Outline of JVARM

–Japanese Veterinary Antimicrobial Resistance Monitoring System–

May 16th 2017

National Veterinary Assay Laboratory (NVAL),

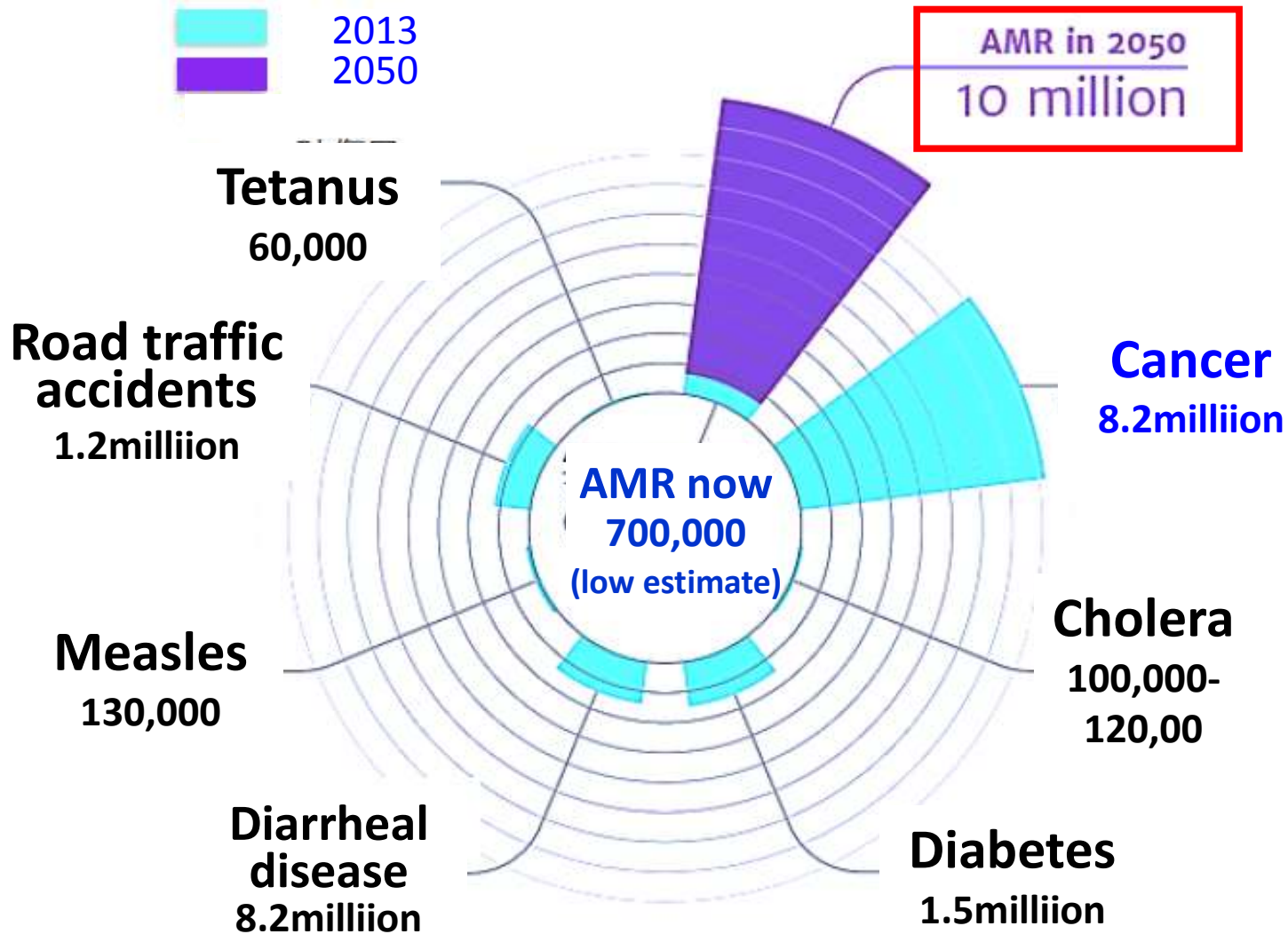
Ministry of Agriculture, Forestry and Fisheries (MAFF)

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.**

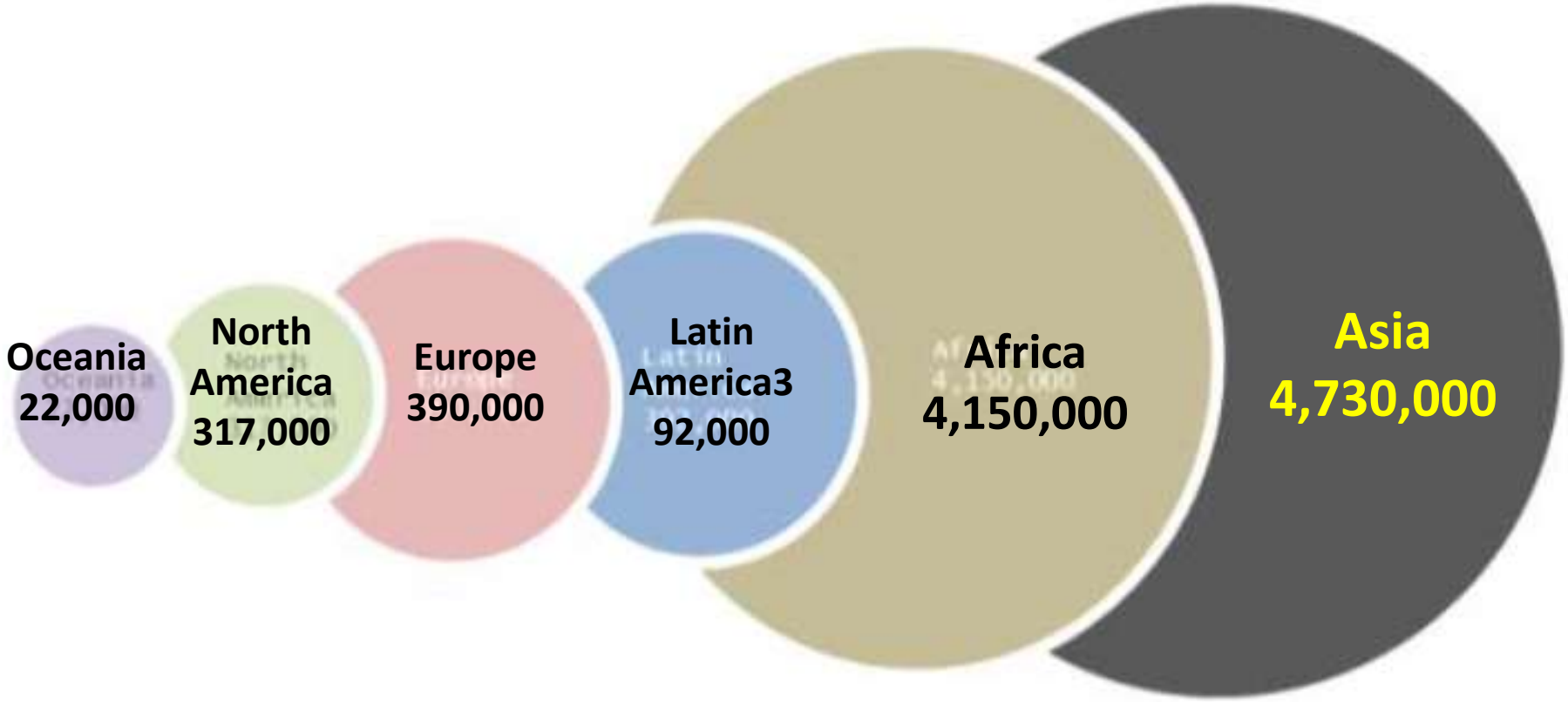
＊There were 120,000 deaths from Tuberculosis in Japan in 1950 (before the introduction of antibiotics)



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

Number of deaths per year attributable to AMR by 2050 if current resistance rates increased by 40%

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



Antimicrobial Resistance in G7 Countries and Beyond, G7 OECD report, Sept. 2015
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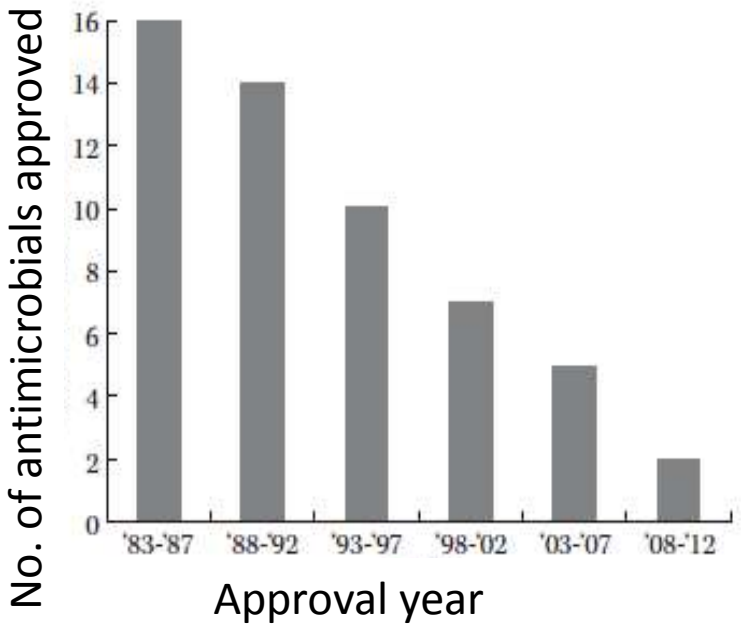
Timeline of antimicrobial marketing in the world

1935 - Prontosil (an oral precursor to sulfanilimide), the first sulfonamide
<1940s> 1942 - benzylpenicillin, the first penicillin
1944 - streptomycin, the first aminoglycoside
1948 - chlortetracycline, the first tetracycline
1949 - chloramphenicol, the first amphenicol
<1950s> 1952 - erythromycin, the first macrolide
1955 - vancomycin, the first glycopeptide
1958 - colistin, the first polymyxin
<1960s> 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
<1980s> 1985 - imipenem/cilastatin, the first carbapenem
1987 - ciprofloxacin, the first 2nd-gen fluoroquinolone
<2000s> 2009 - telavancin, the first Lipoglycopeptide

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



Newly approval antimicrobials in USA

IDSA (Infectious Diseases Society of America); Antibiotic Resistance Fact Sheet 2013

* 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

Selective pressure

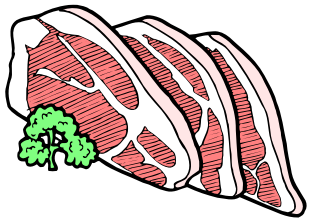
Human

Imported food

Food

One health

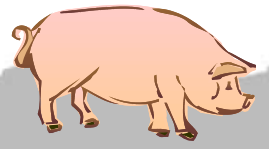
Environment

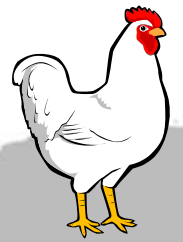


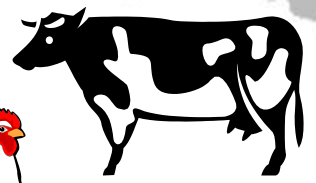
Animal

Selective pressure

Animal







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

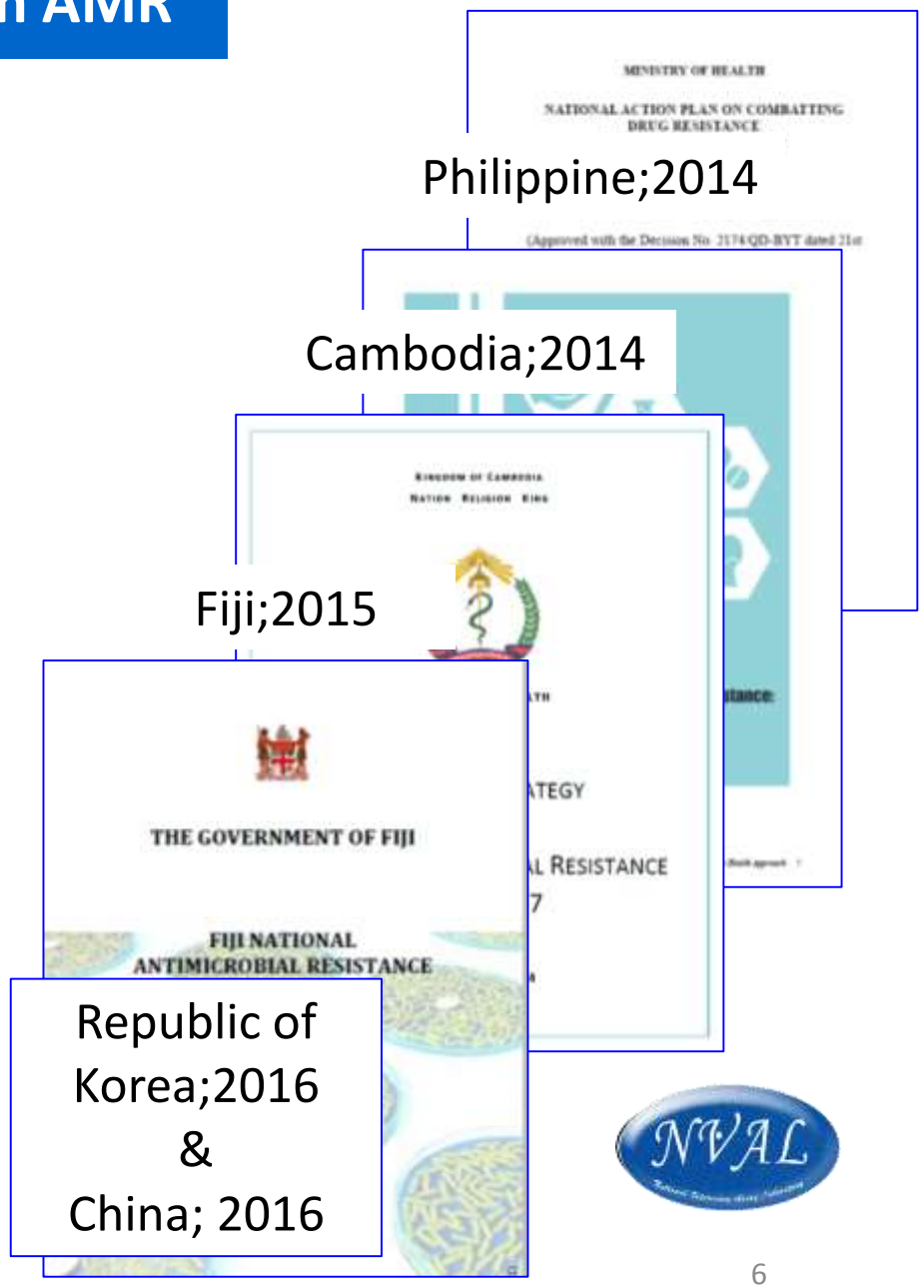
April 5, 2016
The Government of Japan

Vietnam;2013

Philippine;2014

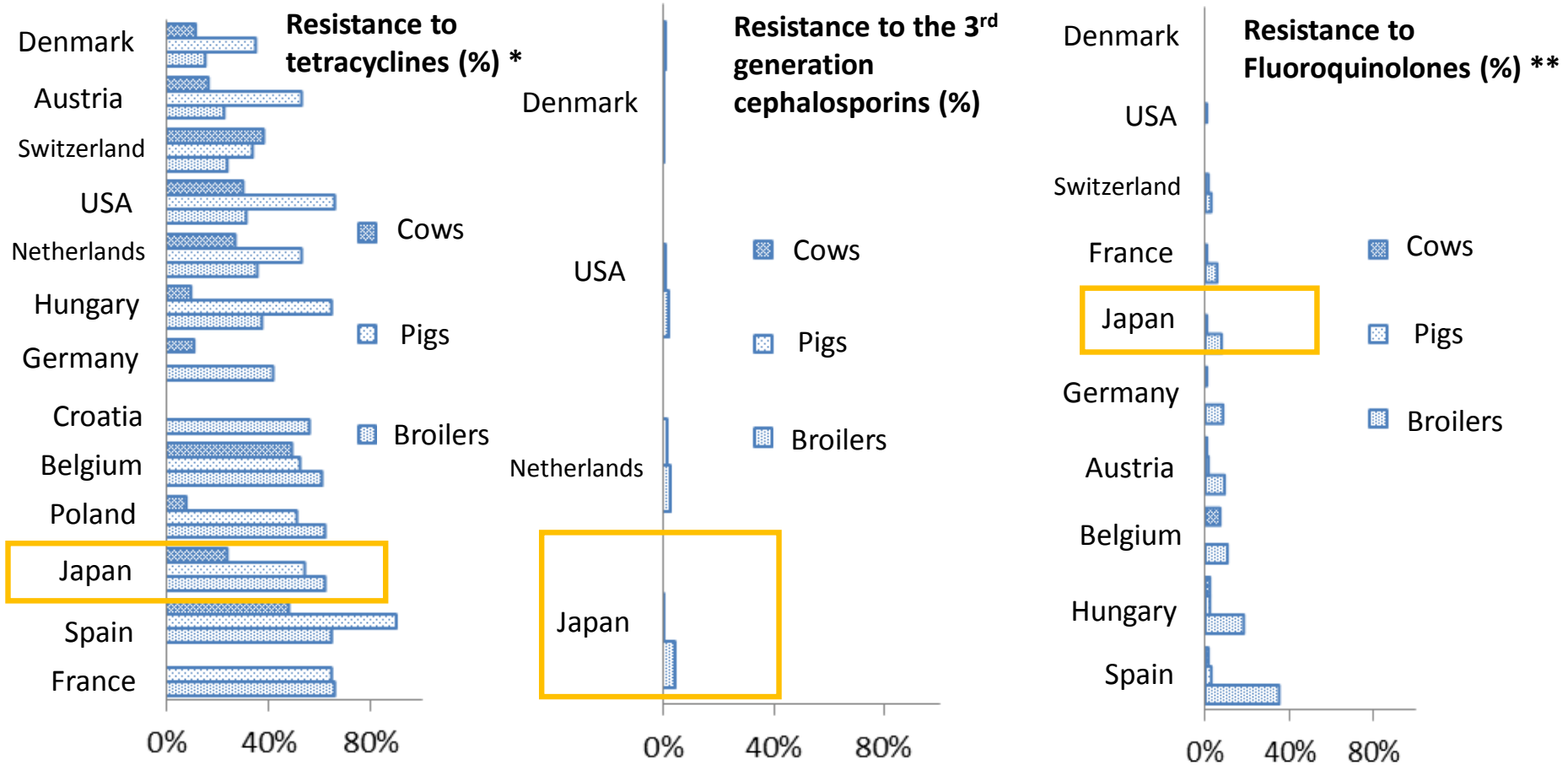
Cambodia;2014

Fiji;2015



Republic of
Korea;2016
&
China; 2016

International comparison of *E.coli* resistance in livestock animals in 2013



* 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

(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)

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

Current Efforts
– AMR Japanese National Action Plan –

6 Key Frameworks

Awareness through education	Surveillance & Monitoring	Infection Prevention & Control
Optimal use of antimicrobials	Research & Development	International Cooperation

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>

% of resistant isolates of specific indicator microorganisms (average of cows, pigs and broilers)		
Indicator	**2014**	**2020 (target)**
% of tetracycline resistance in *E. coli*	45%	33% or less
% of 3rd generation cephalosporin resistance in *E. coli*	1.5%	same level as G7 in 2020
% of fluoroquinolone resistance in *E. coli*	4.7%	same level as G7 in 2020

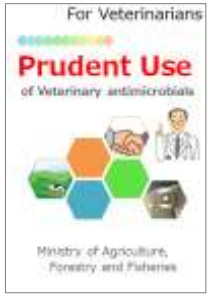
<Humans>

Antimicrobial Use for humans	
Index	**2020 (target)**
Total	Decreased by 33%
Oral cephalosporins, fluoroquinolones, macrolides	Decreased by 50%
Amount of intravenous antimicrobials used	Decreased by 20%

% of resistant isolates of specific indicator microorganisms		
Indicator	**2014**	**2020 (target)**
% of penicillin-resistance in *Streptocuccus pnenumoniae*	48%	15% or less
% of fluoroquinolone resistance in *E. coli*	45%	25% or less
% of methicillin resistance in *Staphylococcus aureus*	51%	20% or less
% of carbapenem resistance in *Pseudomonas aeruginosa*	17%	10% or less
% of carbapenem resistant in *E.coli/Klebsiella pneumoniae*	0.1-0.2%	Same level as 2014

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



NVAL

Number of Livestock in Japan (×1,000 head)

	2006	2008	2009	2012	2014	2016*	Increase / decrease (2016/2006)
Dairy cattle	1,636	1,553	1,500	1,449	1,395	1,345	-17.8
Beef cattle	2,775	2,890	2,923	2,723	2,567	2,479	-10.7
Pigs	9,620	9,745	9,899	9,735	9,537	9,313	-3.2
Layers	180,697	184,773	180,994	178,546	172,349	173,349	-4.1
Broiler*	103,687	102,987	107,141	-	135,747	134,395	29.6

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 **V**eterinary **A**ntimicrobial **R**esistance **M**onitoring (1999～)

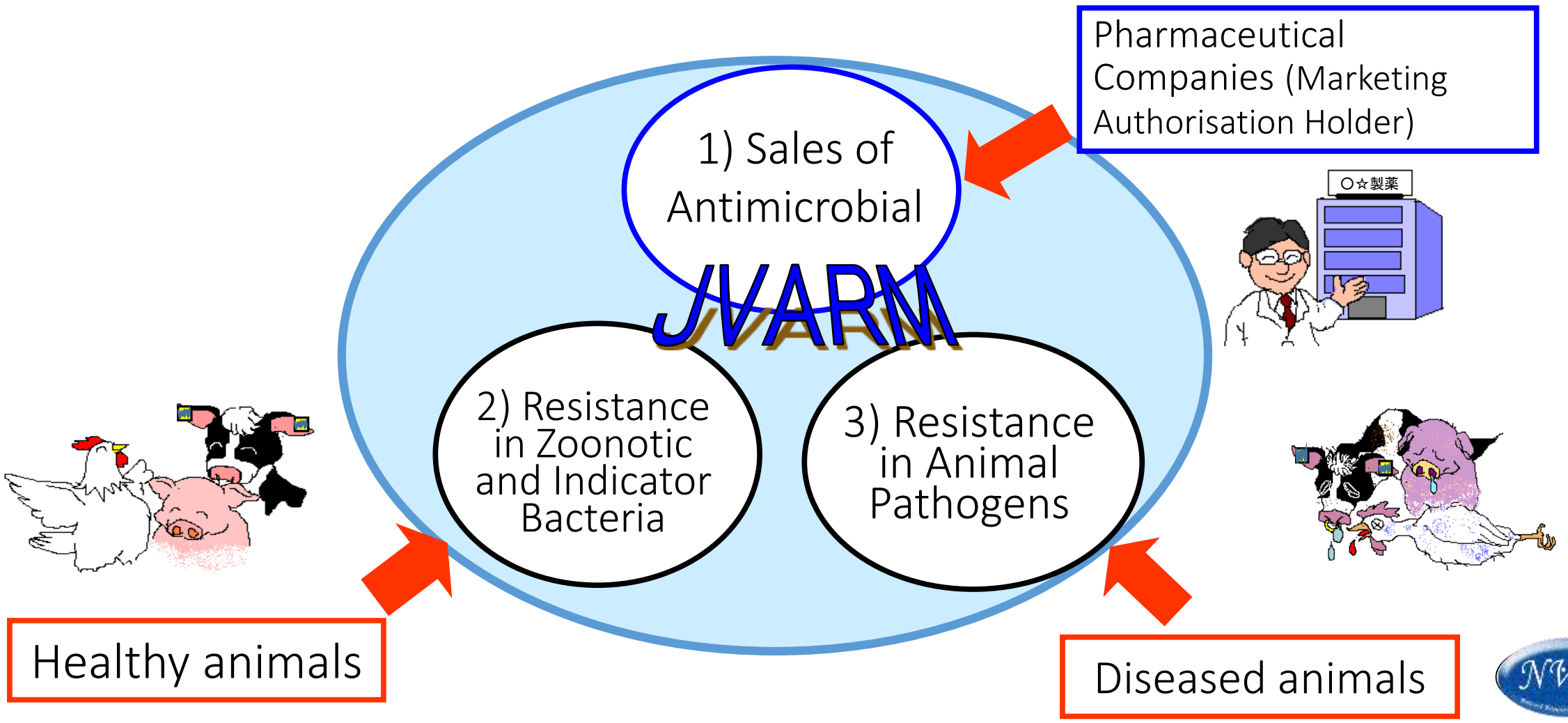
Objectives

- 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



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

http://www.maff.go.jp/nval/iyakutou/hanbaidaka/attach/pdf/h27-koukinzai_re.pdf

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)

Class	Active substance	route of administration	Sales amout (￥1000)	Amounti of active substance (kg)	Estimated Percentages of Sales for Each Animals Species					
					Beef Cattle	Dairy cow	Pig	Broiler	Layer	Dog/Cat
Tetracyclines	Oxytetracycline	oral	383,157	204154	1.8	1.3	84.5	8.1	4.3	
		injection	158,791	1162.7	11.6	5.6	82.5	0.07	0.07	0.09
		total	541,948	205316.7						
	Doxycyclin HCl	oral	520,321	23713.5			84.3	15.6		

http://www.maff.go.jp/nval/iyakutou/hanbaidaka/index.html

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)

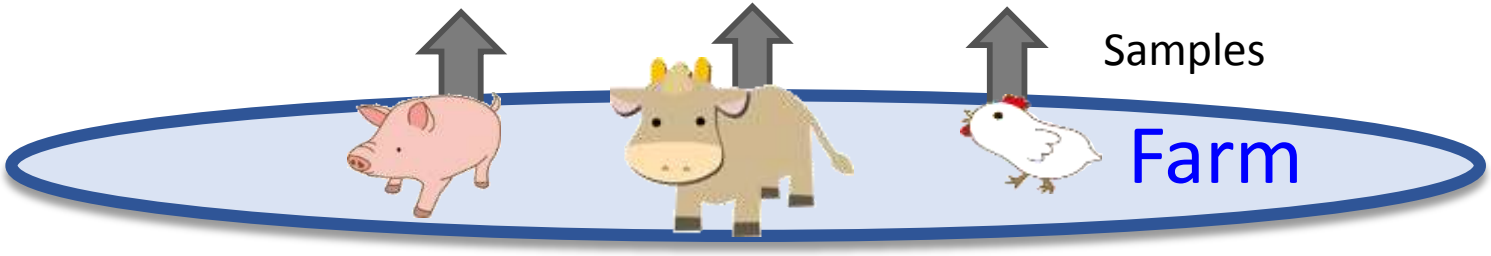
- NVAL（National Veterinary Assay Laboratory）
- FAMIC（Food and Agricultural Materials Inspection Center）(-2015)
  - Sum up, analyze, and evaluate data
  - Research into molecular epidemiology, resistance mechanism

Isolated bacteria, Data

Advice, Training seminar

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

Samples



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

Data ↓ Report ↑

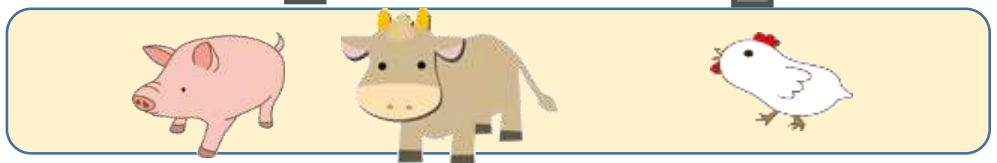
Commission ↓ Data ↑

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

Isolated bacteria, Data ↑ Quality control ↓

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

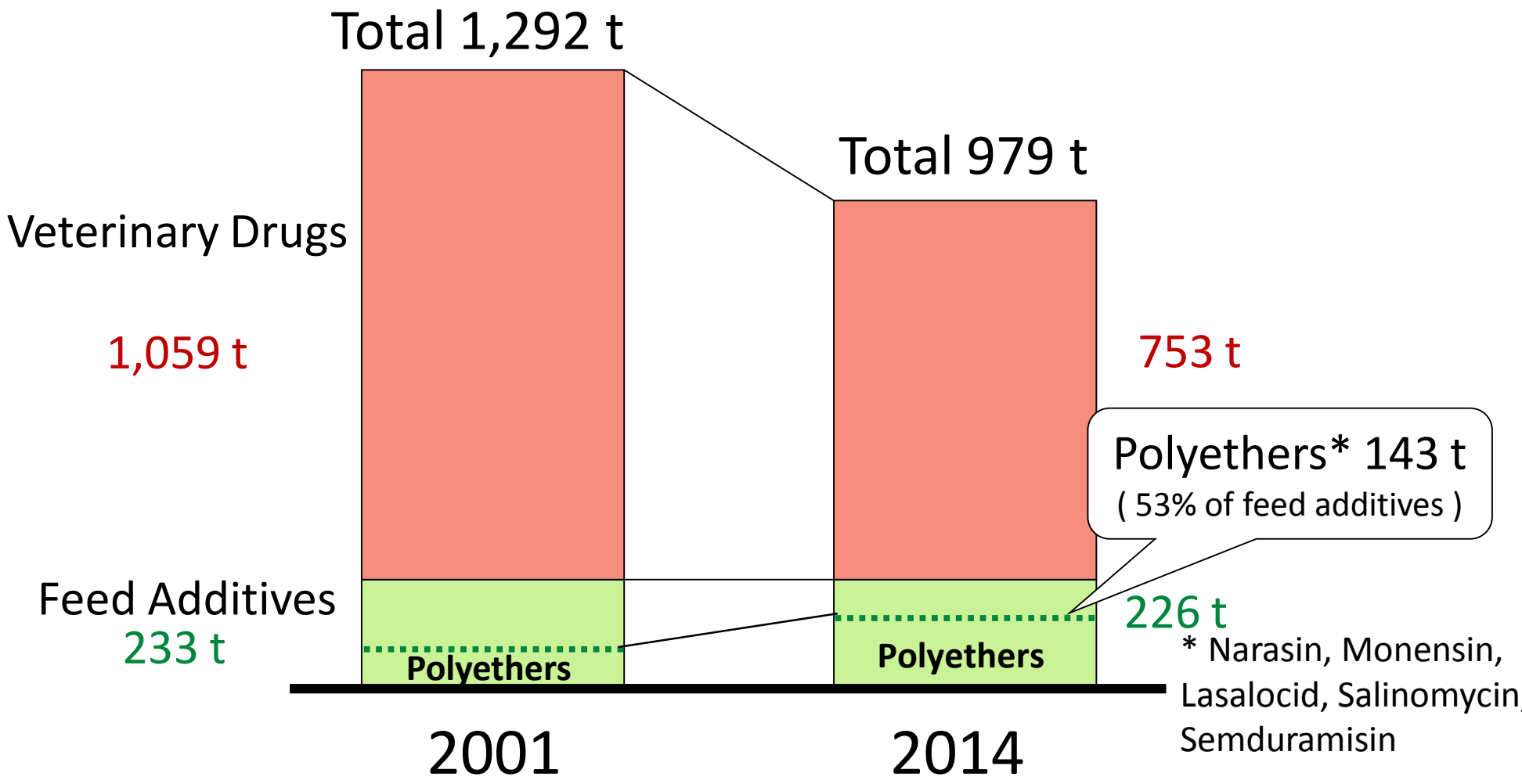
Samples ↑ Samples ↑



Slaughterhouses

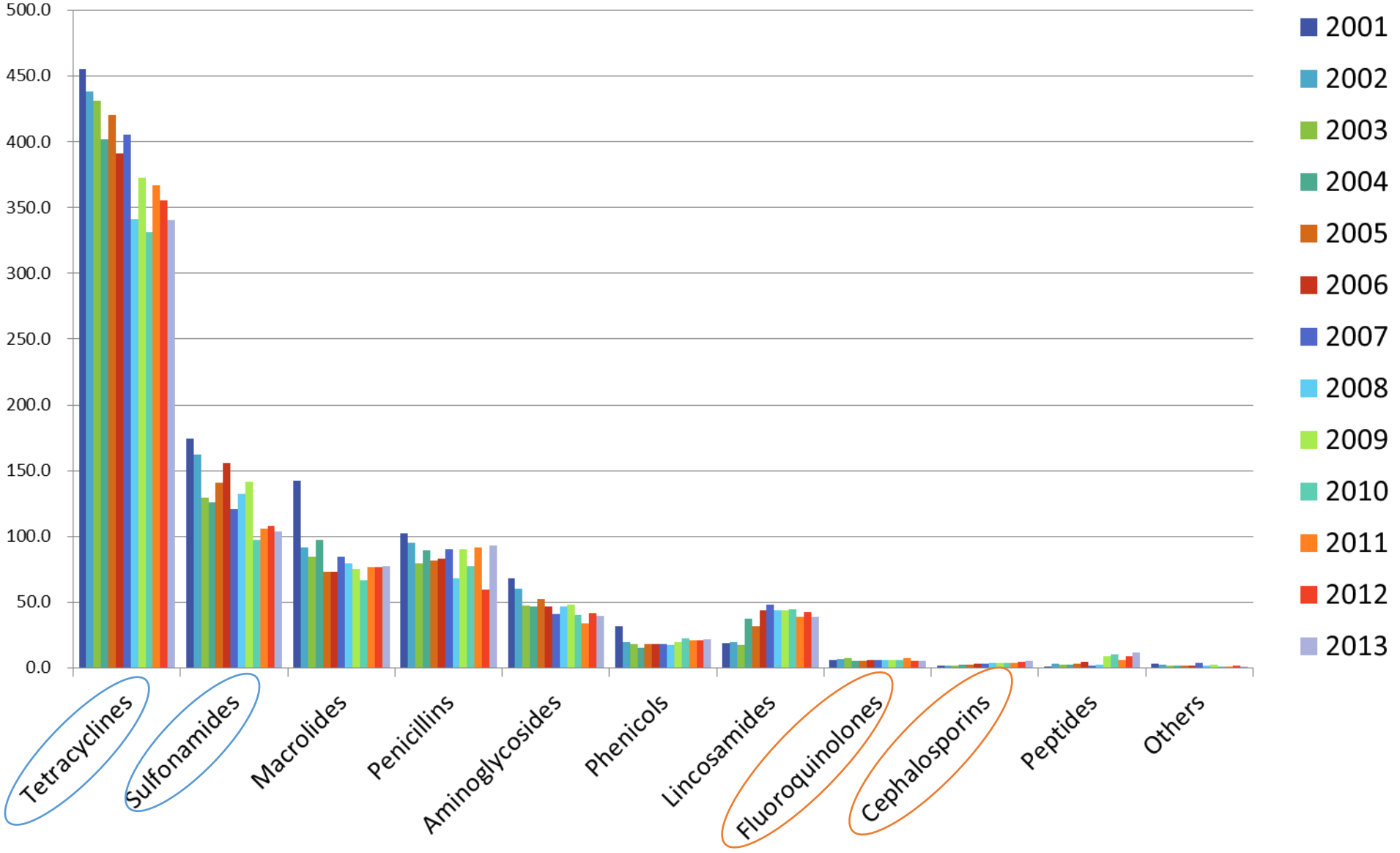
The Sales of Antimicrobials for Animals

* Including food producing animals and companion animals

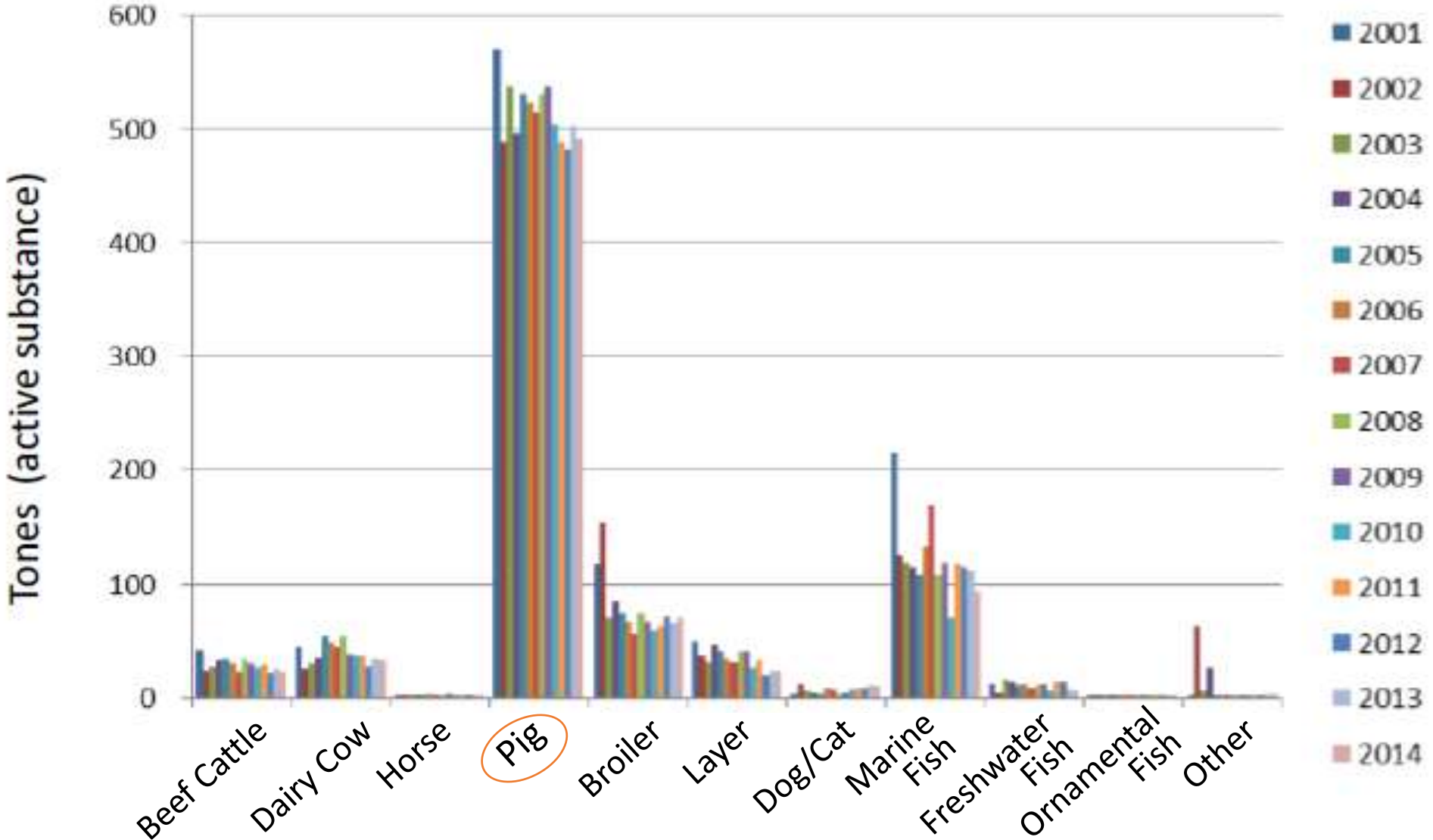


Estimation based on sales/production quantities

Sales of veterinary antimicrobial agents, in tonnes of active substance, during 2001–2013



Sales of veterinary antimicrobial agents by target species, in tonnes of active substance, during 2006–2014



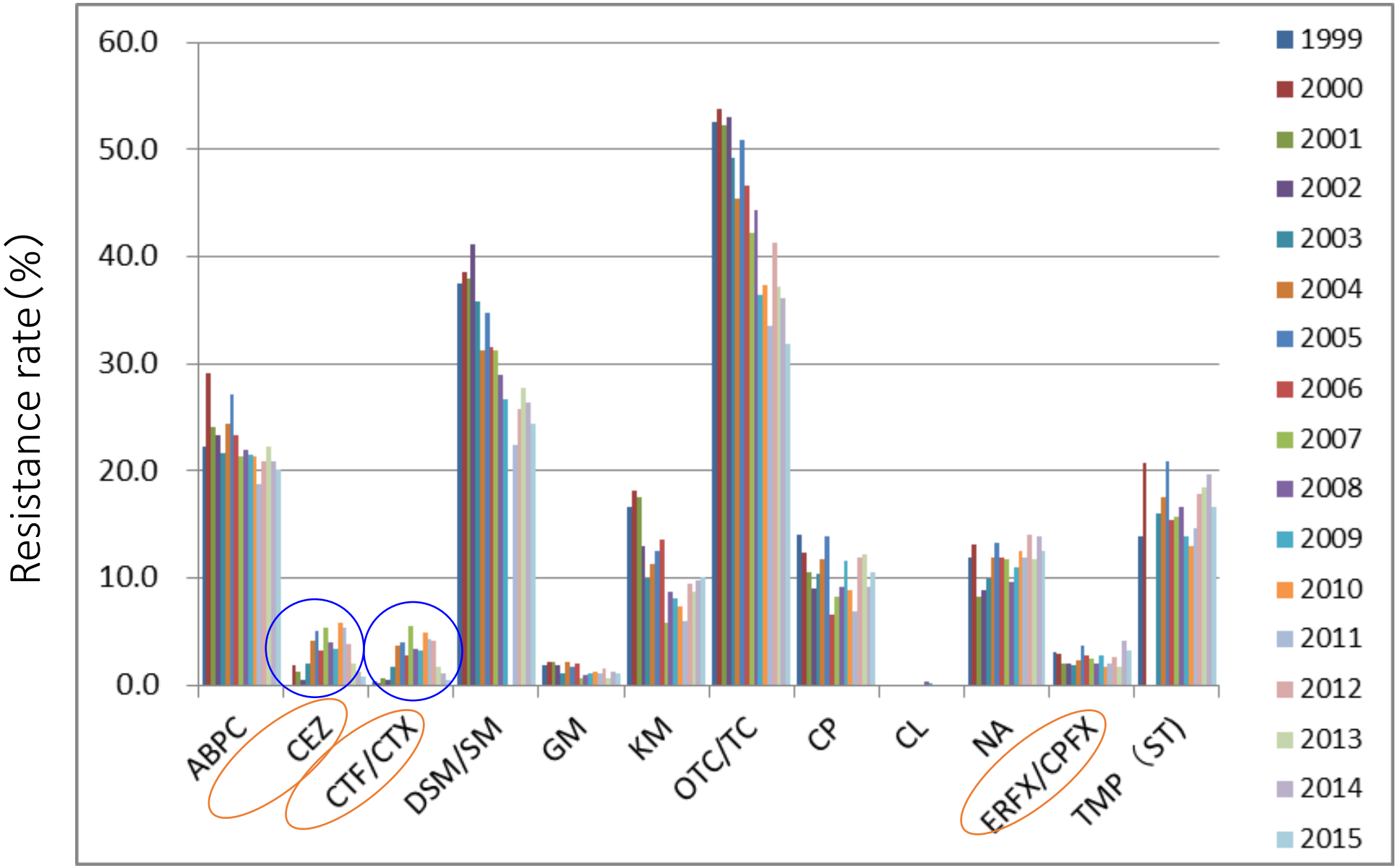
JVARM : Resistance of bacteria (healthy and diseased animals)

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

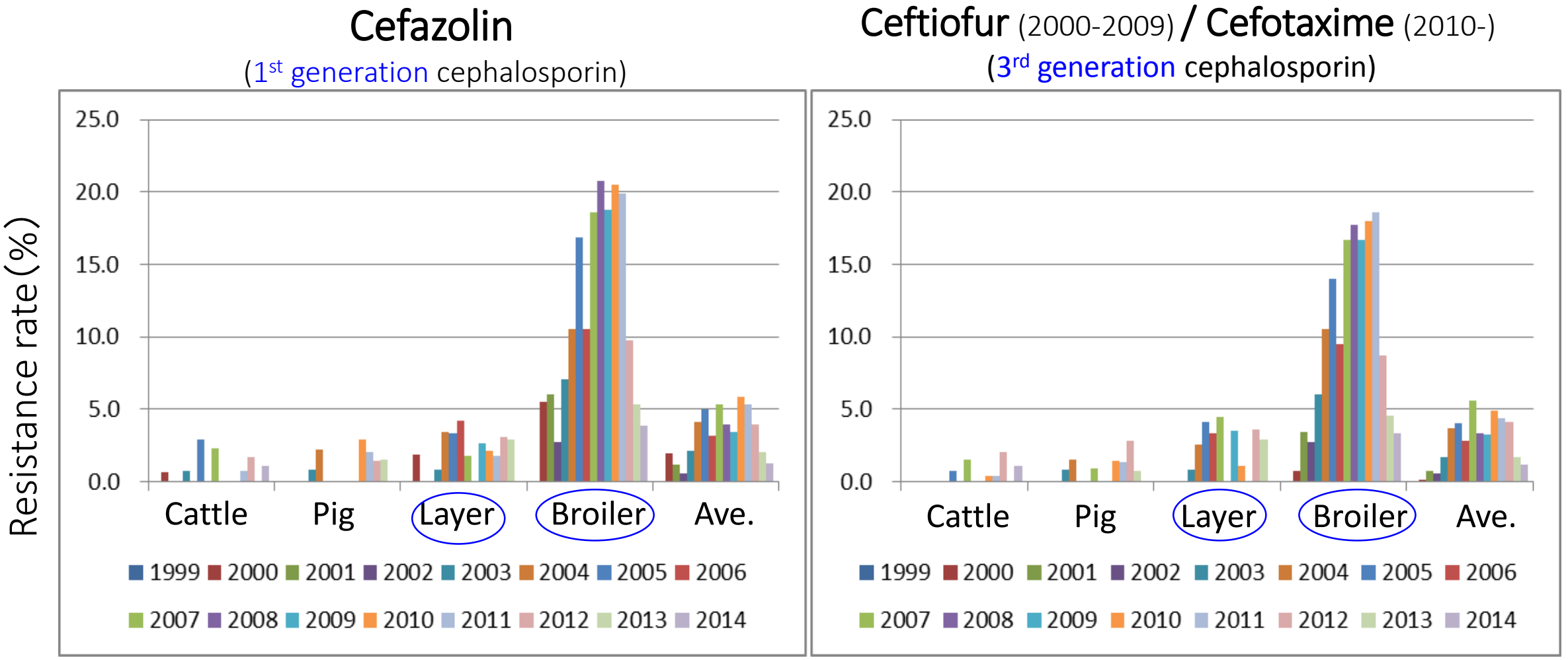
Stage	Year	*E. coli* *	*Entero-coccus* *	*Campylo-bacter*	Healty animal	Clinical isolates	Total
Trial Stage	1999	1,018	1,024	166	124	194	318
1st stage	2000-2003	2,206	1,386	956	183	211	394
2nd stage	2004-2007	1,979	1,920	679	179	482	661
3rd stage	2008-2009	1,295	1,273	390	-	371	371
4th stage	2010-2011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

* Indicator bacteria detected from the healthy animals.

Resistance rate in *E. coli* isolated from healthy animals

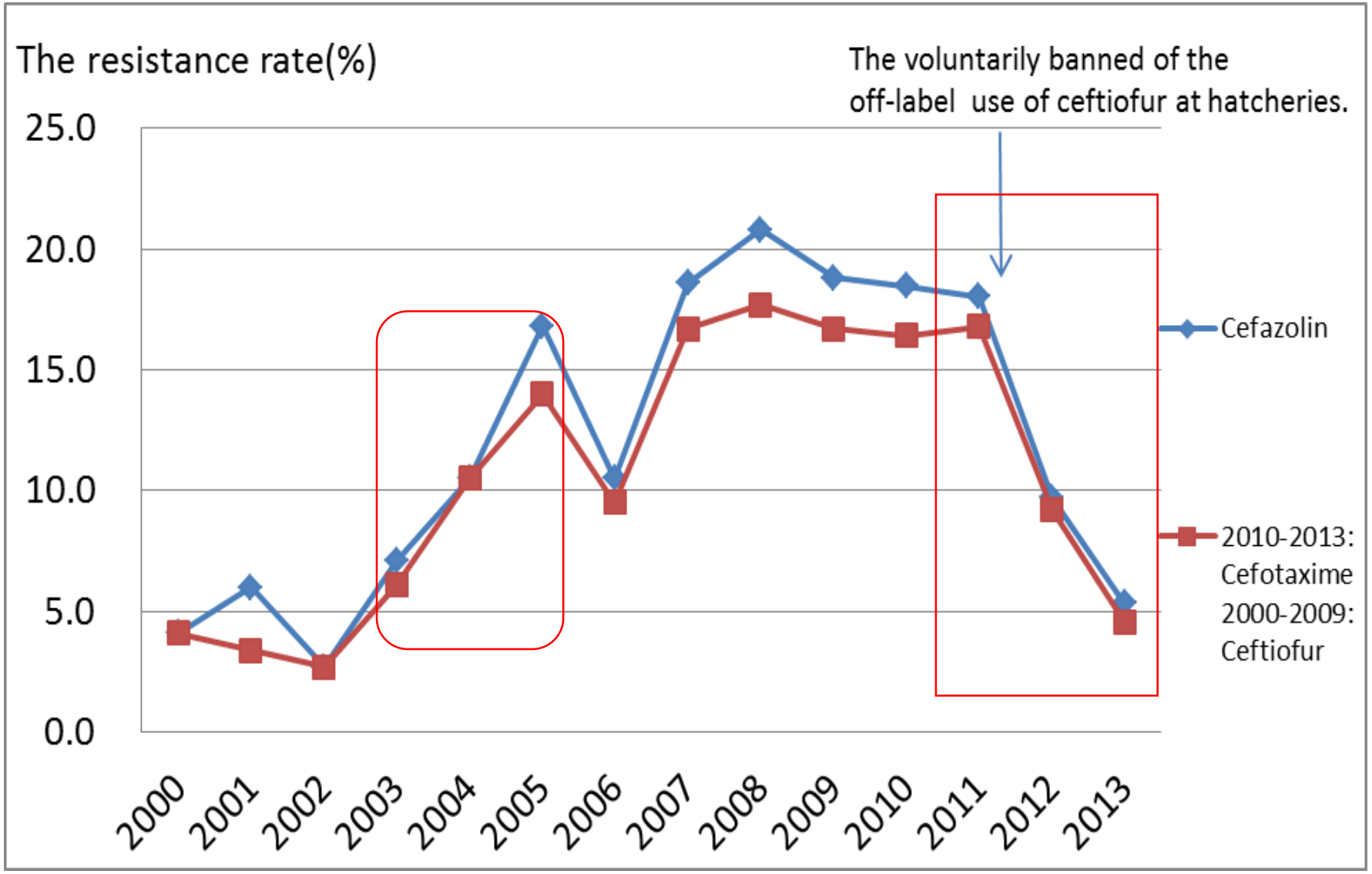


Resistance rate of cephalosporins in *E. coli* isolates from healthy animals



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

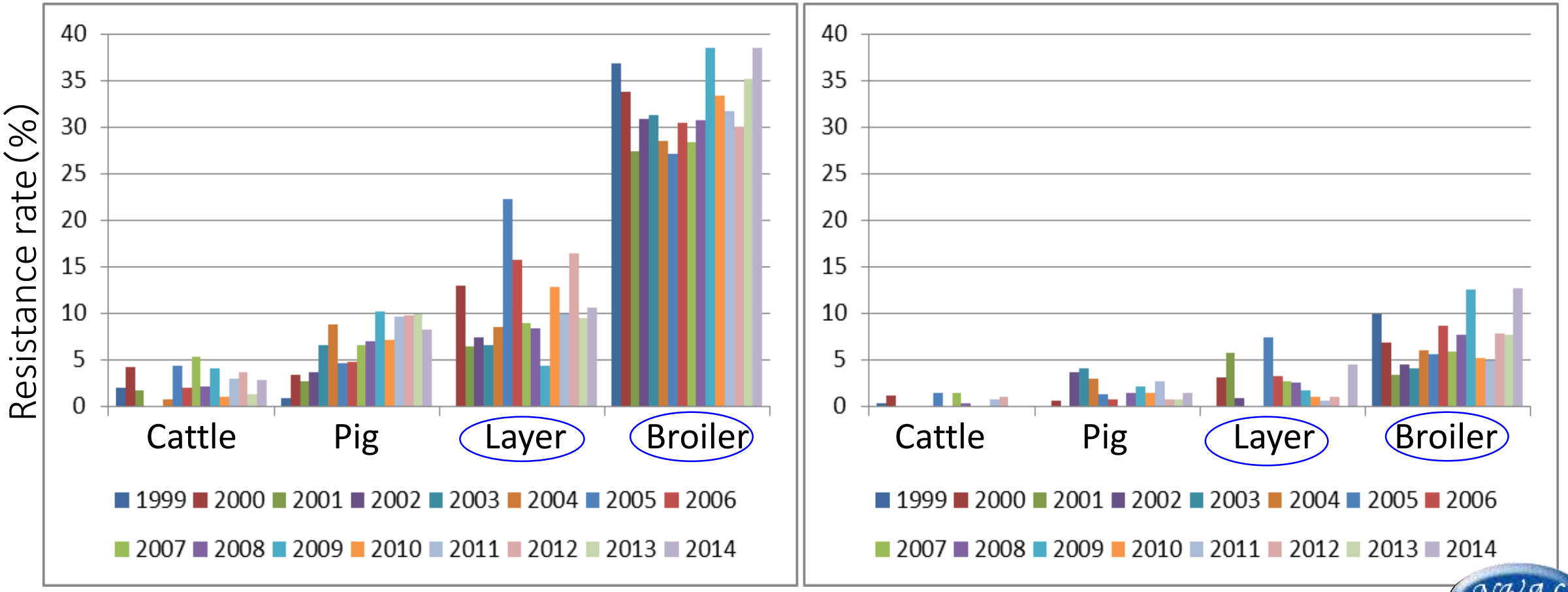


Hiki M et al. Foodborne Pathog Dis. 2015 Jul;12(7):639-43.

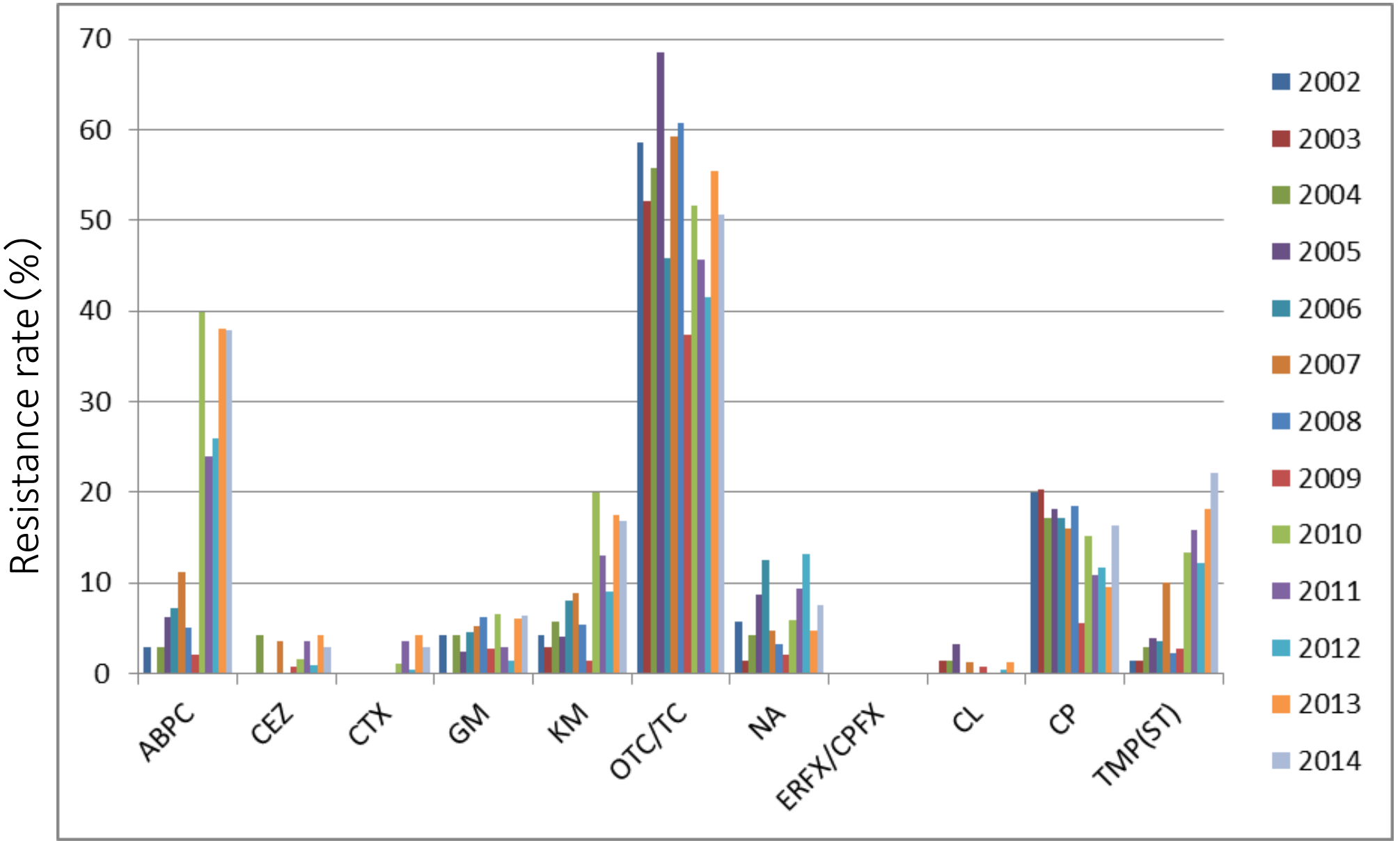
Resistance rate of quinolone in *E. coli* isolates from healthy animals

Nalidixic acid
(Quinolone)

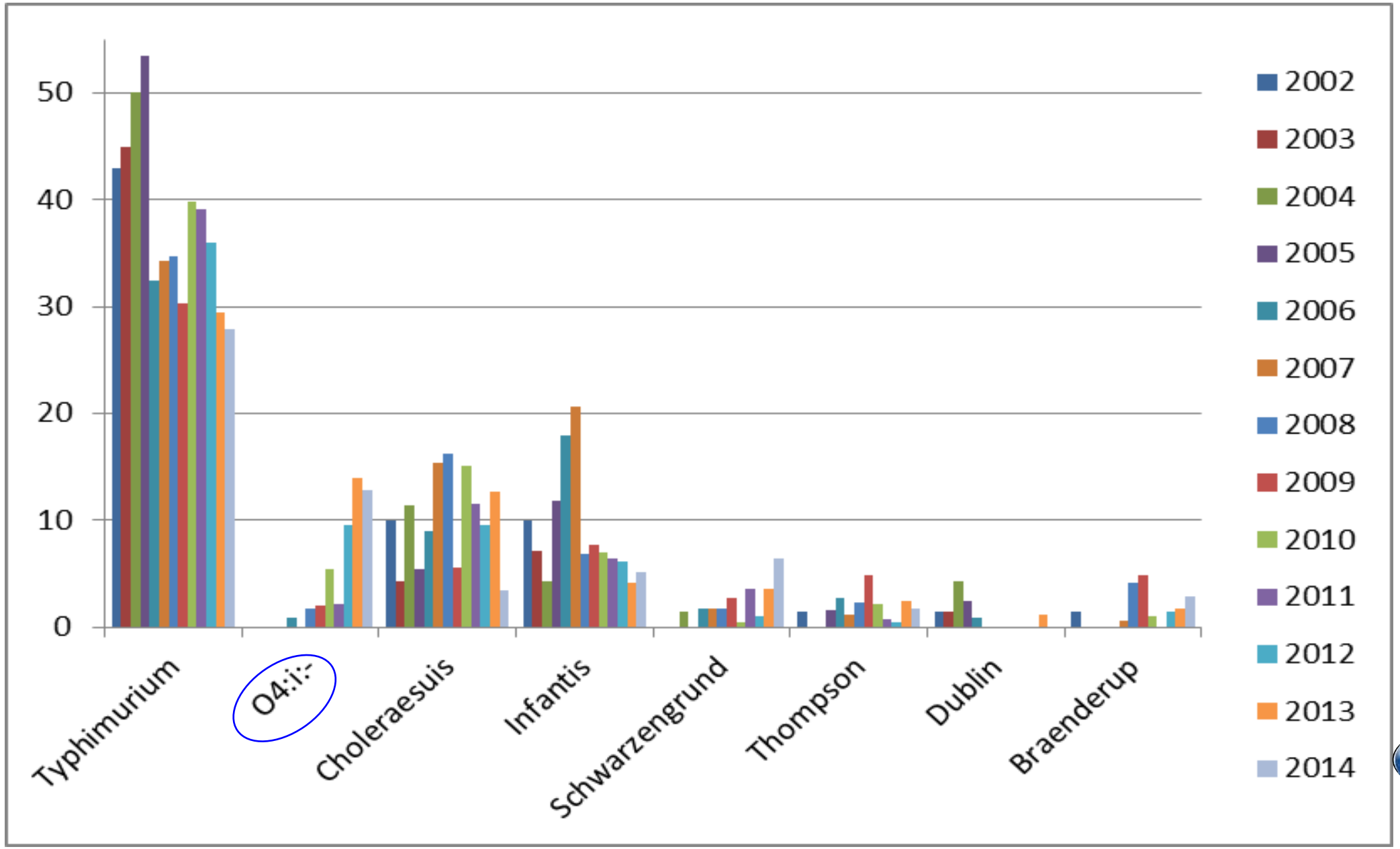
Enrofloxacin (2001-2009) / Ciprofloxacin (2010-)
(Fluoroquinolone)



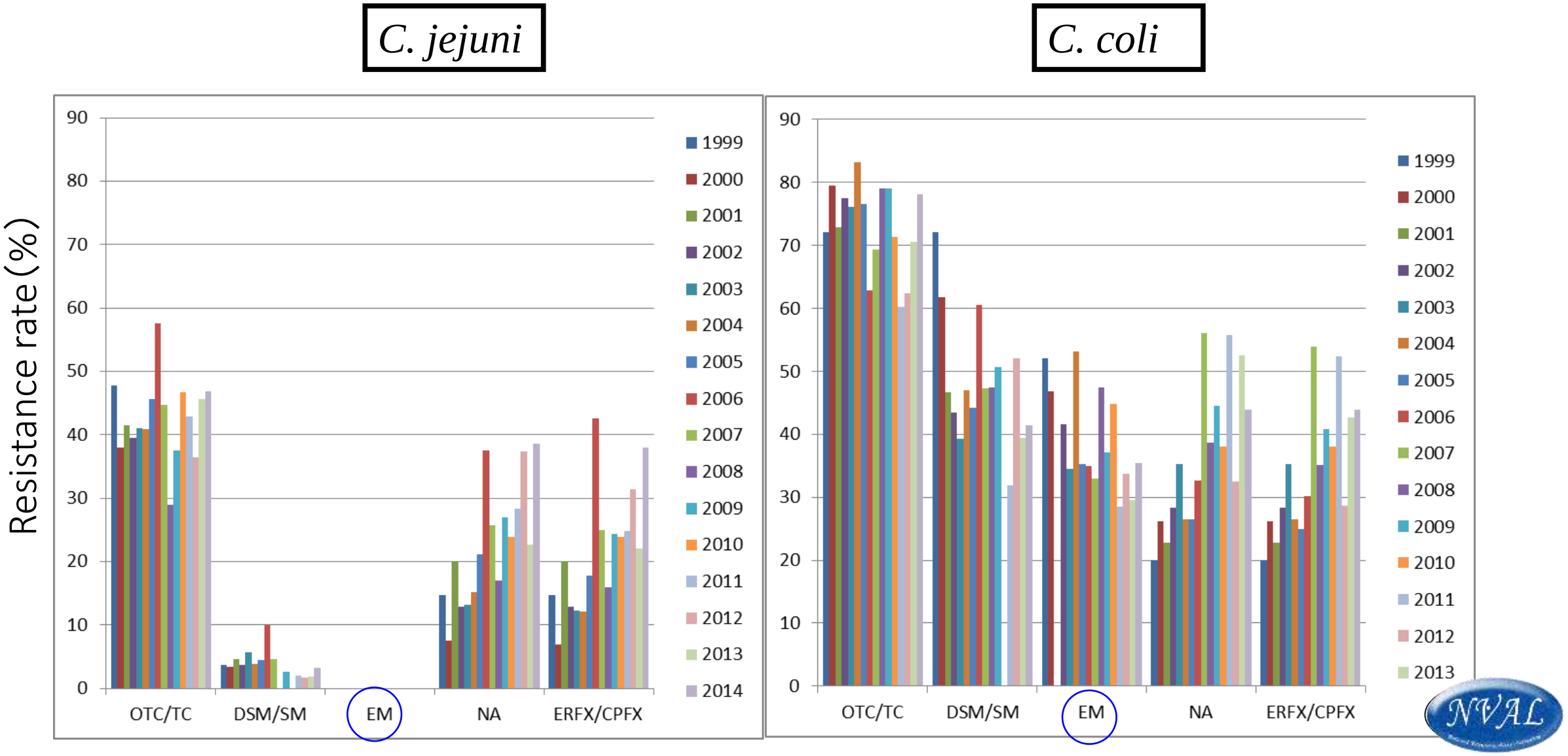
Resistance rate in *Salmonella* isolated from diseased animals (2002-2014)



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

JANIS (Since 2000)

JVARM MIC data (Since 1999)

hospital

hospital

hospital

hospital

MIC data

MIC data

MIC data

JANIS server

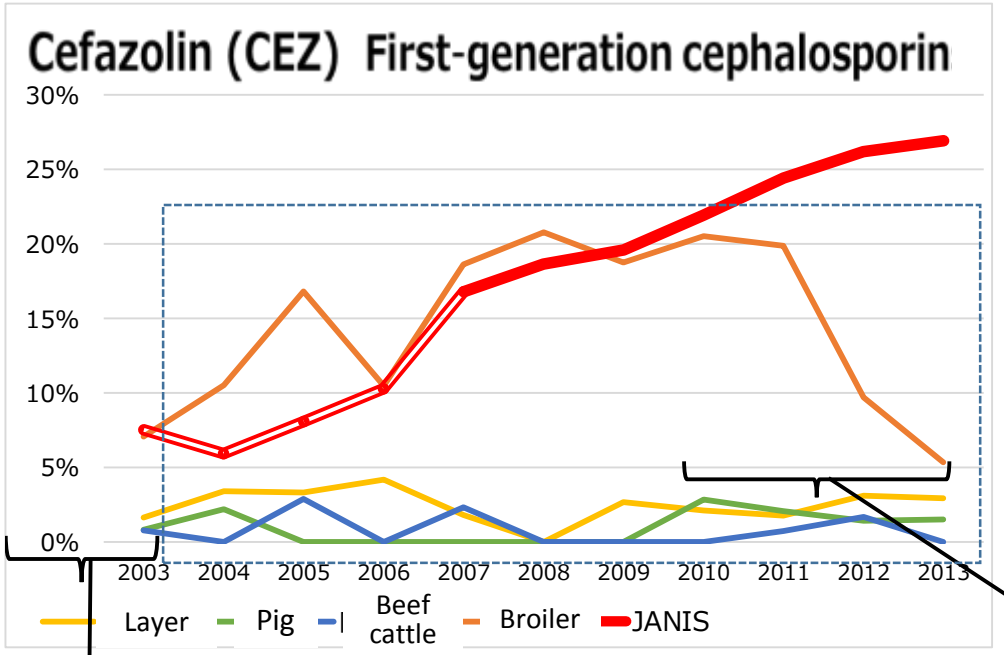
Copy of JANIS Server

Same format

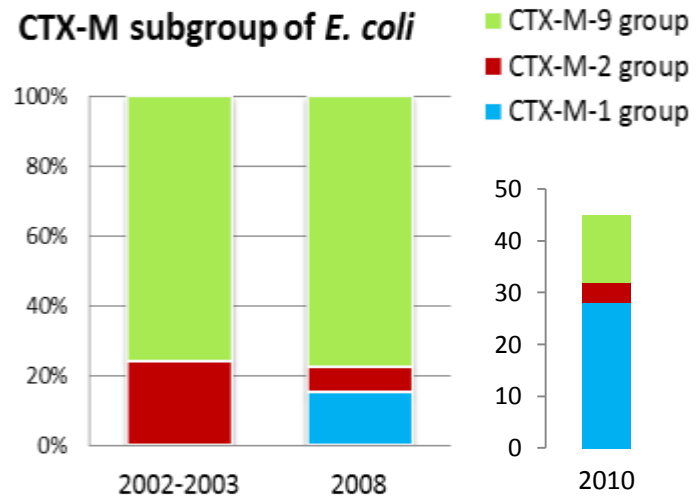
Can calculate

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

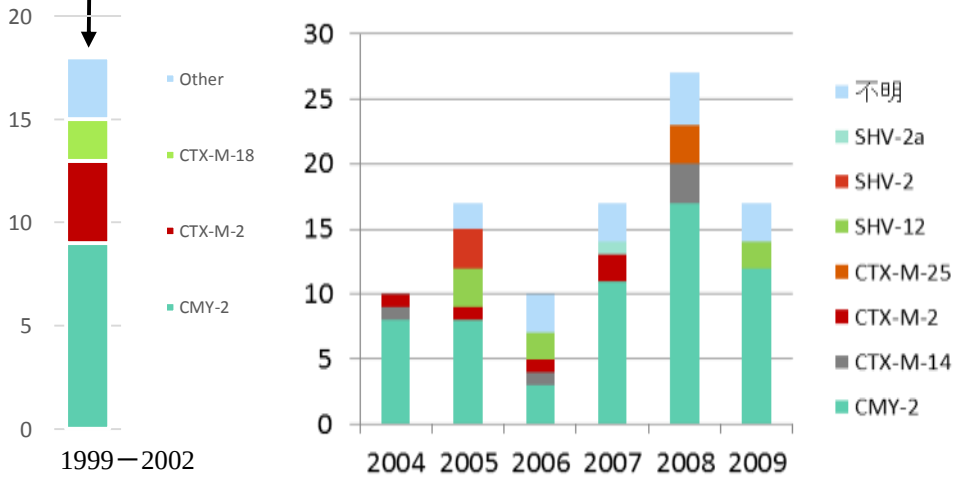
β-Lactamase gene



Isolated from human

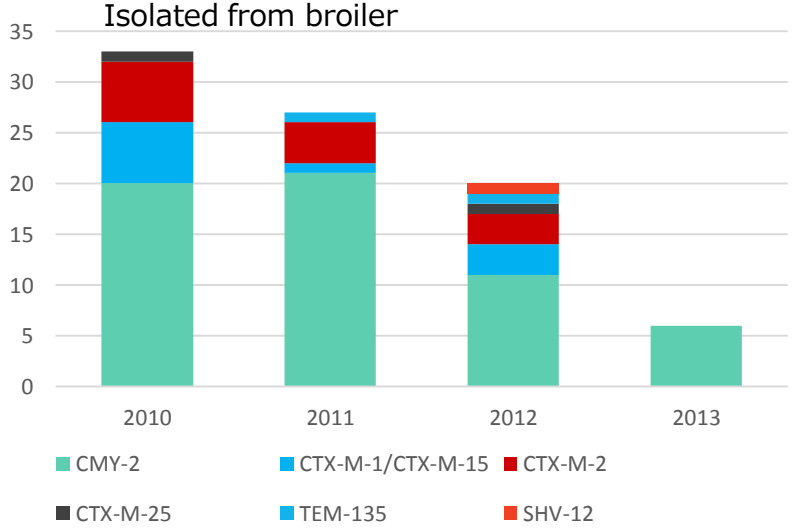


Suzuki S et al. J Antimicrob Chemother. 2009 Jan;63(1):72-9



Kojima A et al. Antimicrob Agents Chemother. 2005 Aug; 49(8): 3533–3537.

Isolated from broiler



Hiki M et al. Foodborne Pathog Dis. 2015 Jul;12(7):639-43.

National antimicrobial resistance monitoring

USA NARMS — FDA, CDC, USDA

National Antimicrobial Resistance Monitoring System

Canada CIPARS — Public Health Agency of Canada

Canadian Integrated Program for Antimicrobial Resistance Surveillance

Denmark DANMAP — NFI, NVI, DMA

Danish Integrated Antimicrobial Resistance Monitoring and Research Programme

UK UK-VARSS — APHA, VMD

UK Antibiotic Resistance and Sales Surveillance Report

France RESAPATH — ANSES

French surveillance netwark for antimicrobial reistance in pathogenic bacteria of animal origin

Sweden SVARM — NVI

Swedish Veterinary Antimicrobial Resistance Monitoring

Norway NORM/NORM-Vet — Norwegian Veterinary Institute

Ussage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

***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

Human sector

JANIS

MAFF

Other Asian member states

JVARM network

NVAL

- AMR central lab
- OIE collaborating center

JVARM

International contribution

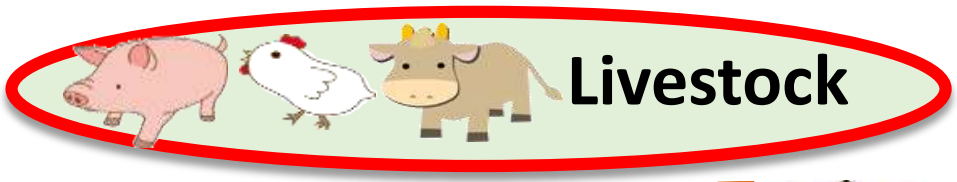
Livestock hygiene service centers

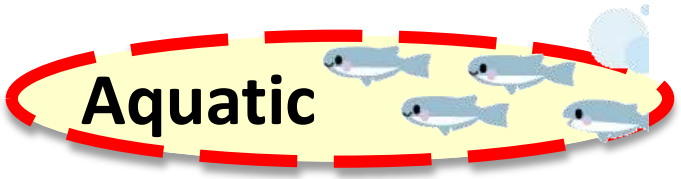
Private test service

Animal hospitals

Academia

Aquatic test facilities





NVAL

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

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

Manufacturer tour

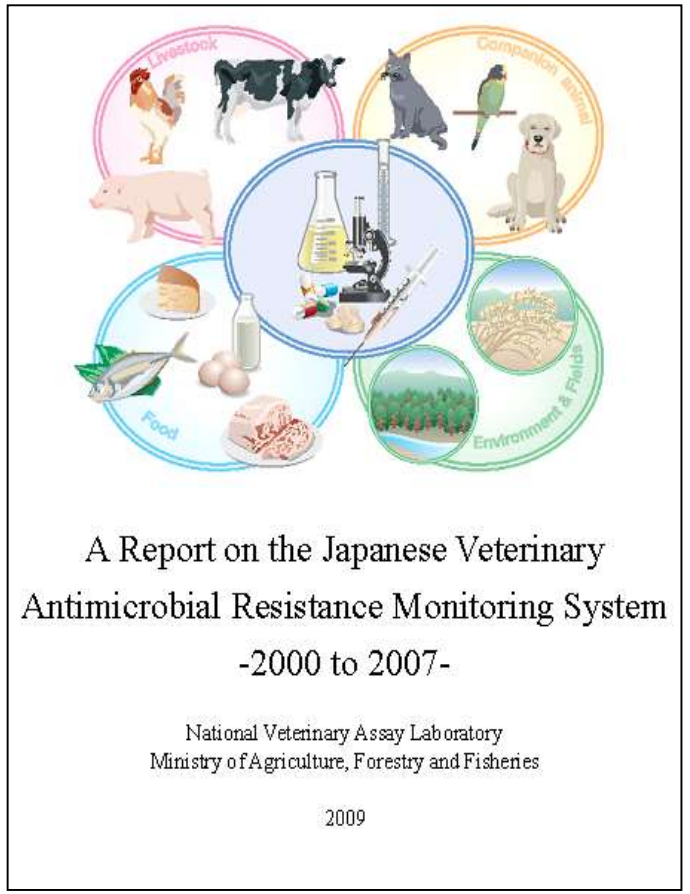
http://www.maff.go.jp/nval/OIE/2016kennsyuu.html

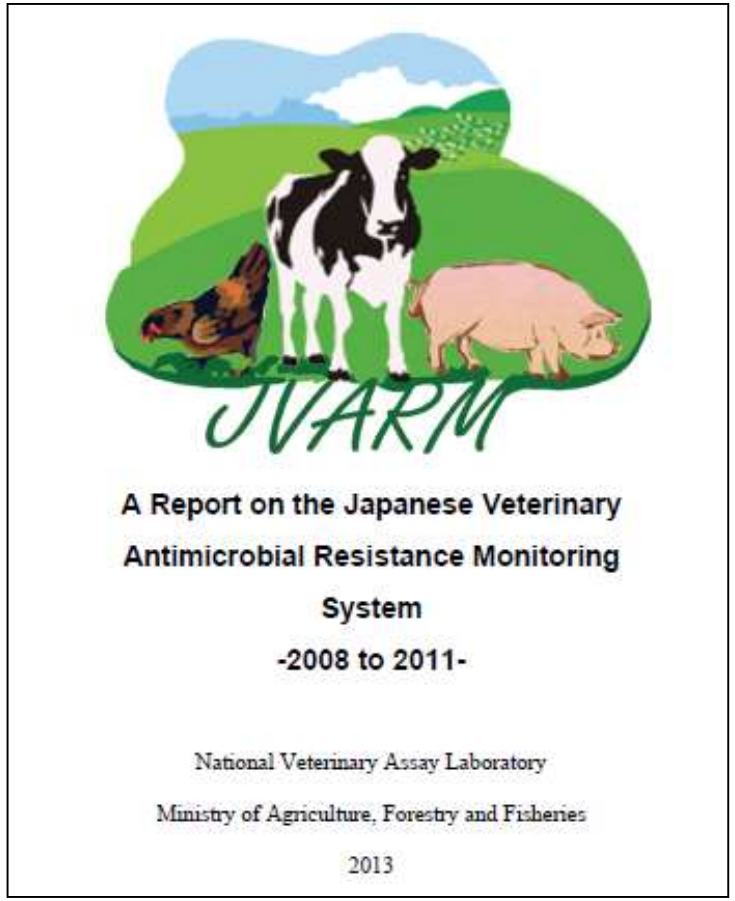
OIE Regional Short-term Training on Antimicrobial Resistance in Tokyo Japan (14th – 18th Nov. 2016)

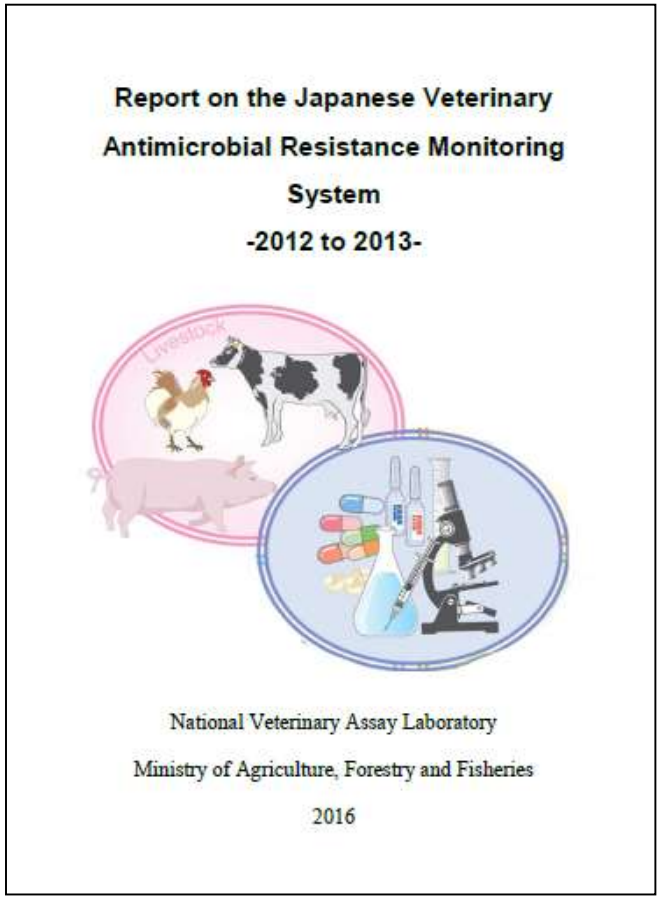
Participants

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

Thank you !







http://www.maff.go.jp/nval/yakuzai/yakuzai_p3.html