Hong Kong, 13-14/11/18

AMR Surveillance Programme in food in China

Junshi Chen

China National Centre for Food Safety Risk Assessment

Surveillance is the key component of global action plan

2015:

Global action plan on antimicrobial resistance (Strategic objective 2: Strengthen the knowledge and evidence base through surveillance and research)

- **Global Antimicrobial Resistance Surveillance System (GLASS)**
- **WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance - with AGISAR 5-Year Strategic Framework to Support Implementation of the Global Action Plan on Antimicrobial Resistance (2015-2019)**

2016:

- **The FAO Action Plan on Antimicrobial Resistance 2016 - 2020 (Focus Area 2: Develop capacity for surveillance and monitoring of Antimicrobial Resistance and antimicrobial use in food and agriculture)**

2016:

- **CCEXEC71 and CAC39 considered: (1) revision of the Code of practice to minimize and contain antimicrobial resistance and development of guidance on integrated surveillance of antimicrobial resistance. (2) establishment of a TFAMR.**

Surveillance of Antimicrobial Use

WHO：

- **Should establish systems to determine the amounts of antimicrobials given to food animals**

WHO/FAO/OIE：

- **AMU is a main driver for AMR**
- **Improved AMU in both humans and animals is needed to combat AMR, includs information on the individual patients (human or animal) and the indication for treatment**

Integrated Surveillance of AMR in Foodborne Microorganisms

Surveillance of AMU

Animal

Human

Surveillance of AMR

Animal

Human

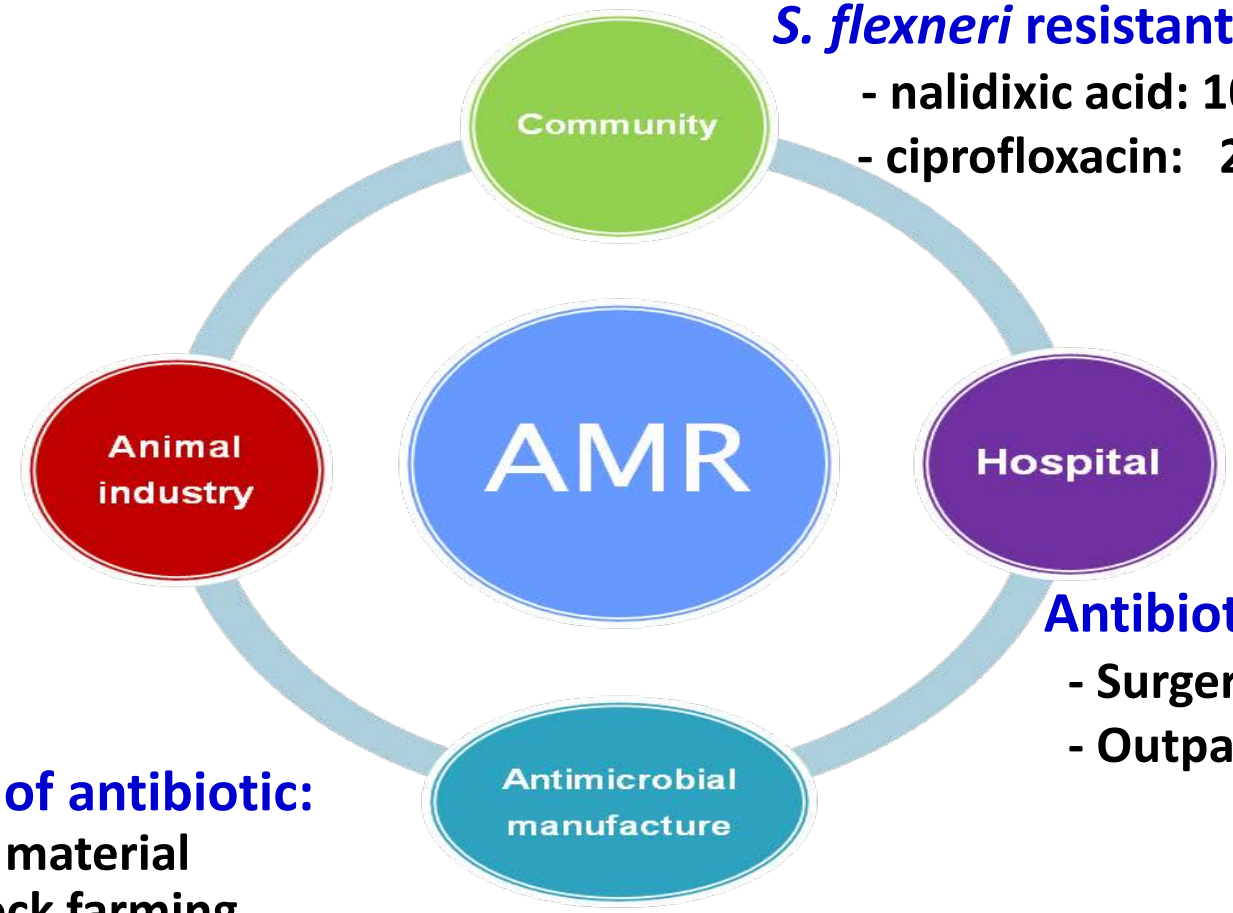
Food

- **WHO:** integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a One Health Approach
- **Codex:** Proposed draft guidelines on integrated Surveillance of antimicrobial resistance (TFAMR EWG COP2)

Link of AMR Emerge in China

***S. flexneri* resistant to**

- nalidixic acid: 100%
- ciprofloxacin: 20%



Antimicrobial use:

> 50,000 tons annually

> 50% as feed additives

Antibiotics use in

- Surgery: 97%～100%
- Outpatients: 20%～30%

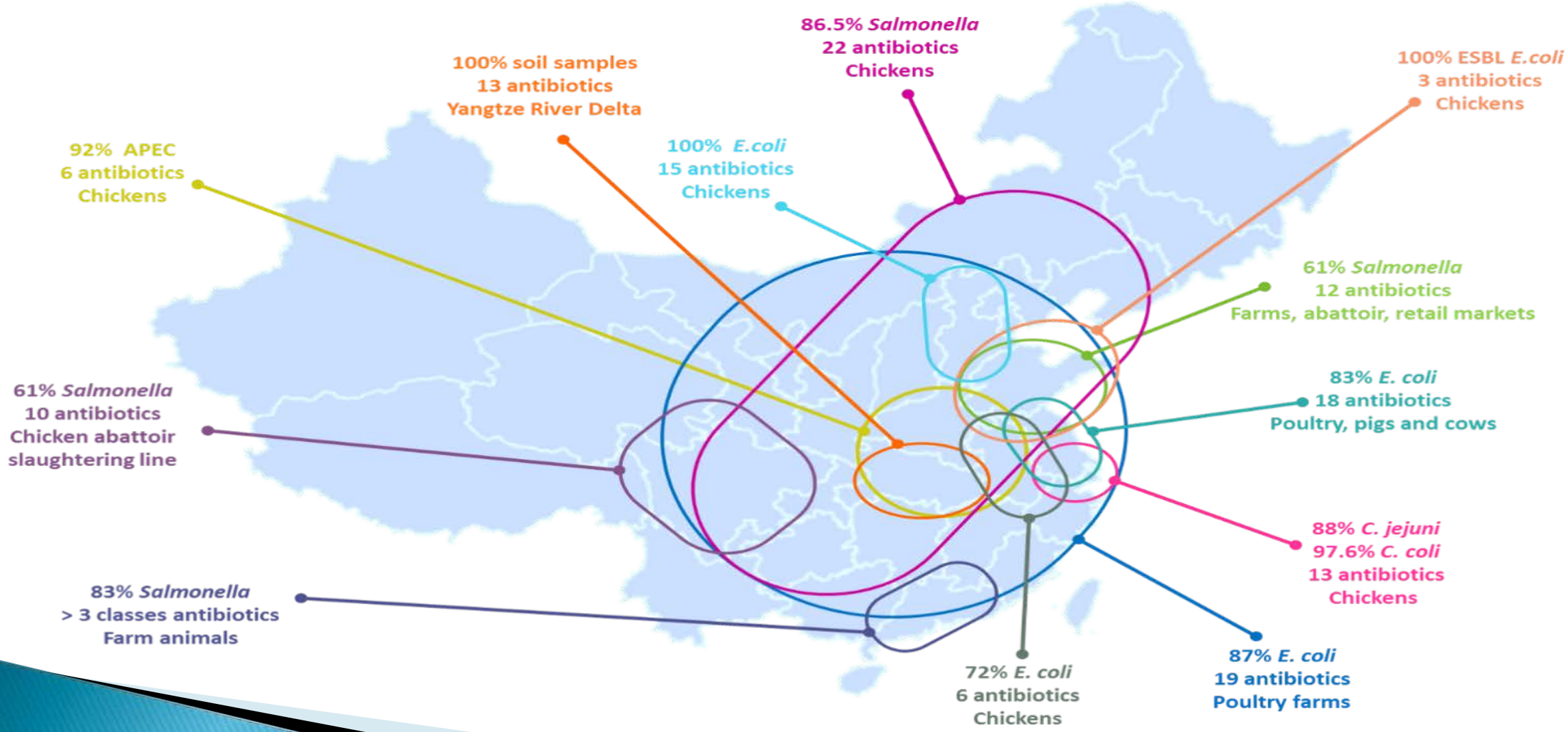
Annual production of antibiotic:

> 210,000 tons raw material

> 46% use in livestock farming

- Li et al. China practical medicine, 2010, 5(1): 159-160.
- Jia et al. Anhui Agriculture Science . 2007, 35 (5) :1368-1370.
- Development report of the veterinary drug Industry in China, 2013.

Multi-drug resistance of *E. coli, Salmonella* and *Campylobacter* isolated from poultry and environment in animal production provinces in China



Xie et al., 2017； Chen et al., 2012; Zhang et al., 2015.

AMR Surveillance Networks in China

全国细菌耐药监测网 CARSS China Antimicrobial Resistance Surveillance System

ce

Surveillance System (1412 hospitals, 2017)

CHINET 中国细菌耐药监测网

China Antimicrobial Surveillance Network (CHINET)

CFSA

d

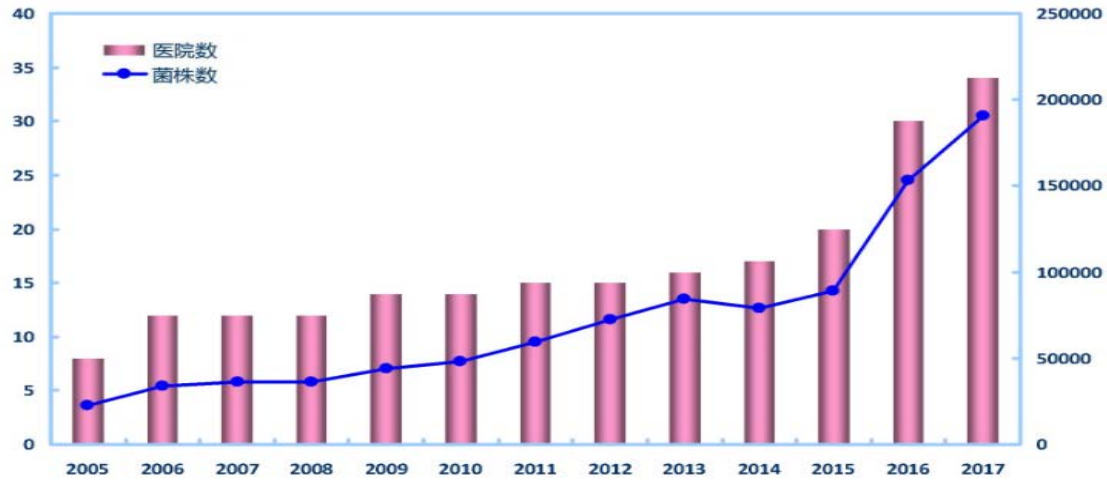
a

Bacteria and antimicrobials monitored mandatory in clinical samples

Bacteria	Antimicrobial agents
Staphylococcus	Penicillin, cefoxitin (or benzimidazole), erythromycin, Clindamycin
Streptococcus pneumonia:	Penicillin, vancomycin, ceftriaxone (or cefotaxime), meropenem
β-hemolytic streptococcus:	erythromycin, Clindamycin
Streptococcus viridans:	Penicillin (ampicillin)
Enterococcus	Penicillin (or ampicillin), gentamicin (high concentration) or Streptomyces(high concentration)
Haemophilus influenza	Ampicillin, SMZco
Enterobacteriaceae (E coli,Klebsiella, Proteus,Enterobacter,Bacillus citrate, Serratia)	Ampicillin, Cefazolin, gentamicin (or tobramycin)
Enterobacteriaceae (Salmonella, Shigella)	Ammonia-ampicillin, ceftriaxone (or cefotaxime), levofloxacin
Pseudomonas aeruginosa	Piperacillin/Tazobactam, ceftazidime, gentamicin (or tobramycin)
Acinetobacter	Ampicillin/Sulbactam, ceftazidime, Imipenem (or Mei Luo pei)South, Niepenand), gentamicin (or tobramycin)
Maltophilia Maltophilia	SMZco
Burkholderia cepacia	SMZco, Meropenem, levofloxacin
Others non- Enterobacteriaceae	Ceftazidime, Gentamycin (or tobramycin)

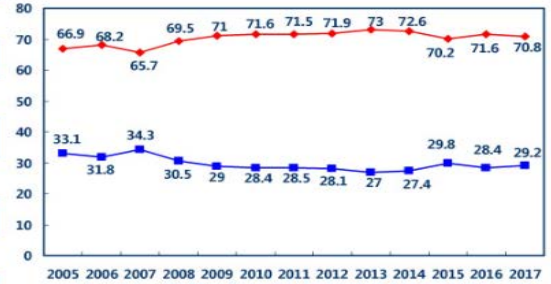
6.jpg

CHINET监测网历年成员单位及监测总菌株数量

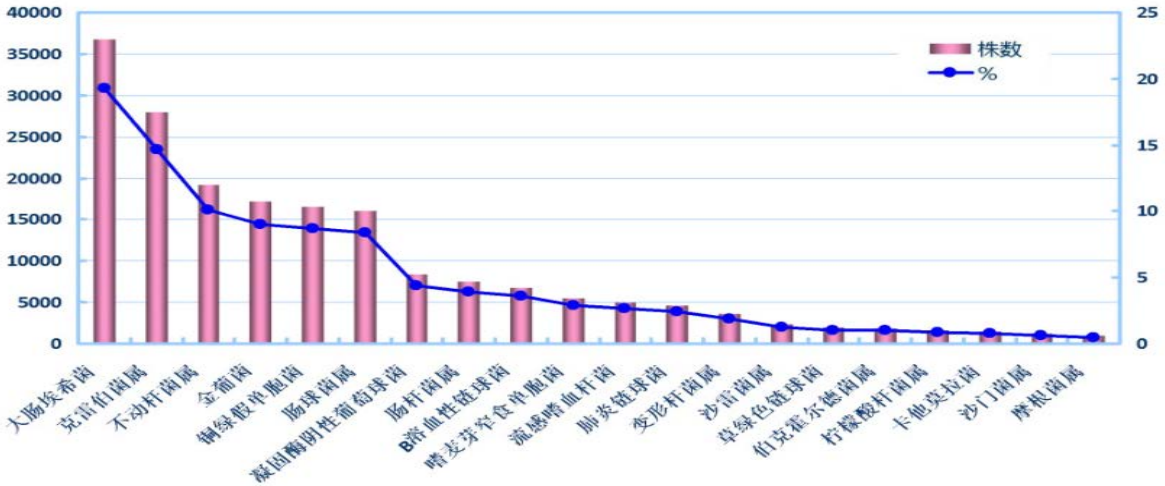


历年革兰阴性菌和阳性菌菌株数及占比

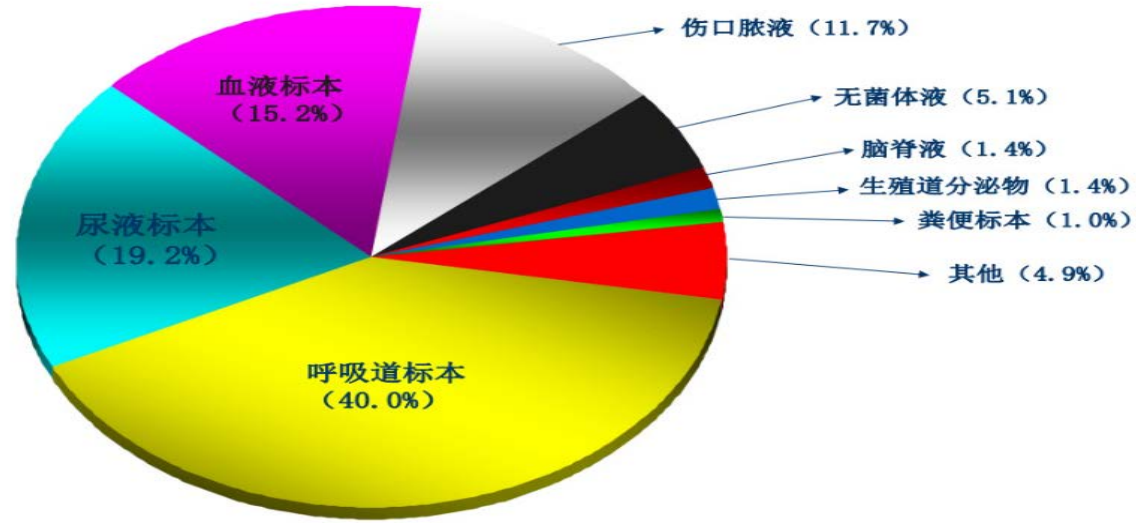
年份	医院数	株数	革兰阴性菌	革兰阳性菌
2005年	8	22774	15244	7530
2006年	12	33811	23062	10749
2007年	12	36001	23637	12364
2008年	12	36216	25184	11032
2009年	14	43670	31002	12668
2010年	14	47850	34282	13568
2011年	15	59287	42415	16872
2012年	15	72397	52043	20354
2013年	16	84572	61709	22863
2014年	17	78955	57320	21635
2015年	20	88778	62297	26481
2016年	30	153084	71.6%	28.4%
2017年	34	190610	70.8%	29.2%



2017年主要临床分离菌种分布（前20位）



190610株临床分离菌在各类标本中的分布



Database on AMR of Animal Origin

Foodborne Pathogen Surveillance

Regular Surveillance

- *E. coli*
- *Salmonella*
- *Staphylococcus aureus*
- *Listeria monocytogenes*
- *Bicillus cereus*
- *Shigella*
- *Vibro parahaemolyticus*
- *Cronobacter*
- *Pseudomonas aeruginosa*

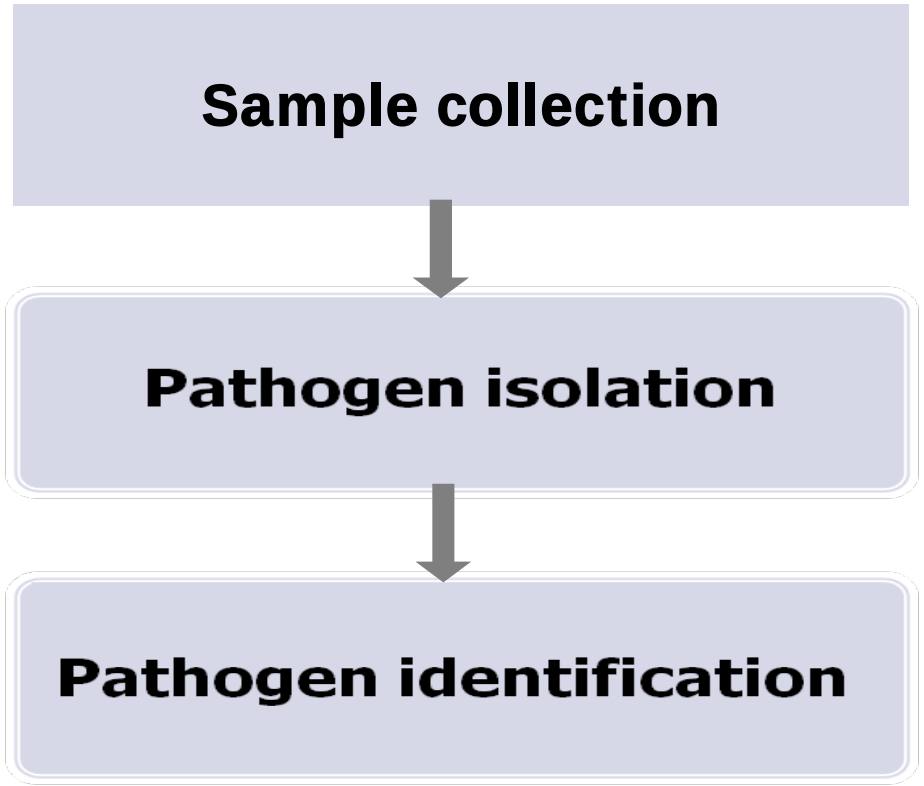
All samples from retailers

Targeted Surveillance

Chicken meats - *Salmonella*
Chicken meats - *Campylobacter*
Aquatic products- *V. parahaemolyticus*
RTE meat - *Listeria monocytogenes*
Infant formula - *Cronobacter*

Pathogen – food combination

Regular Surveillance for Foodborne Pathogens in China



- Further Confirmation
- Antimicrobial susceptibility test and AMR mechanism
- Genetic Characterization
  - PFGE, MLST, MLVA
  - Virulence gene detection
  - Toxic effect on cells
  - Whole genome sequencing

Local CDC → CFSA

(5,000-10,000 isolates per year)

Gene *mcr-1* Positive *Salmonella* Cultured from Foods in Regular Surveillance

Strain	CFSA664	CFSA122	CFSA12	CFSA244	CFSA1096	CFSA231	CFSA629
Serotype	Indiana	Typhimurium	Typhimurium	Typhimurium	London	Derby	Typhimurium
Year	2011	2013	2014	2014	2015	2016	2016
Food	Retail chicken carcass	Retail dumpling	Retail Pork	Retail Pork	Retail Pork	Dumpling	-

CFSA: Data not published

Surveillance of Carbapenem - Resistant *Salmonella* from Retail Foods

Targeted surveillance:

All strains are susceptible to carbapenem

	Ls
	3

	1601
Non-clinical	386

Regular surveillance

Salmonella in retail food, 2013-2015, 32 provinces

Target & Regular

Clinical cases, retail food, environment, pet (2013)

Wang Wei et al, 2016, Hu Yujie et al, 2015.

Antibiotic susceptibility of *S.* Indiana C629 to 23 antibiotics obtained in target surveillance in 2014

Class	Antimicrobial Agent	MIC (mg/L)	R/I/S
Penicillins	Ampicillin	>128	R
Cephalosporins	Cefepime	>16	R
	Cefoxitin	>32	R
	Cefazolin	>32	R
	Cefotaxime	>16	R
	Ceftazidime	>32	R
	Ceftiofur	>32	- [b]
Carbapenems	Imipenem	4	R
	Meropenem	8	R
Polymyxin	Colistin	0.5	S
Folate pathway inhibitors	Trimethoprim/sulfamethoxazole	>8/152	R
Aminoglicosides	Streptomycin	>32	- [b]
	Gentamicin	>32	R
Tetracyclines	Tetracycline	>32	R
	Tigecycline	<0.5	- [b]
β-lactamase inhibitor combinations	Amoxicillin/Clavulanic Acid	>64/32	R
Phenicols	Chloramphenicol	>32	R
	Florfenicol	>16	R
Macrolides	Azithromycin	>64	R
Fluoroquinolones	Nalidixic acid	>128	R
	Ciprofloxacin	>4	R
	Enrofloxacin	>8	R
Mequindox	Mequindoxs	>64	-

Wang wei et al. 2017, DOI 10.1186/s12879-017-2515-5.

Antimicrobial resistant phenotype of C629

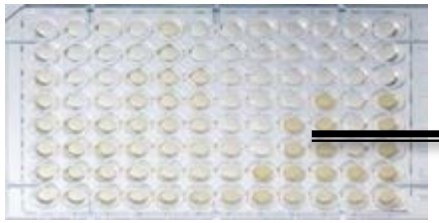
- Carbapenem resistance
- Co-resistance to ciprofloxacin-cefotaxime
- Extended Spectrum β-Lactamases (ESBLs)
- Resistant to antibiotics used in clinical and livestock
- Extensively drug-resistant (XDR)

Wangwei et al. 2017, DOI 10.1186/s12879-017-2515-5.

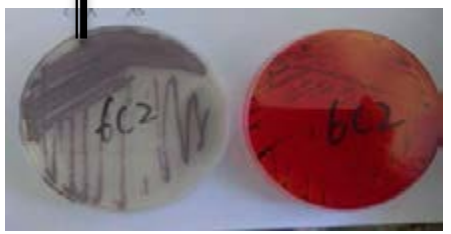
Targeted Surveillance of AMR *Salmonella* from Retail Chicken Carcass

Sampling

Isolation



WGS



Antimicrobial Susceptibility Test

Data Analysis

Distribution of AMR Patterns for Different Salmonella Serovars

Number of Class of Antimicrobials	No. of strains of dominant serovars (Percentage)											
	Total (n=2210)	Enteritidis (n=673)	Indiana (n=365)	Infantis (n=211)	Typhimurium (n=163)	Agona (n=162)	Derby (n=81)	Rissen (n=68)	Dabou (n=58)	Thompson (n=50)	Hadar (n=46)	Others (n=333)
0	438(19.8%)	68(10.1%)	6(1.6%)	16(7.6%)	24(14.7%)	135(83.3%)	7(8.6%)	12(17.6%)	4(6.9%)	19(38.0%)	0(0.0%)	147(44.1%)
1	645(29.2%)	271(40.3%)	12(3.3%)	141(66.8%)	34(20.9%)	9(5.6%)	15(18.5%)	32(47.1%)	43(74.1%)	11(22.0%)	0(0.0%)	77(23.1%)
2	160(7.2%)	20(3.0%)	19(5.2%)	15(7.1%)	9(5.5%)	0(0%)	10(12.3%)	3(4.4%)	11(19.0%)	0(0.0%)	42(91.3%)	31(9.3%)
3	175(7.9%)	128(19.0%)	18(4.9%)	1(0.5%)	10(6.1%)	0(0%)	4(4.9%)	2(2.9%)	0(0.0)	0(0.0%)	2(4.3%)	10(3.0%)
4	198(9.0%)	148(22.0%)	15(4.1%)	0(0%)	16(9.8%)	1(0.6%)	9(11.1%)	2(2.9%)	0(0.0)	0(0.0%)	2(4.3%)	5(1.5%)
5	101(4.6%)	14(2.1%)	25(6.9%)	1(0.5%)	19(11.7%)	6(3.7%)	9(11.1%)	7(10.3%)	0(0.0)	1(2.0%)	0(0.0%)	19(5.7%)
6	209(9.4%)	21(3.1%)	62(17.0%)	37(17.5%)	27(16.6%)	11(6.8%)	3(3.7%)	9(13.2%)	0(0.0)	6(12.0%)	0(0.0%)	33(9.9%)
7	184(8.3%)	3(0.5%)	109(29.9%)	0(0%)	24(14.7%)	0(0%)	24(29.6%)	1(1.5%)	0(0.0)	13(26.0%)	0(0.0%)	10(3.0%)
8	100(4.5%)	0(0%)	99(27.1%)	0(0%)	0(0%)	0(0%)	0(0.0%)	0(0.0%)	0(0.0)	0(0.0%)	0(0.0%)	1(0.3%)
≥3 (MDR)	967(43.8%)	314(46.7%)	328(89.9%)	39(18.5%)	96(58.9%)	18(11.1%)	49(60.5%)	21(30.9%)	0(0.0)	20(40.0%)	4(8.7%)	78(23.4%)
≥5	594(26.9%)	38(5.7%)	295(80.8%)	38(18.0%)	70(42.9%)	17(10.5%)	36(44.4%)	17(25.0%)	0(0.0)	20(40.0%)	0(0.0%)	63(18.9%)

Hu et al. Food Control, 2017, 81C： 46-54.

ESBLs distribution of cefotaxime and ciprofloxacin co-resistant S. Indiana with different antimicrobial resistance profiles

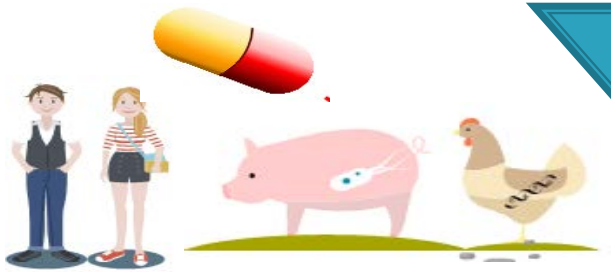
Antimicrobial resistance profile	Number of Isolates	Number of ESBLs
GEN-CHL-CIP-NAL-AMP-SAM-TET-CAZ-CTX-SXT	32	32
GEN-CHL-CIP-NAL-AMP-SAM-TET-CTX-SXT	66	65
GEN-CHL-CIP-NAL-AMP-SAM-TET-CAZ-CTX	11	11
GEN-CHL-CIP-NAL-AMP-SAM-CAZ-CTX-SXT	15	14
GEN-CHL-CIP-NAL-AMP-SAM-CTX-SXT	19	18
CHL-CIP-NAL-AMP-SAM-TET-CTX-SXT	13	13
GEN-CHL-CIP-NAL-AMP-SAM-TET-CTX	9	9
CHL-CIP-NAL-AMP-SAM-CAZ-CTX-SXT	1	0
GEN-CHL-CIP-NAL-AMP-TET-CTX-SXT	1	1
GEN-CIP-NAL-AMP-SAM-TET-CTX-SXT	3	3
GEN-CHL-CIP-NAL-AMP-SAM-CTX	4	4
GEN-CHL-CIP-NAL-AMP-CTX-SXT	2	2
GEN-CIP-NAL-AMP-SAM-CTX-SXT	1	1
CHL-CIP-NAL-AMP-CAZ-CTX-SXT	1	1
GEN-CHL-CIP-NAL-AMP-TET-CTX	1	1
GEN-CIP-NAL-AMP-SAM-TET-CTX	1	1
GEN-CIP-NAL-AMP-CTX-SXT	1	1
CIP-NAL-AMP-SAM-CTX	1	1
CIP-NAL-AMP-TET-CTX	1	1
Total	183	179

Comparisons of resistance to different antimicrobial agents between *Salmonella* isolates recovered from different seasons

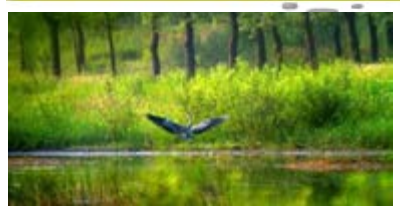
Antimicrobials	No. of resistant isolates				P Value*
	Spring + Winter (n=834)		Summer + Autumn (n=1376)		
Gentamicin	279	33.45%	176	12.79%	<0.001
Chloramphenicol	279	33.45%	246	17.88%	<0.001
Ciprofloxacin	220	26.38%	144	10.47%	<0.001
Nalidixic acid	610	73.14%	950	69.04%	0.04
Ampicillin	500	59.95%	451	32.78%	<0.001
Ampicillin-sulbactam	442	53.00%	399	29.00%	<0.001
Tetracycline	437	52.40%	490	35.61%	<0.001
Ceftazidime	76	9.11%	28	2.03%	<0.001
Cefotaxime	182	21.82%	65	4.72%	<0.001
Trimethoprim-sulfamethoxazole	314	37.65%	300	21.80%	<0.001
Imipenem	0	0.00%	0	0.00%	-

Capacity Building

AMU in Human & Animals



AMR in Human, Animals, Environment

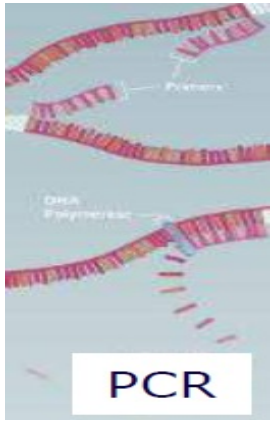


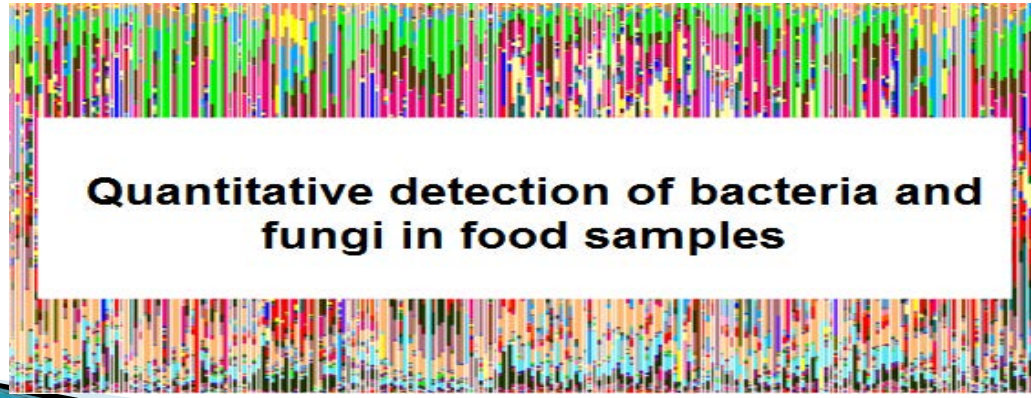
Integrated Surveillance

Data Analysis

Capacity Building in AMR Surveillance: Next Generation Sequencing

DNA Extraction

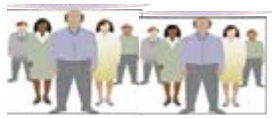




Using Big Data to Fight AMR – Advanced analytics

Surveillance

Farm



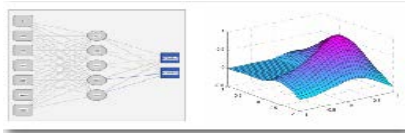
Community

Fork

Hospital

Mategenomics + Machine learning

Sequencing



Machine learning

AMR related gene profiling & tracking

Output

ALERT

+

ACTION

Capacity Building in AMU Surveillance

AMU in humans

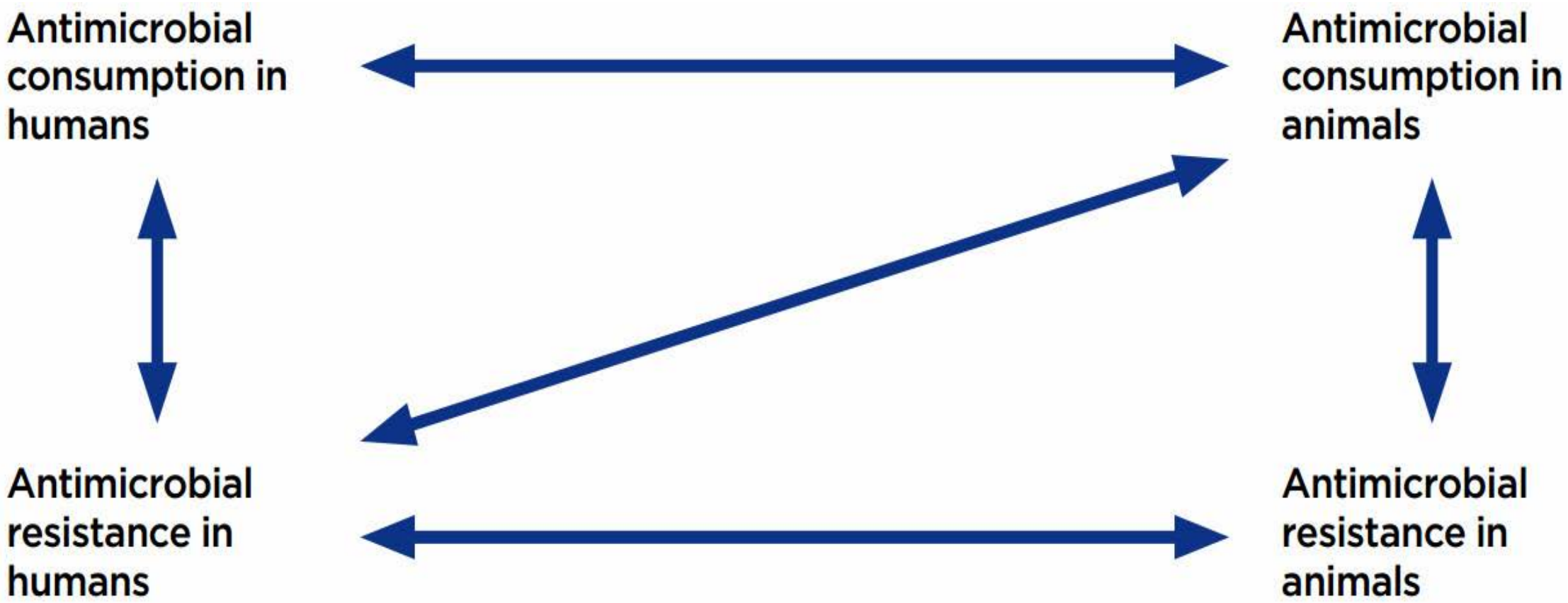
- national antimicrobial sales data
- in hospitals
- in community

AMU in animals

- national antimicrobial sales data
- antimicrobial consumption by animal species
- continuous collection of consumption data by animal species
- data from a sample of farms
- stratification of sales data

Integrated surveillance system at national level is the KEY

Capacity building in data analysis



Impact of AMU on AMR across sectors

http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=a1249.

Conclusion

- The key word of national AMR surveillance is integration.
- AMU should be included as an important part.
- Capacity building in integrated AMR surveillance should include:
  - Plan development
  - Staff training on sampling and analytical methods
  - Quality control
  - Data analysis, and
  - Report preparation and data sharing

Acknowledgement

国家食品安全风险评估中心
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National Natural Science Foundation of China