Change or Die
No Action Today - No Cure Tomorrow

According to WHO and Most Global Experts the Rapidly Growing Threat of Anti-Microbial Resistance May soon Kill Millions, Isolate Countries, Halt International Trade The World is faced with a Transgenerational and Transboundary Scourge
Rio Praaning Prawira Adiningrat, PA Secretary General Annemieke Beylevelt MD, PA Director of Health Policy

Presented to the ASEAN Secretariat on Tuesday 30 July 2013

“If current trends continue unabated, the future is easy to predict. Some experts say we are moving back to the pre-antibiotic era. No. This will be a post-antibiotic era. [...] An end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill.”

Dr Margaret Chan Director-General of the World Health Organization, 14 March 2013
“Antimicrobial resistance (AMR) poses a catastrophic threat. If we don’t act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can’t be treated by antibiotics.”

Professor Dame Sally Davies
Chief Medical Officer, United Kingdom, 11 March 2013

Antibiotics Use in the Agricultural Sector

Source: PA Europe, The Hague
### Antibiotics Use in Human Medicine

Percentage of population reporting antimicrobials use in past year

Source: PA Europe, The Hague.


### Antibiotics Use Across the World

<table>
<thead>
<tr>
<th>Region</th>
<th>Use</th>
<th>Non-Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europe</td>
<td>14–37%</td>
<td>3%</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>47–73%</td>
<td>19%</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>23–51%</td>
<td>30%</td>
</tr>
<tr>
<td>Central Europe</td>
<td>31–61%</td>
<td>6%</td>
</tr>
<tr>
<td>South America</td>
<td>23% (past two weeks)</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>62%, (past four months)</td>
<td></td>
</tr>
<tr>
<td>Middle East</td>
<td>23–46%</td>
<td>39% (Israel 3%)</td>
</tr>
<tr>
<td>Asia</td>
<td>4–75%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Antibiotic Use and AMR Rates

AMR Rates 1990–2000 in selected countries


Spread of Antibiotic-Resistant Bacteria

Spread of Antibiotic-Resistant Bacteria: EU

Proportion of Methicillin Resistant Staphylococcus aureus (MRSA) Isolates in Participating Countries in 2011

Source: Data submitted to TESSy, The European Surveillance System (2013)

Spread of Antibiotic-Resistant Bacteria: EU

Proportion of Aminopenicillins Resistant (R) Escherichia coli Isolates in Participating Countries in 2011

Source: Data submitted to TESSy, The European Surveillance System (2013)
Spread of Antibiotic-Resistant Bacteria: US

Source: The Surveillance Network, U.S.A

5 Main Issues Driving Global AMR

- Overuse
- Underuse
- Non-Use
- Counterfeit and Substandard Antibiotics
- Human Antibiotics Use in Agriculture
European Union: Growing awareness, political preparedness to act, but no progress due to lack of enforcement and resistance among some Member States’ agricultural constituencies.

USA: Growing awareness but rapid increase of (human) antibiotics use for animal growth promotion and disease prevention; no bipartisan AMR approach due to heavy ‘Big Ag’ lobby.

China: Political and scientific awareness, several categories of human antibiotics in animals reportedly lost efficacy, no lessons learnt from Melamine crisis; risk of early AMR Crisis as world’s largest antibiotics producer, user and abuser.

EU Council Decision

In June 2012, the Council adopted the Conclusions on “The impact of antimicrobial resistance in the human health sector and in the veterinary sector – a One Health perspective”:

- Closer cooperation between human and veterinary sectors
- Member States to develop national action plans for AMR
- Education and training of professionals on appropriate use
- Prevention of illegal sales over the internet
- Limited use of Critically Important Antimicrobials
- Limited prophylactic use
- Incentives for animal production systems that improve animal health, reducing antibiotics dependence
- Effective surveillance systems and data collection
United States

“Because it is well established that all uses of antimicrobial drugs, in both humans and animals, contribute to the development of antimicrobial resistance, it is important to use these drugs only when medically necessary [...] FDA is proposing a voluntary initiative to phase in certain changes to how medically important antimicrobial drugs are labeled and used in food-producing animals.

FDA is taking this action to help preserve the effectiveness of medically important antimicrobials for treating disease in humans.” – US Food and Drug Administration (2013)

**Large-scale agriculture and food animal production mainly interested in up to 15% growth promotion, meat-instead-of-fat, and prophylactic antibiotics use**

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China

“There are many problems with the clinical use of antibiotics in our hospitals [...] The resulting rise in drug resistance has gradually become a huge obstacle to good healthcare in this country.” – Ma Xiaowei, Vice-Minister of Health, 2011

**1.3 billion people and up to feed, 80% small holder farmers; lack of education, training, investment; widespread damaging antibiotic/pesticide/fertiliser practices with Government funding. Mix of food safety, food security, informal buyers boycott issues. New responsible Government may forge changes.**
African Union

“The time to act is now to ensure a healthier and better tomorrow [...] the germs that cause disease develop a defense against our drugs because of the way we have been using them.” – Prof. Onyebuchi Chukwu, Nigerian Minister for Health (2011)

Pan-American Health Organisation

“The resistance of the infectious agents of certain diseases to drugs specifically used to combat them is a phenomenon confirmed by scholars [...] From the perspective of global public health, this resistance constitutes an increasing problem that has worsened through the misuse or abuse of antibiotic agents.”

ASEAN

“Inter-country networking, communication and collaboration mechanism shall be developed in promoting rational use of antimicrobials and containment of antimicrobial resistance. Regular inter-country meetings need to be organized to monitor progress.”

Counterfeit Drugs

- Mislabeled products with correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging
- WHO estimates: 1% of medicines in developed world counterfeit, 10% of medicines in developing world
  - But: “Many countries in Africa and parts of Asia and Latin America have areas where more than 30% of the medicines on sale can be counterfeit…”*†‡
- Counterfeit antibiotics account for 28% of all counterfeit medicines† and 5% of the global antibiotics market‡

Counterfeit Drugs – Prevalence by World Region

Factors Driving Spread of Counterfeit Drugs

- Lack of political will/commitment
- Lack of appropriate legislation
- Absence of or weak drug regulation (30% of WHO Member States have no regulation or limited/ineffective capacity)
- Weak enforcement
- High drug prices → huge profits to be made from counterfeits
- Inefficient cooperation between stakeholders, i.e. between regulatory authorities, police, and customs services and the judiciary

Result: high prevalence of counterfeit medicines in developing countries, especially antibacterial agents, particularly in Southeast Asia and Africa
### Prescription Policies and Enforcement

<table>
<thead>
<tr>
<th>Region</th>
<th>Policy</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>Prescription Only</td>
<td>Differences in enforcement between member states</td>
</tr>
<tr>
<td>USA</td>
<td>Prescription Only</td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>Prescription Only</td>
<td>Higher levels of bacterial resistance among most of its key pathogens, compared with Europe and the United States</td>
</tr>
<tr>
<td>Chile</td>
<td>Prescription Only</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>Prescription Only</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>Prescription Only</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>Over the counter</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>Over the counter</td>
<td>High burden of infectious diseases</td>
</tr>
<tr>
<td>Middle East</td>
<td>Mostly over the counter</td>
<td>High rates of non-prescription use of antibiotics</td>
</tr>
<tr>
<td>Asia</td>
<td>Mostly over the counter</td>
<td>Extremely high resistance rates in Vietnam and Bangladesh</td>
</tr>
<tr>
<td>China</td>
<td>Over the counter</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Over the counter</td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>Prescription Only</td>
<td>Difficulties with enforcing prescription policy</td>
</tr>
</tbody>
</table>

**Sources:**

- World Health Organization - The evolving threat of antimicrobial resistance: options for action, 2012 / Morgan DJ et al.
- Non-prescription antimicrobial use worldwide: a systematic review. Lancet Infectious Diseases, 2011
- Alliance for the Prudent Use of Antibiotics. Executive summary: select findings, conclusions, and policy recommendations. Clinical Infectious Diseases, 2005
- Okeke IN, Laxminarayan R, Bhutta ZA, et al. - Antimicrobial resistance in developing countries. Lancet Infectious Diseases, 2005
- Okeke IN, Lamikanra A, Edelman R. - Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerging Infectious Diseases, 1999

### Prescription Policies and Challenges

![Prescription Policies and Challenges](image_url)

### Human vs. Veterinary Antibiotics Use

- In some countries, veterinary antibiotics use far outstrips antibiotics use for human medicine
- US: veterinary use accounts for 80% of total antibiotics sales

**Antimicrobial Drugs Approved for Use in Food-Producing Animals: 2009 Sales and Distribution Data Reported by Drug Class**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Kilograms</th>
<th>Pounds</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOOD-ANIMAL USE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amoxicillin</td>
<td>237,678</td>
<td>521,985</td>
<td>2%</td>
</tr>
<tr>
<td>cephalaxin</td>
<td>41,128</td>
<td>91,111</td>
<td>0%</td>
</tr>
<tr>
<td>non-beta-lactams</td>
<td>3,740,837</td>
<td>8,249,871</td>
<td>23%</td>
</tr>
<tr>
<td>macrolides</td>
<td>115,833</td>
<td>253,371</td>
<td>1%</td>
</tr>
<tr>
<td>penicillins</td>
<td>651,985</td>
<td>1,580,352</td>
<td>5%</td>
</tr>
<tr>
<td>sulfas</td>
<td>610,514</td>
<td>1,345,353</td>
<td>4%</td>
</tr>
<tr>
<td>tetracyclines</td>
<td>517,872</td>
<td>1,141,719</td>
<td>2%</td>
</tr>
<tr>
<td>nitrofurans</td>
<td>6,611,892</td>
<td>10,867,181</td>
<td>28%</td>
</tr>
<tr>
<td>nitrofurans</td>
<td>2,227,386</td>
<td>4,910,501</td>
<td>14%</td>
</tr>
<tr>
<td>nitrofurans</td>
<td>12,607,180</td>
<td>25,098,134</td>
<td>22.0%</td>
</tr>
<tr>
<td>HUMAN MED USE</td>
<td>3,320,080</td>
<td>7,275,255</td>
<td>22.0%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>16,287,290</td>
<td>35,093,279</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: FDA (2010): 2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals

### AMR and Research Results from China

- AMR and the fight against AMR is a dynamic process
- Reduction of antibiotics use results in a reduction in resistant bacteria over time (years)
- Rates of resistance will always remain higher than before introduction of the antibiotic
- The bacteria Campylobacter, MRSA, and E. Coli are currently multi-drug resistant and therefore represent the greatest threat to human health
- The following slides show the development of these resistant bacteria in China
Consequences of Increasing AMR in China

- Efficacy of antibiotics is rapidly decreasing and becoming a threat to public health
- Resistance rates in animals will soon increase up to 100% for most common human antibiotics
- Resistant bacteria will be spread from Chinese animals (via the food chain and through direct contact) to humans and vice versa, and will subsequently spread globally
- This threat has already begun with the emergence of multiresistant Campylobacter, MRSA and E. Coli globally
- Increasing resistance leading up to 100% resistance will cause millions of deaths, similar to the situation before the invention of Penicillin in 1928
- Will dramatically diminish the strength and power of the nation
- Will lead to a triple economic disaster, through higher costs of health care, diminishing workforce and income, and obstacles to international trade and exchange

Consequences of Resistance for Vulnerable Groups

- Vulnerable elderly people and infants with lower or no immunity capacity will die sooner from previously curable infectious diseases, such as pneumonia
- Surgery in general will become very high-risk, as possible antibiotic interventions after operations become limited or nonexistent
- Specialised surgery, e.g. heartvalve surgery, kidney transplants and other transplants will become impossible
- Treatment of patients suffering from any form of cancer will be more life-threatening, as the (temporarily) diminished immune system will not be supported by antibiotics
- Prematurely born babies will have a very small chance of survival
- Apart from the human tragedies, the economic consequences will be devastating
Consequences of AMR Outbreaks

- High human toll
  - US: 99,000 deaths per year due to drug-resistant infections*
  - China: 80,000 deaths per year†
  - EU: 25,000 annual deaths‡
- Huge financial impact
  - US: the annual cost of antibiotic-resistant infections for the healthcare system of approximately $21 billion to $34 billion*
  - China: 80 billion yuan per year†

Both can be expected to rise as AMR continues to spread

Reasons for Failure of AMR Containment Policies

- View of antibiotics as a panacea by the public and medical professionals alike
- Public unawareness of the dire consequences of antibiotics overuse or inadequate use
- Poor surveillance of prescription practices by doctors as well as the influence of the pharmaceutical industry
- Too few quality controls on antibiotics available on the internet
- Poor adoption of alternative growth promoters/animal husbandry practices
- Governance failures, among others due to the influence of industry stakeholders
- Deliberate lack of data on production, use and abuse including regarding growing immunities in animals
- Deliberate lack of consultation, cooperation and joint action throughout the food chain due to resistance among agricultural lobbies

Non-Use in Developing Countries

- Non-availability of antibiotics/lack of access in rural areas
- Non-availability of particular antibiotics, which are then replaced through antibiotics that are available
- Too few doctors/qualified health workers → self-medication through over-the-counter use
- Widespread availability of counterfeit and sub-standard antibiotics with some African countries having over 50% fake antibiotics
“Combatting AMR globally and at regional and national levels requires leadership and support from the political level fostering multistakeholder engagement and empowerment for action.”


**Key Immediate Options for Solutions**

1) Priority for development of alternative products for growth promotion and prevention over development of new molecules which takes at least ten years while bacteria reach immunity within two years under continued present use
   2) Zero use of human antibiotics in animal farming
   3) Higher cost for life saving antibiotics while ensuring availability when necessary
   4) Enforced restriction on use through equating antibiotics to morfins
   5) Establishment of international multistakeholders platform tasked with consensus building, information and communication
Global multi-sectoral multistakeholder platform

Regional Platforms

China

ASEAN

Regional Platforms

Africa

Regional Platforms

EU

Russia

Regional Platforms

America’s

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