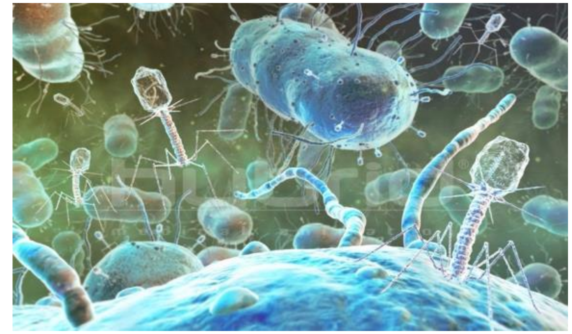



Antibiotics—*Resistance Is Futile!*

Walter Jakubowski & Ryan Reinke

DPR in California

- **Legislation (SB 918 and SB 322)**
  - Modified **Water Code**
  - Finalize **groundwater replenishment** regulations (completed June 2014)
  - Develop **Surface Water Augmentation** regulations (Draft in Sept 2016; Final in Dec 2016)
  - Required an **Expert Panel** to evaluate the feasibility of criteria for DPR

Expert Panel Charge

Per California Water Code Section 13565(a)(1)

- Advise DDW on **public health issues** and **scientific and technical matters** regarding water recycling criteria for DPR.
- Assess **additional areas of research** needed to establish DPR regulatory criteria.

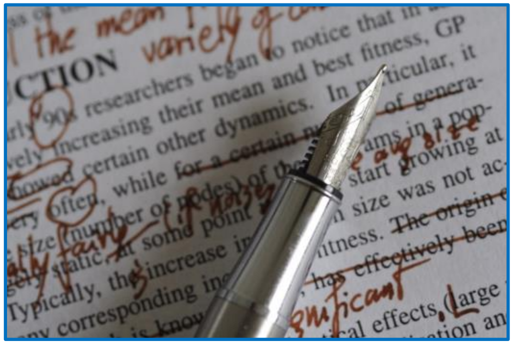
NWRI

Panel Organization

- Sponsored by the SWRCB Division of Drinking Water
- Administered under contract by NWRI

Briefing Paper Topics

1. Bioanalytical Tools for Water Analyses (Bioassays)
2. Quantifying Treatment Facility Reliability
3. Analytical Approaches for Measuring Chemical Water Quality
4. Pathogen Monitoring Methods
5. **Antibiotic Resistant Bacteria and Antibiotic Resistance Genes**
6. Comparative Health Risks
7. Public Health Surveillance



Direct Potable Reuse Briefing Paper

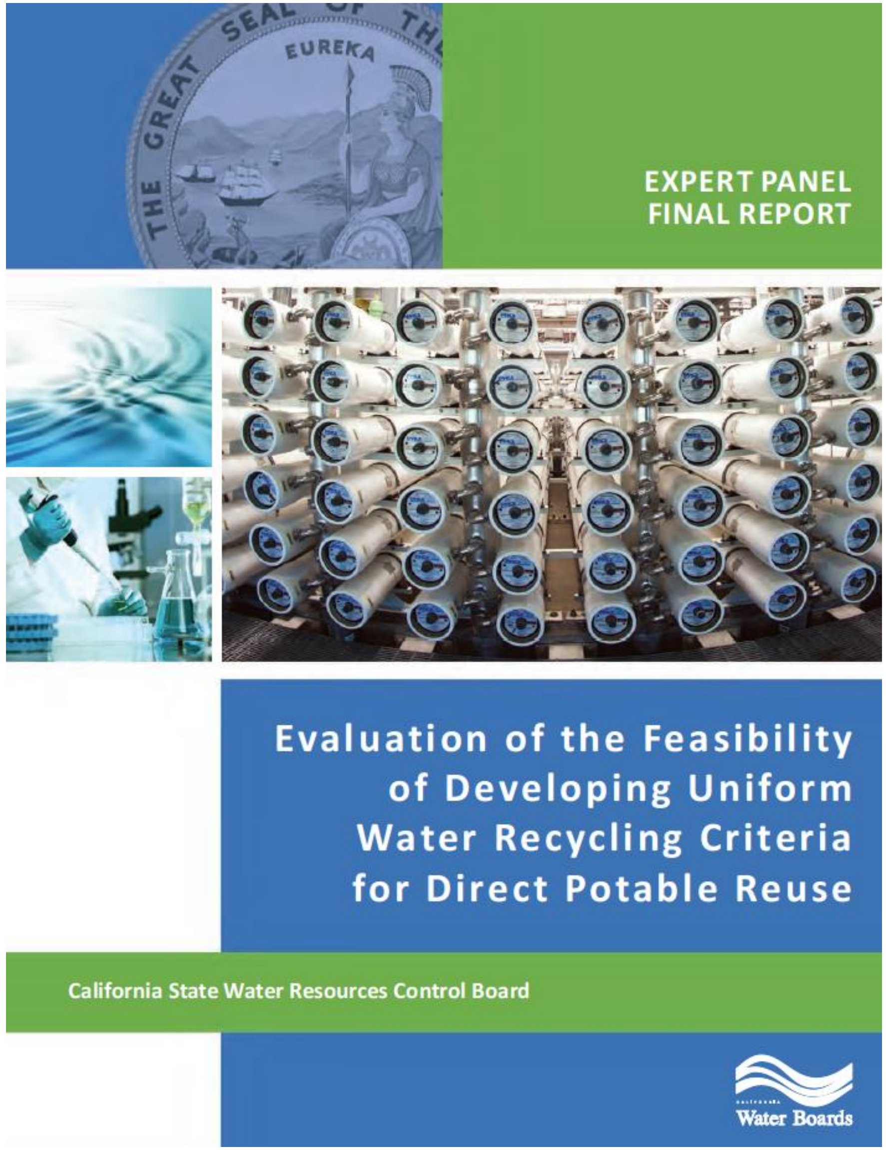
Paper #5
Antibiotic Resistant Bacteria and Antibiotic Resistance Genes

Prepared By:

NWRI Expert Panel
on the Feasibility of Developing Criteria for Direct Potable Reuse

Authored By:

Walter Jakubowski, M.S.
Ryan Reinke, Ph.D.
Kellogg Schwab, Ph.D.



EXPERT PANEL
FINAL REPORT

Evaluation of the Feasibility of Developing Uniform Water Recycling Criteria for Direct Potable Reuse

California State Water Resources Control Board

Water Boards

ARB/ARG Chapter Outline

1. **Introduction**
   - Microbial Resistance
   - Antimicrobials and Antibiotics
   - Antimicrobial Resistance Mechanisms
   - Global and National Burden of Antibiotic Resistance
   - Antibiotic Usage in the U.S.

2. **Community and Environmental Sources/Exposure Routes for ARB/ARG**

3. **Significance of Sources for ARB/ARG Exposure**

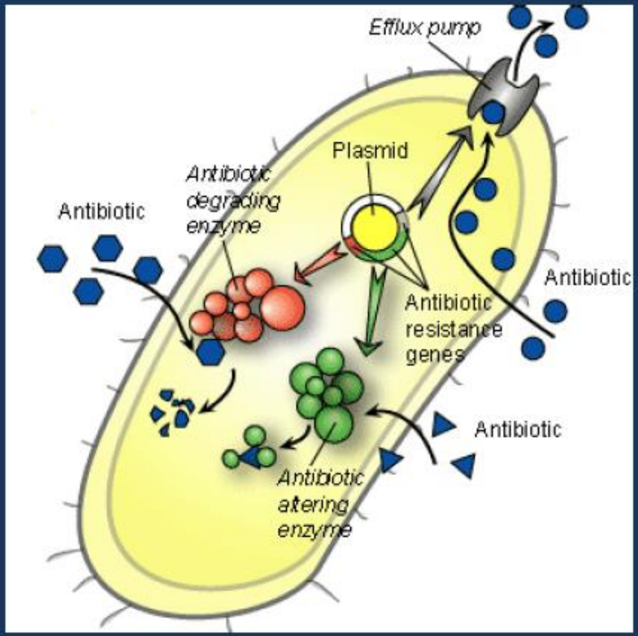
4. **Methods for Assessing Antibiotic Resistance (AR) in Water Matrices**
    - Culture-Based Methods
    - Molecular Methods
5. **Occurrence And Removal of ARB/ARG Through Water And Wastewater Treatment**
    - Occurrence and removal in WWTPs
    - Antibiotic resistance occurrence and removal by drinking water treatment processes
    - Disinfection and advanced oxidation processes
6. **Findings**
7. **Recommendations**

References

Antimicrobials and Antibiotics

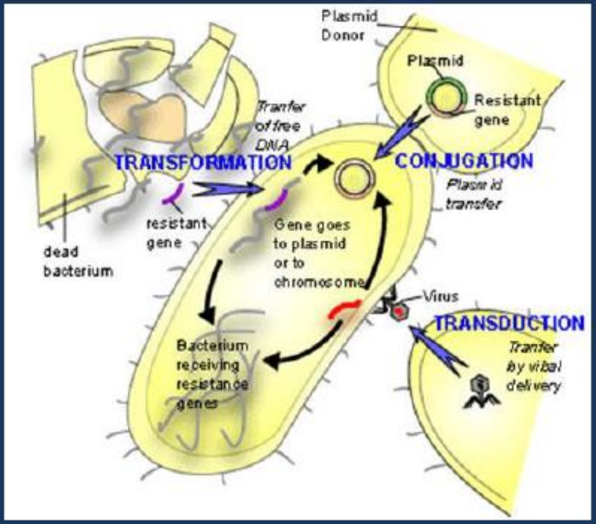
- Antimicrobials—chemicals that kill or limit the growth of microorganisms
- Antibiotics—synthetic or naturally occurring antibacterial compounds used as pharmaceuticals or growth promoters
- Antibiotic Resistance—the ability of bacteria to survive and grow in the presence of a compound that would normally kill them

Antibiotic Resistant Bacteria (ARB)



The ability of a bacterium to prevent an antibiotic from adversely affecting that isolate, strain, or group.

Horizontal Gene Transfer; Antibiotic Resistance Genes (ARGs)



Slide courtesy Jean McLain

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Editorial

A Global Antimicrobial Conservation Fund for Low- and Middle-Income Countries

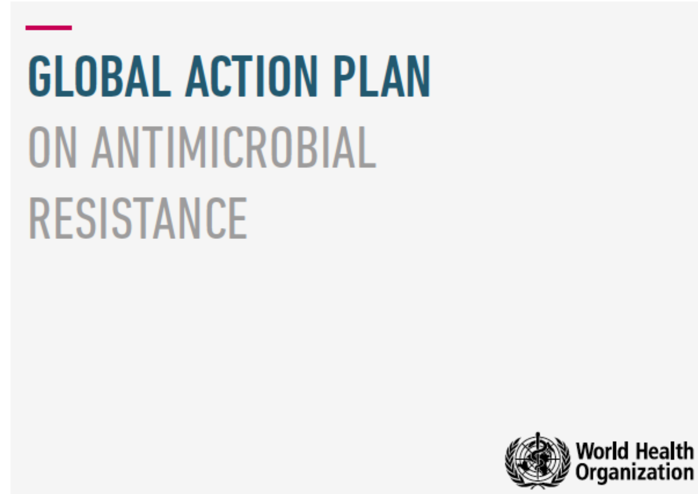
On 21st September 2016, for only the 4th time in history, a health topic will take centre stage at a United Nations General Assembly (UNGA) high-level meeting where heads of state are present. A day-long session has been convened to discuss the global threat from the lack of access to antimicrobials and from increasing antimicrobial resistance (AMR). The main focus will be on antibiotic resistance. The involvement of the UN underlines the significance of this threat to public health, food security, global economic growth, and progress towards the 2030 Sustainable Development Goals.[1]

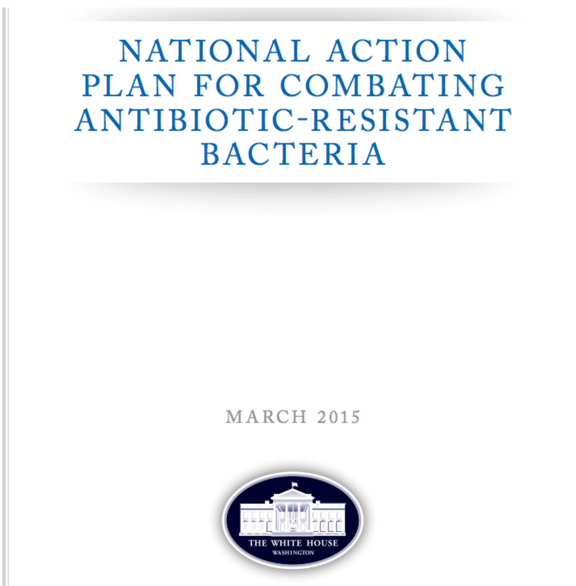
Like climate change, AMR depends on effectively managing global public goods and common resources, in this case antimicrobials, whose use drives resistance, and thereby deprives others of their benefits. Such management requires interdependent action in three areas: conservation, access and innovation (figure 1).

Akin to the reduction in use of fossil fuels to curb pollution levels that impact on climate, conserving antimicrobials to limit development of resistant microbes, thereby ensuring the continuation of their efficacy for all in need, is a critical strategic response. This must occur in parallel with existing efforts to promote greater, appropriate access to antimicrobials for the millions of people who practices. Historically, these practices rely on sub-therapeutic doses of antibiotics for animal growth promotion (AGP), a practice banned in the European Union since 2006, as well as wide scale treatment of healthy animals to prevent them getting sick (metaphylaxis), and hence avoiding reduced productivity. Veterinarian prescribing controls a comparatively small percentage of total use in animals.

Although not confined to LMICs, the drivers of antimicrobial overuse and misuse in human health are multifactorial and magnified in these settings by the still massive burden of infectious diseases, high poverty levels leading to lack of access to clean water, sanitation and hygiene, unregulated access to antimicrobials over-the-counter and from street-sellers without prescription, cultural perceptions of antimicrobials (antibiotics in particular) as confirmation of illness and vindication of being unwell, and lack of education of healthcare professionals and the public in terms of the adverse effects that inappropriate antimicrobial use exacts on the public health. In addition, aggressive marketing and a limited regulatory and enforcement capacity of pharmaceutical company practice can drive overuse in some settings.


ANTIMICROBIAL RESISTANCE
Global Report on Surveillance
2014
World Health Organization


GLOBAL ACTION PLAN
ON ANTIMICROBIAL
RESISTANCE
World Health Organization


NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA
MARCH 2015
THE WHITE HOUSE
WASHINGTON


HHS.gov
U.S. Department of Health & Human Services
Office of the Assistant Secretary for Health
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Public Health Offices
Advisory Committees
HHS Home > ASH > Advisory Committees > Combating Antibiotic-Resistant Bacteria
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)
About Us
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Incentives
National Action Plan on CARB
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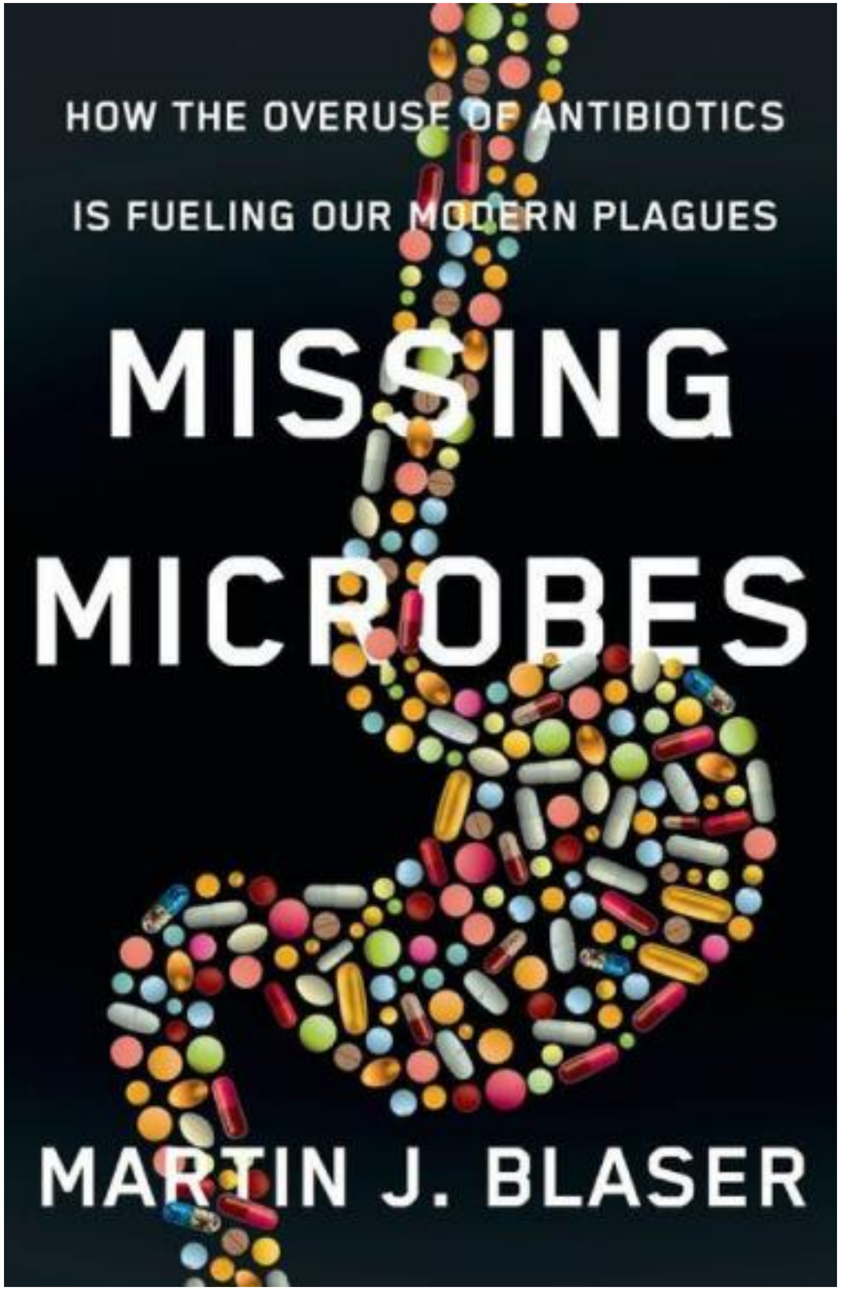
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)
In March 2015, the U.S. Department of Health and Human Services (HHS) announced the establishment of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council). The Advisory Council provides advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the implementation of Executive Order 13676, - PDF including the National Strategy for Combating Antibiotic-Resistant Bacteria - PDF (Strategy) and the National Action Plan for Combating Antibiotic-Resistant Bacteria - PDF (Action Plan).
I would like info on...
The upcoming September 19, 2016 public meeting
About PACCARB
Learn about why PACCARB was established and what it does.


HOW THE OVERUSE OF ANTIBIOTICS
IS FUELING OUR MODERN PLAGUES
MISSING
MICROBES
MARTIN J. BLASER

Working Groups

PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA

The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) has established 5 working groups, based on the 5 goals of the National Action Plan on Combating Antibiotic-Resistant Bacteria (CARB). Each of these working groups has a specific mission, a timeline, and identified membership which includes PACCARB voting members, PACCARB liaison members, and federal officials. The working groups are chaired by PACCARB members. External stakeholders will be invited to provide information as deemed appropriate by the working group chairs.

Working Group #1 on Antibiotic Stewardship

Mission: Provide the full Advisory Council a summary of findings on the federal and non-federal efforts to slow the emergence of resistant bacteria and prevent the spread of resistant infections.

Working Group #2 on One Health Surveillance

Mission: Provide the full Advisory Council a summary of findings on the federal and non-federal efforts to strengthen national One-Health surveillance efforts to combat resistance.

Working Group #3 on Diagnostic Innovations

Mission: Provide the full Advisory Council a summary of findings on the federal and non-federal efforts to advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.

Working Group #4 on Treatment, Prevention, and Control Research & Development

Mission: Provide the full Advisory Council a summary of findings on federal and non-federal efforts to accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.

Working Group #5 on International Collaboration on CARB

Mission: Provide the full Advisory Council a summary of findings on the federal and non-federal efforts to improve international collaboration and capacities for antibiotic resistance, prevention, surveillance, control, and antibiotic research and development.

Content last reviewed on November 10, 2015

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:

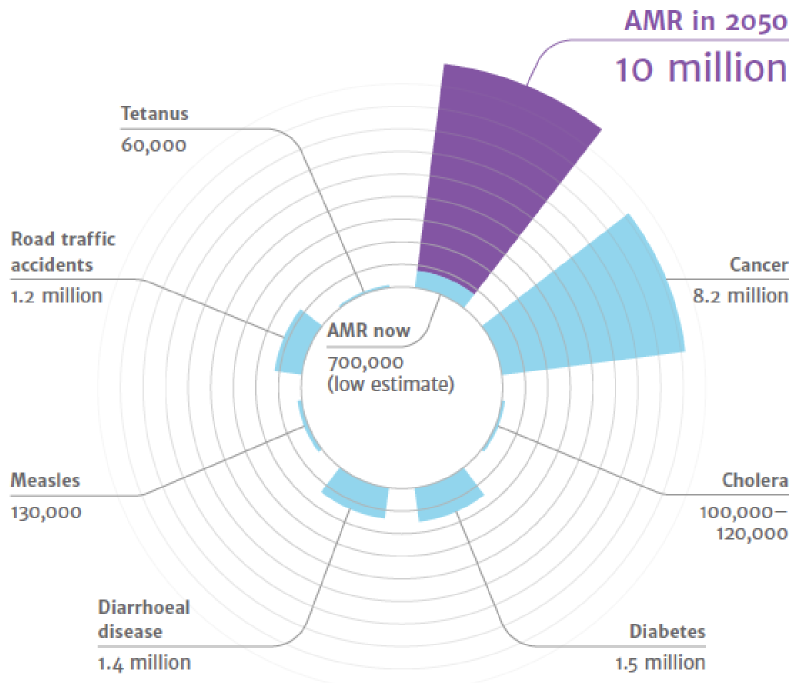
FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2016

DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



Sources:
Diabetes: www.who.int/mediacentre/factsheets/fs312/en/ Cancer: www.who.int/mediacentre/factsheets/fs297/en/
Cholera: www.who.int/mediacentre/factsheets/fs107/en/ Diarrhoeal disease: www.sciencedirect.com/science/article/pii/S0140673612617280
Measles: www.sciencedirect.com/science/article/pii/S0140673612617280 Road traffic accidents: www.who.int/mediacentre/factsheets/fs358/en/
Tetanus: www.sciencedirect.com/science/article/pii/S0140673612617280

Review on Antimicrobial Resistance

Global and National Burden of Antibiotic Resistance

- World—difficult to estimate due to differences in national surveillance and reporting systems

- Europe—estimated at 25,000 deaths annually and cost of 1.5 billion Euros

- United States—2 million infections and 23,000 deaths annually at a direct cost of $20 billion plus $30 billion in productivity losses

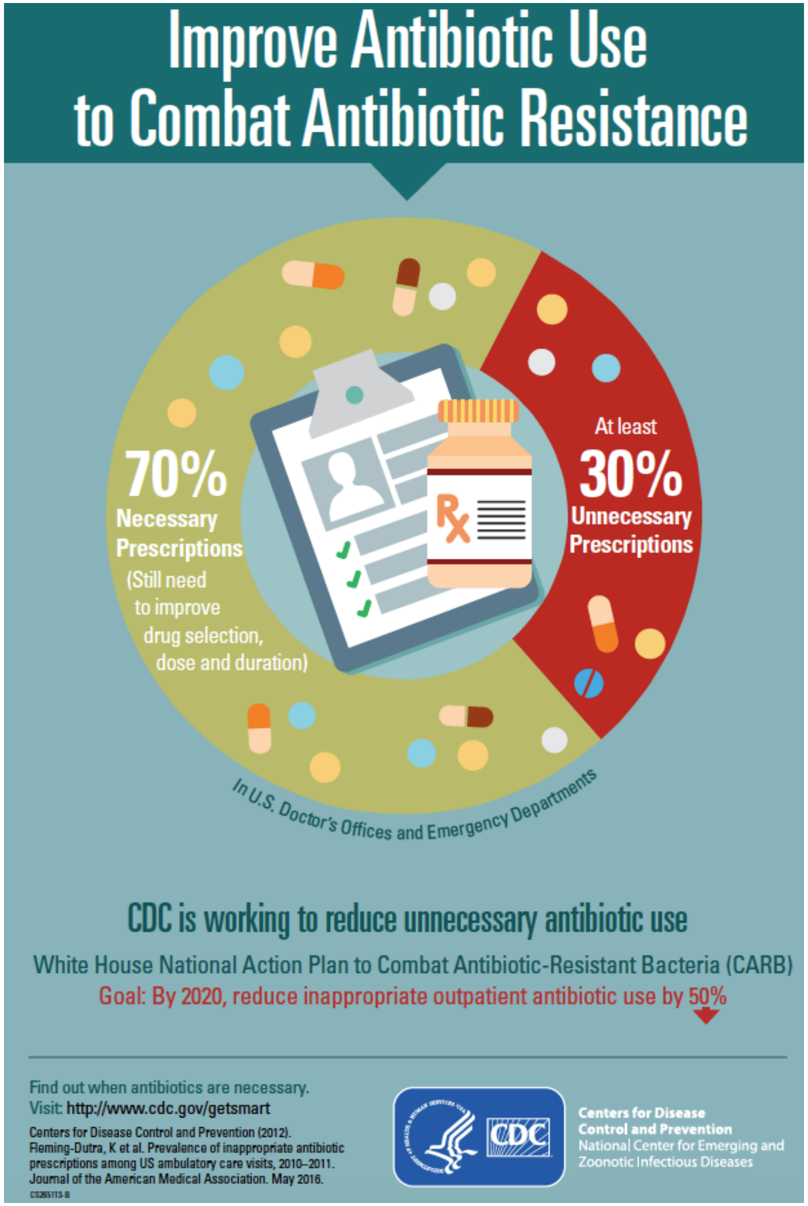
Drug-Resistant Microorganism Threats in the United States[a]

Hazard Level	Microorganism
Urgent a	*Clostridium difficile* (CDIFF)
	Carbapenem-Resistant Enterobacteriaceae (CRE)
	Neisseria gonorrhoeae
Serious	Multidrug-Resistant *Acinetobacter*
	Drug-Resistant *Campylobacter*
	Fluconazole-Resistant *Candida*
	Extended Spectrum beta-lactamase (ESBL) Enterobacteriaceae
	Vancomycin-Resistant *Enterococcus*
	Multidrug-Resistant *Pseudomonas aeruginosa*
	Drug-Resistant Non-Typhoidal *Salmonella enterica*
	Drug-Resistant *Salmonella typhi*
	Drug-Resistant *Shigella*
	Methicillin-Resistant *Staphylococcus aureus* (MRSA)
	Drug-Resistant *Streptococcus pneumoniae*
	Drug-Resistant Tuberculosis
Concerning	Vancomycin-Resistant *Staphylococcus aureus*
	Erythromycin-Resistant Group A *Streptococcus*
	Clindamycin-Resistant Group B *Streptococcus*

[a]Adapted from CDC, 2013

Antibiotic Usage in the United States

- Most are for food-producing animals—33 million pounds in 2014
- California recently passed the most stringent law in the country on usage of antibiotics in food-producing animals
- More than 7.25 million pounds of antibiotics were sold for human consumption in 2011 (about 20% of the total)



Improve Antibiotic Use
to Combat Antibiotic Resistance
70%
Necessary
Prescriptions
(Still need
to improve
drug selection,
dose and duration)
At least
30%
Unnecessary
Prescriptions
In U.S. Doctor's Offices and Emergency Departments
CDC is working to reduce unnecessary antibiotic use
White House National Action Plan to Combat Antibiotic-Resistant Bacteria (CARB)
Goal: By 2020, reduce inappropriate outpatient antibiotic use by 50%
Find out when antibiotics are necessary.
Visit: http://www.cdc.gov/getsmart
Centers for Disease Control and Prevention (2012).
Fleming-Dutra, K et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. Journal of the American Medical Association. May 2016.
CDC
Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

Community and Environmental Sources/Exposure Routes for ARB/ARG

- Land application of animal waste and sewage sludge affects soil and source waters
- Hospital waste

Significance of Sources for ARB/ARG Exposure

Although food-producing animals, hospitals and inappropriate prescribing are all important, there is currently no quantitative method for assessing the risks from these and other sources.

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Get Smart for Healthcare

Get Smart for Healthcare
- Overview and Evidence to Support Stewardship
- Implementation Resources
- Stewardship Program Examples
- Get Smart Week
- Get Smart for Healthcare Buttons

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Antibiotic use in nursing homes

Get Smart About Antibiotics Week: November 18–24, 2013

Did you know?

1. Antibiotic resistance is one of the world's most pressing public health threats.
2. Antibiotics are the most important tool we have to combat life-threatening bacterial diseases, but antibiotics can have side effects.
3. Antibiotic overuse increases the development of drug-resistant germs.
4. Patients, clinicians, healthcare facility administrators, and policy makers must work together to employ effective strategies for improving antibiotic use — ultimately improving medical care and saving lives.

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Scope of the problem in nursing homes

- Antibiotics are among the most commonly prescribed medications in nursing homes.
- Up to 70% of long-term care facilities' residents receive an antibiotic every year.
- Estimates of the cost of antibiotics in the long-term care setting range from $38 million to $137 million per year.
- Among the antibiotic-resistant organisms most commonly found in nursing home populations are multidrug-resistant Gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE).

Download [PDF - 435 KB]

Why focus on nursing homes?

- Many long-term care residents can be "colonized" with bacteria, meaning that germs can live on the skin, wound surfaces or even in the bladder without making the person sick. Challenges with separating colonization from true infection can contribute to antibiotic overuse in this setting.
  - Studies have consistently shown that about 30%-50% of frail, elderly long-term care residents can have a positive urine culture even without any symptoms of a urinary tract infection. Unfortunately, many of these patients are placed inappropriately on antibiotics.
- Poor communication when patients transfer facilities, for example from a nursing home to a hospital, can result in antibiotic misuse.
- Antibiotic-related complications, such as diarrhea from *C. difficile*, can be more severe, difficult to treat, and lead to more hospitalizations and deaths among people over 65 years. Long-term care facility residents are particularly at risk for these complications.

Antibiotic resistance in long-term care is associated with:
- Increased risk of hospitalization
- Increased cost of treatments
- Increased risk of death

Community and Environmental Sources/Exposure Routes for ARB/ARG

- Land application of animal waste and sewage sludge affects soil and source waters
- Hospital waste

Significance of Sources for ARB/ARG Exposure

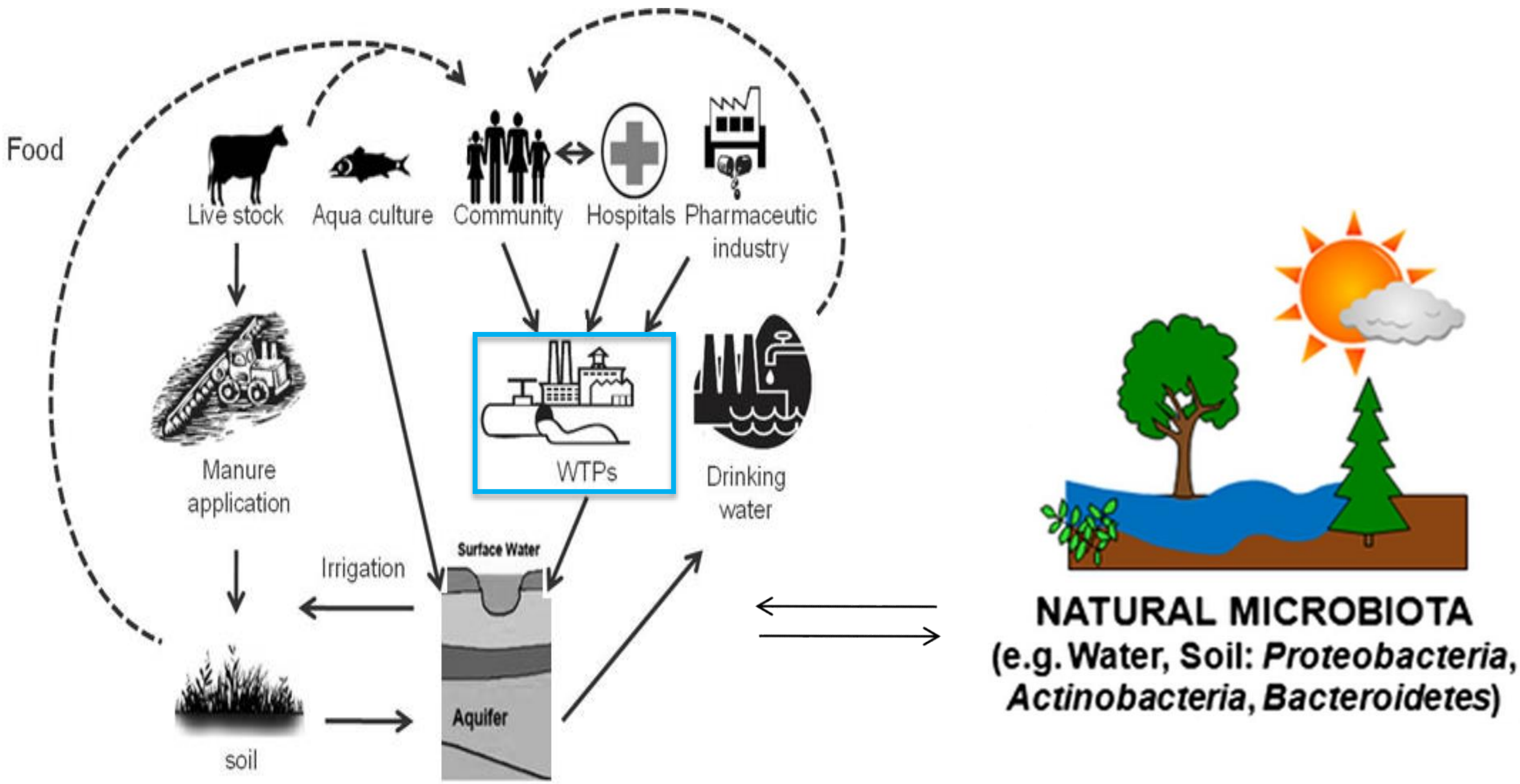
Although food-producing animals, hospitals and inappropriate prescribing are all important, there is currently no quantitative method for assessing the risks from these and other sources.


Superbugs in the Supply Chain:
How pollution from antibiotics factories in India and China is fuelling the global rise of drug-resistant infections
Changing Markets
This report was researched and written by Changing Markets and Ecostorm.
changingmarkets.org
Published in October 2016

Antibiotic Resistance and Water Treatment

Antibiotic Resistance and Water Treatment

Anthropogenic Environmental



Source: http://www.eawag.ch/en/department/surf/projects/antibiotica-resistance/

Antibiotic Resistance

- Study of AR is unlike traditional microbial hazards.
  - ARG in pathogens and non-pathogens can cause adverse affects.
  - The genes themselves can be considered a hazard.
    - Even in the absence of viable microbes.
  - ARG have been found in every environment on earth: with or without anthropogenic influence.

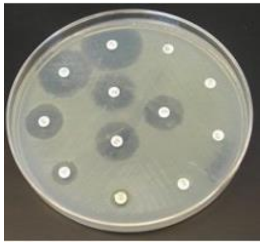
- Gene transfer is important.

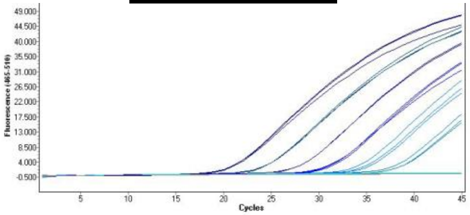
- Risk assessment is difficult with AR.

- Can assess occurrence and quantity.

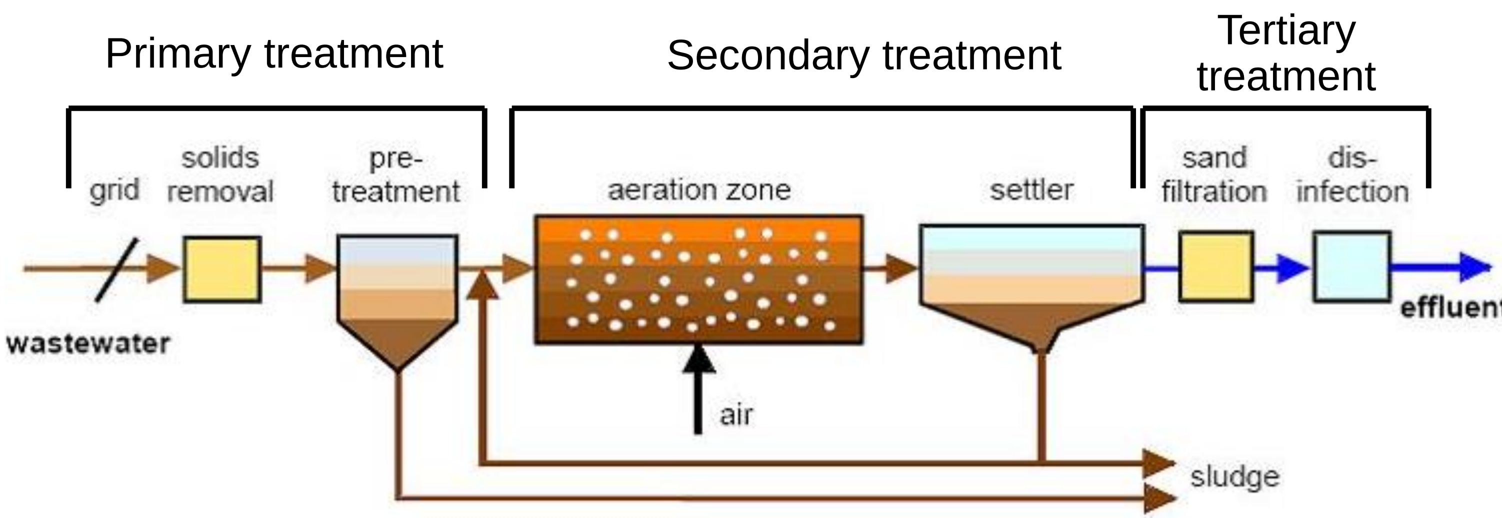
Antibiotic Resistance Methods

- Two basic approaches
  - Culture-based
    - Testing the resistance of culturable bacteria to one or more drugs using culture media with the antibiotic(s) of choice.
    - Will detect more types of resistant mechanisms but from a smaller group of organisms.
  - Molecular
    - PCR is the predominant methodology used.
    - Testing the DNA in a sample for the presence and/or quantity of pre-determined ARG targets.
    - Will detect a smaller number of resistant mechanisms but from a larger number of sources.
  - There are currently no standardized methods for testing AR in water.





Wastewater Treatment



- Activated sludge
- Trickling filter
- Rotating biological contactors

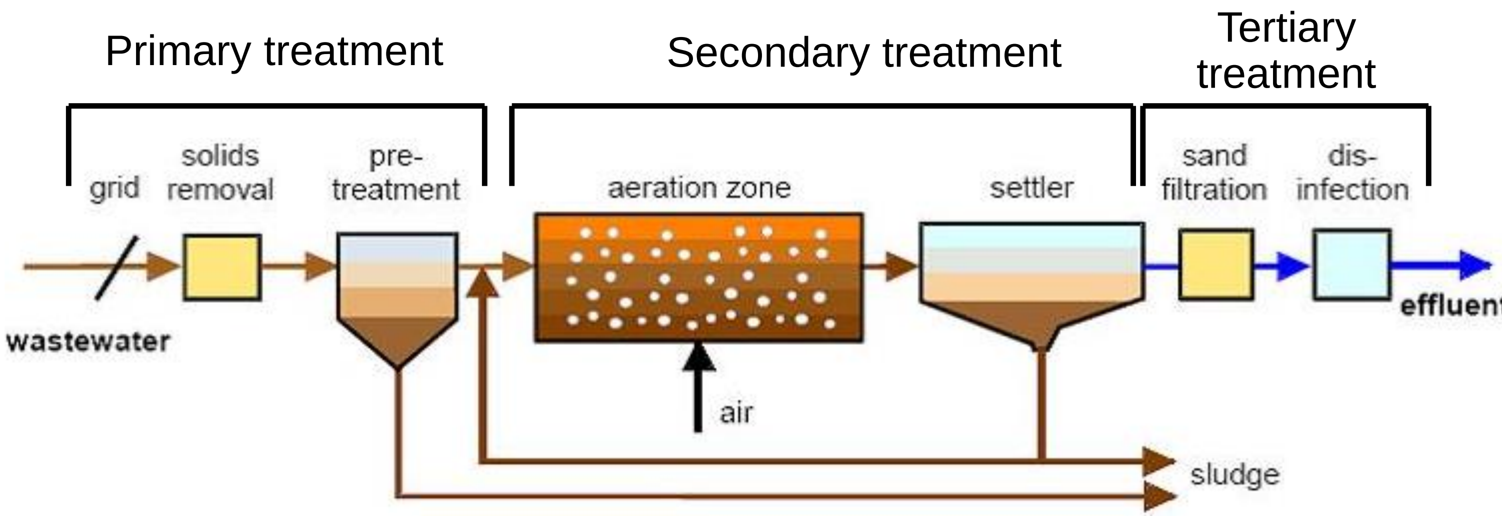
- Media filtration
- Membrane filtration
- Nutrient removal
- Disinfection

Image courtesy of Wikipedia

ARB/ARG in WWTPs

- All clinically relevant ARGs have been found in raw sewage.
- Resistance to β-lactams, tetracycline, macrolides, and sulfa-drugs are the most commonly reported in wastewater matrices.
- Pathogen and indicator removal by wastewater treatment processes has been well studied but ARB/ARG have been have not been as well characterized.

ARB/ARG Removal



<u>Raw sewage AR concentrations</u>

ARGs:

10^7 to 10^{11} copies/100ml

ARB:

10^5 to 10^8 CFU/100ml

<u>AR reductions: raw to 2º</u>

ARGs: <1 to 3-log reduction

ARB: <1 to 5-log reduction

<u>AR reductions: raw to 3º</u>

ARGs: 1 to 7-log reduction

ARB: 1 to 5-log reduction

<u>Factors affecting occurrence and removal:</u>

- **Geographic location.**
- **Type and extent of treatment.**
- **Operational parameters.**
- **Analytical methods and/or AR target.**

Image courtesy of Wikipedia

ARB/ARG in WWTPs

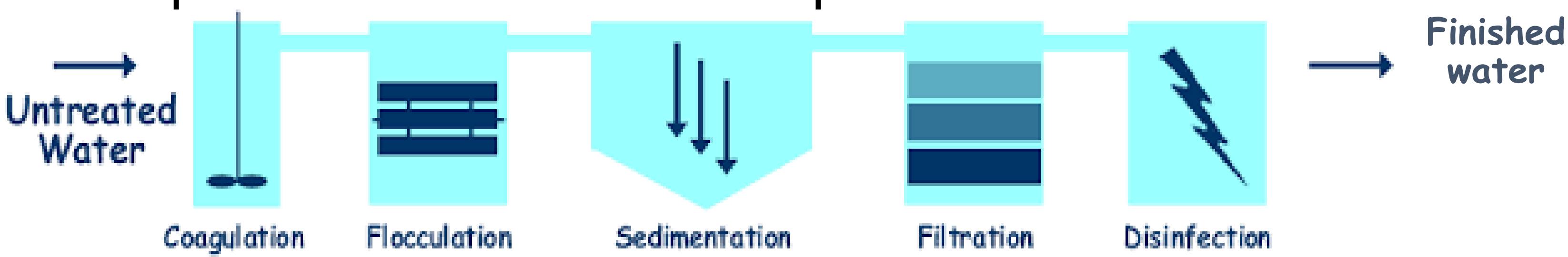
- No consensus on optimal treatment configuration for AR removal.
- Best reported ARG reductions:
  - MBR + disinfection
    - *sul1*= 2-3 log decrease
    - *tet*= 6-7 log decrease
  - Activated sludge + media filtration + UV or Chlorine
    - *sul1*= 2-4 log decrease
    - *tet*= 2-4 log decrease

Potable Water Treatment

Advanced treatments

- Biological aeration
- Membrane filtration
- Activated carbon
- Advanced oxidation

Primary treatment



Source water concentrations

AR Heterotrophs:

ND-10^5/100ml

ARGs:

ND-10^6/100ml

AR reductions from source water

AR Heterotrophs:

4 to 6-log reduction

ARGs:

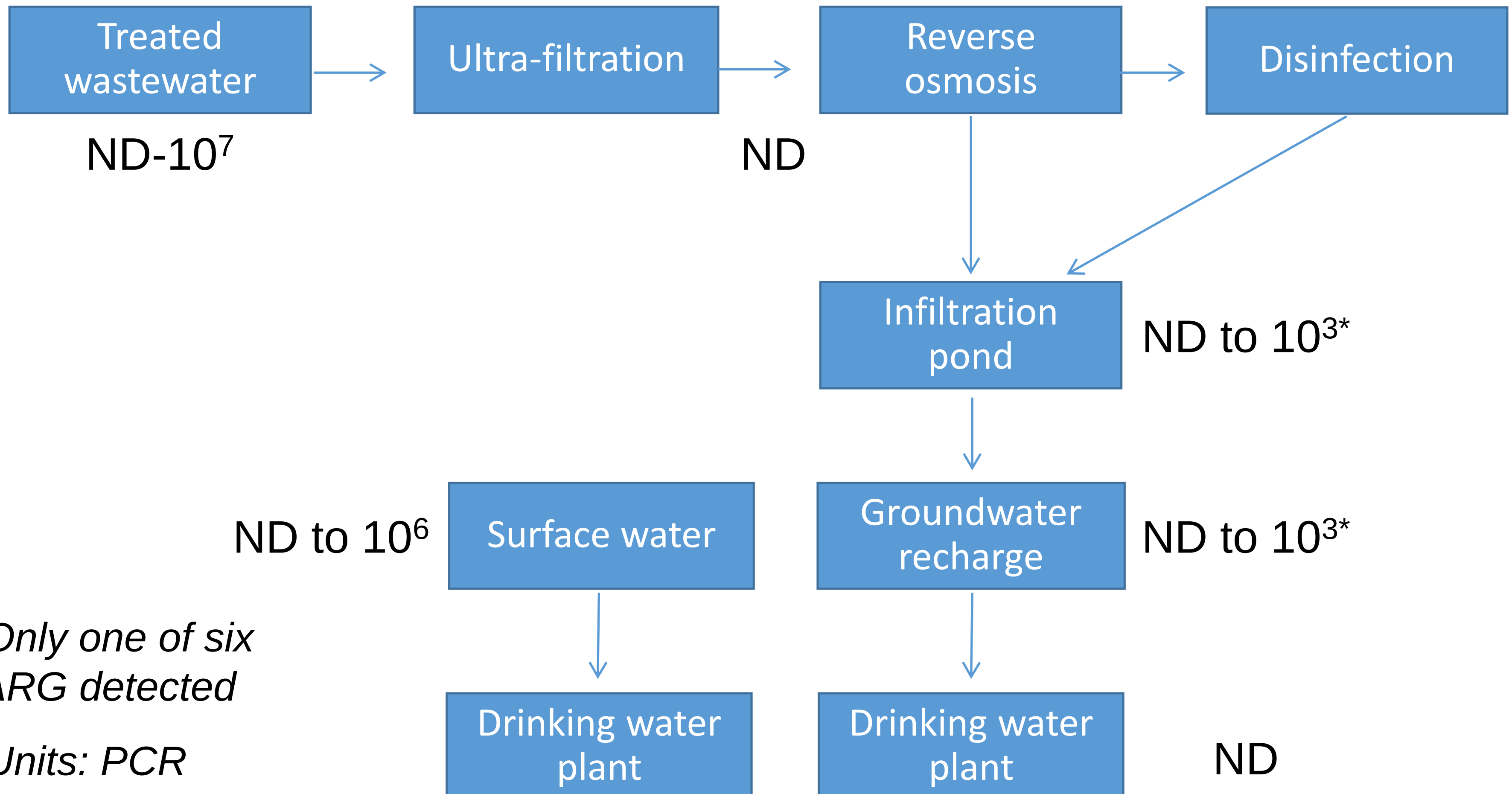
<1 to 2-log

Image courtesy of http://theacesinc.com/2015/03/21/freshening-up-freshwater-systems/

Disinfection/Filtration

Process	Application	Concentration range	ARB $\log_{10}$ removal	ARG $\log_{10}$ removal
Chlorine	Drinking water	15-200 mg x min./L	2-4 logs	NR
	WWTP disinfection (CA title 22)	450 mg x min./L	2- >4 logs	1-2 logs
UV	WWTP disinfection	10-200 mJ/cm^2	4-5 logs	<1-4 logs
Ozone	WWTP disinfection	0.1-200 mg x min./L	2-4 logs	1-3 logs
Ultrafiltration/ nanofiltration	AWTF	NA	NR	4- >5.9 logs
Reverse osmosis	AWTF	NA	NR	NR

ARG Removal by AWTF



* *Only one of six ARG detected*

Units: PCR copies/100 ml

Data from Bockelmann et. al. 2009

DPR Panel Findings

- AR is a **valid and serious** worldwide public health concern.
- ARB and ARG **are found** in wastewater and in other environments not necessarily impacted by wastewater.
- **No standard tests** for ARB/ARG in environmental samples.
- **Determining ARB/ARG concentrations in water** can help assess treatment process removals of antibiotic resistance.
- **Risk levels from ARB/ARG in water unknown**; but, ARB/ARG in waters subjected to DPR treatment **would likely be lower than that from current water sources entering drinking water treatment facilities**.

Findings (con't)

- **WT technologies** (e.g., activated sludge, tertiary filtration, and chlorine disinfection) **reduce ARB and ARG concentrations.**

- The current knowledge base regarding urgent and serious potentially waterborne drug-resistant bacteria **is limited** for known antibiotic resistance determinants and their fate during treatment.

- **Information about the performance of advanced water treatment processes related to ARG removal is limited.**

- **A combination of secondary wastewater treatment and advanced water treatment processes** leading to a finished potable water **is likely to reduce ARB and ARG in recycled water to levels well below those found in conventional treated drinking water.**

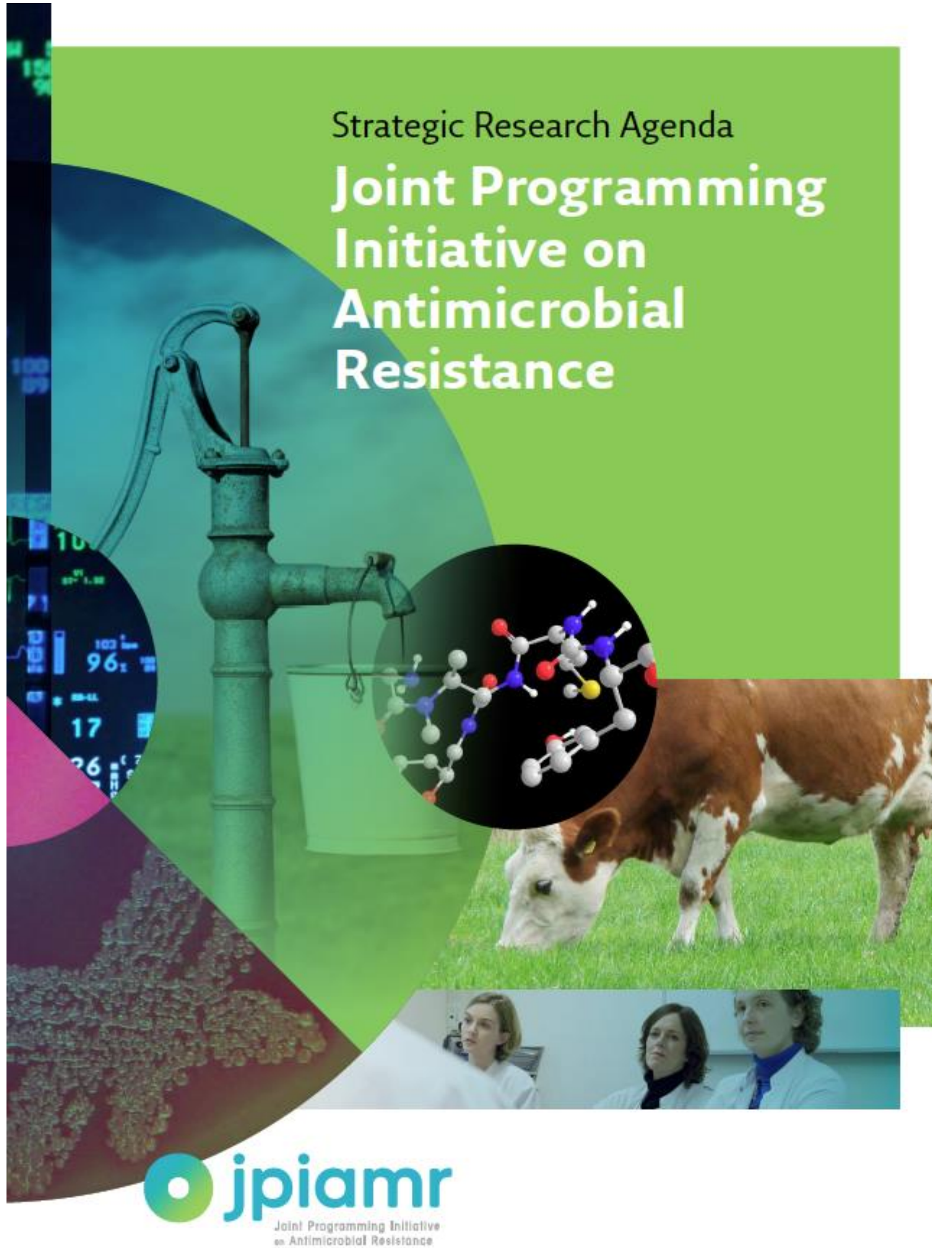
- **Ongoing research** in the U.S., Europe, and Asia **is examining wastewater and other sources** (e.g., hospitals, agriculture) **for ARG and ARB and their removal** by treatment processes.

Recommendations – Research

1. **Research is needed to determine risk to humans and on defining dose-response relationships from ARB and ARG in water** relative to other exposures.

2. **Standardized tests to determine ARB/ARG in potable water and wastewater should be developed.** These tests should be financially and technologically accessible to a majority of water and wastewater treatment agencies.

3. **Characterize and evaluate ARB/ARG removal using advanced water treatment processes**.


Strategic Research Agenda
Joint Programming Initiative on Antimicrobial Resistance
jpiamr
Joint Programming Initiative on Antimicrobial Resistance

Development and Evaluation of Monitoring Methods for Surveillance: Antimicrobial Resistant Bacteria in León, Nicaragua and Chapel Hill, North Carolina

Katy M. Brown[1], Claudia Perez[2], Erick Amaya[2], Daniel Reyes[2], Lydia Abebe[1], Sylvia Becker-dreps[3], Samuel Vilchez[2], and Mark Sobsey[1]

[1]Gillings School of Global Public Health, Dept. of Environ. Sci. and Eng., UNC-Chapel Hill, USA [2] Dept. Microbiology, Faculty of Medical Sciences, University of Nicaragua, León, Nicaragua [3]Dept. Family Med., UNC-Chapel Hill, USA

Average *E. coli* as seen in CHROMagar Orientation™ and proportion of *E. coli* ESBL and KPC producers by sites, León and Chapel Hill

Water Samples Origin	León Sites	*E. Coli* CFU/100 mL	% ESBL *E. coli*	% KPC *E. coli*
Raw Sewage Waters	Hospital Sewage	$5.13x10^6$	31.4	0.2
	Raw Sewage Cocal (Urban)	$2.19x10^7$	3.95	-
	Secondary Effluent Cocal	$3.12x10^6$	4.19	-
	Raw Sewage Sutiaba (Urban and Hospital)	$2.59x10^7$	4.66	0.02
	Secondary Effluent Sutiaba	$1.61x10^6$	1.86	0.01
	Raw Sewage San Isidro (Rural)	$6.44x10^6$	4.02	-
Recreational Waters	Upstream Chiquito River	$2.54x10^7$	3.11	-
	Downstream Chiquito River (Cocal and Sutiaba)	$1.79x10^5$	2.84	-
	Downstream Quezalhuaque River (San Isidro)	$2.66x10^4$	2.56	-
Water Samples Origin	**Chapel Hill sites**	***E. Coli* CFU/100 mL**	**% ESBL *E. coli***	**% KPC *E. coli***
Raw Sewage Waters	Hospital Sewage	$2.00x10^6$	18	12.1
	Raw Sewage	$3.5x10^6$	22	17
	Secondary Effluent	$2.20x10^4$	15	3
Recreational Waters	Upstream Morgan Creek	$4.30x10^2$	19	1.3
	Downstream Morgan Creek	$3.80x10^2$		

WERF1C15

Occurrence, Proliferation, and Persistence of Antibiotics and Antibiotic Resistance during Wastewater Treatment

UNLV

The University of Arizona

Southern Nevada Water Authority

Project Update

February 11, 2016

NSF-PIRE Halting Environmental Antimicrobial Resistance Dissemination (HEARD)

Principal Investigators: Peter Vikesland, Pedro Alvarez, Dina Aga, Amy Pruden, Krista Wigginton

Driving Hypotheses:

1. WWTP influents can be monitored to gauge impacts of local antimicrobial use and disposal practices on the prevalence of resistant organisms and resistance elements.

2. A broad gradient of AR elements and ARB are present in WW effluents across the globe.

3. WW treatment processes and receiving environments can be chosen or modified to mitigate the spread of AR.

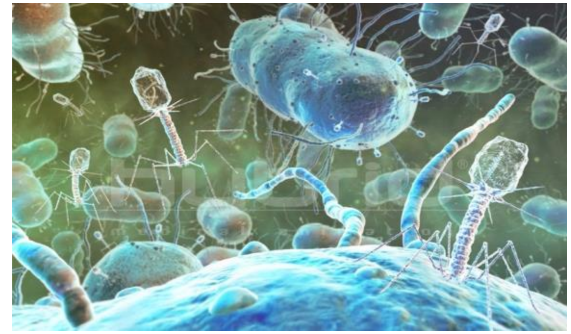
NSF-PIRE-HEARD (cont.)

Research Plan Thrusts

1. Global reconnaissance of antimicrobial drugs, ARB and resistance element fate during WW treatment.

2. The relative roles of WWTPs and receiving environments in resistance dissemination.

3. Advancing WW treatment technologies for antimicrobial drug, ARB and resistance element removal.



Antibiotics—*Resistance Is Futile!*

Walter Jakubowski & Ryan Reinke