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ANIMAL AND HUMAN HEALTH PREVENTION OPPORTUNITIES

Antibiotic Resistance

Antimicrobials (antibiotics, antifungals, antivirals, antimalarials, and anthelmintics) have been instrumental in reducing death and disability from infectious diseases. However, antibiotic resistance is a growing global public health threat. Infections resistant to first and second line antibiotics are becoming more common, which can result in the use of more toxic and often less effective options. Antibiotic resistance is complex with many factors contributing to the issue. In this edition of *Montana One Health*, we will discuss the mechanisms of resistance, contributing causes, and implications.

Mechanisms of Resistance

Antibiotics have different mechanisms of action and not all bacterial species are inherently susceptible to all classes of antibiotics. In addition, all bacteria have the ability to become resistant to the antibiotics created to destroy them. Bacteria have different mechanisms of resistance, intrinsic and acquired.

Intrinsic or natural resistance occurs when bacteria have an innate ability to resist the activity of a particular agent through structural or functional characteristics. Intrinsic resistance mechanisms mean the bacteria were never susceptible to that antibiotic. Mechanisms of intrinsic resistance include inaccessibility of the antibiotic into the bacterial cell, lack of affinity of the antibiotic for the bacterial target, extrusion of the antibiotic by active exporters, and innate production of enzymes that inactivate the antibiotic. Intrinsic resistance mechanisms are important for clinicians to understand so the appropriate antibiotic is selected for the bacterial infection.

Biofilms are another mechanism by which some bacteria can be resistant to antibiotics. A biofilm is an aggregation of bacterial cells firmly attached to a surface surrounded by a slimy protective coating. This coating prevents entry of the antibiotics, reduces concentrations of antibiotics that reach the microorganisms, and reduces oxygen and nutrients for bacteria deep within the biofilm which slows bacterial growth making them less susceptible to the antibiotic.

Acquired resistance occurs when a bacterial population becomes resistant to an antibiotic that they were previously susceptible. Bacteria acquire resistance through mutation of genes involved in normal processes resulting in either vertical gene transfer or horizontal gene transfer. While spontaneous gene mutations for antibiotic resistance are rare, fast growth rate of bacteria can lead to a resistant population in a relatively short timeframe. Once the mutation or resistance gene is present, the genetic material will be passed on directly to all the bacteria's progeny during DNA replication. This process is vertical gene transfer.

Another form of acquired mutation is horizontal gene transfer which occurs when small packets of DNA are transferred between bacteria of the same species or different species. Three mechanisms of horizontal gene transfer can occur, conjugation, transformation, and transduction. Conjugation is the main method of horizontal gene transfer. Conjugation occurs with direct cell-to-cell contact between two bacteria resulting in a small piece of DNA, a plasmid, being transferred. Transformation occurs when bacteria uptake a piece of DNA from the environment, usually from a dead or lysed bacteria. Transduction occurs when bacteria-specific viruses, bacteriophages, transfer DNA between two closely related bacteria. Because bacteria multiply rapidly and many pathways for transferring resistance genes exist, resistance occurs rapidly in evolutionary time.

Causes of Antibiotic Resistance

Just using antibiotics is the biggest factor leading to resistance because any bacteria has the potential to become resistant. Antibiotics will rarely kill all the bacteria so the remaining few have the potential to pass on the resistant genetic material through one of the above described mechanisms. The magnitude and impact of this selective pressure varies, adding to complexity of the issue.

Antibiotic use and misuse in people and animals, often with no professional oversight, is considered the leading cause of antibiotic resistance. Antibiotics are the most commonly prescribed medication in human medicine with up to 50% of all the antibiotics prescribed not needed or not optimally effective as prescribed. In animals, antibiotics are used to prevent, control, and treat disease, and to promote growth in accordance to label instructions and federal regulations specifically the Veterinary Feed Directive. In addition to antibiotic use in human and animals, antibiotic resistance can also be spread person-to-person or from environmental sources such as food and water. Antibiotics can find their way into municipal water supplies from runoff from housing facilities and agricultural practices. Antibiotic-resistant genes are used as markers in genetically modified crops to detect genes of interest and the impact of this process is unknown.

Impacts

Antibiotic resistance is present in every country. In the United States, the Centers for Disease Control and Prevention estimates annually at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die because of these infections. Most of the scientific literature about antibiotic resistance focuses on the human health implications and public health impact. Animal health and welfare is impacted but little research has been done to understand the burden. However, antibiotic resistance has the potential to impact animal health, welfare, and production levels. In addition, economic impacts exist for the individual owner and the economy since food

production is a significant contributor to the world economy. Antibiotic resistance does affect the individual, regardless whether the individual is an animal or a person and economic consequences include increased treatment costs, loss of productivity of animals, and loss to productivity and increased societal costs in people.

Montana Efforts

Formal efforts to address antibiotic resistance in human health care settings is underway. Montana Department of Public Health and Human Services is a member of the Montana Antimicrobial Stewardship Collaborative, which includes representatives from the Montana Hospital Association, Mountain Pacific, and the University of Montana, Skaggs School of Pharmacy. This collaborative is working to effectively implement antimicrobial stewardship programs that meet the Centers for Disease Control and Prevention's "Seven Core Elements of Antibiotic Stewardship" in Montana hospitals. In addition, Montana has an Infectious Disease Physician Network which represents the majority of infectious disease physicians in the state. The network has recently completed a consensus statement for *Clostridium difficile*.

In the next *One Health*, we will discuss how antibiotic resistance is tracked, steps federal agencies are taking to combat resistance in human and veterinary medicine, expand upon Montana's efforts, and address the principles of antibiotic stewardship.

Antibiotic Resistance-Key Points

- Antibiotic resistance is present in every country
- Bacteria become resistant through both intrinsic and acquired mechanisms
- Antibiotic resistance is complex with many contributing factors
- Antibiotic resistance impacts both human and animal health
- Effective antibiotic stewardship requires a One Health collaborative approach

References available on web version. Visit http://www.dphhs.mt.gov/publichealth/publications.shtml.

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