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Why are antibiotic residues in farmed shrimp a big deal?

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By Stephen G. Newman Ph.D.

Amount that would have to be consumed limits any direct significant impact

When antibiotics are used properly, i.e. their use is prescribed by a science-based determination of the underlying cause of mortality, they can be very helpful, if not essential, tools. Photo by Darryl Jory.

The accidental discovery of the antibiotic penicillin, by Alexander Fleming in the late 1920s, reshaped human and animal medicine. Initially the focus was on limiting the impact of infectious disease processes in humans. As their usage increased, it was observed that they also could play an important role in the production of animals and they eventually were deemed essential to provide a burgeoning human population with high quality, safe and cheap animal protein.

Observations of the positive benefits of these antimicrobial substances led to their usage at ever- increasing levels for a variety of benefits, not just for the prevention and/or treatment of disease, but for overall animal robustness and growth. The feeding of antibiotics from birth to slaughter became a standard operating practice for many different animals.

The last 50 years has seen global aquaculture production grow rapidly with most reliable estimates putting total output in 2019 at close to or exceeding the levels that are "hunted (fished)," in the range of 100 million metric tons (MT) per year. This transition from a fishery to a farmed product has brought with it many of the challenges that face terrestrial agriculture as well as some that are uniquely aquatic.

A great deal of research has shed substantial light on what Dr. Fleming "stumbled" upon. Many antibiotics are in use today, with the most powerful being synthetic and frequently derived from natural sources. Commercialization is a very expensive proposition, requiring working with multiple government agencies and a large amount of testing. Once a broad-ranging arsenal of antimicrobial substances was established, the incentives to develop others waned. Today, only a small fraction of what has been spent historically to develop antibiotics has been allocated towards the development of new antimicrobial substances. As their use and availability have increased, it became evident that the pathogens that we were trying to keep from killing humans and animals were developing resistance, limiting the usefulness of these very important tools.

Why the concern about their use?

Conservative estimates are that more than 1 million people a year die from infections with antibiotic-resistant pathogens. By the year 2050, this is estimated to significantly grow to more than 10 million people dying annually. These are deaths that would be preventable if the widespread use of antibiotics (not just abuse) was curtailed.

Most countries regulate, to some extent, what and how antibiotics can be used. Enforcement, though, may be lax or nonexistent, allowing indiscriminate use to flourish. The reasons for this are complex. Focusing on shrimp farming, perhaps the single-largest reason for the widespread use of antibiotics is that the traditional and widely used farming practices are not science-based. All too often when farmers have animal health challenges, they have no idea what is actually going on. While a competent authority may isolate and identify potential pathogens, disease is often multifactorial with multiple pathogens and stressors playing a role. Few farmers, if they look at all, look further than a single possible culprit.

"Researchers examine antimicrobial resistance potential in aquaculture (https://www.aquaculturealliance.org/advocate/researchers-examine-antimicrobial-resistance-potential-aquaculture/?__hstc=236403678.1cefc9f3687d8a706bb9fe69e008c3b9.1681001648127.1681001648127.1681001648127.1&__hssc=236403678.1.1681001648127&__hs

Most farmed shrimp is produced by small farmers in what is largely a poverty-driven production system. They may operate one or two small ponds on their property and have a considerable portion of their wealth tied up in the ponds. Poor outcomes, all too common, are disastrous and many resort to the use of readily available antibiotics, whether legal or not, in an effort to avoid serious financial repercussions. The farmer, often in desperation, uses every tool at his disposal to try and salvage his profits when animals are dying.

When antibiotics are used properly, i.e. their use is prescribed by a science-based determination of the underlying cause of mortality, they can be very helpful, if not essential, tools. Unfortunately, this information is simply not available to most shrimp farmers and they gamble that they will see a benefit and that there will be no easy way that their use of an antibiotic can be determined. It is ironic that physicians also play a role in the overuse of antibiotics by prescribing them in the absence of proof that they are indicated. There are many that think that this is actually the predominant reason for the development of resistance.

In Southeast Asia (where most of the worlds farmed shrimp is produced), a common practice is to pool the harvests from a number of small farmers into a single lot. This ensures that traceability is not always complete and indeed it is often lost. So, a farmer may use a specific antibiotic that his local feed mill, processing plant, animal health consultant or other source recommends – far too often with no regard for the proper usage – and gamble that its presence will not be discovered. Poverty-driven production paradigms are highly susceptible to this abuse. Farmers who would go bankrupt from single crop failures make choices that are understandable, even if irresponsible and in the long run, foolish.

There are two primary issues regarding the use of antibiotics that are of concern. The most important is the development of antimicrobial resistance or AMR. This resistance results in antibiotics not working, and farmers end up using antibiotics that are essential for controlling human disease outbreaks that should not be used elsewhere. The second issue is that of residues. The issue with residues is not one of danger to the health of the consumer. The presence of residues is an indicator that a given antibiotic has been used.

The abuse of antibiotics is widespread: deliberate use of antibiotics that are banned in the country that the final farmed product is destined for; use of excessively high dosages because of "resistance"; generally irresponsible use of poorly formulated products; companies selling products that contain antibiotics that are included to provide the perception of a benefit from the use of products that are not effective as claimed, etc. The end result is that when the shrimp are harvested, there can be detectable residues from the use of these antibiotics in the consumer-ready product.

These can range from the raw, nonmetabolized antibiotics themselves to metabolic byproducts that the consuming animals produce as they degrade and break down the antibiotics. This can and has resulted in crops from an entire country being banned or facing higher levels of regulatory scrutiny that ultimate impact profitability. India currently has a huge problem with this, and knowledgeable sources are saying that the Chinese have begun to ban imports of farmed shrimp from India because of consistently high levels of antibiotic residues (personal communication-Yudee Sim, Speedy Assay, Malaysia). This is not a problem that will resolve itself without major changes to the manner in which shrimp are farmed.

More about AMR

The role of antibiotics in human medicine is critical, with millions of lives being saved every year. The development of new antibiotics is very expensive and time-consuming. Proof of safety and efficacy, metabolic half-lives, the range of usefulness, etc. are among the elements needed to be able to market and sell them. Unfortunately, the development of resistance to these compounds is inevitable.

Today we know that a vast number of antimicrobial substances are produced naturally by bacteria and fungi where they are essential for survival. These compounds are an important tool by which microorganisms ensure access to the nutrients needed for growth. They are chemically diverse and ubiquitous. Microbes live in vast complex assemblages, termed microbiomes, with the composition evolving as the environment around them changes. Antibiotics are a very important element of the evolutionary pressures that drive this change. Only a very small number of these have been exploited commercially.

The use of antibiotics in aquaculture is, as their use is in general, an evolutionary pressure. Abuse can rapidly increase the impact of these pressures, resulting in some microbes becoming refractory (requiring much higher doses for efficacy) or resistant (no dose will kill the target pathogens) to given antibiotics at rates that are problematic. This is typically a result of the presence of a small proportion of the target population for the AMS being present from the onset that contains the genes for resistance. This is why proper use is critical. Specific targeted pathogen loads must be reduced so that the animal's immune system can clean up what is left.

Improper use of antibiotics often fails to do this, and animals can end up being infected with strains that are resistant to most, if not all, commercially available antibiotics.

This resistance can be linked to resistance to other antibiotics. The means by which much of this resistance occurs is through the transfer of small circular loops of DNA, known as plasmids, that readily fuse with each other to create multiple antibiotic-resistant strains. Improper use (much higher doses, shorter application times, stopping the use when the symptoms abate, etc.) can lead to this. Resistance happens even with responsible use, though evidently at a lower frequency. Alternating the use of different classes of antibiotics and monitoring for resistance patterns is important to protect against this. Unfortunately, most shrimp farmers do not do this and the labs that might help them are often the same ones selling them the antibiotics in the first place.

More about residues

From a toxicity standpoint for consumers, while for a few antibiotics there are concerns, including anaphylaxis (severe, potentially life-threatening allergic reaction), the levels of residues found are rarely if ever an issue. The amount of shrimp (or fish) that would have to be consumed to get even close to what might be a therapeutic dose likely limits any direct significant impact that one can expect on the consumer and their microbiome. If an allowable residue limit is 1 ppm, this is equivalent to 1 gram in a metric ton. A thousand times less than this, a ppb, is equivalent to 1 mg in a MT. So, for a compound that has an allowable residue limit of a single part per billion, to get the equivalent of a therapeutic dose (orally), say a gram, one would have to ingest 1,000 MT of shrimp. Clearly this reduces the risk to as close to zero as one can get from having an adverse reaction to the presence of a residue.

It is estimated that U.S. consumers will eat around 150 billion pounds of beef and poultry in 2019. Only recently has the FDA banned the use of a broad range of antibiotics in agriculture that are deemed essential for use in treating human diseases. Even though the legal use of many of these has been restricted to treating diseases and not for use as growth promoters, this is difficult to enforce, as veterinarians have a great deal of discretionary power and can prescribe for prophylaxis (prevention of disease). This ban, however, has not stopped the illicit use of many antibiotics, and residues are common.

Residues are typically allowed at levels based on scientific observations of how compounds are metabolized. They are intended to serve as guidelines for dosages and withdrawal times. Testing every animal is, of course, not possible. Instead, typically at slaughter, random samples are taken to be tested for a wide range of antibiotics and some of the almost 400 chemicals that may find their way into our food chain (primarily pesticides). The number of samples taken is determined by the risk. The risks are determined based largely on the history of the source of the animals. So someone who has violated the law historically will be watched closer than someone who has never done so (or, more accurately, has never been caught).

> ***Farmers who would go bankrupt from single crop failures make choices that are understandable, even if irresponsible and in the long run, foolish.***

It is interesting to note that there are many instances in which meat produced in the United States would not be allowed into some other countries. It is clear that there is a need for a consistent standard to be adopted that takes all of the various elements into consideration to avoid double standards. Many countries, however, have no issues with the same antibiotics being used on humans as on animals. It is a fact that in many of the major shrimp farming countries, antibiotics are freely available without prescription, and veterinary supply houses may warehouse many tons of antibiotics in anticipation of what their customers want to use. This is an irresponsible yet widespread practice.

To sell into a given market, certain tests must be conducted to ensure that there are no indications that a specific antibiotic or group of antibiotics has been used in the current production cycle. These tests are invariably limited by the very nature of how these antibiotics or their metabolic byproducts must be tested for. Testing is done using a statistical approach that is limited and realistically not adequate for the task of finding evidence of improper use at low prevalence levels. As a result, many animals that contain residues still enter the food chain.

The antibiotics that are of the greatest focus are usually synthetic analogs of natural compounds, as these are widely used in treating human disease. Factors such as the species being tested, the tissue being tested, the rearing conditions that the animal faced (temperature, salinity and other parameters), the genetics of the strains, the purity of the antibiotic, its source and the conditions under which it has been stored, the presence of non-target animals in the population, etc. all play roles in the presence of residues at harvest. Residues are currently the primary manner in which the illegal use of AMS is detected.

The common argument is that we should exclude as much as we can from the production environment what is not needed and/or is detrimental. The risks and benefits of this must be considered. Blanket bans on the use of any antibiotic make little sense, given that responsible use of antibiotics where a science-based determination of the underlying cause of a problem can mitigate a great deal of financial damage. In fact, while some may perceive that shrimp farmers are unfairly targeted, they are not. Shrimp are not tested for many compounds that would not be legal if present in U.S.-produced meat.

An additional irony in this whole matter is the presence of, among other things, harmful algal blooms or HABs in shrimp ponds. Shrimp are typically (successfully) farmed in moderately enriched bodies of water where there are complex microbiomes present that lend themselves to optimal production. There are vast numbers of metabolic byproducts excreted by the huge numbers of bacteria, algae, yeast, etc. that are actually the largest biomass present in the ponds.

While we do know what some of these are, this is not even a fraction of a percent of what is present. HABs produce a variety of toxins that can kill fish/shrimp quickly and sicken, or even kill, humans as well. Only a very small number of the total present have been characterized. These are not routinely tested for, despite the fact that it is highly probably that some of them, such as the serine analog BMAA, a potential culprit in certain neurodegenerative diseases, is highly likely to be present in ponds with high levels of cyanophytes (blue-green algae).

It appears certain that, as the planet warms as a result of human induced environmental feedback inhibition (widely referred to as climate change), that the levels and types of toxins will increase. There are many things in all of what we eat that are not known. Ultimately the presence of these toxins is potentially much more harmful to the consumer than levels of antibiotic residues that require the consumption of impossibly huge amounts of shrimp in order to get even enough to be remotely problematic.

The use of antibiotics in farmed shrimp and fish is impacted by where the animals are being exported to and who the consumers are. Not everybody has the same concerns. Antibiotics can remain in an animal for its life cycle, as can metabolites that are not excreted. Each chemical compound has a metabolic pathway for degradation. Some of the many questions that have to be addressed are:

- How they are broken down?
- What they are broken down into?
- How many steps until they are excreted?
- Are they excreted, and if so, how?
- If they are not excreted either partially or in total, then, where are they? And in what form?
- How does the environment impact this?

Analytical testing of "random" samples is how the use of these compounds is policed. What the samples are tested for varies depending on what organizations they might have audit them, what country they are in and where the product is destined to be consumed in. This sampling is not, in reality, adequate to ensure high levels of compliance. This is partly a result of how samples are collected for testing. Testing samples from individual farms before pooling and working closer with all levels of the supply chain would be more effective in ensuring that residue containing product does not find its way into the marketplace.

Ultimately, much tighter regulatory oversight, stiffer penalties for violations in conjunction with better traceability will have to become the norm. The industry needs to quit empowering a system that cannot possibly adequately ensure consumers that they are not consuming adulterated foods.

Perspectives

The use of antibiotics in shrimp farming is constrained because it can be and should be. Resistance to antibiotics poses a threat to all of us. Regulators can and do enact legislation that adopts a zero-residue tolerance level. Enforcing these laws, though, is not straightforward and it is highly unlikely that this is going to change any time in the near future. A balance must be found between what is realistic and what is ideal.

Ideally, antibiotics should only be used on the basis of science-based determinations of the underlying cause of disease. This holds true for the physician in the United States who prescribes antibiotics to help their patients think that something is being done to make them feel better, as well as for the shrimp farmer in Southeast Asia whose financial well-being depends on his small crops. Making physicians accountable will be easier than making shrimp farmers accountable, although neither will address the fact that resistance is more or less inevitable and that there is scant financial incentive to develop new antibiotics.

The reality is that the proper and appropriate use of antibiotics across the spectrum is not a realistic goal. The double standard regarding the safety of food containing residues will persist until there is a universal, binding agreement by all parties to focus on residues of any number of compounds, not just antibiotics, and to develop methods that can detect most (if not more than currently) of the violators.

References available from the author.

Author

STEPHEN G. NEWMAN PH.D.

President and CEO
Aquaintech Inc.
Lynnwood WA, USA
www.probioticsaquaculture.com

sgnewm@aqua-in-tech.com (mailto:sgnewm@aqua-in-tech.com)