

# Food Safety Risk Assessment in Japan ～ Foodborne AMR bacteria ～

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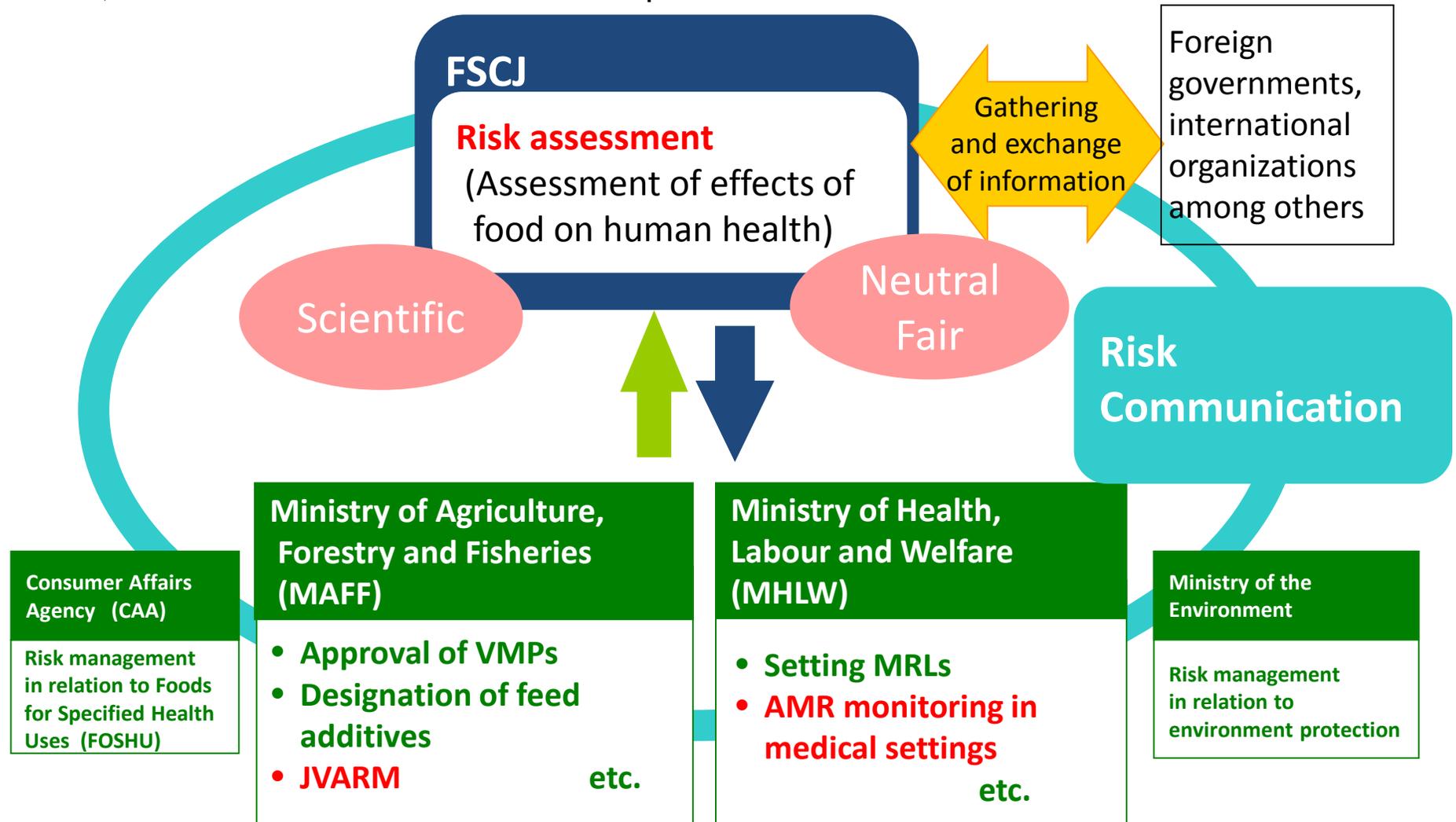
# Topics covered

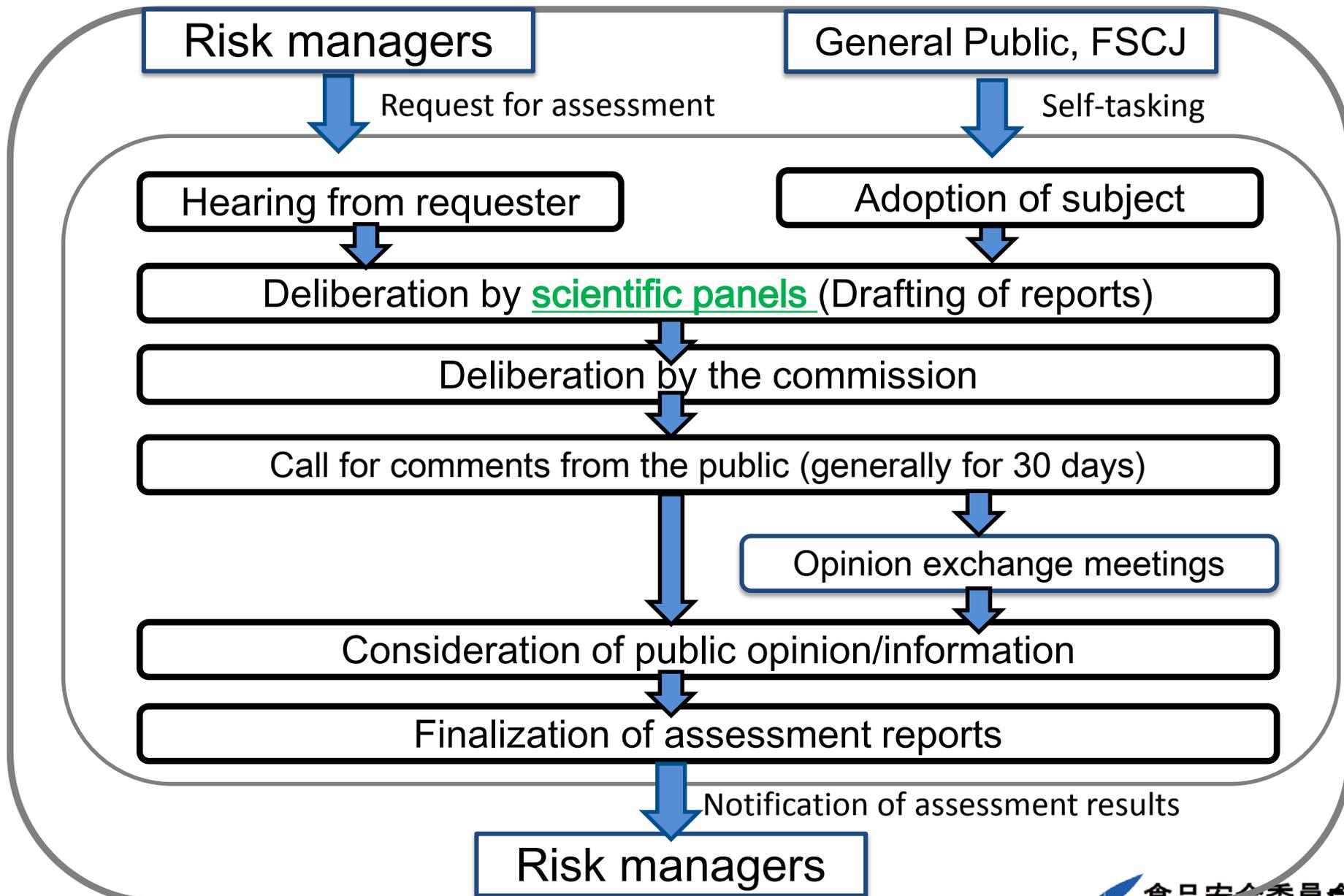
- 1) FSCJ – who we are? how we work?
- 2) Foodborne AMR risk assessment at FSCJ
- 3) 《*Example*》 Colistin risk assessment incl. following FSCJ's research and survey program

- **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)** established as a part of Japanese Cabinet Office, independently from risk managing ministries such as MHLW and MAFF (1 July 2003)

# Relationship between FSCJ and other ministries

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





# Scientific Panels

(on-going as of October 2018)

- Food additives
- Pesticides
- Veterinary Medicinal Products
- Apparatuses, Containers and Packages
- Contaminants in Foods
- Microorganisms and Viruses
- Prions
- Natural Toxins and Mycotoxins

- Genetically Modified Foods
- Novel Foods
- Feeds and Fertilizers

(Working Group)

- Food Additives as Nutrients
- Antimicrobial-Resistant Bacteria
- New Risk Assessment Methodology Development
- Hexavalent Chromium
- Food Allergy (new)
- Flavouring Substances in Foods (new)

# Risk Assessment AMR in FSCJ

- Food Safety Basic Act (Jul. 2003) enforced to protect nation's health
- Risk Analysis introduced to food safety administration inc. AMR issues
- According to the Act, MAFF has requested FSCJ for risk assessment for:

AMR bacteria selected by the use of antimicrobial feed additives and VMP of the same class (Dec. 2003)

【Zinc-bacitracin, monencin Na, etc.:  
26 antibiotics, 11 classes】



Antimicrobial veterinary medicinal products (VMP) on approval and re-examination

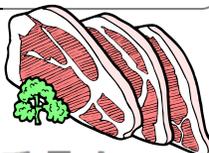
【fluoroquinolones, tulathromycin,  
pirlimycin, etc.】



## FSCJ's task

Possibility and degree of reduction or loss of clinical effectiveness of human antibiotics 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 formulates and implements risk management (RM) measures according to the results



# AMR risk management measures taken by MAFF based on risk assessment results

FACJ risk assessment results	Examples of risk management	
	Veterinary medicinal products	Feed additives
<b>High</b>	<ul style="list-style-type: none"> <li>- Revocation of approval</li> <li>- Temporary ban of use</li> </ul>	<ul style="list-style-type: none"> <li>- Revocation of designation</li> </ul>
<b>Medium</b>	<ul style="list-style-type: none"> <li>- Restriction of the usage</li> <li>- Shortened application periods</li> </ul>	
	<ul style="list-style-type: none"> <li>- Strict use as a second choice drug</li> <li>- Enhanced monitoring (e.g. increasing number of samples)</li> </ul>	
<b>Low</b>	<ul style="list-style-type: none"> <li>- Continued monitoring</li> </ul>	<ul style="list-style-type: none"> <li>- Continued monitoring</li> </ul>
<b>Negligible</b>		

**Food Safety Commission**  
**Establishing assessment guideline**

**“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)**



**< Assessment body >**

**Food Safety Commission**

**“WG on Antimicrobial-resistant Bacteria”**

**(Until 30 Sep. 2004, Joint Expert Committee on  
Feed and Fertilizer, etc./ Microorganisms and Viruses)**

# Assessment Guideline

- Approved by the Commission in 2004
- Based on Codex, VICH, and OIE guidelines
- Aims to assess the effect of food-borne resistant bacteria on human health
- Chapter 1: General Rules
  - Intro, Definitions, etc.
- Chapter 2: Detailed Expositions
  - Hazard identification, Risk Assessment, Other discussions

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<sup>1</sup>. 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 considered in assessment

## Hazard Identification



### Release Assessment

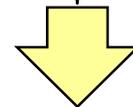
- Emergence of AMR\* bacteria
- Resistance rate, susceptibility
- Other factors

### Exposure Assessment

- Biological feature
- Contamination
- Other factors

### Consequence Assessment

- FSC-CIA\*\* list
- Severity of diseases
- Other factors



## Risk Estimation

\* antimicrobial-resistant

\*\* critically important antimicrobials

Assessment of the effect of food on human health

# FSCJ List of Critically Important Antimicrobials

Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food (13 Apr. 2006, Decision, 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.)



## 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

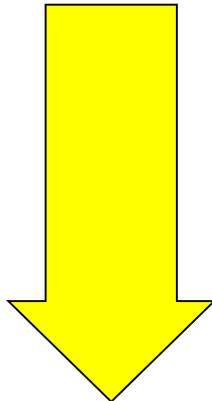
# 3) 《EXAMPLE》 RISK ASSESSMENT REPORT OF COLISTIN SULFATE

**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)**

# Release Assessment

- The degree of possible selection of the hazard was evaluated as "**Medium**". ← More than one "Moderate"

Relevant parameter	Some points from discussion	Concern
1) Emergence	<ul style="list-style-type: none"> <li>- 2% of <i>mcr-1</i> positive <i>E. coli</i> isolates from healthy livestock in 2015</li> <li>- <i>mcr-1</i> can be horizontally transferred among <i>E. coli</i> and other <i>Enterobacteriaceae</i></li> <li>- Uncertainty in fitness cost, role of <i>mcr-1</i> in susceptible isolates</li> </ul>	Moderate
2) Susceptibility	<ul style="list-style-type: none"> <li>- Colistin-susceptibility in <i>E.coli</i> from healthy livestock in 2000-2015 remained high (MIC <math>\geq</math> 4 <math>\mu</math>g/mg: 1.0-4.7%)</li> <li>- Relatively high resistance rate (MIC <math>\geq</math> 4 <math>\mu</math>g/mg) in <i>E.coli</i> (w/ or w/o <i>mcr-1</i>) from diseased livestock (pigs: 40%, cattle: 20%, chickens: 2%)</li> </ul>	Moderate
3) Other factors	<ul style="list-style-type: none"> <li>- Prescription VMP: increase at 3,5 <math>\rightarrow</math> 10 t in 2005-2014</li> <li>- Feed additive: decrease at 32 <math>\rightarrow</math> 28 t in 2005-2015, with high amount of use in pigs and chickens (more <i>mcr-1</i>)</li> </ul>	Moderate

# Exposure Assessment

- The degree of possible human exposure to the resistant bacteria via livestock products was evaluated as “**Low**”.  
One “Moderate” and two “Little”

Relevant parameter	Some points from discussion	Concern
1) Biological properties	<ul style="list-style-type: none"> <li>- <i>E. coli</i> survives occasionally in meat</li> <li>- Unknown colonization of colistin-resistant <i>E. coli</i> in human gut flora</li> <li>- <i>mcr-1</i> has been shown to be transferred among <i>E. coli</i> and <i>Salmonella</i></li> </ul>	Moderate
2) Food contaminations	<ul style="list-style-type: none"> <li>- Colistin-resistant strains have been scarcely isolated from meat, though minced meat with <i>E. coli</i> positive is 60-70%</li> </ul>	Little
3) Other factors	<ul style="list-style-type: none"> <li>- <i>E. coli</i> on/in meat is generally non-pathogenic</li> <li>- Proper cooking reduces a chance of colonization of colistin-resistant <i>E. coli</i></li> </ul>	Little

# Consequence Assessment

- The degree of possible reduction or loss of clinical effectiveness was evaluated as “**High**” ← More than one “Great”

Relevant parameter	Some points from discussion	Concern
1) Importance in clinical use	<ul style="list-style-type: none"> <li>- Ranked as “Critically Important” in FSCJ CIA List</li> <li>- Last resort for CRE infection</li> </ul>	Great
2) Severity of infectious diseases	<ul style="list-style-type: none"> <li>- MDR bacteria with colistin-resistance as a cause of nosocomial infection could have an impact on clinical treatment</li> <li>- Incidence of foodborne (nosocomial) <i>E. coli</i> infection is unknown</li> <li>- Scarce reports of deaths by infection with colistin-resistant <i>E. coli</i></li> </ul>	Moderate
3) Other factors	<ul style="list-style-type: none"> <li>- MDR bacteria with colistin-resistance might lead to loss of alternatives</li> </ul>	Great

# Risk Estimation for colistin sulfate

RA component		<i>E. coli</i>	
Outcome	Release (Score)	Medium (2)	<ul style="list-style-type: none"> <li>• Emergence: Moderate</li> <li>• Susceptibility: Moderate</li> <li>• Other factors: Moderate</li> </ul>
	Exposure (Score)	Low (1)	<ul style="list-style-type: none"> <li>• Biological properties: Moderate</li> <li>• Food contaminations: Little</li> <li>• Other factors: Little</li> </ul>
	Consequence (Score)	<u>High (3)</u>	<ul style="list-style-type: none"> <li>• <u>Importance in clinical use: Great</u></li> <li>• Severity of infectious diseases: Moderate</li> <li>• <u>Other factors: Great</u></li> </ul>
	Total score	(6)	
Risk Estimation results		Medium	

※ 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

To fill data gaps

### 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*)

## Following research and survey program

- Research on the prevalence and characterization of colistin resistant bacteria (FY 2017-2019)
  - Characterization of plasmid-mediated genes associated with colistin resistance among Enterobacteriaceae isolated from food producing animals.
  - Isolation of colistin resistant bacteria from livestock products and from humans
  - Illustrate the effect of the plasmid-mediated genes associated with colistin resistance on MIC

# Completed works so far

(As of 8 August 2017)

Result	Item (Year of notification)	Class/Rank in CIA List		
Medium	Fluoroquinolone for cattle and pigs (2010, 2015), for chickens (2013)	VMP	FQs	I
	Tulathlomyacin (2012) and Gamithlomyacin (2017) for pigs	VMP	15-membered MLs	I
	Ceftiofur (2015) and Cefquinome (2016) for cattle and pigs	VMP	Ceps (3 <sup>rd</sup> & 4 <sup>th</sup> )	I
	Virginiamycin for pigs and chickens (2016)	FA	Streptogramins	II
	Colistin sulfate for livestock (2017)	VMP/FA	Polypeptides	I
Low	Pirlimycin hydrochloride for intramammary infusion (2013)	VMP	Lincosamides	II
	Gamithlomyacin (2014) and Tulathlomyacin (2015) for cattle	VMP	15-membered MLs	I

## Completed works so far – cont'd.

Result	Item (Year of notification)		Class/Rank in CIA List	
Negligible	Monencin-Na (2006), Semduramycin-Na (2013), Lasalocide-Na (2013), Salinomycin (2013), Narasin (2013)	FA	Polyether	-
	Nosiheptide (2012), Enramycin (2014)	FA	Peptides	Ⅲ
	Flavophospholipol (2013)	FA	Phosphoglycolipid	-
	Avilamycin (2014)	FA	Orthosomysins	-
	Florfenicol (2016)	VMP	Phenicol	Ⅱ
	Tylosin tartrate for honeybees (2017)	VMP	16-membered MLs	Ⅲ
No evidence of AMR	Amprolium, Ethopabate, Morantel citrate, Nicarbazin (2013.9.9)	FA	Others (anticoccidial)	-

# 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) Update 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](http://www.fsc.go.jp/english/index.html)

Guidelines

Risk assessment reports



[http://www.fsc.go.jp/english/standard\\_sforriskassessment/antimicrobialresistantbacteria\\_e2.html](http://www.fsc.go.jp/english/standard_sforriskassessment/antimicrobialresistantbacteria_e2.html)



## Antimicrobial-resistant bacteria

- ▶ [Assessment guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals \[September 30, 2004\]\[PDF:95KB\]](#)
- ▶ [Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food Commodities \[April 13, 2006\]\[PDF:251 KB\]](#)

## Risk assessment reports

- ▶ [Risk assessment reports for antimicrobial-resistant bacteria](#)

# Official Journal – *Food Safety*

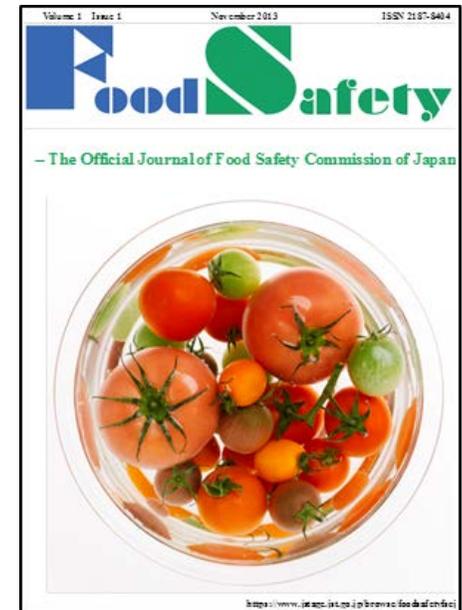
***Food Safety*** is...

A peer-reviewed open-access electronic online journal in English published by the FSCJ.

(published quarterly)

This journal features four types of articles;

- Original articles
- Short communications
- Reviews
- Risk assessments conducted by FSCJ.



For further information, please visit our website:

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Thank you for your kind attention.  
Questions?