



Antimicrobial resistance in aquaculture in the context of one health

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Sebastian G.B. Amyes

MAGIC BULLETS

LOST HORIZONS

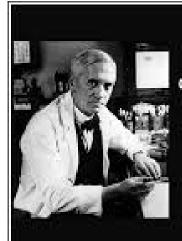
The Rise and Fall of Antibiotics

Understanding resistance is Important...

WORLD SEAL ANTIMICROBIAL

AWARENESS WEEK

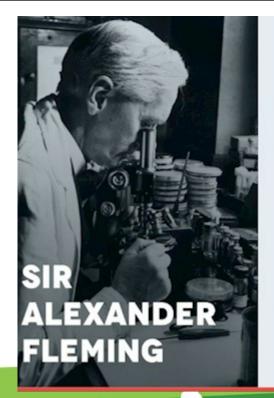
18-24 NOVEMBER



I have been trying to point out that in our lives chance may have an astonishing influence and, if I may offer advice to the young laboratory worker, it would be this - never to neglect an extraordinary appearance or happening.

(Alexander Fleming)

izquotes.com



The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.

I hope this evil can be averted.







Why should we talk about resistance



"Resistance training is just as important as cardio. Train yourself to resist chocolate, pastries, fried foods, beer, pizza...."

Definitions

Multidrug Resistant (MDR)

 Acquired non-susceptibility to at least one agent in three or more antimicrobial categories

Extensively drug resistant (XDR)

 Non-susceptibility to at least one agent in all, but two or fewer antimicrobial categories

Pan drug resistant (PDR)

• Non-susceptibility to all agents in all available antimicrobial categories Exner et al. GMS Hyg Infect Control. 2017; 12: Doc05.

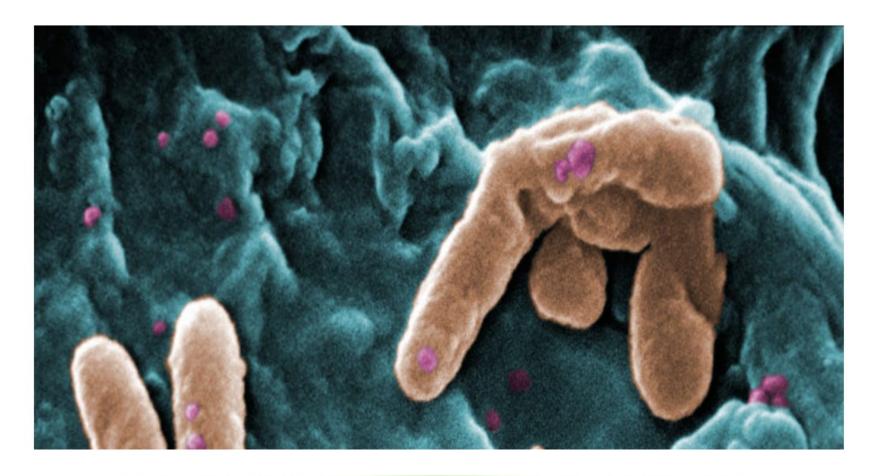
Antimicrobial resistance global threat

- WHO has identified AMR as one among top 10 global public health threats.
- US CDC estimates- two million people affected by AMR infections and 23,000 die every year.
- Europe estimates- ~ half million affected by AMR infections and deaths 33,116 per year.
- In 2011, UN General assembly adopted "Political declaration on antimicrobial resistance".
- WHO, FAO and OIE have developed action plan against AMR

WHO – most important organisms for which new therapeutics are needed

- ESKAPE group
 - Enterococcus faecium
 - Staphylococcus aureus
 - Klebsiella pneumoniae
 - Acinetobacter baumanii
 - Pseudomonas aeruginosa
 - Enterobacter spp
- Cause of most important healthcare associated infections
- Impact:
 - Infections not responding to antibiotics mortality
 - Longer hospital stays

WHO releases list of world's most dangerous superbugs



Priority 1: Critical

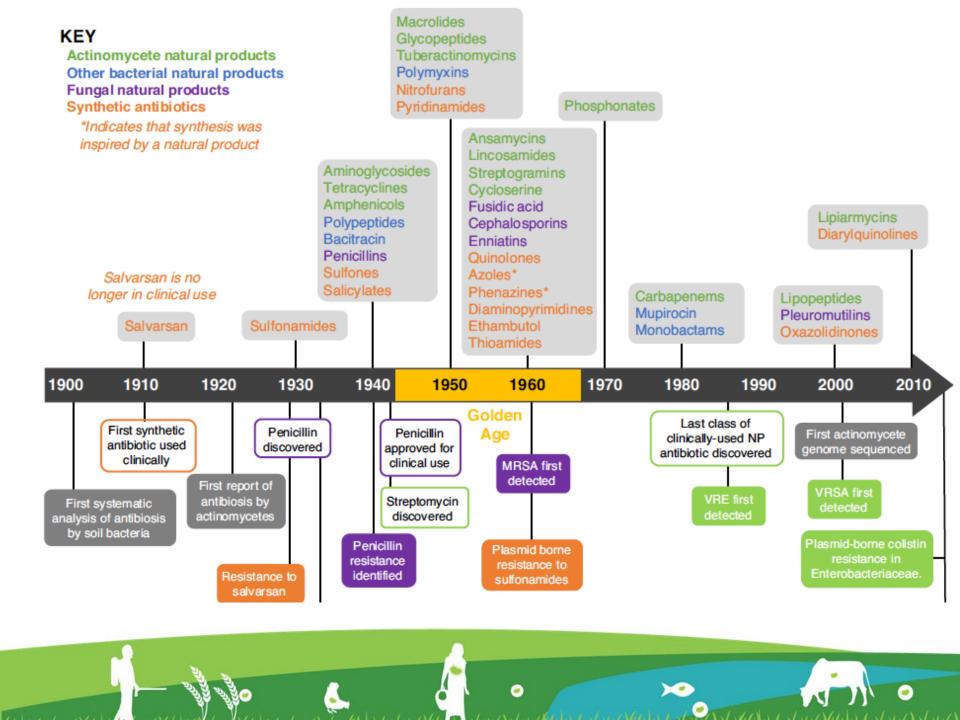
- 1. Acinetobacter baumannii, carbapenem-resistant
- 2. Pseudomonas aeruginosa, carbapenem-resistant
- 3. Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Priority 2: High

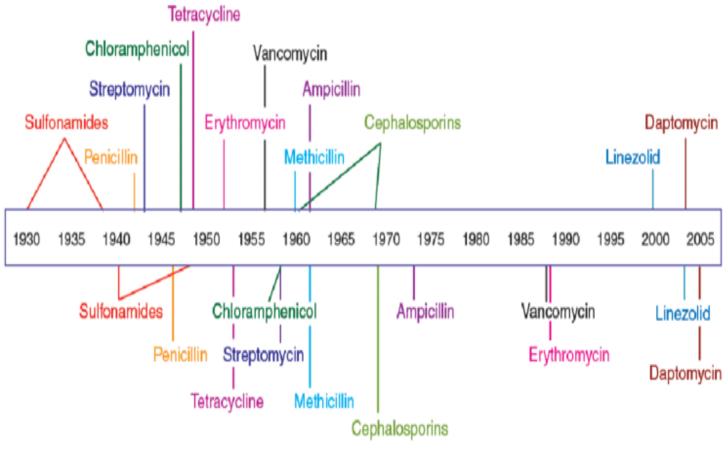
- 4. Enterococcus faecium, vancomycin-resistant
- 5. Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
- 6. *Helicobacter pylori*, clarithromycin-resistant
- 7. Campylobacter spp., fluoroquinolone-resistant
- 8. Salmonellae, fluoroquinolone-resistant
- 9. Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: Medium

- 10. Streptococcus pneumoniae, penicillin-non-susceptible
- 11. Haemophilus influenzae, ampicillin-resistant
- 12. Shigella spp., fluoroquinolone-resistant



Antibiotic deployment



Antibiotic resistance observed



CONSULTATIONS AND WORKSHOPS

Antimicrobial Use in Aquaculture and Antimicrobial Resistance

Report of a Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance

Seoul, Republic of Korea, 13-16 June 2006







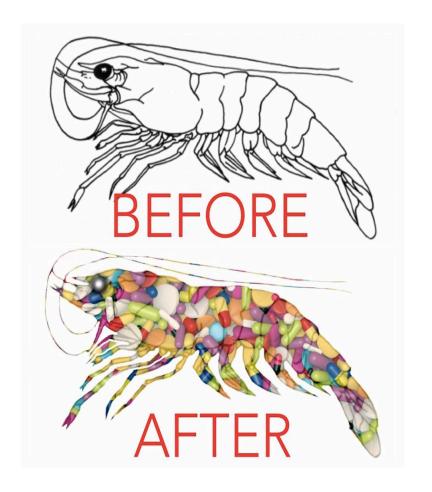
Issued by the World Health Organization in collaboration with the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health

DEPARTMENT OF FOOD SAFETY, ZOONOSES AND FOODBORNE DISEASES
WORLD HEALTH ORGANIZATION
GENEVA, SWITZERLAND

Major risks associated with antimicrobial use in aquaculture

- Antimicrobial residues in fish
- Selection and spread of antimicrobial resistance
 - Pathogens of aquatic animals
 - Fish associated bacteria with zoonotic potential
 - Resistance transfer can happen across bacterial species and genera
 - Aquatic bacteria that may transfer resistance to human pathogens





Publications that raised serious concern

Environmental Microbiology (2006) 8(7), 1137-1144

doi:10.1111/j.1462-2920.2006.01054.x

Minireview

Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment

Felipe C. Cabello

Department of Microbiology and Immunology, New York Medical College, Valhalla, NY 10595, USA.

many developed and developing countries. It is expected that this growth will increase at an even faster rate in the future, stimulated by the depletion of fisheries and the market forces that globalize the sources of food supply



Aquaculture as yet another environmental gateway to the development and globalisation of antimicrobial resistance



Felipe C Cabello, Henry P Godfrey, Alejandro H Buschmann, Humberto J Dölz

Aquaculture uses hundreds of tonnes of antimicrobials annually to prevent and treat bacterial infection. The passage of these antimicrobials into the aquatic environment selects for resistant bacteria and resistance genes and stimulates bacterial mutation, recombination, and horizontal gene transfer. The potential bridging of aquatic and human pathogen resistomes leads to emergence of new antimicrobial-resistant bacteria and global dissemination of them and their antimicrobial resistance genes into animal and human populations. Efforts to prevent antimicrobial overuse in aquaculture must include education of all stakeholders about its detrimental effects on the health of fish, human beings, and the aquatic ecosystem (the notion of One Health), and encouragement of environmentally friendly measures of disease prevention, including vaccines, probiotics, and bacteriophages. Adoption of these measures is a crucial supplement to efforts dealing with antimicrobial resistance by developing new therapeutic agents, if headway is to be made against the increasing problem of antimicrobial resistance in human and veterinary medicine.

Lancet Infect Dis 2016; 16: e127–33

Published Online April 12, 2016 http://dx.doi.org/10.1016/ S1473-3099(16)00100-6

Department of Microbiology and Immunology and Department of Pathology, New York Medical College, Valhalla, New York, NY, USA (Prof F C Cabello MD,

Antimicrobial use in Aquaculture

- Fish contributes to about 7% of global protein intake (FAO, 2020).
- 2017 global antimicrobial consumption in aquaculture- 10,259 tonnes expected to increase to 13,600 tonnes (33% increase) by 2030 (Schar et al.,
 2020).
- Consumption intensity : 157 mg kg^{-1} for catfish, 103 mg kg^{-1} for trout, 59 mg kg^{-1} for tilapia, 46 mg kg^{-1} for shrimp, 27 mg kg^{-1} for salmon, 208 mg kg^{-1} for pooled species.
- Global antimicrobial consumption in 2030 expected to be 236,757 tonnes Application sector wise: humans accounting for 20.5%
 - terrestrial animal production accounting for 73.7% aquaculture accounting for 5.7%

Global antimicrobial consumption

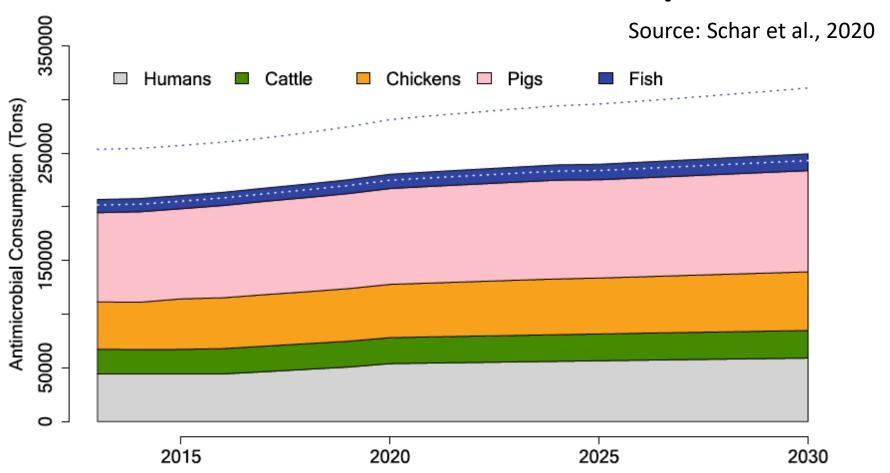


Figure 3. Global antimicrobial consumption, 2013–2030. Dotted lines represent the 95% uncertainty interval for fish.

Antibiotic consumption in aquaculture (Schar et al., 2020)

 In 2017, 93.8% global antibiotic consumption in aquaculture sector was in Asia-Pacific Region, 2.3% in Africa, 1.8% in Europe.
 In 2030, increases would be 50.9% in Africa and 50.6% in Latin America

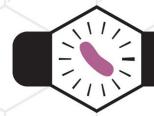
In Asia-Pacific region, antibiotic consumers – Global aquaculture production

China 57.9%	51.2%
India 11.3%	9.9%
Indonesia 8.6%	9.8%
Vietnam 5%	5.7%

• The countries with largest projected increase during 2017-2030 would be Brazil (94%), Saudi Arabia (77%), Australia (61%), Russia (59%) and Indonesia (55%).



Development of Antibiotic Resistance



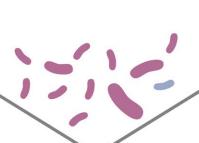
How Antibiotic Resistance Happens

Lots of germs.
A few are drug resistant.

Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.



The drug-resistant bacteria are now allowed to grow and take over.



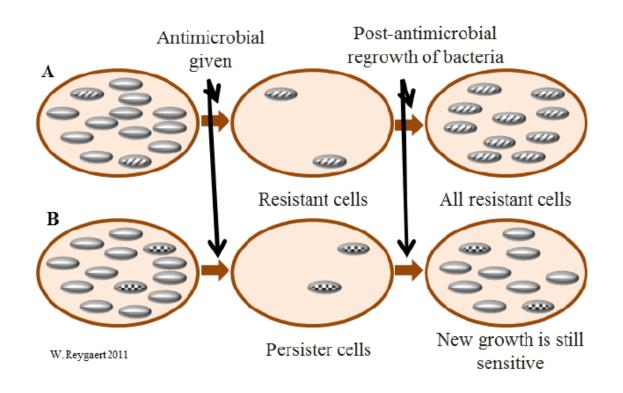
Some bacteria give their drug-resistance to other bacteria, causing more problems.

Image courtesy of CDC / Melissa Brower Centers for Disease Control and Prevention Public Health Image Library http://phil.cdc.gov/phil/home.asp



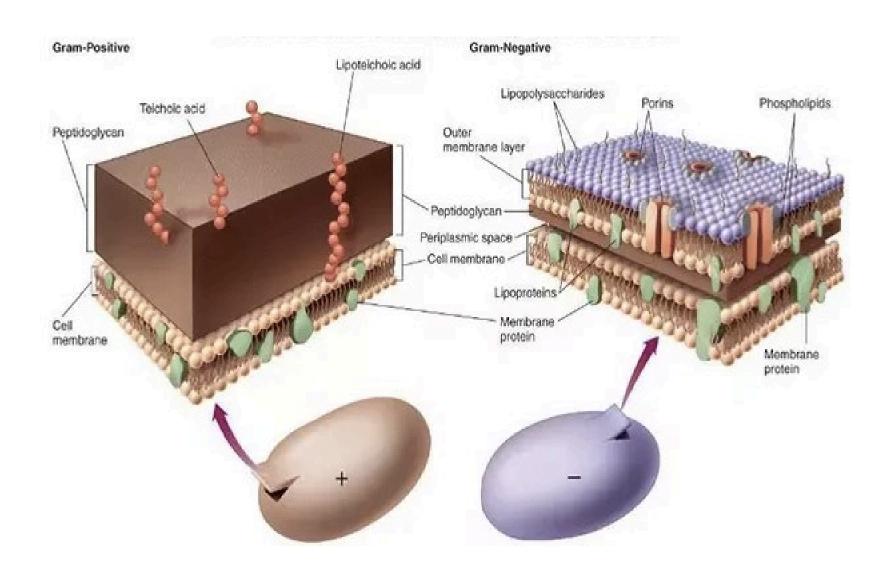


Persistance *vs* resistance ?



Some bacteria have intrinsic resistance

- The intrinsic resistance of a bacterial species to a particular antibiotic: ability to resist the action of that antibiotic as a result of inherent structural or functional characteristics.
- For example: glycopeptide antibiotic vancomycin inhibits peptidoglycan crosslinking by binding to target d-Ala- d-Ala peptides, but in Gram-negative organisms, it cannot cross the outer membrane and access these peptides in the periplasm
- Aeromonas has intrinsic beta-lactamases which makes them resistant to ampicillin.



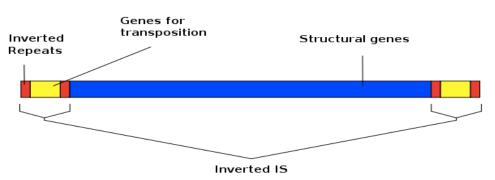
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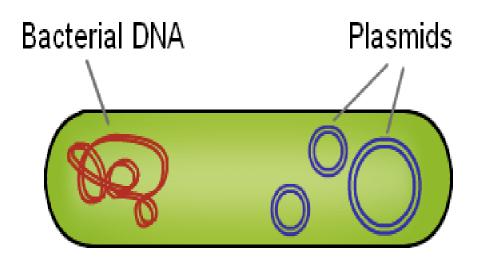


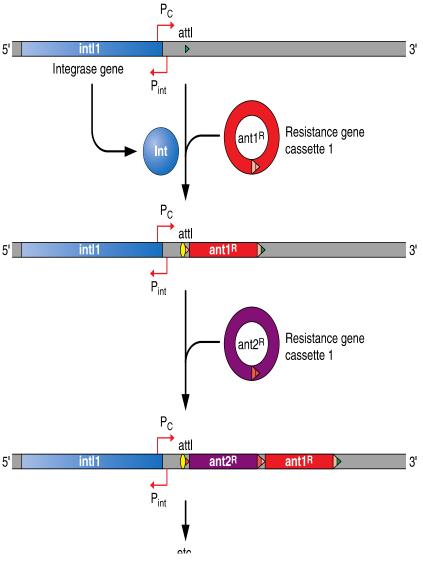
Acquired antimicrobial resistance

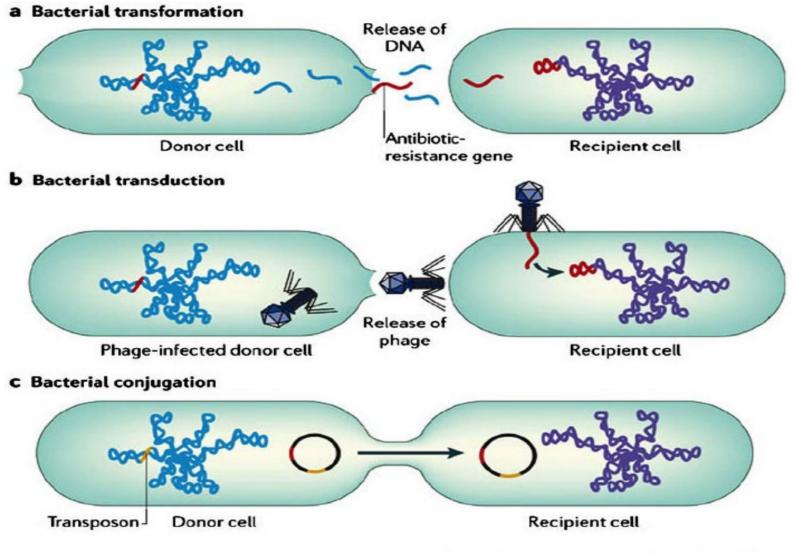
- When microorganisms once sensitive to an antimicrobial agent become resistant to that particular antibiotic, the resistance is acquired
- The acquired resistance could be due to genetic changes such as mutations or acquisition of genes contributing to resistance through horizontal gene transfer
- Mobile genetic elements like plasmids, transposons, bacteriophages contribute to horizontal gene transfer
- Horizontal gene transfer can occur across bacterial genera and species eg from environmental bacteria to human pathogens

Bacterial composite transposon



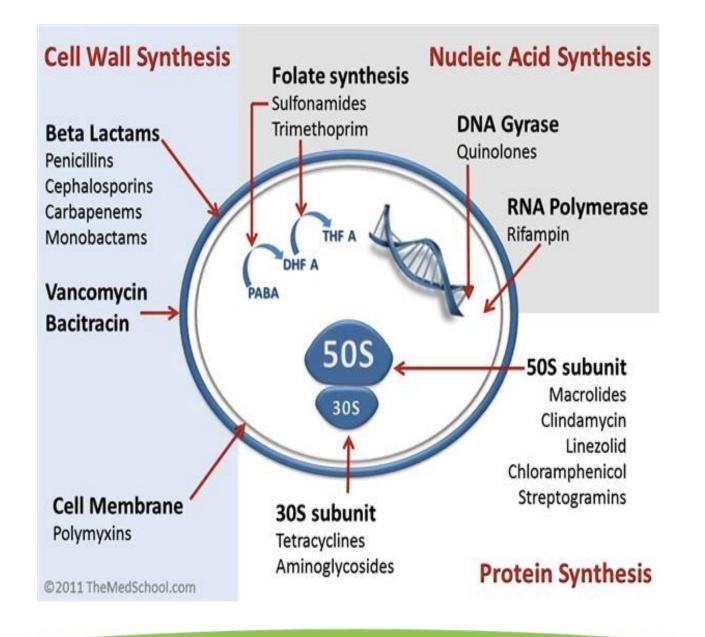




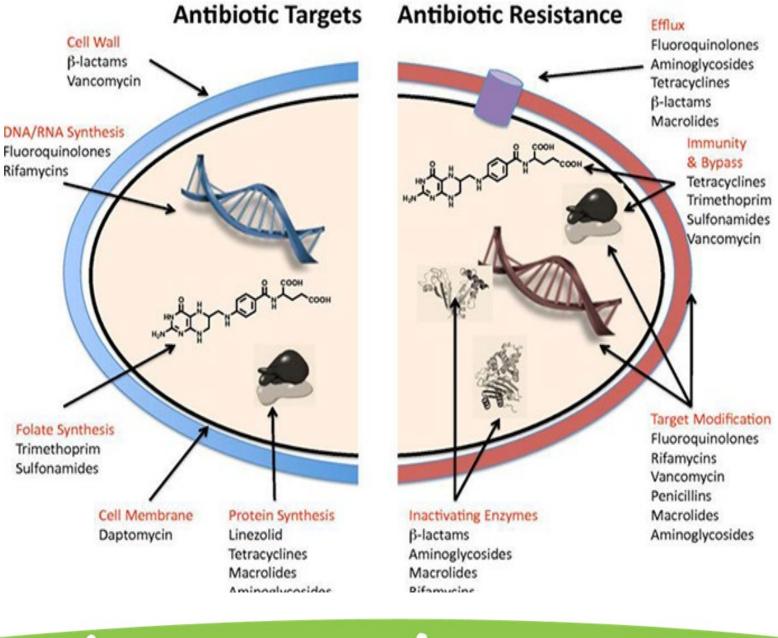


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Phenotypic resistance and mechanisms of resistance

- When identical phenotypic resistance is detected in two isolates eg
 - one from aquatic environment
 - another from a clinical case,
- The two isolates may have different resistance genes with different mechanisms
 - Eg: tetracycline resistance could be due to
 - (a) over production of efflux proteins or
 - (b) production of ribosomal protection proteins
 - (c) production of tetracycline inactivating proteins

Antimicrobial resistance is ancient, natural and is found in environments with no exposure to antibiotics

- Viable multidrug-resistant bacteria have been cultured from the Lechuguilla Cave in New Mexico, isolated for >4 million years (Bhullar et al., 2012)
- Antibiotic resistant marine bacteria have been found as far as 522KM offshore and in deep sea at depths of 8200m (Aminov, 2011)
- Evolution of antibiotic resistance genes predates evolution of Actinomycetes
- Some of the antibiotic resistance genes have not evolved to protect against antibiotics but have other metabolic functions

Resistance genes have other functions in the cell

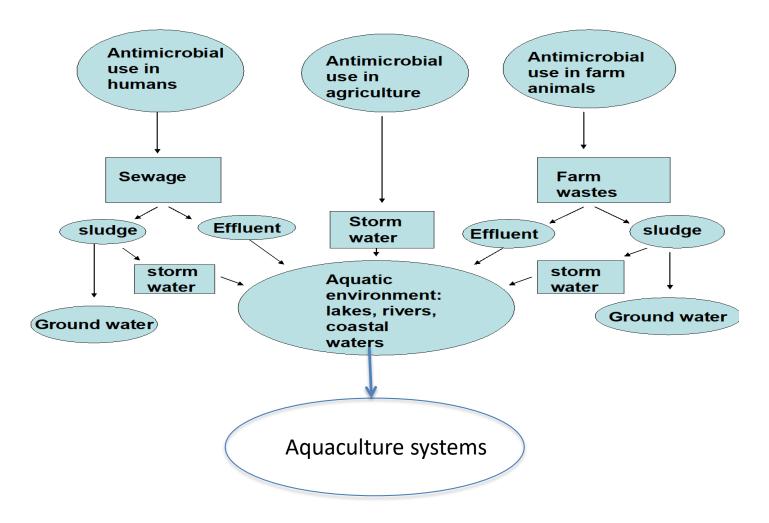
- ampC beta-lactamase is involved in maintaining normal morphology in *Escherichia coli*
- Efflux pumps are involved in efflux of several compounds
- bla_{oxy} beta-lactamase has metabolic function in *Klebsiella oxytoca*

Resistance genes found in environmental bacteria without exposure to antibiotics

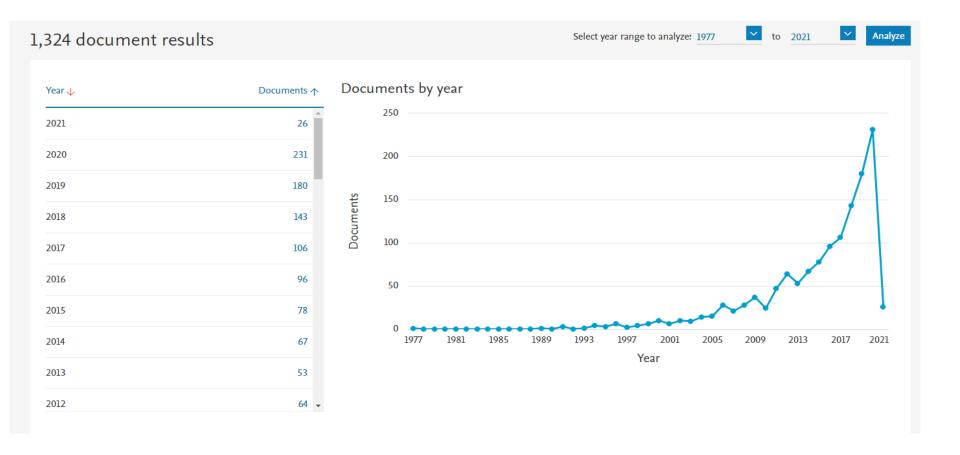
- qnr gene conferring resistance to quinolones are found in marine bacteria like Shewanella algae and Vibrio spp.
- CTX-M beta-lactamase is present in environmental bacteria like Kluyvera

AMR not always related to use of antibiotics in aquaculture

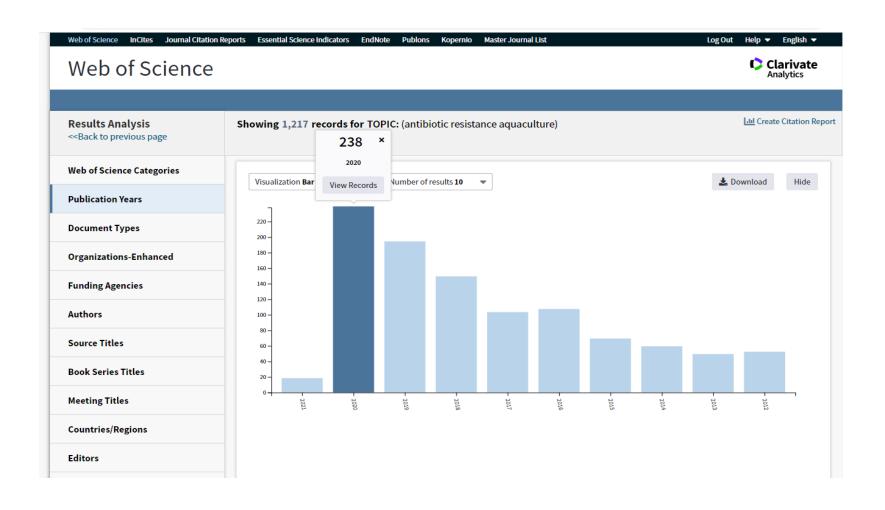
- Culture-independent studies in the Baltic sea, show presence of resistance genes encoding resistance to sulphonamides, trimethoprim, tetracycline, aminoglycoside, chloramphenicol
- Genes encoding multidrug efflux pumps in sediments below fish farms, though some antibiotics like tetracyclines, aminoglycosides and chloramphenicol are not used in this area (Muziasari et al., 2017)
- Most *Vibrio vulnificus* strains isolated from Dutch eel farms showed resistance to cefoxitin, though this antibiotic was not used in eel aquaculture (Haenen et al., 2014)



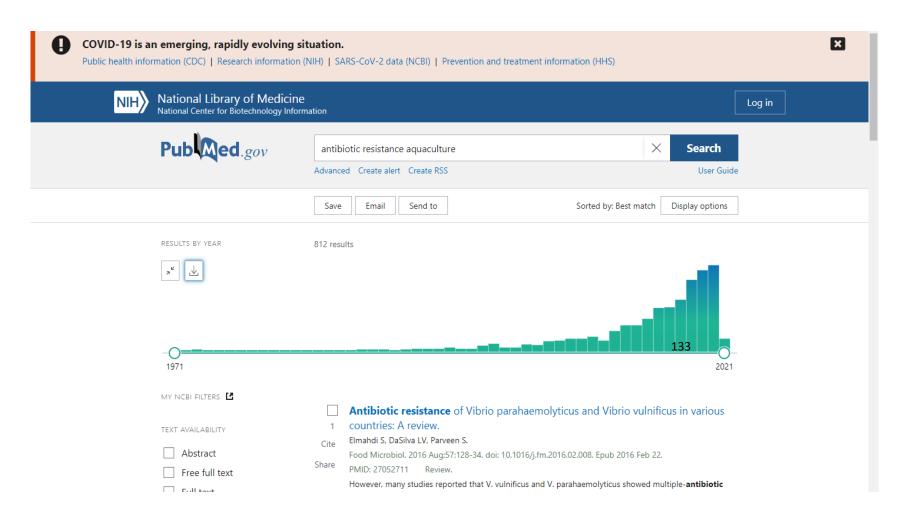
Antimicrobial resistance from all sectors end up in aquatic environment



Web of Science search "Antibiotic resistance aquaculture"

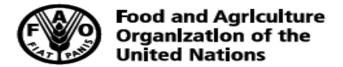


Pubmed search "antibiotic resistance aquaculture"



Aspects not considered in many publications on AMR associated with aquaculture

- Intrinsic resistance in many aquatic bacteria *Aeromonas* to ampicillin
- Selection of antibiotic resistant bacteria due to exposure to chemical pollutants, heavy metals
- AMR introduced into aquaculture environment from other sectors
- Change of microflora that happens during the processing of fish – at retail stage, flora present could be totally different

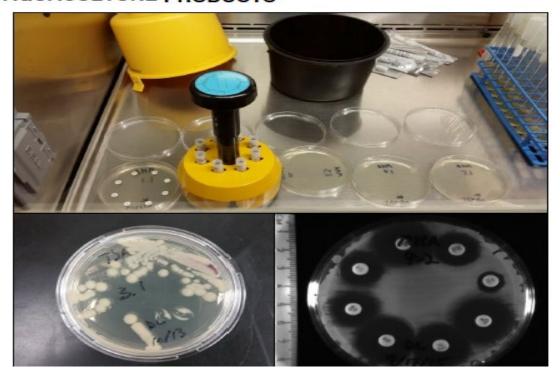


FIAA/C1191 (En)

FAO Fisheries and Aquaculture Circular

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THE PERFORMANCE OF ANTIMICROBIAL SUSCEPTIBILITY TESTING PROGRAMMES RELEVANT TO AQUACULTURE AND AQUACULTURE PRODUCTS





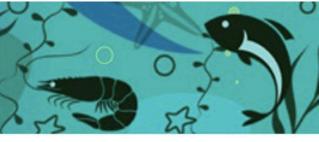
What is the way forward?

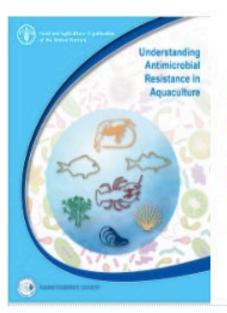
 We need to understand aquatic environment as reservoir of resistance determinants

 Integrated surveillance with human, veterinary and other environments will give a better picture of the selection pressure in different sectors

 One Health approach in collaboration with clinicians and veterinarians is needed to minimize antimicrobial use and selection pressure

Asian Fisheries Science







Volume 33S1 (2020)

Understanding Antimicrobial Resistance in Aquaculture

Full version of Volume 33S

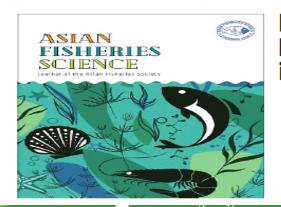
EDITED BY J. RICHARD ARTHUR, MELBA G. BONDAD-REANTASO, IDDYA KARUNASAGAR, CELIA

LAVILLA-PITOGO, BRETT MACKINNON AND DEE MONTGOMERY-BROCK

Date: 2020/12/25

Page: 1-124

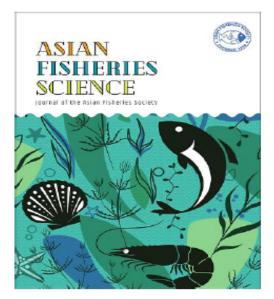




Review of National Residue Control Programme for Aquaculture Drugs in Selected Countries

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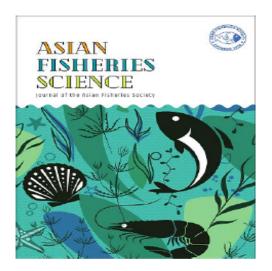
Complexities Involved in Source Attribution of Antimicrobial Resistance Genes Found in Aquaculture Products

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Contact-Zoonotic Bacteria of Warmwater Ornamental and Cultured Fish

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OUTPUTS AND ACTIVITIES OF FAO PROJECT FMM/RAS/298/MUL ON ANTIMICROBIAL RESISTANCE IN FISHERIES AND SUMMARY OF FAO'S RECENT WORK ON ANTIMICROBIAL RESISTANCE IN AQUACULTURE

Melba G. Bondad-Reantaso Rome, Italy

Celia R. Lavilla-Pitogo lloilo, Philippines

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Codex texts on foodborne antimicrobial resistance



Textes du Codex concernant la résistance aux antimicrobiens d'origine alimentaire R

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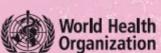
Textos del Codex sobre resistencia a los antimicrobianos transmitida por los alimentos



Food and Agriculture Organization of the United Nations

Organisation des Nations Unies pour l'alimentation et l'agriculture

Organización de las Naciones Unidas para la Alimentación y la Agricultura













Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials

Report of the FAO/WHO/OIE Expert Meeting

FAO Headquarters, Rome, 26-30 November 2007

Critically Important Antimicrobials for Human Medicine

6th Revision 2018

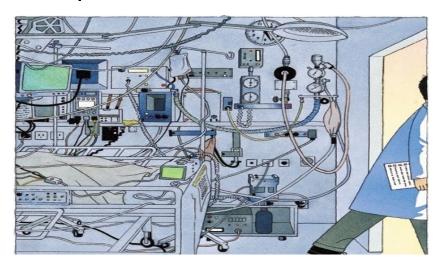
Ranking of medically important antimicrobials for risk management of antimicrobial resistance due to non-human use



- Aquaculture systems are a hub of several AMR pathogens
- Some may possess intrinsic resistance, some others may be selected by antibiotic use; some are derived from antibiotic use in other sectors
- Source of AMR found in aquatic bacteria is hard to trace
- Inter-sectoral collaboration is needed to trace the source of resistance determinants which is very complex

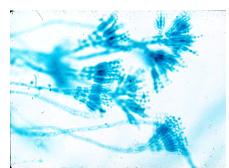
The continuing emergence of multi drug resistant organisms that cause infections in community and health care settings contribute substantially to the morbidity, prolonged hospital stay with increased treatment costs and mortality

Within the hospital, extensive data indicate that ICU's are the epicenter of the phenomenon



The Prophecy that went awry!

"On the whole, the position of antimicrobial agents in microbial therapy is highly satisfactory. The majority of bacterial infections can be cured simply, effectively and cheaply. The mortality and morbidity from bacterial diseases has fallen so low that they are no longer among the important unsolved problems of medicine..."



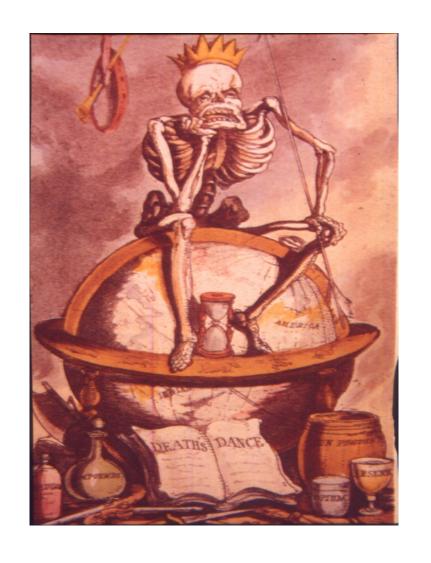
Jawetz E. Annu Rev Microbiol 1956; 10

 Resistance (often multiple) is an increasing threat to successful therapy of both hospital infections, aquaculture and veterinary sector

 Spreading & newly emerging patterns of resistance makes an ideal antibiotic a distant dream

Cause for emerging infections

- Change in human demographics and behavior
- Economic development and change in land use
- Increased transboundary movement of humans and animals
- Microbial adaptation and change
- Breakdown of public health measures and biosecurity in aquaculture and veterinary sector



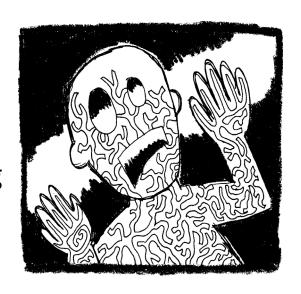
All animals are equal but some are more equal than others

George Orwell



Difficult to treat super bugs!

- Methicillin resistant Staphylococcus aureus
- Vancomycin resistant enterococci or staphylococci
- Extended spectrum beta lactamase producing gram negative bacilli
- Multidrug resistant Pseudomonas or Acinetobacter
- Pan resistant gram negative bacilli (our worst nightmare)



The plague....





Gram Negative Pathogens

Antibiotics with gram negative coverage

- ß lactams Cephalosporins, Ampicillin, Penicillins
- Aminoglycosides
- Flouroquinolones
- Carbapenems
- Trimethoprim sulphamethoxazole
- Tetracyclines
- Macrolides
- Chloramphenicol
- Nalidixic acid

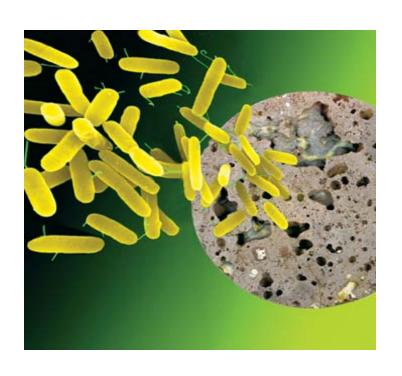


Unintended Consequences of Antibiotic Therapy

 'Collateral damage' is a term used to refer to ecological adverse effects of antibiotic therapy; namely, the selection of drugresistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms

Paterson DL. Clin Infect Dis 2004;38(Suppl 4):S341-S345

ESBL producing organisms



Most common
 E.coli & Klebsiella

Others

Proteus, Enterobacter, Citrobacter, Providencia, Morganella, Shigella, Serratia, Pseudomonas

Pseudomonas

- Are intrinsically resistant to NS penicillins, 1st and 2nd GC & Cotrimoxazole
- Susceptible to aminoglycosides, 3rd and 4th GC, FQ, Aztreonam and ticarcillin/piperacillin
- Cefotaxime and Ceftriaxone are not the ideal 3GC
- Multidrug resistance can emerge during course of treatment



"Know thy enemy and know thyself: In a hundred battles you will never be in peril"

Sun Tzu from "The art of war"

Key factors in control......



Avoid Inadequate
Antibiotic
Therapy

Stop the spread

Combinations that do not go together....

Antibiotics	Organism
Amino glycosides	Streptococcus
TMP/SMX	Klebsiella
Beta lactams	MRSA
Cephalosporin	Enterococcus
1 st generation Cephalosporin	Salmonella
Cefotaxime	Pseudomonas
Cephalosporin	ESBL producing K.pneumo/E.coli
Meropenem	S. maltophilia
Ertapenem	Psudomonas aeruginosa



NATIONAL POLICY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE INDIA



2011

Directorate General of Health Services

Ministry of Health & Family Welfare Nirman Bhawan, New Delhi

- Monitor antimicrobial resistance
- Regulations for use
- National surveillance system for antibiotic resistance,
- Monitoring prescriptions by audits
- Monitoring use of antibiotics

Bad Bugs, No Drugs

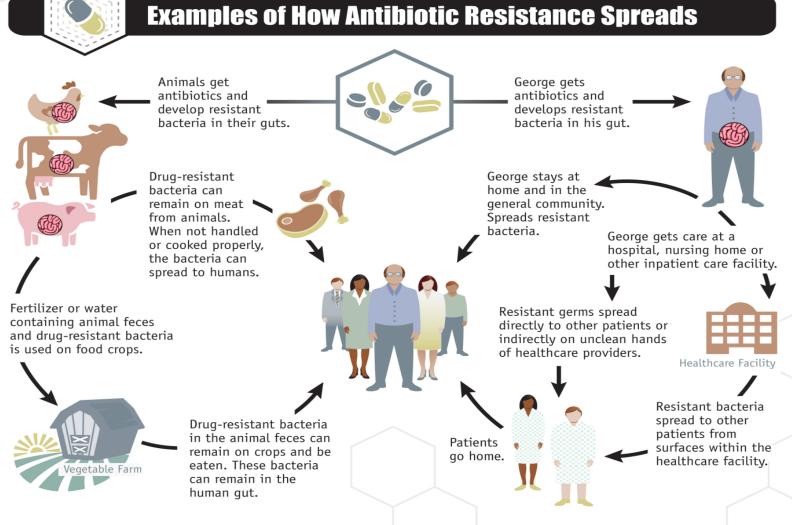
As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews







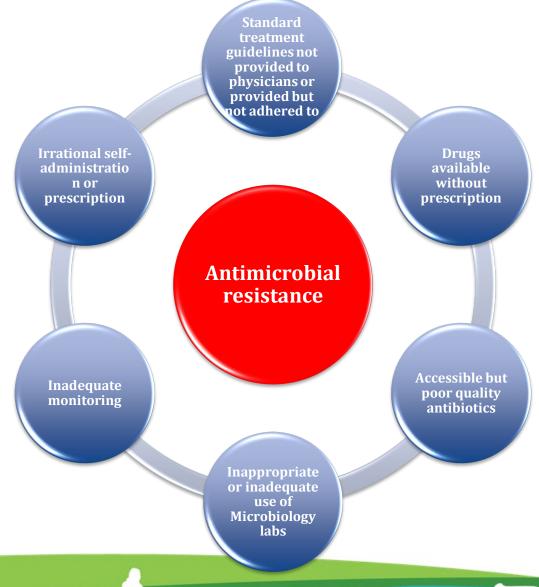




Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

Resistance is accelerated through inappropriate use of

antimicrobials





INSIDE HOSPITALS, THEY CAN BE LURKING....



Colonized patients





Biofilms





Handwash Basins



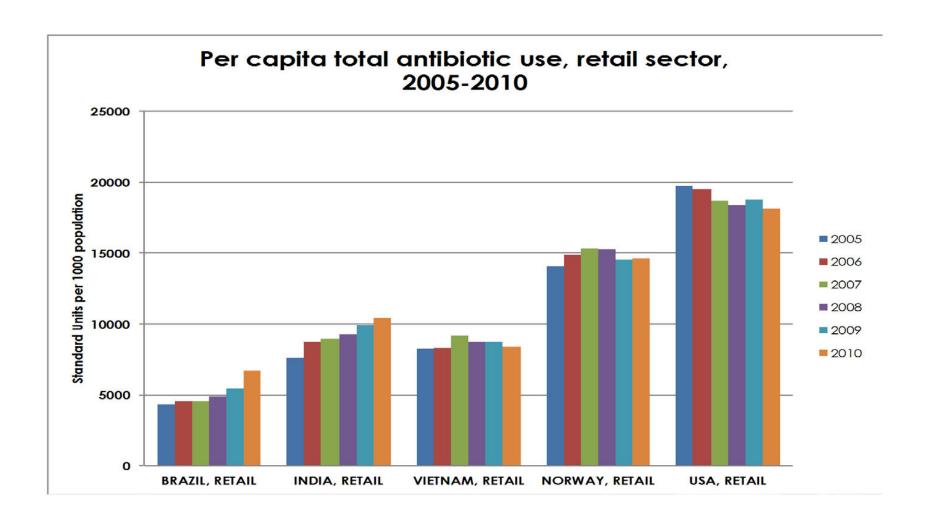
Toilet Rims



Endoscopes



Antibiotic consumption is increasing in developing countries...



ANTIBIOTIC RESISTANCE WHAT YOU CAN DO



Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.



- Only use antibiotics when **prescribed** by a certified health professional
- Always take the **full prescription**, even if you feel better
- 3 Never use left over antibiotics
- 4 Never share antibiotics with others
- Prevent infections by regularly washing your hands, avoiding contact with sick people and keeping your vaccinations up to date

www.who.int/drugresistance

#AntibioticResistance









Preventive strategies

Curtail production, prescription and consumption of antibiotics both in human & veterinary medicine

Education of the general population, of healthcare personnel, veterinarians and pharmacists about means of prevention and proper Rx of infections

Offering access to clean, affordable water and sanitation to all people

Promoting vaccination, and by introducing animal breeding and foodproduction processes which render the use of antibiotics unnecessary

THANK YOU

ANTIBIOTICS USE-RESPONSIBLY



Hospital wastes seed carbapenem-resistance pathogens to Indian urban water systems



