One Health Approach on AMR surveillance in Korea

Food Microbiology division, NIFDS, MFDS
• Antimicrobial resistance is a global public health concern and food safety issue
Threats of AMR

- Deaths attributable to AMR every year
  
  It is estimated that the burden of deaths from AMR is growing into 10 million lives each year by 2050, unless action is taken.

Modified from Jim O’Neill Report, 2016
Threats of AMR

Origins and channels of contamination

Ministry of Health & Welfare (KCDC)

MAFRA / Ministry of Oceans and Fisheries

Min. Food & Drug Safety

Resistant bacteria

Misuse

Antibiotics

Direct contact

Improper handling or cooking

Horticulture/farming/fishery products

Feces, fertilizers

Feces, disposal of medicines

Food

Environment

People

Medical institutions

Spreading within medical institutions

Local community

Ministry of Environment
History of the national AMR management program

NVRQS (Ministry of agriculture)
- Monitoring of antimicrobial resistance on the food-animals and meats

Asia Pacific Foundation for Infectious Disease (Samsung Medical Center)
- Control of antimicrobial resistance in hospitals through integrated antimicrobial stewardship program

NFRDI Ministry of marine affairs and fisheries
- Monitoring of antimicrobial resistance for aquaculture and introduction of organic marine production system

Drug resistance Division (KCDC)
- Surveillance of antimicrobial resistant pathogens in community

Seoul National University / Korea University
- Risk analysis of critically important veterinary antimicrobials
- Risk analysis of antimicrobial resistant bacteria

Enterobacteria Division(KCDC)
- Establishment for national FoodNet for antimicrobial resistance

Korea Food and Drug Administration
- General management & budget allocation
- Development of network for integrated antimicrobial resistance management
- Construction of information share portal
- Management of expert committee for antimicrobial resistance
- Public relation and education
- Invitation of Codex AMR TF
- Research for foodborne antimicrobial resistant bacteria

Korea consumer agency
- Antibiotic resistance monitoring for animal farm environment and impact assessment
- Surveillance of antimicrobial resistant bacteria from animal farm environment

Yonsei University (21 University hospital)
- Devising strategies to reduce antibiotic resistance in clinical medicine

Korea consumer affairs institute / Yonsei University
- Survey for awareness of antimicrobial resistance
- Evaluation of the effect of public relation and contents development

Yonsei University / Culture collection of antimicrobial resistant microbes
- Construction of Culture collection of antimicrobial resistant microbes

Kosin University
- Analysis of antimicrobial resistance gene

Clinical field

Prime Minister’s Office
- Mediation & evaluation of tasks of governmental departments

Ministry of Health and Welfare
- Revision of regulations
- Public relation & Education

Center for Disease Control & Prevention
- Antimicrobial resistance management
- Hospital infection management

Health Insurance Review & Assessment Service
- Monitoring antibiotics prescribing rate & amount of hospitals

Hospital, Medical college, Academic society
- Regional research institute of public health and env.
- Management & surveillance on antibiotic resistance
- Management & surveillance on nosocomial infection

Non-clinical field

Korea Food and Drug Administration
- Invitation of CODEX TFAMR
- Consumer education

Ministry of Environment
- Management of residual drugs in environment
- Collection of used drugs in household

Ministry of Food, Agriculture, Forestry and Fisheries (Livestock)
- Trace system of antimicrobials for animal
- Mandatory system of prescription for animal HACCP for livestock

Ministry for Food, Agriculture, Forestry and Fisheries (Aquaculture)
- HACCP for aquaculture
- Diffusion of vaccine
- Guideline of using antimicrobials

National Institute of Environmental Research
- Monitoring of residual drugs in environment

Animal, plant & fisheries quarantine & inspection agency
- Monitoring of antimicrobial resistant bacteria & amount of antimicrobials used

National Fisheries Research & Development Institute
- Monitoring of antimicrobial resistant bacteria & amount of antimicrobials used
Non-clinical discussion bodies (2013~2016)

- Monitoring of antimicrobial-resistance in each sector after the end of “National Antibiotics-resistance Safety Management Program”

Resistance rate in clinical sector
- Ministry of Health & Welfare
- Korea Center for Disease & Control
- HIRA

Resistance rate of imported or distributed food products
- Ministry of Food & Drug Safety (MFDS)
- National Institute of Food & Drug Safety (NIFDS)

Resistance rate in farming and fishery sectors
- MAFRA
- Animal and Plant Quarantine Agency
- Ministry of Oceans and Fisheries
- National Institute of Fisheries Science

Residues in the environment and resistance
- Ministry of Environment
- National Institute of Environmental Research

Management of antibiotics-resistance Non-clinical discussion bodies
National action plan of Korea (2016~)

- WHO presented a global action plan and urged national-level actions (2015).
- Developed and implemented the National Action Plan on AMR

MoHW (Oversight)

- Antibiotics-resistance advisory committee
- Good Antibiotics Usage Campaign HQ

KCDC

- Dedicated departments

MFDS (Non-human oversight)

- MAFRA (animal oversight)
- Ministry of Oceans and Fisheries
- Ministry of Environment

Korea Institute of Drug Safety & Risk Management

Animal and Plant Quarantine Agency

National Institute of Fisheries Science

National Institute of Environmental Research
One health approach fight AMR (2017~)

- Surveillance of Antimicrobial drug usage
- Research on Multi-drug resistance
- Interaction and translocation of among Human-animal-environment
- Control and treatment

Ministry of Environment
Ministry of Health & Welfare
Ministry of Science & ICT
Ministry of Oceans & Fisheries
Ministry of Food & Drug Safety
Ministry of Agriculture, Food & Rural Affairs
Major outcomes of national AMR management programs
Major outcomes of National programs

• **Ban** of adding antimicrobials in *animal feed* (*MAFRA, 2011*)

• Provide **government subsidies** for *organic* live stock farms (2008)

• Expansion of **HACCP** certified farms

• Adoption of **seafood traceability** system
  (*Ministry of Oceans and Fisheries, 2008*)

• Adoption of **mandatory prescription by veterinarians** (*MAFRA, 2013*)

• **Public relation and education** (2003~)

• Medicinal waste recovery system (*MoE, 2010*)
Major outcomes of National programs

Sales (tons)

-200
0
200
400
600
800
1000
1200
1400


- total
- tetracyclines
- sulfonamides
- penicillins
- aminoglycosides
- macrolides
- quinolones
- inophores
- polypeptides
- phenicols
- pleuromutilins
- quinoxalines
- lincosamides
- cephalosporins
- streptomycins
- glycolipid
- others
Major outcomes of public relation & education

- Guidelines for public education

- Educations on animal and aqua farms for prudent use of antimicrobials
Major outcomes of public relation & education

- Public educations (TV shows)

- Public educations (leaflets)
Major outcomes of public relation & education

- Collection and dispose of unused drugs
Monitoring outcome reporting

- Published integrated, non-clinical national antibiotics usage and resistance statistics report (livestock, farm products, and fishery products)
- Published via the website (www.mfds.go.kr)
Future directions

- Establish and implement national antibiotics-resistance management action plan (2016~)

**Vision**

Reduce the use of antibiotics, use a proper amount, and prevent distribution of resistant bacteria

⇒ Protect the public from antibiotic-resistance.

**Target**

<table>
<thead>
<tr>
<th>[Human]</th>
<th>- Compared to 2015, by 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Reduce the volume of antibiotics usage by 20%</td>
<td></td>
</tr>
<tr>
<td>▪ Reduce the volume of antibiotics prescription for upper airway infection by 50%.</td>
<td></td>
</tr>
<tr>
<td>▪ Reduce the volume of antibiotics prescription for respiratory diseases by 20%.</td>
<td></td>
</tr>
<tr>
<td>▪ Reduce the resistance of <em>Staphylococcus aureus</em> against methicillin by 20%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>[Non-human]</th>
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<tr>
<td>▪ Increase the number of antibiotics items for prescription by veterinarians by two folds</td>
</tr>
<tr>
<td>▪ Chicken: Reduce the resistance to fluoro-quinolone against colon bacteria by 10%</td>
</tr>
</tbody>
</table>
The Codex *ad hoc* Intergovernmental Task Force on *Antimicrobial Resistance (TFAMR)* established in the Codex Alimentarius Commission (CAC) in 2006

- The 1st through 4th Codex TFAMR held in Korea (2007~2010)
  - Guidelines on *risk assessment of foodborne antimicrobial resistance*

- The 5th Codex TFAMR holding in Jeju, Korea in 2017

- The 6th Codex TFAMR holding in Busan, Korea in 2018
  - Revision of the *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CAC-PCP 61-2005)
  - Propose draft *Guidelines on integrated surveillance of antimicrobial resistance*
CODEX *ad hoc* TF AMR

**CODEX TFAMR**

- **Executive Committee**
  - General Subject Committee
    - General Principles (France)
    - Food Contaminants (Netherlands)
    - Food Hygiene (USA)
    - Food Labeling (Canada)
    - Methods of Analysis and Sampling (Hungary)
    - Pesticide Residues (China)
    - Residues of Veterinary Drugs in Food (USA)
    - Food Import and Export Inspection and Certification System
    - Nutrition and Foods for Special Dietary Uses (Germany)
    - Food Additives (China)
  - Commodity Committee
    - Milk and Milk Products (New Zealand)
    - Cocoa Products and Chocolate (Switzerland)
    - Processed Fruits and Vegetables (USA)
    - Meat and Poultry Hygiene (New Zealand)
    - Fish and Fishery Products (Norway)
    - Fresh Fruit and Vegetables (Mexico)
    - Fats and Oils (United Kingdom)
    - Sugars (United Kingdom) Adjoined
    - Cereals, Pulses and Legumes (USA) Adjoined
    - Vegetables Proteins (Canada) Adjoined
    - Natural Mineral Waters (Switzerland) Adjoined
  - *ad hoc* Intergovernmental Task Force
    - Foods Derived from Biotechnology (Japan)
    - Quick Frozen Food (Thailand)
    - Antimicrobial Resistance (Korea)
  - Regional Coordinating Committee
    - Asia (Korea)
    - Africa (Uganda)
    - Europe (Slovak Republic)
    - Latin America and Caribbean (Dominican Republic)
    - Near East (Egypt)
    - North America and the Southwest Pacific (Canada)
Characteristics of ESBL-producing *Salmonella* from food samples
Salmonella Virchow isolated from human

- *Salmonella* Virchow strains from human feces samples had been gradually increasing during 2010-2014

**Figure.** Temporal distribution of *Salmonella enterica* serotype Virchow isolates in South Korea, 2005–2014.

Reference from: JS Kim et al., 2016, EID 22(1):68-70
Distribution of *Salmonella* serotype

- *Salmonella* spp. isolated from food samples During 2014 - 2017

*Salmonella* spp. (108)

ESBL-producing *Salmonella* spp. (8)

*others (19) : S. Augustenborg (1), S. Braenderup (3), S. Coeln (1), S. Derby (2), S. Edinburg (1), S. I 4,[5],12:i:- (1), S. Livingstone(4), S. Newport (2), S. Ohio (1), S. Richmond(1), S. Sandiego(1), S. Schwarzengrund(1)
AMR analysis and genotyping tools (1)

- Antimicrobial resistance test: automated MIC determination (Trek Sensititre)

- Conventional PCR: identified antimicrobial genes
AMR analysis and genotyping tools (2)

- **MLST (Multi Locus Sequence Typing)**

  - PCR > Sequencing > Allele assignment at mist.net > ST assignment at mist.net

  - ST239

- **PFGE (Pulsed Field Gel Electrophoresis)**

  - Bacteria
  - Add to buffer to make suspension
  - Add molten agarose to make plug
  - Agarose plug filled with bacteria
  - Lysis cells
  - Step 3
  - Electrophoresis
  - DNA fragments
  - Whole, genomic DNA
  - Step 4
  - Enzyme digest
Illumina Miseq Sequencing

NexteraXT index kit with V2 chemical

Removing adapter sequences using Trimmomatic

SPAdes3.12.0 for De novo assembly

Quality control and annotation

Apply different bioinformatic pipelines to characterize the genome
Bioinformatic tools

Overview of Services

- Workflows
  - Bacterial Analysis Pipeline (Batch Upload)
- Phenotyping
  - ResFinder
  - Phenol萃取
  - PathogenFinder
  - VenerealFinder
  - RestrictionModificationFinder
- Typing
  - KmerFinder
  - SpecialFinder
  - MLST
  - PhenolFinder
  - PLA:J
  - SerotypeFinder
  - Primer
  - O-Typing
  - R-Typing
  - SCCmecFinder
- Phylogeny
  - CBB Phylogeny
  - Neighbor

- ResFinder
- PlasmidFinder
- MLST
- ISFinder

• BRIG
• Seqsero: Predicting Salmonella serotype
• BRIG
• PATRIC
• Rast
Genetic relation among ESBL-producing *Salmonella*

- *Salmonella* Virchow isolated from chicken meat during 2014-2016 showed very similar PFGE patterns, the same clonal sequence type (ST16)

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Year</th>
<th>Source</th>
<th>Serotype</th>
<th>Bla genes</th>
<th>Inc group</th>
<th>MLST type</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF6489</td>
<td>2015</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Virchow</td>
<td>CTX-M-15</td>
<td>HI2, HI2A, Q1</td>
<td>ST16</td>
</tr>
<tr>
<td>MF6490</td>
<td>2015</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Virchow</td>
<td>CTX-M-15</td>
<td>HI2, HI2A, Q1</td>
<td>ST16</td>
</tr>
<tr>
<td>MF7758</td>
<td>2016</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Virchow</td>
<td>CTX-M-15</td>
<td>HI2, HI2A, Q1</td>
<td>ST16</td>
</tr>
<tr>
<td>MF4257</td>
<td>2014</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Virchow</td>
<td>CTX-M-15</td>
<td>HI2, HI2A, Q1, Y</td>
<td>ST16</td>
</tr>
<tr>
<td>MF4259</td>
<td>2014</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Virchow</td>
<td>CTX-M-15</td>
<td>HI2, HI2A, Q1</td>
<td>ST16</td>
</tr>
<tr>
<td>MF8451</td>
<td>2017</td>
<td>Chicken meat (Brazil)</td>
<td><em>S.</em> Heidelberg</td>
<td>CTX-M-8</td>
<td>A/C2, X1</td>
<td>ST15</td>
</tr>
<tr>
<td>MF5430</td>
<td>2015</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Newport</td>
<td>CTX-M-15, TEM-1B</td>
<td>FIA, FIB, FII, Q1, X1</td>
<td>ST166</td>
</tr>
<tr>
<td>MF5419</td>
<td>2015</td>
<td>Chicken meat (Korea)</td>
<td><em>S.</em> Enteritidis</td>
<td>CTX-M-15</td>
<td>FIB(S), FII(S), Q1</td>
<td>ST11</td>
</tr>
</tbody>
</table>
Genetic relation among ESBL-producing Salmonella

- Genetic relation of ESBL-producing Salmonella by PFGE

- Genetic relation of ESBL-producing Salmonella by FastTree method on PATRIC
Genetic characteristic

- $\text{bla}_{\text{CTX-M-15}}$ carrying contigs of Salmonella Virchow were compared by BRIG
One health approach

- **PFGE Comparison between Salmonella Virchow isolates from human and food samples**
  - which dose it prefer clonal spread or horizontal transfer
Conclusion

- Korean government tried to slow down the spread of resistance by “national antimicrobial-resistance management program” started since 2003.

- **National Action Plan on Antimicrobial Residence** in accordance with WHO’s global action plan propositions since 2016 engaged in clinical and non-clinical national programs as part of the **ONE-HEALTH** approach.

- Major outcomes of last 15 yrs of National AMR management Programs include banning addition of antibiotics to animal feeds and introduction of mandatory prescription by vets.

- Due to the ban on mixing in the feed, which resulted in a significant reduction in the usage of tetracycline, it turned out that the resistance against this drug reduced significantly.

- MFDS (NIFDS) is planning to continue its role of AMR management, including overseeing non-clinical areas such as livestock, fishery, environment, and foods, to reduce the AMR and ensure proper use of antibiotics.
Thank you!