



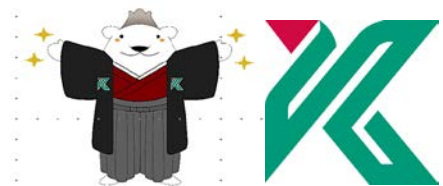
Sakurajima "Cherry blossom Island" is an active composite volcano and a former island in Kagoshima Prefecture

National Action Plans on Antimicrobial Resistance in Japan

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Disclosure

- I have no potential conflict of interest to this symposium.
- I am a member of a university hospital in Japan and this symposium does not indicate the policy of the government of Japan.





World Health
Organization

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE



- The **WHO** featured antimicrobial resistance (AMR) on the World Health Day 2011 and called upon the international community to devote global efforts under the **One Health approach**, which addresses both human and animal health together.
- In 2015, the World Health Assembly endorsed the **Global Action Plan on Antimicrobial Resistance**, and urged **all Member States to develop relevant national action plans** within two years.



- At the **G7 Summit 2015**, **antimicrobial resistance** was taken up as one of the key issues.
- The G7 Health Ministers welcomed the formulation of the Global Action Plan by WHO and discussed the necessity of **strengthening the One Health approach** and of **research and development for new drugs**.
- Assuming the G7 presidency for 2016, **Japan** as the host country of G7 summit is determined **to intensify its efforts in measures against AMR**.



The Government of Japan formulated the National Action Plan on AMR (2016-2020) in April 2016.

This National Action Plan is structured around goals in the following six areas:

1. Public Awareness and Education
2. Surveillance and Monitoring
3. Infection Prevention and Control
4. Appropriate Use of Antimicrobials
5. Research and Development
6. International Cooperation.

**National Action Plan on
Antimicrobial Resistance (AMR)**

2016-2020

April 5, 2016

The Government of Japan

This action plan specified the outcome indices of the antimicrobial resistance and the antimicrobial use

Public Awareness and Education

Goal 1

Improve Public Awareness and Understanding, and Promote Education and Training of Professionals

- According to the questionnaire, about half of Japanese citizens (58063/135137, 43.0%) believed antibiotics are effective for viral diseases.

<https://news.yahoo.co.jp/polls/domestic/25663/result>

- The reasons for taking antibiotics were colds (713/1566, 45.5%), influenza (180/1566, 11.6%) and fever (168/1566, 10.7%).

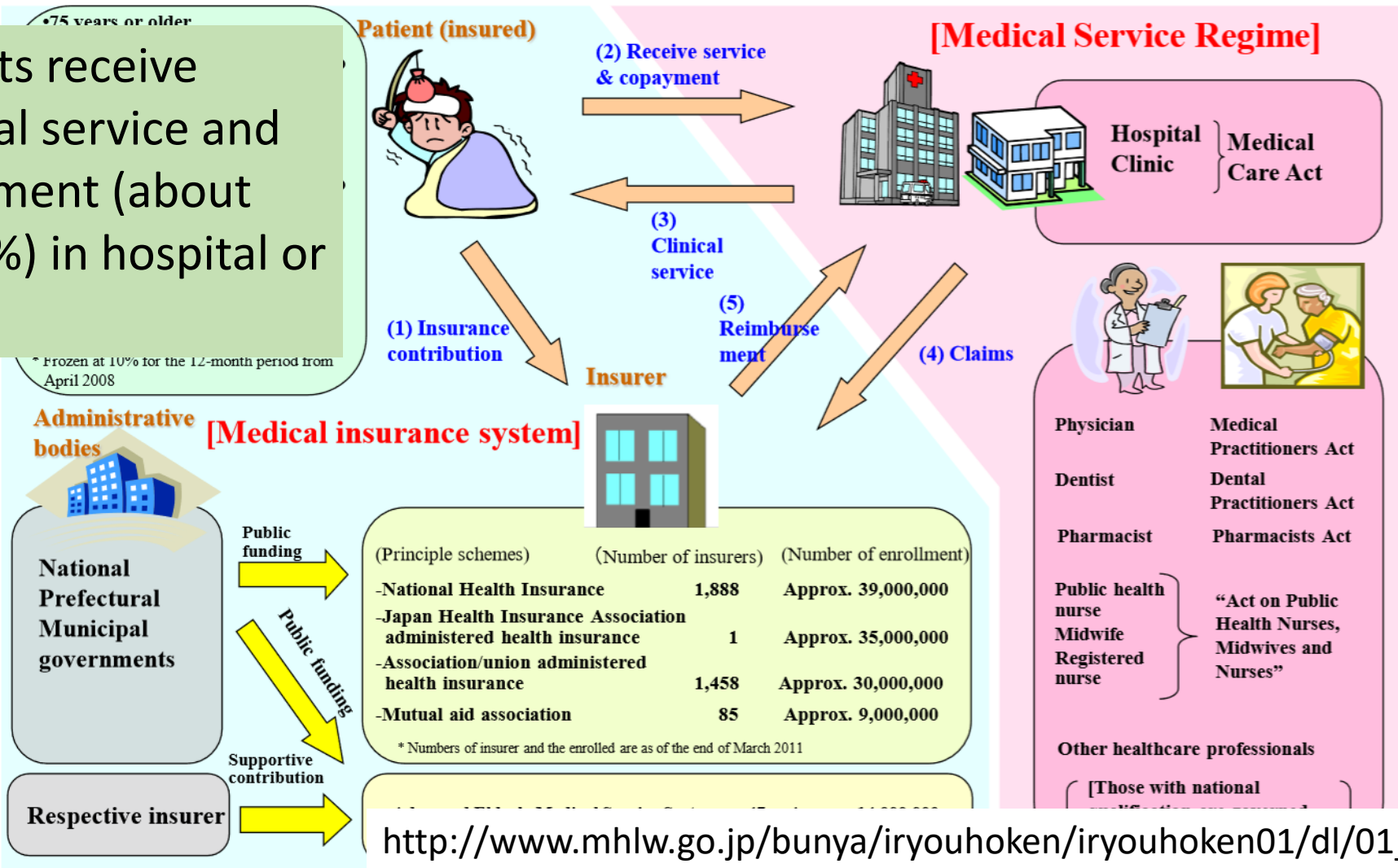
Omagari T. Study on public awareness about drug resistance. Health Labour Sciences Research Grant of Japan Report 2016.

In Japan, a universal healthcare insurance system extending to all citizens has been set up.

Overview of Medical Service Regime in Japan

Patients receive medical service and copayment (about 10-30%) in hospital or clinic.

* Frozen at 10% for the 12-month period from April 2008



http://www.mhlw.go.jp/bunya/iryuhoken/iryuhoken01/dl/01_eng.pdf

Antimicrobials can not be obtained without a prescription from healthcare institutions.

Ministry of Health, Labour and Welfare of Japan create tools which aid proper awareness and understanding of antimicrobial stewardship and infection prevention and control for the purpose of raising the public awareness of AMR

“Go through measures against AMR!”

“There is something everyone can do”



This poster appeals that

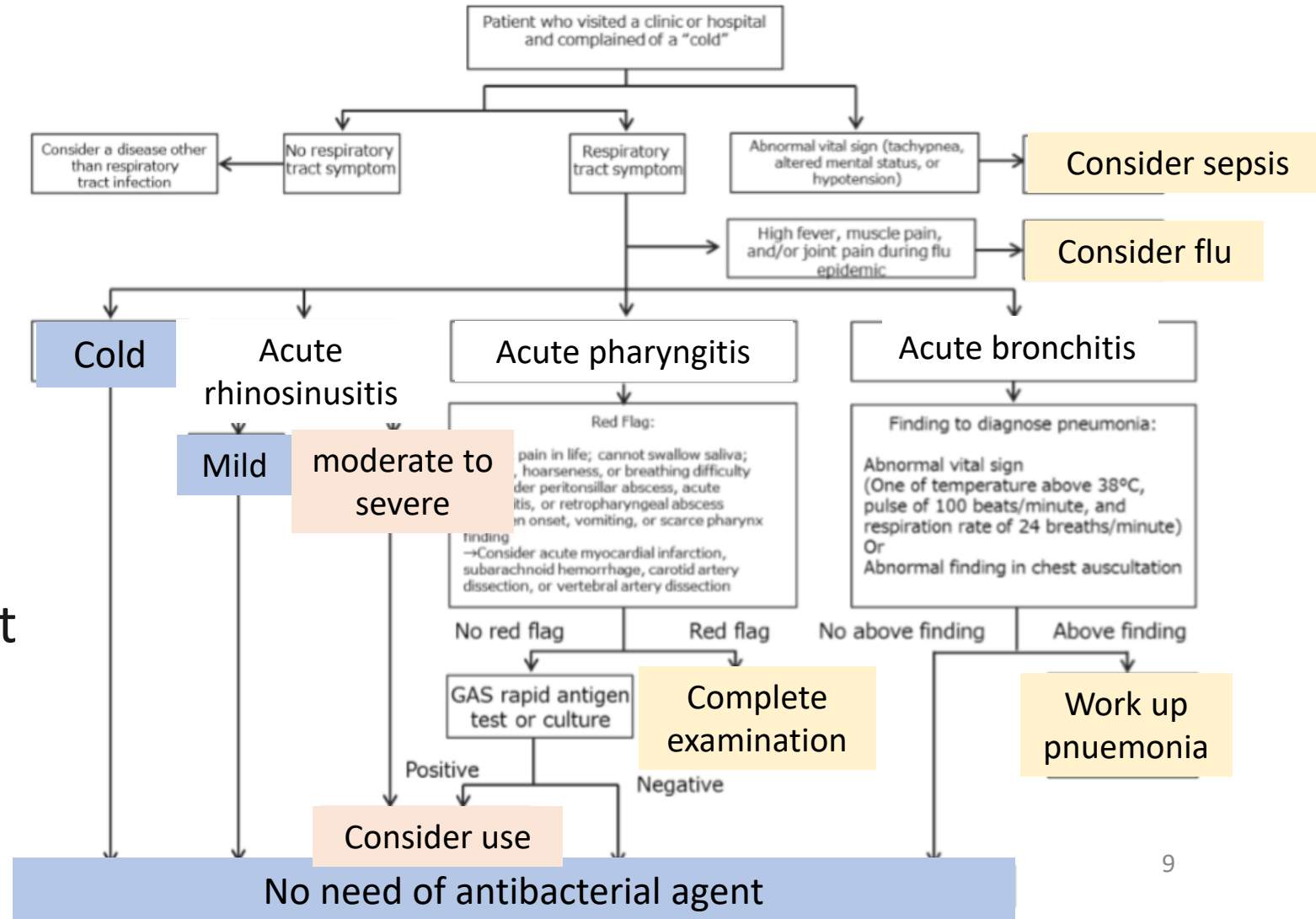
- ✓ Performing hand hygiene and cough etiquette is important for infection prevention
- ✓ Antibiotics are not effective for most cases of the common cold, and unnecessary use of antimicrobials breeds the emergence of antimicrobial-resistant organisms.

He is AMuRo, the hero of the Japanese anime Gundam.

Manual of Antimicrobial Stewardship

- This manual has been prepared for **medical staff conducting outpatient clinical practice** by **Ministry of Health, Labour and Welfare of Japan**.

- This manual is focused on **acute respiratory tract infection and acute diarrhea, which are considered to be particularly frequent use of unnecessary antibacterial drugs.**
- Several **example sentences** when explaining to the patient not to use antibiotics is also described in this manual.



- In **the pediatric medical treatment fee**, an addition will be created that contributes to the proper use of antibiotics (after April 2018)
 - when examining a child who was consulted with acute upper respiratory tract infection or acute diarrhea without the necessity of antibiotic administration.
 - It will be calculated (800yen≒7 US dollars per examination) **against the explanation of the reason why antimicrobials are unnecessary.**

Surveillance and Monitoring 1

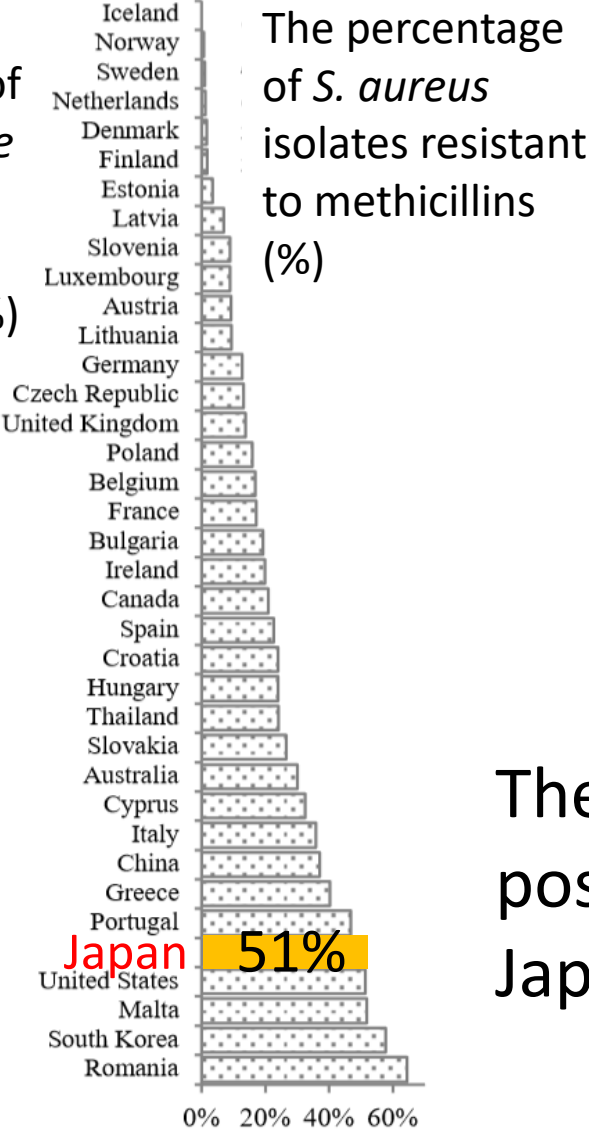
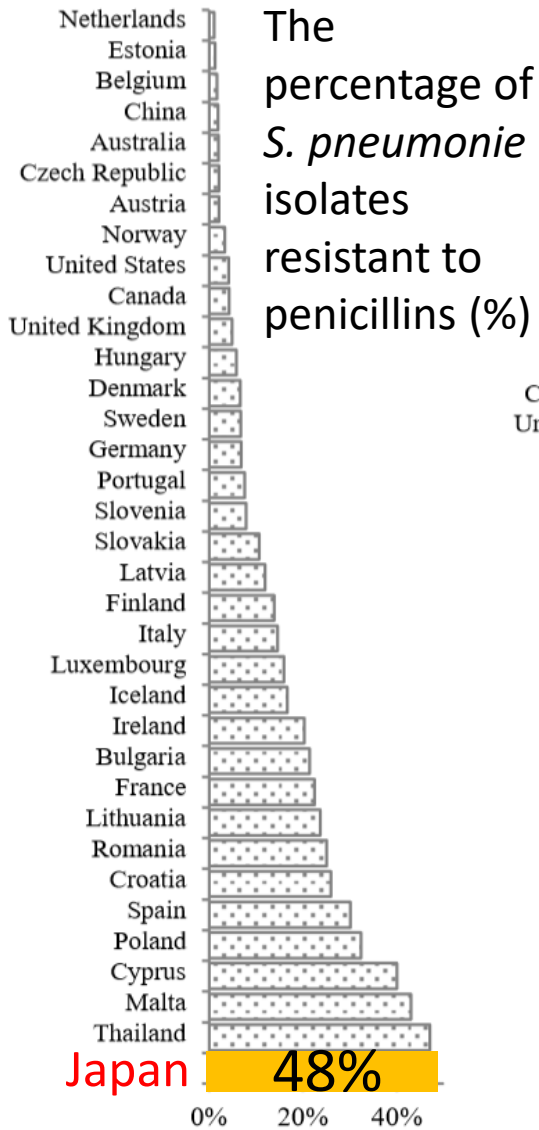
Goal 2

Monitor Antimicrobial Resistance and Use of Antimicrobials Continuously, and Understand the Signs of Change and Spread of Antimicrobial Resistance Appropriately

◆ One of the strategies in this area is to strengthen the surveillance of antimicrobial resistance in healthcare and nursing care

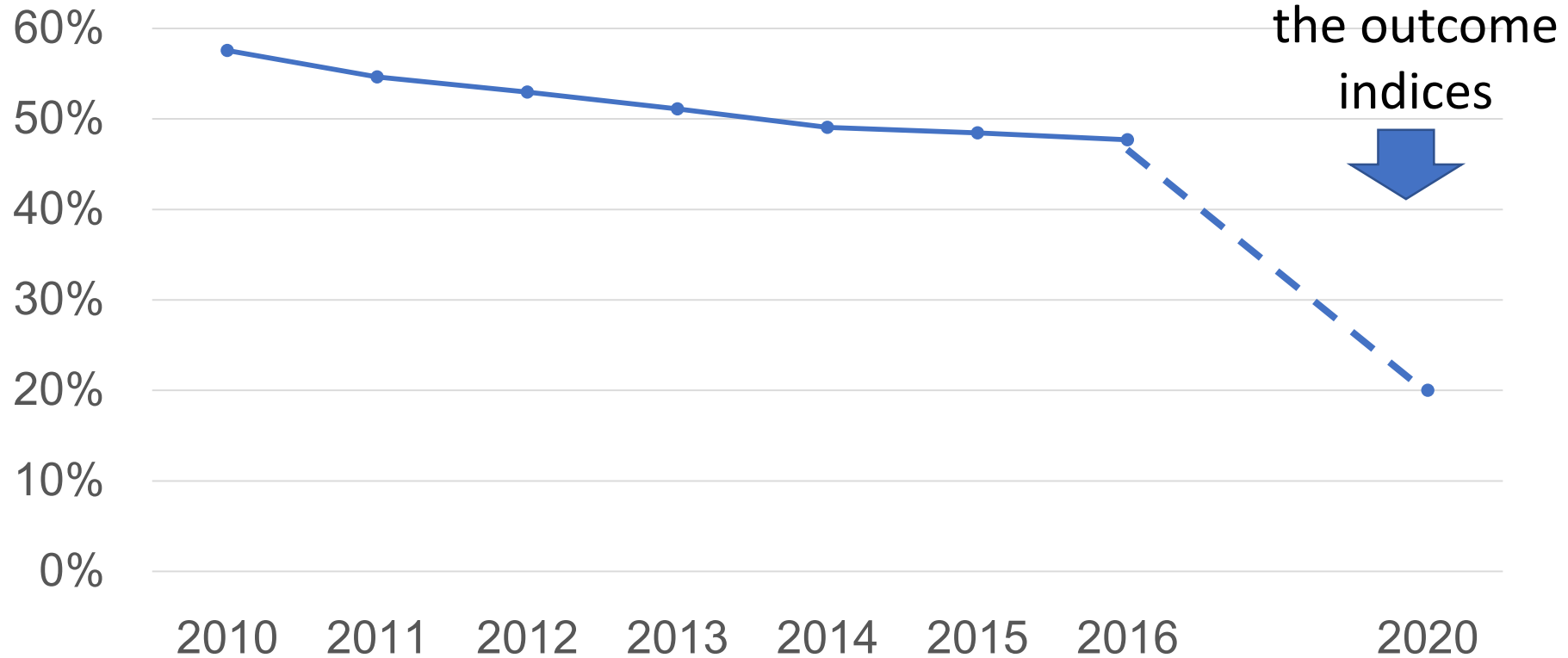
- The Japan Nosocomial Infections Surveillance (JANIS) which monitors the trends of AMR in healthcare is operated by Ministry of Health, Labor and Welfare of Japan.
- About 1700 facilities (20% of medical institutions in Japan) participated in JANIS, and about 800,000 samples were counted at 2016.

International comparison of antimicrobial resistance proportions in major Gram-positive bacteria in humans



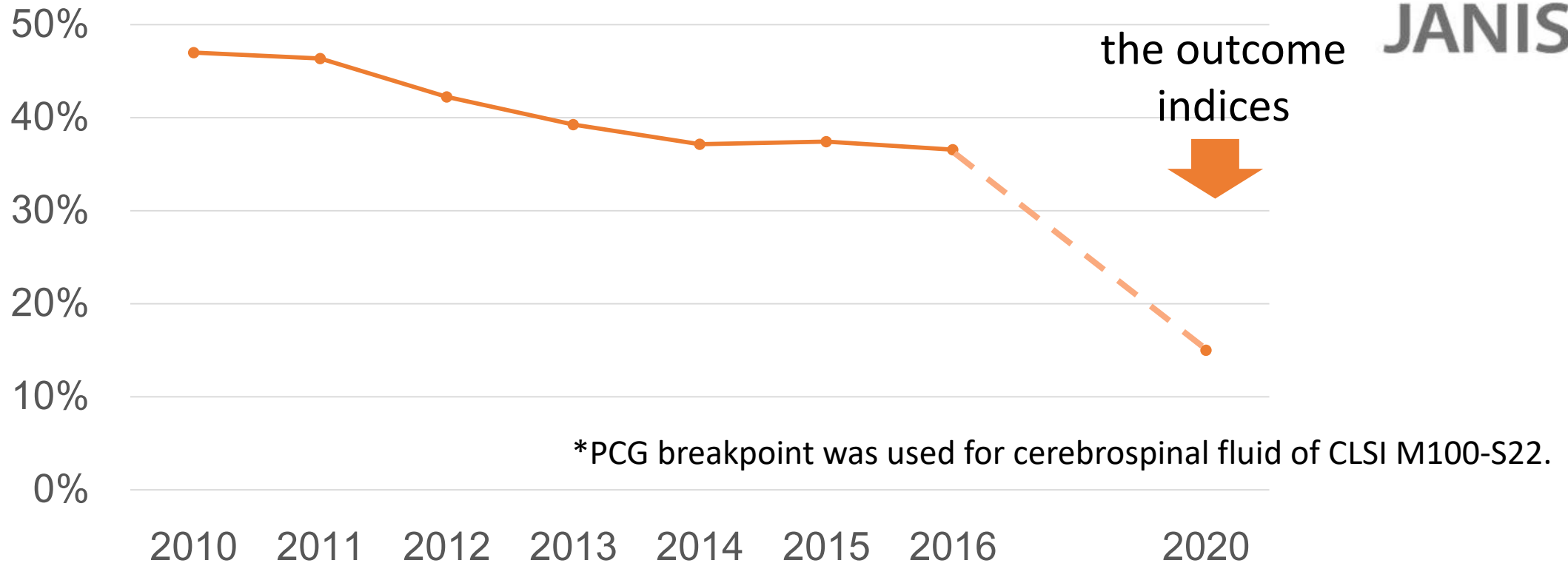
The proportions of AMR in Gram-positive bacteria are higher in Japan than in the other countries.

The methicillin resistance of *S. aureus* in JANIS



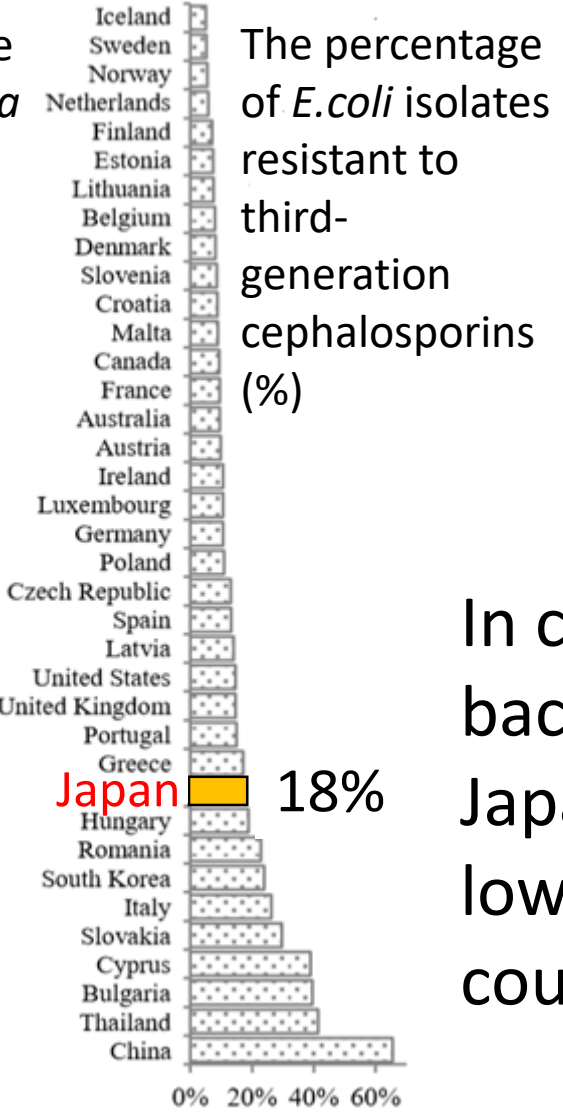
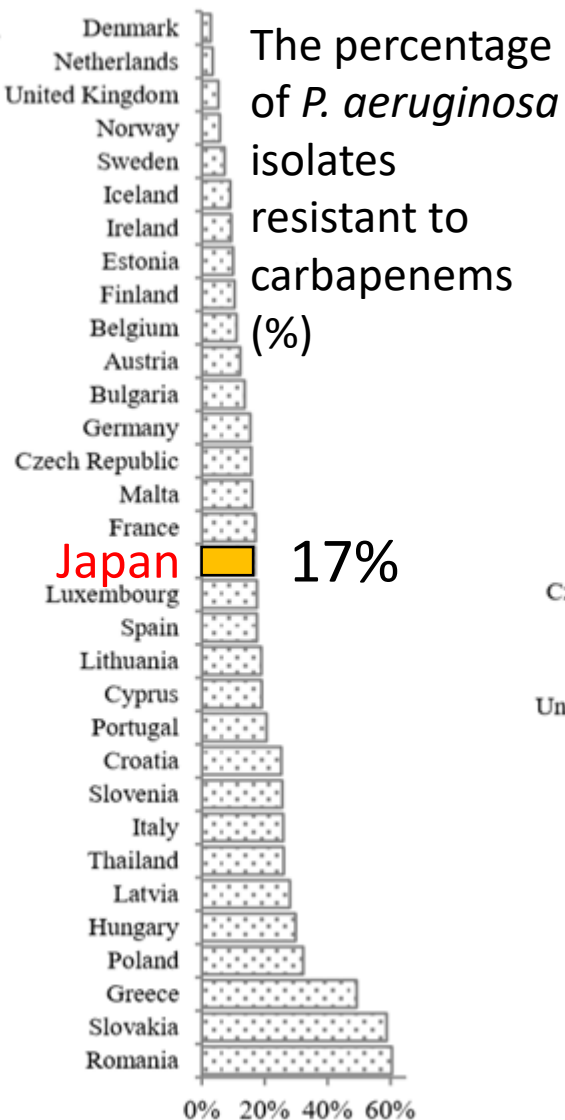
- The methicillin resistance of *S. aureus* in JANIS decreased from 58% at 2010 to 48% at 2016.
- The outcome indices of the methicillin resistance of *S. aureus* to 20% or less at 2020. It may be very challenging!

The penicillin resistance of *S. pneumoniae* in JANIS



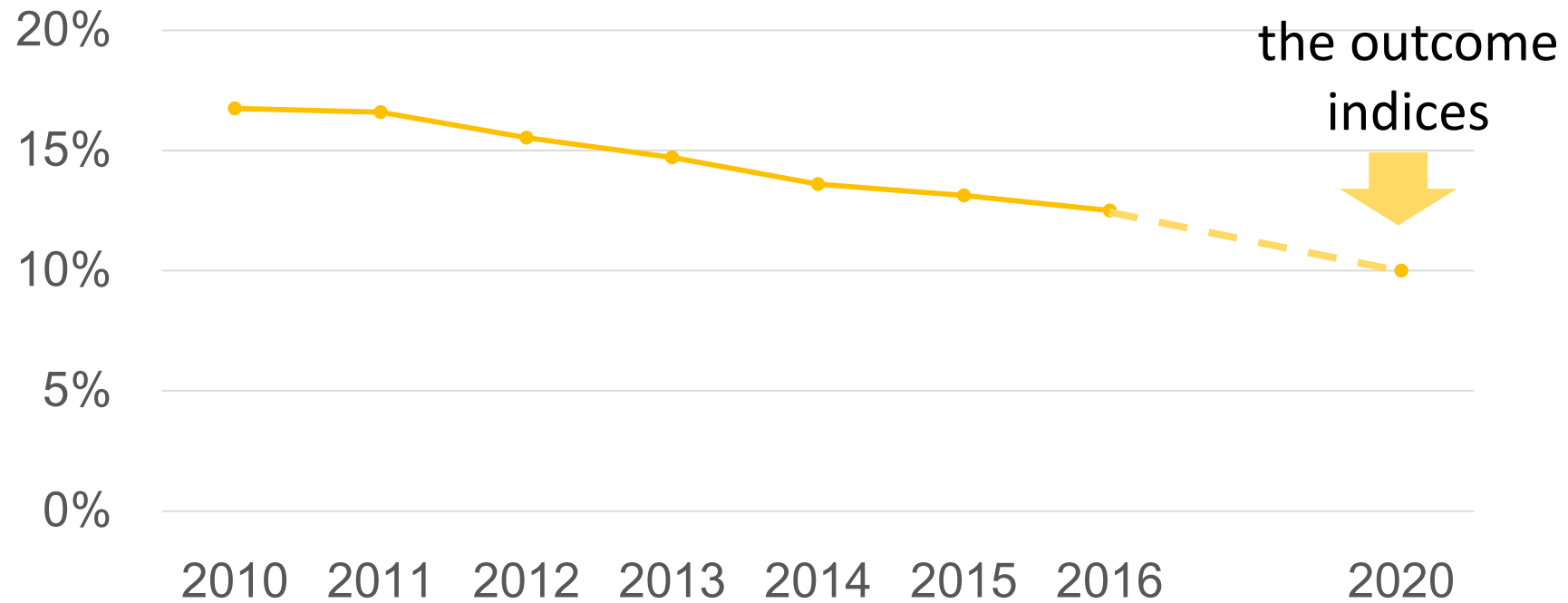
- The penicillin resistance of *S. pneumoniae* in JANIS decreased from 47% at 2010 to 37% at 2016.
- The outcome indices of the penicillin resistance of *S. pneumoniae* to 15% or less at 2020. It also may be very challenging!

International comparison of antimicrobial resistance proportions in major Gram-negative bacteria in humans



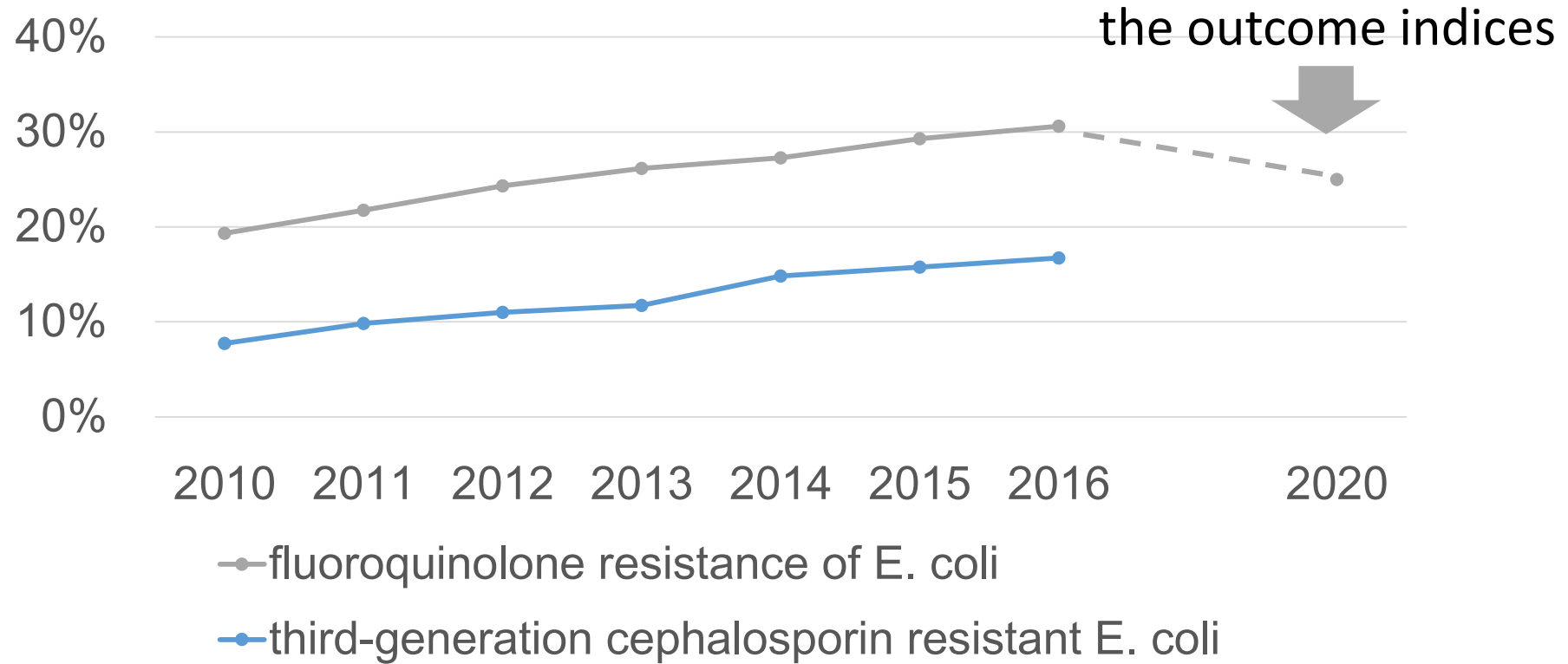
In contrast, for Gram-negative bacteria, the proportion of AMR in Japan, maintain levels equal to or lower than those in the other countries.

the carbapenem resistance of *P. aeruginosa* in JANIS



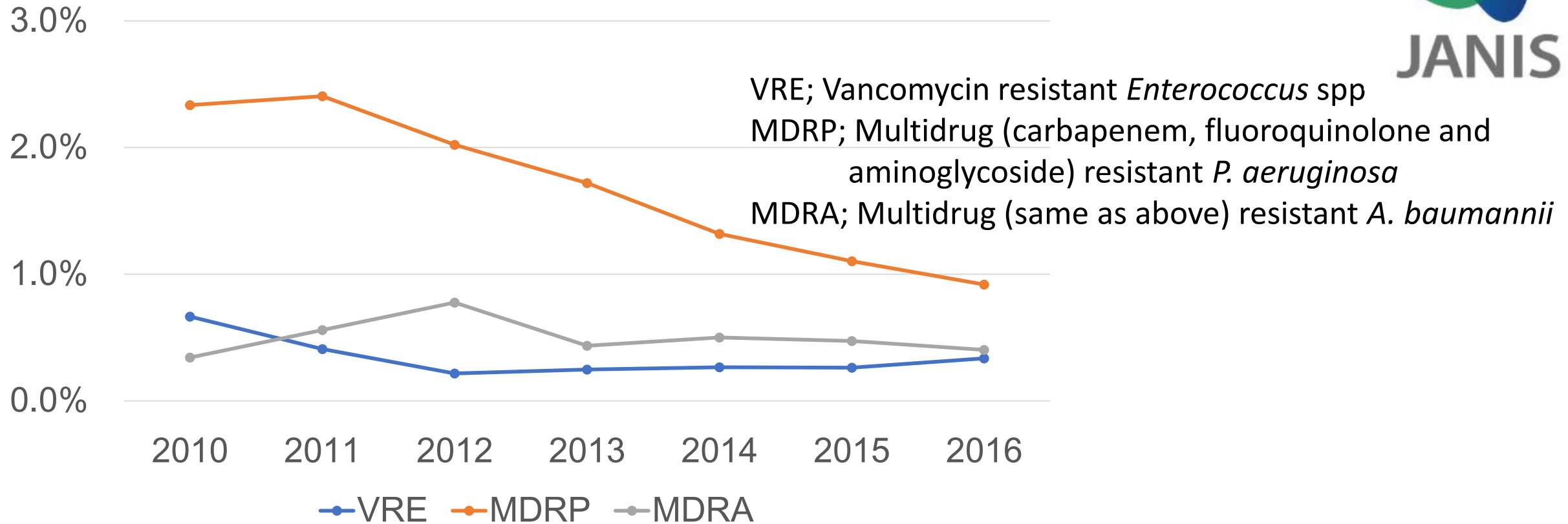
- The imipenem resistance of *P. aeruginosa* in JANIS decreased from 17% at 2010 to 13% at 2016.
- The outcome indices of the carbapenem resistance of *P. aeruginosa* to 10% or less at 2020. It may be reasonable.

The fluoroquinolone and 3rd -generation cephalosporin resistance of *E. coli* in JANIS

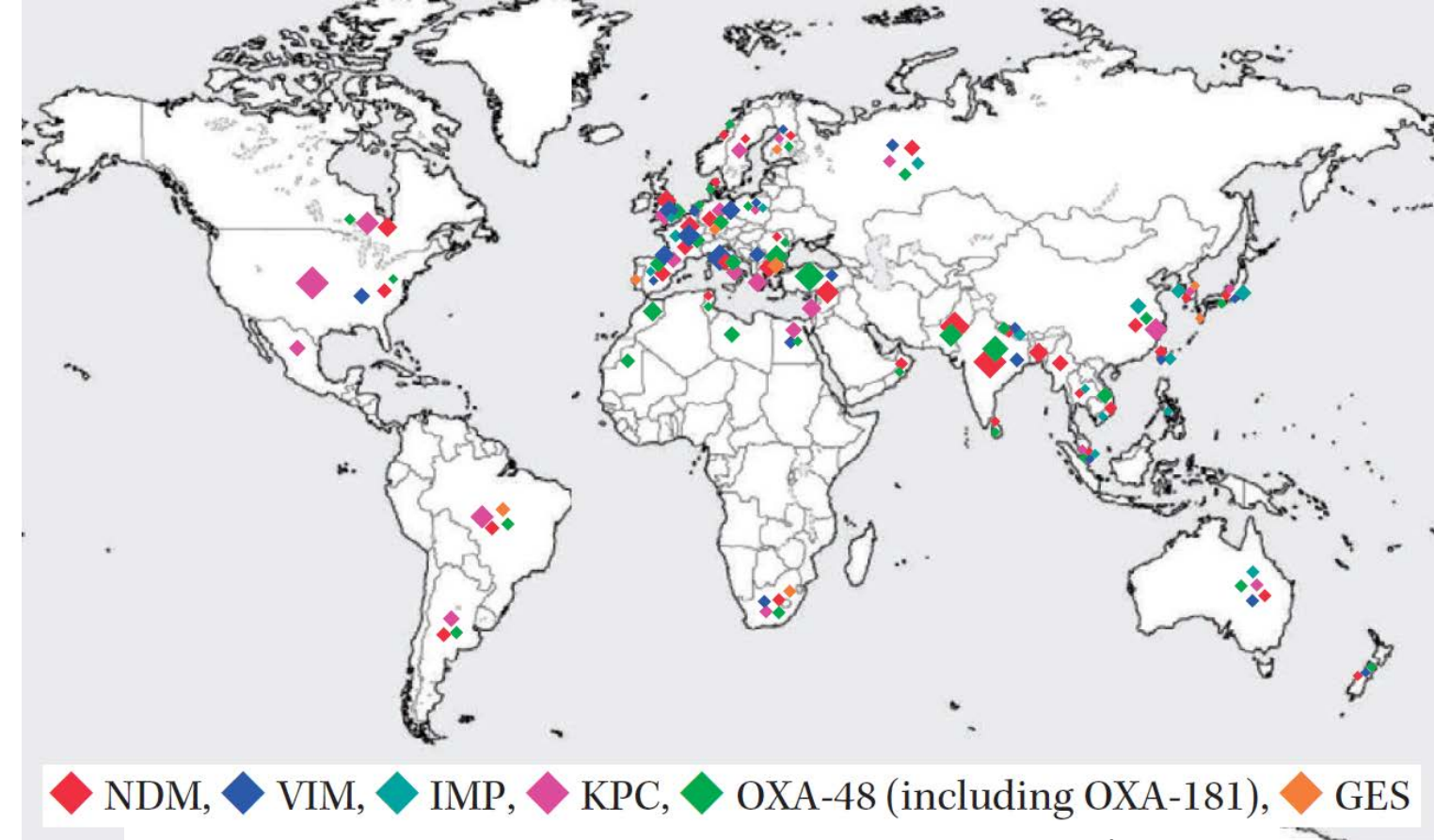


- The fluoroquinolone and 3rd -generation cephalosporin resistance of *E. coli* in JANIS was increasing.
- The outcome indices of the fluoroquinolone resistance of *E. coli* to 25% or less at 2020.

The rate of VRE, MDRP and MDRA in JANIS



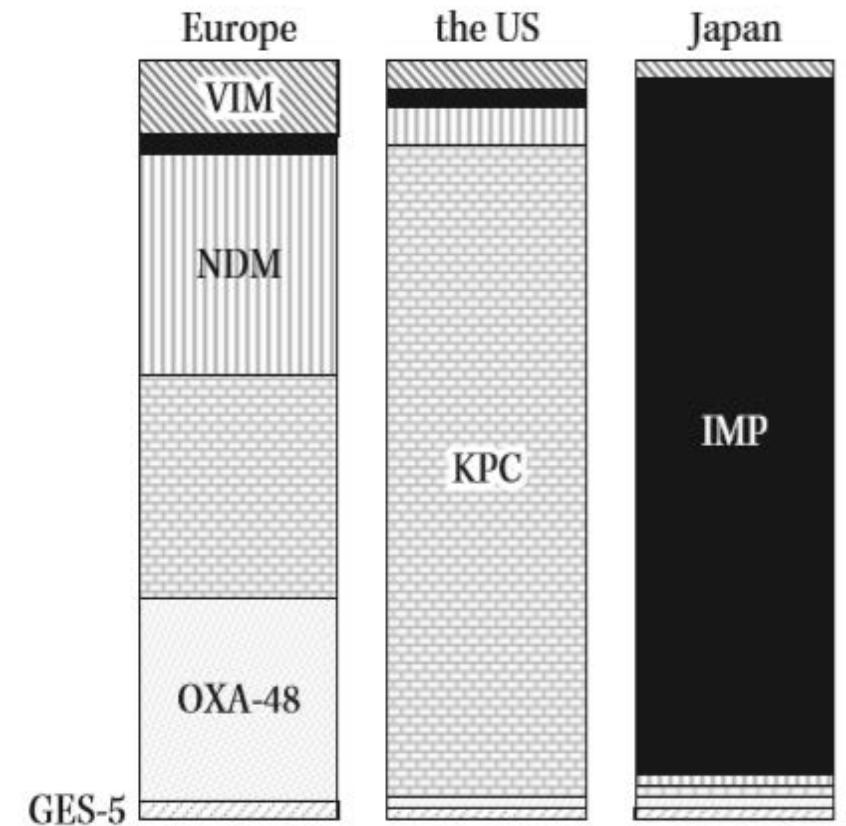
- The rate of MDRP (among *P. aeruginosa*) in JANIS decreased from 2.5% at 2011 to 0.9% at 2016.
- The rate of VRE (among *Enterococcus* spp) and MDRA (among *A. baumannii*) in JANIS were very low in Japan.



◆ NDM, ◆ VIM, ◆ IMP, ◆ KPC, ◆ OXA-48 (including OXA-181), ◆ GES

Global distribution of carbapenemases found in CRE/CPEs.

◆ The size represents the rough numbers of reported cases at 2014.



Arakawa Y. Jpn. J. Chemother. 2015 (in Japanese)

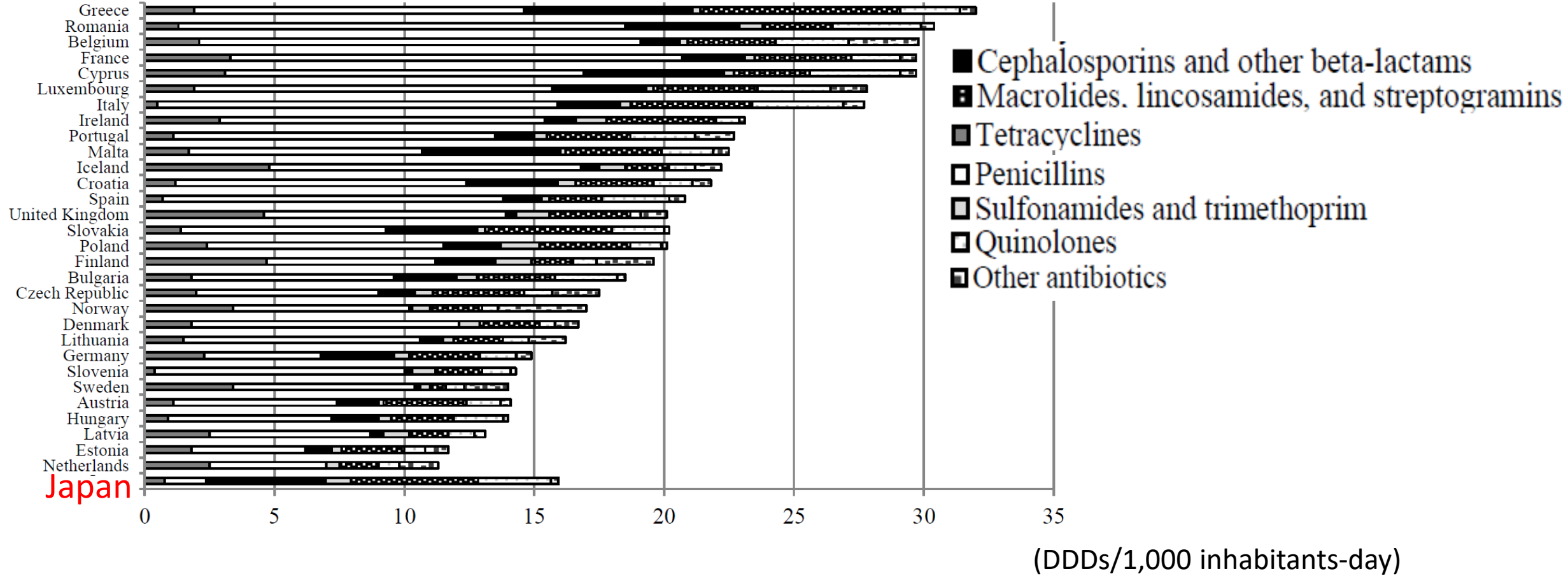
- The prevalence of **CRE (carbapenem-resistant *Enterobacteriaceae*)** remains low with a percentage of 0.2% in Japan.
- The frequency of CPE (carbapenemase producing *Enterobacteriaceae*) is about 30% of CRE.
- **IMP metallo- β -lactamase** is the most prevalent form of CPE in Japan and there is the difference in the isolation frequency between Japan and Europe or the US.

- The National Epidemiological Surveillance of Infectious Disease (NESID) is based on the Act on Prevention of Infectious Diseases.
- Medical doctors in Japan **must report** all cases of **the infection of VRE, MDRA and CRE** to public health centers when diagnose according this law.
- The public health institutes at all prefecture in Japan can **analyze the carbapenemase genotypes** of strains isolated from patients suffering from CRE infection.

Surveillance and Monitoring 2

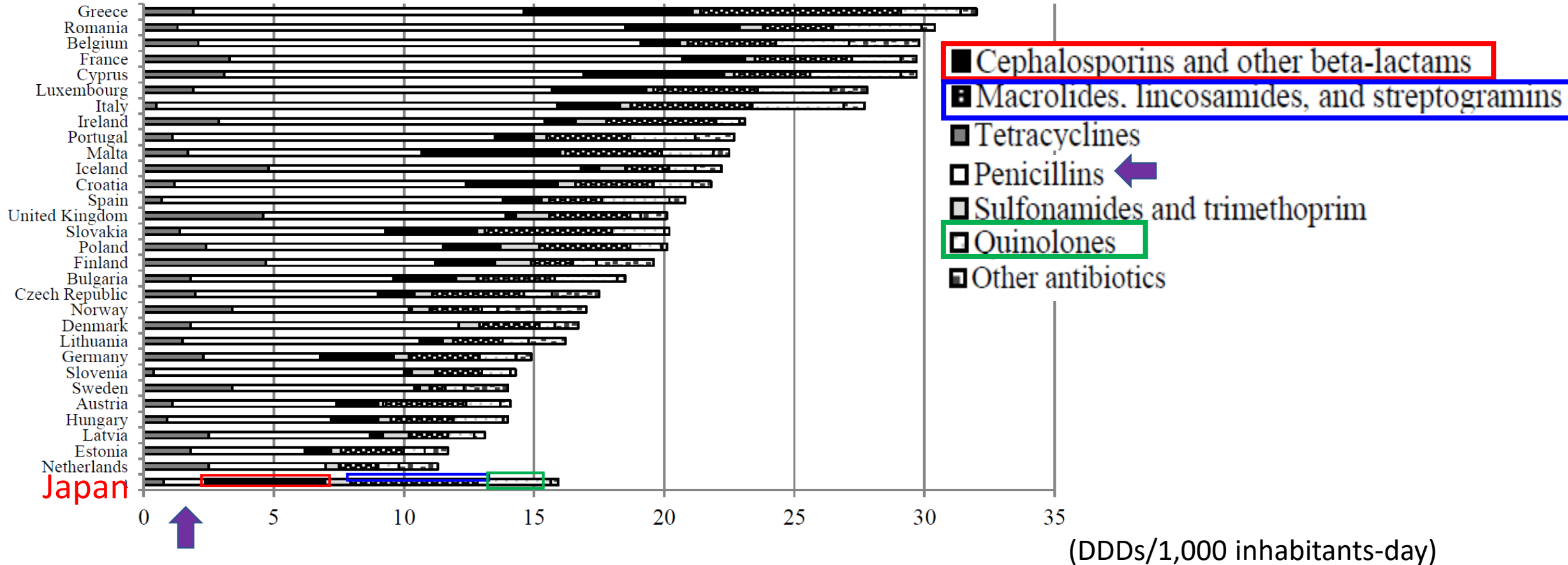
- ◆ Other strategy in this area is to monitor the trend of the antimicrobial use at medical institutions by
 - Developing surveillance methods to monitor antimicrobial use in medical institutions
 - Exploring the application of big data collected in the National Database for Prescription and National Health Check-up (NDB)

Comparison of antibiotic use for humans in EU countries and Japan



- Total antibiotic use in humans in Japan is a relatively small figure compared to Europe.

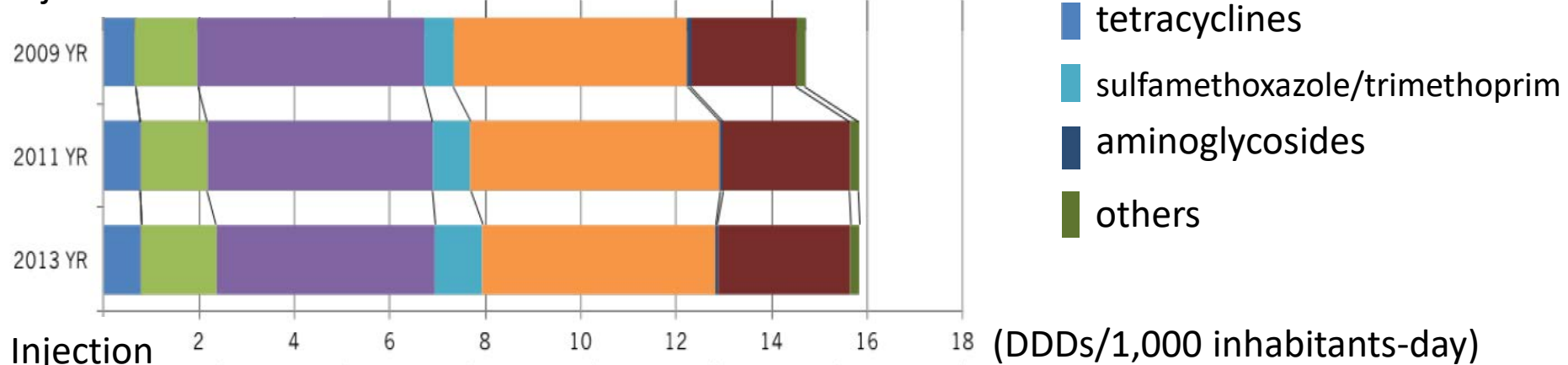
Comparison of antibiotic use for humans in EU countries and Japan



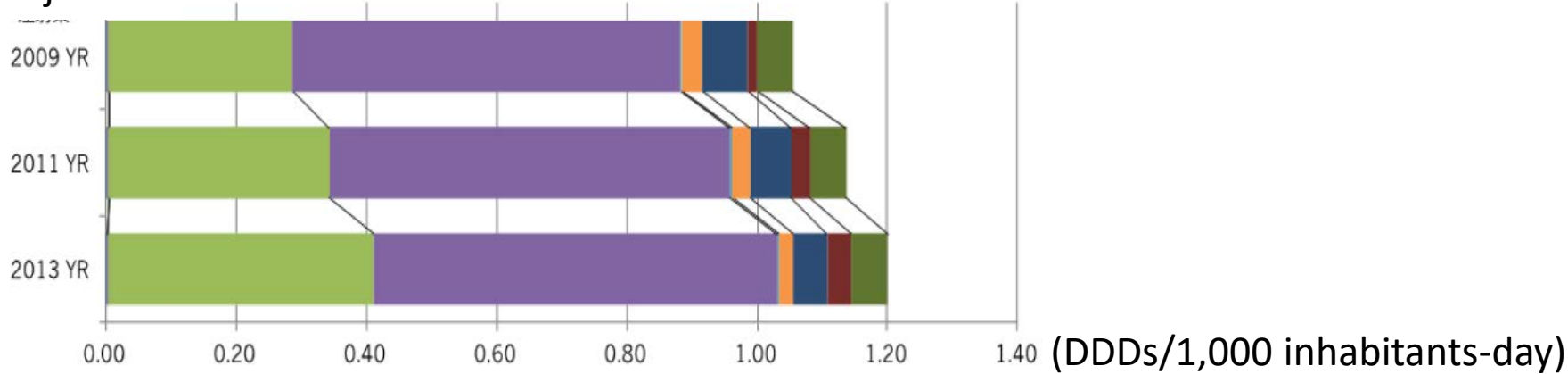
- However, some specific classes of broad-spectrum oral antibiotics including **cephalosporins** (more than 60% of them were third-generation), **macrolides** and **fluoroquinolones** were frequently used in Japan, and **penicillins** are less frequently used compared to the other EU countries.

The population-weighted antimicrobial use density (AUD) in Japan

Injection and Oral

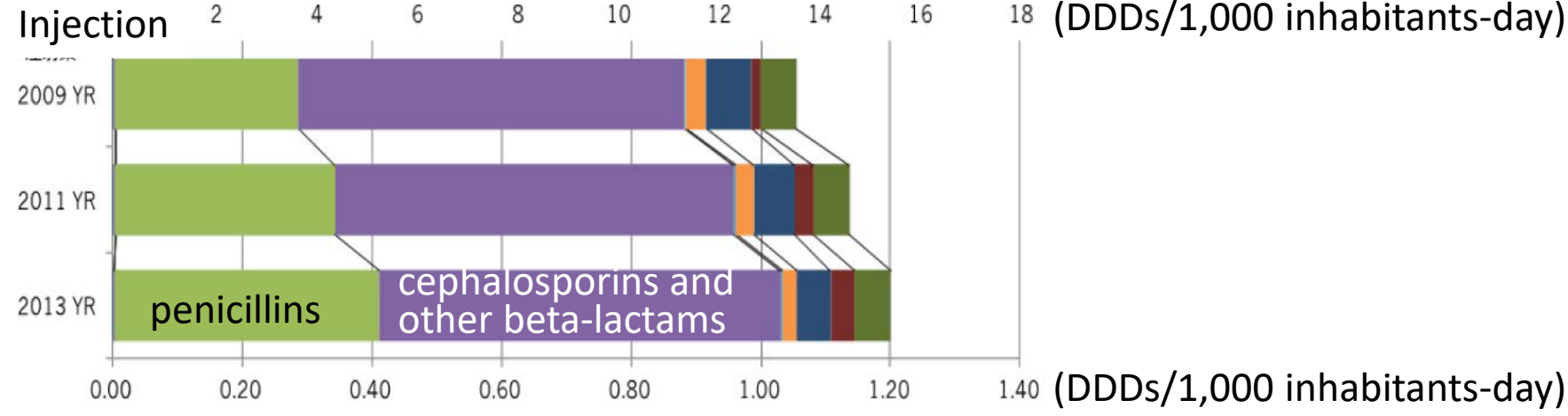
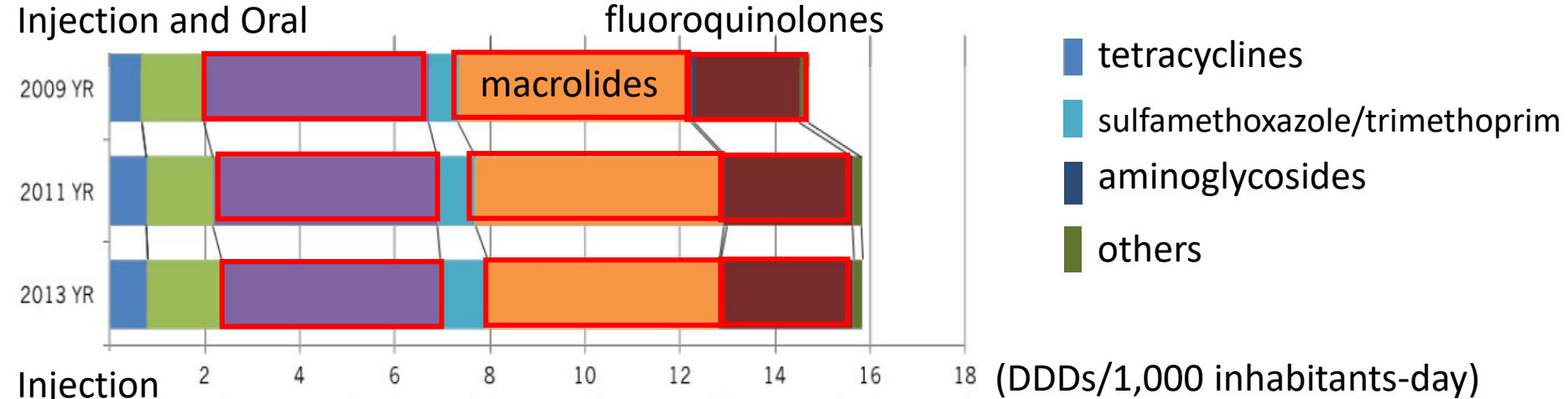


Injection



- The average **oral medication accounted for 93%** of the total antibacterial drugs suggesting that these were used among outpatients and residents in nursing care facilities.

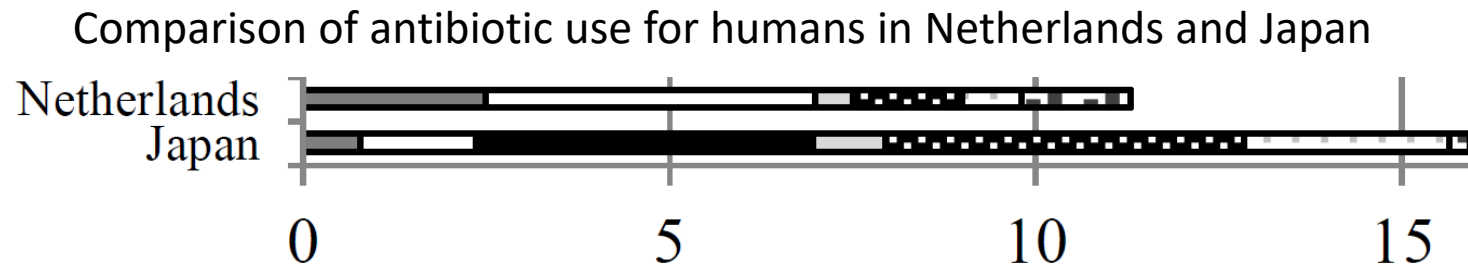
The population-weighted antimicrobial use density (AUD) in Japan



- The third generation cephalosporins, macrolides and fluoroquinolones accounted for 77% of oral antibacterial drugs.

The outcome indices of the antimicrobial use

- Reduce in 2020 **to two-thirds** of the level in 2013
 - In the Netherlands, where the AUD is the smallest in Europe, approximately two-thirds the level in Japan.



- Reduce the use of **oral cephalosporins, quinolones, and macrolides** in 2020 **by 50%** from the level in 2013
- Reduce the use of **intravenous antimicrobials** in 2020 **by 20%** from the level in 2013

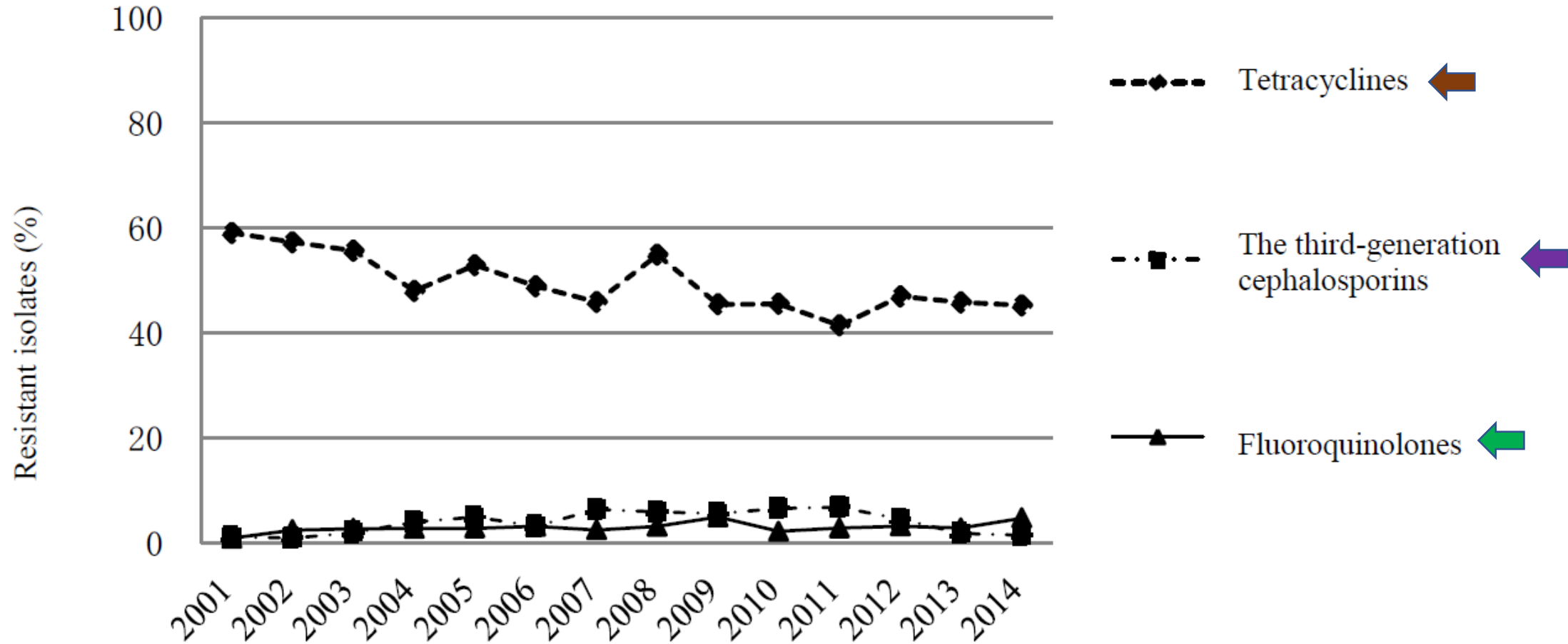
Surveillance and Monitoring 3

The Japanese government is working to

- ◆ Strengthen Surveillance and Monitoring in the Fields of Veterinary Medicine, Livestock Production and Aquaculture
- ◆ Implement Integrated One Health Surveillance Including Humans, Animals, Food, and the Environment

- Tetracyclines are largely used in livestock.
- The amount of antimicrobial use for livestock in 2013 decreased by 25% from that in 2001 (1059 tons → 796 tons).

Trends in antimicrobial resistance in *Escherichia coli* of livestock animal origin in Japan



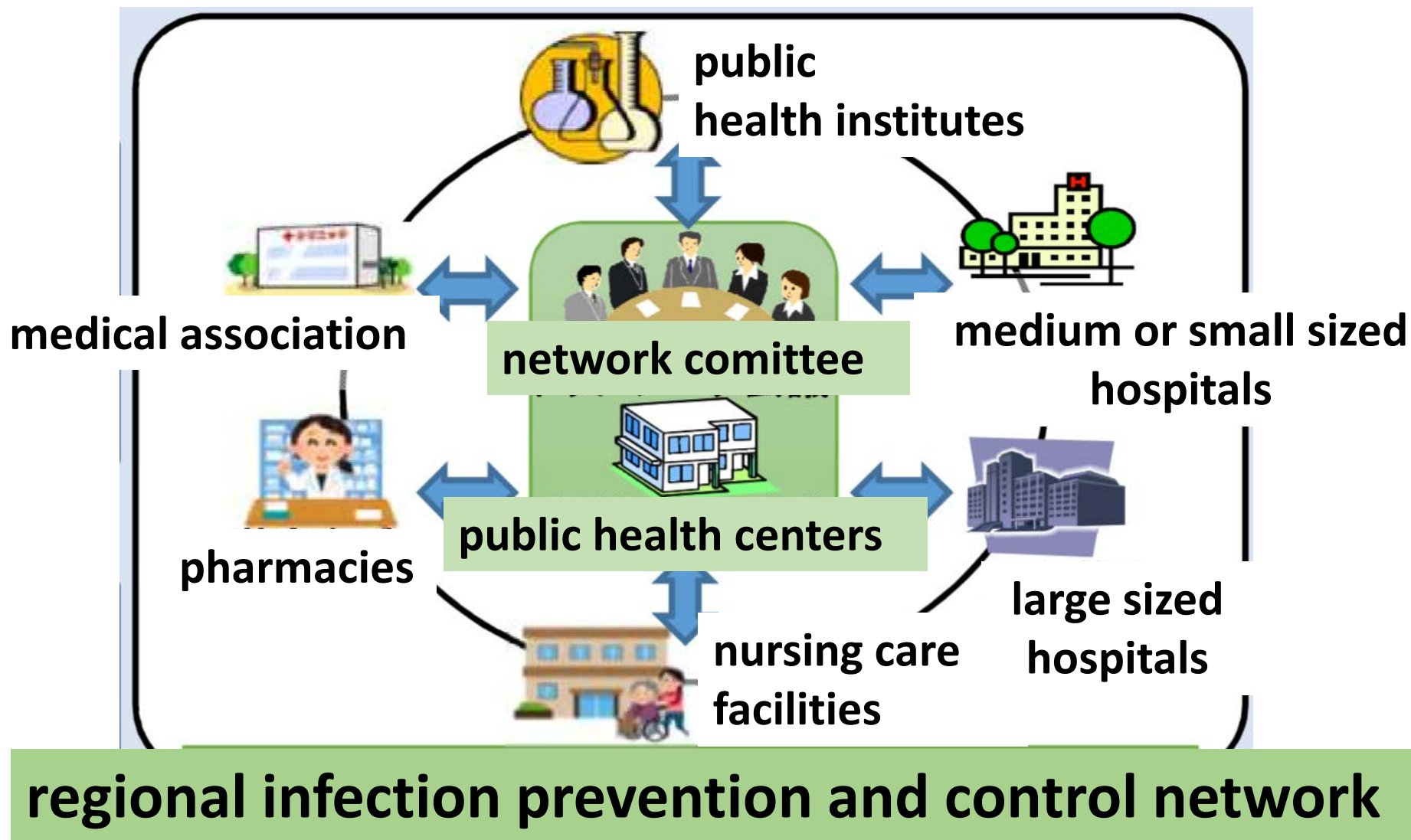
- The percentages of isolates resistant to **tetracyclines**, **third-generation cephalosporins**, and **fluoroquinolones** in *E. coli* of animal origin in Japan in 2014 are **45%**, **1.5%**, and **4.7%** respectively and these are decreasing.

Infection Prevention and Control

Goal 3

Prevent the Spread of Antimicrobial-resistant Organisms by Implementing Appropriate Infection Prevention and Control

- The goal includes to expand activities in cooperation with regional hospitals and related organizations, and to develop a comprehensive regional infection prevention and control network.



- In Japan, it is possible to calculate **the additional medical fee of infection prevention** from 2012 (5000 yen≒ 45 US dollars per one hospitalization) by
 - arranging **certificated nurse for infection control**
 - performing **infection control round** for the wards every week
 - promoting **antimicrobial stewardship** measures including the mandatory **pre-authorization or prospective audit and feedback** for specified antibiotics use
 - established to **support** infection control of **small and medium-sized medical institutions**.
 - **evaluating between facilities** that calculate this additional fee



Kagoshima Infection Control Network (KICN)

- established at 2004.
- joins 76 medical facilities, public health centers and public health institutes at Kagoshima prefecture.
- supported by Kagoshima Prefecture Medical Association.
- the activities of this network are
 - Information sharing among members by mailing list
 - Consideration of outbreak case of each facility
 - Multicenter survey of multidrug-resistant bacteria
 - Questionnaire on infection control for medical institute and nursing facilities



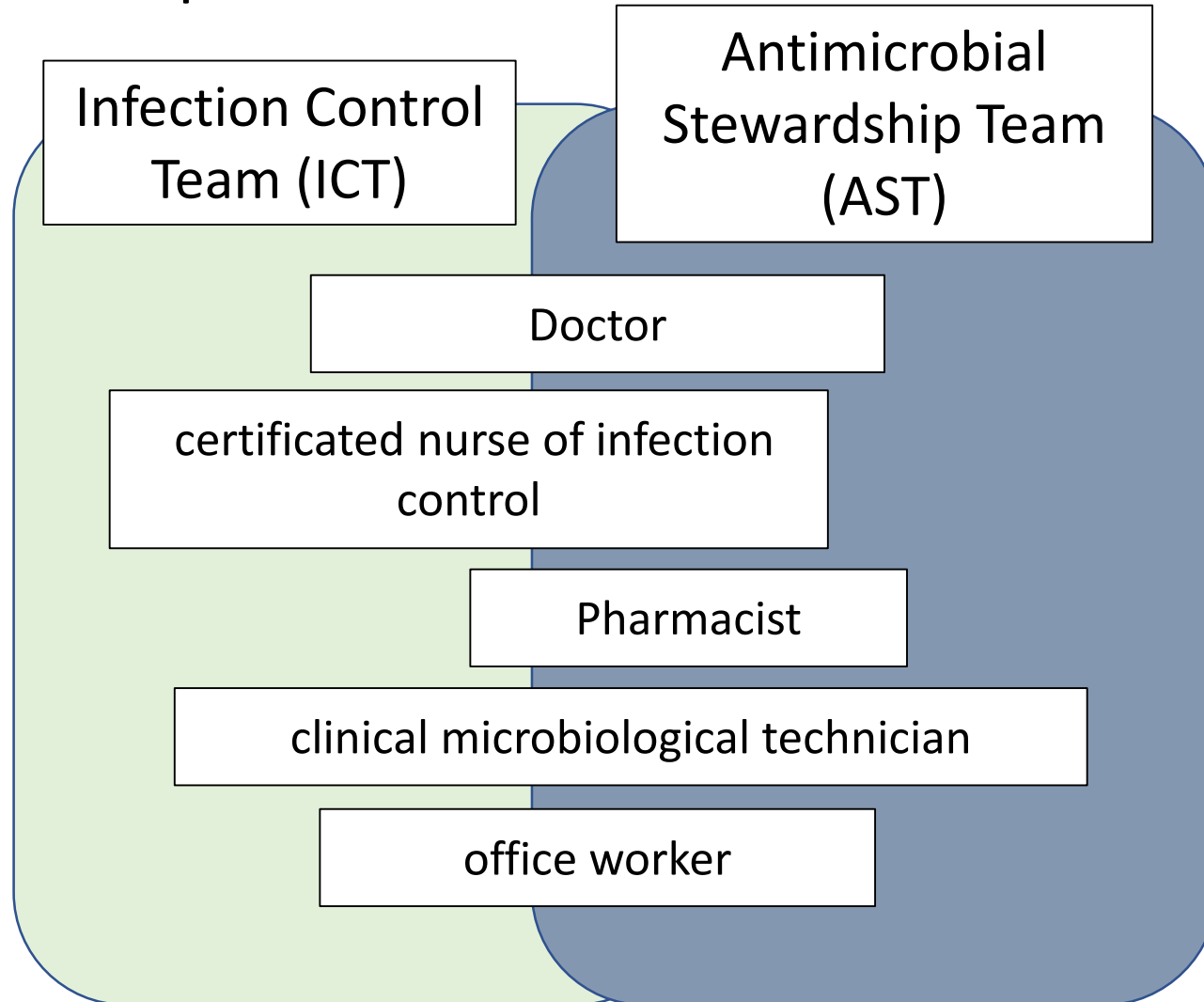
Appropriate Use of Antimicrobials

Goal 3

Promote Appropriate Use of Antimicrobials in the Fields of Healthcare, Livestock Production and Aquaculture

- In hospital setting, the efforts including operation of antimicrobial stewardship teams have been initiated in addition to the surveillance of AMR and infection prevention and control.

- It will be possible to calculate the additional medical fee about the support of antimicrobial stewardship (1000 yen \approx 9 US dollars per one hospitalization) after April 2018.



As with Infection Control Team, Antimicrobial Stewardship Team (AST) consists of four professionals: doctor, certified nurse, pharmacist, clinical microbiological technician.

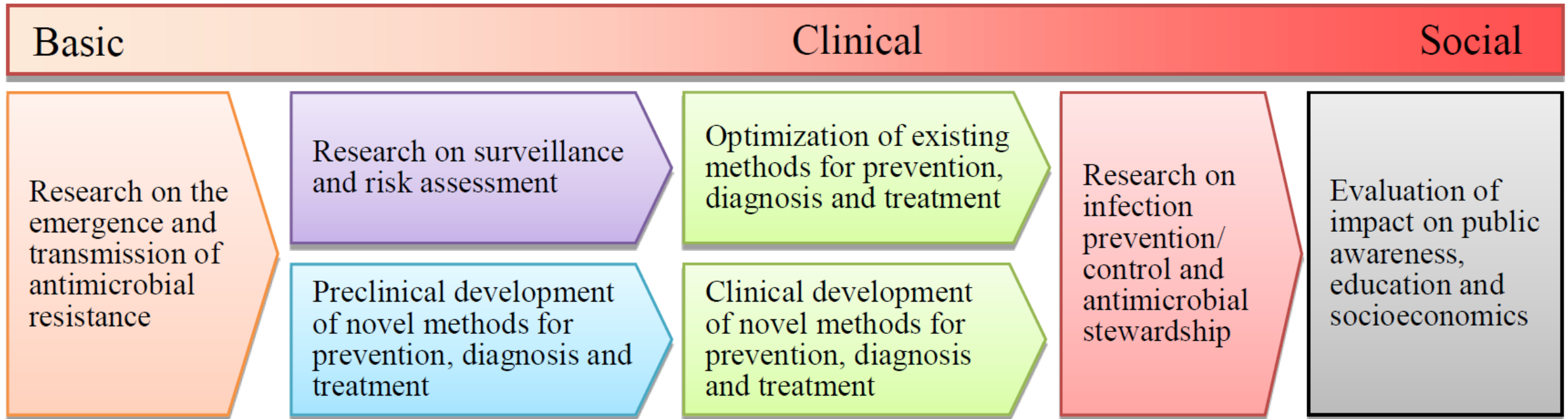
The Activities required for AST

- Monitoring patients **using wide-spectrum antibiotics** and those **with bacteremia or immunocompromised**
 - Evaluation about the **appropriateness of antimicrobial drugs** and **feedback** to the attending physician
 - Asking to **conduct microbial examination** or **therapeutic drug monitoring** if necessary .
- Developing a system that allows **microbiological testing** to be used properly
- Evaluating **process indicators** such as antimicrobial use situation and blood culture submission status and **outcome measures** such as antimicrobial resistance rate and antibiotic usage

Research and Development

Goal 5

Promote Research on Antimicrobial Resistance and Foster Research and Development to Secure the Means to Prevent, Diagnose and Treat the Antimicrobial-resistant Infections



International Cooperation

Goal 6

Enhance Global Multidisciplinary Countermeasures against Antimicrobial Resistance

It was added to fulfill Japan's responsibilities for the international community as the host country for 2016 G7 Ise-Shima Summit to demonstrate leaders' role in Asia region etc.



Conclusions 1

- The Government of Japan formulated the National Action Plan on AMR in 2016.
- The proportions of AMR in Gram-positive bacteria including PRSP and MRSA are higher in Japan than in the other countries.
In contrast, for Gram-negative bacteria, these maintain levels equal to or lower than those in the other countries.

Conclusions 2

- In hospital setting, the efforts including operation of antimicrobial stewardship teams have been initiated, in addition to the surveillance of AMR and infection prevention and control.
- The state of antimicrobial use counts 90% of the prescription among outpatients and residents in nursing care facilities.
It is necessary to carry out further surveillance for outpatient departments and nursing care facilities.