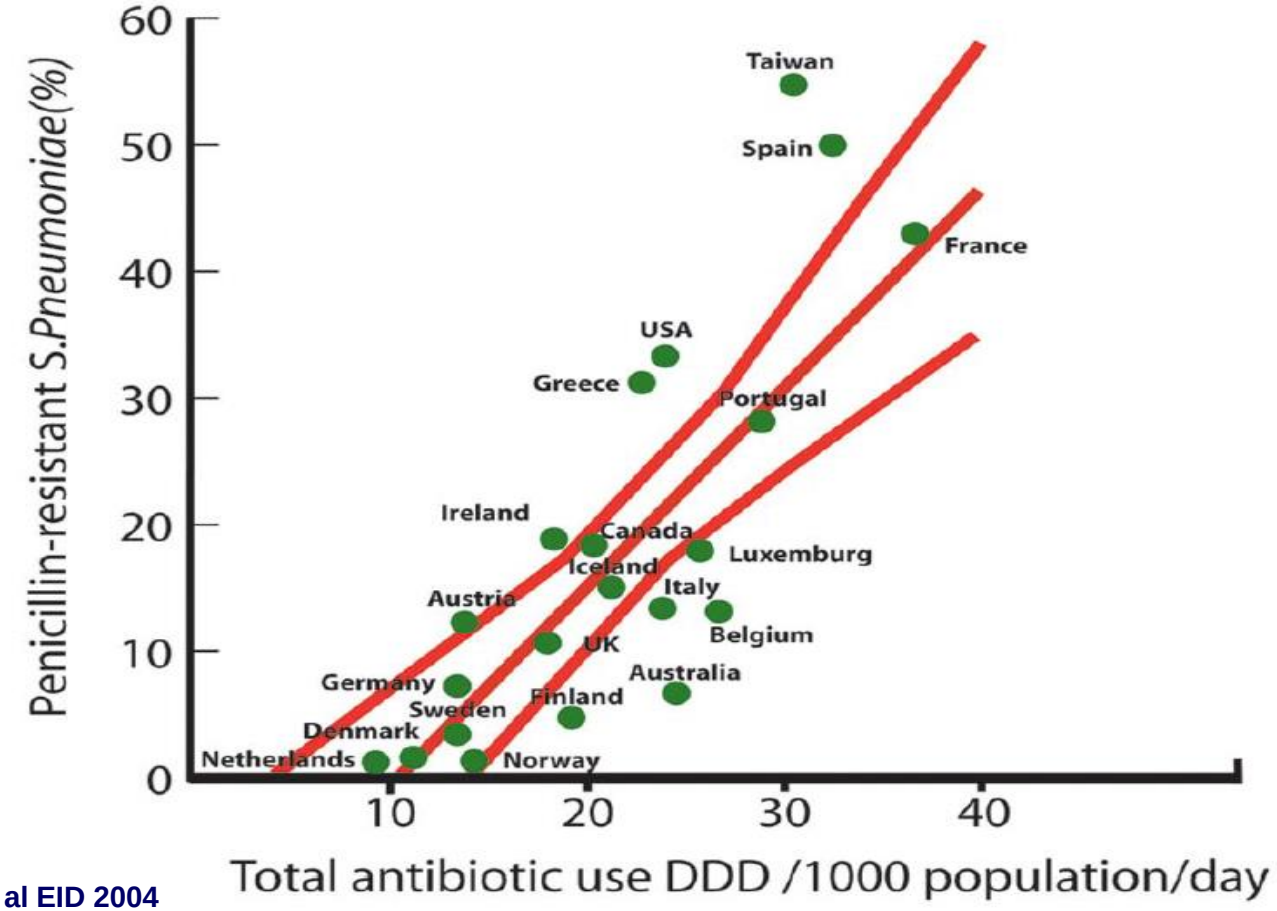
AMR control in Japan

Haruo Watanabe

Unavoidable reality: more use of antimicrobials results in more resistance



From Albrich et al EID 2004

Antimicrobial drug resistance is recognized as a world wide problem

Recent problems: Emerging Carbapenem-resistant enterobacteriaceae (CRE)

Emergence of NDM-1 resistant strains in India

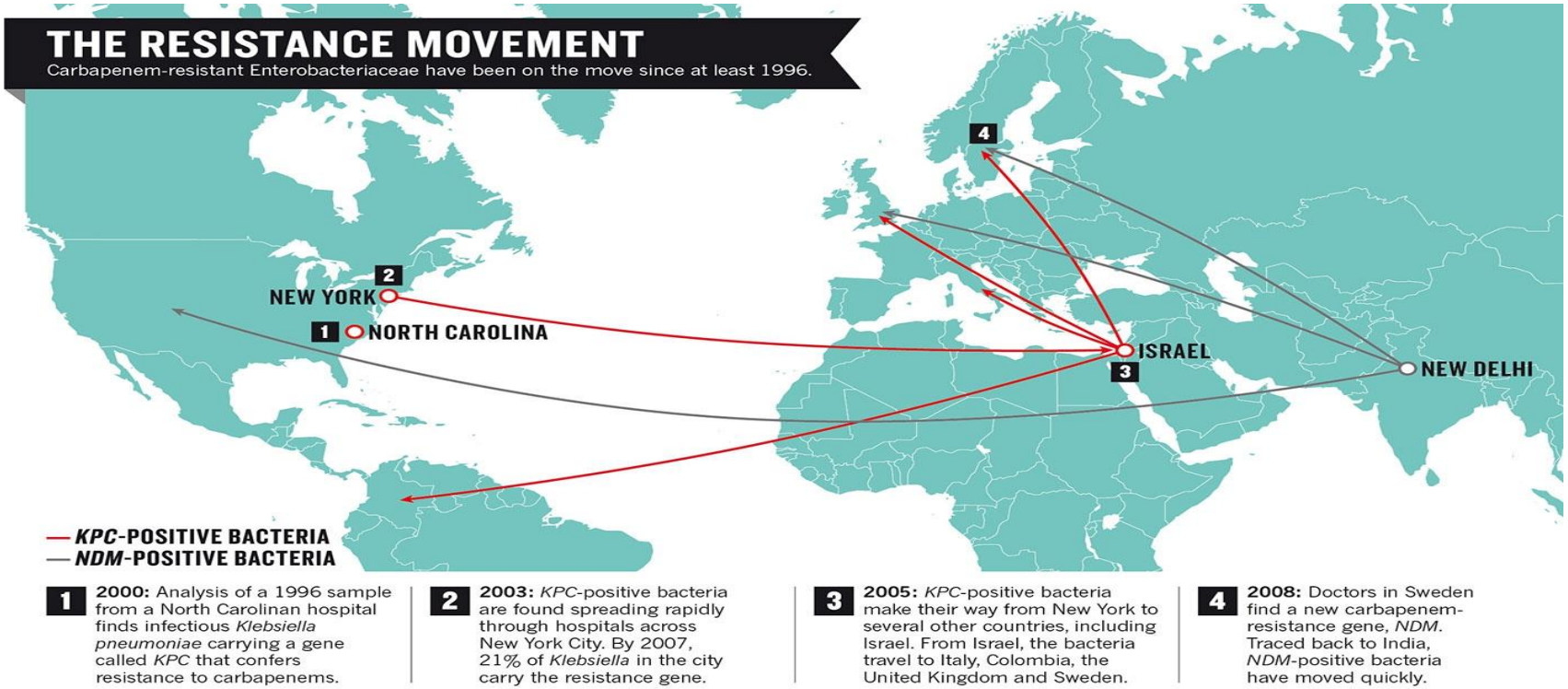
Superbug; 10-fold increase of "Nightmare Bacteria; CRE" of *E.coli* (NDM-1) and *K.pneumoniae* (KPC) during these 10 years in USA

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

Lancet Infect Dis Aug. 11, 2010

Superbug CRE a growing threat among young children、CBS News



Drug resistance is not a problem of one country,
which spreads beyond countries immediately.

Nature 2013. 499:394

Limited choice of antibiotics for treatment of infections with this bacteria:
Last-resort antibiotics for treating infections due to CRE:

Colistin and Tigecycline

（CIA:Critically Important Agents designated by AGISAR, WHO)

Colistin was found in 1950 by Japanese researcher. It fell out of favor due to its nephrotoxicity to human

Emergence and dissemination of plasmid-mediated colistin resistant(*mcr-1*) Enrerobacteriaceae bacteria

(Yi-Yun Liu et al; published on line; Lancet Infectious *Dis*、*November 18, 2015)*

High frequent isolation of *mcr-1* positive *E.coli* in China

（*mcr-1* gene: phosphoethanolamine transferase enzyme family, which modifies LPS, a target by colistin ）

Data:

21% of *E.coli* isolates of food animal feces (pig)

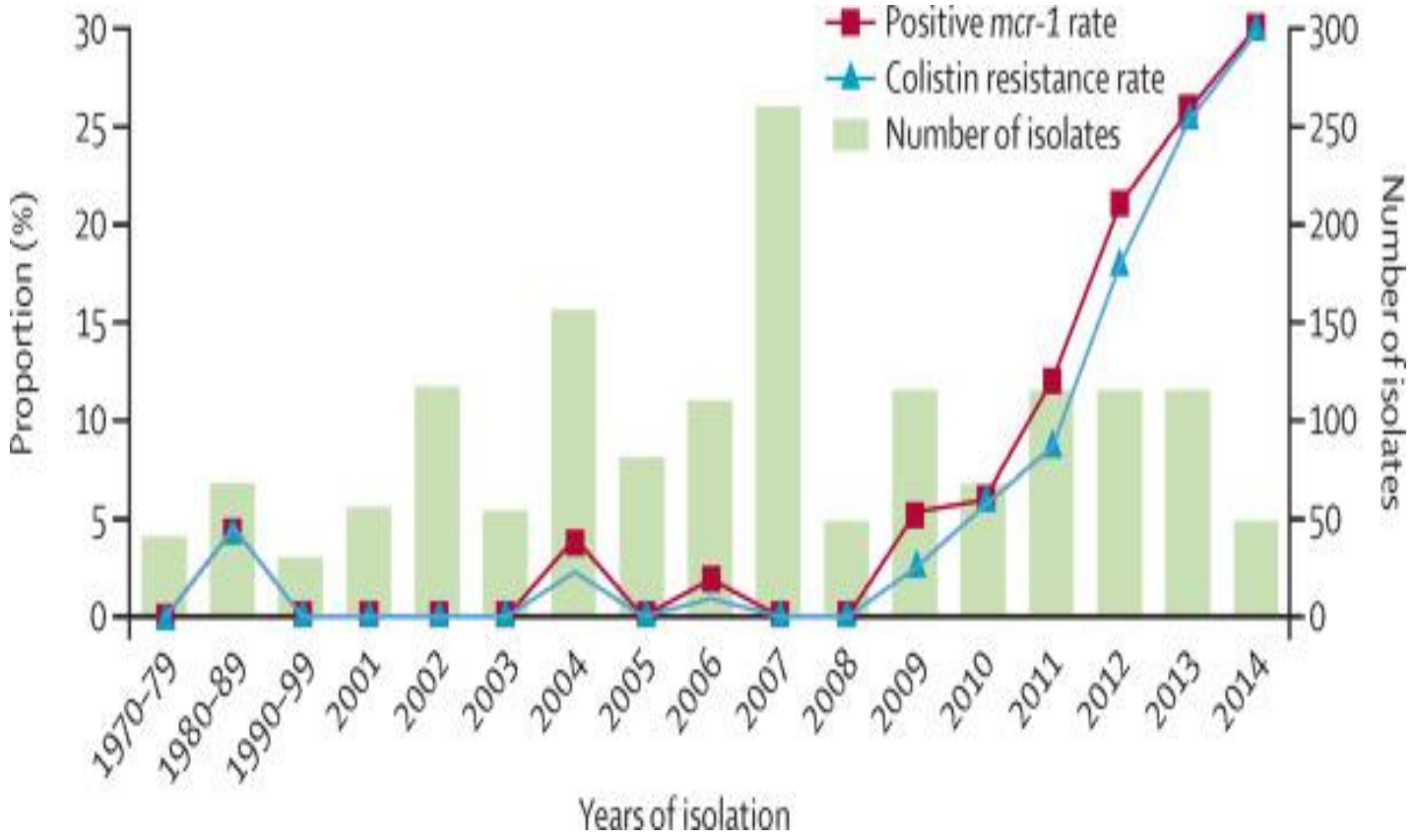
15% of *E.coli* of retail meats (pork and chicken)

1% of *E.coli* of inpatient

Subsequently, isolation of *mcr-1* carrying strains in *E.coli, K. pneumonia, Salmonella* and etc. has been reported from various countries including Asia, EU and others.

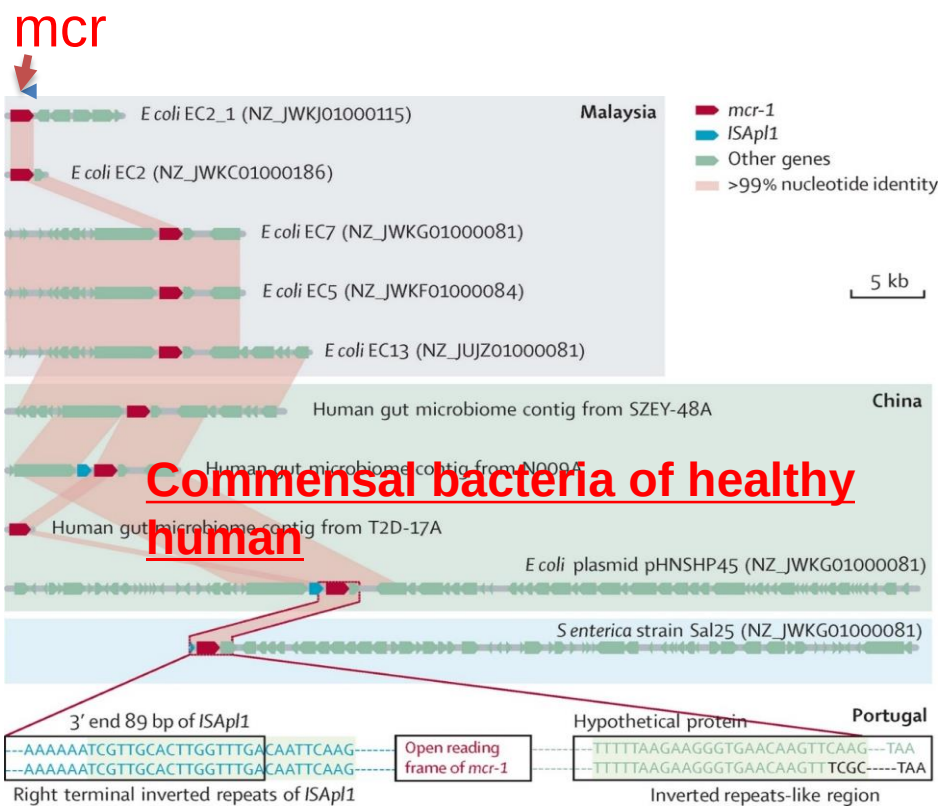
Presence of *mcr-1* and colistin resistance in *Escherichia coli* of chicken origin during 1970–2014 in China

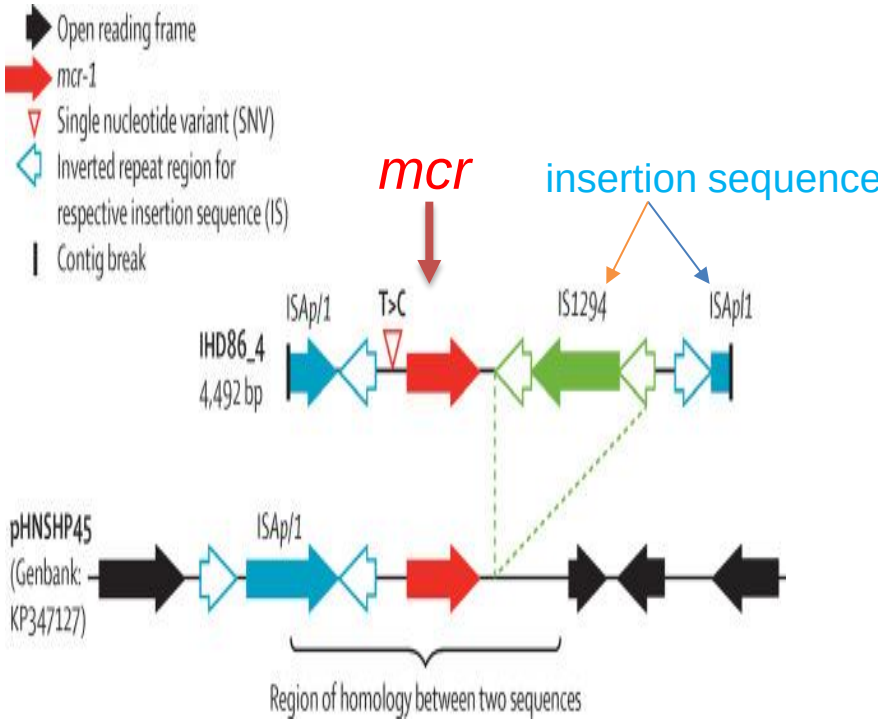
(Shen Zhanggi et al. Lancet. Infect. Dis. 16:293. 2016)



Mcr-1 strains were isolated in 1980s. The proportion of *mcr-1* positive *E.coli* increased from 2009, which may be due to the increased use of colistin during the past 5 years (annual use of colistin; ranging 2470 to 2875 metric tons by the Lancet Inf. Dis. paper).

Detection of *mcr-1* gene from human commensal gut flora of healthy persons (Yongfei Hu et al. Lancet Infect Disease 16:146, 2016)

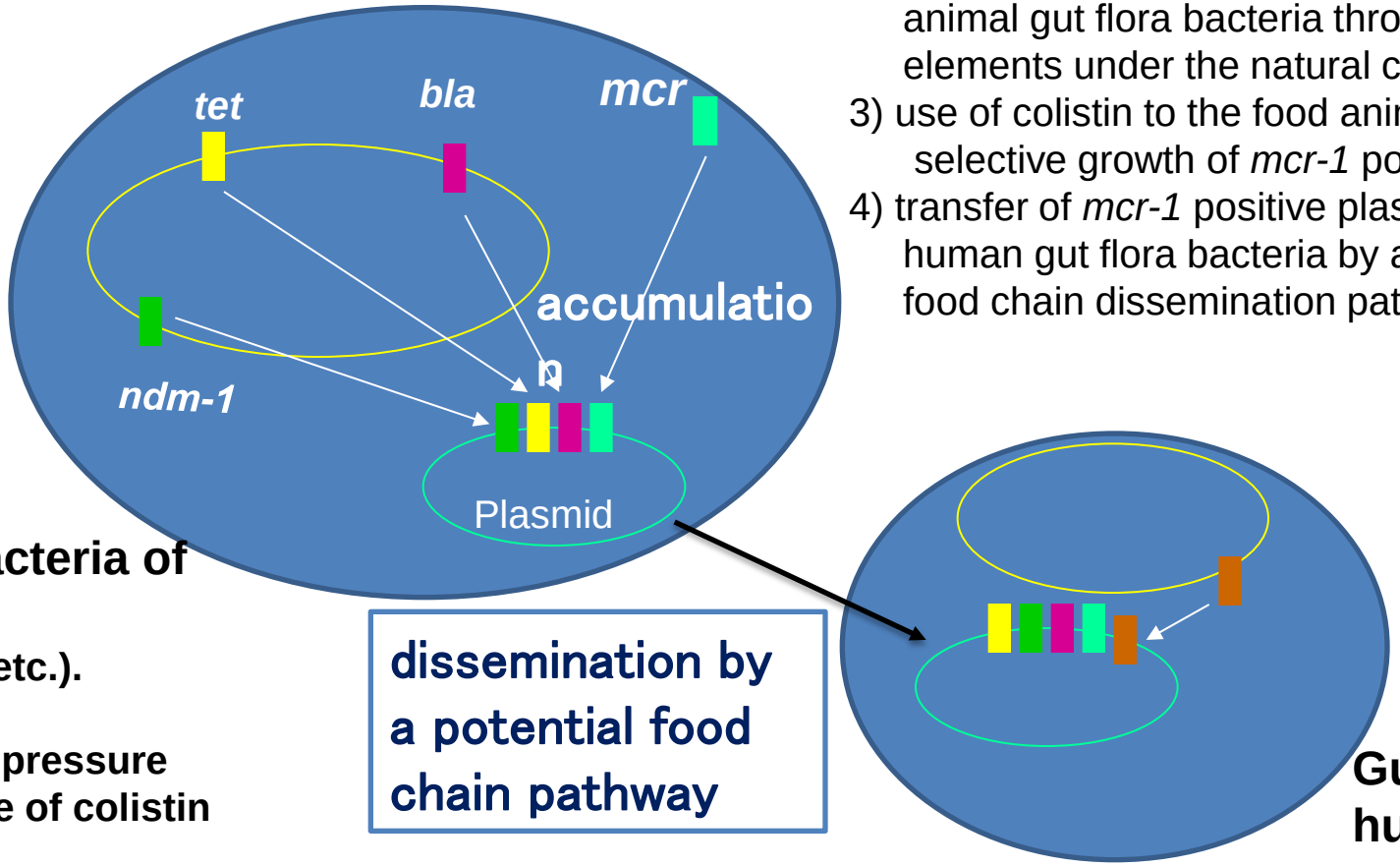




***mcr-1* gene existed in the human commensal gut flora of healthy persons. The gene was flanked by insertion sequences, indicating *mcr-1* gene can be transposed as mobile elements. The gene may have been introduced into the human flora (mirobiome) through the food chain dissemination pathway. The *mcr-1* gene in the human flora has a potential to be disseminated among human when colistin is used as a selective pressure.**

Genetic background: dissemination of *mcr-1* gene

1) emergence of *mcr-1* gene in somewhere (probably originated from some bacteria)
2) accumulation of *mcr-1* gene on the plasmid with other resistance genes in animal gut flora bacteria through mobile elements under the natural conditions
3) use of colistin to the food animals and selective growth of *mcr-1* positive strains
4) transfer of *mcr-1* positive plasmid into human gut flora bacteria by a potential food chain dissemination pathway



Flora bacteria of animals
(chicken etc.).

Selective pressure by the use of colistin

dissemination by a potential food chain pathway

Gut flora of human

The mcr-1 positive strains will cause diseases

WHO activity for AMR

- The appearance of superbug induced big concerns about the AMR.
- G7, G20, WHO and others discussed on the countermeasures to combat with AMR

Global action plan(GAP)-AMR

In 2014, WHO created a draft of Global action plan for AMR under the support of AMR-STAG(Strategic and Technical Advisory Group)

In 2015, 68th WHA resolution: Global action plan for AMR adopted

Global commitment formalised through a series of high-level meetings - G7, UNGA

AMR with the following priority areas of action :

1) Improve awareness and understanding of AMR;
2) Strengthen surveillance in human health, animal health and agriculture sectors
3) Strengthen infection prevention and control (IPC) practices in healthcare facilities;
4) Promoting rational use of antimicrobials across sectors; and
5) Promoting investments in AMR and related research

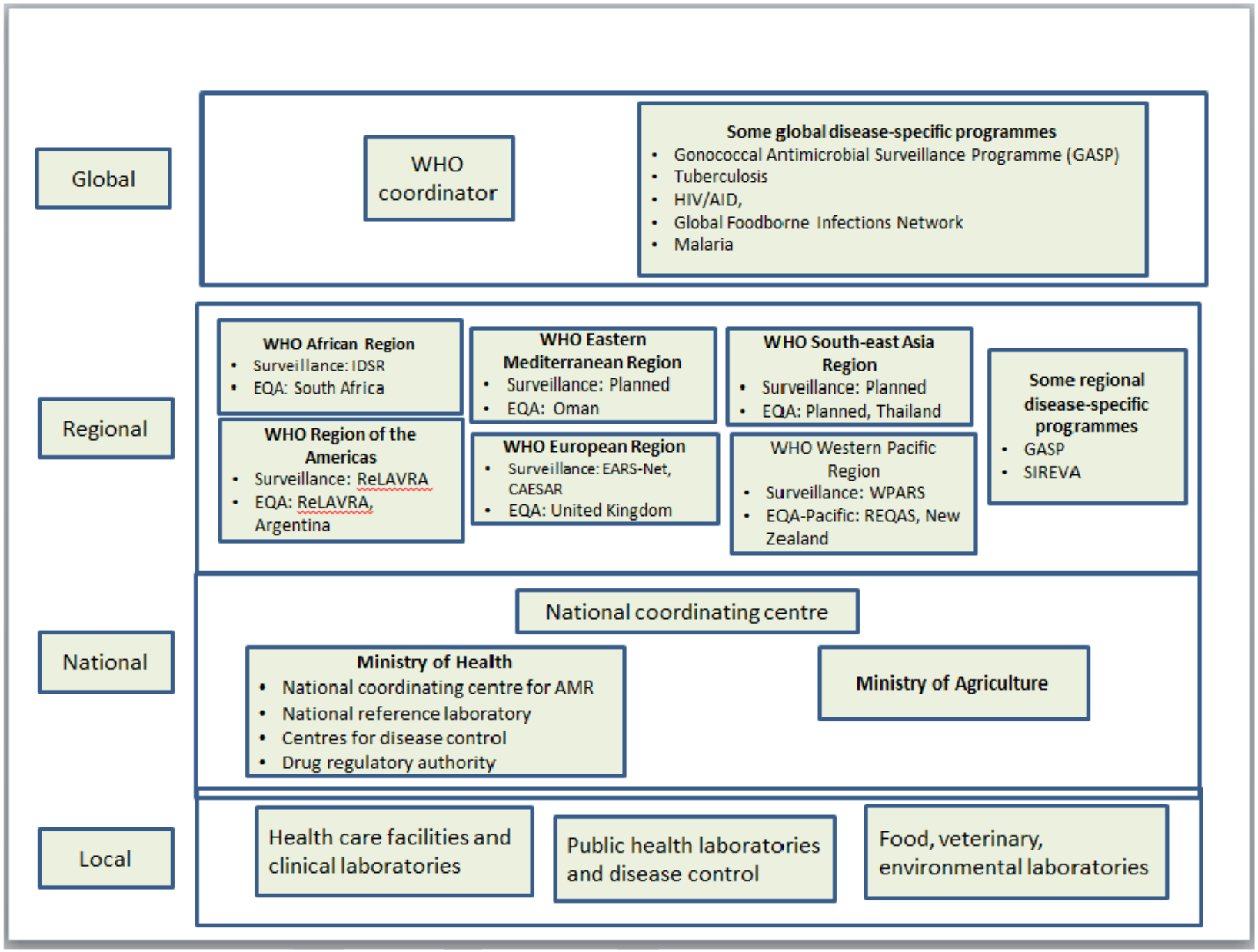
- to develop National Action Plan (NAP) aligned with GAP-AMR by May 2017
- WHO is to report on the development, implementation in WHA
- monitoring and evaluation of NAP-AMR and GAP-AMR.

Development and implementation of NAP

- **Action from countries:**
  - Create a coordination mechanism applying the One-Health approach body involving:
    - Human, animal, food sectors
    - Agricultural and environmental sectors
    - Partners from the civil society organizations (industry associations, professional organizations, association and private sectors)
  - Review to identify challenges and needs in 2016
  - Timeline of deliverables in NAP will be as appropriate to each country's context and circumstances
  - Develop comprehensive policies that cover all pillars of the Global Action Plan for AMR

Annex 2. Strategic framework for global surveillance of AMR

WHO strategy for AMR surveillance in human and agriculture



Surveillance system in Japan

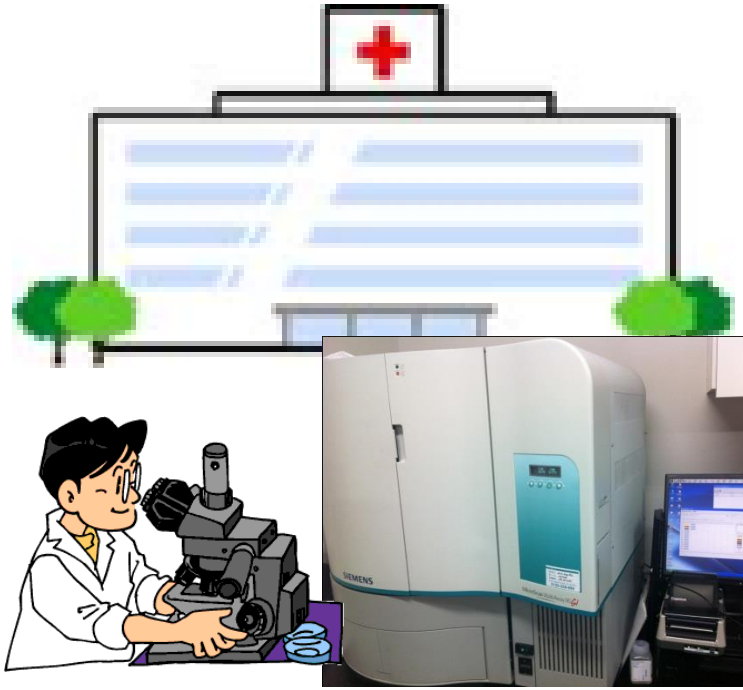
Human side: JANIS

Animal side: JVARM

Japan Nosocomial Infections Surveillance (JANIS)

- Organized by Ministry of Health, Labour and Welfare
- Established in 2000, system renewal in 2007
- Consists of five divisions
  - **Clinical Laboratory Division (CL)**
  - **Antimicrobial Resistant Infections Division (ARI)**
  - Surgical Site Infections Division (SSI)
  - Intensive Care Unit Division (ICU)
  - Neonatal Intensive Care Unit Division (NICU)

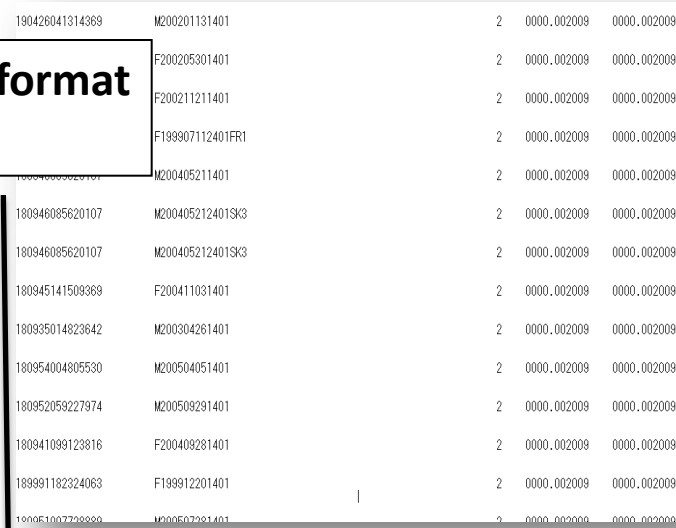
Data collection and return to the users

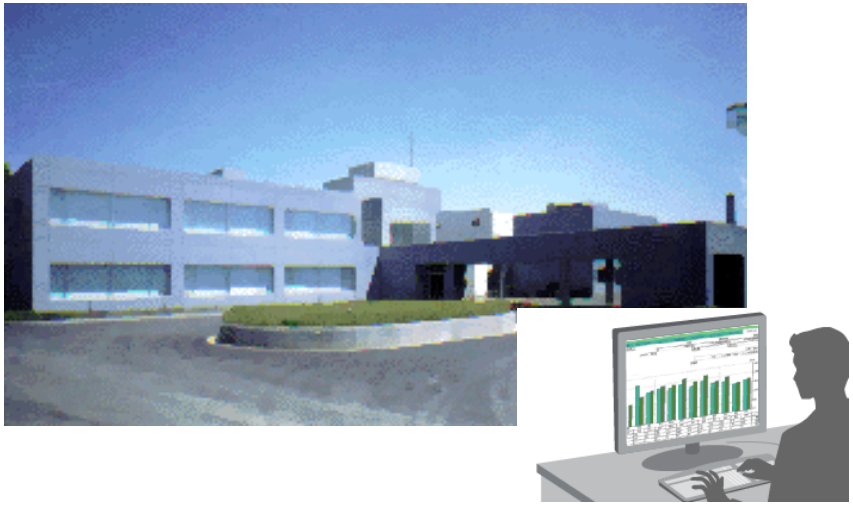


Clinical laboratory in participating hospitals

Convert all electrical data in the hospital into the JANIS format

JANIS format data

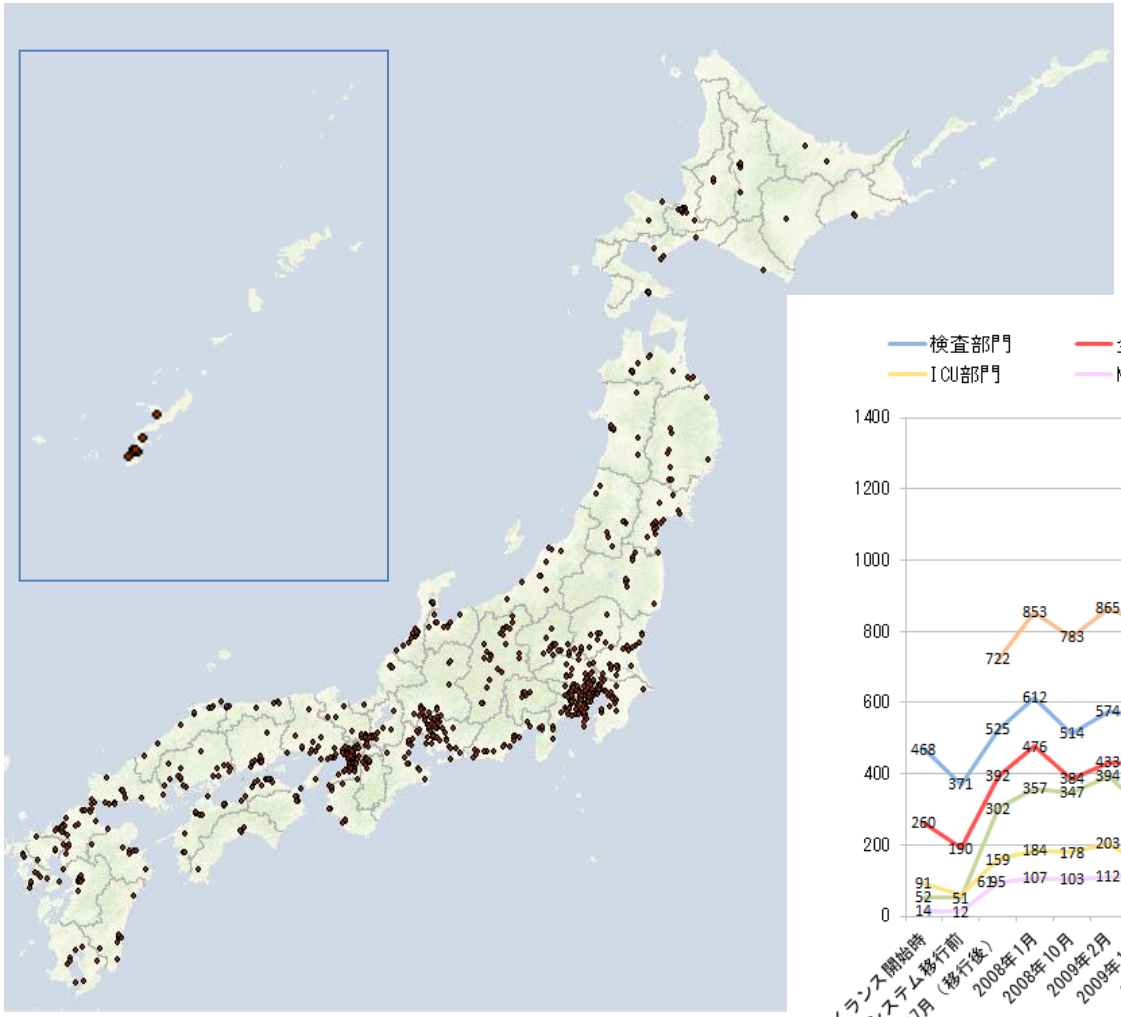




National Institute of Infectious Diseases(NIID)

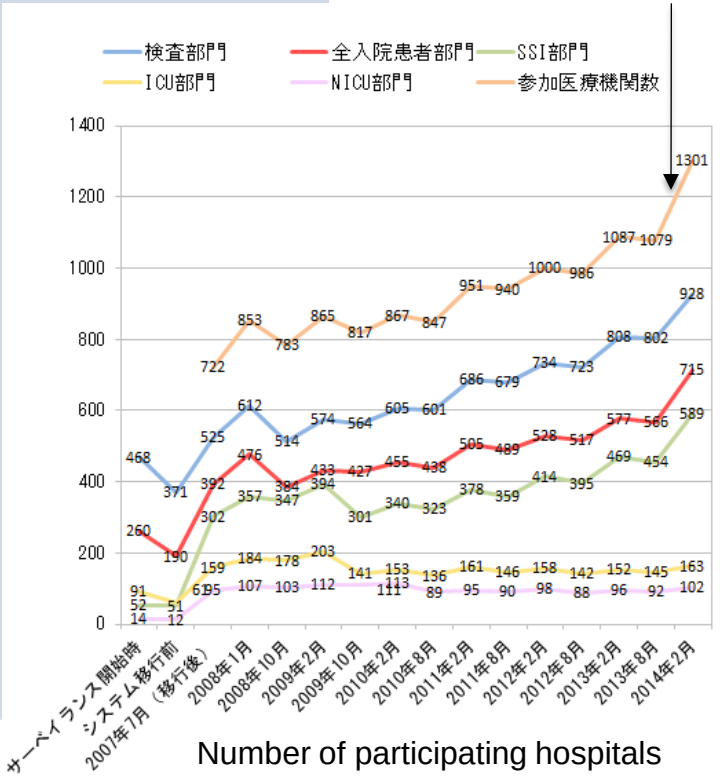
- Compile data from all hospitals
- Analyze and publish the summary, periodically in the website of NIID
- Each hospital will know its present situation of drug resistance, comparing with the average, and use the date for the improvement in the hospital

Participating hospitals in JANIS



Approximately 1,300 hospitals with >200 beds are participating

Reimbursement of infection control fee



Number of participating hospitals

Total

Clinical Laboratory Division

Antimicrobial-Resistant Bacterial Infections Division

SSI Division

ICU Division

NICU Division

New participants are recruited every year.
(A total number of hospitals in Japan is about 8,000)

Numbers of isolates cultured at participating hospitals

Samples	No of samples	No of culture-positive samples	No of cultured isolates
Respiratory tract	1,488,882	942,330	1,978,204
Urine	621,446	325,947	497,438
Stool	401,659	198,141	392,408
Blood	1,562,028	200,174	226,460
Spinal fluid	63,505	3,262	3,633
Others	1,000,110	460,798	817,695
Total	5,137,630	2,130,652	3,915,838

Open report 2014

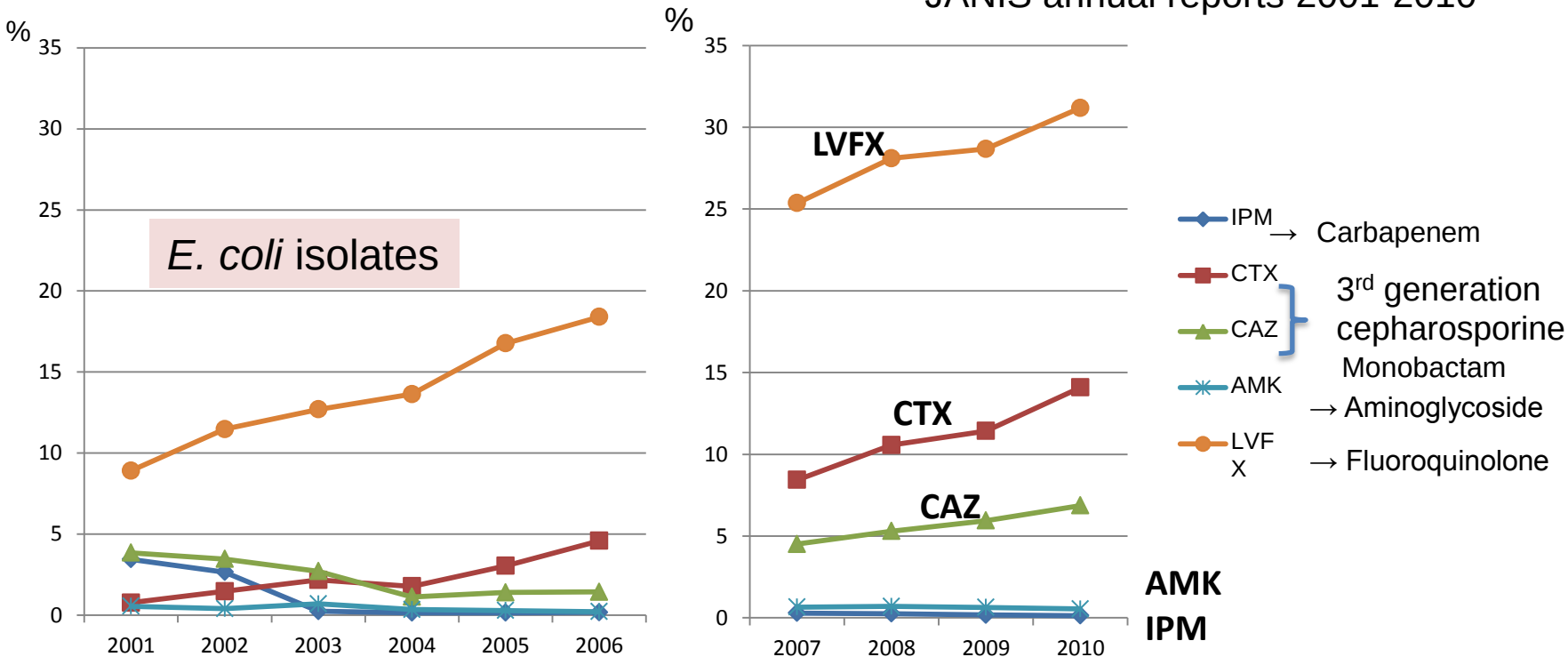
MRSA/*S. aureus*	60%
VRE/*Enterococcus* spp.	0.5–1.0%
Carbapenem resistant *P. aeruginosa*/*P. aeruginosa*	17–20%
MDRP/*Pseudomonas aeruginosa*	3%
Fluoroquinolones resistant *E. coli*/*E. coli*	25–30%
3rd generation cepharosporine resistant *E. coli*/*E. coli*	10%
Carbapenem resistant *E. coli* (IPM,NDM-1,KPC etc)	0.1%
3rd Cep. Resistant *K. pneumoniae*	5%
Carbapenem resistant *K.* pneumoniae	0.2%
Multidrug-resistant *Acinetobacter*/*Acinetobacter*	0.1%

Clinical Laboratory Division

Multidrug-resistant *E. coli* of human clinical isolates

Rates of *E. coli* nonsusceptible to clinically important antimicrobial drugs

JANIS annual reports 2001-2010



- Resistance of 3rd generation cepharosporines and fluoroquinolones has been increased dramatically in these decades
- Pandemic of CTX-M type ESBL-producing *E. coli* O25 ST131 was found

Trend of frequency of drug resistance in *Acinetobacter* spp.

Year	*A. baumannii*	*A. calcoaceticus*	*A. lwoffii*	*Acinetobacter* sp.	Total
2007	10/8,273 (0.12%)	1/545 (0.18%)	1/1,354 (0.07%)	12/3,403 (0.35%)	24/13,575 (0.18%)
2008	26/16,721 (0.16%)	0/1,033	1/3,320 (0.03%)	14/7,356 (0.19%)	41/28,430 (0.14%)
2009	20/17,212 (0.12%)	0/661	4/3,393 (0.12%)	9/8,386 (0.11%)	33/29,652 (0.11%)
Total	56/42,206 (0.13%)	1/2,239 (0.04%)	6/8,067 (0.07%)	35/19,145 (0.18%)	98/71,657 (0.14%)

From JANIS data

General view of JVARM

1．Purpose
- Nationwide monitoring of antimicrobial resistance
- Monitoring of veterinary antimicrobial use
- Data submitted to risk evaluation/risk management
- Reflection of data to prudent use of antimicrobials

2．Established in 1999 , organized by Ministry of Agriculture

3．Achievement system
- Network of prefectural Livestock Hygiene Service Centers

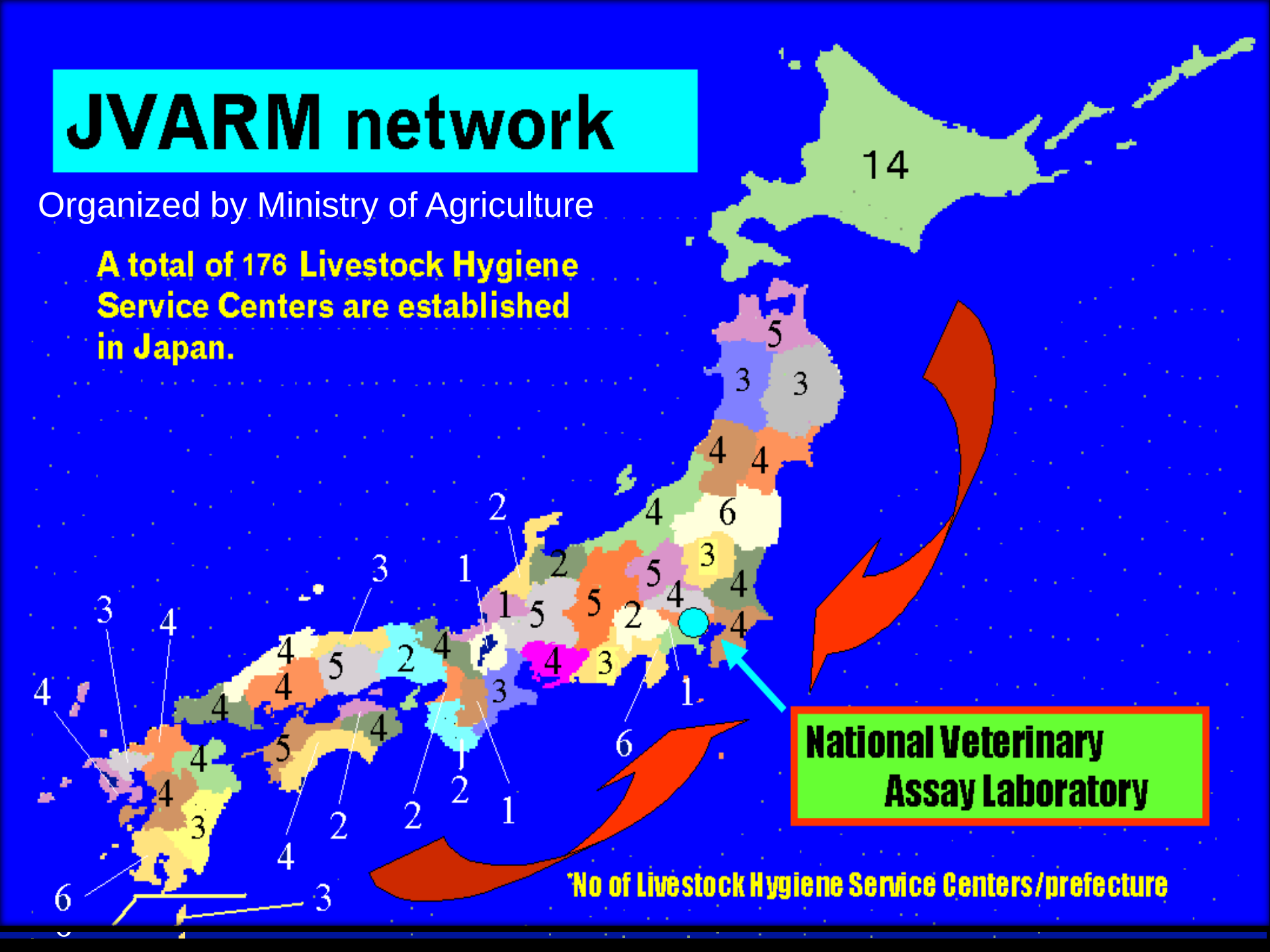
4．Targeted bacterial species
- Indicator bacteria （*E.coli* & *Enterococcus*）
- food-born pathogen （*Salmonella* & *Campylobacter*）

5．Publication
- Animal Hygiene Weekly
- HP （http://www.maff.go.jp/nval/english/）

JVARM network

Organized by Ministry of Agriculture

A total of 176 Livestock Hygiene Service Centers are established in Japan.

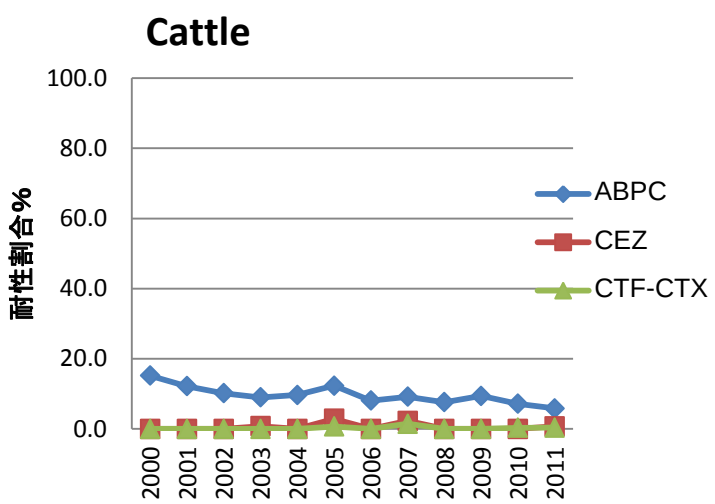


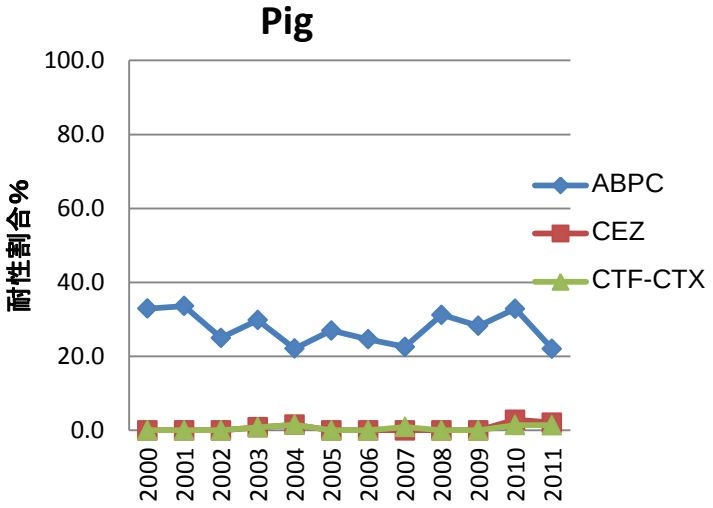
Total number of bacterial isolates examined from animal feaces in 1999 to 2009

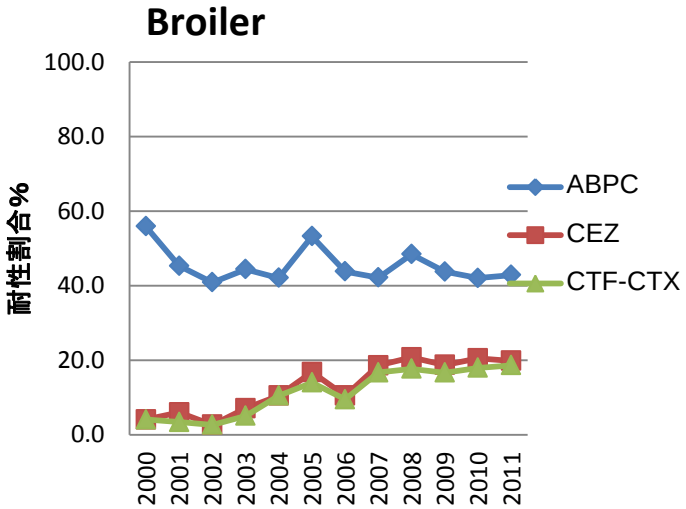
year	*E. coli**	*Enterococcus**	*Campylobacter*	*Salmonella*		
				Non-diagnostic	Diagnostic	Total
1999	1,018	1,024	166	124	194	318
2000	620	556	302	91	–	91
2001	580	302	239	22	60	82
2002	532	242	168	50	79	129
2003	475	286	247	20	72	92
2004	511	513	219	35	73	108
2005	518	562	158	41	128	169
2006	500	421	83	64	111	175
2007	450	424	223	39	170	209
2008	683	707	157	–	222	222
2009	612	566	233	–	149	149
TOTAL	6,499	5,603	2,195	486	1,258	1,744

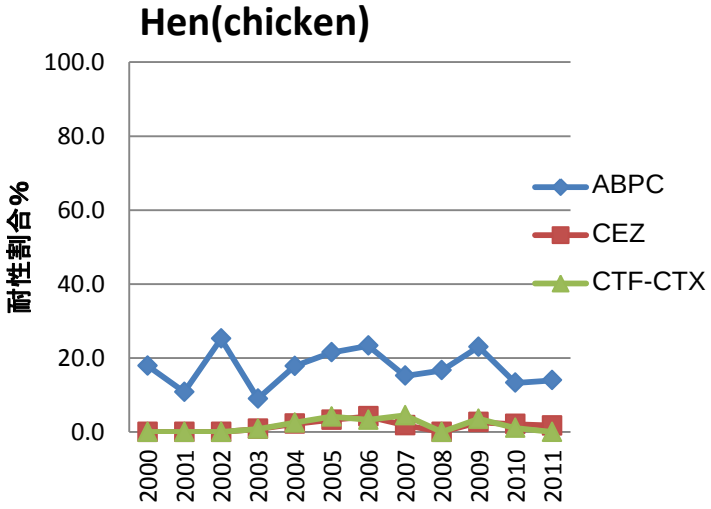
* indicator bacteria

Trend of β-lactum resistant *E.coli* rate among livestock



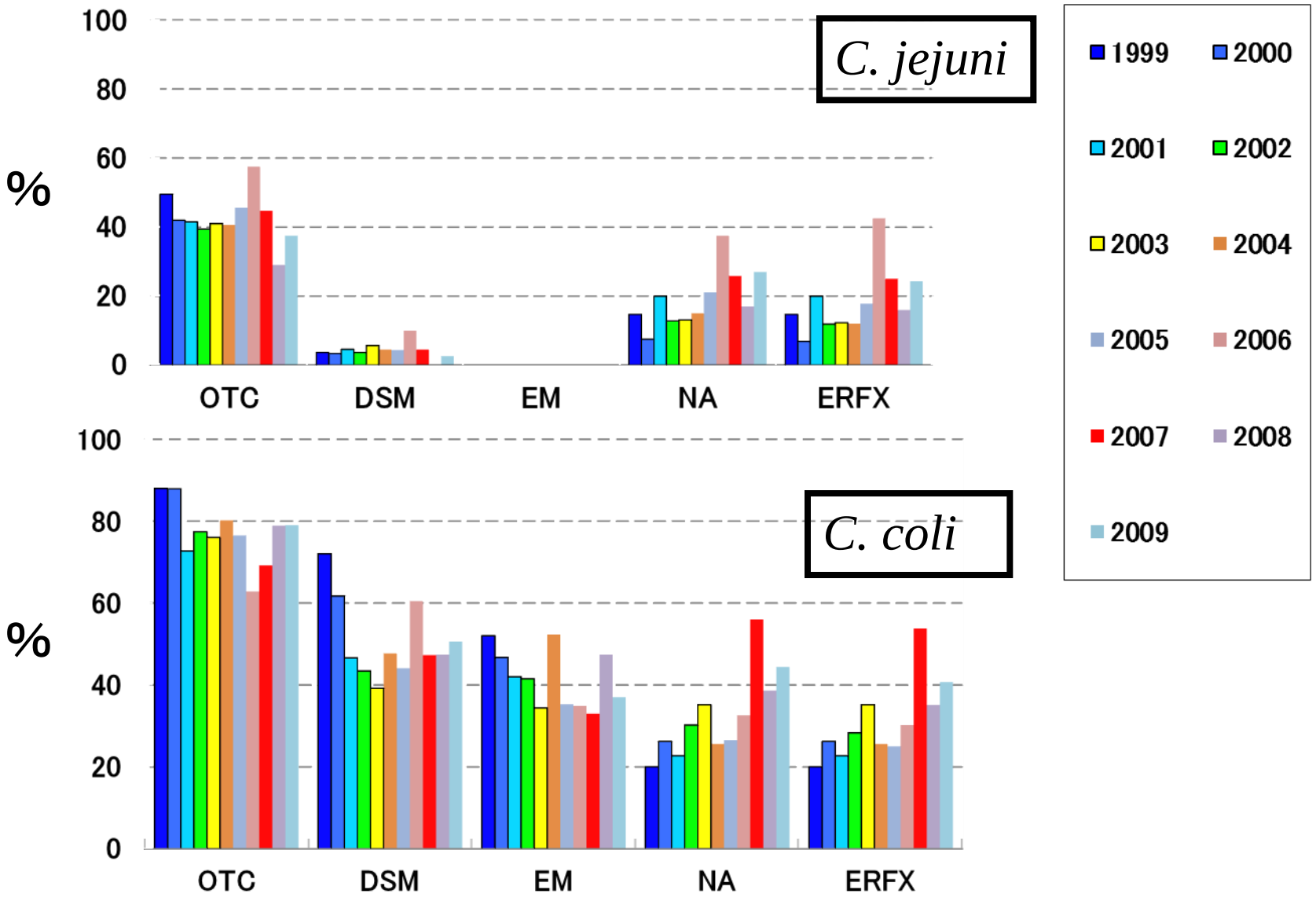






ABPC：Ampicillin、CEZ：Cefazolin、CTF-CTX：2000～2009Y(CTF;Ceftioful：2010~2011Y(CTX; Cefotaxim）

Resistance rate: *Campylobacter*



Integration of data between JANIS and JVARM

(Comparison of antibiotic resistance between human and animal origin)

Data of JVARM

Convert of JVARM data into JANIS format

Server of data between JANIS and JVARM

Data of JANIS and JVARM are combined and analyzed

JANIS data

Hosp

Hosp

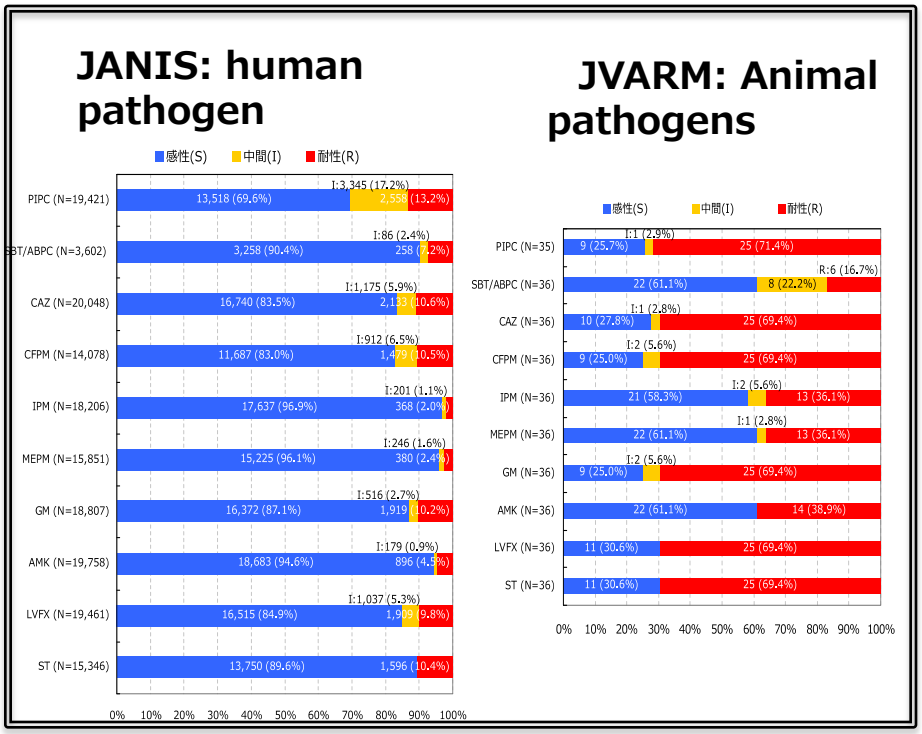
Hosp

Hosp

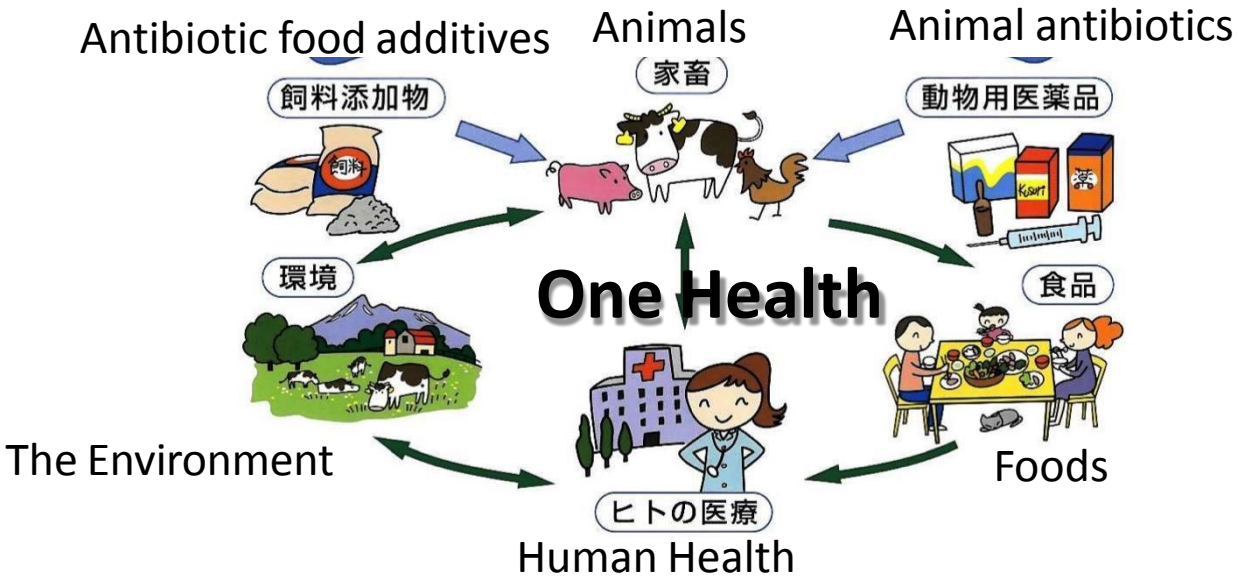
Hosp

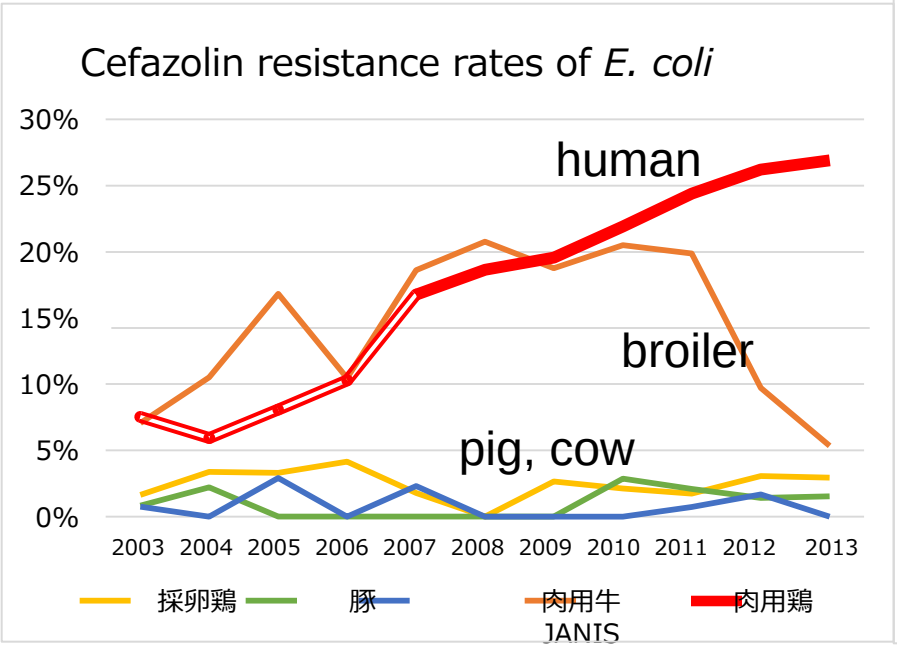
Hosp

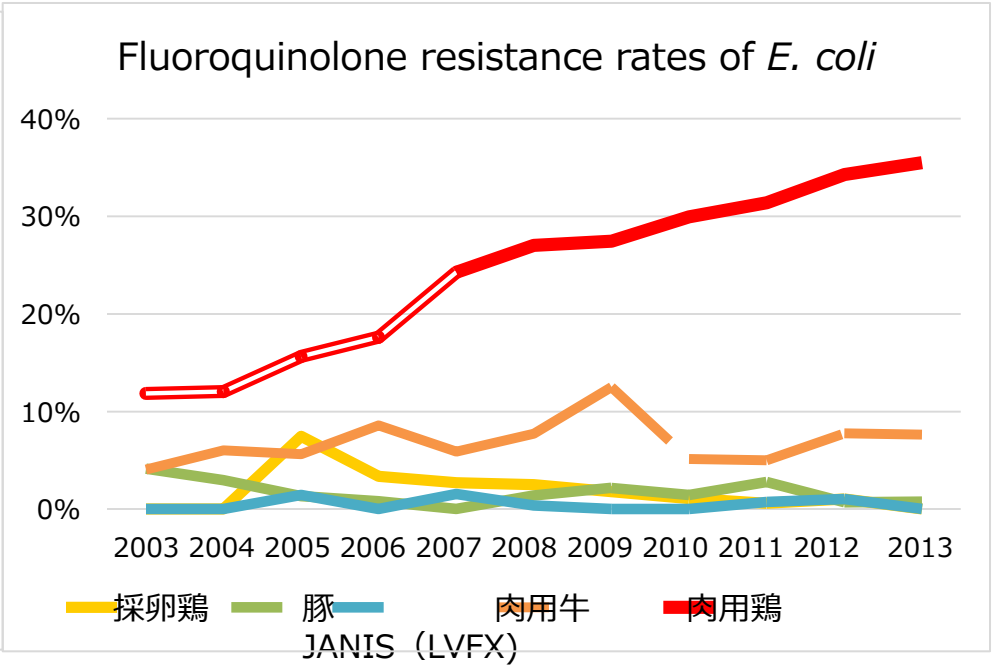
JANIS Server



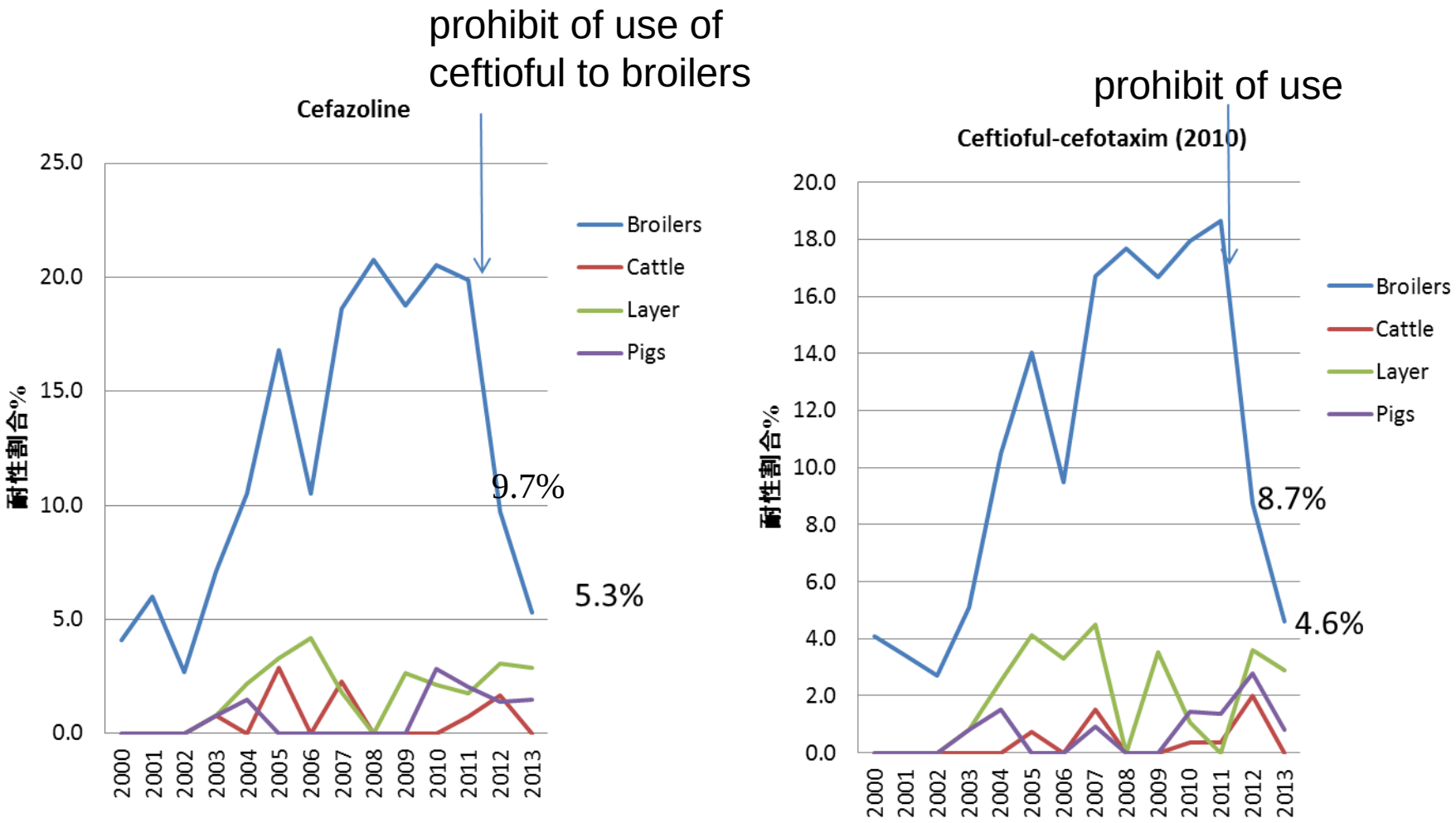
Cooperation with animal sectors







Reduction of cephalosporin resistant *E. coli* of broiler origin after the stop of use of antibiotics administration to broilers



Prohibit of the use of antibiotics has a great impact to the reduction of AMR in the feces of broilers

Transmission of drug resistant strains or genes

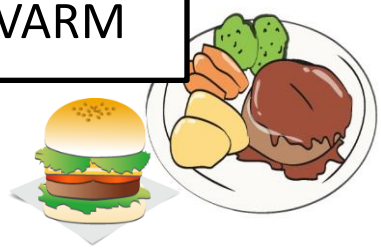
Integration of JANIS and JVARM: surveillance

Use of antibiotics for human

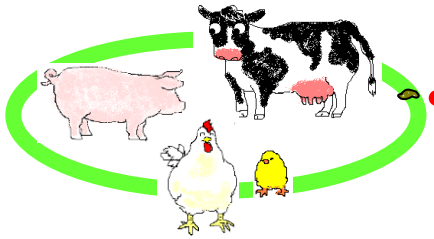
JANIS

JVARM

Selective pressure



Selective pressure

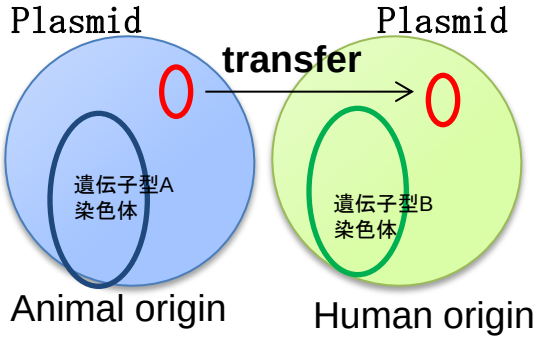


Use in agriculture

Selective pressure

Use for animals: therapeutic and growth promotion

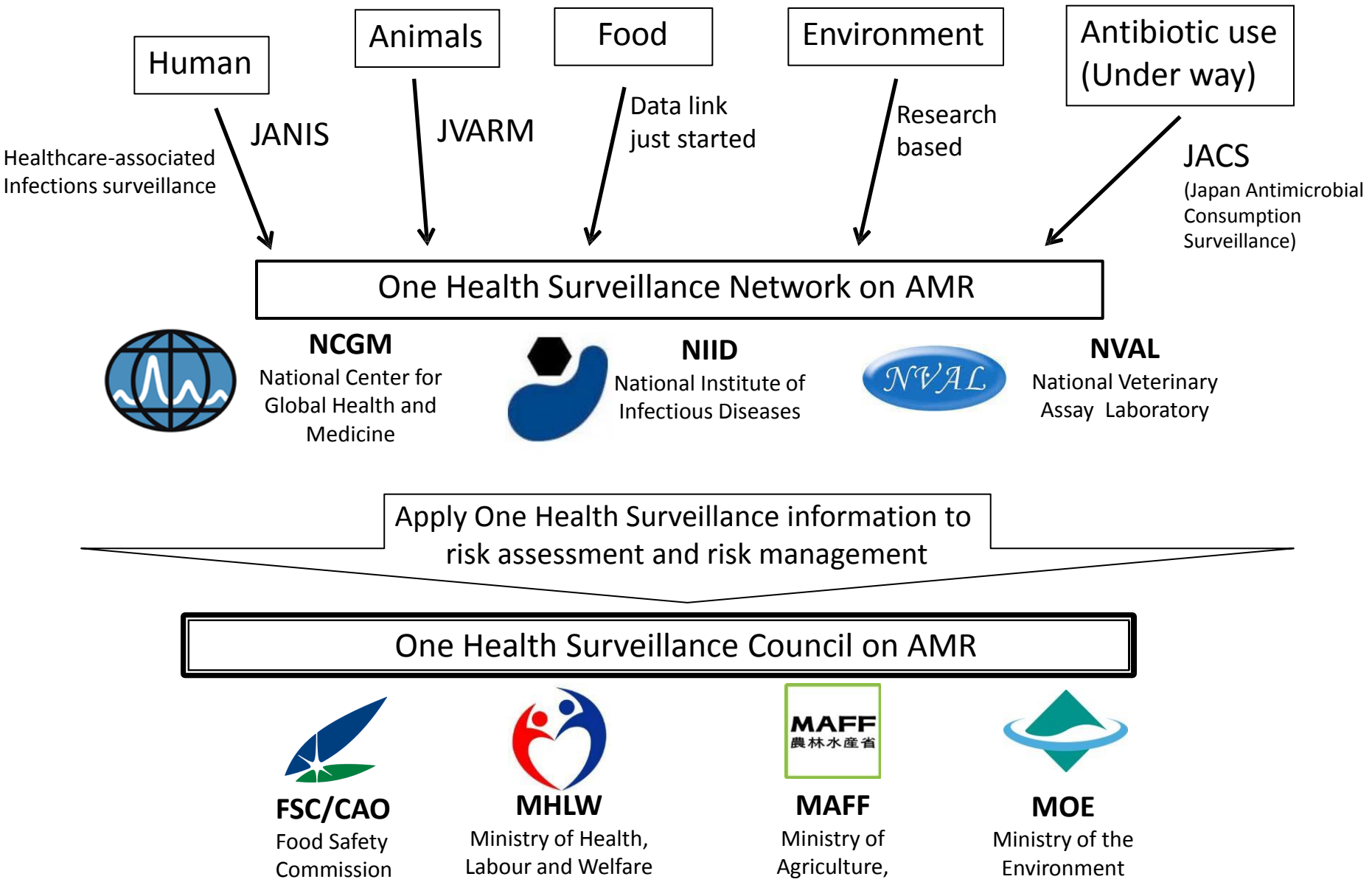
Research project



Construction of plasmid genome data

Data base of genome of plasmids conferring drug resistance genes isolated from different species, sources, isolation years and etc.

Current development: One Health Surveillance



AMR action plan in Japan,2016-2020

Six Areas and Goals for Countermeasures on AMR Fields

1 . **Public Awareness and Education** ; Improve public awareness and understanding, and promote education and training of professionals

2. **Surveillance and Monitoring** ; continuously monitor antimicrobial resistance and use of antimicrobials, and appropriately understand the signs of change and spread of antimicrobial resistance

3. **Infection Prevention and Control** ; prevent the spread of antimicrobial-resistant organisms by Implementing appropriate Infection prevention and control

4. **Appropriate Use of Antimicrobials**; promote appropriate use of antimicrobials in the fields of healthcare, livestock production and aquaculture

5. **Research and Development** ; promote research on antimicrobial resistance and foster research and development to secure the means to prevent, diagnose and treat the antimicrobial-resistant Infections

6. **International Cooperation** ; enhance global multidisciplinary countermeasures against antimicrobial resistance

Please see the details in the web site of MOH in Japan

http://www.maff.go.jp/nval/english/pdf/japan_nationalactionplan_on_antimicrobial_resistance.pdf

OUTCOME INDICES FOR THE ACTION PLAN

The following outcome indices are specified for this action plan.

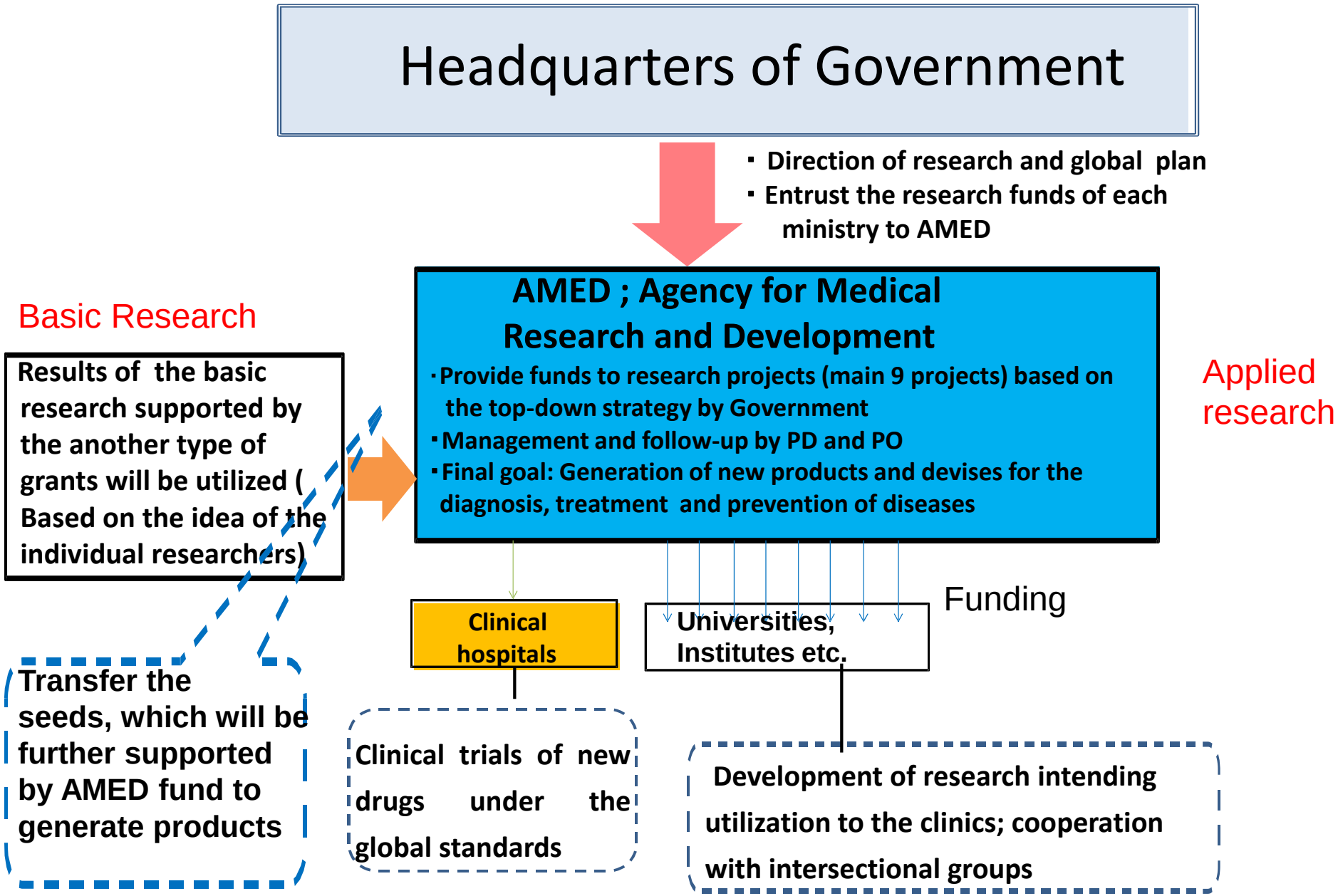
HUMAN-RELATED INDICES

1. Lower the penicillin resistance of *Streptococcus pneumoniae* to 15% or less in 2020
2. Lower the methicillin resistance of *Staphylococcus aureus* to 20% or less in 2020
3. Lower the fluoroquinolone resistance of *Escherichia coli* to 25% or less in 2020
4. Lower the carbapenem (imipenem) resistance of *Pseudomonas aeruginosa* to 10% or less in 2020
5. Maintain the carbapenem resistance of *Escherichia coli* and *Klebsiella pneumoniae* at 0.2% or less in 2020[104]
6. Reduce the antimicrobial use per day per 1,000 inhabitants in 2020 to two-thirds of the level in 2013[105]
7. Reduce the use of oral cephalosporins, quinolones, and macrolides per day per 1,000 inhabitants in 2020 by 50% from the level in 2013
8. Reduce the use of intravenous antimicrobials per day per 1,000 inhabitants in 2020 by 20% from the level in 2013

ANIMAL-RELATED INDICES

1. Lower the tetracycline resistance of *Escherichia coli* to 33% or less[106]
2. Maintain the third-generation cephalosporin resistance of *Escherichia coli* at the same level as in the other G7 countries as of 2020[107]
3. Maintain the fluoroquinolone resistance of *Escherichia coli* at the same level as in the

New Policy for the research development and innovation: New funding agency(AMED) operated from April 1, 2015



Major Projects in the Infectious disease-associated fields

Promote the research on whole genome analysis, data-base construction , and relation between epidemiological information and genome information of pathogens, toward the development of diagnosis, treatment and prevention

Influenza

Novel influenza such as H7N9 emerged in China, which may invade into Japan. Rapid response is required

Dengue fever

Endemic Dengue fever has recently occurred in Japan in 70 years. Japan has a risk for Dengue fever. Rapid response is required

Drug resistance

Incident of CRE is increasing worldwide. WHO will announce the global action plan to combat the drug resistance in 2015. Each country is required to make a nationak plan.

Enteric infections (Norovirus etc)

Norovirus infection is most prevalent among enteric infections in Japan. Preventative method such as vaccine is required in Japan

Rapid response

EID such as Ebola etc

J－GRID overseas sites

Collaboration

NIID

PHI (prefectural health insitutes)

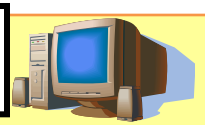
・Promote genome analysis of pathogens and construction of data base,

Develop and improve the national response for the control of EID

Analysis of genome data of pathogens

Analyze rapidly the change of virulence and drug resistance
Compare the international and national isolates and trace back the origins
Predict the endemic or pandemic strains

Identification of drug targets



Contributions to development

・Development of diagnostic devises , drugs for treatment, vaccines for prevention of infectious diseases