Risk analysis of foodborne antimicrobial resistance (AMR)

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Introduction

• Antimicrobial resistance (AMR) is major global public health concern & food safety issue

• Risk Analysis :-
  • assess risk to human health from foodborne AMR microorganisms or determinants
  • determine risk management options (RMOs) to control risk
Framework for foodborne AMR risk analysis

- Preliminary risk management activities
- “Risk assessment”
- “Risk management (options)”
- “Risk communication”
- Surveillance use of antimicrobial agents & AMR
Framework for foodborne AMR risk analysis

Figure 1. Framework for Foodborne AMR Risk Analysis

- Identification of an AMR food safety issue
- Development of a risk profile
- Ranking of the food safety issues for risk assessment/risk management priority
- Establishment of preliminary risk management goals
- Establishment of a risk assessment policy and commissioning of a risk assessment
- Hazard identification
- Exposure assessment
- Hazard characterization
- Risk characterization
- Consideration of the risk assessment results
- Implementation of risk management decisions
- Monitoring and review of risk management measures
- No action

Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR-risk analysis.

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Preliminary risk management activities

Figure 1. Framework for Foodborne AMR Risk Analysis

Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR-risk analysis.

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Preliminary risk management activities

- Immediate (and/or provisional) decision
- Development of a risk profile
- Ranking of the food safety issues for risk assessment/risk management priority
- Establishment of preliminary risk management goals
- Establishment of a risk assessment policy and commissioning of a risk assessment

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Preliminary risk management activities

- Responsibility of “Risk manager”
- Scope & magnitude of “AMR food safety issue”
- Commence activities to control identified risk
Preliminary risk management activities

1. Identify “AMR food safety issue”
   • combination of “Hazard” vs. “Food commodity”

2. Develop a foodborne AMR risk profile
   • current knowledge of AMR food safety issue

3. Rank the food safety issues

4. Prioritise risk assessment and management
Preliminary risk management activities

5. Establish preliminary risk management goal
   • decide goal to have :-
     • Risk assessment ?
     • Immediate action ? or No action ?

6. Establish a risk assessment policy
   • communicate with risk assessor & stakeholders

7. Commission a foodborne AMR risk assessment
   • Risk question?, Quantitative vs. Qualitative
   • transparent, timeline, scientific
Foodborne AMR risk assessment

Figure 1. Framework for Foodborne AMR Risk Analysis

Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR-risk analysis.

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Foodborne AMR risk assessment
Foodborne AMR risk assessment

- consider risk profile and risk assessment policy
- step of foodborne AMR risk assessment
  1. Hazard identification
  2. Exposure assessment
  3. Hazard characterization
  4. Risk characterization
Foodborne AMR risk assessment

1. Hazard Identification

Hazard Characterization

Exposure Assessment

4. Risk Characterization

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- Type of risk assessment
  - quantitative vs. qualitative
  - depending upon purpose of RA & risk question
  - quantitative should be used to the greatest extent possible without discounting the utility of available qualitative information

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Foodborne AMR risk assessment

1. Hazard Identification
   - Hazard Characterization
   - Exposure Assessment

4. Risk Characterization
Foodborne AMR risk assessment

Hazard identification

• Describe the foodborne AMR hazard
• Review literature & information of AMR food safety issue (hazard + commodity)
• Biology of AMR microorganisms & determinants
Foodborne AMR risk assessment

1. Hazard Identification

Hazard Characterization  Exposure Assessment

4. Risk Characterization
Foodborne AMR risk assessment

Exposure assessment

Objective

• An estimate of the magnitude of exposure to AMRM/AMRD
Foodborne AMR risk assessment

Exposure assessment

Figure 2a. Considerations for Exposure Assessment in a Foodborne AMR Risk Assessment – the Exposure Pathway
Foodborne AMR risk assessment

Exposure assessment

1. Pre-harvest step
   • input: Selecting & Disseminating AMRM/AMRD
   • output: Prevalence & Concentration of AMRM/AMRD at slaughter/harvest
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Exposure pathway

Prevalence  P  P  P  P

Concentration  C  C  C  C

Step 1

Step 2

Step 3

Retail

Consumption Prob. & Dose

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Exposure pathway

Parent stock

Broiler

Slaughter house

Retail

Consumption

Prob. & Dose

Prevalence

Concentration

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Exposure pathway

- Dynamic of concentration of organisms
  - Growth
  - Inactivation
- Steps in food supplied chain are connected to each other as output and input
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Exposure pathway

- Output of Preceding step is input of Current step
- Output of Current step is input of Subsequent step
- So on and so forth “From farm to fork”
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Exposure pathway

Steps in food supplied chain

Preceding → Current → Subsequent

Current_1 → Current_2 → Current_3
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Exposure pathway

Steps in food supplied chain

\[ \mu_i = f_i \left( \mu_{i-1}, y_{ij} \right) \]

No. of steps : \( i = 1 - m \)

No. of variables in each step : \( j = 1 - n \)
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Exposure pathway

Steps in food supplied chain

\[
\mu_0 \xrightarrow{f_1(\mu_0, y_{1,1}, y_{1,2}, \ldots, y_{1,n})} \mu_1 \xrightarrow{f_2(\mu_1, y_{2,1}, y_{2,2}, \ldots, y_{2,n})} \mu_2 \xrightarrow{f_m(\mu_1, y_{2,1}, y_{2,2}, \ldots, y_{2,n})} \mu_m
\]

\[
\mu_1 = f_1(\mu_0, y_{1,1}, y_{1,2}, \ldots, y_{1,n})
\]

\[
\mu_2 = f_2(\mu_1, y_{2,1}, y_{2,2}, \ldots, y_{2,n})
\]

\[
\vdots
\]

\[
\mu_m = f_m(\mu_1, y_{2,1}, y_{2,2}, \ldots, y_{2,n})
\]

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Exposure pathway

Steps in food supplied chain

Step 1 : Growth

\[ \mu_1 = f_1(\mu_0, y_{1,1}, y_{1,2}, \ldots, y_{1,n}) \quad L(t) = A + C \cdot e^{-e^{-B(t-M)}} \]

\( \mu_1 : L(t) \)

\( f_1 : A + C \cdot e^{-B(t-M)} \)

\( \mu_0 : A \)

\( y_{1,1} : B, \quad y_{1,2} : C, \quad y_{1,3} : M \)
Foodborne AMR risk assessment

Exposure pathway

Steps in food supplied chain

Step 2 : Inactivation

\[ \mu_2 = f_2(\mu_1, y_{2,1}, y_{2,2}, \ldots, y_{2,n}) \]

\[ \log N_t = \log N_0 - \frac{t}{D_T} \]

- \[ \mu_2 : \log N_t \]
- \[ f_2 : \log N_0 - \frac{t}{D_T} \]
- \[ \mu_1 : L(t) = \log N_0 \]
- \[ y_{2,1} : t, \quad y_{2,2} : D_T \]
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Exposure assessment

2. Post-harvest step

• input: Commodity processing, Consumer, Consumption, Microbial factor

• output: Likelihood & Level of AMRM/AMRD in food at the point of consumption

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Exposure assessment

2. Post-harvest step

2.1 Likelihood of AMRM/AMRD in food ($P_E$)

• Prevalence of AMRM/AMRD

• Concentration of AMRM/AMRD

• Consumption of food
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Exposure assessment

2. Post-harvest step

2.2 Level (dose) of AMRM/AMRD in food

- Concentration of AMRM/AMRD
- Consumption of food
- Dose = Concentration x Consumption
- colony-forming unit (cfu) = cfu/g x g
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Exposure assessment

How to get these data

• Published sources

• Experiment

• Predictive microbiology
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Exposure assessment

Quality of Data

- Lack of knowledge brings about estimation
- Total uncertainty
  - Uncertainty (inadequate sample size)
  - Variability (natural phenomena)
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Exposure assessment

Probability distribution
  • Point estimate
  • Interval estimate

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Exposure assessment

2.1 Likelihood of exposure \( (P_E) \)

\[
P_E = P \left(1 - e^{-m \times 10^C} \right) = 0.3987
\]

\( P_E \) = Probability (Likelihood) of Exposure

\( P \) = Prevalence of AMRM/AMRD (%)

\( C \) = Concentration of AMRM/AMRD (cfu/g)

\( m \) = Consumption (g)
Foodborne AMR risk assessment

Exposure assessment

Model and Data analysis

Monte Carlo technique
  • combine distributions in models
  • considering both uncertainty & variability

Simulation
  • do numerous iterations
  • converge to a more stable value
Foodborne AMR risk assessment

Exposure assessment

2.1 Probability of exposure ($P_E$)
CAC's Risk Assessment

1. Hazard Identification

Hazard Characterization

Exposure Assessment

Likelihood: $P_E$

Level: Dose

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Foodborne AMR risk assessment

1. Hazard Identification

Hazard Characterization

Exposure Assessment

4. Risk Characterization
Foodborne AMR risk assessment

Hazard characterization

Objective

• An estimate of the adverse health effects related to resistance conditional on disease and infection with AMRM
Foodborne AMR risk assessment

Hazard characterization

1. Characteristics of the hazard, food matrix and host to determine the probability of disease in humans upon exposure to AMRM/AMRD
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Hazard characterization

2. Also includes the characteristics of the acquired resistance so as to estimate the additional consequences that can occur when humans are exposed to resistant pathogens, such as increased frequency & severity of disease

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Hazard characterization

Major related factors

- Microbiological factor
- Host factor
- Food matrix factor
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Hazard characterization

Fundamental epidemiological concept

Agent

Disease

Host

Environment

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Hazard characterization

Major related factors

- Microbiological
  - Survival in environment and host
  - Factors affecting growth and survival
  - Virulence factors
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Hazard characterization

Major related factors

• Host
  • Demographic and socioeconomic factors
  • Genetic factors
  • Health and Immunity factors
Foodborne AMR risk assessment

Hazard characterization

Major related factors

• Food Matrix
  • Food composition
  • Food condition
  • Consumption
  • Micro-environment
Foodborne AMR risk assessment

Hazard characterization

Pathogenesis

- Exposure
- Infection
- Illness
- Recovery, sequel, or death
Foodborne AMR risk assessment

Hazard characterization

Pathogenesis

Exposure → Infection → Illness → Recovery

Chronic → Death
Foodborne AMR risk assessment

Hazard characterization

• Determine the number of cases with a foodborne disease based on exposure is similar to non-AMR microbiological risk assessment except that potential increased virulence of AMRM and selection effects in patients treated with the antimicrobial agents should be incorporated into the assessment
Foodborne AMR risk assessment

Hazard characterization

- The risk outcome
  - Like microbiological risk assessments will focus on diseases except, in this case, the focus is specifically on disease attributed to AMRM/AMRD
Foodborne AMR risk assessment

Hazard characterization

• The risk outcome
  • Considers the subsequent risk of treatment failure or other complications as a result of infection from microorganisms that have acquired resistance
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Hazard characterization

Dose-response models

• Human-feeding trial
• US. Risk assessment of *S. Enteritidis*
• Health Canada *S. Enteritidis*
• Epidemiological data worldwide
Foodborne AMR risk assessment

Hazard characterization

Epidemiological data

- Similar to the real foodborne outbreaks
- Water, cheese, ice cream, ham, beef, salad, soup, chicken etc.
- 33 outbreaks: Japan (9), North America (11)
- 7 serovar. $\leq S. Enteritidis$ (12), $S. Typhimurium$ (3)
- Beta-Poisson
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Hazard characterization

Outbreak of *Salmonella* Enteritidis & *Salmonella* spp.
Comparison of Dose-response curves

Outbreak curve $\alpha = 0.1324$ $\beta = 51.45$
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Hazard characterization

- Using epidemiological data
- Beta-Poisson model
  - $\alpha = 0.1324$ (0.0763 - 0.2274)
  - $\beta = 51.45$ (38.49 - 57.96)

$$P(D) = 1 - \left[ 1 + \frac{\text{Dose}}{\beta} \right]^{-\alpha}$$
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Hazard characterization

• Compared to a non-AMR hazard characterization, AMR hazard characterization outcomes can be a series of additional consequences that occur following the initiating infection event
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Hazard characterization

• AMR hazard characterization step estimates the probability of infection and then, conditional to this event, the probability of disease

• The other consequences that occur because infection is from a resistant microorganism are additional conditional probabilities, as disease is conditional on infection

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Foodborne AMR risk assessment
Hazard characterization

Figure 2b. Considerations for Hazard Characterization in a Foodborne AMR Risk Assessment

- Qualitative description translating exposure level to probability of disease
- Semi-quantitative models translating exposure level to probability of disease
- Quantitative models translating exposure level to probability of disease

Disease related to pathogens:
- Increased frequency of infection/disease
- Increased treatment failures and loss of treatment options
- Increased severity of infection/disease (prolonged duration, increased hospitalizations, increased mortality)

Adverse health effects related to resistance:
Estimates of the further outcomes that can occur as a result of disease due to AMR pathogens

The objective is to arrive at an estimate of the adverse health effects related to resistance conditional on disease and infection with an AMRM.

AMRM = antimicrobial resistant microorganism

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Hazard characterization

Hazard characterization pathway

Exposure

Infection

“Disease” related to pathogen

“Adverse health effects” related to resistance

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Hazard characterization

Adverse health effects related to resistance

\[ Pr = P(D) \times Pf \]

Pr : Probability of getting “adverse health effect” related to resistance

P(D) : Probability of getting “disease” related to pathogen (non-AMR risk assessment)

Pf : Probability of treatment failure related to resistance

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1. Hazard Identification

- Hazard Characterization
- Exposure Assessment

Pr = P(D) x Pf

PE = P * (1 - e^{-m * 10^c})

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1. Hazard Identification
   
   Hazard Characterization  Exposure Assessment

4. Risk Characterization
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Risk characterization

• Considers the key findings from :-
  • hazard identification
  • exposure assessment and
  • hazard characterization
  • to estimate the risk.

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Foodborne AMR risk assessment

Risk characterization

- Final stage of risk assessment
- Overall evaluation of the likelihood that the population will suffer adverse effects as a result of the AMRM/AMRD in food
- Integrate 2\textsuperscript{nd} and 3\textsuperscript{rd} step
  \begin{itemize}
    \item 2\textsuperscript{nd} Hazard Characterization : Pr
    \item 3\textsuperscript{rd} Exposure assessment : P_E, D
  \end{itemize}
Risk estimate

\[ P_i = P_E \times Pr \]

\[ P_i = 0.4091 \times 1.62 \times 10^{-5} \]

\[ = 6.63 \times 10^{-6} \]
Foodborne AMR risk assessment

1. Hazard Identification

   Hazard Characterization   Exposure Assessment

4. Risk Characterization

\[ P_i = P_E \times Pr \]
Foodborne AMR risk assessment

Risk characterization

- Output from Monte Carlo Simulation
- Mean of Risk estimate $= 4.57 \times 10^{-5}$
Foodborne AMR risk management

Figure 1. Framework for Foodborne AMR Risk Analysis

Identification of an AMR food safety issue

- Development of a risk profile
  - Ranking of the food safety issues for risk assessment/risk management priority
  - Establishment of preliminary risk management goals
  - Establishment of a risk assessment policy and commissioning of a risk assessment
  - Hazard identification
    - Exposure assessment
    - Hazard characterization
    - Risk characterization

Risk management

- Identification, evaluation, and selection of risk management options
  - Consideration of the risk assessment results
    - Implementation of risk management decisions
    - Monitoring and review of risk management measures
    - No action

Risk communication

Surveillance of AMR and other sources of information

Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR-risk analysis.

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Foodborne AMR risk management

1. Consideration of the foodborne AMR risk assessment results
2. Identification of foodborne AMR RMOs
3. Evaluation of foodborne AMR RMOs
4. Selection of foodborne AMR RMOs
5. Implementation of foodborne AMR risk management decision
6. Monitoring and review of foodborne AMR risk management measures

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Surveillance of use of antimicrobial agents and AMRM/AMRD

Figure 1. Framework for Foodborne AMR Risk Analysis

Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR-risk analysis.
Surveillance of use of antimicrobial agents and AMRM/AMRD

- Baseline data that is useful for all parts of the risk analysis process
- Use of standardized and validated antimicrobial susceptibility testing methods and harmonised interpretive criteria
Foodborne AMR risk management

Figure 1. Framework for Foodborne AMR Risk Analysis

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    - Risk characterization
  - Consideration of the risk assessment results
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    - Monitoring and review of risk management measures

Surveillance of AMR and other sources of information

Risk communication

Risk management

Preliminary risk management activities

Immediate (and/or provisional) decision

Note: The boxes in grey highlight the key decision points in the framework of foodborne AMR-risk analysis.

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Foodborne AMR risk communication

• An open process, in which the food safety issue is clearly identified and communicated by the risk managers to risk assessors as well as affected consumers and industry at the national / regional level

• Promoted at the earliest opportunity and integrated into all phases of a risk analysis
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