Drivers of Antimicrobial Resistance in Bacteria Associated with Aquatic Animals

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Chair OIE ad hoc Committee on Responsible Use of Antimicrobial Agents in Aquaculture
Why should we be concerned about antibiotic resistance?

Resistance in bacteria associated with diseases of aquatic animals.

Resistance in bacteria present on food derived from aquatic animals.

Contribution of aquaculture to the gene pool of antibiotic resistance determinants in the environmental microflora.
Resistance in bacteria associated with diseases of aquatic animals

Reduction of *therapeutic options* for disease control in aquatic animals - we have only very few antibiotics for aquatic animals

Globally aquaculture is a major supplier of dietary protein - loss of *economic viability* of food production.

There is strong evidence that this is a very real risk.
Resistance in bacteria present on food derived from aquatic animals

Resistance in bacteria that can infect humans, require antibiotic therapy when infecting humans.

Small number of zoonotic bacteria found in aquatic animals.

- The most common zoonotic bacteria (*V. parahaemolyticus*) do not cause infections in humans that respond to antibiotic therapy.

- Zoonotic bacteria present at point-of-sale may derive from post-harvest processing.

Risk very much less significant than for terrestrial animals
Environmental gene pool of antibiotic resistance determinants

Risk for humans associated with elevated frequencies of resistance determinants in the environmental microflora.

Investigations complicated by the fact that ALL uses of antibiotics (human, veterinary and aquatic) contribute to this gene pool.

Factors influencing the persistence and maintenance of determinants in environmental gene pool little understood.
Fundamental Observation

Antibiotics have a role in the natural ecology of bacteria.

Antibiotic resistance is a natural property of bacterial populations even in those environments that have not been impacted by human use.

The presence of antibiotic resistant bacteria cannot be taken as evidence of the use of antibiotics.
Fundamental Rule

The presence of sufficient concentrations of antimicrobial agents in any environment exerts a selective pressure for the emergence of an increased frequency of bacteria resistant to that agent.
The primary driver of increased frequencies of antimicrobial resistance is the use of antibiotics by humans
Antibiotic resistance and aquaculture

If the basic driver of antimicrobial agent resistance is antimicrobial agent use can we

Reduce our use
Eliminate inappropriate use
Make our use more effective
What do we mean by Resistance?

Clinical resistance

Phenotypic resistance

Genetic resistance
Clinical resistance

“A bacterium can be considered as clinically resistant if, as a result of its reduced susceptibility to an agent, it can continue to contribute to the morbidity and mortality in a population during and after the administration of a course of therapy with that agent to that population.”

Difficult to establish in aquaculture
Varies with treatment, environment and host

Sensitive/Intermediate/Resistant (S/I/R)
Phenotypic resistance

Less susceptible than other members of its species in *in-vitro* laboratory tests

**Easy** to determine and does not **vary** but

No necessary clinical relevance

Wild-type (WT)/ Non wild-type (NWT)
Genetic resistance

Possession of a gene sequence known to encode reduced susceptibility to an agent.

Useful for detailed studies of resistance determinant epidemiology
How do we use antibiotics?

Why do we use antibiotics?

How can we reduce our use?

How can we improve our use?
How do we use antibiotics

Classification of antibiotic administrations

**Therapeutic**
Administration to an individual or group of individuals that are experiencing an infection.

**Prophylactic**
Administration to an uninfected individual or group of individuals to prevent them being infected.

**Growth promotion**
Administration of sub-therapeutic doses to an uninfected population with the aim to facilitate faster growth.
In-feed metaphylactic administration

The administration of antibiotic medicated feed to a population containing some infected individuals.

Normally initiated after mortalities start to rise and/or after the presence of a specific disease-associated bacterium has been confirmed.

Treatments that are metaphylactic at a population level may be therapeutic or prophylactic at an individual level.
Very few antibiotics are used or are licensed for use in European aquaculture.

- **Oxytetracycline** (poor bioavailability)
- **Florfenicol**
- **Early generation quinolones** (oxolinic acid, flumequine)
- **Potentiated sulfonamides** (poor palatability)
- **Amoxicillin** (poor efficacy)
Why do we use antibiotics?

The aim of aquaculture is not to rear fish **BUT** to **make money** from rearing fish

Antibiotic use in aquaculture is a technique of protecting **profits** not protecting **fish**
Why do we use antibiotics?

For a farmer the use of antibiotics in aquaculture is to attempt to reduce economic losses that may result from infectious disease epizootics that may occur.

The decision to treat is always a gamble.
Making a better bet

It is easy
For a farmer to know that his/her fish are dying.

It is less easy
To predict the economic impact of the epizootic.
To know why they are dying - this requires the diagnostic skills of a trained HCP.
To know how to minimise the losses and how effective any treatment might be.
Factors that influence the decision to treat

Beliefs

Role of bacteria in disease
The power of antibiotics

Availability of

Diagnostic advice
Susceptibility test data
Simplistic Belief

Bacteria CAUSE disease

Antibiotics KILL bacteria

Therefore

Antibiotics CURE disease
Causality

*Aeromonas salmonicida* is *always* present in fish suffering furunculosis

Not all fish from which *Aeromonas salmonicida* can be isolated are suffering from furunculosis

The presence of *Aeromonas salmonicida* results in disease *only* in specific environmental conditions.
General principle

Healthy animals don’t get sick

In nearly all infectious disease outbreaks environmental stressors play a role

The importance of the infecting bacterium may vary from major and very significant to minor and largely irrelevant
Etiology and Therapy

IF

The bacterium is a major causal factor - antibiotic therapy may be a cost-effective and prudent response.

BUT

If the environmental factors are not addressed - the effect on mortalities will only be short term.

IF

The bacterium is an opportunistic invader of very stressed animals antibiotic therapy is unlikely to be a cost-effective or prudent response.
Industry-wide epizootics

* Aeromonas salmonicida* in Scotland and Norway
* Piscirickettsia salmonis* in Chile

Massive quantities of antibiotics did not stop the epizootics.

Attempts to deal with industry-wide epizootics by the administration of antibiotics were ineffective and economically and environmentally unsustainable.
Tuberculosis deaths in UK

![Graph showing the decline of tuberculosis deaths in the UK from 1850 to 1950, with a significant decline post-1950 due to the introduction of streptomycin and BCG vaccinations.](image-url)
TAKE HOME MESSAGE 1

Failure to fully appreciate the role of environmental stressors in disease and
Exaggeration of the importance of the isolation of bacteria and
Excessive belief in the power of antibiotics

Lead to the imprudent and ineffective use of antibiotics

These beliefs drive antibiotic resistance.
Diagnosis

The etiology of diseases associated with infectious agents is always multifactorial.

Morbidity or mortality emerges from the complex interaction between an infectious agent, a host, their environment and their history.

Diagnosis is not simply the identification of an infectious agent.

It is an attempt to provide an adequate description of the factors contributing to the etiology of a disease event.
Consequences

Diagnosis from a distance will tend to exaggerate the importance of the bacterial component of the etiology.

Use of high-tech molecular proxy methods for bacterial identification will tend to exaggerate the importance of diagnosis from a distance.

This effect will tend to lead to inappropriate, imprudent, ineffective and excessive use of antibiotics.
Structural relationship with health care professionals (HCP)
Prevention is better than cure

How is the HCP integrated into the production, management and husbandry processes?

If the HCP is involved from THE BEGINNING of the production cycle they can input to many factors that may reduce disease-associated losses.

If the HCP is consulted ONLY AFTER mortalities start to rise all they can do is to recommend treatment – antibiotics.
TAKE HOME MESSAGE 2

Lack of on-site diagnostic investigations and Failure to build disease control measures into production planning lead to the imprudent and ineffective use of antibiotics. These practices drive antibiotic resistance.
Effective therapy

Antibiotic therapy can only be effective in reducing losses if

Bacterial infection plays a major role in those losses and

Sufficient concentration of antibiotic can be delivered to the right place in the right fish to inhibit (or kill) the infecting bacterium

Efficiency of the administration
Susceptibility of the bacterium
Efficiency of in-feed administrations
(pharmacokinetics PK)

Dose and duration

Effect of environment factors (temperature, salinity)

Effect of infected hosts (species-dependent PK)

Limited empirical evidence

Clinical outcomes

Minimising resistance selection
Marketing authorizations

Establish that

a specified dose regimen delivered using a specified antibiotic-containing product

will control losses resulting from

a specified bacterial infection of a specified species

under specified environmental conditions
Problems with MA

MAs are specific
but disease conditions encountered in aquaculture are diverse

MA are expensive and time-consuming to produce

We have too few MAs
Bacterial susceptibility (pharmacodynamics PD)

Antibiotic treatment of an infection with a bacterium can have **no value**

If

The bacterium is resistant

But

It will still exert a selective pressure for the emergence of increased frequencies of resistance
Susceptibility testing

Two part process

**Generation** of *in-vitro* susceptibility measures

Standardised and internationally harmonised test protocols are essential

**Interpretation** of *in-vitro* susceptibility measures

Application of clinical breakpoints or epidemiological...
Number of laboratories using particular cut-off values for *Aeromonas salmonicida*

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Monitoring and surveillance of antimicrobial agent resistance in microorganisms associated with farmed aquatic animals

Smith, P., Alday-Sanz, V., Matysczak, J., Moulin, G., Lavilla-Pitogo, C.R., Prater, D.

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Conclusion

Many laboratories are providing inadequate and misleading susceptibility data.

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Rapid response

Susceptibility tests should be performed for all therapies.

Therapy is most efficient if started early in epizootic.

Susceptibility testing takes time.

Antibiotic chosen before susceptibility test results available.

Susceptibility data is used to confirm or alter choice of agent.
Lack of optimised dose regimen and Lack of adequate and relevant susceptibility data Lead to the imprudent and ineffective use of antibiotics These inadequacies drive antibiotic resistance
Many improvements in education, practices and provision of technical services can be made that will reduce the rate of increases in the frequencies of antibiotic resistance.

A first step in promoting those changes is implementation of programmes that monitor and survey antibiotic use and antibiotic resistance.