Risk assessment of the use of antimicrobial agents as feed additives in Japan ~ Foodborne AMR bacteria ~

Food Safety Commission Secretariat
Cabinet Office, Government of Japan
Topics covered

1) Risk analysis framework

2) Foodborne AMR risk assessment at FSCJ

3) *Example* Risk assessment report of colistin sulfate
1) RISK ANALYSIS FRAMEWORK
Relationship between FSCJ and other ministries

Request for risk assessment
Notification of risk assessment/opinion/recommendation

FSCJ @ Cabinet Office

Risk assessment
(Assessment of effects of food on human health)

Scientific

Neutral
Fair

Risk
Communication

Ministry of Agriculture, Forestry and Fisheries (MAFF)
- Approval of VMPs
- Designation of feed additives
- JVARM etc.

Ministry of Health, Labour and Welfare (MHLW)
- Setting MRLs in Food
- AMR monitoring in medical settings etc.

Consumer Affairs Agency (CAA)
Risk management in relation to Foods for Specified Health Uses (FOSHU)

Ministry of the Environment
Risk management in relation to environment protection

Foreign governments, international organizations among others

Gathering and exchange of information
Legislative framework

- Food Safety Basic Act enforced (1 July 2003)
  - Principle: protection of our citizen’s health is a top priority

- Introduction of Risk Analysis to food safety administration

- Food Safety Commission of Japan (FSCJ) was established as a part of Japanese Cabinet Office, independently from risk managing ministries such as MHLW and MAFF (1 July 2003)
What we do

1. Assessment of human health risks associated with food
2. Research and survey program
3. Risk communication
4. Monitoring of risk managers’ food safety policies
5. Emergency responses for food safety crises
6. International collaboration
Organizational structure of FSCJ

- Food Safety Commission (The Commission)
- Planning Committee
  - Scientific Panels (Expert Committees, Working Groups*)
- Secretariat

*Working Group: An ad-hoc panel established for an extensive discussion on a specific topic.
Flow of assessment

Risk managers

Request for assessment

General Public, FSCJ

Self-tasking

Hearing from requester

Adoption of subject

Deliberation by scientific panels (Drafting of reports)

Opinion exchange meetings

Deliberation by the commission

Consideration of public opinion/information

Finalization of assessment reports

Call for comments from the public (generally for 30 days)

Notification of assessment results

Risk managers
2) FOODBORNE AMR RISK ASSESSMENT AT FSCJ
Risk assessment regarding foodborne AMR at FSCJ

- In the risk analysis framework set out by the **Food Safety Basic Act**, MAFF has requested FSCJ for AMR risk assessment.

AMR bacteria selected by the use of antimicrobial feed additives and VMP of the same class (Dec. 2003)【26 antibiotics, 11 classes: e.g. Zinc-bacitracin, monencin Na, etc.】

Antimicrobial veterinary medicinal products (VMP) on approval and re-examination【e.g. fluoroquinolones, tulathromycin, pirlimycin, etc.】

FSCJ’s task

Possibility and degree of **reduction/loss of clinical effectiveness** of human antimicrobials when a person has developed an **infectious disease** due to AMR bacteria selected in animals and transmitted via food, using the Guideline & CIA List.

- MAFF develops and implements risk management measures according to the results.
Food Safety Commission

Establishing the WG and Assessment Guideline

<Assessment body>

Food Safety Commission

“WG on Antimicrobial-Resistant Bacteria”
(Until 30 Sep. 2015, Joint Expert Committee on Feed and Fertilizer, etc./Microorganisms and Viruses)

“Assessment Guideline for the Effect of Food on Human Health regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Producing Animals”
(30 Sep. 2004, Decision, FSCJ)
• Decided by the Commission in 2004
• Based on OIE guidelines in reference to Codex, VICH.
• Aims to assess the effect of foodborne AMR bacteria on human health
• Chapter 1: General Rules
  – Intro, Definitions, etc.
• Chapter 2: Detailed Expositions
  – Hazard Identification, Risk Assessment, Other discussions

Assessment Guideline

Approved by the Food Safety Commission on September 30, 2004

Assessment guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals

Chapter 1 General Rules

1. Introduction

Antimicrobials have been used in the process of food animal or fish farming in Japan for more than half a century. The purposes are either to “improve feed efficiency and promote growth, etc. in food animal” as “feed additives” based on the “Law Concerning Safety Assurance and Quality Improvement of Feeds (Law No. 35, 1953) or to “treat diseases” as “veterinary medicinal products” based on the “Pharmaceutical Affairs Law” (Law No. 145, 1960).

It is well known that antimicrobial-resistant bacteria are selected by the use of antimicrobials. Therefore these days, both in Japan and abroad, there are questions regarding the potential of these antimicrobial-resistant bacteria, especially in farming, to be selected for resistance and to spread that resistance among humans through food commodities; thus, affecting human health. The Office International des Epizooties (OIE), Food and Agriculture Organization of the United Nations / World Health Organization (FAO / WHO), and various international organizations in the European Union (EU) and the U.S., etc. have been performing investigations to develop risk analyses and preparing guidelines regarding antimicrobial-resistant bacteria derived from food animals, and, in some cases, actually working on risk analyses. Moreover, from the aspect of health protection in both animals and humans, the “responsible and prudent use” of veterinary antimicrobials, in order to suppress and reduce the selection of antimicrobial resistance, as well as the collection of further information regarding antimicrobial-resistant bacteria, have been encouraged, mainly by
Factors to be considered in assessment

Release Assessment
- Emergence of AMR bacteria
- Resistance rate, susceptibility
- Other factors

Exposure Assessment
- Biological feature
- Contamination
- Other factors

Consequence Assessment
- FSCJ’s CIA* List
- Severity of diseases
- Other factors

Risk Estimation

* critically important antimicrobials

Assessment of the effect of food on human health

Hazard Identification
FSCJ List of Critically Important Antimicrobials
Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food (13 Apr. 2006, Decision; revised in 2014, FSCJ)

I: Critically important
The antimicrobial is used as the sole medicine for treatment of a specific human disease, or few alternatives are available.
(e.g. 15-membered macrolides, fluoroquinolones, 3rd- & 4th-generation cephalosporins, etc.)

II: Highly important
Alternative antimicrobials are available for treatment of human diseases due to the antimicrobial-resistant bacteria, but their number is extremely limited compared to those ranked as III.
(e.g. Streptomycin, 2nd-generation cephalosporins, erythromycin, etc.)

III: Important
Alternative antimicrobials are available sufficiently either from the same or other classes of the antimicrobial, for treatment of human diseases due to the antimicrobial-resistant bacteria.
(e.g. Kanamycin, sulfonamides, 1st-generation cephalosporins, etc.)
## Completed works so far

(As of 8 August 2017)

<table>
<thead>
<tr>
<th>Result</th>
<th>Item (Year of notification)</th>
<th>Class/Rank in CIA List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>Fluoloquinolone for cattle and pigs (2010, 2015), for chickens (2013)</td>
<td>VMP</td>
</tr>
<tr>
<td></td>
<td>Tulathlomycin (2012) and Gamithlomycin (2017) for pigs</td>
<td>VMP</td>
</tr>
<tr>
<td></td>
<td>Ceftiofur (2015) and Cefquinome (2016) for cattle and pigs</td>
<td>VMP</td>
</tr>
<tr>
<td></td>
<td>Virginiamycin for pigs and chickens (2016)</td>
<td>FA</td>
</tr>
<tr>
<td></td>
<td>Colistin sulfate for livestock (2017)</td>
<td>VMP/FA</td>
</tr>
<tr>
<td>Low</td>
<td>Pirlimycin hydrochloride for</td>
<td>VMP</td>
</tr>
<tr>
<td></td>
<td>Tulathlomycin (2015) for cattle</td>
<td>MLS</td>
</tr>
</tbody>
</table>

** Why categorize drugs as High, Medium, Low?**

The categorization is based on the risk associated with using antibiotics in livestock. High-risk antibiotics are those that are more likely to lead to antibiotic resistance. Medium-risk antibiotics are those with moderate risk, and Low-risk antibiotics are those with minimal risk.
## Completed works so far – cont’d.

<table>
<thead>
<tr>
<th>Result</th>
<th>Item (Year of notification)</th>
<th>Class/Rank in CIA List</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flavophospholipol (2013)</td>
<td>FA Phosphoglycolipid</td>
</tr>
<tr>
<td></td>
<td>Avilamycin (2014)</td>
<td>FA Orthosomysins</td>
</tr>
<tr>
<td></td>
<td>Flriferonicol (2016)</td>
<td>VMP Phenicols</td>
</tr>
<tr>
<td></td>
<td>Tylosin tartrate for honeybees (2017)</td>
<td>VMP 16-membered MLs</td>
</tr>
<tr>
<td>No evidence of AMR</td>
<td>Amprolium, Ethopabate, Morantel citrate, Nicarbazin (2013.9.9)</td>
<td>FA Others (anticoccidial)</td>
</tr>
</tbody>
</table>
### AMR risk management measures taken by MAFF based on risk assessment results

<table>
<thead>
<tr>
<th>FACJ risk assessment results</th>
<th>Examples of risk management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Veterinary medicinal products</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>- Revocation of approval</td>
</tr>
<tr>
<td></td>
<td>- Temporary ban of use</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>- Restriction of the usage</td>
</tr>
<tr>
<td></td>
<td>- Shortened application periods</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>- Strict use as a second choice drug</td>
</tr>
<tr>
<td></td>
<td>- Enhanced monitoring (e.g. increasing number of samples)</td>
</tr>
<tr>
<td><strong>Negligible</strong></td>
<td>- Continued monitoring</td>
</tr>
</tbody>
</table>
Antimicrobial-resistant Bacteria Arising from the Use of Colistin Sulfate in the Livestock (Antimicrobial-resistant Bacteria)

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment on antimicrobial-resistant bacteria arising from the use of colistin sulfate, which is used as a feed additive and veterinary medicinal products in the livestock. Both *Salmonella* and *E. coli* were considered as potential antimicrobial-resistant bacteria to be selected under the use of colistin sulfate in the livestock. As only limited reports were available on the colistin-resistance in *Salmonella*, FSCJ conducted a risk assessment focusing on *E. coli* as a hazard, on which the information was rather available. In the release assessment, the degree of possible selection of the hazard was evaluated as “Medium”. Considering proper cooking of the livestock products, the degree of possible human exposure to the resistant bacteria via livestock products was evaluated as “Low”. The degree of
Example of our risk assessment: Colistin sulfate in the livestock (Jan. 2017)

【Hazard Identification】
AMR bacteria arising from the use of colistin sulfate in livestock, potentially affecting human health via food

Criteria for a hazard:
- Found in target animals
- Selected and gain resistance by colistin use
- Transmitted by food to humans
- Human infectious disease for which colistin can be used

⇒ Data availability on susceptibility to colistin & resistance genes?

Commensal *E. coli*
(Not enough information for *Salmonella* to conduct a risk assessment)
## Risk Estimation for colistin sulfate

<table>
<thead>
<tr>
<th>RA component</th>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Emergence: Moderate</td>
</tr>
<tr>
<td></td>
<td>• Susceptibility: Moderate</td>
</tr>
<tr>
<td></td>
<td>• Other factors: Moderate</td>
</tr>
<tr>
<td>Release (Score)</td>
<td>Medium (2)</td>
</tr>
<tr>
<td></td>
<td>• Biological properties: Moderate</td>
</tr>
<tr>
<td></td>
<td>• Food contaminations: Little</td>
</tr>
<tr>
<td></td>
<td>• Other factors: Little</td>
</tr>
<tr>
<td>Exposure (Score)</td>
<td>Low (1)</td>
</tr>
<tr>
<td></td>
<td>• Importance in clinical use: Great</td>
</tr>
<tr>
<td></td>
<td>• Severity of infectious diseases: Moderate</td>
</tr>
<tr>
<td></td>
<td>• Other factors: Great</td>
</tr>
<tr>
<td>Consequence (Score)</td>
<td>High (3)</td>
</tr>
<tr>
<td></td>
<td>• Importance in clinical use: Great</td>
</tr>
<tr>
<td></td>
<td>• Severity of infectious diseases: Moderate</td>
</tr>
<tr>
<td></td>
<td>• Other factors: Great</td>
</tr>
<tr>
<td>Total score</td>
<td>(6)</td>
</tr>
<tr>
<td>Risk Estimation results</td>
<td>Medium</td>
</tr>
</tbody>
</table>

※ Result of each RA component is expressed as “high (3)”; “medium (2)”; and “low (1)”, and the Risk Estimation is a sum of these components. RA is comprehensively described by the total score: 8-9 (High); **5-7 (Medium)**; 2-4 (Low); and 0-1 (Negligible).
Foodborne AMR risk assessment:
Other discussions on colistin sulfate

- Considering the importance of colistin in human medicine, stricter risk management for colistin as feed additive should be carefully considered.
- Cooperate with relevant risk management agencies to continue monitoring of AMR bacteria (esp. *mcr-1*)
- Collect state-of-the-art scientific knowledge on *mcr-1* and other colistin resistance genes

Following collaborative actions by respective agencies

- Guidelines on risk management measures to tighten the use of antimicrobials as feed additive; ban the use of colistin as feed additive
- Collaborative AMR monitoring among human, food and animals (i.e. One Health surveillance)
- Research project on colistin and the resistance gene (*mcr-1*)
### Risk management options based on risk assessment

~~ Feed Additives ~~

<table>
<thead>
<tr>
<th>Risk Assessment Result</th>
<th>Risk Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Revocation of designation</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Continued monitoring</td>
</tr>
<tr>
<td>Negligible</td>
<td></td>
</tr>
<tr>
<td>No evidence of AMR</td>
<td></td>
</tr>
</tbody>
</table>

- Virginiamycin
- Colistin
  → Revoke the designation

- Monencin
- Smduramycin
- Lasalocide
- Salinomycin
- Narasin etc.
Way Forward
(FSCJ AMR Action Plan 2016-2020)

Tasks

(1) Data and information
• Needed for RA (e.g. aquaculture)
• State-of-the-art information

(2) International affairs
• Review of the GL and CIA List ← GAP (e.g. WHO CIA List revision)

(3) Info dissemination / communication
• Public awareness-raising activities
• Int’l cooperation in the area of RA

Actions

1 Risk assessment
(1) Complete by 2020 on the items requested
(2) Review the past reports (e.g. colistin)
(3) Review the GL and CIA List

2 Info collection for RA
(1) Conduct research
(2) Join the OH Surveillance
(3) Intra-/inter-governmental communication and collaboration with relevant agencies

3 Others
(1) Respond to emerging issues
   - Collaboration with RM agencies
(2) Enhance communication on AMR
English Website of FSCJ: www.fsc.go.jp/english/index.html

Guidelines

Risk assessment reports

http://www.fsc.go.jp/english/standardsforriskassessment/antimicrobialresistantbacteria_e2.html
Official Journal – Food Safety

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