Antibiotics for Animals:
The Antibiotic Resistance Issue

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Contents

Summary

The use of antibiotics in subtherapeutic quantities in animal feeds is believed by some to contribute importantly to antibiotic resistance of bacteria in the intestinal tract of humans, and to affect human health adversely. This document addresses the antibiotic-resistance issue, with the following conclusions:

1. Therapeutic doses of antibiotics generally have greater effects than subtherapeutic doses, but both tend to suppress the more sensitive bacteria and permit the more resistant bacteria to multiply.

2. Bacteria resistant to an antibiotic may not be eliminated from the intestinal tract of an animal before marketing, even though the antibiotic has not been used during most of the life span of the animal.

3. Eliminating the subtherapeutic use of an antibiotic, while allowing therapeutic use to continue, would not result in disappearance of antibiotic-resistant intestinal bacteria from animals, nor would it eliminate the possibility of transfer of antibiotic-resistant intestinal bacteria from animals to humans, or the possibility of transfer of resistance factors from intestinal bacteria of animals to bacteria in humans.

4. Banning all animal uses of antibiotics, both therapeutic and subtherapeutic, would assure a reduction in human exposure to antibiotic-resistant bacteria from animals at the cost of reduced efficiency in animal production and increased prices of animal products for consumers.

5. Even if all resistance to antibiotics could be eliminated, disease-causing organisms would not disappear from animals, nor would their ability to cause human disease be nullified. The propensity of *Salmonella* bacteria to cause human disease appears to be far more important than resistance or nonresistance to antibiotics. The death rates from infections with antibiotic-resistant and antibiotic-sensitive strains of *Salmonella* appear to be similar, to judge from the total numbers of cases and deaths reported in published U.S. data from the Centers for Disease Control.

6. National Center for Health Statistics data based on death certificates are considered by some to underestimate the numbers of human fatalities in the United States from intestinal infections due to *Salmonella* because they do not take into account the deaths to which salmonellosis may have made a secondary contribution. Moreover, some deaths due to salmonellosis may be attributed to other causes. Centers for Disease Control data are thought to overestimate the numbers of fatalities because deaths among persons infected with *Salmonella* are generally attributed to salmonellosis, whether or not that is the cause.

7. Irradiating packaged meats and eggs with low doses of ionizing energy as they leave the processing lines would improve human health by essentially closing the pathway through which the principal transfer of both antibiotic-sensitive and antibiotic-resistant disease-causing bacteria from animals to humans is thought to occur. At the same time, it would retain the benefits of the antibiotics for animals, the increased efficiencies in production, and the lower costs of meats and eggs for consumers.

Introduction

Antibiotics are used for therapeutic purposes in animals, as well as in humans. The controversy over use of antibiotics in animal agriculture revolves principally around the feeding of subtherapeutic levels of antibiotics to improve animal performance. The subtherapeutic use of penicillin and tetracyclines in animal agriculture is controversial because these antibiotics are important in human medicine. Among the bacteria, certain species of *Salmonella* have received most of the attention because these bacteria

infect both humans and animals, and they are a major cause of human intestinal disease in the United States. Species of *Staphylococcus*, *Campylobacter*, and *Listeria* are also important causes of foodborne infections.

Animal products have been known for many years to be a source of bacteria that cause foodborne infections in humans, but evidence that the use of antibiotics in animals has been responsible for human infections with antibiotic-resistant bacteria has been difficult to obtain. Good evidence was obtained in a recent outbreak of salmonellosis from hamburger derived from dairy cattle in California. In a technical assessment of the California study, Spika et al. (1987) concluded "that food animals are a major source of antimicrobial-resistant salmonella infections in humans and that these infections are associated with antimicrobial use on farms." Amplifying on this conclusion, an editor in the meat processing industry (Bjorklis, 1987) wrote that "Now the heaviest, and perhaps final artillery in the war has been fired. The federal Centers for Disease Control, in a study published in the March 5 edition of the *New England Journal of Medicine*, states that feeding antibiotics to meat-producing livestock does indeed lead to the promulgation of antibiotic-resistant strains of the *salmonella* bacterium, and that food animals are a 'major source' of antimicrobial-resistant salmonella infections in humans. . . . In essence, the theories are no longer theories. They're facts. . . . It is time to give consumers the safety they demand—and have a right to—in their meat supply. It is time to halt subtherapeutic feeding. Completely.'"

The expansive generalization quoted from the technical article and the reaction of the editor epitomize the basis for the erroneous perception that resistance to antibiotics developed from subtherapeutic use of

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' According to Swartz et al. (1989), the contaminated hamburger in the study by Spika et al. (1987) was traced to dairy cows that probably had been receiving illegal therapeutic doses of chloramphenicol rather than the subtherapeutic doses indicted by Bjorklis (1987).

these substances is the root cause of human intestinal disease problems.

The emergence of strains of intestinal bacteria that are resistant to an antibiotic used in sufficient concentrations in animals is not a matter of scientific controversy. From the very beginnings of antibiotic use in animals, the consumption of feeds containing effective concentrations of antibiotics has been known to result in large numbers of resistant bacteria in the intestinal tract. Development of a population of antibiotic-resistant bacteria occurs simultaneously with increased growth and improved health of the treated animals, which implies that most of these antibiotic-resistant bacteria are not harmful.

Similarly, no scientific controversy exists regarding the possibility that resistant bacteria may be transferred to humans through the food system and that under appropriate circumstances some of these resistant bacteria may have adverse effects on human health. Although many billions of animals have been treated with antibiotics during the nearly 4 decades of antibiotic use in animal agriculture, there is little evidence of detrimental effects on humans caused by the antibiotic resistance of intestinal bacteria derived from animals.

The focus on antibiotic resistance has tended to obscure the fact that although resistance to one or more antibiotics may modify some properties of disease-causing bacteria, the basic hazard is the bacteria. Elimination of all antibiotic resistance, irrespective of the cause, would not eliminate the capability of the bacteria to cause human disease.

The purpose of this document is to provide the basis for a clearer understanding through a brief review of the relevant scientific background. The three antibiotic-resistance-related issues addressed are: (1) subtherapeutic versus therapeutic doses of antibiotics, (2) the health risk from resistant and nonresistant bacteria, and (3) mortality estimates and statistics.

Subtherapeutic Versus Therapeutic Doses of Antibiotics

Subtherapeutic doses of antibiotics are relatively low doses that are used to reduce mortality and morbidity and to improve animal performance in terms of production and efficiency of feed use. Subtherapeutic doses

are often used for extended periods of time and are invariably supplied in the diet. Therapeutic doses are relatively high doses used to treat diseased animals. Therapeutic doses characteristically are used for

shorter times than subtherapeutic doses. They may be administered in the diet or in other ways.

The distinction between subtherapeutic and therapeutic doses varies among bacteria and among antibiotics. Different individuals make the distinction at different doses. For example, Hays et al. (1981) used 50 grams per ton of feed as a general figure for the upper limit for subtherapeutic uses. In the United Kingdom, the upper limit is considered to be 200 grams per ton according to Swartz et al. (1989).

Subtherapeutic use of antibiotics in animal feeds has come under heavy criticism. The following chain of reasoning has been advanced in support of a proposal to discontinue subtherapeutic use: (1) Subtherapeutic use of antibiotics in animal feeds is the principal offender in development of antibiotic-resistant bacteria. (2) If subtherapeutic use were eliminated, the level of resistance of bacteria harbored by animals would be reduced significantly. (3) The reduced resistance of animal bacteria to antibiotics would result in an improvement in human health because the probability of transfer of antibiotic-resistant bacteria from animals to people would be reduced.

In contrast to the supposed propensity of subtherapeutic doses to promote the development of antibiotic-resistant strains of bacteria, therapeutic doses are viewed by some as "bullets" that act quickly and decisively and then are gone. This perception of the consequences of therapeutic versus subtherapeutic doses of antibiotics in animal husbandry appears to be an inference based upon the principle that when a *systemic* infection occurs, the proper way to treat it is to use large doses of an antibiotic to eliminate the invading organism quickly. Lower doses administered over longer periods of time are considered to favor the emergence of resistant organisms, which may prolong the infection and perhaps lead to failure of the treatment.

For example, Ahmed et al. (1984) of the Natural Resources Defense Council petitioned the Secretary of Health and Human Services to ban the subtherapeutic use of penicillin and tetracyclines in animal feeds as an imminent hazard to public health. In the petition, they argued that because therapeutic treatment of animals with antibiotics is episodic in nature and of limited duration, "It is reasonable to assume that such use [of antibiotics] does not contribute significantly, if at all, to the longterm, sustained development of antibiotic-resistant bacterial strains in animals." On the basis of this assumption, the authors of the petition suggested the intermittent use of antibiotics at therapeutic levels as an alternative to more or less continuous use at subtherapeutic levels in animal feeds.

Resistance does not develop automatically in all species of initially sensitive bacteria when their host is treated with specific antibiotics. Moreover, some species of bacteria are intrinsically resistant to specific antibiotics. For those combinations in which some sensitivity to a given antibiotic exists, however, relatively low concentrations of the antibiotic inhibit the more antibiotic-sensitive members of the bacterial population. Responding to the decreased competition, the more resistant bacteria then multiply and comprise an increasing proportion of the total population (Gordon et al., 1959; Kobland et al., 1987).

In some instances, the development of resistance is rapid (Levy et al., 1976; Starr and Reynolds, 1951), and high levels of resistance may be attained within as little as 2 days. For such a rapid change, resistant organisms presumably must be present in the original bacterial population, needing only inhibition of their nonresistant competitors to permit them to multiply.

In other instances, resistance develops after a period during which there is no apparent effect (Guinee, 1971). This behavior presumably is observed when resistant organisms are absent initially, but develop within the treated population or are introduced from an outside source after the antibiotic treatment is underway.

Where development of resistance to an antibiotic is concerned, the distinction between subtherapeutic and therapeutic doses is a matter of degree. Therapeutic doses have a greater inhibitory capability than do subtherapeutic doses. For example, Gordon et al. (1959) and Kobland et al. (1987) found that the proportion of resistant intestinal bacteria was higher with therapeutic than subtherapeutic doses of antibiotics. Thus, depending upon the magnitude of the therapeutic dose and the sensitivity of the bacterial strain concerned, therapeutic doses might result in (1) the development of a higher proportion of resistant organisms within a given length of time than are developed by subtherapeutic doses or (2) the inhibition of all of the infecting organisms or such a high proportion of them that other body defenses can eliminate the remaining organisms.

Bacteria that cause intestinal disease are normally eliminated in time as a result of body defenses, including competition with the preexisting population of better adapted intestinal bacteria. Figure 1 shows the results of an experiment in which chickens were fed different amounts of chlortetracycline in the diet and, after 3 days of antibiotic treatment, were infected artificially with a mixture of sensitive and chlortetracycline-resistant *Salmonella*. In the absence of chlortetracycline, elimination of the resistant *Salmonella* was complete 20 days after infection. With chlortetracycline in the diet, the chickens had not
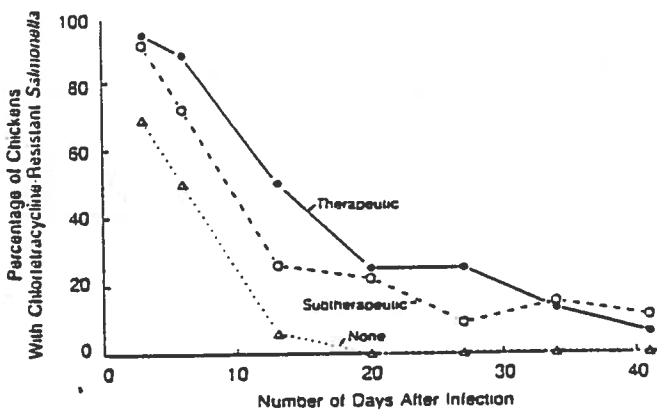
Figure 1. Percentage of chickens found infected with chlortetracycline-resistant *Salmonella* when tested different lengths of time after infection with a mixture of sensitive and resistant *Salmonella* while the chickens were receiving (a) no chlortetracycline, (b) therapeutic doses of chlortetracycline (550 ppm) in the feed in three 5-day periods with 2 days between each period, or (c) subtherapeutic doses of chlortetracycline (average of treatments with 55, 110, and 220 ppm) in the feed continuously. The antibiotic treatments began 3 days before the chickens were infected with *Salmonella* (Kobland et al., 1987).

eliminated the chlortetracycline-resistant bacteria by the end of the experiment (41 days after infection). The bacteria were eliminated more slowly with therapeutic than with subtherapeutic doses. By the end of the experiment, however, the proportion of the chickens still infected with resistant *Salmonella* was lower with therapeutic doses (which had been discontinued at the end of Day 22) than with subtherapeutic doses (which were supplied continuously throughout the experiment). In the presence of chlortetracycline, the resistant *Salmonella* evidently persisted throughout a substantial portion of the 45- to 55-day life span of broiler chickens.

Figure 2 shows the persistence of chlortetracycline resistance in swine. In this instance, two herds were involved. The one that received no antibiotics for any purpose had previously received antibiotics at subtherapeutic and therapeutic levels as needed. Percentages of fecal coliform bacteria that were resistant to tetracycline ranged from 72 to 82% in the first year without antibiotics and had dropped only to 42% in the 10th year without antibiotics.

Another study was made of an isolated swine herd that had been established by caesarean section of the sows to avoid contamination of the pigs with antibiotic-resistant and other bacteria at birth (Langlois et al., 1986). When the herd was sampled after 9 years during

which there had been intermittent therapeutic use of streptomycin but no subtherapeutic use of any antibiotic, 73% of the fecal coliform bacteria tested were resistant to streptomycin. Some of the pigs sampled had not been treated therapeutically with streptomycin during the year before sampling, but more than 80% had been treated at some time during the year. The time from birth to marketing for pigs is about 5.5 to 6.5 months. Thus, under some circumstances, bacterial resistance developed from therapeutic use of antibiotics in market pigs may not diappear before slaughter.

The opportunity for continual reinfection and cross-infection of animals from fecal material (Harry, 1962) and feeds (Durand et al., 1987) is probably one reason for the long residence time of antibiotic-resistant intestinal bacteria. The reinfection may contribute also to the development of well-adapted strains that compete well with the preexisting nonresistant strains and may persist indefinitely. For example, in the swine herd from caesarean-derived pigs, 70% of the fecal coliform bacteria were found resistant to tetracyclines even though the herd had been kept in isolation and no tetracyclines had ever been used (Langlois et al., 1986). The resistance to tetracycline must have been derived from some incidental introduction of well-adapted tetracycline-resistant bacteria because resistance to streptomycin has not been found to confer resistance to tetracycline.

In 1969, a government-sponsored committee in the United Kingdom (Swann, 1969) recommended dis-
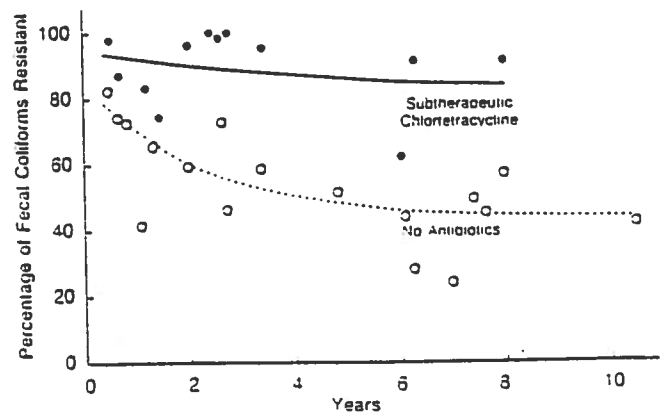

Figure 2. Percentage of fecal coliform bacteria resistant to tetracycline in two experimental herds of swine in Kentucky. In one herd, chlortetracycline was used continuously in the feed at a subtherapeutic level. In the other, no antibiotics were used for any purpose. Before the experiment was started, both herds received antibiotics as feed additives and as injectables when needed (Hays and Black, 1985).

continuing the subtherapeutic usage of antibiotics employed in human medicine (including penicillin and the tetracyclines) as well as those antibiotics that result in cross-resistance with antibiotics used in human medicine. This recommendation was accepted, and two classes of antibiotics were established: (1) those that may be used as feed additives without prescription and (2) those restricted to use only upon the advice and prescription of a veterinarian. Other European countries have adopted similar policies. Studies made in the United Kingdom since the implementation of the Swann Report (Smith, 1975; Walton, 1986; Swartz et al., 1989) indicate that the use restriction has not reduced the prevalence of bacterial resistance to the antibiotics of concern. These findings are consistent with the results of experimental work by Langlois et al. (1986) in the United States.

Health Risk From Resistant and Nonresistant Bacteria

The property of antibiotic resistance in disease-causing bacteria appears to have three principal implications for human health. First, the resistance will make the antibiotic or antibiotics in question ineffective against a human infection caused by the bacteria. Second, if a person is using the antibiotic or antibiotics for some other reason, the antibiotic may result in an infection far more serious than otherwise would have resulted because the antibiotic will eliminate bacteria that could have suppressed the antibiotic-resistant disease-causing bacteria by competitive inhibition. Third, antibiotic-resistant bacteria may be more or less virulent than antibiotic-sensitive bacteria. Some background information is needed to provide appropriate perspective on all of these issues.

It is true that if bacteria causing an intestinal infection are resistant to an antibiotic, that antibiotic will be ineffective against the specific bacteria that cause the infection. Antibiotics, however, are not the treatment of choice for the common primary intestinal infections with Salmonella species. The natural defenses of the body and the competitive effects of the myriads of other better adapted intestinal bacteria eliminate the infecting bacteria in almost all instances.

If a person is using an antibiotic for some other reason at or shortly before the time of contracting an intestinal infection, the severity of the infection may be increased if the infecting strain of bacteria is resistant to the antibiotic used. Theoretically, a similar but lesser effect might be found with use of an antibiotic to which an infecting bacterium is sensitive. If the infecting strain is sensitive to the antibiotic, the use of the antibiotic may favor the acquisition of antibiotic resistance (Aserkoff and Bennett, 1969). With both resistant and sensitive strains, the use of an antibiotic may be expected to increase the length of time the bacteria are excreted following infection, thus increasing the potential for transfer of the organisms from infected persons to others.

The situation is different in the relatively small number of infections in which the bacteria breach the body's defenses and circulate in the blood. Then an antibiotic is needed, and if the bacteria are resistant to the antibiotic used, the treatment will be ineffective. In such situations, sensitivity tests must be performed to determine the antibiotic of choice for treating the infection. Swartz et al. (1989) estimated that 2% of the Salmonella infections of the sort reported to the Centers for Disease Control are a direct result of antibiotic use by persons who are infected with antibiotic-resistant Salmonella.

The third potential human-health implication of antibiotic resistance in infecting bacteria is that a change in virulence may be associated with the acquisition of the resistance. This is the crucial issue for people who contract intestinal infections, but who are not using antibiotics. Direct experimental work on this question has been done on animals. For example, in research with chicks (Smith and Tucker, 1979), the virulence of Salmonella with and without plasmids conferring resistance to various antibiotics was tested.[2] The antibiotic-resistance plasmids employed were derived from bacteria that had caused serious epidemics

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[2] Resistance of bacteria to antibiotics is often conferred by antibiotic-resistance plasmids, which are small bits of DNA that are independent of the chromosomes and can be added to or removed from bacteria or transferred from one bacterium to another under appropriate conditions.

in various countries. When these plasmids were added to strains of two *Salmonella* species, the virulence of the *Salmonella* recipients was unchanged in some instances, but in most instances was decreased. When the plasmids were removed, the virulence of the *Salmonella* was unaffected in some instances, but increased in others. This evidence indicates that the possession of the antibiotic-resistance plasmids was involved in the decreased virulence of the bacteria.

Swartz et al. (1989) reviewed the research on virulence, and concluded that the experimental situations in which reduced virulence after the acquisition of antibiotic-resistance plasmids had been demonstrated "are unlikely to reflect the importance of selective pressures in nature." They noted that the resistance plasmids might also contain genes that code for increased virulence, which would make the antibiotic-resistant strains more virulent than the sensitive strains.

Because experiments on virulence cannot be conducted with human subjects, indirect evidence based upon observations made in studies of disease outbreaks must be relied upon to gauge the effect of antibiotic resistance on virulence. According to a review by Holmberg et al. (1984), 312 persons infected with antibiotic-resistant *Salmonella* were investigated in 17 outbreaks from 1971 through 1983, and 13 died. Corresponding figures for antibiotic-sensitive *Salmonella* were 19 outbreaks, 1912 persons investigated, and 4 deaths. According to a later review by Holmberg et al. (1987), 461 persons infected with antibiotic-resistant *Salmonella* were investigated in 13 outbreaks from 1970 through 1981, and 37 died. Corresponding figures for antibiotic-sensitive *Salmonella* were 17 outbreaks, 1523 persons investigated, and 5 deaths.

The 1984 paper by Holmberg et al. listed 18 outbreaks that had been traced to foods derived from animals, and to judge from the information given on years, serotypes, and resistance to antibiotics, 14 of these outbreaks were included among those listed in the 1987 paper. The 1984 paper did not include mortality data on individual outbreaks. Accordingly, we have used as a starting point for our calculations the data in the 1987 paper. To update the record, we have added data published more recently by Spika et al. (1987), Ryan et al. (1987), and St. Louis et al. (1988).[3] (All these publications are from the Centers for Disease

Control.) The totals we derive in this way are 19,770 cases of infections with antibiotic-resistant strains (92 deaths) and 4,149 cases of infections with antibiotic-sensitive strains (18 deaths). The death rate with the antibiotic-resistant strains (0.465%) does not differ significantly from the death rate with the antibiotic-sensitive strains (0.434%). In fact, the probability exceeds 70% that differences in mortality rates this great or greater would occur even though the true death rates were equal.

Antibiotic therapy probably was used in some of the cases in which the bacteria had entered the bloodstream. Effectiveness of the antibiotics used as well as virulence of the bacteria thus could have been involved in the mortality recorded in such cases.

In another investigation, Tolley et al. (1987) examined data from Illinois (including the results of the massive 1985 outbreak of salmonellosis in the Chicago area), England, Wales, and the Netherlands, as well as the data published by Holmberg et al. (1984). Their conclusion was "that antibiotic resistant *Salmonella* is no more mortality producing than antibiotic sensitive strains." In their work, Tolley et al. (1987) used preliminary Centers for Disease Control data that attributed more deaths to salmonellosis in the Chicago outbreak than did Illinois state officials or a later summary published jointly by officials from the Centers for Disease Control and the Illinois Department of Health (Ryan et al., 1987). As was true with all the other analyses mentioned, Tolley and coworkers made their calculations on the basis of epidemiologic data that included persons taking antibiotics as well as those not taking antibiotics.

Ahmed et al. (1984) based their petition to the Secretary of Health and Human Services to ban the subtherapeutic use of penicillin and tetracyclines in animal feeds on the data by Holmberg et al. (1984) indicating a death rate 21 times greater from antibiotic-resistant than from antibiotic-sensitive *Salmonella*. On the basis of a more comprehensive study, Swartz et al. (1989) estimated that the death rate was from zero to four times greater from resistant than from sensitive *Salmonella*.

To obtain their estimates, Swartz et al. (1989) used the method of averaging the death rates by outbreaks without regard to the numbers of cases involved. This approach gives undue weight to outbreaks involving small numbers of cases. We have given equal weight to all cases, and have averaged the death rates over all cases. This approach is in accordance with the statistical method used to judge whether the death rates differ significantly between the outbreaks due to antibiotic-resistant and antibiotic-sensitive strains; however, it would tend to overlook the effects of

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[3] According to Blake and Potter (1989), almost all of the *Salmonella* strains tested were sensitive to antibiotics in the egg-associated outbreaks of salmonellosis reviewed by St. Louis et al. (1988). We therefore have classified the data as representing a consequence of antibiotic-sensitive *Salmonella*. Swartz et al. (1989) made a similar decision.

differences in virulence among strains, should these be distributed unevenly between outbreaks with large and small numbers of cases.

The ratio of the risk from antibiotic-resistant to antibiotic-sensitive bacteria is basic to understanding and decision-making. Because of the importance of the ratio and the variability of the fatality rate from one outbreak to the next, a periodic summary from official sources could be useful. Such a summary would need to include the relevant information on all out-breaks that are systematically investigated.

Two and perhaps three separate risk ratios are needed to provide an appropriate perspective of the resistance issue. One is for people who have not taken an antibiotic recently. A second is for people who are taking or have recently taken an antibiotic to which the infecting organism is resistant. A possible third is for people who are taking or have recently taken an antibiotic to which the infecting organism is sensitive. The reason for the third is that the ability of the population of intestinal bacteria to eliminate disease-causing invaders by competition is likely to be reduced by any antibiotic.

Mortality Estimates and Statistics

Continuing estimates of mortality from intestinal infections with bacteria are issued by individuals associated with certain U.S. government agencies. For example, Cohen and Tauxe (1986) of the Centers for Disease Control estimated that *Salmonella* annually account for more than 500 deaths. In a private communication, Tauxe (1988) estimated 1,000 to 2,000 deaths annually. Holmberg (1985), also of the Centers for Disease Control, stated that there are as many as 2,000 deaths annually from *Salmonella* and as many as 2,100 deaths annually from *Campylobacter.* Bennett et al. (1987) of the Centers for Disease Control estimated the number of deaths in 1985 as 2,000 from salmonellosis and 10,800 from all intestinal infections. Reporting information received from the Food and Drug Administration, Moser (1987) gave the estimated number of deaths from salmonellosis in 1985 as more than 1,000.

The Cohen and Tauxe (1986) estimate of more than 500 deaths per year from salmonellosis was obtained by multiplying the total number of cases reported to the Centers for Disease Control (a case was defined as an individual from whom *Salmonella* was isolated) by the ratio of 7 deaths to 503 cases in a particular study made in 1979. The total number of cases reported annually from outbreaks plus isolated cases was said to exceed 40,000. Because many cases are not reported to the Centers for Disease Control, 40,000 may be considered an underestimate of the true total number of cases. Although many of the unreported cases would be expected to be relatively mild, some deaths no doubt would occur, so that the total number of deaths would be expected to exceed the number estimated by Cohen

and Tauxe if the death rate in the instance quoted was representative of the total. Some of the more generous estimates of death may have resulted from attempts to take the deaths from unreported cases into account.

An independent estimate of total fatalities from salmonellosis may be obtained from the records of the National Center for Health Statistics (NCHS, 1989), which collects death certificates for the entire country. The Center estimates that certificates are completed for more than 99% of the deaths. The Health Statistics data show an average of 96 deaths from salmonellosis per year in the period from 1980 through 1986 (the most recent year for which data are available). The total number of deaths from all intestinal infections, including cholera, typhoid fever, paratyphoid fever, salmonellosis, shigellosis, other bacterial food poisonings, amoebiasis, other protozoal intestinal diseases, intestinal infections due to other organisms, and ill-defined intestinal infections, averaged 472 per year during the same period. Thus, even the Cohen and Tauxe (1986) low estimate of 500 deaths from salmonellosis exceeds the total number of deaths reported on death certificates for salmonellosis plus all other intestinal infections, whether bacterial, protozoal, or ill defined.

The wide difference in estimates between the two sources of information appears to stem primarily from differences in methods of reporting. The result is probable underestimates by the the National Center for Health Statistics and probable overestimates by the Centers for Disease Control.

For salmonellosis, for example, the National Center for Health Statistics reports as deaths due to salmonel-

losis only those deaths stated to be attributable to that cause. No account is taken of the deaths to which salmonellosis may have contributed, but which were considered to have been caused primarily by something else. Tauxe (1988) and Swartz et al. (1989) criticize the data further on the basis that the wrong cause sometimes is given for deaths actually due to salmonellosis. The improbability that underestimates in the National Center for Health Statistics data are responsible for all the difference between these data and the estimates from Centers for Disease Control is suggested by calculations indicating that 81% of the salmonellosis deaths were assigned to other causes if the Cohen and Tauxe (1986) estimate of 500 deaths per year is correct, and 95% of the salmonellosis deaths were assigned to other causes if the Bennett estimate of 2,000 deaths is correct.

On the other hand, some of the Centers for Disease Control data are overestimates because the figures represent the total numbers of deaths among persons infected with salmonellosis and not necessarily the number who died of salmonellosis (Swartz et al. 1989). The disparity between the two estimates of mortality rate may be considerable. For example, Swartz et al. (1989) obtained information from the Centers for Disease Control indicating that in an outbreak in which the Centers had reported eight deaths among about 600 patients with salmonellosis, salmonellosis was clearly the cause of one death. It played an unknown role in three deaths, and no role in four deaths. In another outbreak involving 16,659 confirmed cases (Ryan et al., 1987), 18 deaths occurred. A review of the death certificates suggested that salmonellosis probably caused 2 deaths, was possibly related to 12 deaths, and was not related to 4 deaths.

The Remedy

To remedy the human disease problems attributed to resistance to antibiotics generated by the use of penicillin and tetracyclines in animal agriculture, Ahmed et al. (1984) recommended banning the subtherapeutic use of these antibiotics in animal feeds. Swartz et al. (1989) developed estimates indicating a greater human risk from antibiotic-resistant than from antibiotic-sensitive *Salmonella*, but they stopped short of direct recommendations.

Not emphasized by either Ahmed et al. (1984) or Swartz et al. (1989) was the fact that *Salmonella* that would become sensitive to penicillin and tetracyclines as a result of banning the subtherapeutic use of these antibiotics would still be capable of causing salmonellosis in humans. The "remedy" probably would enjoy only partial success for this reason, as well as the additional reasons that therapeutic use of antibiotics in animals also causes resistance, and the need for therapeutic use of penicillin and tetracyclines very likely would increase after a ban on subtherapeutic use, as appears to have occurred in the United Kingdom.

An alternative remedy of potentially greater effectiveness would be to irradiate packaged meats and eggs with ionizing energy as they leave the processing lines to inactivate both the antibiotic-resistant and sensitive *Salmonella* and most other disease-causing bacteria, as well as the parasites present (Josephson

et al., 1989). Although such treatment would not prevent recontamination of the products or transfer of the organisms among humans, it would largely eliminate what has been suggested as the major pathway by which animals contribute to human salmonellosis, namely, the transmission of the bacteria from animals to humans by way of food products.

While largely eliminating the human hazards associated with the presence of disease-causing microorganisms and parasites in meats and eggs, the adoption of this alternative would have the additional advantages of retaining the benefits to animals resulting from the subtherapeutic use of antibiotics, as well as the economic benefits accruing to consumers from such use (Hays et al., 1981). The beginnings of movement to exploit the potential of ionizing energy may be found in the Food and Drug Administration's approval for the use of up to 1 kilogray of ionizing energy to eliminate trichina parasites from pork and a U.S. Department of Agriculture petition now before the Food and Drug Administration to irradiate poultry with 3 kilograys of ionizing energy to control bacterial contamination.

Proper cooking kills all the disease-causing bacteria and parasites that may occur in meats and eggs. This remedy has long been available, but it is not always used.

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