antibiotics. 2002. The need to improve antimicrobial use in agriculture: ecological and human health consequences. Clinical Infect Dis. 34(suppl.3):S71-S144. Available at: http://www.journals.uchicago.edu/CID/journal/contents/v34nS3.html.

Several lines of evidence now link agricultural antibiotic* use to resistant infections in humans:

- Human studies tracing drug-resistant human infections to specific livestock and poultry operations.
- Timeline studies that find specific drug resistance in animal-associated bacteria prior to emergence of the same resistance in human pathogens.
- More circumstantial evidence linking drug resistant bacteria on foods to use of antibiotics in food animals
- Studies of farmers and handlers of food animals receiving antibiotics showing that they are rapidly colonized with bacteria resistant to the same agents.
- Microbiological studies showing drug resistant bacteria from food animals may colonize the human gut and transfer resistance genes to pathogens or other bacteria present there, laying groundwork for future resistant infections.
- Studies suggesting ecological spread of antibiotic resistance.

1. **Human (epidemiological) studies tracing drug-resistant human infections to specific livestock and poultry operations.** Evidence from controlled human studies, as well as disease outbreaks, directly traces human infections to specific livestock operations. A quarter century ago, Levy et al. conducted a controlled study in members of a farm family documenting the rise and fall of tetracycline-resistant intestinal bacteria, directly correlating it with the family giving and then removing tetracycline-enhanced feed to their chickens.[1]

   In 2000, Fey et al. published evidence that a strain of *Salmonella* infecting a 12-year old Nebraska boy was identical to one found in cattle on his father's farm – the bacteria was uniquely resistant to 13 different antimicrobials.[2] Another outbreak of *Salmonella* food poisoning resistant to multiple antibiotics was traced back to a fast food chain, and ultimately to dairy farms serving as the source for its hamburger.[3] Similarly, in 1998, eleven patients in Denmark were hospitalized and 2 died in an outbreak of multidrug-resistant *Salmonella* food poisoning traced back to a swine herd.[4] Canada's largest outbreak of waterborne disease, in Walkerton, Ontario, infected 1,346 and

* For the purpose of this document, the term "antibiotic" is used interchangeably with "antimicrobial".

claimed the lives of six people; it was traced to bacterial contamination from runoff of livestock farms into the source of drinking water for the nearby towns.[5]

2. **Timeline studies finding specific drug resistance in animal-associated bacteria *prior to* emergence of the same resistance in human pathogens.** Since 1986, fluoroquinolone antibiotics (FQs) have been use to treat various human infections, including serious cases of foodborne illness caused by *Campylobacter jejuni (C. jejuni)*. Prior to 1995, *C. jejuni* in humans showed approximately 1.3% resistance to antibiotics from the quinolone class (which includes fluoroquinolones). At that point, no fluoroquinolones had yet been approved for use in food-producing animals. In 1995, a fluoroquinolone antibiotic was approved for poultry use in the U.S. By 1998, *C. jejuni* bacteria isolated from Americans were 10.2% resistant to quinolones[6]; the latest figures, reported by the Centers for Disease Control, put resistance levels at approximately 19%[7]. Similar results have been found around the world.[8] However, in Australia – where fluoroquinolones have never been licensed for use in food production animals – there was no fluoroquinolone resistance detected among Campylobacter isolates known to be acquired locally (not from travel abroad).[9]

   Science linking fluoroquinolone use in food animals to the appearance of bacterial resistance isn't confined to Campylobacter. Spread of quinolone-resistant strains of Salmonella DT104, with subsequent cases of human infection, also is so linked.[10] *Salmonella DT104* is a dangerous strain of *Salmonella* resistant to multiple drugs. It emerged in cattle in 1988 in the U.K[11], then spread rapidly through food animals over several continents. Prevalence of *DT104* in humans in the U.S. was less than 1% between 1979 and 1980. In 1996 the prevalence rose to 34%[12].

   Vancomycin is another critical drug in human medicine. In Europe, where avoparcin – a sister drug to vancomycin – was approved for use in farm animals, high levels of vancomycin-resistant bacteria have been found in community residents. In the United States, where avoparcin has not been used in the animals, vancomycin-resistance is confined primarily to hospitals.[13]

3. **More circumstantial evidence linking drug-resistant bacteria in foods to use of antimicrobials in food animals.** Approximately 70% of all antibiotics used in the U.S. are given to food animals for purposes other than treating infection[14]. When nontherapeutic levels of drugs are put into animal feed, it creates fertile grounds for the selection of drug-resistant bacteria. Many antibiotics given to animals are the same as, or closely related to, medically important human drugs.

   Several studies have measured levels of antimicrobial resistant bacteria present on retail meats. A 2003 Consumer Reports study looked at nearly 500 fresh, whole chicken broilers bought at supermarkets across the country. *Campylobacter* and *Salmonella* were found in 42% and 12% of the chicken tested, respectively. One very disturbing result of the study indicated that 26% of the *Campylobacter* was resistant to fluoroquinolones and 20% resistant to erythromycin, both of which are first lines of defense against foodborne illness in humans[15]. In another recent study of 200 samples of retail ground meat, 20% contained *Salmonella.* The majority of the *Salmonella* isolated (84%) were resistant to at least one antimicrobial, and more than half were resistant to greater than three antimicrobials. Disturbingly, 16% of the isolates were resistant to ceftriaxone, the drug of choice used to treat children with serious *Salmonella* illnesses.[16] In Belgium where dioxin-contaminated chicken feed was discovered, causing the subsequent removal of all chicken and eggs from the market for several weeks, a significant decline of 40% in the number of human *Campylobacter* infections followed that removal.[17] A control test, conducted by Sorenson et al., with test volunteers to study the persistence of ingested resistant bacteria found the bacteria persisted in the stools for up to 14 days after the initial ingestion.[18] Finally, Manges et al. studied urinary tract infections in California, Michigan and Minnesota. Nearly one half of the community-acquired infections that were resistant to a particular drug were caused by one specific type of *Escherichia coli* bacteria. The authors suggested that the possible explanation for this was the ingestion of contaminated food.[19]

4. **Studies of farmers and handlers of food animals receiving antibiotics showing that they are rapidly colonized with bacteria resistant to the same agents.** Farm workers and their families are exposed to antimicrobials and antimicrobial-resistant bacteria throughout the farming environment - in the feed, water, waste and in the air. As mentioned, Levy et al. conducted a controlled study to observe the transfer of tetracycline-resistant bacteria from a family's chicken farm to the farm family. Prior to giving chickens tetracycline in the feed, there was little or no

tetracycline-resistant bacteria present. Within two weeks of starting the chickens on this feed, 90% of the chickens excreted tetracycline-resistant organisms. Nearly half of the farm family also began to excrete tetracycline-resistant organisms. When the tetracycline feed was removed, the levels of resistant organisms being excreted decreased in the farm family and in the chickens.[1]

An epidemic in a hospital nursery infecting several infants was traced back to a pregnant mother who had worked on her father's farm amongst sick calves. The bacteria causing the epidemic was cultured and shown to be the same strain that was infecting the calves on the farm.[20] One study of the poultry environment found very high levels of bacteria resistant to Quinupristin-dalfopristin, a drug recently released for use in the human population to fight bacteria resistant to most other drugs available. The authors surmise that the use of a sister antimicrobial, virginiamycin, used in the poultry industry to improve growth as well as for other purposes, may have selected for the high rates of resistance found (as high as 78%).[21] Van den Bogaard et al. studied bacteria from three different groups of farmers, slaughterers, and the poultry these groups worked with to identify the bacteria present and the antimicrobial resistances of each. Exact matches were found between a chicken farmer and a broiler on the farm, as well as from a turkey farmer and a turkey on the farm.[22]

5. **Microbiological studies showing that drug resistant bacteria from food animals may colonize the human gut and transfer their resistance genes to ordinary pathogens or other bacteria present in the human gut, thereby causing harm at a later date.** Bacteria are very promiscuous and can rapidly share genes across species. Numerous studies have demonstrated this phenomenon in the laboratory environment but relatively few studies have been done to demonstrate the occurrence in nature. Some studies have been conducted on *Bacteroides*, bacteria that make up about 20-30% of the normal microorganisms present in the human colon.[23] *Bacteroides* may become opportunistic pathogens causing life-threatening infections in humans if they are released from the colon during abdominal trauma or surgery. It is becoming increasingly difficult to treat *Bacteroides* infections in humans due to high levels of resistance.[24]

   One study found that tetracycline-resistance genes were transferred between *Prevotella*, bacteria that normally colonize livestock, and *Bacteroides* in humans.[25] A retrospective study found that over the last 3 decades, tetracycline resistance has gone from nearly 30% of the *Bacteroides* strains carrying the resistance gene to over 80% of *Bacteroides* now carrying the resistance gene. With erythromycin resistance, the change has gone from less than 2% of the *Bacterioides* strains carrying the resistance gene to 23%. The authors conclude that this supports the hypothesis for extensive gene transfer between bacterial species within the human colon.[24]

6. **Studies suggesting ecological spread of antimicrobial resistance.** As much as 75% of the antimicrobials that are fed to farm animals may be excreted unmetabolized into the waste.[26] Food animal waste in the United States exceeds two trillion pounds annually by some estimates,[27] and this waste is either spread on farm lands and/or stored in waste lagoons that have been found often to leak or overflow.

   Studies have found surface water, ground water, and soil in the vicinity of large confined animal feeding operations (CAFOs) contaminated with antimicrobials as well as antimicrobial-resistant bacteria. Contamination of the surface or ground water has implications for public health concerns if this water is linked to drinking water sources. One study found antimicrobials used on poultry and swine in CAFOs in nearby streams and monitoring wells.[28] In a study by the United States Geological Survey, antimicrobial residues were found in 48% of 139 streams surveyed nationwide, many of which were located downstream from animal agriculture operations.[29] Chee-Sanford et al., found tetracycline-resistance genes in groundwater underlying two swine farms and 250 meters downstream from the farms. In addition, they discovered tetracycline resistance in soil organisms.[26] Winokur et al. found multi-drug resistant E. coli in surface waters in Eastern Iowa and concluded that "these studies identify significant environmental contamination with these organisms".[30] As mentioned earlier, the largest multi-bacterial waterborne outbreak in Canada, which infected 1,346 people, sending 65 to the hospital and claiming the lives of six of those patients, was traced back to bacterial contamination from runoff of livestock farms into the source of drinking water for the nearby towns.[5]

   Studies have also found antimicrobials as well as antimicrobial-resistant bacteria aerosolized in the farming environment,[31,32,33] with potential transmission to farmers, farmworkers and nearby residents.

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