Risk assessment of antimicrobial resistance

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Methodological aspects for AMR Risk Assessment

**General** principles for Risk Assessments apply
Hazard Identification

What exactly is the hazard with AMR?

- The drug, i.e. residues of the drug?
- The bacterial species?
- The resistance determinant, i.e. the resistance gene?
- The DNA carrying the resistance gene (Plasmid, Integron etc.)?
Hazard Identification

Aim: to describe the foodborne AMR hazard of concern

Specific strains or genotypes of foodborne microorganisms that may pose risks by a particular combination of

- food commodity,
- AMR microorganism and / or determinants and
- antimicrobial agents which are affected by resistance.
Information on the biology of AMR microorganisms / determinants within different environments / niches e.g.

- interactions with other bacteria
  - in animal feeds,
  - aquaculture or
  - the gut environment
  - in food matrices

Information on susceptible strains of the same organisms or related AMR microorganisms and / or determinants are useful.
Hazard Identification (Annex 2)

1.1 Identification of **hazard of concern**: foodborne AMR microorganisms and / or determinants

1.2 **Microorganisms** and **resistance** related information

- Potential human pathogens (phenotypic and genotypic characterization) that are likely to acquire resistance in non-human hosts
- Commensals with AMR determinants (phenotypic and genotypic characterization) and the ability to transfer them to human pathogens
- Mechanisms of AMR, location of AMR determinants, frequency of transfer and prevalence among human and non-human microflora
- Co- and cross-resistance and importance of other antimicrobial agents whose efficacy is likely to be compromised
- Pathogenicity, virulence and their linkage to resistance
1.3 The **antimicrobial agent** and its properties

- **Description** of the antimicrobial agent – name, formulation, etc.
- **Class** of antimicrobial agent
- **Mode of action** and spectrum of activity
- **Pharmacokinetics** of the antimicrobial agent
- Existing or potential human and non-human uses of the antimicrobial agents and related drugs
Hazard characterisation

Which adverse health effects could be relevant?

Qualitative description
Semi-quantitative model
Quantitative model

translating exposure to AMRM into the probability of infection / subsequent disease

Disease related to pathogens

Increased frequency of infection / disease
Increased treatment failures and loss of treatment options
Increased severity of infection / disease

Estimation of diseases and infections (= adverse health effects) related to AMRM

Risk Assessment
1. Hazard identification
2. Hazard characterisation
3. Exposure assessment
4. Risk characterisation

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Hazard Characterisation (Annex 2)

3.1 **Human** host and **adverse health effects**

- Host factors and susceptible **population**
- **Nature** of the infection, disease
- **Diagnostic** aspects
- **Epidemiological** pattern (outbreak or sporadic)
- Antimicrobial **therapy** and hospitalization
- **Importance** of the antimicrobial agents
- Increased **frequency** of infections and **treatment failures**
- Increased **severity** of infections (duration↑, frequency↑, hospitalization↑, mortality↓)
- **Persistence** of hazards in humans

3.2 **Food** matrix related factors **influencing survival** of microorganism in the gut

3.3 **Dose-response relationship** between exposure and probability of outcome

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Hazard Characterization

Various disease outcomes associated with the factor are identified.
Two approaches used to estimate the disease burden:

- **Exposure based approach**
  - Assessment of the exposure of the study population to the risk factor is made.
  - Dose-response relationship for the given hazard is defined.
  - Exposure and dose-response are combined to produce estimates of outcome.

- **Outcome-based approach**
  - Disease outcome data are obtained.
  - The fraction attributable to the risk factor of interest is estimated.

Exposure assessment

The fundamental activities in exposure assessment:

(a) clear depiction or drawing of the exposure pathway

(b) detailing the necessary data requirements

(c) summarising the data.

Adapted from: Codex Alimentarius, CAC/GL 77-2011

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Exposure Assessment

Antimicrobial resistant microorganism (AMRM) / Antimicrobial resistance determinant (AMRD)

Three major players

| Selection of resistant bacteria in primary production/pre-harvest | Transmission of bacteria to meat during slaughter and processing | Handling and preparation of food in public or household environment |

Risk Assessment

1. Hazard identification
2. Hazard characterisation
3. Exposure assessment
4. Risk characterisation
Sources of information: Antimicrobials sold in the EU 2015 (EMA 2017)

Sales of antimicrobial agents by antimicrobial class as percentage of the total sales for food-producing species, in mg/PCU, aggregated by 30 European countries, for 2015.
But: where, when and for how long were these drugs used?

- Sales data reflect overall use but have limited analytical value
- Exposure of animals needs to be measured on a species or production type level

Number of treatments highly depend on production level/stage

- **Amount** of substance alone is a poor measure.
Risk Characterization

Risk characterization considers the key findings from

- hazard identification,
- hazard characterization
- exposure assessment

to estimate the risk.

The **form** and the **outputs** will **vary** from assessment to assessment as a function of the risk management **request**!
Qualitative risk assessment - example

<table>
<thead>
<tr>
<th>Hazard characterisation</th>
<th>Exposure assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negligible</td>
</tr>
<tr>
<td>Negligible</td>
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<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Severe</td>
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</tbody>
</table>
Quantitative risk assessment in AMR - challenges

- Bacterial concentrations are not constant over time
- Bacterial growth is determined by many factors
- Bacteria interact (horizontal gene transfer, competition) with varying intensity
- Resistance determinants can be carried by different bacterial species
- Knowledge of processes on presence and concentration of bacteria is still limited

More information can be found here: McEwen SA
Quantitative human health risk assessments of antimicrobial use in animals and selection of resistance: a review of publicly available reports.
Rev Sci Tech 2012 Apr;31(1):261-76
Summary

AMR risk assessment follows **general** risk assessment **principles**

**Codex alimentarius guideline** can and should be used

**Major challenges**

- **Complexity** of biology
  - Horizontal gene transfer within/between species
  - Cross and co-resistance
  - Bacterial growth

- AMR is related to **human** and **veterinary medicine**
  - Veterinary / food chain share needs to be determined

- Complex **exposure patterns**
  - Environment / Contact to animals / Contact to humans / Food

- **Shortage** on quantitative **data**
Thank you for your attention

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