EXHIBIT H

TO DECLARATION OF
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INSTITUTE OF MEDICINE

REPORT OF A STUDY

Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed

1988

PREFACE

In 1980, at the request of the Food and Drug Administration (FDA), a committee of the Assembly of Life Sciences of the National Research Council (NRC) prepared a report evaluating the effects on human health of the use of penicillin and two tetracyclines (chlortetracycline and oxytetracycline) at subtherapeutic concentrations[1] in animal feed. That committee concluded that the postulated hazards to human health from such use of antimicrobials had been neither proved nor disproved. It drew the conclusion largely because a direct detailed epidemiologic investigation of the hazards had not been feasible and in part because it was impossible to ascertain prior antimicrobial exposures of individual animal sources of meat products for human consumption. The committee recommended various epidemiologic studies (especially of human illness due to salmonellae and pathogenic Escherichia coli) and monitoring and surveillance of the occurrence of antimicrobial resistance of enteric bacteria in humans, animals, and foodstuffs.

Several years later, in 1987, FDA asked the Institute of Medicine to conduct an independent review of the human health consequences and the risk associated with the use of penicillin and the tetracyclines at subtherapeutic concentrations in animal feed. The Institute established a committee and gave it a tightly drawn charge: specifically, to perform "a quantitative risk assessment" of those consequences--to "assess the adequacy of existing human health data and use such data to arrive at an estimate of

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[1] The Center for Veterinary Medicine considers any extended use of antibiotics in feed at 200 g/ton or less beyond 2 weeks as "subtherapeutic use," whether it is for growth enhancement or disease prevention. "Use levels are generally 200 g or less of penicillin or tetracycline per ton of feed, but dosage units will vary by species. Levels approved for growth claims and disease prophylaxis are usually lower than those approved for disease treatment; however, there is some overlap in the claims for dose levels of 200 g per ton or less." There is more concern in the agency "with the length of time the antibiotic is used in feed than in the level of drug." (FDA personal correspondence, April 26, 1988)

risk, the basis of which will be justified." If complete quantification of human health risks was not possible because of inadequacies of the available data, the committee was to evaluate the scientific information that had become available since the 1980 report and make judgments about the magnitude of the risks. The committee has not addressed risk management, nor any aspects related to policymaking because this was not part of its charge.

In its risk assessment, the committee was to address the following questions:

- Does the subtherapeutic use of penicillin and the tetracyclines in animal feed result in an increased frequency of antimicrobial resistance in pathogens, particularly foodborne pathogens? If so, can the increase in frequency be reliably estimated and compared with the increases associated with other sources of resistance?

- Does antimicrobial resistance increase (or diminish) the ability of foodborne pathogens to cause disease, change the number of foodborne pathogens (dose) needed to produce disease, or alter the severity of disease caused by foodborne pathogens?

- Does the subtherapeutic use of penicillin and the tetracyclines in animal feed result in increased prevalence of pathogens in the animals so fed and in foods derived from them?

- Does antibiotic resistance attributable to subtherapeutic use in feed increase the incidence of foodborne infectious disease in humans or complicate its medical management?

The current committee is well aware of the longstanding uncertainty of the benefits of the subtherapeutic use of antimicrobials in animal feed and its possible restriction in this country and abroad, and it understands the need for a risk assessment as a foundation for risk management in FDA's decision-making (rule-making) regarding the use of feed additives.

It is inherently difficult to relate human morbidity and mortality associated with a specific antibiotic-resistant bacterial pathogen directly to that pathogen's origin in livestock (or poultry) on a farm or in a feedlot and to administration of subtherapeutic amounts (as opposed to treatment amounts) of penicillin and the tetracyclines to the animals. Unequivocal direct evidence linking mortality to the postulated initial events is not available--certainly not in sufficient quantity to establish a cause-and-effect relationship. For want of direct evidence, the committee has

approached its task indirectly by developing a risk model, using the most reliable data available for the individual elements involved, including annual numbers of reported cases of specified infections, fractions of cases due to bacterial strains that show antibiotic resistance, mortality rates, fractions of deaths associated with bacterial strains of farm origin, and fractions of antibiotic-resistant strains of farm origin caused by subtherapeutic use of antibiotics in animal feed. Although some bacterial pathogens (salmonellae, Campylobacter jejuni, enterohemorrhagic E. coli, and Yersinia enterocolitica) are commonly foodborne and of animal origin, salmonella infections are the only ones that have been reportable for many years and for which incidence figures and antimicrobial-susceptibility data have been collected. Salmonellosis has therefore been selected for the risk assessment model, although we acknowledge that several other human infections would also be relevant to our charge.

The committee is particularly conscious of the limitations and inherent weaknesses of the data base used in the risk assessment model. Where an assumption or estimate had to be made, we have stated its basis. We are aware that some estimates used in the model are weaker than others; for example, the fraction of antibiotic-resistant strains of farm origin attributable to subtherapeutic use of antibiotics (or penicillin and the tetracyclines specifically). Because some data for the model were only estimates, we considered a range of values (low, mid-range, and high) for each element and expressed the final risk estimates (deaths per year) as minimum, median, and maximum.

In addition to the risk assessment, the committee has reviewed further new information pertinent to human health that might be related to subtherapeutic use of antibiotics in animal feed. Some of the new information addresses study possibilities identified by the former NRC committee on subtherapeutic antibiotic use in animal feeds. Some of it deals with the biologic impact of antibiotic resistance in bacteria and the use of molecular biologic techniques in identifying clonal features of isolates obtained from farm animals, from foodstuffs derived from livestock and farm animals, and from infected humans. Some of it reflects followup experience in European countries that have, in the last 10-20 years, by regulatory action prohibited use in animal feed of subtherapeutic concentrations of antibiotics that are used in treatment of humans. Much of this information provides only circumstantial evidence bearing on the question under consideration. Some of the facts even appear to be mutually contradictory.

The committee has not addressed any cost-benefit aspects of the issues related to this problem, nor has it made any recommendations regarding regulatory strategies or policies. It hopes that its report on the subtherapeutic use of

penicillin and the tetracyclines in animal feed will be useful to FDA in its consideration of the risk involved and appropriate risk management. The committee stresses the continuing need for more extensive gathering of detailed epidemiologic information to define the human health risks more sharply.

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CONCLUSIONS

The committee has reviewed the extensive and sometimes conflicting literature pertaining to possible human health risks associated with the use of subtherapeutic concentrations of penicillin and the tetracyclines (and other antimicrobials) in animal feed. It evaluated investigations of the molecular nature of plasmids, transposons, and other bacterial antimicrobial-resistance determinants and their transfer; data on the extent of antimicrobial resistance in Salmonella species (and in other enteric pathogens) isolated from humans and farm animals; epidemiologic studies in humans and farm animals; data on reported cases of human illness and deaths due to Salmonella transmitted to humans from farm animals via meat and poultry products; information on the extent of subtherapeutic use of penicillin, the tetracyclines, and other antimicrobials in animal feed; and data from Great Britain on the effects of the restrictions placed some years ago on the use of antimicrobials in animal feeds in those countries.

The committee also reviewed the available published reports dealing with four subjects recommended for further study in the 1980 report of the National Research Council Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds: the effects of subtherapeutic and therapeutic doses of antimicrobials on the prevalence of antimicrobial-resistent enteric bacteria (including salmonellae) in farm animals; the extent of carriage of resistance-factor-containing bacteria in vegetarians and nonvegetarians (to ascertain the extent to which such carriage is associated with meat consumption); the extent of carriage of resistance-factor-containing Enterobacteriaceae in abattoir workers, their families, and neighborhood controls (to assess the association with occupational exposure to bacteria from animal sources); and the prevalence of urinary tract infections (and urinary tract infections due to resistance-plasmid-containing Enterobacteriaceae) in female workers in poultry-processing plants and a control group of women without contact with farm animals or their unprocessed meat products.

We consulted with and heard testimony from the epidemiology staff of the Centers for Disease Control, other medical epidemiologists, veterinarians, representatives of

the Animal Health Institute, microbiologists, and representatives of the pharmaceutical industry.

Using all the resources noted above, we were unable to find a substantial body of direct evidence that established the existence of a definite human health hazard in the use of subtherapeutic concentrations of penicillin and the tetracyclines in animal feeds. However, we believe that important--but as yet scant--data indicate the flow of distinct salmonella strains from farm animals, through the food processing chain, to humans in whom they cause clinical salmonellosis. In the one compelling instance of such a clear link, the multiple-antibiotic-resistant S. newport originated in farm animals exposed to chloramphenicol, a drug not approved by the Food and Drug Administration for use in feed. The committee believes that the molecular fingerprinting techniques used in this study can provide (when unique markers are present) the direct evidence needed to trace the source of antibacterial-resistant bacteria to human infection. If records of amounts of antibiotic use are maintained on farms producing food for human consumption, better evidence can be established for incriminating subtherapeutic/therapeutic doses in disease outbreaks.

The committee believes that there is indirect evidence implicating subtherapeutic use of antimicrobials in producing resistance in infectious bacteria that causes a potential human health hazard. The evidence is of several kinds:

- There are extensive experimental data on the properties of R plasmids and their capacity for transfer of antimicrobial-resistance determinants, both in the test tube and in the intestinal tract, particularly in the presence of antimicrobial selective pressure.

- There is evidence of widespread use of subtherapeutic concentrations of penicillin and the tetracyclines (and other antimicrobials) on farms and feedlots.

- There is ample evidence of high levels of antimicrobial resistance among animal isolates of salmonellae.

- Animal and poultry carcasses in meat-processing plants are often contaminated with Escherichia coli and other enteric pathogens. Few data are available on the frequency of antimicrobial resistance among such isolates. If the prevalence of antimicrobial resistance among reported isolates from diagnostic laboratories is a true representation of antimicrobial resistance in farm animals going to slaughter, the frequency of resistance among enteric pathogens in animal and poultry carcasses would be expected to be high. However, if the salmonella isolates reported

from diagnostic laboratories are principally from animals that are ill and have received antimicrobials, the figures would clearly overestimate the frequency of resistant isolates from meat and poultry carcasses.

o Handling and ingestion of improperly cooked, packaged frozen or refrigerated meat and poultry contaminated with bacterial pathogens provides exposure to an infecting inoculum.

o Experience with antimicrobial drugs in humans over the last 45 years has revealed the emergence of resistant strains associated with extensive drug use and the need to avoid unnecessary and prolonged use, particularly "prophylactic" use without clear and proven indications.

In addition, the committee has used the results provided by the risk assessment model presented to estimate quantitatively the possible risk of mortality associated with antibiotic-resistant salmonellae due to the subtherapeutic use of penicillin or the tetracyclines in animals. In the 1980 NRC report, the Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds concluded that "the postulated hazards to human health from a subtherapeutic use of antimicrobials in animal feeds were neither proven nor disproven." In other words, the risk of human health as a result of subtherapeutic use of antimicrobials in feed was not estimated.

We found the available data base on some aspects of the problem to be limited in quality and quantity; indeed, the data had not been gathered prospectively for the purpose of this type of analysis. The committee has used what it considers the best available information, indicating, where appropriate, the inherent weaknesses in the data. Admittedly, in some instances, we used only the best estimates available in the risk assessment. The assessment does indicate the presence of risk. Although it does not provide a distinct numerical "answer" to the question of the magnitude of the human health risk involved, it does provide some indication of the probable size of the risk in terms of numerical estimates or ranges. These are presented below as numbers of deaths per year attributable to the subtherapeutic use of antimicrobials (or penicillin and tetracyclines) in the listing of specific conclusions:

BIOLOGIC IMPACTS

o Use of each new antimicrobial agent over the last half-century has eventually mobilized genes that encode resistance to the agent and disseminated them widely through

the world's interconnecting bacterial populations. Use of the antimicrobial agent disseminates the resistance genes in stages, each of which begins with a rare molecular event that facilitates further dissemination. Although use of antimicrobials in a patient or the patient's neighbors might have triggered overgrowth and clinical manifestation of the resistant strain, the evolution and delivery of its resistance genome was the result of prior use in many, probably distant, bacterial populations.

o Results of surveys of isolates of salmonellae from animals and humans in the United States and restriction-endonuclease fragment patterns of resistance plasmids from selected isolates suggest that clones of resistant salmonellae are endemic in animals and sporadic or occasionally epidemic in humans.

o Herds of farm animals given subtherapeutic amounts of antimicrobial agents have more antimicrobial-resistant intestinal bacteria than herds given no antimicrobials.

o The most important determinant in the selection of antimicrobial-resistant strains in a bacterial population is exposure of that population to antimicrobials. Total duration and concentration of antimicrobial use are important in selection for resistance. Any measure that fails to reduce total use appreciably is unlikely to affect the prevalence of antimicrobial-resistant strains.

o Resistance to antimicrobial drugs among salmonella strains can interfere with the efficacy of antimicrobial therapy of human salmonellosis. (Such resistance is usually R-plasmid-mediated, so it can involve other drugs, such as trimethoprim-sulfamethoxazole, chloramphenicol, and ampicillin.) Although such interference with the efficacy of therapy almost certainly occurs (i.e., patients are treated with an antimicrobial that is ineffective because of drug resistance), it is probably quite uncommon in nontyphoidal salmonellosis.

o The available data are inadequate to conclude that either subtherapeutic or therapeutic concentrations of antimicrobials are more selective of drug-resistant bacteria. On theoretical grounds, it is likely that therapeutic and subtherapeutic dosages exert equal selective pressure for clonal expansion of resistance, but subtherapeutic dosages exert more pressure for conjugative transfer of drug resistance, because of the dosages and the durations of administration.

o Animal and poultry products (including veal, beef, pork, chicken, eggs, and milk) are the principal sources of human nontyphoidal salmonellosis. Also, some E. coli serotypes can also be found in the intestinal flora both of humans and of farm animals. Thus, there could be an interconnecting link between these two large pools of enteric microorganisms, facilitated by the high frequency of contamination of animal and poultry carcasses in slaughterhouses. Such a potential link would provide a means of movement of R plasmids of farm origin to the human alimentary tract. The interconnection, because of its nature, would constitute an almost exclusively one-way passage.

o The overall prevalence of resistance to any of five commonly used antimicrobials is about 4 times as great in collections of salmonella isolates from farm animal and poultry (65%) as those in collections of isolates from humans (15.5%). This difference suggests that the predominant pool of resistant salmonellae is in farm animals. Because ultimately almost all human infections with nontyphoidal salmonellae result from strains originating in farm animals, the antimicrobial resistance observed in human isolates most likely is derived from the animal pool of resistance genes, rather than from selection due to antimicrobial use in humans.

EPIDEMIOLOGIC FINDINGS

o Evidence is sparse that directly links the use of penicillin and tetracycline in subtherapeutic concentrations in animal feeds to human infections. Several studies have yielded reliable evidence of spread, from farm animals and poultry to humans, of E. coli strains in which antimicrobial resistance had been induced by administration of subtherapeutic concentrations of antimicrobials as feed additives. There is evidence from only one study of the direct spread of multiple-antimicrobial-resistant salmonellae from farm animals to humans via meat products. However, the antimicrobial used on the farm was chloramphenicol, a drug not approved by FDA as a feed additive in animals used for food production. It might be difficult, or impossible, to provide a total chain of evidence directly relating the majority of cases of human infection with antimicrobial-resistant salmonellae to a source on the farm or feedlot or to relate the presence of the resistance to the use of specific antimicrobials in subtherapeutic concentrations in feed. By the time a detailed investigation of an outbreak of human salmonellosis occurs, evidence of prior antimicrobial use patterns might not be available.

o It has not been possible to determine whether antimicrobial resistance of salmonellae caused by the administration of subtherapeutic concentrations of antimicrobials in animal feed increases the number of cases of human salmonellosis.

o Whether the presence of antimicrobial resistance in salmonellae increases virulence is uncertain; the available data are limited and conflicting. In special circumstances, as when R plasmids are linked with virulence genes (e.g., those for enterotoxin or hemolysin in E. coli), selection by antimicrobial agents might promote spread of virulent strains; however, such an occurrence has only rarely been reported. It is not clear whether the overall prevalence of salmonellae in food products is increased by virtue of antimicrobial resistance. However, the incidence of human salmonellosis in the United States is increasing, and the increase is unlikely to be an artifact of better reporting. As long as most strains of Salmonella are susceptible to the antimicrobials to which they are exposed, subtherapeutic administration of antimicrobials might reduce the prevalence of salmonellae in meat and poultry products that humans ingest. However, as the prevalence of resistant strains increases because of repeated and prolonged exposure to antimicrobials, subtherapeutic administration might actually favor the increase by suppressing the normal competing flora and promoting R-plasmid spread. Direct proof of this pattern in salmonellae in farm animals is lacking.

o The current frequency of R-plasmid-mediated antimicrobial resistance among isolates of E. coli and salmonellae in the intestinal contents of farm animals and poultry is high--much higher than in human isolates. It would be difficult to predict the period required, after curtailment of the use of subtherapeutic concentrations of penicillin and the tetracyclines in animal feed, for R-plasmid-mediated antimicrobial resistance to decrease in any extent in salmonellae and E. coli strains. Major decreases might occur only after the passage of years, in view of (1) the current degree of resistance, (2) the extensive environmental contamination on farms and feedlots with resistant organisms, (3) the prolonged prior subtherapeutic use of antimicrobials, which has allowed extensive permeation of resistance genes (transposons) throughout the highly colonization-adapted coliform flora of farm animals, and (4) the need to introduce competing, antimicrobial-susceptible coliform bacteria. Results of studies in confined populations of swine indicate that it could take many years for major decreases in levels of resistance to occur.

o Although the extent of antimicrobial resistance among salmonella strains isolated from humans is probably growing, it is still low enough for suitable intervention to forestall possible further increases and eventually to lower the overall extent of antimicrobial resistance.

ANTIBIOTIC USE PATTERNS

o The use of subtherapeutic dosages of penicillin and the tetracyclines in animal feeds is extensive in the United States. Such use is for the purpose of either growth promotion or disease prevention and often continues for a substantial portion of the growth cycle of farm animals. The specific rationale for use in a given herd at a given time is not always clear. Of over 31 million pounds of antimicrobials produced each year in the United States, about 42-48% is designated for addition to animal feeds or other unspecified (minor) uses. The best estimates (they are only estimates) indicate that penicillin and the tetracyclines account for almost 60% of the antimicrobials sold to the feed trade (and presumably ultimately used on farms and in feedlots). Of the total amount of tetracyclines produced in this country, for use in both humans and animals, approximately 70% is sold for use in livestock and poultry feeds. An estimated 88% of all antimicrobial use in livestock and poultry is in subtherapeutic concentrations. Thus, subtherapeutic use of penicillin, the tetracyclines, and other antimicrobials in animal feeds--which accounts for some 40% of antimicrobial production in the United States--constitutes a sizable segment of the total antimicrobial selective pressure (for resistant enteric microorganisms) exerted on the combined human and farm-animal intestinal bacterial populations.

o Interpretation of the results in Great Britain after banning the subtherapeutic use of penicillin and the tetracyclines in animal feed is difficult, in part because total farm use of these antimicrobials might not have decreased because use could have taken the form of therapeutic or prophylactic doses in feed for disease treatment or prevention as prescribed by a veterinarian. The appearance of new epidemic strains of antimicrobial-resistant salmonella serotypes during the period of interdiction of subtherapeutic use further confounds interpretation. It might take years for dilution of antimicrobial-resistant strains of Salmonella and E. coli in the farm animal population before any substantial changes might be observable.

RISK ANALYSIS

o The committee has been unable to find substantial direct evidence that bacterial resistance resulting from the use of subtherapeutic concentrations of penicillin or the tetracyclines in animal feed causes an excess risk to human health as a result of consumption of food products derived from the treated animals, as a result of contact with such animals, or as a result of exposure to an environment contaminated by resistant enteric bacteria from such animals. Lacking this direct evidence, the committee turned to the tools of risk assessment to develop some quantitative estimate of the probable risk to human health associated with this form of the subtherapeutic use of these antimicrobials.

o Use of penicillin and the tetracyclines in subtherapeutic concentrations in animal feed has led to increased antimicrobial resistance in foodborne commensals and pathogens. The risk analysis in this report focused only on human infection with salmonella serotypes, because available data on other species were insufficient. The committee has not assessed the potential risk to human health associated with drug resistance in other gram-negative bacillary species (Campylobacter jejuni, Yersinia enterocolitica, and enterohemorrhagic E. coli) of animal origin, because the data on human cases are too limited and because antimicrobial susceptibility data on those bacteria are not routinely obtained.

o Because the committee's risk assessments are based on estimates using sparse data, these estimates should be interpreted and used with caution. Such estimates are best seen as scientific hypotheses about the possible extent of a problem. This does not mean that they are "hypothetical" in the weak sense of being speculative. Rather, they are hypotheses that are consistent with all available information and scientific understanding, but they have not been tested by traditional scientific methods. All the estimates presented in this report should be viewed in that perspective.

o Annual numbers of deaths from salmonellosis attributable to subtherapeutic uses of any antimicrobials for prophylaxis and growth promotion have been estimated. The likeliest estimate is 70 deaths per year.

o The likeliest estimate of mortality from salmonellosis attributable to subtherapeutic uses of penicillin/ampicillin and/or tetracycline for prophylaxis and growth promotion is 40 deaths per year. Caveat--these are not necessarily "excess deaths," but rather estimates of the

yearly mortality attributable to salmonellosis of the indicated origin. The deaths might to some extent replace deaths (in the same patients or others) that occur from infections due to salmonellae susceptible to penicillin/ampicillin and tetracycline if subtherapeutic dosages of these antimicrobials had not been used in animal feed. Estimation of such "replacement" of deaths is not possible with the evidence at hand.

o The likeliest estimate of mortality from salmonellosis attributable to subtherapeutic uses of any antimicrobial for growth promotion only is 20 deaths per year. As in the preceding (and following) estimates, the caveat regarding "excess deaths" applies.

o The likeliest estimate of mortality from salmonellosis attributable to subtherapeutic uses of penicillin/ampicillin and/or tetracycline only for growth promotion is 15 deaths per year.

o The likeliest estimate of mortality from salmonellosis in the "etiologic fraction" attributable to subtherapeutic uses of any antimicrobial for prophylaxis and growth promotion is 6 deaths per year. The "etiologic fraction" is the proportion of persons exposed to an antimicrobial-resistant salmonella strain who are at increased risk of illness by virtue of recent use of antimicrobial drugs for whatever reason. Therefore, such deaths can be considered as "excess deaths"; i.e., they would not occur if the infecting salmonella strain were not antimicrobial-resistant and if its multiplication were not promoted, presumably, by suppression of growth of the competing normal antimicrobial-susceptible normal flora. In the same way, the number of foodborne pathogens (inoculum size) needed to precipitate disease might have been decreased. Whether a similar effect can be produced by prior antimicrobial use in persons infected with antimicrobial-susceptible salmonellae (due to possible differential antimicrobial susceptibility between susceptible salmonellae and normal components of the intestinal flora) is unknown, and the committee has not been able to find data bearing on this question.

o The likeliest estimate of mortality from salmonellosis in the "etiologic fraction" attributable to subtherapeutic uses of penicillin/ampicillin and/or tetracycline for prophylaxis and growth promotion is 6 deaths per year.

o The likeliest estimate of mortality from salmonellosis in the "etiologic faction" attributable to

subtherapeutic uses of any antimicrobial only for growth promotion is 2 deaths per year.

o The likeliest estimate of mortality from salmonellosis in the "etiologic fraction" attributable to subtherapeutic uses of penicillin/ampicillin and/or tetracycline only for growth promotion is 2 deaths per year.

o Infections with antimicrobial-resistant strains of Salmonella are more often fatal than infections with susceptible Salmonella. Therefore, the increased difficulty of providing effective therapy for human disease can be estimated. The increased difficulty in providing effective treatment may be due to increased virulence of antimicrobial-resistant strains, to the presence of resistance to one of the antimicrobials ordinarily used to treat such infections when they are severe or when they occur in particularly vulnerable persons, or to some other factor. The likeliest estimate of mortality from salmonellosis arising because of increased difficulty of treatment attributable to subtherapeutic uses of any antimicrobial for prophylaxis and growth promotion is 40 deaths per year.

o The likeliest estimate of mortality from salmonellosis arising because of increased difficulty of treatment attributable to subtherapeutic uses of penicillin/ampicillin and/or tetracycline for prophylaxis and growth promotion is 20 deaths per year.

o The likeliest estimate of mortality from salmonellosis arising because of increased difficulty of treatment attributable to subtherapeutic uses of any antimicrobial only for growth promotion is 8 deaths per year.

o The likeliest estimate of mortality form salmonellosis arising because of increased difficulty of treatment attributable to subtherapeutic uses of penicillin/ampicillin and/or the tetracyclines only for growth promotion is 8 deaths per year.

o Evaluation of the foregoing estimates of mortality from salmonellosis attributable to subtherapeutic uses of antimicrobials in animal feed requires consideration in a broader context. What possible benefits accrue from such subtherapeutic use of antimicrobials in food production? Would human deaths from salmonellosis be reduced by the discontinuation of subtherapeutic use of penicillin/ampicillin and/or the tetracyclines? The committee's thesis is that, although some deaths due to antimicrobial-resistant strains might be "replaced" by deaths due to susceptible strains, the total number of deaths would decrease, however,

this cannot now be proved. The committee offers no recommendations regarding policy-making because that was not part of its mandate.