Outline of JVARM
–Japanese Veterinary Antimicrobial Resistance Monitoring System–

May 16th 2017

National Veterinary Assay Laboratory (NVAL),
Ministry of Agriculture, Forestry and Fisheries (MAFF)
JAPAN
Deaths attributable to AMR every year compared to other major causes of death

- Globally, a conservative estimate suggests that the death caused by AMR may be 700,000 in 2013.
- If no appropriate policies are put in place, (if current rates of resistance increased by 40%), the deaths attributable to AMR could be 10 million per year in 2050.

* There were 120,000 deaths from Tuberculosis in Japan in 1950 (before the introduction of antibiotics)

Antimicrobial Resistance in G7 Countries and Beyond, G7 OECD report, Sept. 2015; By UK Review on AMR. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations 2014
Antimicrobial Resistance in G7 Countries and Beyond, G7 OECD report, Sept. 2015
By UK Review on AMR. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations 2014

- Only 0.7 million of these additional deaths would occur in North America or Europe, with the largest numbers in Africa and Asia.

Number of deaths per year attributable to AMR by 2050 if current resistance rates increased by 40%
Timeline of antimicrobial marketing in the world

1935 - Prontosil (an oral precursor to sulfanilimide), the first sulfonamide

1942 - benzylpenicillin, the first penicillin
1944 - streptomycin, the first aminoglycoside
1948 - chlortetracycline, the first tetracycline
1949 - chloramphenicol, the first amphenicol

1952 - erythromycin, the first macrolide
1955 - vancomycin, the first glycopeptide
1958 - colistin, the first polymyxin

1960 - metronidazole, the first nitroimidazole
1961 - ampicillin
1961 - trimethoprim, the first dihydrofolate reductase inhibitor
1964 - Cefalotin, the first cephalosporin
1967 - Nalidixic acid, the first quinolone
1968 - clindamycin, the second lincosamide

1985 - imipenem/cilastatin, the first carbapenem
1987 - ciprofloxacin, the first 2nd-gen fluoroquinolone

2009 - telavancin, the first Lipoglycopeptide

The years show when a given drug was released onto the pharmaceutical market. (Wikipedia)

* In 1980s, the threat by new antimicrobial-resistant bacteria began to rise predominantly in hospital settings.
Possible transmission routes of resistant bacteria (resistant gene)

- Human
- Food
- Environment
- Animal

Selective pressure

One health

Imported food

Selective pressure
Development of Action Plans on AMR

【WHO Global Action Plan on AMR】
(2015.5)

【Japanese Action Plan on AMR】
(2016.4)

National Action Plan on Antimicrobial Resistance (AMR)
2016-2020

April 5, 2016
The Government of Japan

Vietnam; 2013
Philippine; 2014
Cambodia; 2014
Fiji; 2015
Republic of Korea; 2016
& China; 2016
# International comparison of *E. coli* resistance in livestock animals in 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>Resistance to tetracyclines (%)</th>
<th>Resistance to the 3rd generation cephalosporins (%)</th>
<th>Resistance to Fluoroquinolones (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No data on pigs in Germany and Croatia, cows in Croatia and France  ** No data on cows in Switzerland and France, pigs in Germany and Belgium

The % of *E. coli* resistant to tetracyclines, the third-generation cephalosporins, and fluoroquinolones in Japan are at comparable levels to those in EU and USA

(Ref: JVARM 2013, NARMS 2013, Scientific report of EFSA and ECDC EU summary report on AMR in zoonotic and indicator bacteria from humans, animals and food in 2013, DANMAP2013)
Our commitment

1. Strengthening the **One Health Approach**
   (e.g., collaboration between human and animal monitoring)
2. Further promoting the **risk assessment based policies**
   (e.g., prudent use)
3. **Working with OIE and other international organizations to contribute to the Asian region**
### Numerical Targets

#### <Animals>

<table>
<thead>
<tr>
<th>% of resistant isolates of specific indicator microorganisms (average of cows, pigs and broilers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator</td>
</tr>
<tr>
<td>% of tetracycline resistance in <em>E. coli</em></td>
</tr>
<tr>
<td>% of 3rd generation cephalosporin resistance in <em>E. coli</em></td>
</tr>
<tr>
<td>% of fluoroquinolone resistance in <em>E. coli</em></td>
</tr>
</tbody>
</table>

#### <Humans>

<table>
<thead>
<tr>
<th>Antimicrobial Use for humans</th>
<th>% of resistant isolates of specific indicator microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index</strong></td>
<td><strong>2020 (target)</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Decreased by 33%</td>
</tr>
<tr>
<td>Oral cephalosporins, fluoroquinolones, macrolides</td>
<td>Decreased by 50%</td>
</tr>
<tr>
<td>Amount of intravenous antimicrobials used</td>
<td>Decreased by 20%</td>
</tr>
<tr>
<td><em>% of penicillin-resistance in Streptococcus pneumoniae</em></td>
<td>48%</td>
</tr>
<tr>
<td><em>% of fluoroquinolone resistance in E. coli</em></td>
<td>45%</td>
</tr>
<tr>
<td><em>% of methicillin resistance in Staphylococcus aureus</em></td>
<td>51%</td>
</tr>
<tr>
<td><em>% of carbapenem resistance in Pseudomonas aeruginosa</em></td>
<td>17%</td>
</tr>
<tr>
<td><em>% of carbapenem resistant in E.coli/Klebsiella pneumoniae</em></td>
<td>0.1-0.2%</td>
</tr>
</tbody>
</table>
To Control the Antimicrobial Resistance

1. Collection of Information (Monitoring, Surveillance)
2. Risk Analysis of Antimicrobial Resistance
3. Responsible and Prudent Use of antimicrobials
4. Improve Public Awareness and Understanding, and Promote Education and Training of Professionals
## Number of Livestock in Japan (×1,000 head)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy cattle</td>
<td>1,636</td>
<td>1,553</td>
<td>1,500</td>
<td>1,449</td>
<td>1,395</td>
<td>1,345</td>
<td>-17.8</td>
</tr>
<tr>
<td>Beef cattle</td>
<td>2,775</td>
<td>2,890</td>
<td>2,923</td>
<td>2,723</td>
<td>2,567</td>
<td>2,479</td>
<td>-10.7</td>
</tr>
<tr>
<td>Pigs</td>
<td>9,620</td>
<td>9,745</td>
<td>9,899</td>
<td>9,735</td>
<td>9,537</td>
<td>9,313</td>
<td>-3.2</td>
</tr>
<tr>
<td>Layers</td>
<td>180,697</td>
<td>184,773</td>
<td>180,994</td>
<td>178,546</td>
<td>172,349</td>
<td>173,349</td>
<td>-4.1</td>
</tr>
<tr>
<td>Broiler*</td>
<td>103,687</td>
<td>102,987</td>
<td>107,141</td>
<td>-</td>
<td>135,747</td>
<td>134,395</td>
<td>29.6</td>
</tr>
</tbody>
</table>

The survey has been conducted as of Feb. 1st every year by the method of self-reporting through mail-in surveys for farmers. (Statistics on Livestock, Statistics Department, MAFF)

*Figures of 2016 are approximate data.
Livestock Hygiene Service Centers

- 47 prefectures
- Each prefecture has several Livestock Hygiene Service Centers (LHSC)
- Total No. of the LHSC; 170
  Total No. of the Vets. ; 2,084
  (at 2015.3.31)
- Role of the LHSC
  - Annual inspections under ‘Domestic Animal Infectious Disease Control Law’
  - Check, guide, advise for farms
  - Prevent livestock infectious diseases etc.
JVARM
Japanese Veterinary Antimicrobial Resistance Monitoring (1999〜)

Objectives

● monitor the occurrence of antimicrobial resistance bacteria in food-producing animals
● monitor the usage of antimicrobials in animals
● to identify the efficacy of antimicrobials in food-producing animals
● to ascertain the public health problem
● to promote the prudent use of such antimicrobials

1) Nationwide monitoring of antimicrobial resistance
2) Monitoring of veterinary antimicrobial sales
JVARM
Japanese Veterinary Antimicrobial Resistance Monitoring System

1) Sales of Antimicrobial

2) Resistance in Zoonotic and Indicator Bacteria

3) Resistance in Animal Pathogens

Healthy animals

Diseased animals

Pharmaceutical Companies (Marketing Authorisation Holder)
Monitoring of Antimicrobial Sales

Under the Pharmaceutical and Medical Device Act
(formerly known as Pharmaceutical Affairs Law)

Pharmaceutical companies (Marketing Authorization Holder)

Report (total sales amount)  Format

National Veterinary Assay Laboratory

Summing up, Analysis, Evaluation

Report on the website of NVAL

Report from the Marketing Authorization Holder

● Sales amount
● The name of antimicrobials
● Annual weight in kilograms of the active ingredients
● The route of administration
● Target animal species
● Estimated percentages of sales for each animal species

etc.
Collates analyses and evaluates the data
Publishes the data in an annual report and posts it on the Web

e.g. Sales Amount and Sales Volume of Antimicrobials. (2005)

<table>
<thead>
<tr>
<th>Class</th>
<th>Active substance</th>
<th>route of administration</th>
<th>Sales amount (¥1000)</th>
<th>Amount of active substance (kg)</th>
<th>Estimated Percentages of Sales for Each Animals Species</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Beef Cattle</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Oxytetracycline</td>
<td>oral</td>
<td>383,157</td>
<td>1.8</td>
<td>84.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>injection</td>
<td>158,791</td>
<td>11.6</td>
<td>82.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>total</td>
<td>541,948</td>
<td></td>
<td>[205316.7]</td>
</tr>
<tr>
<td>Doxycyclin HCl</td>
<td></td>
<td>oral</td>
<td>520,321</td>
<td></td>
<td>84.3</td>
</tr>
</tbody>
</table>

Feed Additives

- Commenced to use in the 1950s
- All of antimicrobial feed additives must be subjected to National Assay before distribution
- National assay is conducted by Food and Agricultural Materials Inspection Center (FAMIC)
- Total usage amount of antimicrobial drugs is much greater than that of antimicrobial feed additives in Japan

Antimicrobial drugs are given priority as risk factor associated with bacterial antimicrobial resistance
Monitoring System in Farm (2000+)

Target bacteria;
- Indicator (*E. coli*, *Enterococcus spp.*), Zoonotic bacteria (*Salmonella spp.*, *Campylobacter spp.*) (-2015)
- Animal pathogen (Clinical isolate; *Salmonella*, *Stapylococcus*, *Actinobacillus pleuropneumoniae* etc.)

- **MAFF** (Ministry of Agriculture, Forestry and Fisheries of Japan)
  - Design risk managements and provide the data for risk assessments to FSC
  - Report (Every year)

- **NVAL** (National Veterinary Assay Laboratory)
  - **FAMIC** (Food and Agricultural Materials Inspection Center) (-2015)
  - Sum up, analyze, and evaluate data
  - Research into molecular epidemiology, resistance mechanism
  - Isolated bacteria, Data
  - Advice, Training seminar

- **Livestock Hygiene Service Center** (170 centers)
  - Collect feces in farm, isolate and identify bacteria, and measure MIC
  - Samples

**JVARM; Monitoring of Antimicrobial Resistance**
Monitoring System in Slaughterhouses (2012-)

MAFF added the monitoring in slaughterhouses since 2012.

Target bacteria;
- Indicator (E. coli, Enterococcus spp.), Zoonotic bacteria (Salmonella spp., Campylobacter spp.)

- **MAFF** (Ministry of Agriculture, Forestry and Fisheries of Japan)
  - Design risk managements and provide the data for risk assessments to FSC

- **NVAL** (National Veterinary Assay Laboratory)

- **FAMIC** (Food and Agricultural Materials Inspection Center)
  - Analyze, and evaluate data
  - Research into molecular epidemiology, resistance mechanism

- **Private-sector institution**
  - Collect feces in Slaughterhouses, isolate and identify bacteria, and measure MIC

- **Samples**

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**JVARM; Monitoring of Antimicrobial Resistance**
The Sales of Antimicrobials for Animals

* Including food producing animals and companion animals

**Estimation based on sales/production quantities**
Sales of veterinary antimicrobial agents, in tonnes of active substance, during 2001–2013

JVARM: Sales of Antimicrobials
Sales of veterinary antimicrobial agents by target species, in tonnes of active substance, during 2006–2014
**JVARM : Resistance of bacteria (healthy and diseased animals)**

Total number of isolates examined (1999-2015) for the basic study; **27,240**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Year</th>
<th>E. coli*</th>
<th>Enterococcus*</th>
<th>Campylobacter</th>
<th>Healthy animal</th>
<th>Clinical isolates</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Stage</td>
<td>1999</td>
<td>1,018</td>
<td>1,024</td>
<td>166</td>
<td>124</td>
<td>194</td>
<td>318</td>
</tr>
<tr>
<td>1st stage</td>
<td>2000-2003</td>
<td>2,206</td>
<td>1,386</td>
<td>956</td>
<td>183</td>
<td>211</td>
<td>394</td>
</tr>
<tr>
<td>2nd stage</td>
<td>2004-2007</td>
<td>1,979</td>
<td>1,920</td>
<td>679</td>
<td>179</td>
<td>482</td>
<td>661</td>
</tr>
<tr>
<td>3rd stage</td>
<td>2008-2009</td>
<td>1,295</td>
<td>1,273</td>
<td>390</td>
<td>-</td>
<td>371</td>
<td>371</td>
</tr>
<tr>
<td>4th stage</td>
<td>2010-2011</td>
<td>1,567</td>
<td>1,432</td>
<td>540</td>
<td>-</td>
<td>325</td>
<td>325</td>
</tr>
<tr>
<td>5th stage</td>
<td>2012-2013</td>
<td>1,481</td>
<td>1,486</td>
<td>464</td>
<td>-</td>
<td>369</td>
<td>369</td>
</tr>
<tr>
<td>6th stage</td>
<td>2014-2015</td>
<td>1,333</td>
<td>1,400</td>
<td>464</td>
<td>-</td>
<td>343</td>
<td>343</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>10,879</strong></td>
<td><strong>9,921</strong></td>
<td><strong>3,659</strong></td>
<td><strong>486</strong></td>
<td><strong>2,295</strong></td>
<td><strong>2,781</strong></td>
</tr>
</tbody>
</table>

*Indicator bacteria detected from the healthy animals.*
Resistance rate in *E. coli* isolated from healthy animals
In Japan, cephalosporins have **NOT** been approved for poultry, however, resistance rate was obviously increasing in Layer and Broiler.
The resistance rate of cephalosporin in *E. coli* isolates from healthy broilers

The voluntarily banned of the off-label use of ceftiofur at hatcheries.

Resistance rate of quinolone in *E. coli* isolates from healthy animals

<table>
<thead>
<tr>
<th></th>
<th>Cattle</th>
<th>Pig</th>
<th>Layer</th>
<th>Broiler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalidixic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resistance rate (%)</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Nalidixic acid (Quinolone)**
- **Enrofloxacin (2001-2009) / Ciprofloxacin (2010-)**

(Fluoroquinolone)
Resistance rate in *Salmonella* isolated from diseased animals (2002-2014)
Serotypes of *Salmonella* isolated from diseased animal (2002-2014)
Resistance rate in *Campylobacter* isolated from healthy animals (1999-2014)
Integration of human and animal data

JANIS: Japan Nosocomial Infectious Surveillance

Can calculate
- SIR judgment from MIC
- Resistant rate
- Multi-antimicrobial resistant rate

Same format

Copy of JANIS Server

JVARM MIC data
(Since 1999)

hospital

hospital

hospital

hospital

MIC data

MIC data

MIC data

hospital

JANIS server

(Since 2000)
**β-Lactamase gene**

### Cefazolin (CEZ) First-generation cephalosporin

- **Layer**
- **Pig**
- **Beef cattle**
- **Broiler**
- **JANIS**


### Isolated from human

**CTX-M subgroup of E. coli**

- CTX-M-9 group
- CTX-M-2 group
- CTX-M-1 group


### Isolated from broiler

- CTX-M-18
- CTX-M-2
- CMY-2
- Other

## National antimicrobial resistance monitoring

<table>
<thead>
<tr>
<th>Country</th>
<th>System</th>
<th>Agency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>NARMS</td>
<td>FDA, CDC, USDA</td>
<td>National Antimicrobial Resistance Monitoring System</td>
</tr>
<tr>
<td>Canada</td>
<td>CIPARS</td>
<td>Public Health Agency of Canada</td>
<td>Canadian Integrated Program for Antimicrobial Resistance Surveillance</td>
</tr>
<tr>
<td>Denmark</td>
<td>DANMAP</td>
<td>NFI, NVI, DMA</td>
<td>Danish Integrated Antimicrobial Resistance Monitoring and Research Programme</td>
</tr>
<tr>
<td>UK</td>
<td>UK-VARSS</td>
<td>APHA, VMD</td>
<td>UK Antibiotic Resistance and Sales Surveillance Report</td>
</tr>
<tr>
<td>France</td>
<td>RESAPATH</td>
<td>ANSES</td>
<td>French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin</td>
</tr>
<tr>
<td>Sweden</td>
<td>SVARM</td>
<td>NVI</td>
<td>Swedish Veterinary Antimicrobial Resistance Monitoring</td>
</tr>
<tr>
<td>Norway</td>
<td>NORM/NORM-Vet</td>
<td>Norwegian Veterinary Institute</td>
<td>Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway</td>
</tr>
<tr>
<td>ASEAN</td>
<td>ATLASS</td>
<td>in the future</td>
<td></td>
</tr>
</tbody>
</table>

* ASEAN ATLASS in the future
Significance of Nationwide Monitoring

- To understand the baseline of antimicrobial resistance prevalence in bacteria
- To compare the data between humans and animals
- To provide data for the risk assessment

Prefectural Livestock Hygiene Service Center

- To take the interest in the antimicrobial resistance in animals
- To improve the lab technique concerning antimicrobial resistance
Summary

- AMR should be considered comprehensively with regard to human health, animal health, food hygiene, etc.

- It is important to decide the appropriate risk management strategy based on the scientific risk assessments.

- It is essential to evaluate the efficacy of each risk management option continuously after implementation and revise them if needed.

- Improve Public Awareness and Understanding, and Promote Education and Training of Professionals
Laboratory Training Course

〈Antimicrobial Sensitivity Tests〉
1) Disk diffusion methods, 2) Agar dilution method, 3) Broth microdilution method

〈Bacterial identification〉 Isolation and Identification of E. coli and Salmonella

AMR OneHealth Seminar 2016 in NVAL
1. National Action Plan on AMR (JMAFF)
2. Risk Assessment for foodborne antimicrobial-resistant bacteria (Food Safety Commission)
3. One health approach from JANIS (National Institute of Infectious Diseases)
4. AMR situation in Salmonella and E. coli (National Institute of Animal Health)

Presentation from participants
- current situation of their country on AMR

OIE Regional Short-term Training on Antimicrobial Resistance in Tokyo Japan (14th – 18th Nov. 2016)

Participants

Cambodia
Chinese Taipei
Hong Kong SAR, China
Mongolia
Myanmar
Philippines
Thailand
Vietnam

OIE
NVAL
Thank you!

A Report on the Japanese Veterinary Antimicrobial Resistance Monitoring System
-2000 to 2007-
National Veterinary Assay Laboratory
Ministry of Agriculture, Forestry and Fisheries
2009

A Report on the Japanese Veterinary Antimicrobial Resistance Monitoring System
-2008 to 2011-
National Veterinary Assay Laboratory
Ministry of Agriculture, Forestry and Fisheries
2013

Report on the Japanese Veterinary Antimicrobial Resistance Monitoring System
-2012 to 2013-
National Veterinary Assay Laboratory
Ministry of Agriculture, Forestry and Fisheries
2013