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Antimicrobial Resistance Risk Assessment in Food Safety

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ABSTRACT

Microbiological risk assessments generally focus on estimating adverse human health risks from exposures to human pathogenic microbes. The assessment of potential human health risks posed by pathogens that have acquired resistance to antimicrobial drugs is a new application of risk assessment that is closely related to microbiological risk assessment. Antimicrobial resistance risk assessment is a risk analytical process that focuses on resistance determinants as hazardous agents that might lead to drug-resistant microbial infections in humans exposed to bacteria carrying the determinants. Antimicrobial-resistant infections could occur directly from actively invading or opportunistic pathogens or indirectly from the transfer of resistance genes to other bacteria. Here, we discuss risk assessment models that might be employed to estimate risks from drug-resistant bacteria in the animal food pathway and the types of models and data that may be used for microbiological risk assessments or antimicrobial resistance risk assessments.

In recent decades, an alarming increase in the prevalence of bacteria resistant to antimicrobial drugs has been documented *(8, 21).* For example, in 1993 less than 0.5% of enterococcus strains recovered in hospitals were resistant to the antibiotic vancomycin. By 1999, the prevalence rose to nearly 25% of enterococci in hospitals *(39).* Additionally, dramatic increases in resistance have been observed for methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae (24, 45).* The increasing resistance has created a paradox in which ''more antimicrobial agents are available to us than at any time in the antibiotic era, yet the number of these agents with efficacy against the bacteria causing common, hospital-acquired, life-threatening bloodstream infections has progressively diminished'' *(30).* Consequently, in their action plans U.S. and international public health agencies have targeted antimicrobial resistance as one of the most pressing public health needs *(8, 44, 53).*

A basic tenet of microbiology is that antimicrobial treatment of a bacterial population in vitro or in vivo can select for cells carrying either acquired or intrinsic resistance to the antimicrobial drug. Under continued dosing of an antimicrobial drug, a resistant subpopulation of cells can continue dividing and eventually overtake the susceptible bacteria, thereby decreasing the likelihood of effective treatment. Even in infections that are symptomatically cured, resistant bacteria can be retained or shed by the infected individuals and can contribute to reservoirs of resistant bacteria in the population.

Most of the opportunity for the selection of antimicrobial-resistant bacteria of human concern occurs from the treatment of infected patients with antibiotics *(11, 27).* In addition to direct pathways to increased prevalence of resistance in the human population, there has been a long-standing concern for potential indirect pathways to antimicrobial drug resistance among human pathogens and opportunistic pathogens. An indirect pathway of primary concern is in the food animal pathway, i.e., the potential contribution to human antimicrobial drug resistance of certain uses of antimicrobial drugs in food animal agriculture. The call for risk assessments in the food safety pathway is based on a hypothesis that low concentrations of antimicrobial drugs as animal feed or water additives for growth promotion exert a cumulative selective pressure that in turn increases the proportion of drug-resistant human or zoonotic pathogens in relevant food commodities *(9, 23, 28, 32, 48, 49).*

Contemporary applications of antimicrobial drugs in food animals that may be factors in pathways to human antimicrobial drug resistance include (i) drug therapy to control an existing infection in a particular animal, (ii) metaphylaxis, in which a group of animals might be preventively treated upon observations of infection in one or more members of the group, (iii) prophylaxis as a normal preventive measure prior to surgery or prior to conditions known to greatly increase the risk of infection, and (iv) growth promotion to enhance the production features of a herd or flock *(42, 46).* This last use has drawn the greatest concern for potential contributions to antimicrobial drug resistance from both the biomedical community and the public *(2, 3, 23).* The first three uses are generally of lesser concern because (i) food animals with frank illness or infection do not enter the food pathway until the illness has resolved and drug withdrawal periods have been met and (ii) a significantly smaller proportion of the flock or herd is treated at any one time compared with large-scale application for growth promotion.

The public health implications of foodborne exposure

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TABLE 1. *Potential adverse human health consequences based on hazard identification*

Endpoint	Endpoint class
Infection from an antimicrobial drug–resistant pathogen or commersal organism	Morbidity
Long-term complications from infections	Morbidity
Antimicrobial drug–resistant infection from pathogens or commensals leading to death	Mortality
Transfer of resistance genes to secondary pathogens or commensals	Quality of life[a]
Increased prevalence of antimicrobial drug–resistance genes in the population	Quality of life[a]
Limited choice of drugs for treatment of infections	Quality of life

[a] Leads to a second risk assessment process focusing on a hazard presented by a resistant bacterial strain other than the one initially identified, considered a hazard transfer.

of humans to drug-resistant microorganisms emerging from food animal applications of antimicrobial drugs were recognized soon after the use of these drugs in food animals began *(29, 43).* Public health issues and the potential application of risk assessment to antimicrobial drug resistance have been revisited several times by both governmental and nongovernmental organizations *(2, 8, 53).* Human health risk assessment is the process by which the likelihood that exposure to a biological, chemical, or physical agent will result in harm to exposed individuals is estimated. Risk assessments are needed by public health agencies to inform regulatory decision making about mitigating potential adverse impacts of antimicrobial drug resistance on both animal and human health. In addition, risk assessment has been proposed as a primary approach by which antimicrobial drug resistance can be addressed in human food safety reviews for new animal drugs *(48, 49).*

Here, we present an overview of the basic elements of antimicrobial resistance risk assessment (ARRA). The objective of the paper is not to introduce or document ARRA policies of the U.S. Food and Drug Administration; rather, the general theory and recent development of ARRA is discussed. Distinctions between ARRA and the related activity of microbiological risk assessment (MRA) *(12, 18, 26)* are discussed as necessary.

HISTORICAL BASIS FOR ARRA

MRA for food safety analysis began in the 1800s *(37).* Although MRA has advanced recently into a well-characterized and defined process *(12, 18, 19),* ARRA is in its infancy. Proposed models for both MRA and ARRA have their origins in health risk assessment for chemical and radiation hazards developed for environmental (including foodborne) exposure pathways. In particular, the review of governmental risk assessment by the National Academy of Sciences, *Risk Assessment in the Federal Government: Managing the Process,* provided a framework for most contemporary health risk assessments *(34).* Elements of the risk assessment paradigm described in this 1983 report are hazard identification, dose-response assessment, exposure assessment, and risk characterization *(34).* The four steps of risk assessment described in this report have been the subject of much debate, revision, and analysis *(35, 36);* however, the scientific principles underlying the paradigm remain recognizable throughout most health risk assessments.

Why is there a need for a food safety ARRA model that elaborates on the generalized MRA in food safety risk analysis? First, in ARRAs for food animal uses of antimicrobial drugs, ''the nature of the risk to human health due to antimicrobial use in animal husbandry is inherently indirect'' *(7).* Second, the nature of the hazard is difficult to characterize as a single agent. For example, Salisbury et al. *(40)* recommended that three interrelated hazards be assessed separately: (i) the antibiotic, (ii) the antibiotic-resistant bacteria, and (iii) the genetic determinants for antibiotic resistance (antibiotic resistance genes). The corresponding adverse consequences of exposures to these hazards are (i) emergence of antibiotic-resistant bacteria, (ii) spread of antibiotic-resistant bacteria, resulting in human exposure or infection, and (iii) transfer of antibiotic-resistance genes to other bacteria *(40).* The list of possible adverse consequences might also include the cumulative impact from the loss of choice of antimicrobial drugs, i.e., an adverse consequence expressed as a societal value (Table 1). The concern for a loss of therapeutic choices is implicit in the debate about uses of antimicrobial drugs in food animals. Additionally, this consequence spans both risk assessment and risk management issues, suggesting that the hazard might be defined as the very concept of using similar antimicrobial drugs in animals and humans. Clearly, MRA and ARRA are scientifically overlapping processes; however, ARRA is not simply an MRA in which a portion of the bacteria of interest are coincidently resistant to a particular antimicrobial drug.

ARRA RISK ASSESSMENT

Because MRA and ARRA are relatively new areas of risk assessment, much recent discussion has focused on the development of risk analytical paradigms for these processes. For example, the Codex Alimentarius Commission recently recommended a classical four-step risk assessment model for MRA *(15, 38).* The Office International des Epizooties (OIE) of the World Organization for Animal Health adopted the Covello and Merkhofer model *(17)* of risk assessment in which exposure assessment is partitioned into release assessment, focusing on source terms in exposure assessment, and exposure assessment, focusing on the exposure factors governing the human individual and population exposures *(1).* This paradigm also moves hazard identification outside of the risk assessment process, as a separate risk management step (Fig. 1).

Two conceptual models that might serve as generalized

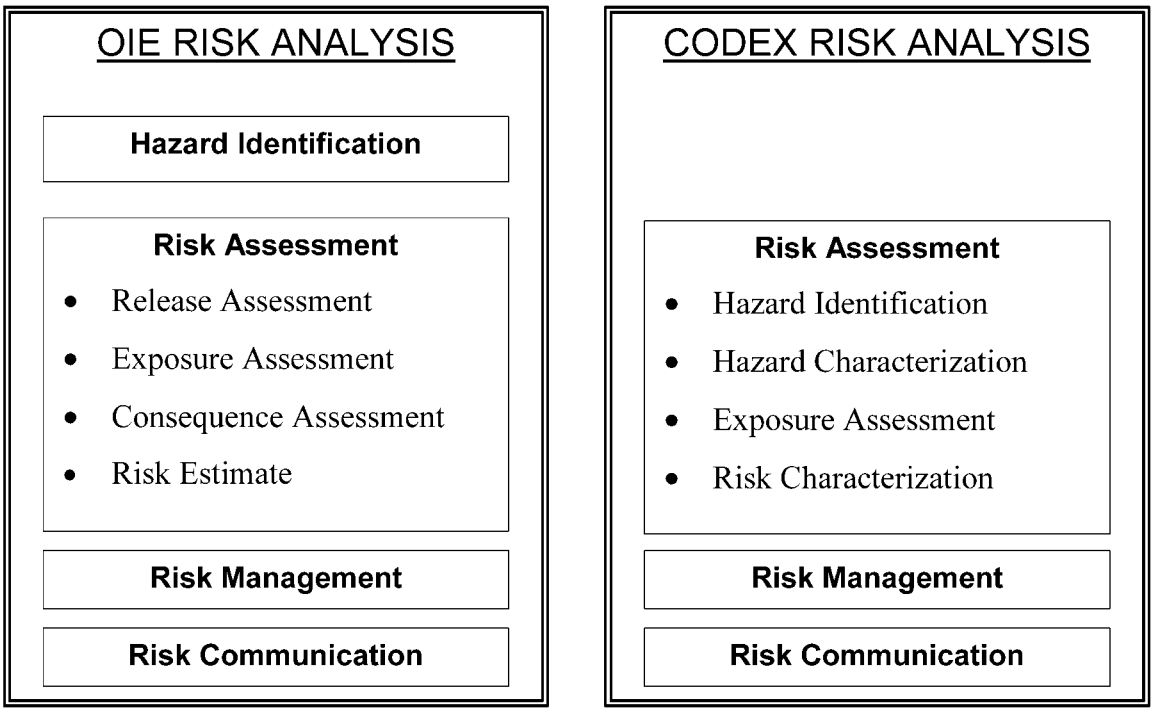

FIGURE 1. *Proposed paradigms of risk analysis for antimicrobial resistance resulting from animal uses of antimicrobial drugs. Risk analysis nominally encompasses the activities of risk assessment, risk management, and risk communication. In the OIE model, hazard identification is part of risk analysis that is performed apart from the risk assessment process.*

starting points for food safety ARRA include a direct pathway (Fig. 2) and an indirect pathway (Fig. 3). A key principle in ARRAs is that antimicrobial-resistant infections are generally not detected unless treatment has been sought using the antimicrobial drug of concern. In other words, an infection from a resistant strain of bacteria is not detectable unless a deliberate lab test is performed or it is otherwise inferred by the failure of an antimicrobial drug to attenuate the infection. Conversely, there can be proportions of the exposed populations that either carry the relevant bacteria asymptomatically or have recovered from mild unreported illness caused by the resistant strains.

HAZARD IDENTIFICATION AND ASSESSMENT

The hazardous agent in ARRA, at the finest level of detail, is one or more microbial genes that code for resistance to an antimicrobial drug. The identification of the hazardous agent is complicated by the following: (i) resistance to an antimicrobial drug can occur through different and possibly overlapping genetic and biochemical mechanisms of action, (ii) one or multiple genes might be necessary for expression of resistance, (iii) the resistance genes might be located in either chromosomal or extrachromosomal (plasmid) DNA, and (iv) the reservoirs for resistance genes might include bacterial strains other than the original strain of interest. Hazard identification is further complicated by the fact that the bacterium carrying the resistance genes need not be intrinsically pathogenic in humans or animals. Some gram-positive or gram-negative bacteria are normally commensal but can become opportunistic pathogens under certain conditions. Thus, this situation differs markedly from the hazard assessment in MRA, for which the hazardous agent is typically specified as a pathogenic bacterium or its toxin *(13, 25, 31, 33, 41).*

Additional problems are encountered in ARRAs when estimating the extent of adverse human health effects. In MRA, the adverse health effect of interest is acute enteric disease, septicemia, or other manifestations of microbiological infection. The prevalence of human disease can sometimes be estimated from the public health surveillance networks and studies of self-reported illnesses. For most scenarios, there is a direct cause-and-effect relationship between consumption of food commodities harboring the microbe of concern and the foodborne illness in question. In MRA, a relatively small proportion of foodborne illness is attributed to carriers of a pathogenic bacterium who do not themselves experience disease. In contrast, the antimicrobial resistance gene(s) that is the focus of an ARRA can be carried by humans without apparent adverse health effects. Human antimicrobial-resistant infections can have a delayed onset, whether experienced by the carrier or by secondarily exposed individuals, e.g., through direct or indirect pathways. In this scenario, the the hazard can best be estimated by measuring the reservoir of antimicrobial resistance genes through sampling intestinal flora from healthy human volunteers. In MRA, such studies are usually undertaken for dose-response assessment phases of the risk assessment to estimate a median infective dose.

EXPOSURE ASSESSMENT

Exposure assessment is the process by which the intensity, duration, and frequency of human contact with the hazardous agent are determined *(34, 35).* Exposure assessment for any biological, chemical, or physical agent is typ-

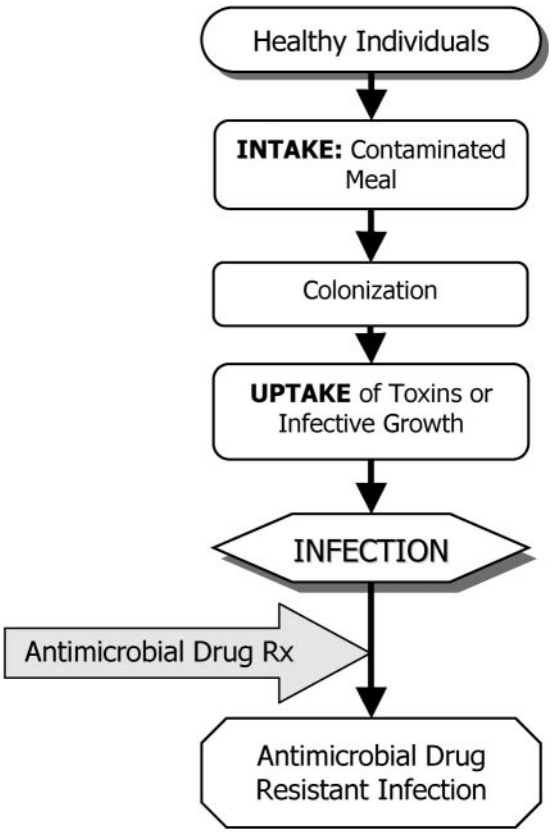

FIGURE 2. *Conceptual model of a direct foodborne pathway of antimicrobial-resistant pathogenic bacterial infections. In this conceptualization, the individual consumes a contaminated meal and is colonized by the bacterial strain in question, potentially leading to gastrointestinal disease, the mechanisms of which depends on the pathogen of interest. The endpoint of antimicrobial-resistant infection is often not detected until treatment with the specific antimicrobial drug has failed. This pathway is closely related to those in MRA, which generally concern pathogenic bacteria. The primary difference is the focus in ARRA on the drug-resistant pathogen. This figure does not show competing human-oriented pathways of contamination and infection.*

ically the broadest intellectual undertaking among the phases of risk assessment. For example, exposure assessment begins with an evaluation of microscopic factors that could enhance the release of resistant bacteria, follows the transport and fate of resistant bacteria in macroscopic environmental pathways ''from farm to fork,'' and ends at microscopic factors that might improve the chances for this bacterium to colonize humans (Fig. 4). Both MRA and ARRA have the potential feature of communicability: humans participate not only as the exposed population but also as part of the fate and transport mechanisms in exposure. For example, person-to-person contact may factor significantly in the risk of exposure of drug-resistant commensal bacterial strains *(8, 10).*

The concentration of the hazardous agent both within the exposure pathway and at the exposure boundary can significantly increase or decrease with time after the original exposure because of growth or death of the bacteria, respectively. Thus, exposure assessment in MRA and ARRA is generally thought to differ from exposure assessment in chemical or physical agent risk assessments. However, there are many instances in radiological risk assessment in which the most toxic radionuclide ''grows in'' from the radioactive decay of its parent radionuclide and instances in chemical risk assessments in which the accumulation of a toxic chemical occurs after release of less toxic precursors. In addition, both radiological and chemical risk assessments often deal with decay (i.e., deathlike processes). Thus, there are probably lessons to be learned from more established radiological and chemical risk assessment processes that might be useful in developing models for quantitative ARRAs.

For most gastrointestinal or systemic infections, population growth of the colonizing organisms is required before the infection or the toxicity from the infection is observable as clinical signs and symptoms. Ultimately, the original concentration of bacteria, host immune system factors, and gut microenvironmental factors are at play in producing optimal conditions for colonization of the host *(47).* The selection pressure of the antimicrobial drug itself is necessary for the resistant bacterium to cause illness.

Exposure to the antimicrobial resistance genes can occur through indirect pathways (Fig. 3). For example, resistant commensal bacteria, such as enterococcus species that have acquired resistance genes, can colonize the animal or human gut without health consequences until the opportunity for infection is presented. The opportunistic infection might occur in the colonized host, or infection might occur by secondary spread and colonization of individuals who are at risk of opportunistic infection. Such a situation is commonly observed in nosocomial disease, in which one of the most likely sources of infection by antimicrobial-resistant bacteria is the contamination of immunocompromised individuals through invasive medical procedures involving carriers of the antimicrobial-resistant opportunistic pathogen *(13, 16, 20, 22, 24).*

In some risk assessments, it might be useful to subdivide exposure assessment, capturing the properties of the sources of hazardous agents in a release assessment and the properties governing the interface of the hazardous agent with the human receptor in an exposure assessment. This partitioning would be particularly useful in situations where the overall exposure assessment might be highly complicated by multiple processes, pathways, and external factors. The OIE recently recommended partitioning release and exposure in risk assessments for antimicrobial drugs in veterinary use (Fig. 1) *(40).* A similar approach was recently proposed by the U.S. Food and Drug Administration *(14, 51).* The OIE model might be particularly relevant in food animal risk assessments because the source terms relevant to food animal production can be compartmentalized within release assessment, and human exposure factors can be defined and characterized in the exposure assessment. The subdivision of exposure into release and exposure might also facilitate risk management.

Release assessment. Release assessment in food safety ARRA includes factors in animal agricultural affecting the shedding of antimicrobial-resistant bacteria. The release of

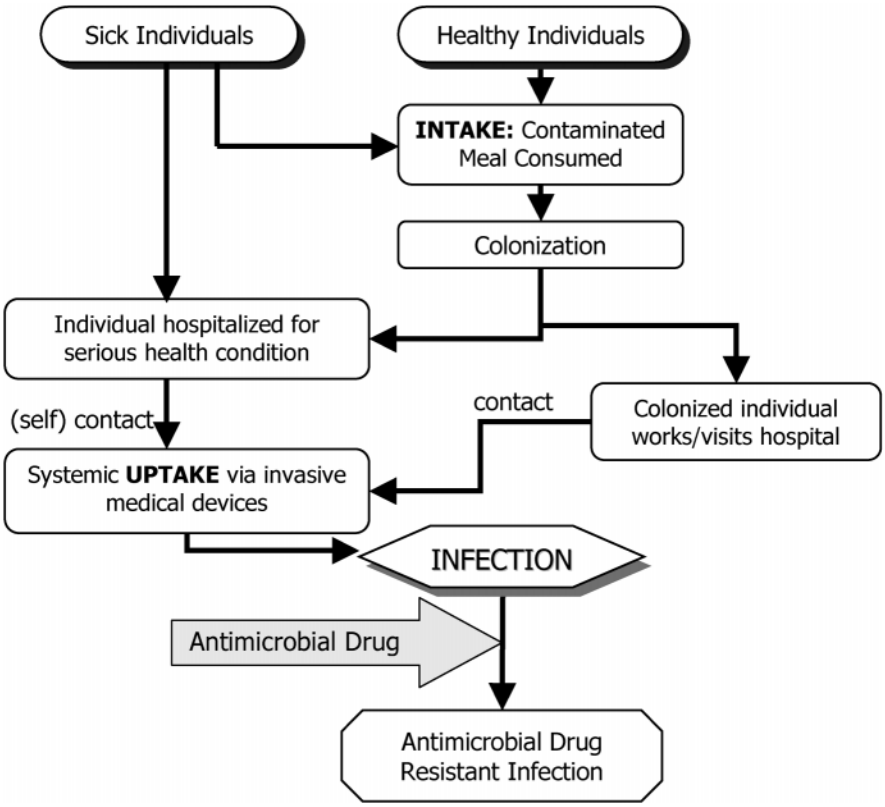

FIGURE 3. *A potential conceptual model of an indirect foodborne antimicrobial-resistant nosocomial infection by commensal bacteria. In this conceptualization, ill individuals might enter the hospital before colonization by a commensal strain. Colonization of the ill individual might occur (i) through consumption of a contaminated meal (intake) or (ii) through systemic self-contamination by contact with an indwelling venous or urinary catheter or a respirator tube. In a second pathway, a healthy individual might by coincidence be hospitalized soon after colonization. Hospital staff and visitors also can spread contamination to medical devices, increasing the opportunity for infection.*

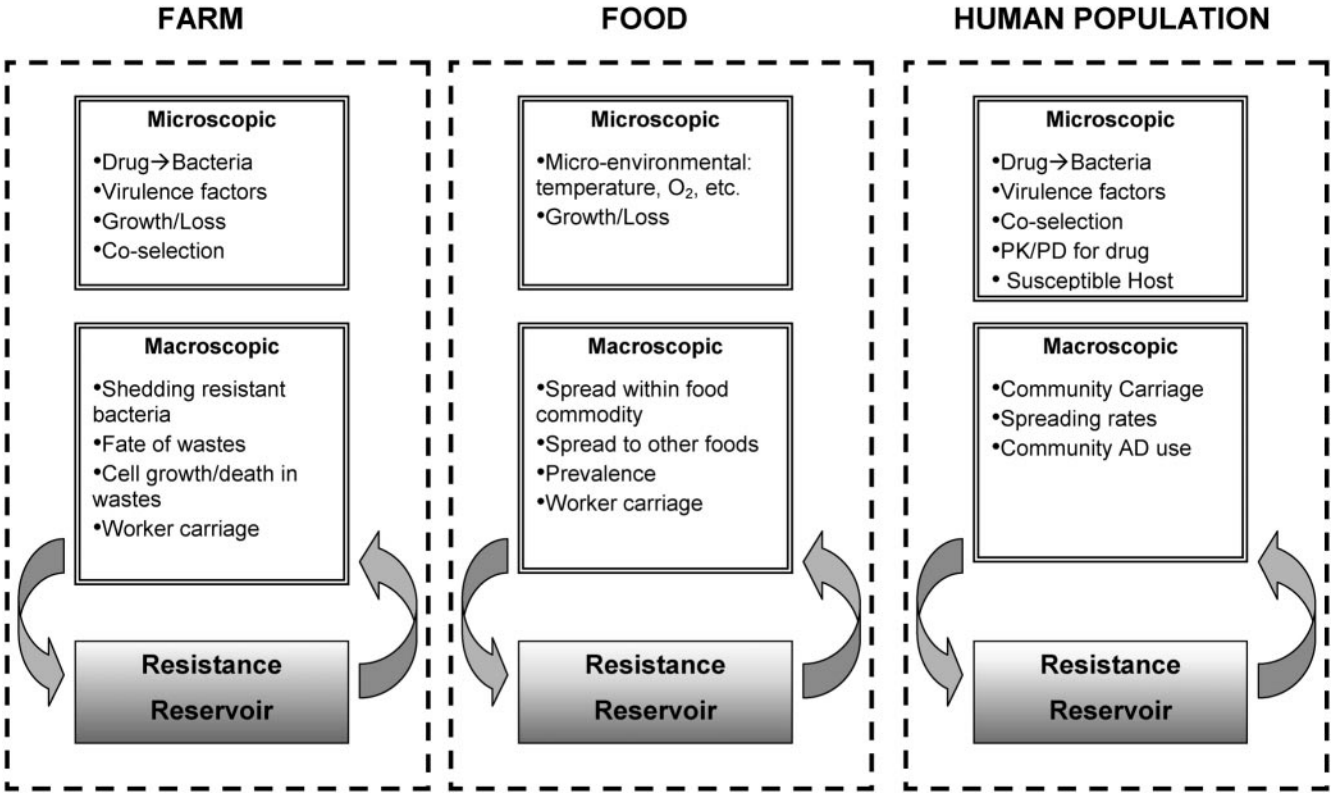

FIGURE 4. *Breadth of coverage for exposure assessment in ARRA. Exposure assessment is a broad scientific undertaking beginning at the microscopic level in the food animal and ending at human microscopic and macroscopic levels. Some proposals for MRA and ARRA in food animal pathways advocate partitioning exposure assessments into release and exposure portions to capture the factors leading to the release of bacteria from the food animal and the factors involved in assessing exposure at the human level. The figure includes only a portion of the complexity of exposure assessment because it focuses on only food animal pathways.*

TABLE 2. *Typical quantitative models for consequence assessments*

Model	Function (probability of infection)	Parameters
Simple exponential	$Pr = 1 - \exp[-\kappa \log_{10}(dose)]$	κ = host microorganism interaction probability: the fraction of microorganisms ingested that survive to initiate infection
Beta-Poisson	$Pr = 1 - [1 + (dose/\beta)]^{-\epsilon}$	ϵ, β = parameters affecting the shape of the curve
Weibull-gamma	$Pr = 1 - [1 + (dose^{\chi}/\beta]^{-\epsilon}$	ϵ, β, χ = parameters affecting the shape of the curve: if $\chi = 1$, then the model reduces to Beta-Poisson; if $\epsilon = 1$, the model reduces to log-logistic

bacteria carrying a resistance gene, in a macroscopic sense, is ultimately related to the presence of antimicrobial drugs in the food animals. In various studies, researchers have attempted to quantify the effect of antimicrobial drugs, either as growth promoters or as therapeutics, on the release of pathogenic bacteria (shedding) from food animals *(5)*. Recently, the Veterinary Medical Advisory Committee of the U.S. Food and Drug Administration reviewed the use of pathogen load research for providing information in new animal drug applications for antimicrobial drugs *(50)*.

The convenience of compartmentalizing release and exposure assessment may be driven by regulatory risk management considerations. For example, if a regulatory agency has inspection authority at the slaughter level in meat processing, then it might be useful to encapsulate the inspection-driven information gathering process within the release assessment. In an iterative risk assessment–risk management cycle, the inspection data might be used to seamlessly update the release assessment. Similarly, data to inform the exposure assessment portion of the risk assessment might be collected (managed) in the food processing portion of the human food production chain. The relevant information collected would be applied to food pathway analyses and could reveal human-derived exposure factors such as spread of resistant bacteria during food preparation. Public health inspection and surveillance data might be used to update the exposure portion of the risk assessment model. Ultimately, the exact boundary between release and exposure could depend on the convenience of risk assessment modeling and on risk management policies designed to address specific regulations.

Exposure assessment following release assessment. In the partitioned risk assessment model, exposure assessment might begin in the human-driven exposure pathways. Thus, when meat leaves the slaughterhouse and is sent for packaging, the processes that alter the abundance of resistant (and susceptible) bacteria on the carcass, during packaging of cuts for retail sale, and during preparation for human consumption are driven largely by human behavioral factors and hygienic controls. In other words, animal behaviors and animal husbandry factors that can increase the shedding of bacteria in food animals are no longer applicable when the processing of the animals and animal food products begins. The animal and husbandry factors influence the releases of bacteria but not the amplification of bacterial populations on the way to the table.

Analysis of the human portion of the exposure pathway is itself a highly complicated process. Analysis of human exposure factors in ARRA closely resemble the analogous processes in MRA. The important factors include the distribution of the hazardous agents in the population for secondary exposure of humans, i.e., the pathways of exposure. For example, cutting board surfaces originally contaminated by bacteria from the food commodity of interest are a source for contamination of other foods. Contamination of prepared food by point-of-preparation or point-of-service activities is generally thought to account for a significant proportion of foodborne illness.

CONSEQUENCE (DOSE-RESPONSE) ASSESSMENT

Once a hazard is identified, dose-response assessments or hazard characterizations are usually performed to characterize the relationship between the dose of a hazardous agent and the risk of adverse health effects. For biological agents, the desired information is a population measure related to the likelihood of infection, e.g., the median infectious dose (ID_{50}). Dose-response relationships obtained in animal or human clinical studies or human epidemiology are fundamental in quantitative risk assessments for estimating the consequences and subsequently the risk to members of the exposed population. In an idealized world, a priori characterization of the dose-response relationship is necessary to complete a quantitative risk assessment. In most circumstances involving resistant pathogens or commensal bacteria, human dose-response relationships cannot be safely or ethically determined. It is often necessary in public health policy to collapse details of dose-response relationships into a single proportionality constant between the dose and observed effect.

In consequence assessment or dose-response assessment for MRA, some useful data are available from human volunteer studies using weakly virulent strains of diarrhea-causing pathogens. The results of these human studies have been used to compare dose-response assessment inferred from epidemiology with experiment data as a reality check. For example, many studies have been conducted with *E. coli* strains having a range of virulence *(52)*. These empirical studies can crudely estimate ID_{50}s for the bacteria in question; however, human volunteer studies and epidemiology have been of limited value in identifying the best analytical models of dose and response. Proposed mathematical models of dose-response assessment include the exponential, beta-Poisson, and Weibull functions (Table 2). Thus far, no single quantitative model can capture ade-

quately all the dose-response features over the diverse species of bacteria and a range of virulence within species.

At this early stage of methods development for ARRA, each combination of antimicrobial drug and bacteria species could benefit from specific and quantitative consequence assessment. However, until enough data are compiled from human or animal studies, risk assessments probably will necessarily default to ecological or case-control epidemiological methods, e.g., ratio methods. For example, the recent risk assessment for fluoroquinolone-resistant *Campylobacter jejuni* from animal applications of fluoroquinolones relied on ecological methods to construct a probability model for risk estimation *(49).*

The particular circumstances created by commensal bacteria raise new uncertainties and difficulties in consequence assessment. For example, by definition, ''commensal'' means that a significant population of bacteria may already be resident in the human intestinal tract or on the skin. These bacteria are normally benign, but when the opportunity for infection presents itself, either susceptible or resistant commensal bacteria can become a major health threat to the individual. Consequence assessment becomes complicated by the possibility that antimicrobial-resistant and susceptible cells of the same strain might differ in virulence, leading to different likelihoods of morbidity or mortality *(47).* Antimicrobial-resistant infection (the consequence) is brought about by treatment with an antimicrobial drug. The need for intervention ''outside'' of the risk pathway to experience this consequence can greatly complicate consequence assessments because the intervention process itself has a variable effect on the selection of resistant bacteria. A robust combination of the dose-consequence relationships for ARRAs is yet to appear in the scientific literature.

RISK ESTIMATION (RISK CHARACTERIZATION)

Risk estimation or characterization is the process by which a qualitative or quantitative estimation of the probability of occurrence and severity of potential or known adverse consequences is made based on the properties of the hazard and information from the release, exposure, and consequence assessments. Risk estimation integrates the other phases of the risk assessment to give a thorough characterization of the risk in question and its attendant uncertainties. Risk estimation or characterization requires broad analytical skills on the part of the risk analysis team to bridge the diverse scientific disciplines involved and to develop decisive conclusions about the quality of the assumptions, data, and models used in the risk assessment.

Emerging areas in risk assessment are likely to have fewer data and models from which the risk can be characterized. Nevertheless, there is often a pressing need for public health agencies to be proactive in protecting the public health. Thus, sometimes the combined expert judgment of scientists from within public health agencies, academia, and the public or industrial stakeholders is the state of the art for a novel hazard. The analytic and deliberative processes used among stakeholders and risk analysts to characterize risks to members of the general public has been promoted as a fundamental part of risk analysis in a democratic society *(36).* In the absence of adequate quantitative information, expert opinion of risk estimates is often believed to be better than no risk estimate at all for emerging health hazards.

High-quality risk estimations or risk characterizations provide detailed discussions of uncertainties in the data, assumptions, and models used throughout the risk assessments. There are numerous instances of both data and model uncertainty in ARRAs. For example, pathways of multiple and overlapping resistance, possible overlapping biochemical means of selecting for a given set of resistance genes, and numerous indirect pathways for exposure and release of resistant organism are often cited as contributing to the uncertainties associated with ARRAs. Additionally, the quantitative nature of the transfer of resistance genes within the animal or human gut is largely unknown. Exposure pathway analyses often reveal large uncertainties, particularly when the focus is on understanding one strain of bacteria from among many competing strains. The problem may be further complicated by strains that are commensal, which may contribute to widespread exposure but have no immediate consequence. For example, if a resistant strain can colonize humans and remain part of the intestinal flora for a protracted period of time, the resistant infection might be distantly separated over time from the original exposure. In this case, risk assessment begins to take on features similar to latent health risks from chemical or radiation carcinogens, in which the exposure event(s) might be greatly removed in time from the eventual consequence.

Given that the final risk characterization or risk estimation process is uncertain and often based on a deliberative process, most public health professionals prefer to make risk estimates that err on the side of conservative estimations of risk as opposed to seeking generalized average risks to larger segments of the population. Ideally, risk assessment provides the basis for a solid risk management program that will encourage the subsequent gathering of new information about exposures, consequences, and the extent of adverse health outcomes. The new information can then be used to reduce the uncertainties in the risk estimates. The reiterative process between risk assessment and risk management is one in which the risk assessment poses the testable hypothesis, and after application of the risk management program, the next risk assessment refines risk estimates and improves the risk characterization models based on the newly acquired knowledge. In a manner analogous to the basic science cycles of hypothesis generation, basic experimentation, and replication that allow formulation of a theory, the risk characterization and risk management cycle eventually allows establishment of a metascientific theory for the health risk of interest.

THE FUTURE OF ARRA

Although there is much emerging knowledge about the basic microbiology of resistance that will eventually contribute significantly to building quantitative ARRAs, the more immediate need is to characterize the adverse human health consequences from antimicrobial resistance in the

food pathway. Steps taken by public health agencies and research groups toward improved data for risk assessments include the development of epidemiological surveillance networks such as the National Antimicrobial Resistance Monitoring System *(6).* Previously, large-scale studies such as the SENTRY and ICARE databases have reported epidemiological findings on the frequencies of various resistance types and resistant strains. Other data are needed to improve uncertainty estimation for resistance reservoirs that may occur in long-term care facilities and for the rates of transfer of resistance from human carriers to sensitive subpopulations. The recent interest of public health agencies in defining the scope of antimicrobial resistance and the impact of risk management strategies on reducing the burden of antimicrobial resistance in the human population has fostered development of surveillance databases and compilations of samples.

When compared with risk assessments for chronic low-dose effects such as those associated with chemical exposure, the observations of human health risks and intermediate stages of exposure in ARRA are made closer to real time, a feature common to acute health risk assessments. This real-time approach is an advantage in terms of both validating risk assessment models and using observations to make iterative adjustments to risk assessment models to account for new practices and new observations. When based on observations from public health surveillance, overly conservative models can be adjusted downward in terms of overall risk estimates. Conversely, well-designed risk management programs offer the possibility for detecting emerging mechanisms of resistance and the movement of resistance genes into new pathways and pathogens early in the process. This early detection is particularly important because antimicrobial resistance is a ''moving target'' and seldom has been reliably forecast. Thus, the compelling need for reliable ARRA models is likely to remain for years to come.

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