Antimicrobial Resistance in Food Safety
The Role of WHO to address this issue Globally

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Introduction

- The emergence and spread of antibiotic resistance is one of the greatest public health threats of the 21st century.

- Antibiotics are a unique class of drugs since they have effects on both the individual and society. Use and misuse of antibiotics by individuals leads to selection of antibiotic resistance in bacteria that may spread to others and thus compromise effective treatment also for other members of society.

- The frequency of antibiotic resistance, especially multidrug resistance, continues to increase globally leading to higher health-care costs, failed treatments, and deaths.
AMR in Food Safety Perspective

- Widespread use of antimicrobials in livestock production …not only from therapeutic purposes
- Same classes of antimicrobials are used both in humans and animals.
- Few new antibiotics are being developed to replace those becoming ineffective through resistance
- Food is generally considered to be the most important vector for spread of resistance between humans and animals
- Globalization of food trade, need for international action
Discovery of antibiotics: a faltering pipeline

How does antibiotic resistance develop?

- Some bacteria are naturally resistant; new resistances also arise spontaneously by chance mutations and these resistant strains then multiply.

- Some resistances can be passed from one bacterium to another, spreading resistance between species. Loops of DNA (called plasmids) carry the resistance genes from one bacterium to another.

- When an antibiotic is given, it kills the sensitive bacteria, but any resistant ones can survive and multiply.

- The more antibiotics are used (in animals and agriculture as well as in man) the greater will be the "selective pressure", favoring resistant strains. This is an example of Darwin's Theory of evolution, operating the "survival of the fittest".

- Antibiotics don't 'cause' resistance; rather, they create an environment which favors the growth of resistant variants which already exist in nature or arise by chance.
Resistance is a Consequence of Usage

- The widespread use of antibiotics both inside and outside of medicine is playing a significant role in the emergence of resistant bacteria.

- Selective pressure from the use of antimicrobials is a major driving force behind the emergence of resistance.

- This resistance will "resist" to phylogenetic, geographic or ecologic barriers; therefore once resistance emerge, resistant bacteria can be found in different ecosystems.
More than 50% of all antimicrobials are used non-therapeutically in animal husbandry

Use of antimicrobials in food animals can lead to Antimicrobial Resistance (AMR) in human pathogen.

- In industrial production, antibiotics are added to drinking water to decrease diseases of crowding and as growth promoters
  - When microbes are exposed to antibiotics, the bacteria resistant to these drugs live to reproduce which resulted in Antimicrobial Resistance

Antibiotics…"the more you use them, the faster you lose them"
Ceftiofur in ovo use and prevalence of ceftiofur resistance among retail chicken *Escherichia coli*, and retail chicken and human clinical *Salmonella enterica* serovar Heidelberg isolates during 2003–2008 in Québec, Canada

Summary on the importance of the animal reservoir

- Larger selective pressure

- Most important reservoir for antimicrobial resistant *Salmonella* and *Campylobacter*.

- An increasingly important reservoir for MRSA

- Important, but not quantified reservoir for E. coli

- Transferable genes
More than one decade (2 decades?...) of WHO Activities on Containment of Food-related Antimicrobial Resistance
The First alert…1990

- Realising that modern livestock production throughout the world relied heavily on the use of antimicrobial substances (treatment, prophylaxis, growth promotion), WHO already in 1990 called for action.

- This was the first alert pointing at an increase of antimicrobial resistance in zoonotic and foodborne pathogens and the first call for action, intersectoral collaboration and harmonization of methods for monitoring and surveillance across sectors.

- An international, multidisciplinary working group was established by WHO to elaborate guidelines for uniform, regular and systematic monitoring and surveillance of antimicrobial resistance susceptibility testing worldwide.

- The result was The Guidelines for Surveillance and Control of Antimicrobial Resistance (WHO, 1990).
The guidelines stated that "The occurrence of antimicrobial resistant pathogenic bacteria in clinical materials, as well as in the normal flora of humans, in food and the environment urgently require elucidation to solve the problem encountered in treating the numerous infections due to such bacteria. ".

As a result, a WHO Working Group on Antimicrobial Resistance was established and held its first meeting at the Central Veterinary Laboratory in Weybridge in 1991.

The WG elaborated a small pilot project on "surveillance and assessment of antimicrobial resistance in microorganisms derived from animals, public and environmental health, and clinical medicine" by applying a common methodology (1992).
In 1997 WHO convened an expert meeting on “The Medical Impact of the Use of Antimicrobials in Food Animals”

The experts acknowledged that antimicrobial use can select resistant forms of bacteria in the ecosystem and resistant bacteria and resistance genes can be exchanged between human, animal and other ecosystems. The following adverse consequences of selecting resistant bacteria in animals were identified:

1. Transfer of resistant pathogens to humans via direct contact with animals or through the consumption of contaminated food or water.
2. Transfer of resistance genes to human bacteria.
3. Increased incidence of human infections caused by resistant pathogens.
1998 WHA Resolution

WHA 51.17

- Concerned by the extensive use of antibiotics in food production, which may further accelerate the development of antimicrobial resistance rendering treatment ineffective,

- the World Health Assembly urges Member States

  • to develop programs for monitoring and containment of antimicrobial resistance

  • to take measures to encourage the reduced use of antimicrobials in food-animal production"
Preserving effectiveness of anti-microbial therapy: globally

WHO Global Strategy for Containment of Antimicrobial Resistance

September 2001
The five key areas: global strategy for containment of antimicrobial resistance

- Rational drug use and regulation
- Infection prevention
- Surveillance
- Research and development
- Agriculture/Animal husbandry
WHO Global Principles for the Containment of AMR in food-animals

To minimise the public health impact of the use of antimicrobial agents in food animals

and provide recommendations for their safe and effective use in veterinary medicine.

Large consultation incl. stakeholders

As chapter in the publication on WHO Global strategy on Containment of Antimicrobial Resistance - 2001
WHO Global strategy for Prevention and Control of Foodborne Antimicrobial Resistance-1

- National and international interdisciplinary cooperation

- Prudent use of antimicrobial agents in all sectors
  - No use of antimicrobial agents for growth promotion
    - EU banned all growth promoters as of January 1, 2006
  - A good regulatory system for approval and licensing
  - Prescription-only
  - Practitioners not having economic profit from prescription
  - Routine prophylactic use of antimicrobials should be never be used as a substitute for health management
  - Accurate diagnosis and antimicrobial susceptibility testing
  - Appropriate antimicrobial product and administration route

- Infection control
  - Successful disease control relies on a holistic approach encompassing hygiene, animal husbandry and management, nutrition, animal welfare, and vaccination
WHO Global strategy for Prevention and Control of Foodborne Antimicrobial Resistance-2

- Antimicrobials identified as critically important in human medicine (WHO, 1998, 2005, 2007) to be used in animals only if justified
  - Fluoroquinolones, 3 + 4 generation cephalosporins

- Monitoring of antimicrobial resistance and antimicrobial usage in human and animals
  - Useful information on prevalence and trends
  - Input for risk assessment and risk management
  - A basis for choosing, implementing and evaluating interventions
Joint FAO/WHO/OIE consultative process on Non-human use of antimicrobials and antimicrobial resistance (Requested by Codex)

- 1rst Workshop on scientific risk Assessment, Geneva, December, 2003
- 2nd workshop on risk management options, Oslo, March 2004
- Joint Expert Consultation on use of antimicrobials in aquaculture and antimicrobial resistance, Seoul, June 2006
- Joint Expert Consultation on critically important antimicrobials, Rome 2007
WHO-panel on impacts of growth promoter termination in Denmark (2003)

- Independent interdisciplinary review panel;
- Assessed impacts on human health, AH and welfare, animal production and economic consequences.
Achievements 1997-2010

- International collaboration established
  - Codex, FAO, OIE, WHO
- 15+ expert meetings and consultations
- Codex Ad Hoc Intergovernmental task Force on Antimicrobial resistance (2007-2010)
- WHO list of Critically Important Antimicrobials for Human Heath developed
- Establishment of an Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)
Integrating Surveillance Systems
AGISAR

A group of experts working in veterinary, food and public health disciplines advising WHO on ensuring globally containment of foodborne antimicrobial resistance through integrated surveillance of antimicrobial usage and antimicrobial resistance in the animal, food and human sectors.
First AGISAR meeting
Copenhagen, June 2009

1) Update the WHO list of critically important antimicrobials (CIA) for human medicine

2) Develop a WHO strategic plan for containment of food-borne AMR
Integrated surveillance a key element of AGISAR- AMR Containment strategy

- Documentation of the situation
- Identification of trends
- Input data for:
  - Establishing associations antimicrobial usage and antimicrobial resistance
  - Risk assessment
  - Evaluation of effectiveness of interventions
- Identify need for interventions
- Basis for focused and targeted research
- Basis for communication
Governance of AGISAR

- Organizations
- Networks
- Institutes
- Universities
- Individuals

World Health Organization

Secretariat

Usage Monitoring Subcommittee
AMR Monitoring Subcommittee
Cap. Building & Country Pilot Projects Subcommittee

Steering Committee (Chairs & Co-Chairs of Subcommittees)

Data Management & Software Dev. Subcommittee
Discuss emerging antimicrobial threats from the food-chain (ESBL *E. coli*)

Discuss WHO-AGISAR’s role in promoting global harmonization of antimicrobial usage monitoring and antimicrobial resistance

Define future work plans for the four WHO-AGISAR working subcommittees
Antimicrobial Usage Monitoring SC

The main aim of the sub-committee’s work is to support and promote collection of standardized data on the usage of antibacterial agents for humans and animals, including aquatic species at regional/national levels.

Approach:
- Identify the AM products on the market
- Identify channels of AM distribution that give representative data coverage
- Decide on which AM to be included
- Decide which data to collect for each product
- Decide on confidentiality politics
- Selection of sources for population data (denominator)
Software Development and Data Management SC

Objective: improve the data management and analysis capabilities of the WHONET software in order to support the WHO AGISAR’s objectives for integrated surveillance of AMR

- Inventory of websites and reports for integrated surveillance of antimicrobial resistance
- Identification of a useful set of fields and code lists from existing surveillance programs and use them as a basis for discussion and planning.
- Development 2 sets of codes/fields
  - 1) fairly comprehensive set of fields/codes to support a variety of surveillance needs and projects
  - 2) a short list of highest priority fields/codes recommended for implementation by most surveillance program.
Phase I: Determine specifications for the AGISAR software

Phase II: Implement specifications into the software based on WHONET

Phase III: Dessemination of the software.

- DANMAP 2008 report
- NORM/NORM-VET 2008 report
- CIPARS 2006 report
- NARMS (USDA) 2006 report
- NARMS (FDA) 2007 report
- FINRES-Vet 2006 report
- MARAN 2007 report
- SVARM 2007 report
- Others

• General information
• Sample Categories
• Antimicrobial and sample selection
• Measurement fields (data collection)
• Suggested output format (data analysis)

Expert advices from AGISAR members
Antimicrobial Resistance Monitoring SC

- Develop recommendations for international harmonization of integrated AMR monitoring systems of food borne bacteria, including both pathogenic and commensal organisms.

- Provide guidance on surveillance and monitoring priorities and minimum requirements for integrated monitoring systems and for AGISAR pilot monitoring projects.

- Provide guidance on sampling strategies.

- Disseminate guidelines and standards on laboratory testing methods and quality assurance.

- Propose components of reporting and information sharing systems that permit regional and international comparison of findings.

- Communicate recommendations through GFN training courses, AGISAR pilot projects, and through other partnerships.
Objectives: Facilitate capacity building through GFN for the integrated surveillance of foodborne pathogens and commensal antimicrobial drug usage and AMR across sectors (animal, food, human), particularly in developing countries.

- Identify and make available relevant resources for antimicrobial usage monitoring and integrated antimicrobial resistance surveillance
- Identify potential training sites for AGISAR/GFN
- Develop and facilitate implementation of training modules for postgraduate interdisciplinary intersectoral audiences
- Encourage participation in external quality control systems to address proficiency/data gaps in laboratories monitoring AMR in foodborne pathogens during AGISAR/GFN training courses.

Facilitate pilot studies focusing on integrated surveillance of AMR in foodborne pathogens and commensals, as well as antimicrobial drug use, with appropriate interventions in one or more developing countries (China, Kenya, Columbia).
Global Foodborne Infections Network (GFN)

A network of professionals working in veterinary, food and public health disciplines committed to enhancing capacity of countries to conduct integrated surveillance of foodborne and other enteric infections, incl. antimicrobial resistance

GFN Steering Committee
GFN main activities

- (Inter)national Training Activities
- External Quality Assurance System (EQAS)
- Country Data Bank (CDB)
- Reference Services
- Focused Regional and National Projects
- Communication

- ~ 1 600 Members
- > 700 Institutions
- 177 Member States
(Inter)national Training Courses

Microbiology training
- Global/Region-specific pathogens (e.g. Salmonella, Campylobacter, E. coli, V. cholerae, S. Typhi, Brucella, Shigella, Listeria, C. botulinum)
- Quality assurance
- Biosafety
- Antimicrobial Susceptibility Testing

Epidemiology training
- Outbreak detection and response
- Evaluation of surveillance systems
- Study design
- Source attribution
- Burden of disease

Joint Epidemiology and Laboratory
- Joint case studies
- Integrated surveillance
- Risk assessment
- Country Plans of Action
- Advocacy and communication
- Information sharing networks
AMR Containment: The way forward

- *The WHO list of critically important antimicrobials* updated every two years.

- Harmonized protocols for monitoring antimicrobial usage and resistance in animal, food, and human developed and disseminated.

- Software to support data collection and analysis developed and disseminated.

- Support WHO capacity-building activities in Member countries through GFN training courses.

- Data generated through country pilot projects (Kenya, China, Columbia) and add AMR data to the GFN country databank.
More information at:

http://www.who.int/foodborne_disease/resistance

:: General information
:: Codex ad hoc Intergovernmental Task Force of Antimicrobial Resistance
:: List of Critically Important Antimicrobials
:: WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)
:: Publications
:: Meetings