



AMU and AMR Activities in Animals

Taiwan
October 10th, 2019

2019/10/10

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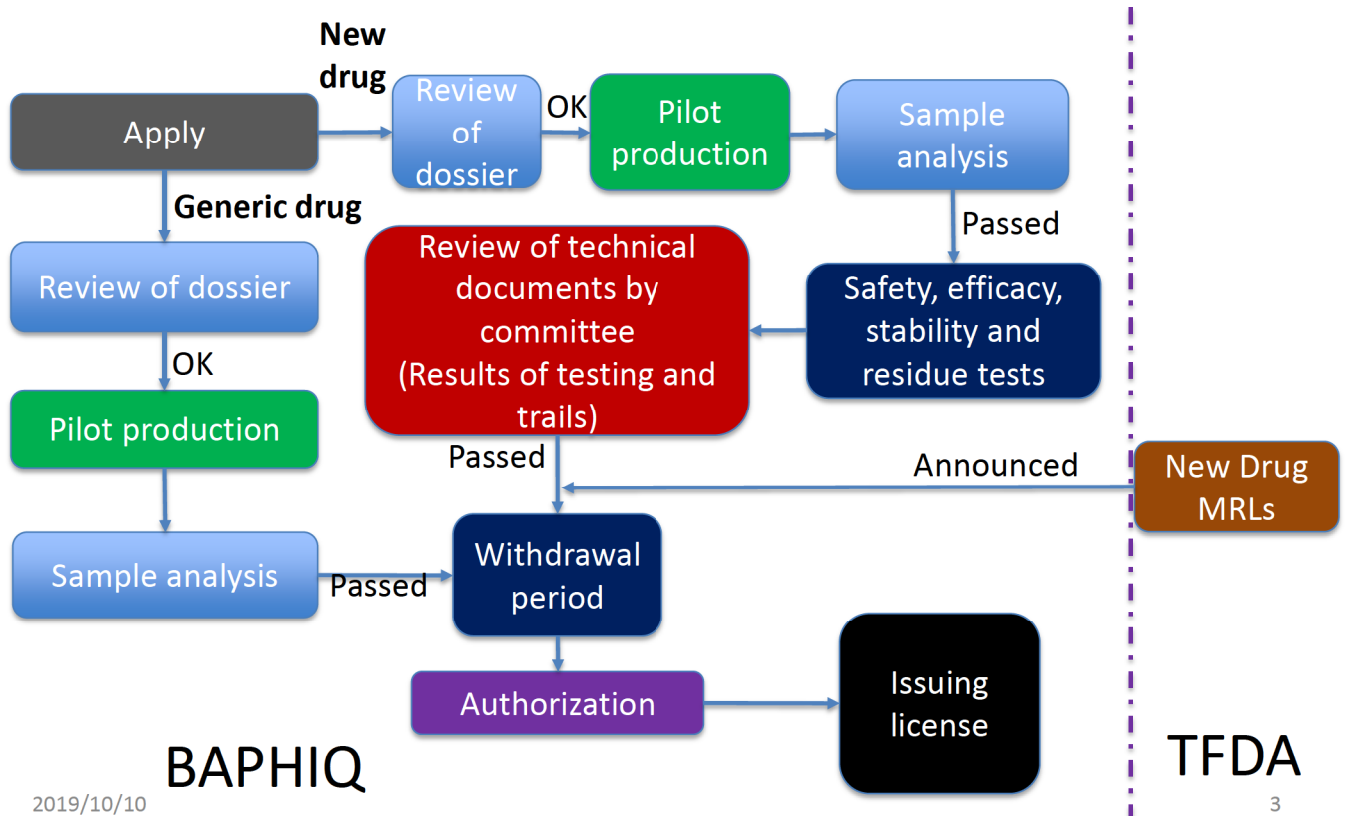
Strategies

- Strict review and approval of new antibiotic using for production animals
 - Critical antibiotics for human medicine (X)
 - MRLs set up by FDA before the approval
- Prudent use of antibiotics
- Phasing out antimicrobial growth promoters (AGPs)
- AMU and AMR surveillance
- Developing antibiotic alternatives (ATA)

2019/10/10

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Process of antibiotic approval for animal use



Regulations for use of antibiotics

- Veterinary Drugs Control Act
- Registration of Veterinary Drugs
- Guideline for Use of Veterinary Drugs
- The sale, utilization, and management of prescription drugs by the veterinarian (or veterinarian assistant)

Use of antibiotics

- Prescription was required for animal use
- Based on
 - A diagnosis and corresponding prescription made by the veterinarian/veterinarian assistant
 - Advises by LADIAs (local animal disease inspection authorities)
- Decreasing the use of fluoroquinolones
 - Suspension of new registration
 - Banning of oral applications

2019/10/10

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Antimicrobial growth promoters (AGPs)

- As of Oct., 2019, 36 AGPs have been delisted

Drug	Drug	Drug	Drug
Avoparcin	Buquinolate	Destomycin A	Chlortetracycline
Kanamycin	Halofuginone	Hygromycin B	Colistin
Kitasamycin	Levamisole hydrochloride	Morantel citrate	Neomycin
Lasalocid	Robenidine	Nystatin	Oxytetracycline
Salinomycin	Thyroprotein	Lincomycin	Olaquinox
Spiramycin	Halquinol	Spectionmycin	Roxarsone
Streptomycin	Nitrovin	Virginiamycin	Dimetridazole
Sulfathiazole	Ronidazole	Penicillin	Carbadox
Arprinocid	Thiopeptin	Bacitracin	Arsanilic acid

- Remaining 9 items are under annual reviews

2019/10/10

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Surveillance

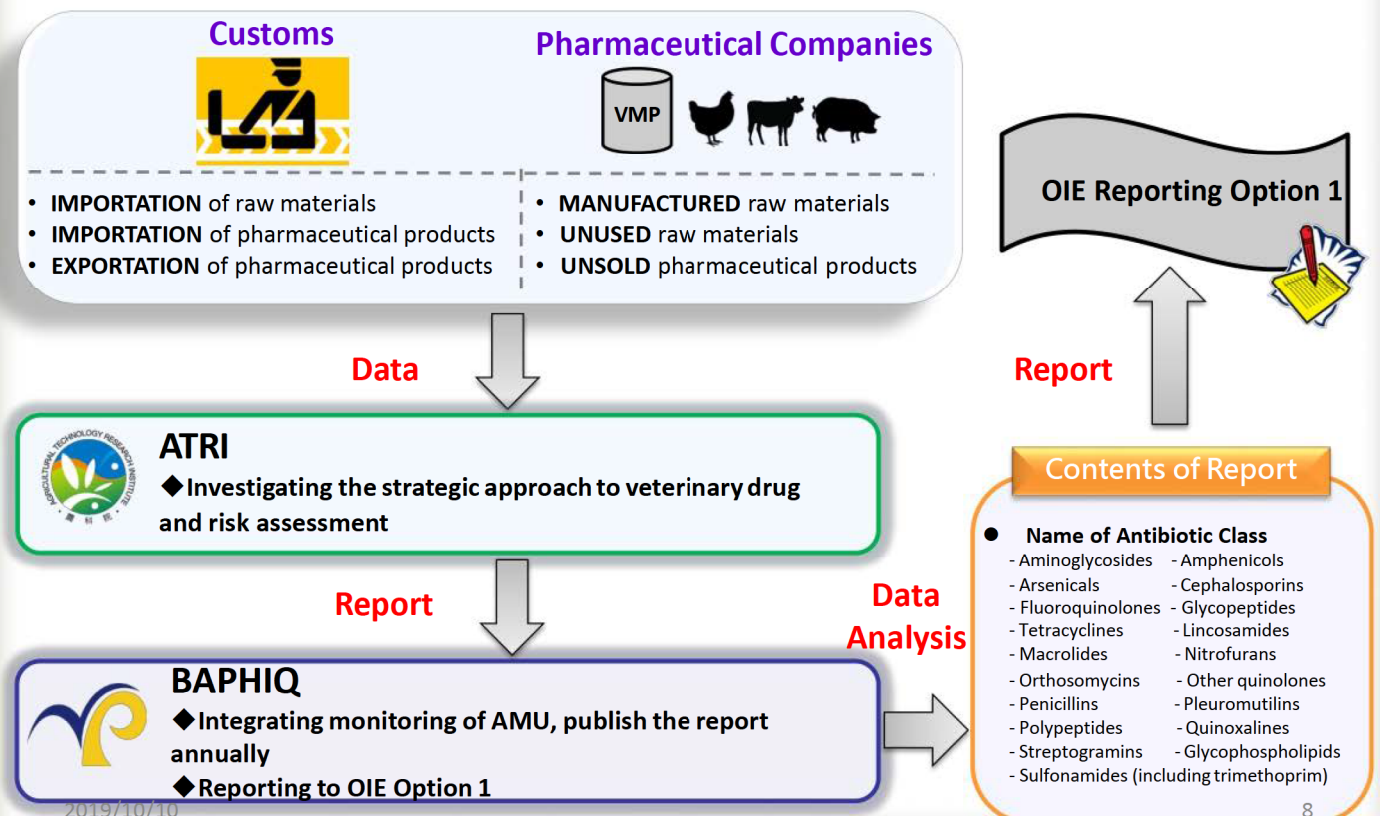
- Antimicrobial products on market
 - To identify substandard, spurious, falsely labelled, falsified and counterfeit antimicrobials
 - Penalties for counterfeit/substandard products are enforced
- AMU (antimicrobial use)
- AMR (antimicrobial resistance)

2019/10/10

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AMU Surveillance

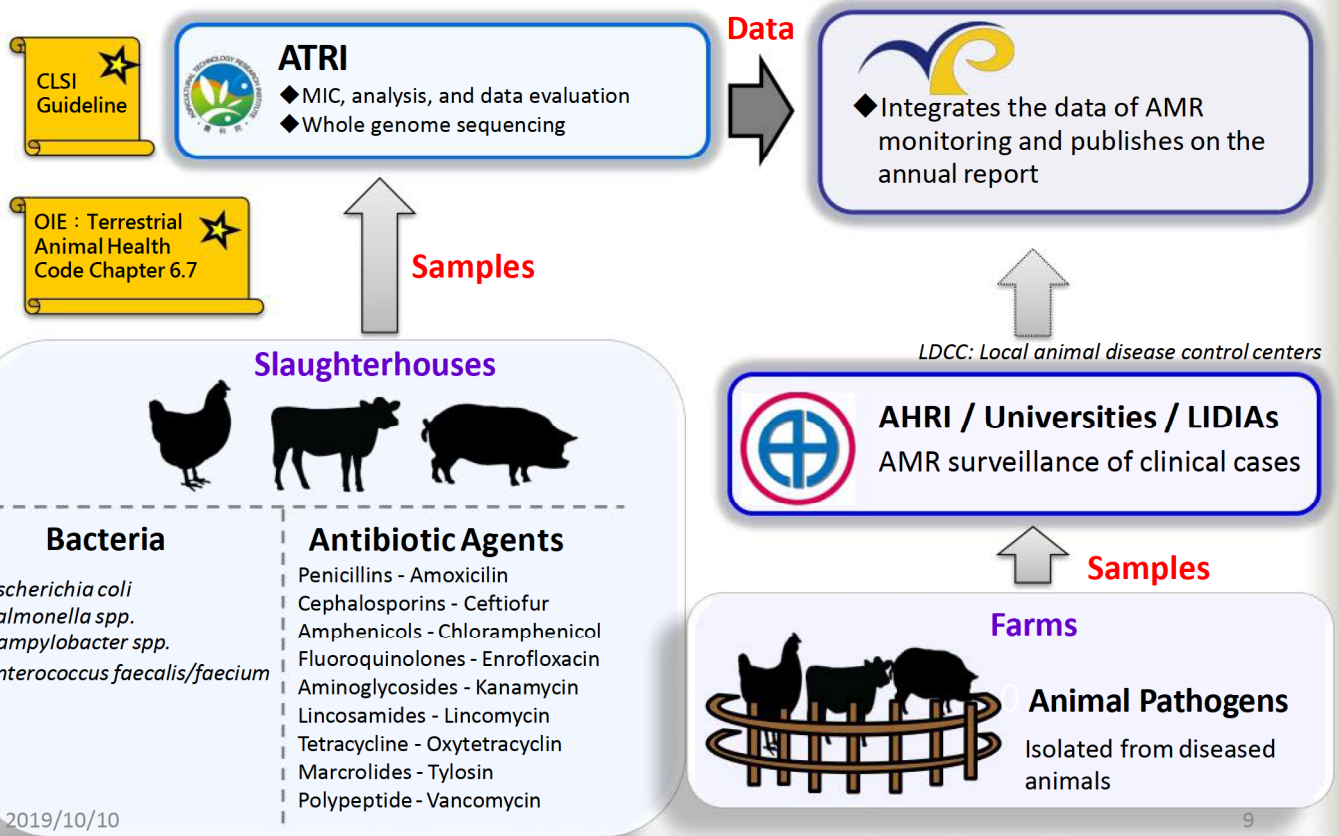
VETERINARY MEDICINAL PRODUCTS (VMP)



2019/10/10

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AMR Surveillance



One Health Approach Collaboration

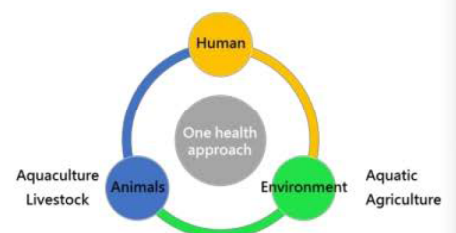
- National Action Plan (draft) on AMR (2020-2024)
 - To decrease the risk for AMR in a collaborative way with stakeholders by improving the production system for livestock and aquaculture



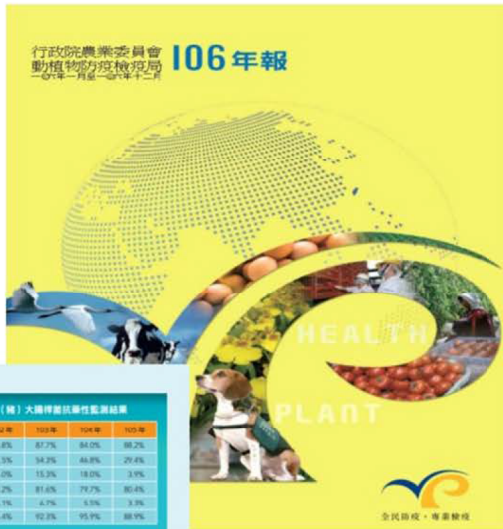
2018 Draft



2017 Cross-departmental meeting

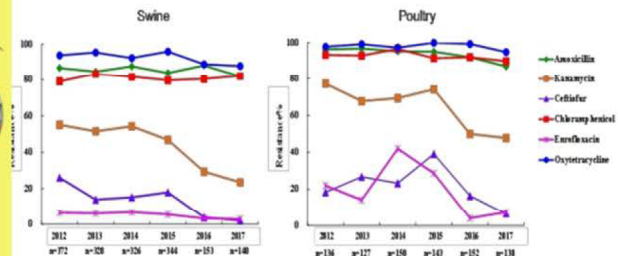


Awareness

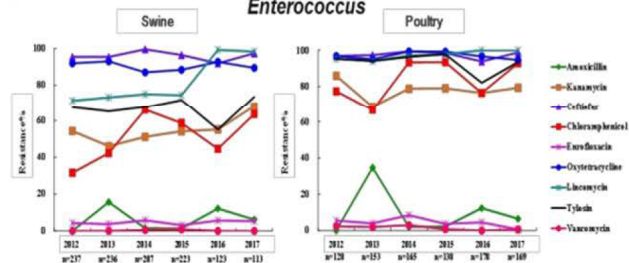


Annual AMR Surveillance Report

Escherichia coli



Enterococcus



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Conclusions

- AMR activities launched in Taiwan progressively promote the decrements of antimicrobial resistance, including kanamycin, ceftiofur, and enrofloxacin.
- The 4 years national action plan on AMR is in line with the global trend and will be executed in 2020.
- Mutual collaboration on AMR will be conducted continuously either with public health sectors or international organizations.

Thanks for your attention !



October 11, 2019
George Washington University

Phenotypic and Genotypic Surveillance of Antimicrobial Resistance in Taiwan



Tsai-Ling Yang Lauderdale (楊采蓮)
National Institute of Infectious Diseases and Vaccinology (NIIDV)
National Health Research Institutes (NHRI)

Research Units at NHRI



Institutes	Research Center
National Institute of Cancer Research	Immunology Research Center
Institute of Cellular and System Medicine	Center for Neuropsychiatric Research
Institute of Population Sciences	
Institute of Biotechnology and Pharmaceutical Research	
Institute of Molecular and Genomic Medicine	
National Institute of Environmental Health Sciences	
Institute of Biomedical Engineering and Nanomedicine	
National Institute of Infectious Diseases and Vaccinology	



Our AMR Surveillance Projects



Taiwan Surveillance of Antimicrobial Resistance (TSAR)

- Target: Clinical bacterial isolates from hospital **inpatients** and **outpatients**
- Objective: Monitor AMR trend in different patient groups and help detect emerging resistance
- Goal: Provide data to promote judicious antibiotic use and support intervention advocacy efforts

Survey of antibiotic-resistant bacteria in the community

- Target: Indicator and zoonotic bacteria in **retail meat**
- Objective: Investigate the prevalence of AM-resistant bacteria in the food supply and their association with clinical human isolates
- Goal: Identify potential reservoirs of AM-resistant bacteria that may be transmitted via the food chain to humans directly or indirectly



TSAR Background & History

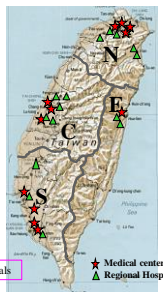


- In 1998, **Dr. Monto Ho (何曼德院士)** established the “Microbial Infections Reference Laboratory (MIRL)” to carry out the mission of “Research and control of antimicrobial resistance (AMR)” in Taiwan through “**Surveillance, Research, Service, and Advocacy**”
- In the same year, Dr. Ho implemented the **TSAR** (Taiwan Surveillance of Antimicrobial Resistance) project (PI: Dr. L. Clifford McDonald 1998-2000).

TSAR Progress

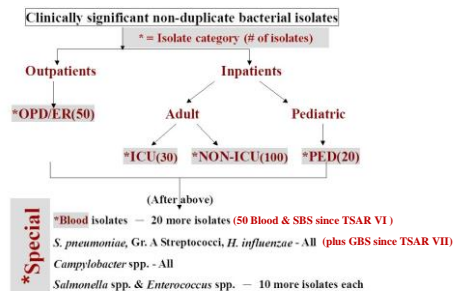


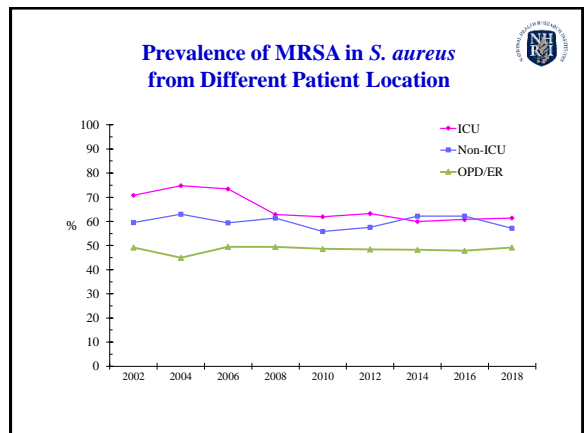
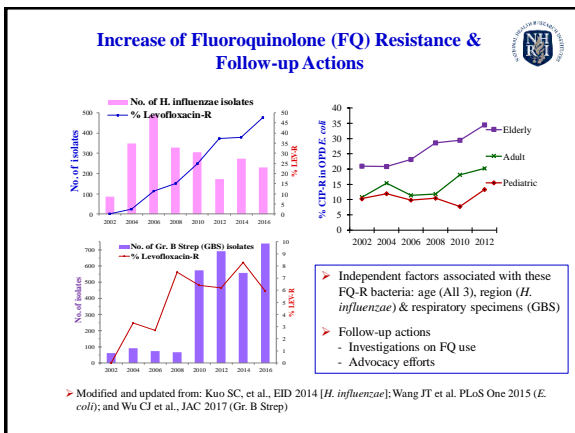
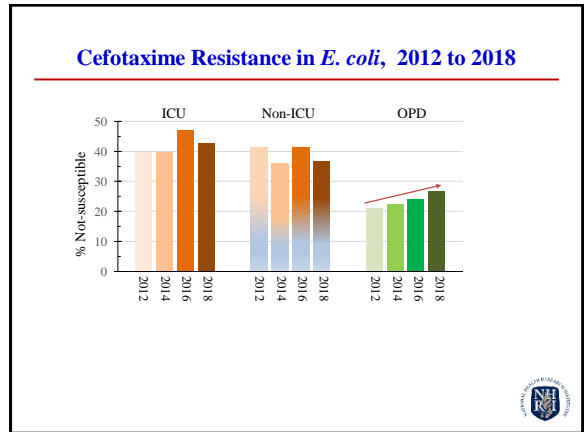
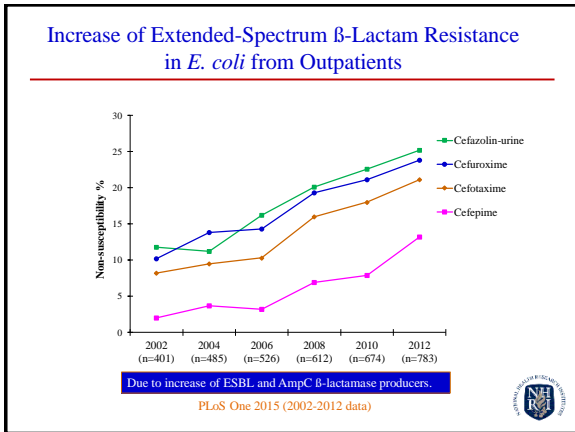
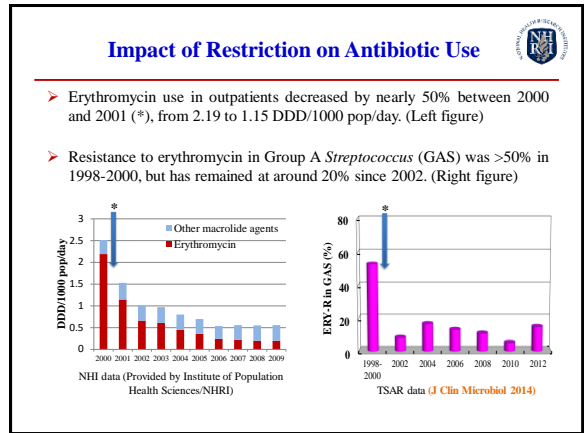
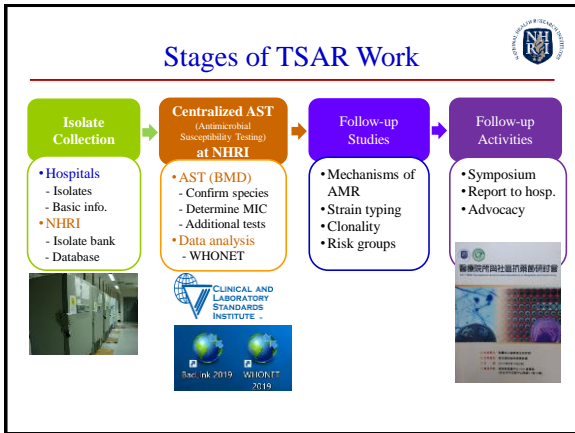
TSAR	Collection time	No. of Hospitals	No. of isolates
I	Oct-Dec 1998	44	~6000
II	Mar-May 2000	21	~3200
III	Jul-Sep 2002	26	~6000
IV	Jul-Sep 2004	26	~6500
V	Jul-Sep 2006	25	~6300
VI	Jul-Sep 2008	26	~7300
VII	Jul-Sep 2010	26	~7400
VIII	Jul-Sep 2012	27	~8000
IX	Jul-Sep 2014	26	~7600
X	Jul-Sep 2016	25	~7600
XI	Jul-Sep 2018	25	~7500

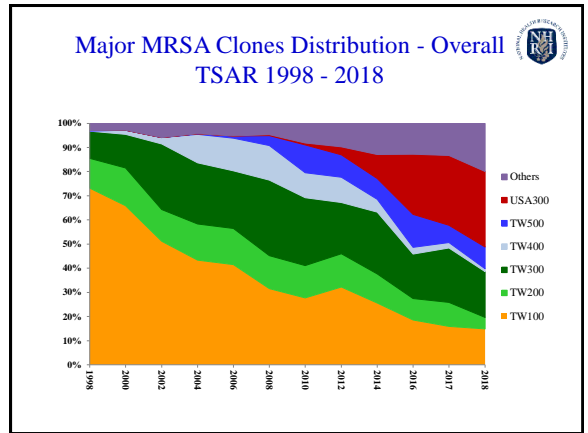
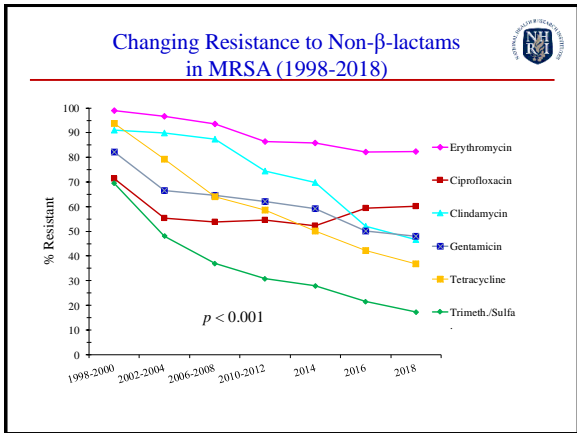


TSAR III ~ XI: Similar isolate collection protocol & participating hospitals

TSAR III ~ XI Collection Protocol



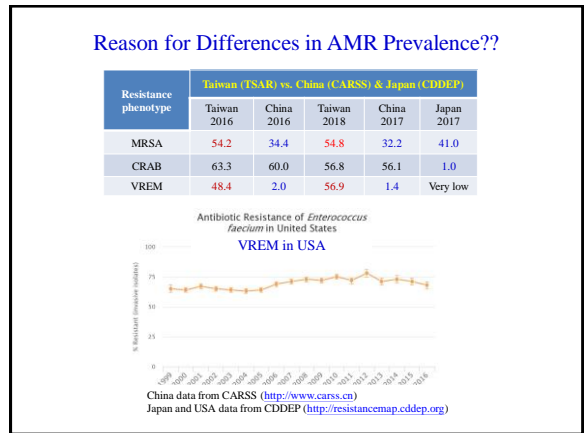
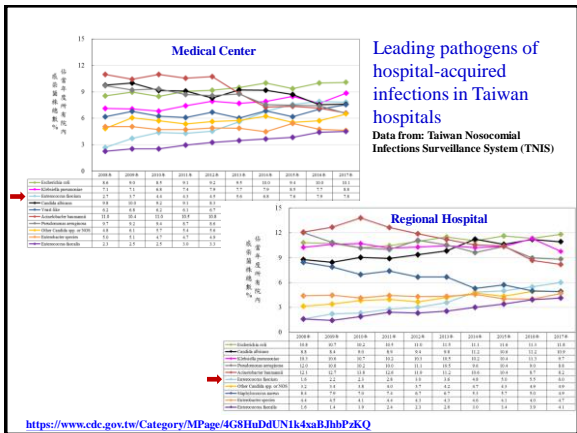
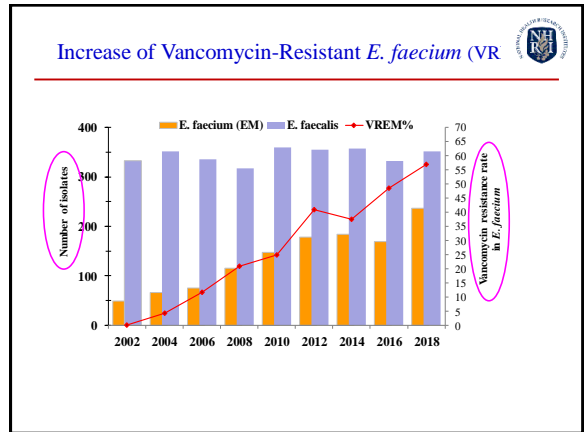




Characteristics of Predominant MRSA Clones : Taiwan

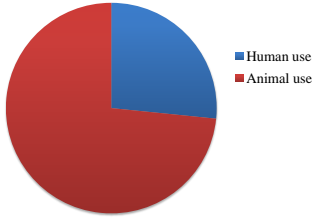
Clone	Main Genotype ST/SCCmecI/spa-CC*	pfst	% of Isolates Resistant					
			CIP	CLI	ERY	GEN	TCY	SXT
TW100	ST239/III/spa-CC037	0	99.8	89.9	99.8	99.2	99.2	99.2
TW200	ST59/IV/spa-CC437	13.6	2.4	93.7	94.5	59.9	52.8	1.1
TW300	ST59/Vt/spa-CC437	96.6	3.3	93.9	94.2	22.2	54.1	1.2
TW400	ST5/II/spa-CC002	0	99.4	99.1	99.7	97.6	3.8	1.8
TW500	ST45/IV or V-like/spa-CC1081	1.2	75.9	6.9	43.6	53.3	61.9	1.4
USA300	ST8/IVa/spa-CC008	91.8	96.4	4.6	92.8	13.1	8.4	0.6

* Sequence type (ST) from MLST or inferred/SCCmec type or subtype/spa type clonal complex (spa-CC)



Antimicrobial Use in Non-Human Sector

% of use in Taiwan (1997-1999)



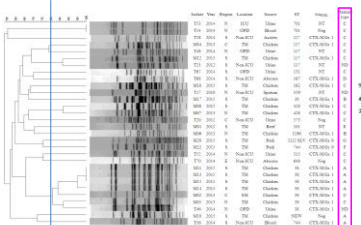
Among approximate 1300 tons of antibiotics produced and imported/year
Chang SC et al., Infection Control 2003 (article in Chinese)

Retail Meat Survey

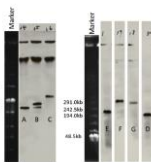
- Survey of ground beef, chicken and pork purchased from supermarkets and traditional markets
- Ongoing since 2012
- Primary target:
 - Fluoroquinolone-resistant and ESBL/AmpC producing *E. coli*
 - Investigate the relatedness of livestock-associated-MRSA strains



plasmid-mediated colistin resistance gene *mcr-1*-Positive *E. coli* from Humans & Retail Meat



PFGE of XbaI digested genomic DNA.
Isolate: T=TSAR; M=Meat



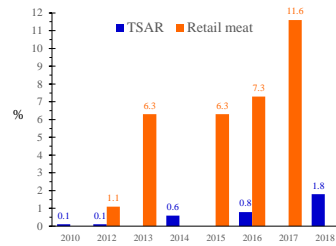
Plasmid profiles from S1 nuclease assay



Discussions with ID experts & government agencies

Kuo SC et al., J Antimicrob Chemother 2016

Prevalence of *mcr-1* in *E. coli* Isolates: TSAR vs. Retail Meat



Antibiotic consumptions outside Taiwan's National Health Insurance in the outpatient clinics/pharmacies

Shu-Chen Kuo, NHRI, Taiwan



NHI



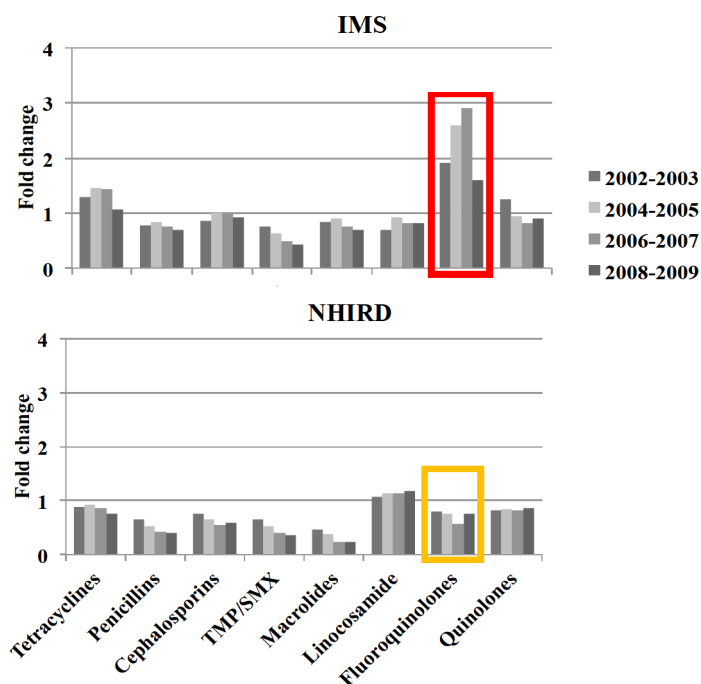
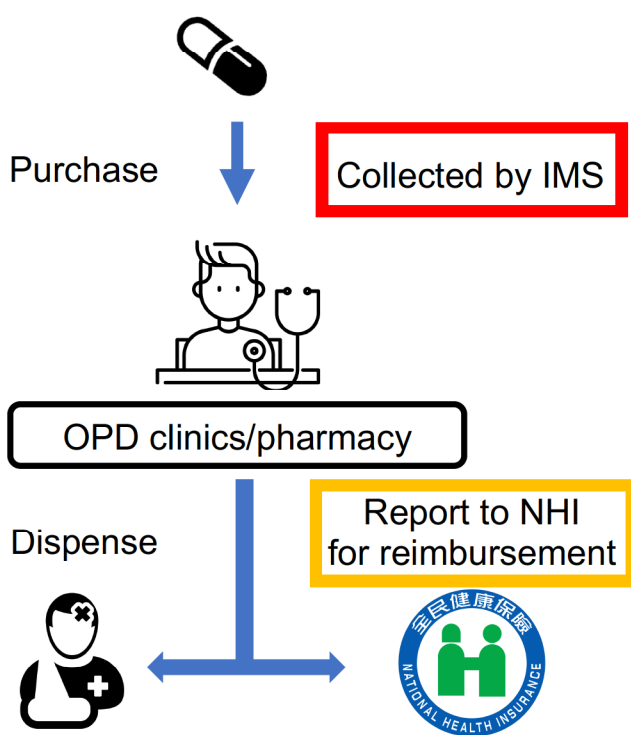
TSAR



IQVIA
(IMS)

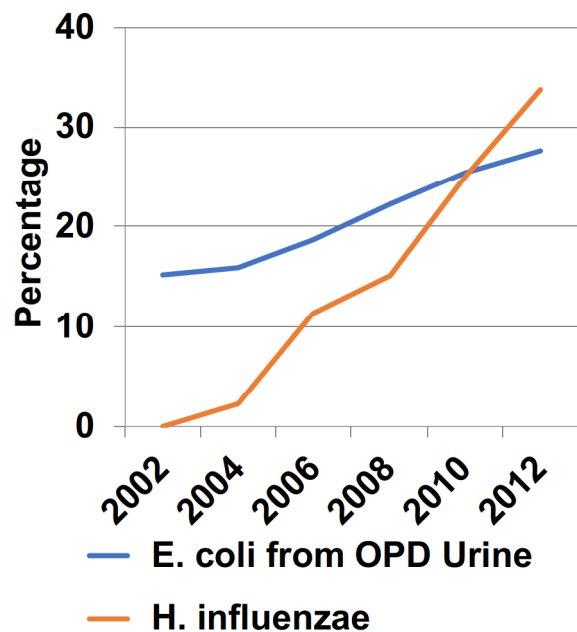
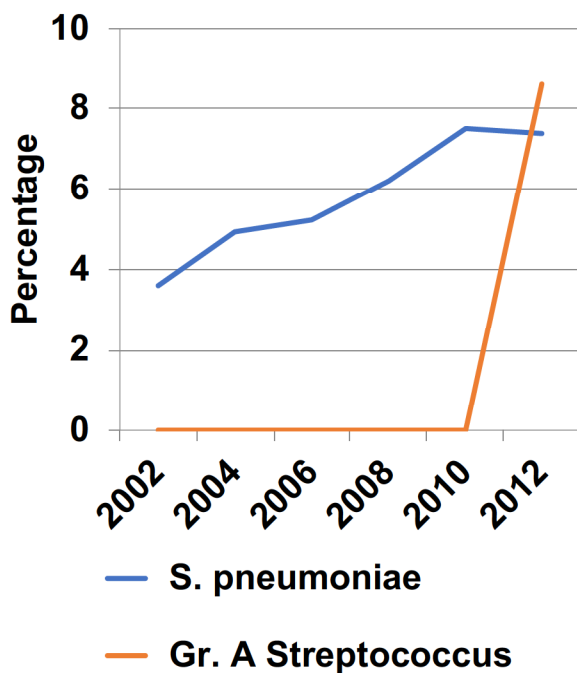
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Discrepancies indicated
OPD antibiotic use were often not reported to NHI.



2000-2001 as the reference,
Purchase increases
Reported Dispensation decreases

Possible consequences: increasing fluoroquinolone resistance in community-acquired bacteria



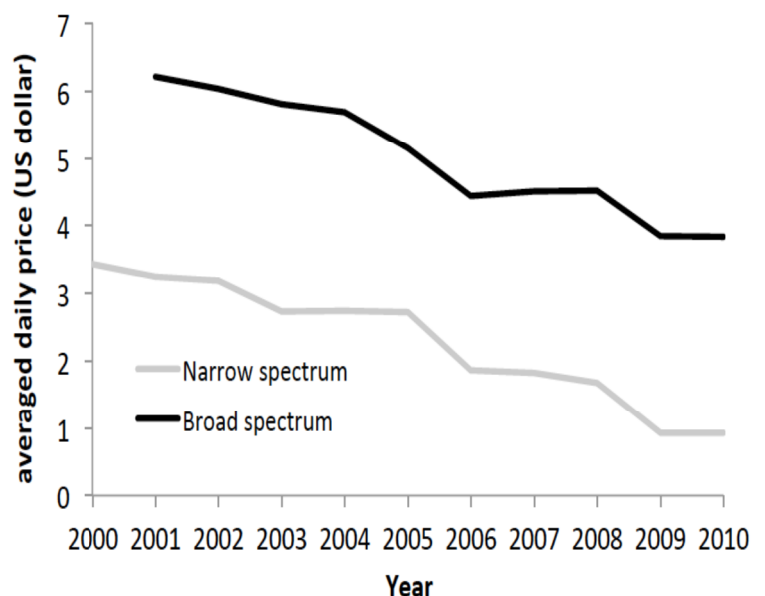
Data from Taiwan Surveillance of Antimicrobial Resistance (TSAR) program

3

Possible causes of unreported use of antibiotics

- Thorough scrutiny and heavy fines by NHI
 - Most report only some drugs but not all
 - Avoid reporting antibiotics
- Low price of antibiotics
- Easy to buy antibiotic without prescription in pharmacies
- Defensive medical decision making

Daily price of fluoroquinolones



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Thank you for your attention

Antibiotic consumption and resistance data are available in **TANK**

An interactive website

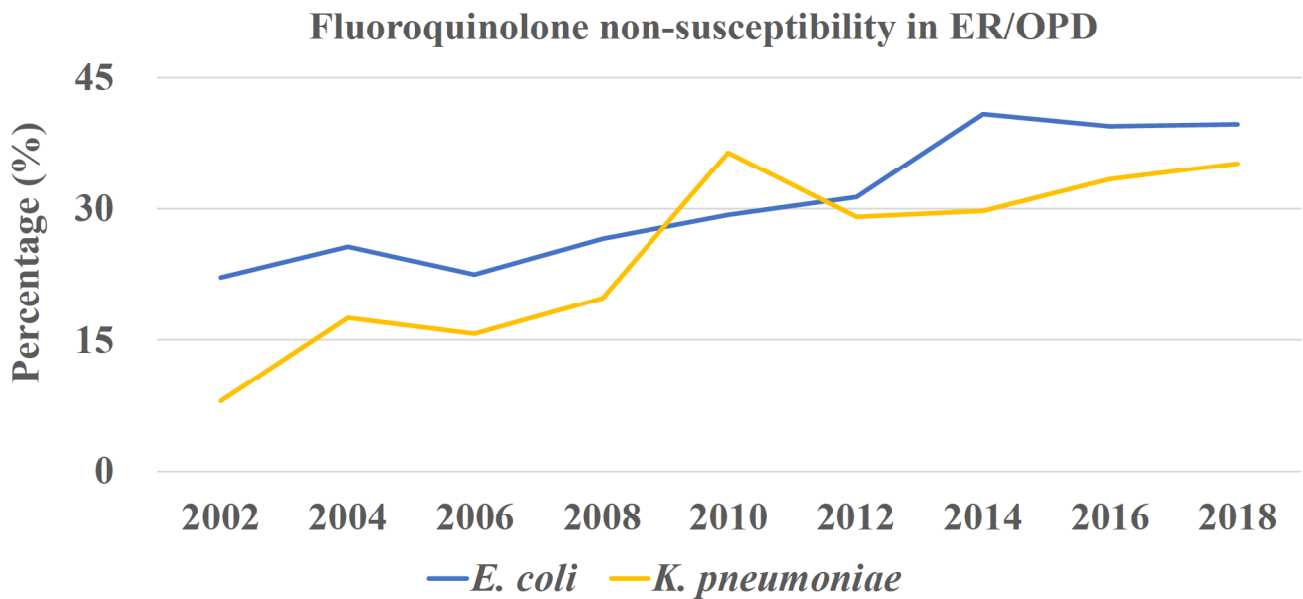
Sharing AMR data from Taiwan



Taiwan Antimicrobial Resistance Network



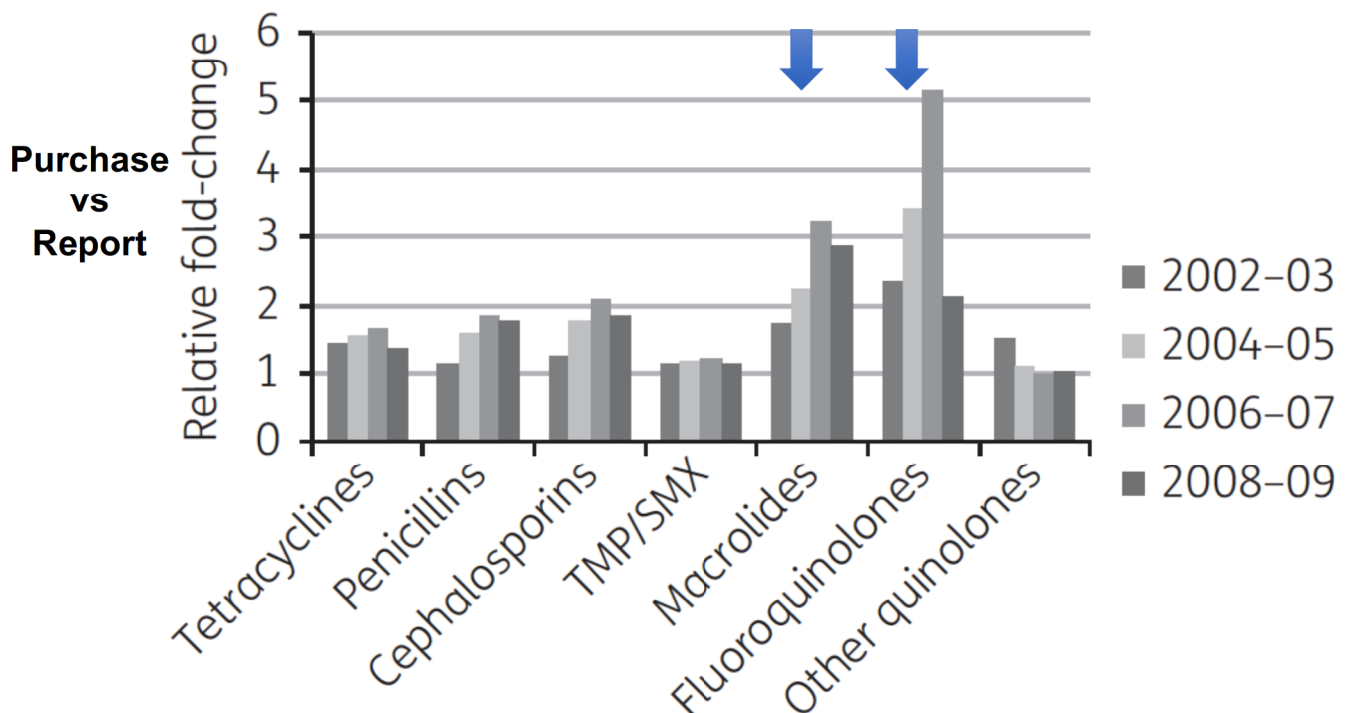
Possible consequences: increasing fluoroquinolone resistance in the OPD till now



CLSI 2019 criteria, TSAR data

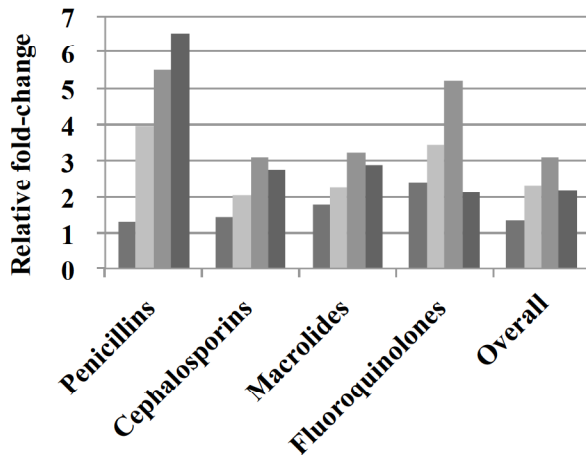
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Some of macrolides and fluoroquinolones were used without reporting

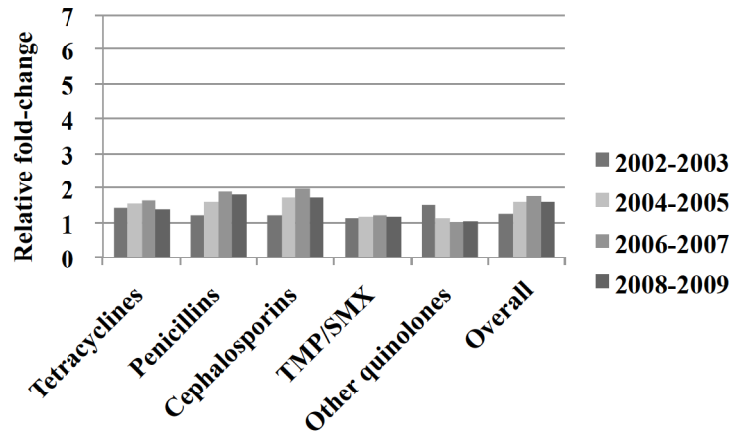


Highly regulated drugs were prone to be prescribed outside NHI

Highly regulated drugs



First-line drugs



Change of purchase / change of dispensation (report to NHI)

The higher the ratio, the greater the private use



Taiwan Antimicrobial Resistance Network



Databases

NHIRD

TSAR

TNIS

IMS

Targets



Infection intensity



Resistance rate

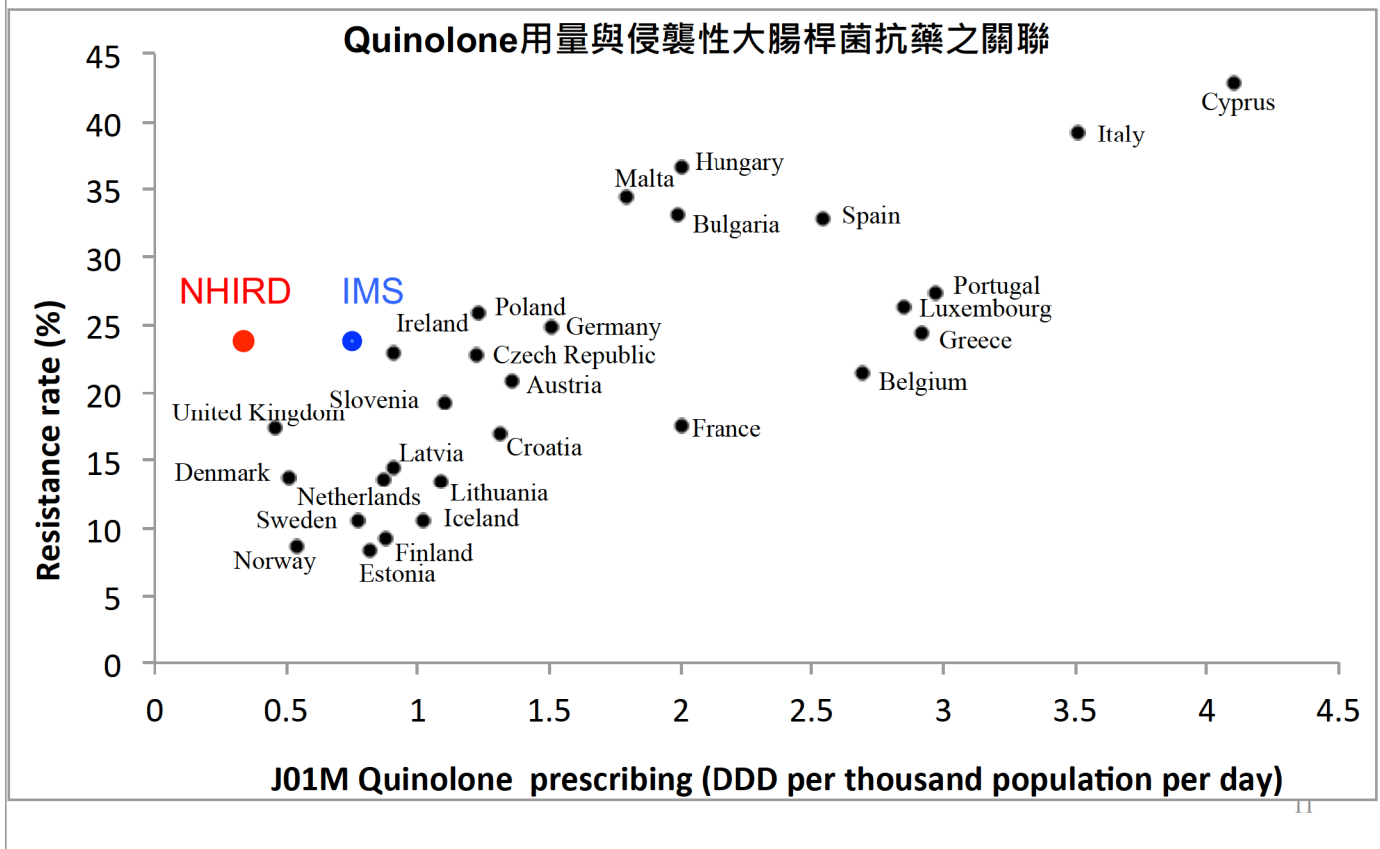


Antibiotic use

Aims

- NHRI integrated 4 databases to create TANK
- An interactive website,
- Data free to all
- Facilitate AMR studies

Did private use explain the high FQ resistance?



TFDA' s Managements of Antibiotics in Taiwan

Ming-Mei Wu
Deputy Director,
Division of Medicinal Products
TFDA
2019.10.11



衛生福利部
食品藥物管理署
Food and Drug Administration

<http://www.fda.gov.tw/>

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Outline

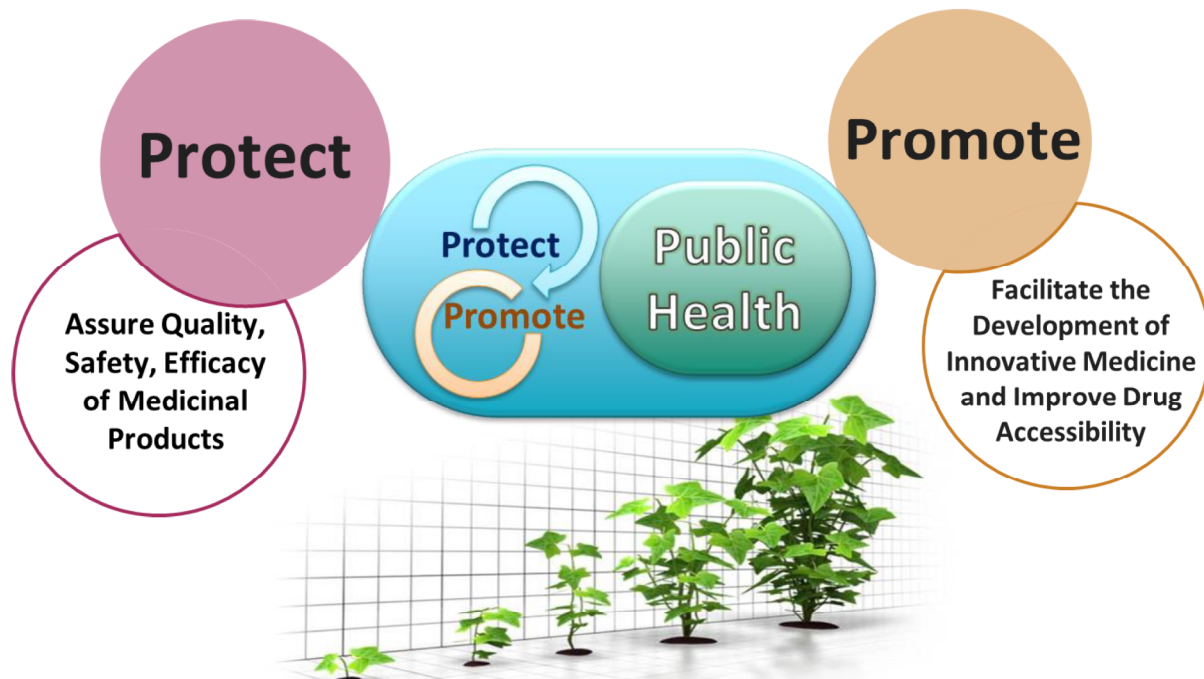
- Introduction TFDA
- Life Cycle Management of Antibiotics
- Managements of Antibiotics Use in Human
- Public Education
- Antibiotics in Foods (*briefly*)
- SWOT Analysis of AMR
- Conclusion

FDA

2

Mission of Taiwan FDA

Division of Medicinal Product



Profession

Service

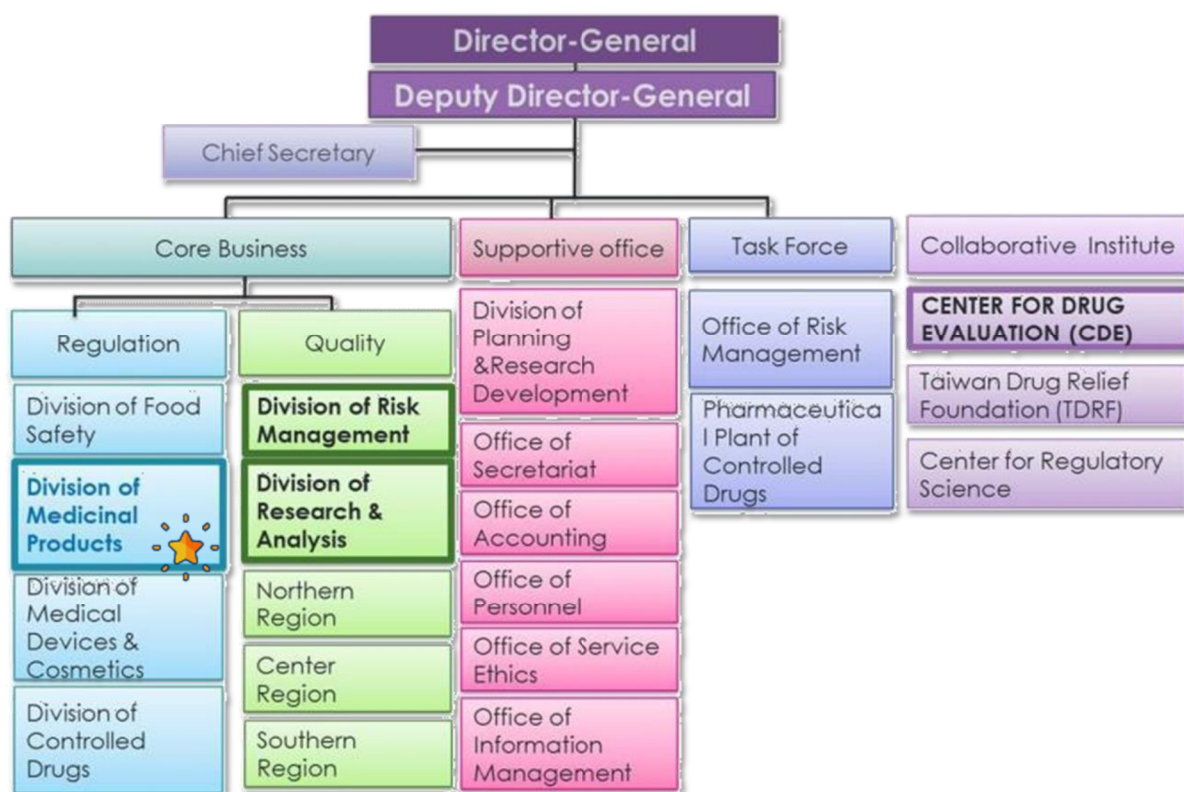
Quality

Innovation



3

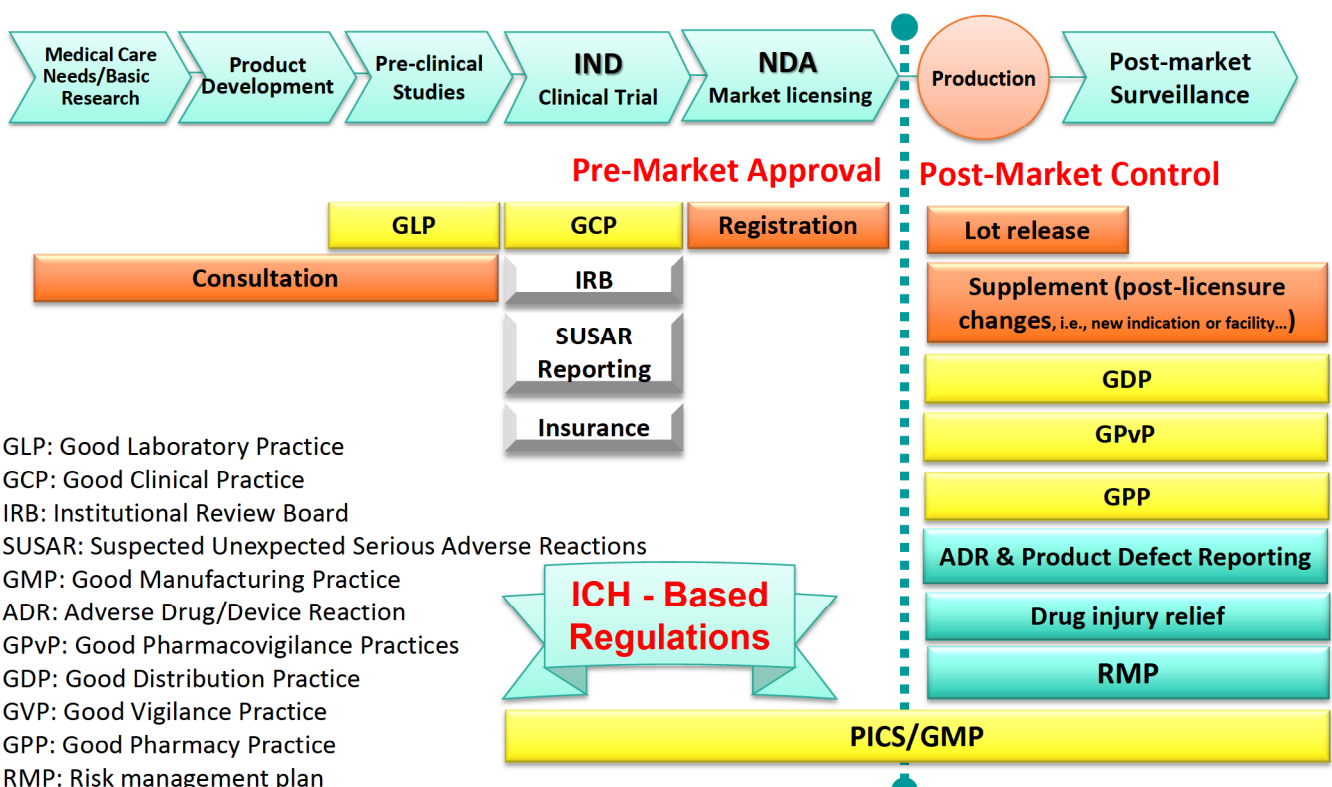
TFDA Organizational Chart



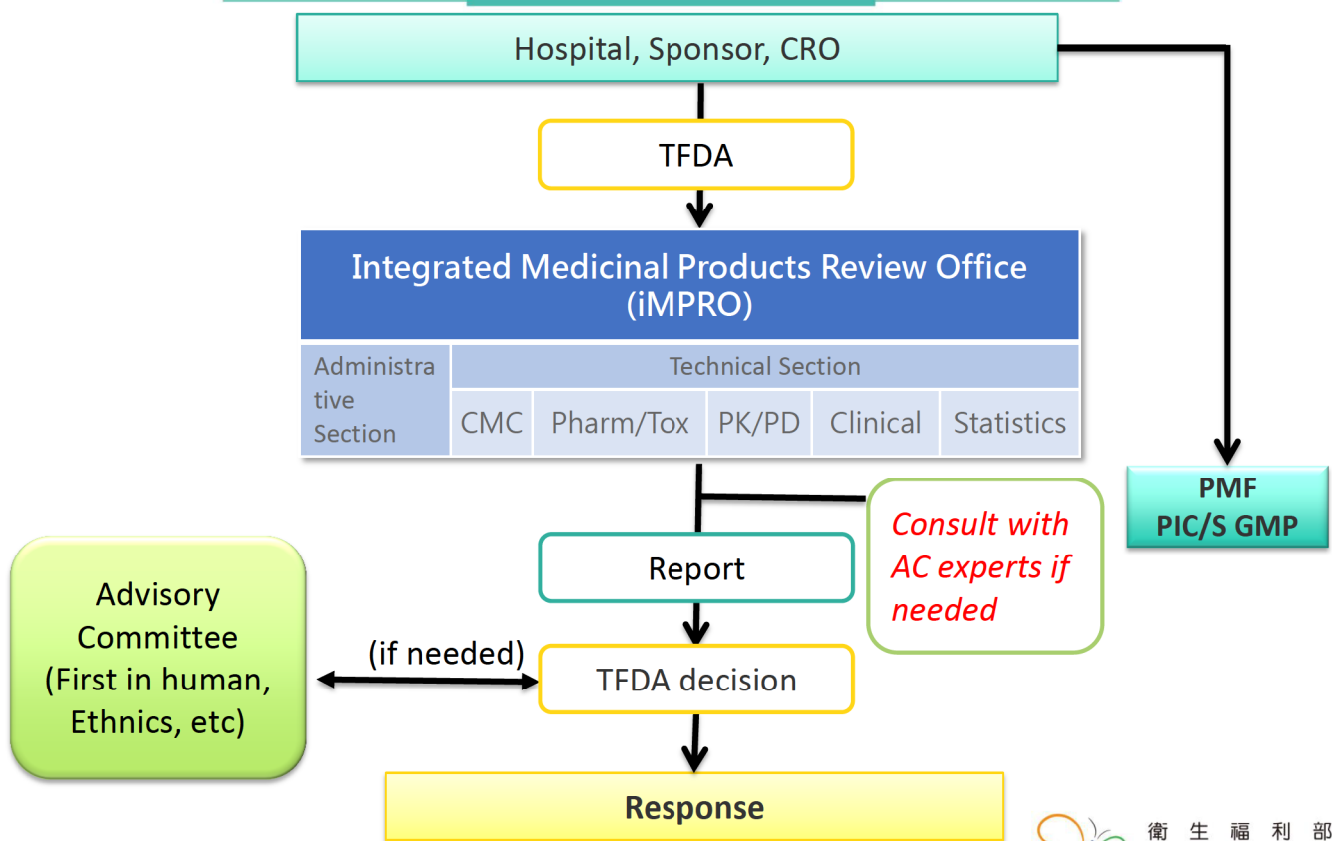
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Life Cycle Management of Antibiotics

Life Cycle Management of Medicinal Products



Approaches on NDA applications-Review Process (including Antibiotic Drug)



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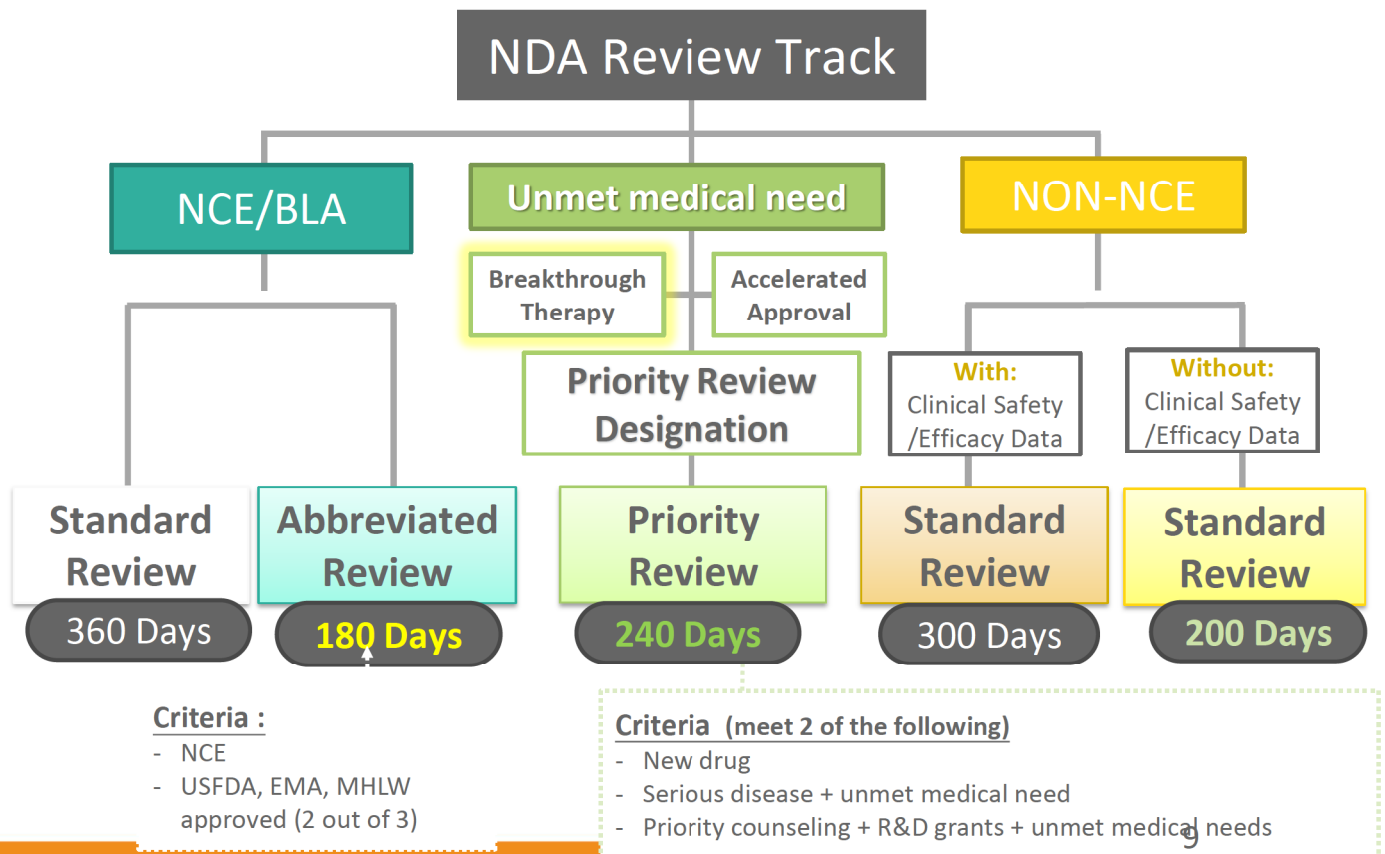
Expedite Review Mechanisms

Expedite Review Mechanisms

- Abbreviated review
- Priority review

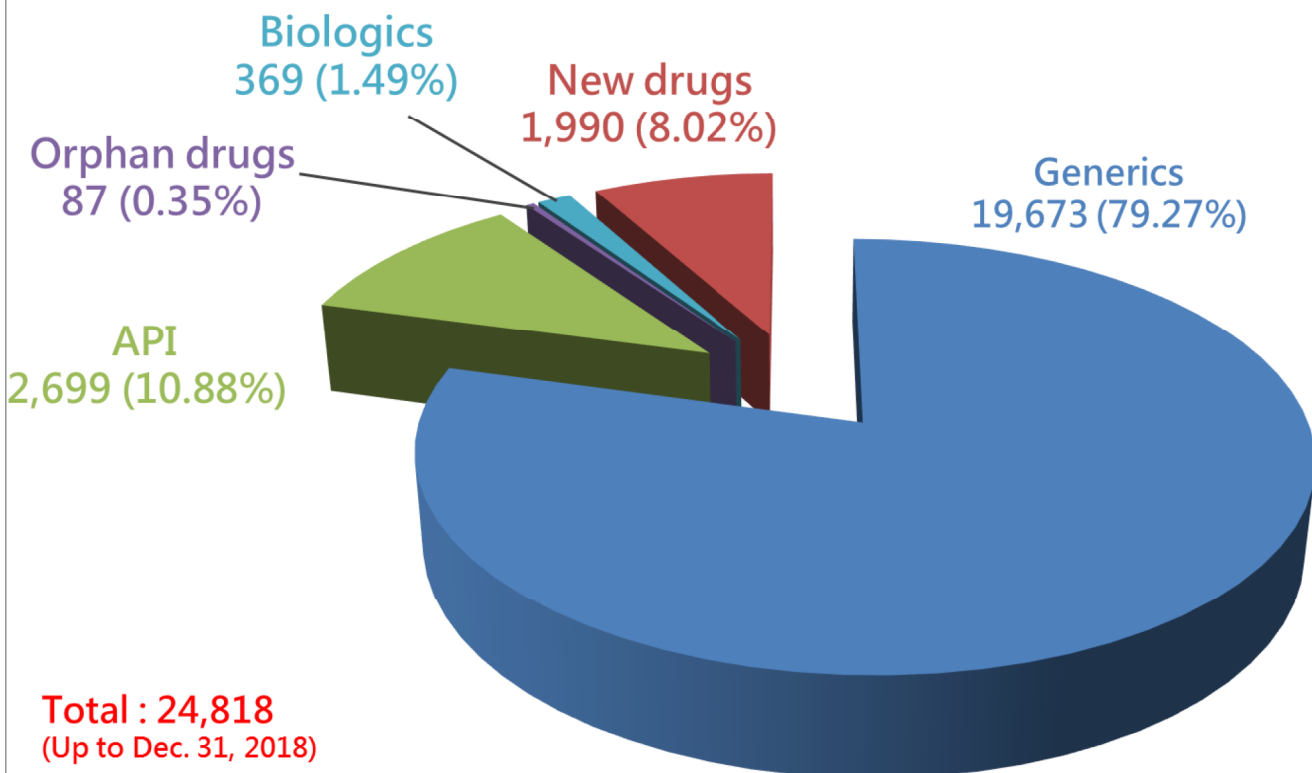
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Expedite Review Programs for NDA



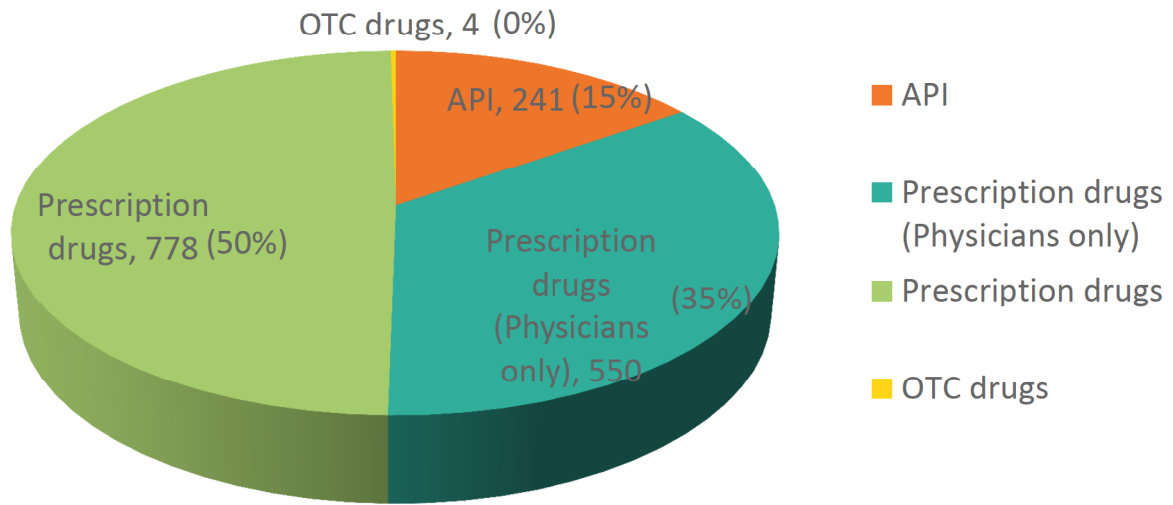
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Approved Pharmaceutical Licenses in Taiwan

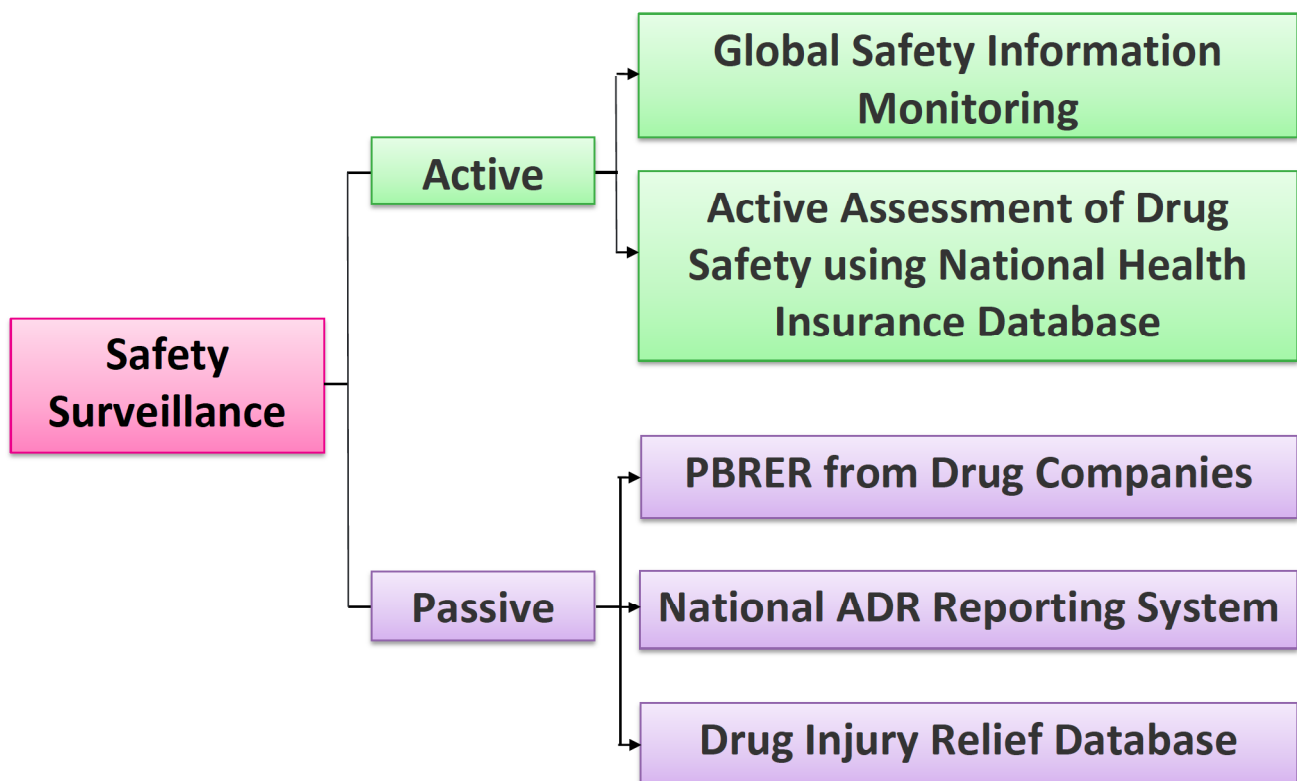


Approved Pharmaceutical Licenses for Antimicrobials

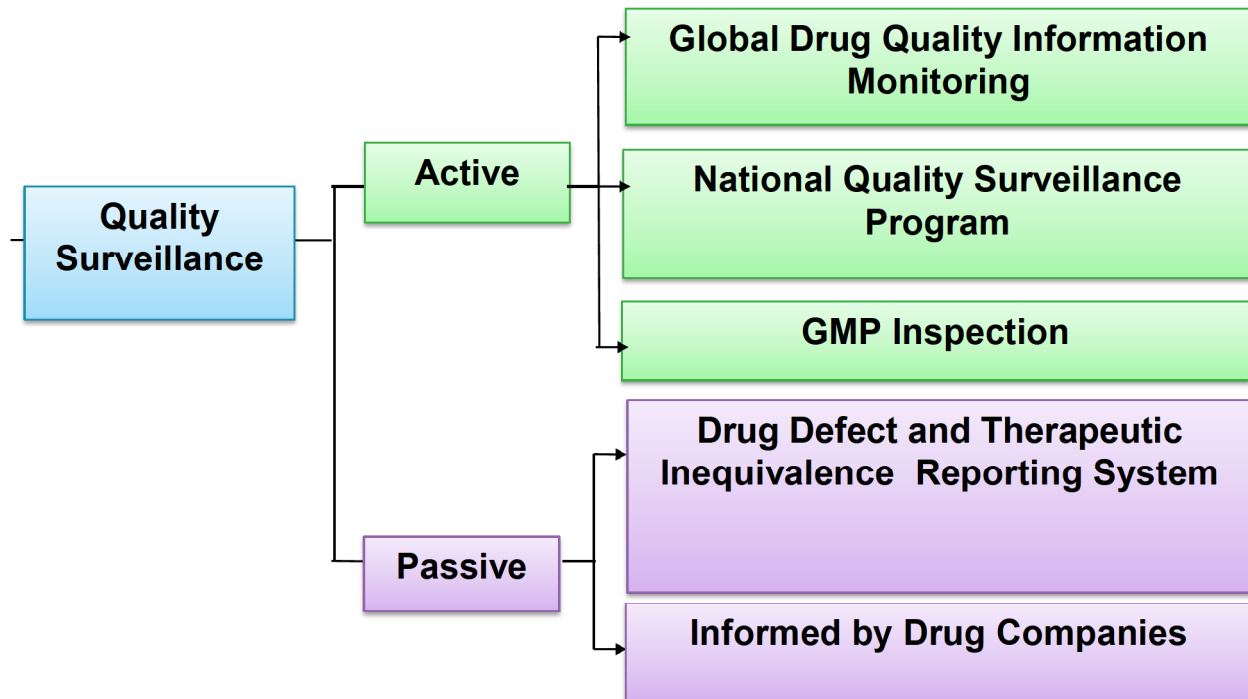
Numbers of the Licenses for Antibiotics (1573 in total)



Post-Market Safety Surveillance



Post-Market Quality Surveillance



Managements of Antibiotics Use in Human

Improve the Accessibility of Antibiotics

Drug Supply Information Platform

The List of Essential Drugs

Drug Supply Information Platform

- Since 2011 TFDA has established the mechanism for drug shortage report and management.
- If medical professionals or pharmaceutical traders discover the potential risk of drug shortage, they could report it to the Drug Supply Information Platform (<http://dsms.fda.gov.tw/>) in order to prevent and solve the problems.



The screenshot shows the homepage of the Drug Supply Information Platform (藥品供應資訊平台). The header includes the FDA logo and navigation links: 首頁, 設置宗旨, 公告資訊, 公開徵求供應廠商, 建議使用替代藥品品質, 無替代藥品品質. Below the header is a banner image of red and blue capsules. A '最新消息' (Latest News) section lists several drug shortage reports with dates and details, such as Bacillus Calmette-Guerin injection and GONADOTROPIN CHORIONIC injection. At the bottom, there are two prominent green buttons: '通報系統 我要通報' (Reporting System I want to report) and '相關連結' (Related Links), along with an 'FAQ' button.

The list of essential drugs

- TFDA amended the list of essential drugs (including antibiotics) in 2017. The list will be revised every two years according to the WHO announcements.
- If the pharmaceutical traders, who hold the market permit licenses for the essential drugs, estimate that they cannot keep manufacturing, importing, or supplying the drugs in the future, they should report to TFDA at least 6 months before, in order to protect the public health.
- After receiving the notification, TFDA will publish the alert on the internet or website. If necessary, special import or manufacture permits will be granted for alternative drugs.
- TFDA has also established Drug Supply Information Platform so that the industry, medical institutes and associations could report the cases online.

Antibiotic Abuse Prevention

Professional Training

Raise the Penalty

Reinforcing Inspections of pharmacies:

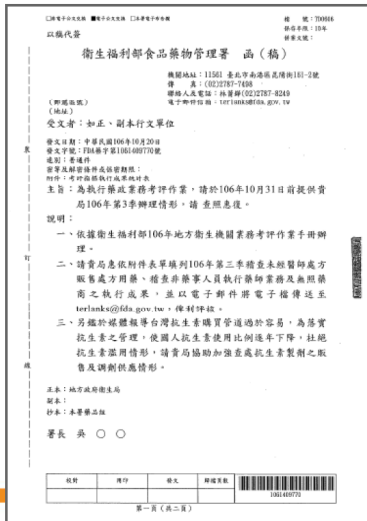
Professional Training

Official Letters

TFDA has sent several official letters to pharmaceutical association and local health bureau and urge them to follow relevant regulations

Training Conferences

Provide trainings during the Annual Meeting of Pharmaceutical Professionals



Raise the Penalty

- Selling antibiotics without prescriptions is against Article 50 of Pharmaceutical Affair Act and could be fined from 30,000 to 2,000,000 TWD if the person has committed the offense repeatedly.

Highlights for the amendments of PAA in 2015

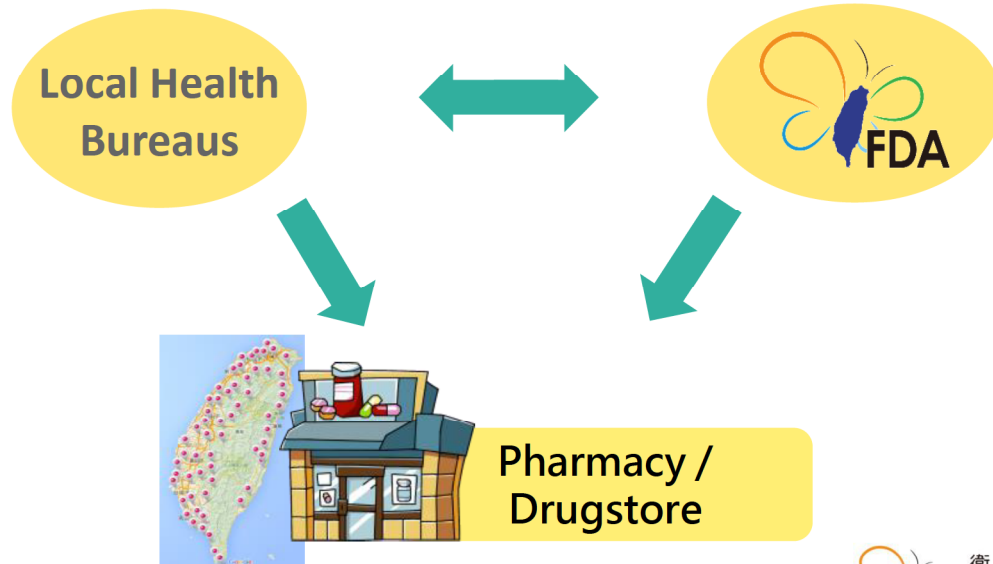
Manufacture or import counterfeit or prohibited drugs	10 years in jail plus paying up to \$100M TWD fine
If causing death	Life imprisonment or minimum 10 years in prison plus paying up to \$200M TWD fine
If causing serious injuries	Minimum 7 years in jail plus paying up to \$150M TWD fine
Illegal profits	Return the illegal profits or pay by mortgage
Selling antibiotics without prescriptions	Minimum \$30,000 and up to \$2,000,000 TWD fine

Other penalties for committing offenses against PAA →

Reinforcing Inspections of the Pharmacies

Reinforcing Inspections

Work with local health bureau and emphasize inspections against selling antibiotics



Reinforcing Inspections of the pharmacies:

Provided by local health bureau

Year	2012	2013	2014	2015	2016	2017	2018
Number of the inspections	27,651	26,200	26,688	12,797	15,162	16,276	15,017
Number of the offenses	36	51	97	127	97	102	50
Offense rate	0.13%	0.19%	0.36%	0.99%	0.64%	0.62%	0.33%

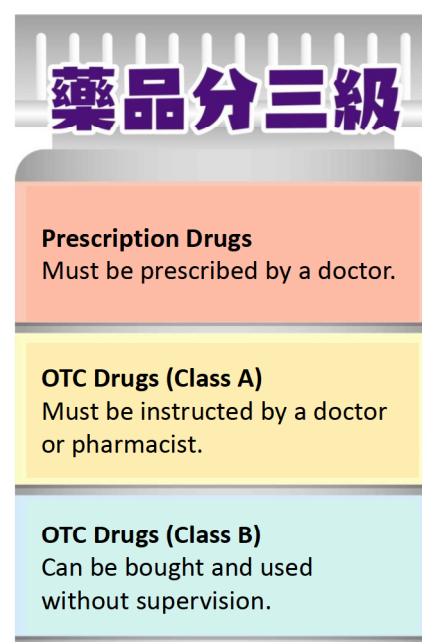
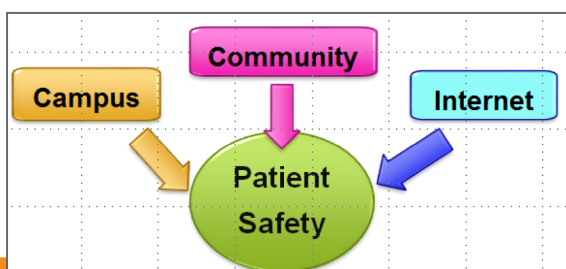
Public Education

Public Education

To help patients understand how their medicines work and why they have to take them

- Health education principals
- --- 「Drug classification and How to read drug labeling」

- Building a supportive environment for correct medication-use.
- ◆ Medication resource centers.
- ◆ Campuses.
- ◆ Community medication consulting stations.



E-Learning Public Education

- URL: <http://www.fda.gov.tw/TC/site.aspx?sid=3670>
- Provides information and official materials about medication-use for different groups of users.
- Groups include : children, teenagers, women, elders, etc.
- Information include : Chinese herbal medicine interactions and travel medicines.



Antibiotics in Foods (*briefly*)

Competent Authority



Council of Agriculture (COA)

Veterinary Drugs Control Act

- Veterinary Drug License
- Monitoring Veterinary Drug Residue on farms
- Education and Management on Farmers

Farms

Bidding auction

Slaughterhouses

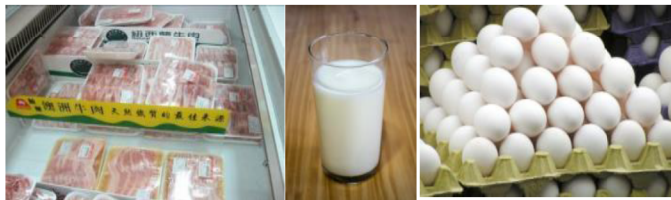
Consumers

Food businesses

Ministry of Health and Welfare (MOHW)

Act Governing Food Safety and Sanitation

- Standards for veterinary drug residue limits in foods
- Monitoring Veterinary Drug Residue on Food industry



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FDA Food and Drug Administration

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Establish the maximum residue limits(MRLs) for animal products

Standards for Veterinary Drug Residue Limits in foods

■ Background:

- according to Article 15 of the Act Governing Food Safety and Sanitation
- established by MOHW

■ Principles:

- consistent with international standards
- Based on Scientific evidences
- in coordination with the COA's requirement for using veterinary drug.
- depend on the dietary pattern and total dietary intake in Taiwan

■ Procedures:

- MOHW receives an application
- submit to MOHW's advisory committee for review
- the draft MRLs will be published for public consultation for 60 days
- publish and enter into force

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Food Samples and Testing Methods

Food Samples

- The food samples were collected from food manufacturers, wholesalers, restaurants, hypermarkets, supermarkets, traditional markets and importers and inspected by local health bureaus.

Testing Methods

- The samples were tested according to the recommended methods announced by MOHW and TFDA. The testing items include : Chloramphenicol, tetracycline, sulfonamide and Quinolone, antiprotozoal, beta-indolamines, antibiotics and their metabolites, nitrofurantoin metabolites, beta Receptor, ionic anticoccidial drugs, aglycosides, tylosin, flunixin and tolfenamic acid, amphibious, carbadane, etc.

Testing result for residues in foods (2015- 2019 July)

Year	2015	2016	2017	2018	2019 (.July)
Number of inspections	1,745	2,278	2,732	3,580	2,235



● Following measures for the disqualified products

- Vertical connection: Urge the traders to withdraw and recall the disqualified products, and track the upstream suppliers.
- Horizontal connection: Provide information to Council of Agriculture to enhance the upstream managements

SWOT Analysis of AMR

from TFDA' s perspective

Strength

Internal (Government Factors)

- Well trained health professionals and reviewers
- Comprehensive regulatory environment, e.g. PAA and Regulations for Registration of Medicinal Products.
- Announced several guidelines regarding pharmaceutical practices, e.g. Good Pharmacy Practice and Good Clinical Practice.

Strength (cont.)

Internal (Government Factors)

- Well-structured cross-sector governmental collaboration.
- Biomedical research and development are emphasized and promoted recently, e.g. the 5+2 industries innovation plan.
- Compliances with international standards, e.g. ICH.

Weakness

Internal (Government Factors)

- Limited/insufficient human and financial resources for implementation.
- No record of antibiotics distributed to or dispensed from the community pharmacies.
- AMR is not set in the national development plan.

Opportunities

External (Non-Government Factors)

- Development of a coordinated global surveillance system.
- Increased interest and funding from international sources.
- The public still respects government authorities
- Frequently attending or hosting international conferences or meetings to facilitate communications and regulatory harmonization.

Threats

External (Non-Governmental Factors)

- Easily accessed to the medical resources. The public are used to go to doctors and take drugs.
- Insufficient public awareness of antibiotic resistance.
- Pharmaceutical companies withdraw from antibiotics R&D.
- Isolated from international community and resources.

Conclusion

TFDA' s Managements of Antibiotics Use in human

- TFDA manage antibiotics use in human from three different directions.
 - Ensuring efficacy, safety, quality of the antibiotics
 - Ensuring sufficient and reasonable distribution of the antibiotics
 - Promoting public education about medication safety
- The management of antibiotic residue in foods.
- SWOT Analysis of AMR in Taiwan