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FACT SHEET ON THE LATEST SCIENCE LINKING USE OF ANTIMICROBIALS IN ANIMAL AGRICULTURE TO INCREASING ANTIMICROBIAL RESISTANCE IN HUMANS

March, 2003

There is an emerging scientific consensus that overuse of antimicrobials in animal agriculture contributes to antimicrobial resistance that is transmitted to humans. In 2000 the Alliance for the Prudent Use of Antibiotics (APUA) convened a Scientific Advisory Panel consisting of experts from human and veterinary medicine, public health, microbiology, biostatistics, and risk analysis. Over the course of two years the Panel conducted a comprehensive review of over 500 of the latest scientific studies on the human health impacts of antimicrobial use in agriculture. The Panel's report appeared as a supplement to the peer-reviewed journal *Clinical Infectious Diseases* in 2002. Publication of this report was a seminal event, compiling and bringing together in one document disparate scientific and medical evidence. This fact sheet will draw upon the APUA report, as well as other studies published contemporaneously or subsequent to that report.

There are several lines of evidence linking antimicrobial use in agriculture to resistant infections in humans, including the following.

1. **Direct epidemiological evidence tracing resistant human infections to specific livestock and poultry operations.**

Controlled studies as well as outbreak investigations have revealed evidence directly tracing human infections to specific livestock operations. As early as 1976, Levy et al. conducted a controlled study of the rise and fall of tetracycline-resistant intestinal coliforms in members of a farm family, that established a direct correlation to the use and subsequent removal of tetracycline-supplemented feed with the family's chickens [Levy, 1976]. Fey et al. discovered that a strain of *Salmonella* infecting a 12-year old boy in Nebraska was identical to one found in cattle on the father's farm – the bacteria was uniquely resistant to 13 different antimicrobials [Fey, 2000]. An outbreak of a multidrug-resistant *Salmonella* food poisoning incident was traced back to a fast food chain and ultimately to the source of the meat – the dairy farms where the cattle were raised [Spika, 1987]. Eleven patients were hospitalized and 2 died in an outbreak of multidrug-resistant *Salmonella* food poisoning in Denmark in 1998 that was traced back to a swine herd [Molbak, 1999]. 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 [Health Canada, 2000].

2. **Temporal studies finding that specific drug resistance in animal-associated bacteria emerged prior to appearance of the same resistance in human pathogens.**

In 1995 a fluoroquinolone was approved for use in poultry in the U.S. Prior to this approval there were no uses of fluoroquinolones in food-producing animals. Fluoroquinolones (FQs) were used in human medicine since 1986 for treatment of various illnesses, including an important foodborne illness caused by the bacteria *Campylobacter jejuni (C. jejuni)*. Prior to 1995, *C. jejuni* in humans showed an approximate 1.3% resistance to quinolones. In 1998, two years after its availability for use in poultry, the resistance level jumped to 10.2% [Smith, 1999]. Similar results have been found in other countries around the world [Engberg, 2001]. The latest figures, reported by the Centers for Disease Control, put the resistance levels at approximately 19% [Anderson, 2002]. In Europe, where avoparcin, a sister drug to vancomycin (a critical drug in human medicine), was approved for use in farm animals, high levels of vancomycin-resistant bacteria were found in many members of the community. Whereas, in the United States, where avoparcin has not been used in the animal industry, vancomycin-resistance is primarily confined to the hospital environment [Van den Boggard, 2000]. A multidrug resistant *Salmonella*, *Salmonella DT104*, emerged in cattle in 1988 in the U.K. [Akkina, 1999]. It spread rapidly through other food animals over several continents. In the U.S., between 1979 and 1980 the prevalence of DT104 was less than 1% in humans, whereas in 1996 the prevalence rose to 34% [Glynn, 1998].

3. **Circumstantial evidence linking antimicrobial resistance in food products to use of antimicrobials in food animals.**

It has been estimated that approximately 70% of all antimicrobials used in the United States are administered to food animals for purposes other than for therapy [Mellon, 2001]. Many of the antimicrobials given to animals are the same as, or closely related to, medically important human drugs. When nontherapeutic levels of antimicrobials are fed to food animals, they set up the perfect breeding ground for the selection of antimicrobial resistant bacteria. Several studies have been carried out to measure the 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 [Consumer Reports, 2003]. 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 [White, 2001]. 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 [Vellinga, 2002]. 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 [Sorenson, 2001]. 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 [Manges, 2001].

4. Studies showing that farmers and other handlers of food animals receiving antimicrobials 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 above, 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 the 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 [Levy, 1976]. 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 [Lyons, 1980]. 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, in the poultry industry used to improve growth in poultry, as well as for other purposes, may have selected for the high rates of resistance found (as high as 78%) [Hayes, 2001]. 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 [Van den Bogaard, 2001]. Studies have also found antimicrobials as well as antimicrobial-resistant bacteria aerosolized in the farming environment [Zahn, 2001].

5. Studies showing that antimicrobial-resistant bacteria from food animals may colonize the human gut and transfer 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 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 [Wang, 2000]. *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 [Shoemaker, 2001]. One study found that tetracycline-resistance genes were transferred between *Prevotella*, bacteria that normally colonize livestock, and *Bacteroides* in humans [Nikolich, 1994]. One 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 strains carrying the resistance gene to 23% carriage. The authors conclude that this supports the hypothesis for extensive gene transfer between bacterial species within the human colon [Shoemaker, 2001].

6. Potential 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 [Chee-Sanford, 2001]. Animal waste in the United States exceeds two trillion pounds by some estimates

[USDA Ag. Census data, 1997] and this waste is either spread on farm lands and/or stored in waste lagoons that have been found 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 levels of antimicrobials used on poultry and swine at CAFOs in nearby streams and monitoring wells [Campagnolo, 2002]. In a recent 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 [Kolpin, 2001]. 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 [Chee-Sanford, 2001]. 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 [Health Canada, 2000].

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