

Antibiotic Resistance: Implications on Genetic Improvement and Disease Resistance.

D. Hurnik, University of Prince Edward Island

What are Antibiotics ?

Antibiotics are compounds that kill bacteria and are generally used to reduce bacterial infections in animals and people. The initial discovery of penicillin started the ‘antibiotic’ age, and revolutionized the practice of medicine. Prior to the use of antibiotics medicine relied on supporting the patient until the body’s immune system either controlled the infection or the patient died. Recently the term antibiotic is being replaced with ‘**antimicrobial**’. The difference is that technically, an antibiotic kills all life, where as an antimicrobial kills microbial life. The rest of the document will use the term, ‘antimicrobial’ as synonymous with the conventional term ‘antibiotic’.

Antimicrobial compounds are mostly isolated from natural compounds found in nature. Their use in the ecosystem is for organisms, (animals, plants, fungi etc.) to fight off bacterial infections. It is a dynamic system where bacteria continually evolve to find new ways to cause infections, and other organisms evolve to fight the bacteria. The mechanism is in many ways identical to the population genetics dynamics we use in livestock improvement.

Why antimicrobial resistance?

Antimicrobial products in the ecosystem exert selection pressure on bacteria to evolve around them. Those bacterial subpopulations that survive treatment or environmental pressure are the ones to become next generation of pathogens. Resistance can be gradual with an incremental tolerance to antimicrobial medications. Overtime the genes associated with resistance become fixed and a more permanent resistance becomes established¹. One key way bacteria differ from mammals, is that they trade genes between species and new resistant strains can evolve quite quickly and resistance can move between species including from animals to man.

Sources of Antimicrobial Selection pressure

Direct Treatment of animals/humans

The treatment of disease by selectively targeting bacteria, directly aids in the evolution of resistant bacteria by allowing the survival of those bacteria that tolerate the antimicrobial given. Practices in human medicine considered to enhance the development of antimicrobial resistance are: not taking the antimicrobials for the full treatment time, the superfluous use of antimicrobial medications for diseases that are viral or non-infectious and lack of hygiene in clinical settings that allow resistant bacteria to infect new patients and spreading infections to the general population.

Practices of concern in veterinary medicine parallel those of human medicine when individual animals are treated both in hospitals and in the home². As well, when treatment of large groups of animals such as in agricultural practice³ there is general concern in the use of low doses of medications (sub therapeutic dosages) for growth promotion and production efficiency.

Cross Species Infection and Contamination.

Bacteria for the most part adapt to specific species and so resistant infections often remain problematic only in those species. Many arguments against the control of antimicrobial use in veterinary medicine rely on this premise. There are, however, pathogens (zoonoses) that reside in animals and can infect people⁴. Enteric bacteria such as salmonella species, e coli, yersinia and skin pathogens such as staphylococcus species can cross infect people and carry with them their resistance patterns⁵. Exchange of antimicrobial resistance genes between bacterial species can further maintain the resistance patterns in the human populations⁶.

Environmental Contamination

There is increasing evidence that antimicrobials used by humans and given to animals continue to remain active in the ecosystem⁷, and exert selection pressure on the microbes that are ubiquitous in the general environment.⁸ Increasingly, data is becoming evident that antimicrobials and associated resistance spread to the ecosystem. An increasingly relevant field of veterinary medicine is ecosystem health.

Emerging Trends and their Impact on Agriculture

There is a restriction of antimicrobial use in some regions. The EU had lead with policies and regulations that restrict the use of antimicrobials for growth promotion and disease prevention (prophylaxis). They have shifted antimicrobial use to more specific therapeutic use. Evidence is accumulating that this has led to a reduction of general antimicrobial resistance in key monitored bacterial species⁹. This policy has however come at considerable financial loss to producers and an increase in clinical disease. Similar policies in North America have not been addressed at a regulatory level but are increasing in private branding and market differentiation activities.

There also appears to be a trend to avoid use of antimicrobials that are important for human use. This has resulted in failure to approve key antimicrobials for animal use, and a lack of will by major pharmaceutical companies to innovate new antimicrobial products for agricultural use.

Response of the Agricultural Community

The following responses have been undertaken in response to society's current antimicrobial phobia.

Health Management

Herd Health policies that reduce the need for antimicrobial use. Two key policies have been found to be effective. Vaccination that raises specific immunity to pathogens has been a growth area for the pharmaceutical industry, and many new products have come onto the market for those purposes. Pathogen eradication has been an effective disease control at the country, region or individual farm level. This has increasingly been a crucial production strategy. Genetic companies and Genetic suppliers who have been able to provide animals free of key diseases have been clear winners of such policies.

Because disease is a dynamic field new trends have emerged that have increased the need and desire for antimicrobials. New diseases continue to emerge and our ability to react with adequate vaccines and control strategies is slower than desired. In swine immunosuppressive diseases such as PRRS virus and Porcine Cirrovirus has caused a significant increase in treatment of secondary infections.

The commodity based economics of livestock production is such that margins are always tight and producers need all technological tools to remain competitive. Antimicrobial use remains a cost effective method to maintain production standards.

Antimicrobial Alternatives

Intensive research is focused on finding alternatives to antimicrobial use in livestock and these involve the use of:

- probiotics for competitive exclusion of pathogens.
- Feed or water acidification,
- increased used of Zinc or Copper feed additives,
- Herbal extracts that have antimicrobial properties
- Immunomodulators that can increase immune response and limit disease

Many of these processes work in a more specific method and we will not likely find one product that will replace the use of antimicrobials. This field will likely remain a marketing opportunity well into the future.

Selection for Disease Resistance

There is increasing effort put into selection of animals for more resistance to disease. There is without question a genetic basis for disease resistance which is both specific to certain pathogens and of a more general nature¹⁰. In the past attempts to select for disease resistant animals has not received as much priority because we have relied on medications to control our animal health problems, and focus has been on selection for more direct economic traits such as fast growth and fertility.

The above noted changes in antimicrobial trends are changing those selection dynamics and research and progress is being made in selection for disease resistance. Selection has been made in two general areas.

Specific Pathogen Resistance

Pathogens often cause disease because of individual genetic factors. For example enteropathogenic e coli will infect pigs that have the F4 pilus antigen receptor. Those pig genotypes that do not carry the gene do not develop post weaning colibacillosis in the same manner as receptor carriers.

New research looking at receptors in macrophages has determined that not only is there variation in animals, but this variation may have some breed differences¹¹. This type of research will significantly impact genetic selection and the research budgets of genetic suppliers.

General Disease Resistance

Methods to evaluate immune response of pigs has been determined and found to be effective in a university setting¹². Pigs with an increased immune response are however at more risk of immune mediated diseases such as non-infections arthritis. The greatest difficulty has been is a method to measure the immune system of swine in a consistent manner on farm¹³, as well involve the use of products that are licensed for use in the food chain.

Methods to create in vitro test such as automated proliferation assays provide some promise¹⁴ and some research has led to identifiable differences between breeds. The challenge will be to generate a simple enough output that can be used for selection purposes.

More sophisticated molecular selection techniques have promise for disease resistance selection¹⁵, and more research is needed put such methods in widespread genetic use¹⁶.

The use of molecular traceability methods to determine parentage and breeding values for animals that do not develop disease in a pathogen challenge is a further tool that will be used once molecular tools for parentage analysis become more affordable and available for general use.

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