

ANTIMICROBIAL RESISTANCE: A SILENT KILLER PANDEMIC



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Antibiotic-Resistant Infections Threaten Modern Medicine

Millions of people in the United States receive care that can be complicated by bacterial and fungal infections. Without antibiotics, we are not able to safely offer some life-saving medical advances.



Sepsis Treatment

Anyone can get an infection and almost any infection can lead to sepsis — the body's extreme response to an infection. Without timely treatment with antibiotics, sepsis can rapidly lead to tissue damage, organ failure, and death

**AT LEAST
1.7M**

adults develop sepsis each year.

Do I need to worry?

Surgery

Patients who have surgery are at risk for surgical site infections. Without effective antibiotics to prevent and treat surgical infections, many surgeries would not be possible today.

1.2M

women had a cesarean section (C-section) in 2017. Antibiotics are recommended to help prevent infection.



What about my parents?



Chronic Conditions

Chronic conditions (e.g., diabetes) put people at higher risk for infection. These conditions and some medicines used to treat them can weaken the immune system (how the body fights infection).

**MORE THAN
30M**

people have diabetes. Antibiotics are used to treat common infections in these patients.

Transplant patients?

Antibiotic-Resistant Infections Threaten Modern Medicine



Organ Transplants

Organ transplant recipients are more vulnerable to infections because they undergo complex surgery. Recipients also receive medicine to suppress (weaken) the immune system, increasing risk of infection.

MORE THAN
33,000

organ transplants were performed in 2016.
Antibiotics help organ transplants remain possible.

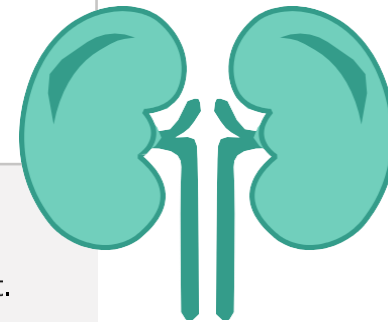
Dialysis patients

Dialysis for Advanced Kidney Disease

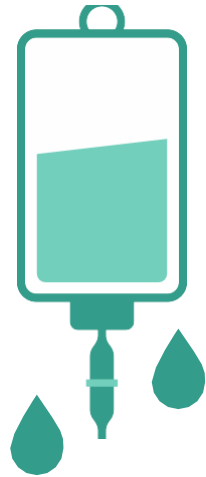
Patients who receive dialysis treatment have a higher risk of infection, the second leading cause of death in dialysis patients.

MORE THAN
500,000

patients received dialysis treatment in 2016. Antibiotics are critical to treat infections in patients receiving life-saving dialysis treatment.



Cancer care compromised?



Cancer Care

People receiving chemotherapy for cancer are often at risk for developing an infection during treatment. Infection can quickly become serious for these patients.

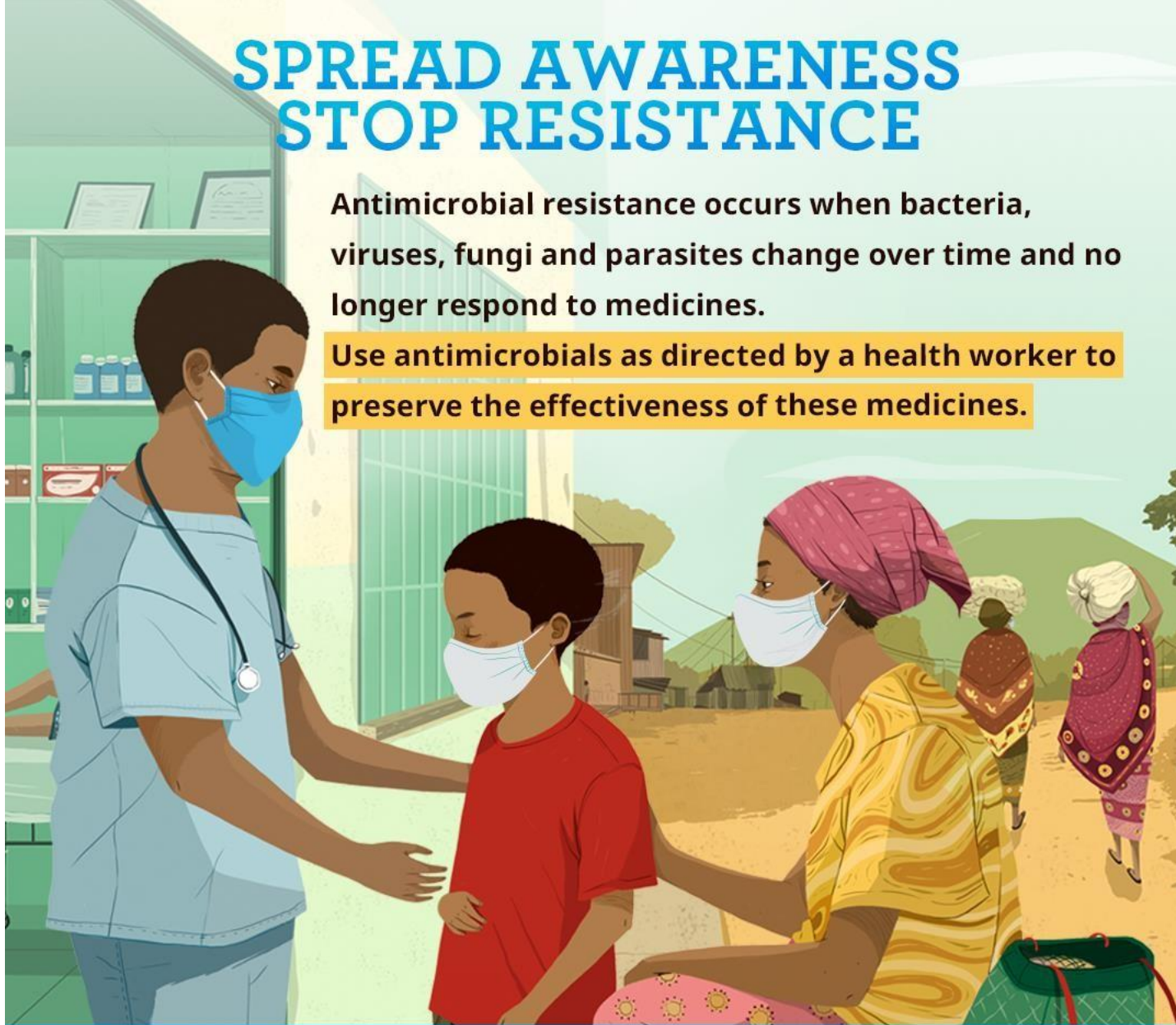
**AROUND
650,000**

people receive outpatient chemotherapy each year. Antibiotics are necessary to protect these patients.

SPREAD AWARENESS STOP RESISTANCE

Antimicrobial resistance occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines.

Use antimicrobials as directed by a health worker to preserve the effectiveness of these medicines.



World Health
Organization



Antibiotics
Antivirals
Antifungals
Antiparasitics

Interconnected world

A ONE HEALTH CHALLENGE

The Interconnected Threat of Antibiotic Resistance

Resistance happens when germs (bacteria and fungi) defeat the drugs designed to kill them. Any antibiotic use—in people, animals, or crops—can lead to resistance. Resistant germs are a One Health problem—they can spread between people, animals, and the environment (e.g., water, soil).



Examples of How Antibiotic Resistance Affects Humans, Animals & the Environment

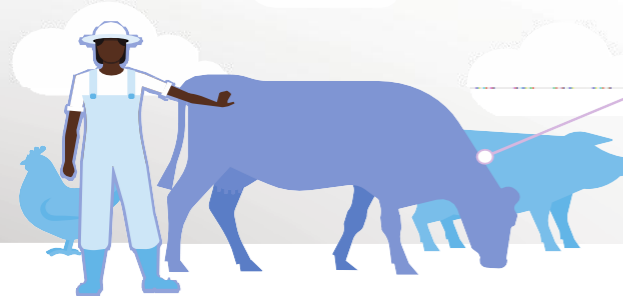
People

Some types of antibiotic-resistant germs can spread person to person. "Nightmare bacteria" carbapenem-resistant Enterobacteriaceae (CRE) can also survive and grow in sink drains at healthcare facilities and spread to patients and to the environment through the wastewater.



Animals

Resistant germs can spread between animals and people through food or contact with animals. For example, *Salmonella* Heidelberg bacteria can make both cattle and people sick.



Environment

Antibiotic-resistant germs can spread in the environment. *Aspergillus fumigatus*, a common mold, can make people with weak immune systems sick. In 2018, resistant *A. fumigatus* was reported in three patients. It was also found in U.S. crop fields treated with fungicides that are similar to antifungals used in human medicine.



Its not just us?

SPREAD AWARENESS STOP RESISTANCE

1 in 10 patients get an infection while receiving care.

Health workers can reduce the spread of infections by ensuring their hands, instruments and environment are kept clean.



World Health
Organization



Antibiotics
Antivirals
Antifungals
Antiparasitics

SPREAD AWARENESS STOP RESISTANCE

Substandard and falsified medicines contribute to antimicrobial resistance.

Increased regulation and enforcement promotes availability of quality medicines for all.



World Health
Organization



Antibiotics
Antivirals
Antifungals
Antiparasitics

Abuse and misuse data

**STOP
THE OVERUSE OF
ANTIBIOTICS**



Why should we talk about resistance



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

Understanding resistance is Important...



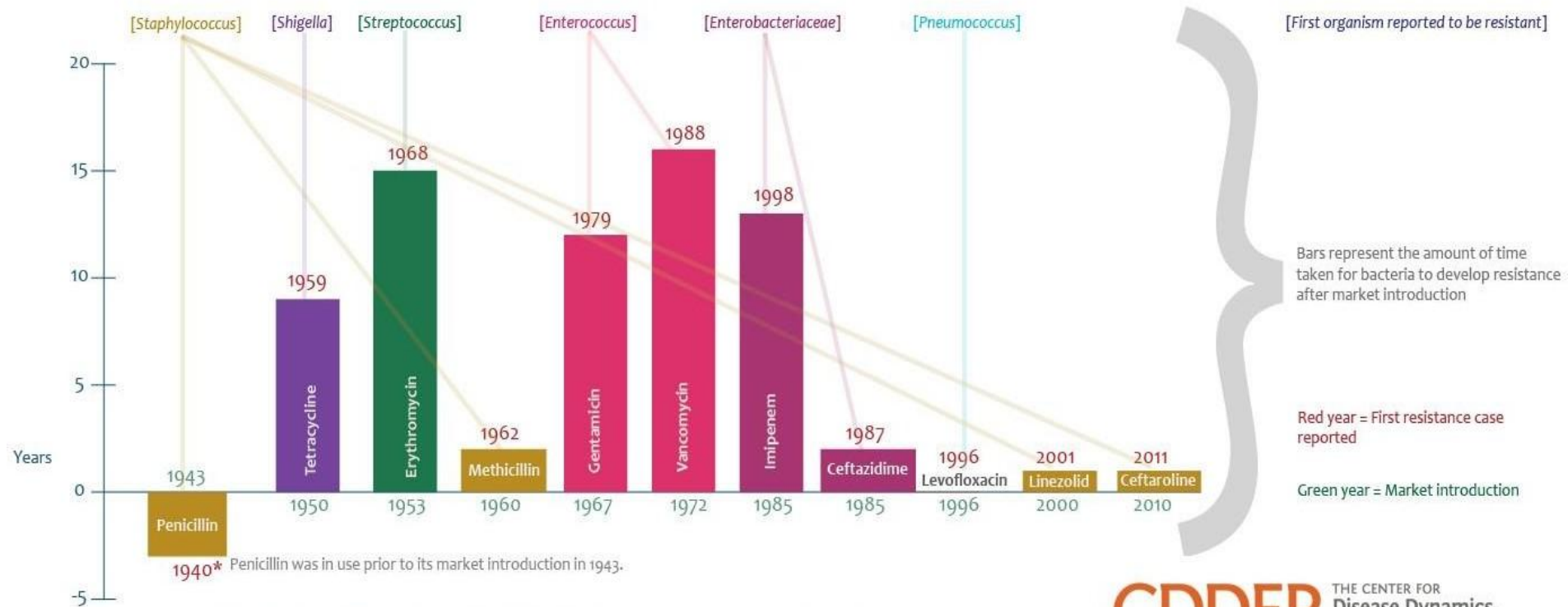
The silent tsunami facing modern medicine

- Has been the topic of numerous international health & political summits
- Great deal of data exists in the form of reports & guidelines to tackle antibiotic resistance
- Still, the problem of resistance, esp MDR- GNB continues to increase with every passing day

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1943	Penicillin-resistant <i>Streptococcus pneumoniae</i> ¹⁰	1967
		Penicillinase-producing <i>Neisseria gonorrhoeae</i> ¹¹	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant <i>Enterococcus faecium</i> ^{12,13}	1988
		Vancomycin-resistant <i>Staphylococcus aureus</i> ¹⁴	2002
Amphotericin B	1959	Amphotericin B-resistant <i>Candida auris</i> ¹⁵	2016
Methicillin	1960	Methicillin-resistant <i>Staphylococcus aureus</i> ¹⁶	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing <i>Escherichia coli</i> ¹⁷	1983
Azithromycin	1980	Azithromycin-resistant <i>Neisseria gonorrhoeae</i> ¹⁸	2011
Imipenem	1985	<i>Klebsiella pneumoniae</i> carbapenemase (KPC)-producing <i>Klebsiella pneumoniae</i> ¹⁹	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant <i>Neisseria gonorrhoeae</i> ²⁰	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant <i>Candida</i> ²¹	1988
Caspofungin	2001	Caspofungin-resistant <i>Candida</i> ²²	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant <i>Staphylococcus aureus</i> ²³	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing <i>Klebsiella pneumoniae</i> ²⁴	2015

Timeline of Antibiotic Introduction & Resistance

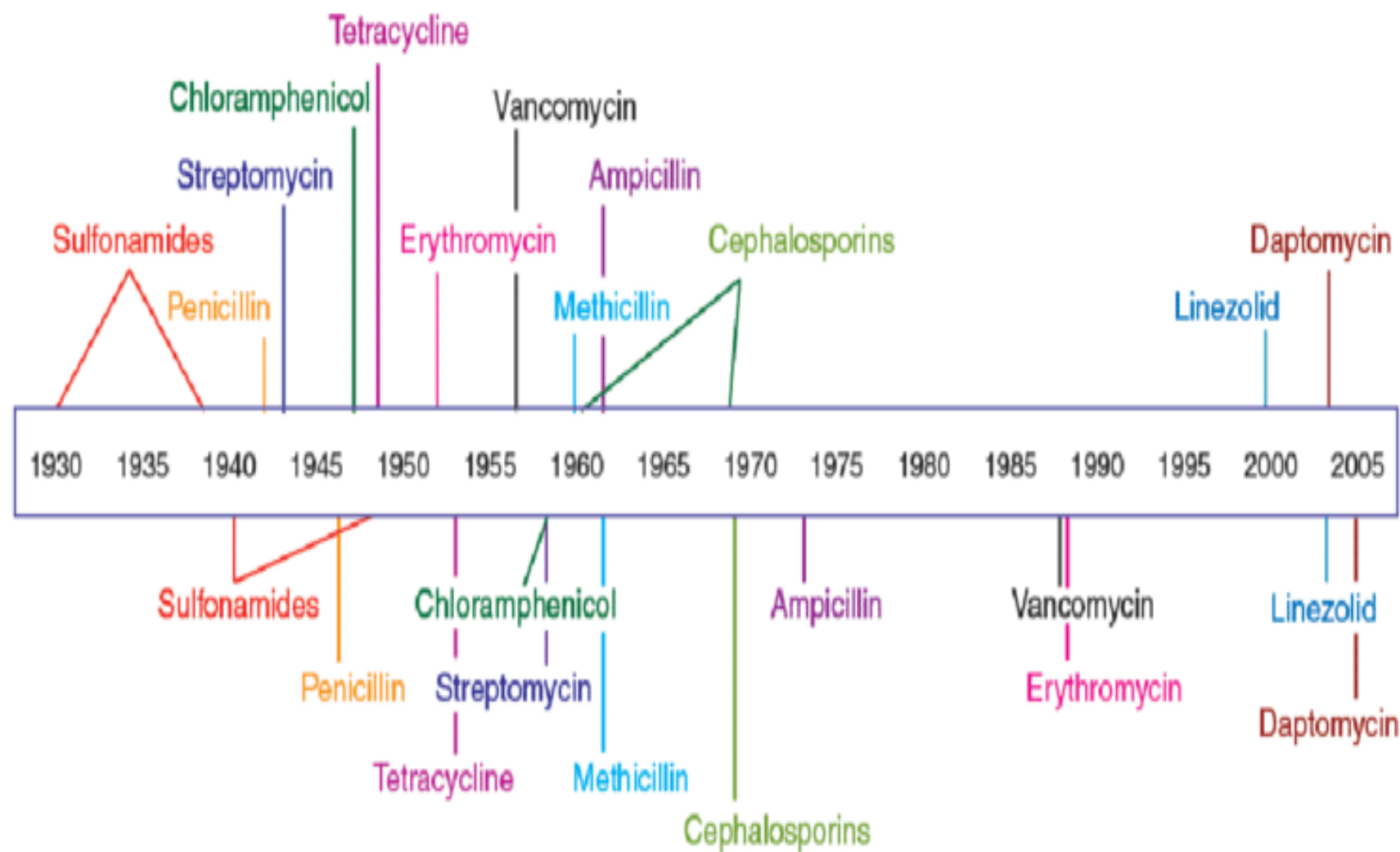
First reported cases of bacterial resistance against key antibiotics




Data source: Antibiotic Resistance Threats in the United States, 2013.
US Centers for Disease Control and Prevention (CDC).



Antibiotic deployment



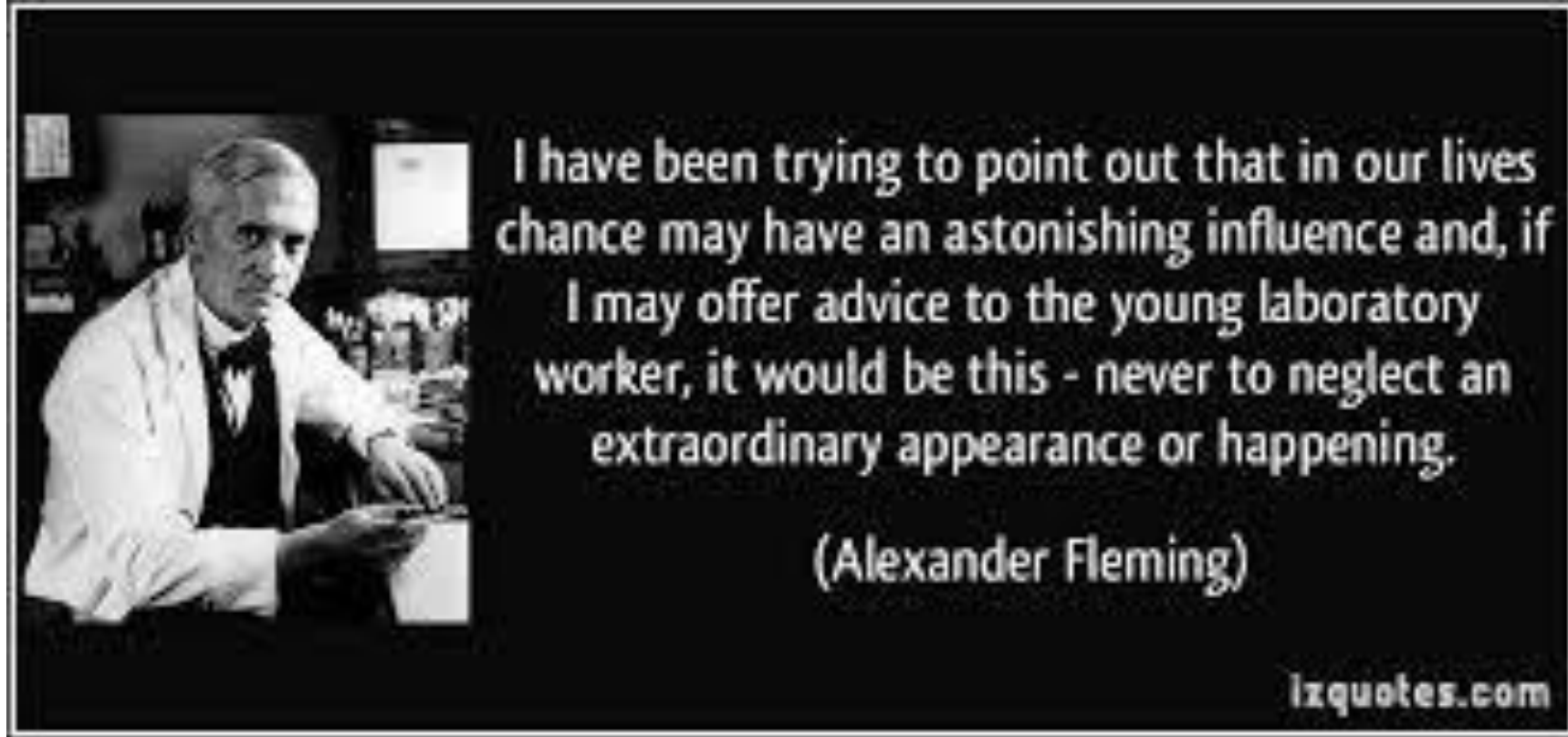
Antibiotic resistance observed

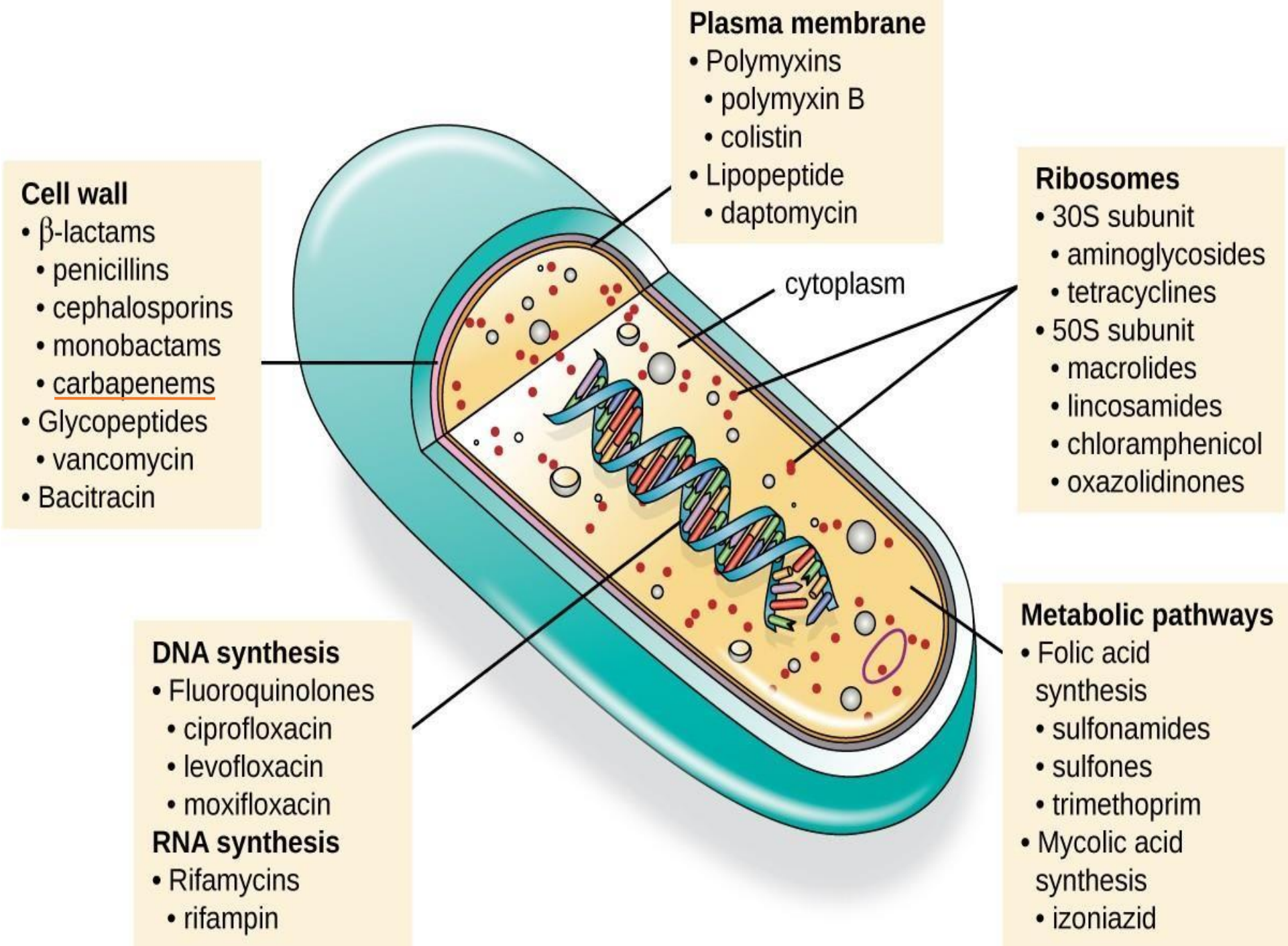


A post-antibiotic era means,
in effect, an end to modern
medicine as we know it.
Things as common as strep
throat or a child's scratched
knee could once again kill.

Former Dir. Gen- WHO
Dr Margaret Chan

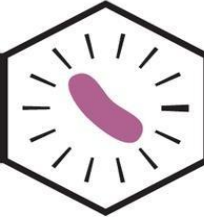
Mechanisms of antibiotic action





Antibiotic resistance is when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them.
It does not mean your body is resistant to antibiotics.

Development of Antibiotic Resistance



How Antibiotic Resistance Happens

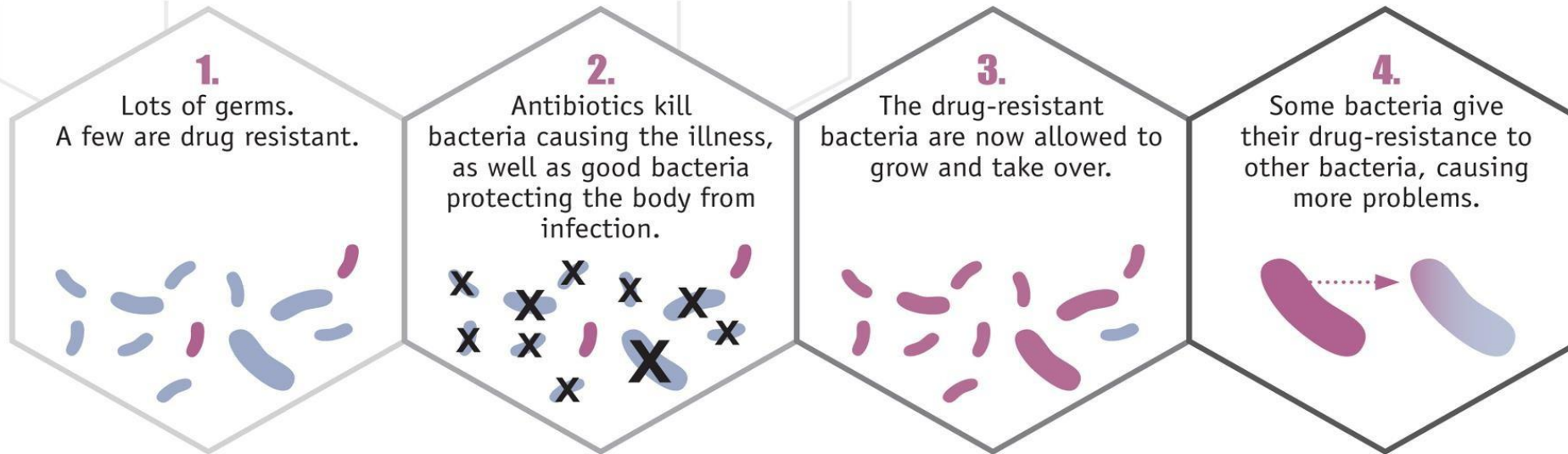
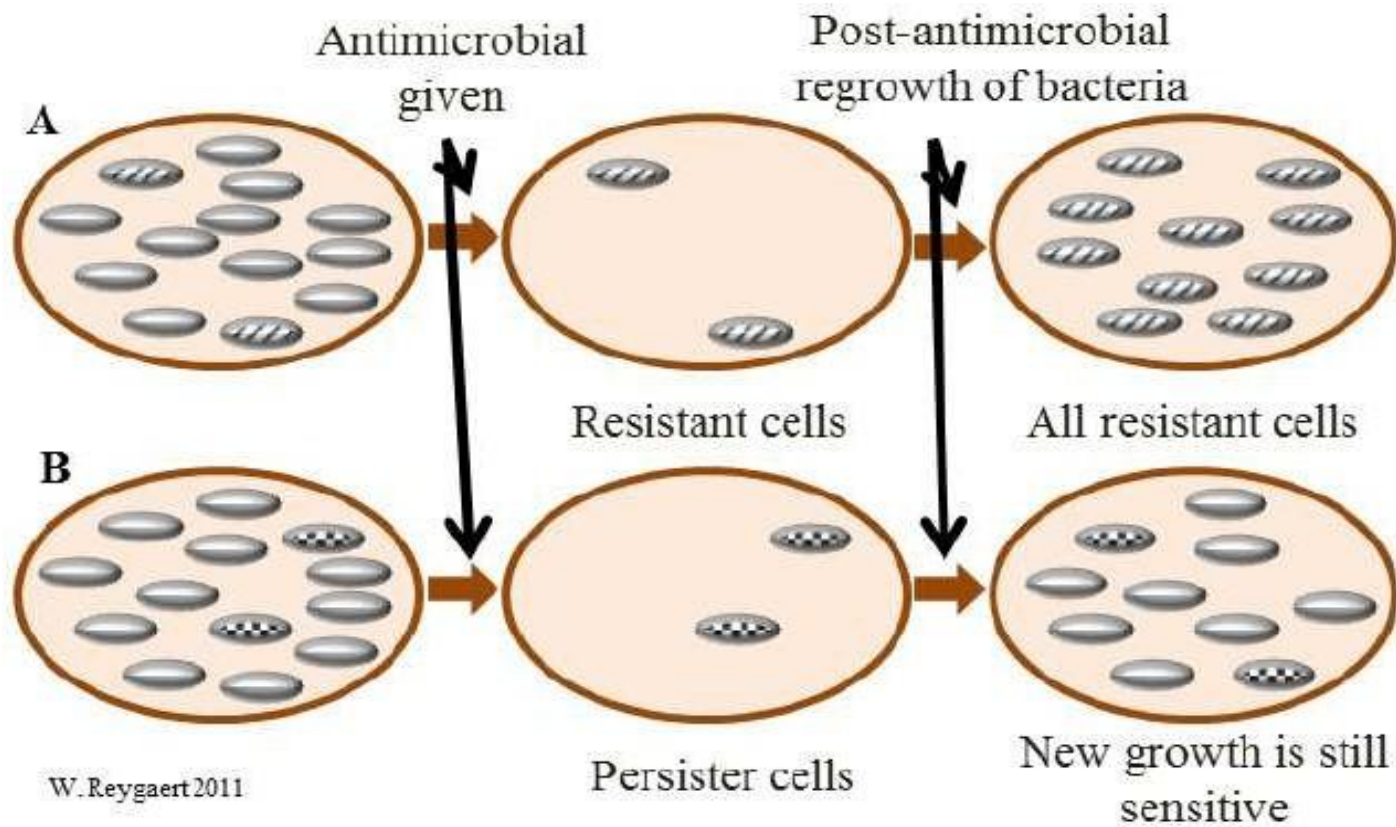


Image courtesy of CDC / Melissa Brower
Centers for Disease Control and Prevention Public Health Image Library
<http://phil.cdc.gov/phil/home.asp>

Persistence vs resistance ?



Development of Antibiotic Resistance

- **Selective advantage**

- Bacteria that contain resistance mechanisms can survive and multiply when exposed to antibiotics

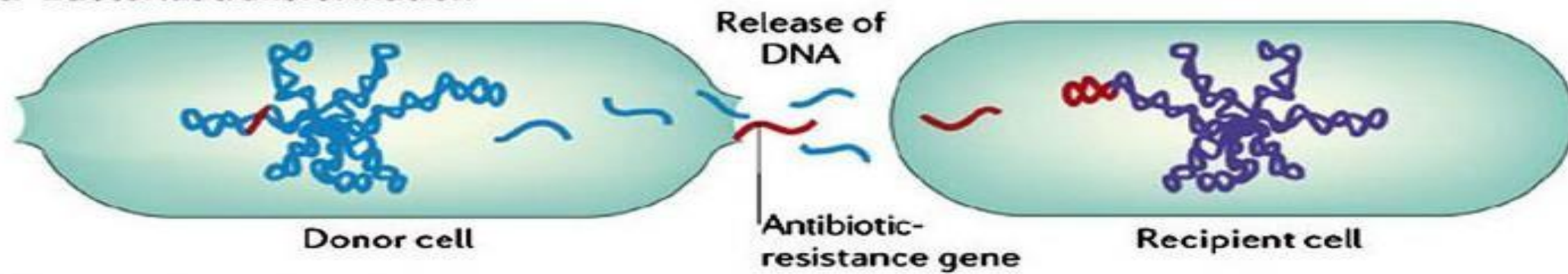
- **Gene transfer**

- Allows bacteria to share genes that cause antibiotic resistance

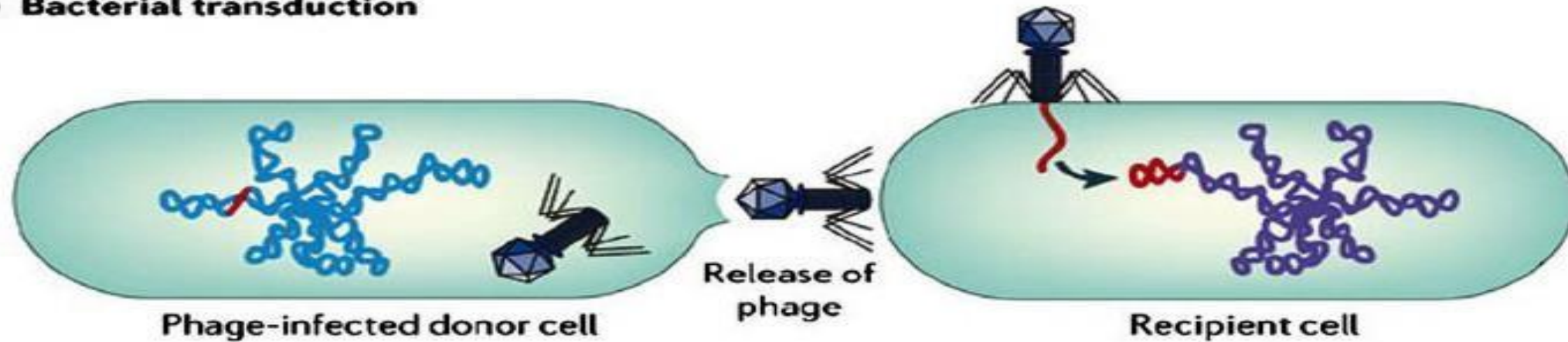
- **Cross-resistance**

- Changes in bacteria which create resistance to one antibiotic may cause resistance to other antibiotics as well

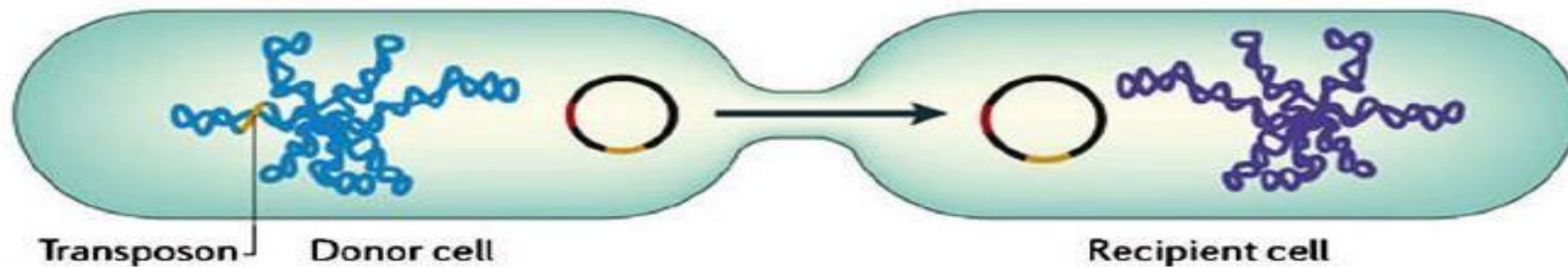
a Bacterial transformation



b Bacterial transduction

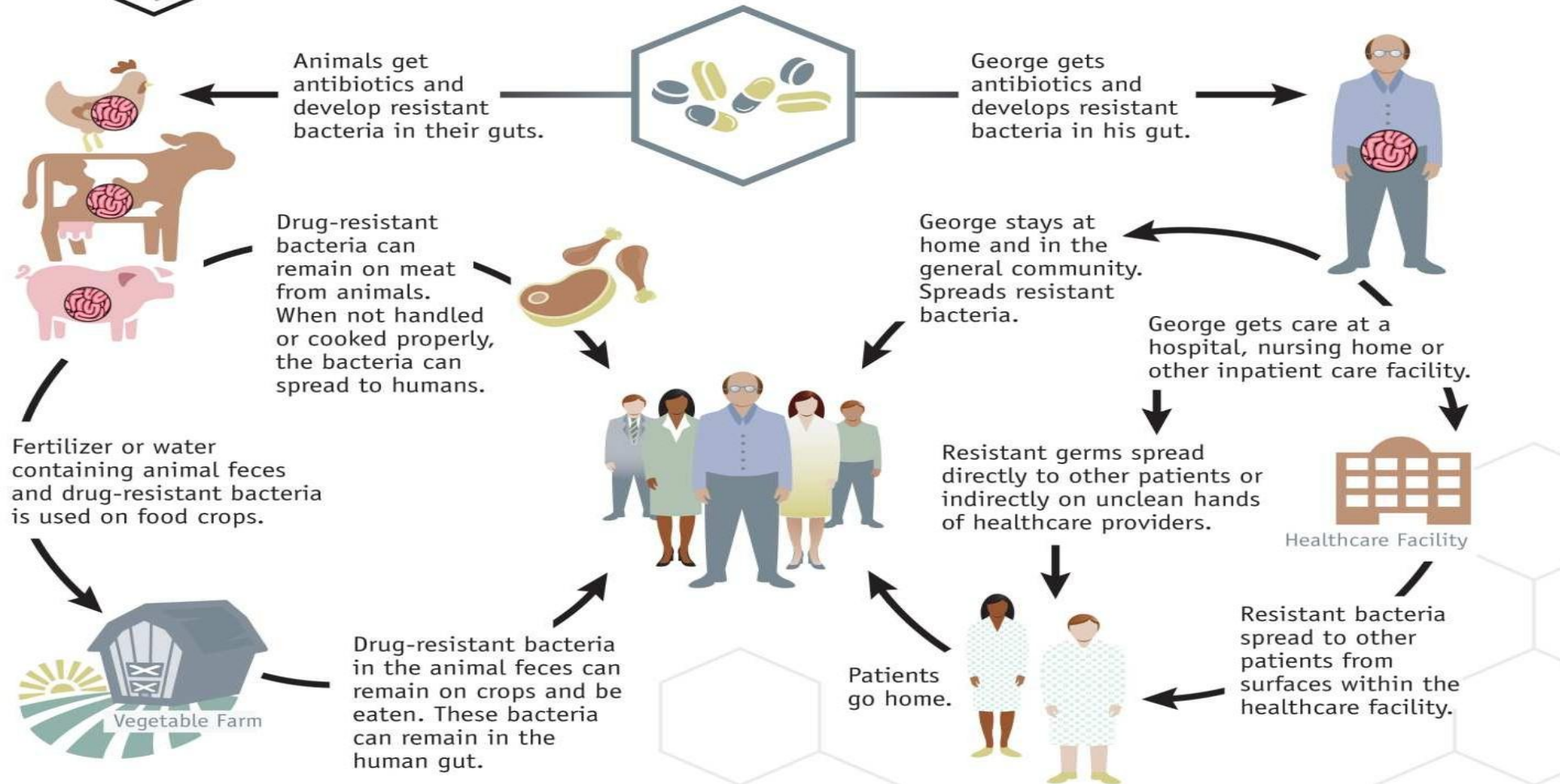


c Bacterial conjugation



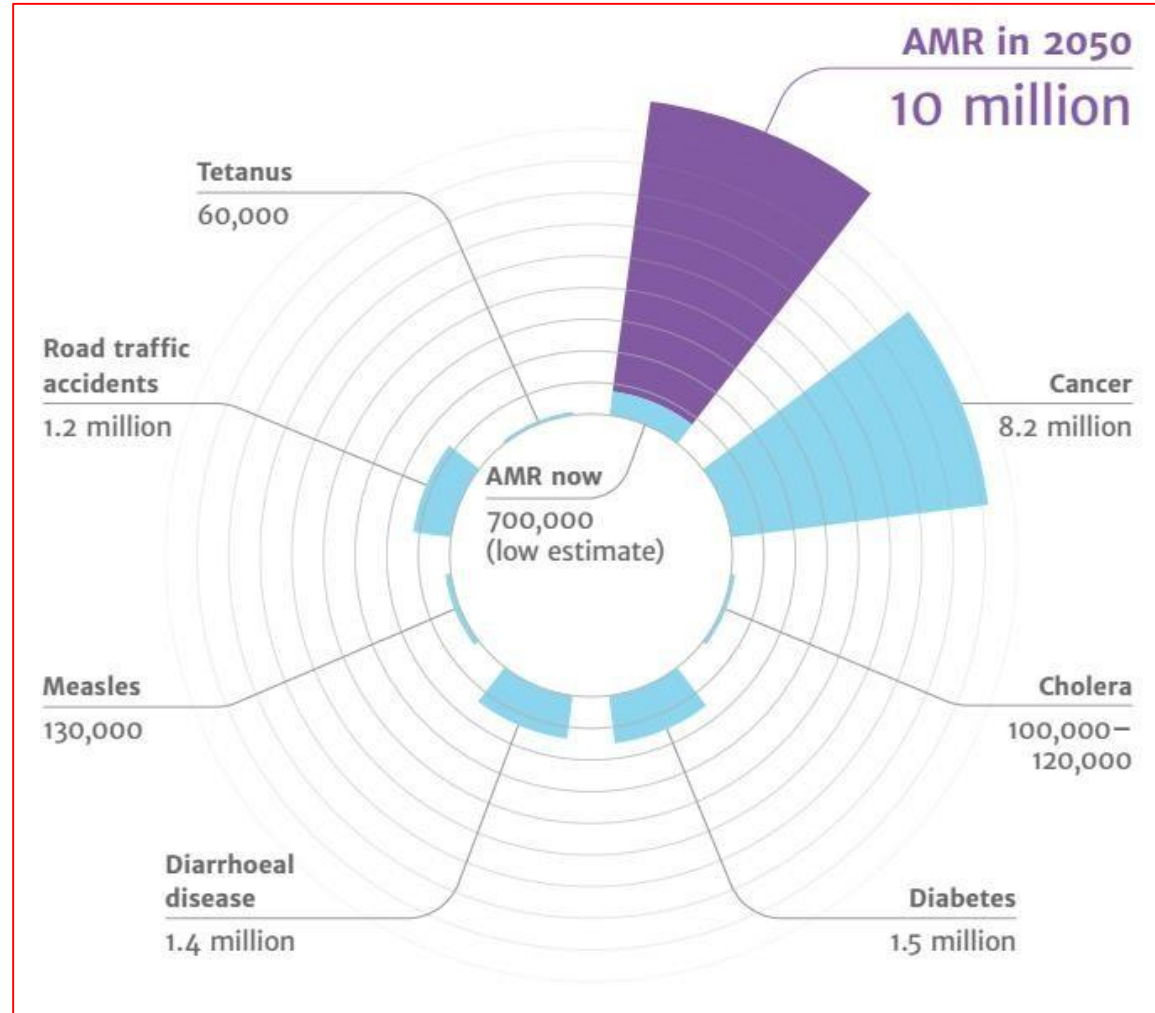


Examples of How Antibiotic Resistance Spreads



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

Deaths Attributable to AMR Every Year



AMR, antimicrobial resistance

O'Neill J (Chair). Review on Antimicrobial Resistance. May 2016. Available from:

http://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [Accessed August 2016].

Resistance in microbes is a natural phenomenon



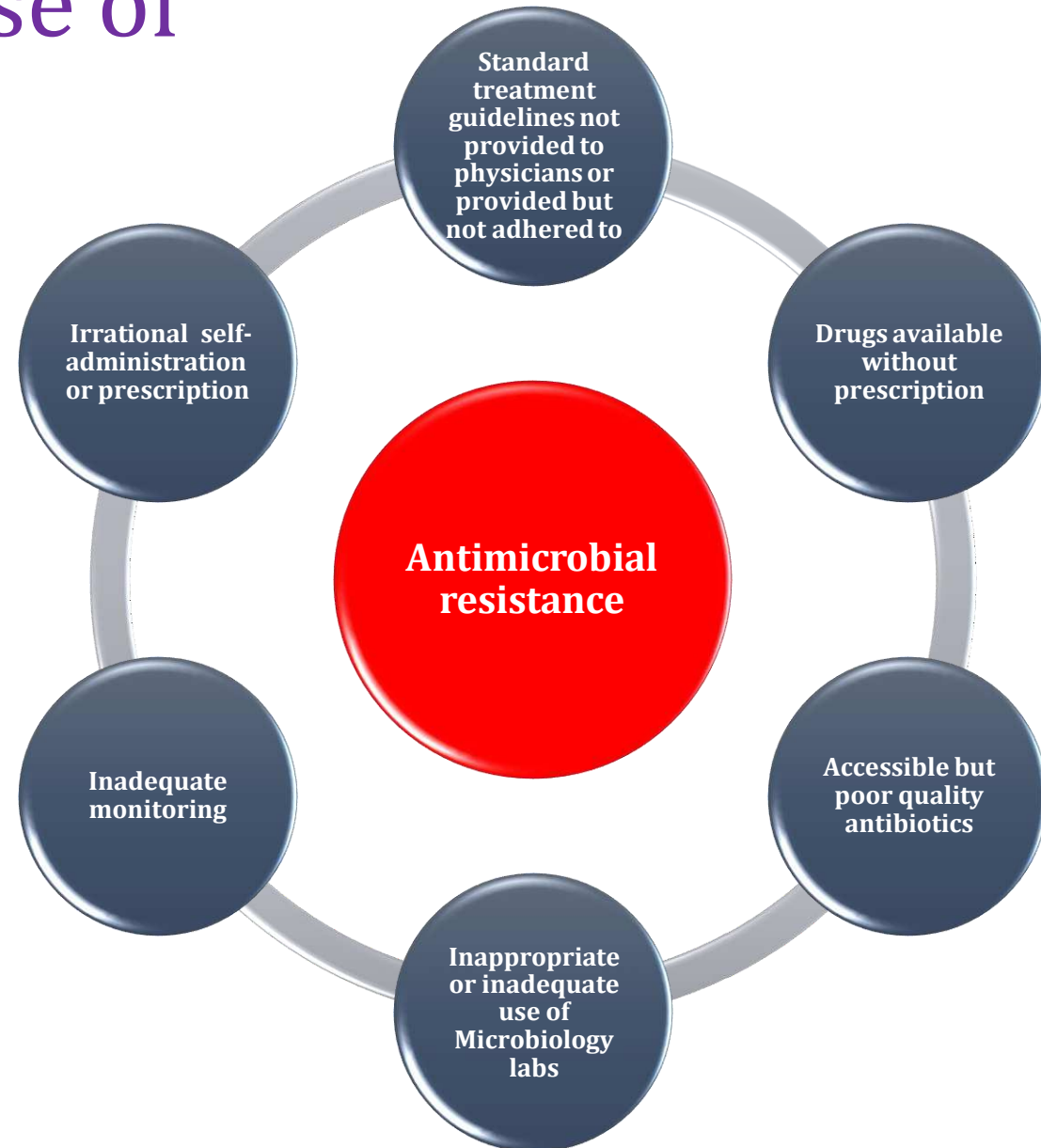
Resistance is unresponsiveness to antimicrobial agents in standard doses

A natural biological unstoppable phenomenon

Resistance is generally slow to reverse or irreversible

All antimicrobial agents have the potential to select drug-resistant subpopulations of microorganisms

Resistance is accelerated through inappropriate use of antimicrobials



Resistance is fallout of inappropriate use of antimicrobials in different settings

Therapeutic and non-therapeutic (e.g. as growth promoters)

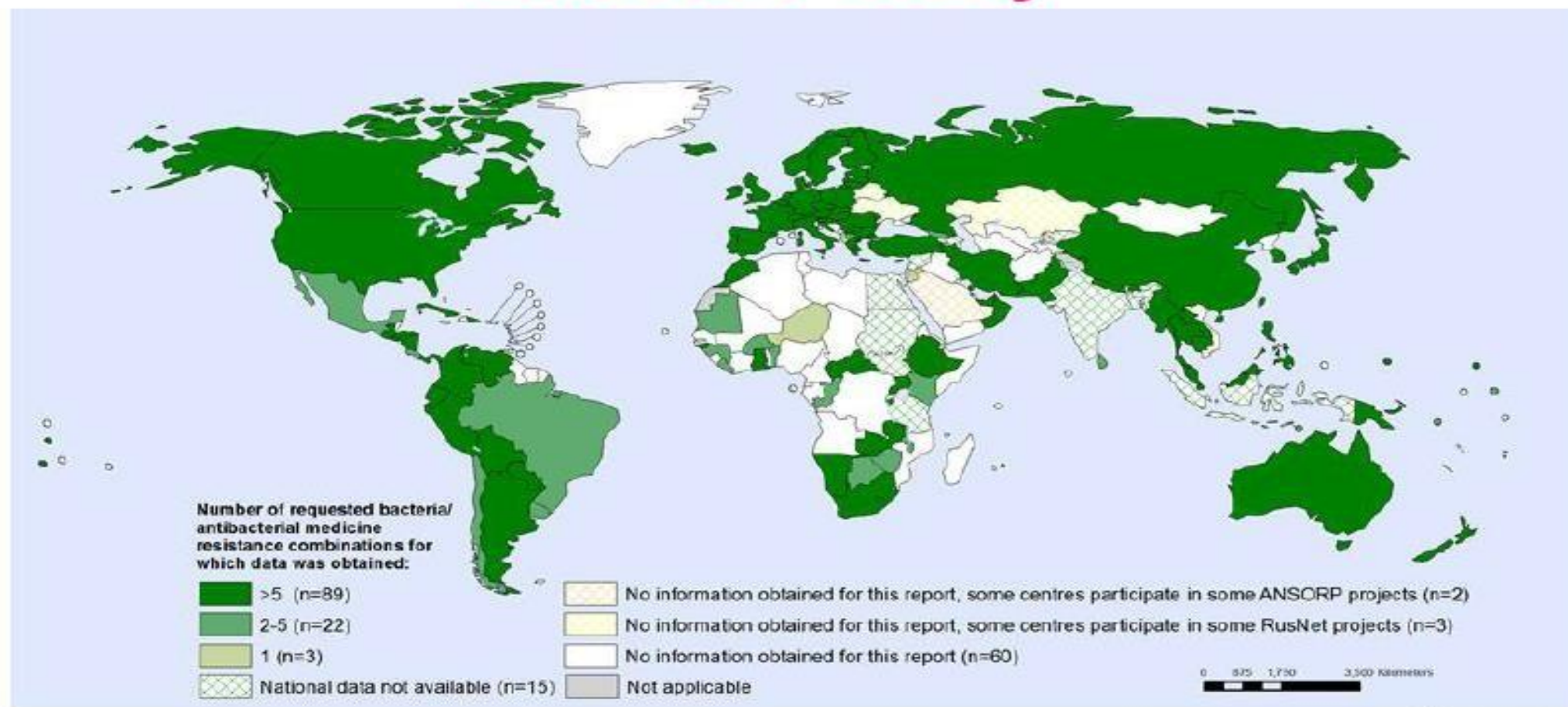
In community acquired infections

In hospital-associated infections

- Irrational use of antibiotics is the greatest driver of resistance
 - **50%** of antibiotics are prescribed inappropriately
 - **50%** of patients have poor compliance
 - **50%** of populations do not have access to essential antibiotics



Data is Patchy



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

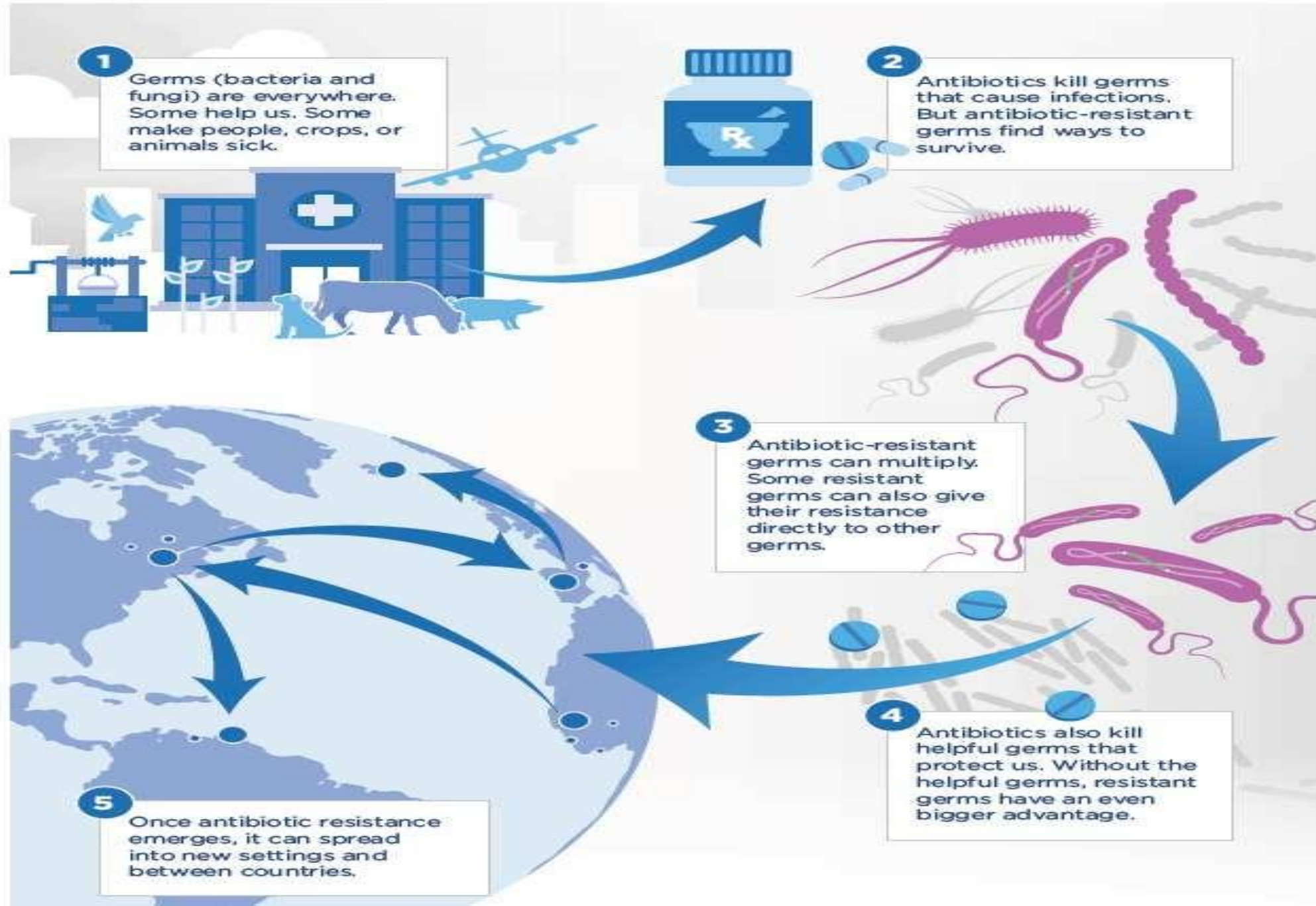
Data Source: World Health Organization
Map Production: Health Statistics and
Information Systems (HSI)
World Health Organization



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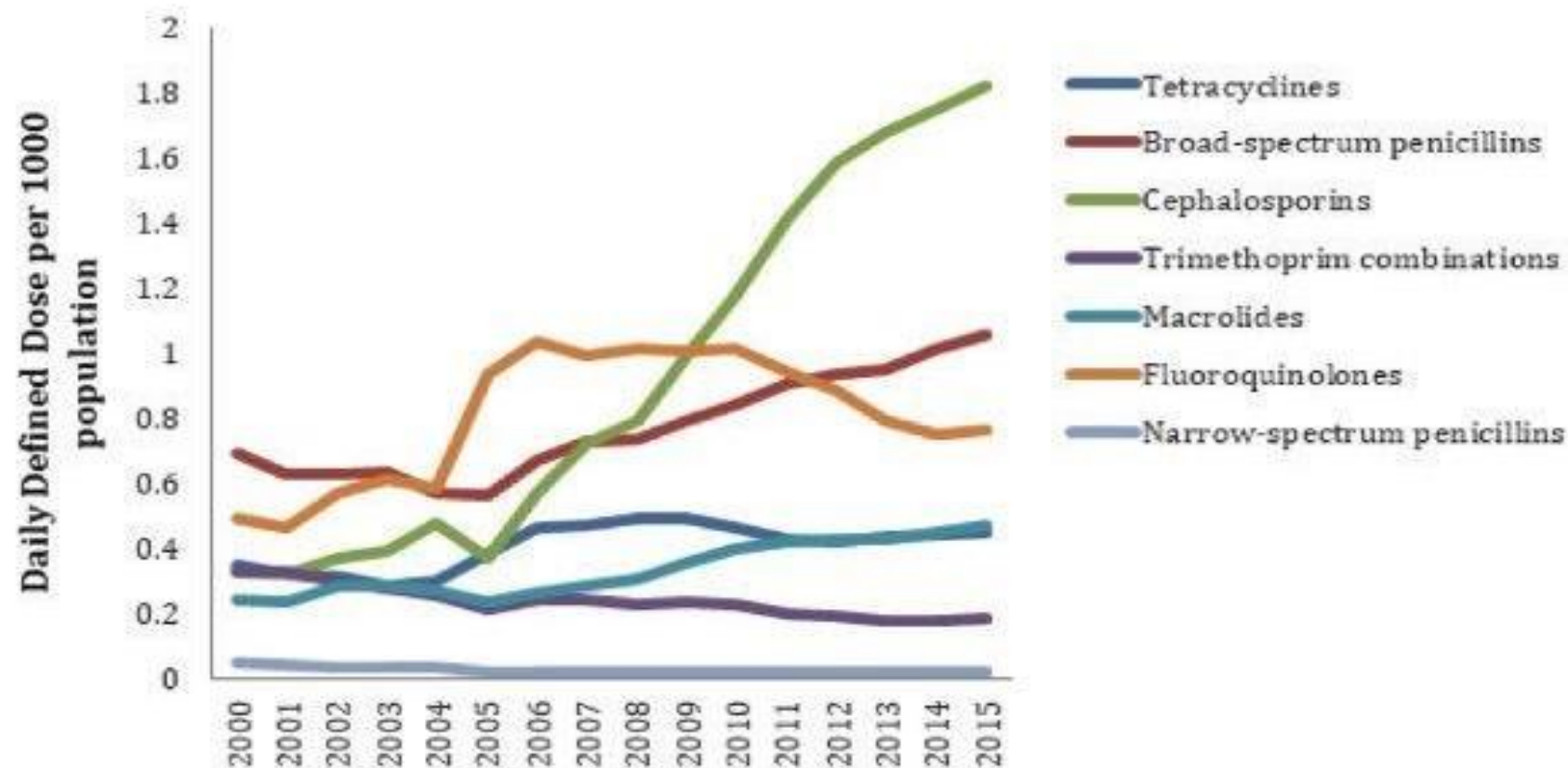
**Available National Data* on Resistance for Nine
Selected Bacteria/Antibacterial Drug Combinations, 2013**

How Antibiotic Resistance Spreads



Impact on current and future patients

- **Antibiotic use contributes to the development of antibiotic resistance**
 - For most medicines, side effects are limited to the individual patient
 - Resistance developed from exposure to an antibiotic may affect the patient, but also affects future patients and the wider community
 - This reduces the number of effective antibiotics available to treat infections



Origins of resistance

3.1. Natural resistance

3.2. Acquired resistance

Intrinsic resistance?

Intrinsic resistance: Large numbers of bacteria, both commensals and pathogens, naturally tend to be resistant to certain classes of antimicrobial agents

Table 2. Examples of bacteria with intrinsic resistance.

Organism	Intrinsic resistance
<i>Bacteroides</i> (anaerobes)	aminoglycosides, many β -lactams, quinolones
All gram positives	aztreonam
Enterococci	aminoglycosides, cephalosporins, lincosamides
<i>Listeria monocytogenes</i>	cephalosporins
All gram negatives	glycopeptides, lipopeptides
<i>Escherichia coli</i>	macrolides
<i>Klebsiella</i> spp.	ampicillin
<i>Serratia marcescens</i>	macrolides
<i>Pseudomonas aeruginosa</i>	sulfonamides, ampicillin, 1 st and 2 nd generation cephalosporins, chloramphenicol, tetracycline
<i>Stenotrophomonas maltophilia</i>	aminoglycosides, β -lactams, carbapenems, quinolones
<i>Acinetobacter</i> spp.	ampicillin, glycopeptides

Name of the Organism	Antibiotics
<i>Citrobacter freundii</i>	A, AUG, CZ, CEF
<i>Citrobacter koseri</i>	A
<i>Klebsiella aerogenes</i>	A, AUG, CZ, CEF
<i>Enterobacter cloacae complex</i>	A, AUG, CZ, CEF
<i>Klebsiella pneumonia</i>	A
<i>Morganella morganii</i>	A, AUG, CZ, COLI, CEF, TGC, NIF
<i>Proteus mirabilis</i>	TGC, NIF, COLI
<i>Proteus penneri</i>	A, CZ, CEF, TGC, NIF, COLI
<i>Proteus vulgaris</i>	A, CZ, CEF, TGC, NIF, COLI
<i>Providencia rettgeri</i>	A, AUG, CZ, TGC, NIF, COLI
<i>Providencia stuartii</i>	A, AUG, CZ, TGC, NIF, COLI
<i>Serratia marcescens</i>	A, AUG, CZ, CEF, NIF, COLI
<i>Enterococcus gallinarum</i> and <i>cassiliflavus</i>	V
<i>Candida glabrata</i>	FLU

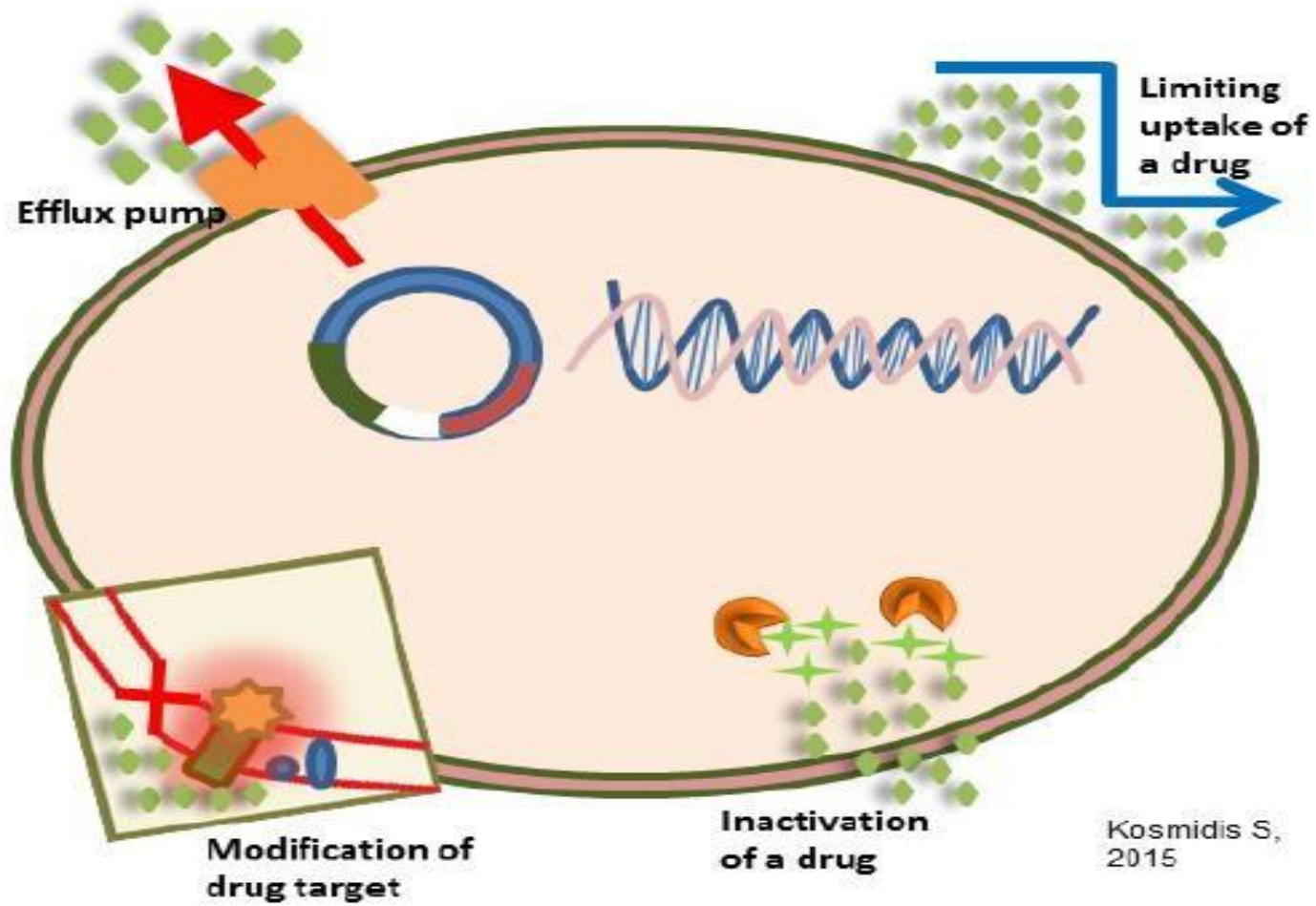


Figure 2. General antimicrobial resistance mechanisms.

What should we worry about?



Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris* (*C. auris*)
- *Clostridioides difficile* (*C. difficile*)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae* (*N. gonorrhoeae*)

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa* (*P. aeruginosa*)
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae* (*S. pneumoniae*)
- Drug-resistant Tuberculosis (TB)

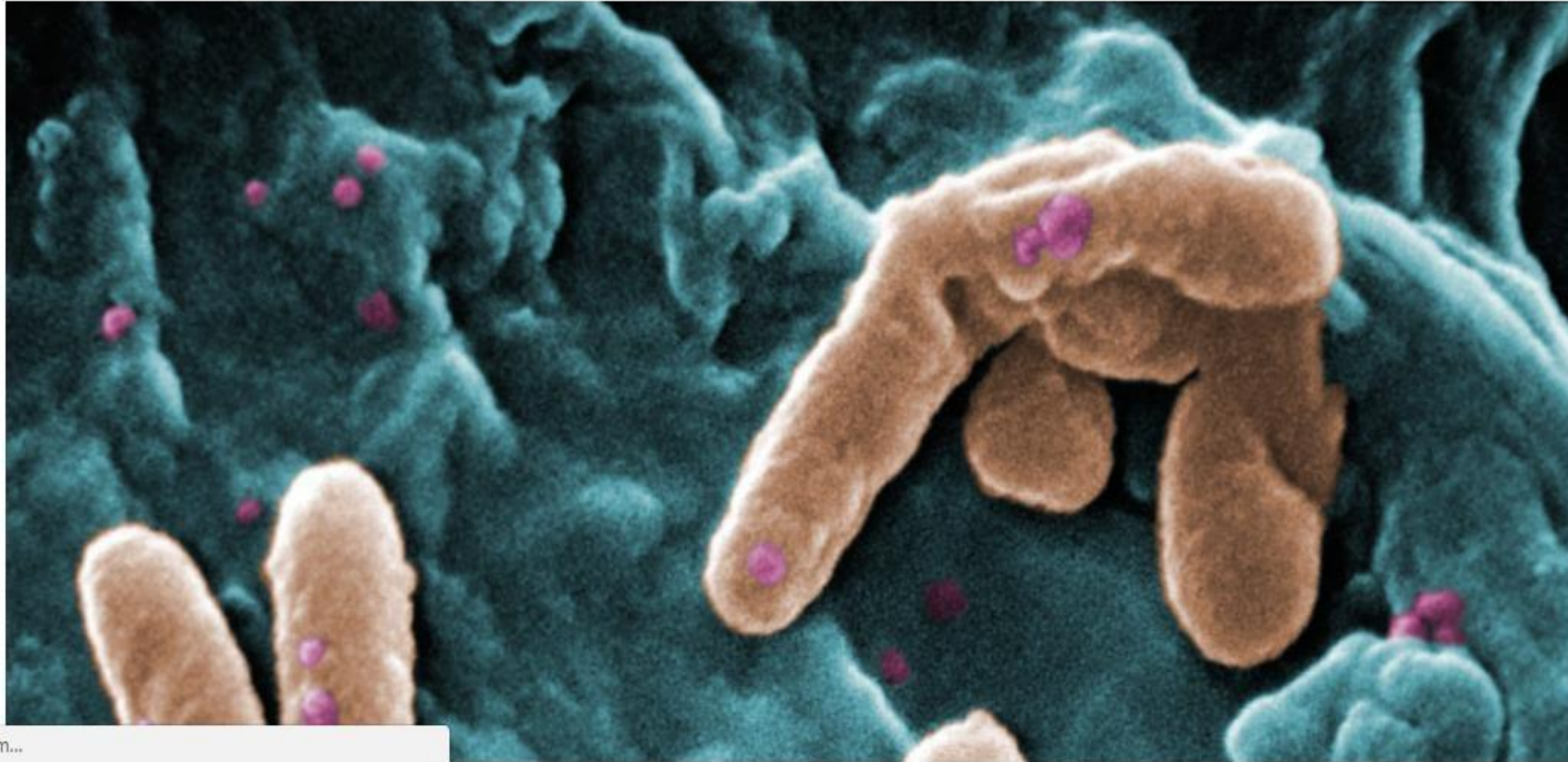
Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus* (*A. fumigatus*)
- Drug-resistant *Mycoplasma genitalium* (*M. genitalium*)
- Drug-resistant *Bordetella pertussis* (*B. pertussis*)

WHO releases list of world's most dangerous superbugs



om...

- **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

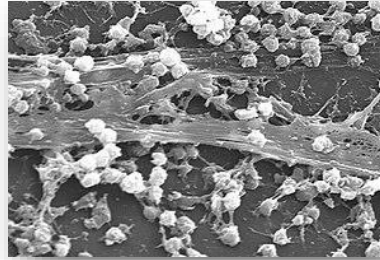
HABITATS AND RESERVOIRS OF (ANTIBIOTIC- RESISTANT) GNB

Name of pathogen	Natural reservoirs and sites of colonization	Transmission paths	Types of infection
<i>Klebsiella</i> spp.	Gastrointestinal (GI) and respiratory tract of humans and animals; fruit, vegetables, dairy products; wood pulp, paper mills, water storage tanks, surface water, sinks/drainage [196]	Contact, ingestion of contaminated food and water, bathing, aerosols/droplets (inhalation)	Sepsis, urinary tract infections, pneumonia, endocarditis, intraabdominal infections, skin and soft tissue infections, ocular infections, meningitis/brain abscess
Other <i>Enterobacteriaceae</i> spp. (rod-shaped)	Lower GI tract of humans and animals; plants; dairy products, raw meat; soil, water, sewage, sinks/drainage; also dry surfaces [196, 197]	Contact, faecal/oral, ingestion of contaminated food and water, aerosols/droplets, contaminated infusions/parenteral	Urinary tract infections, GI infections (diarrhoea), sepsis, intraabdominal infections
<i>Acinetobacter</i> spp.	Human skin and mucous membranes, pets/animals; vegetables, fish and shrimp farms; sewage, dump sites, waste water treatment plants, sinks/drainage; petroleum hydrocarbons; soil; warm and humid environments, but also able to survive in a dry environment [198, 199, 200]	Contact, ingestion of contaminated water and food, aerosols/droplets	Suppurative infections in any organ system, dominating respiratory infections, and soft tissue infections, rarely meningitis, ocular infections, native or prosthetic valve endocarditis, osteomyelitis; septic arthritis, pancreatic and liver abscesses, sepsis
<i>P. aeruginosa</i>	Human skin, upper respiratory system, GI tract; raw milk; moist environments including water (sinks/drainage), soil, plants [201]	Contact, ingestion of contaminated water, aerosols/droplets (inhalation)	Usually do not cause infections in healthy people; infections in any organ system, dominating sepsis, acute and chronic lung infections, ocular infections

INSIDE HOSPITALS, THEY CAN BE LURKING....



Colonized patients



Biofilms



Hosp Linen



Keyboards



Handwash Basins



Toilet Rims



Endoscopes

Problem

- Rising incomes and increasing access to antibiotics are saving lives (although lack of access still kills more people than antibiotic resistance)
- But are not a good substitute for public health

SIX CORE MEASURES FOR PREVENTION OF CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE* IN ACUTE AND LONG-TERM CARE FACILITIES

1. Hand Hygiene
2. Contact Precautions
3. Patient and staff cohorting
4. Minimize use of invasive devices
5. Promote antimicrobial stewardship
6. Screening

For more information:

CDC 2012 CRE Toolkit: <http://www.cdc.gov/hai/organisms/cre/cre-toolkit/>



Infection prevention and control: Prevent infections and reduce the spread of germs



Tracking and data: Share data and improve data collection



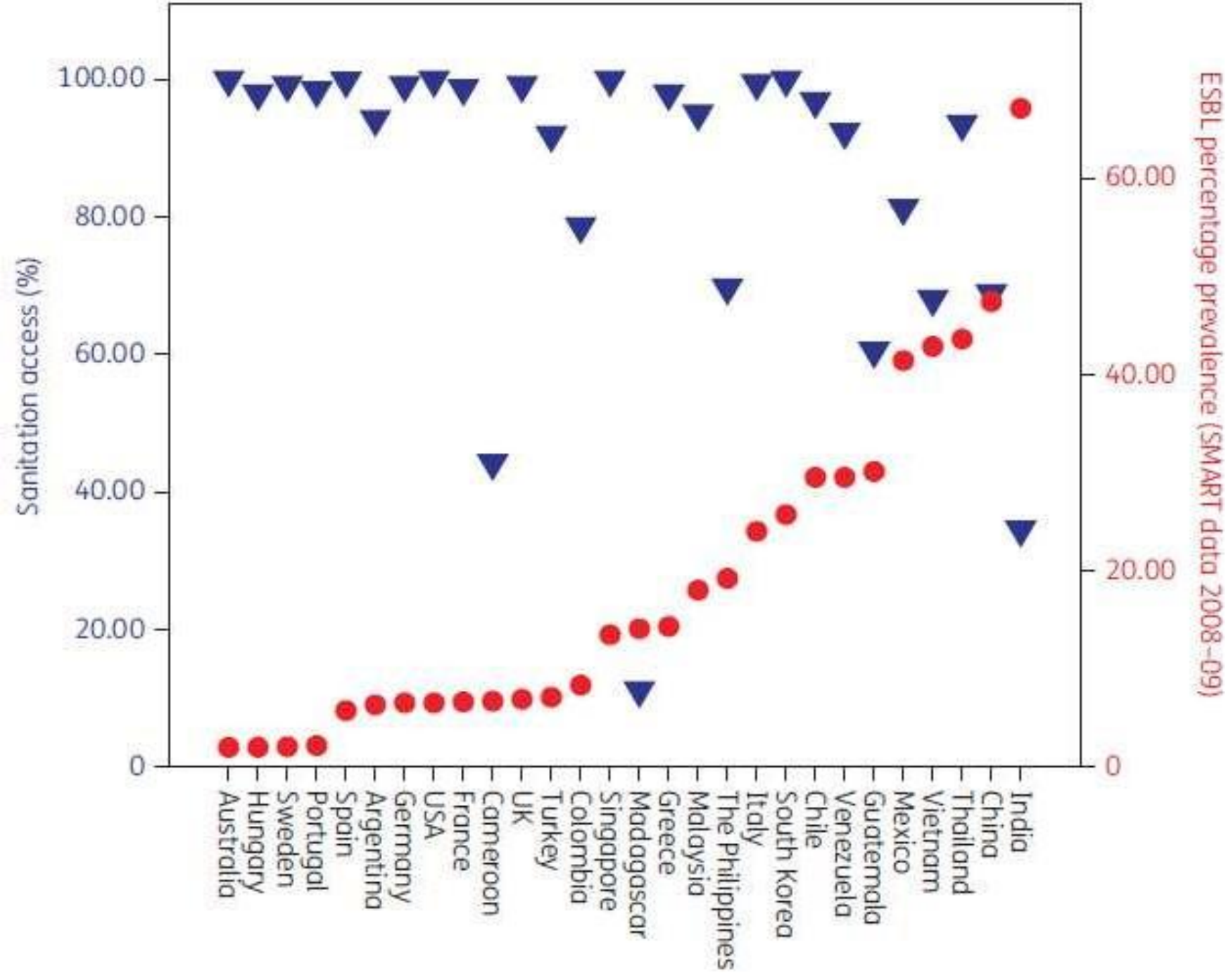
Antibiotic use and access: Improve appropriate use of antibiotics, reduce unnecessary use (called antibiotic stewardship), and ensure improved access to antibiotics



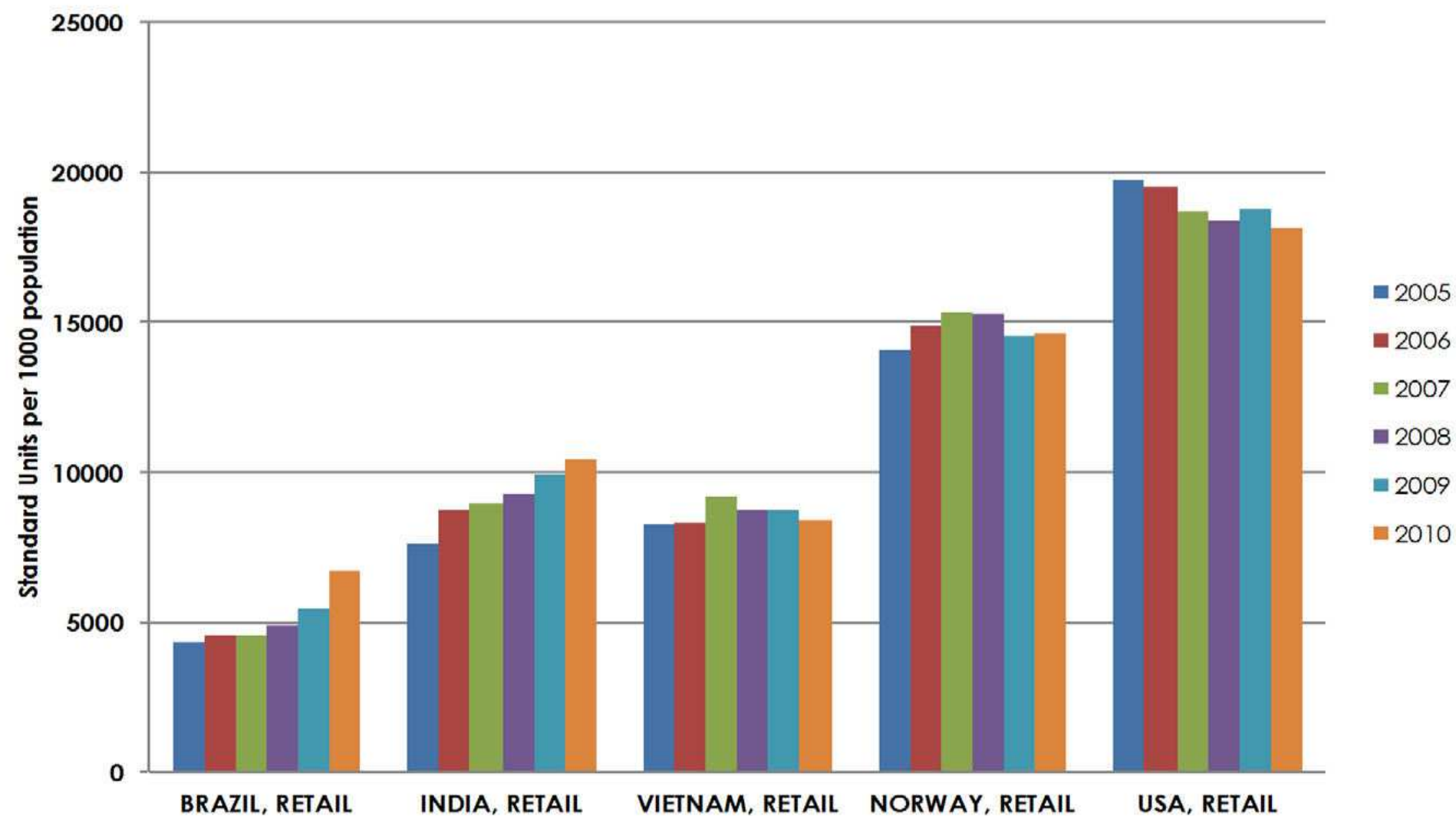
Vaccines, therapeutics, and diagnostics: Invest in development and improved access to vaccines, therapeutics, and diagnostics for better prevention, treatment, and detection



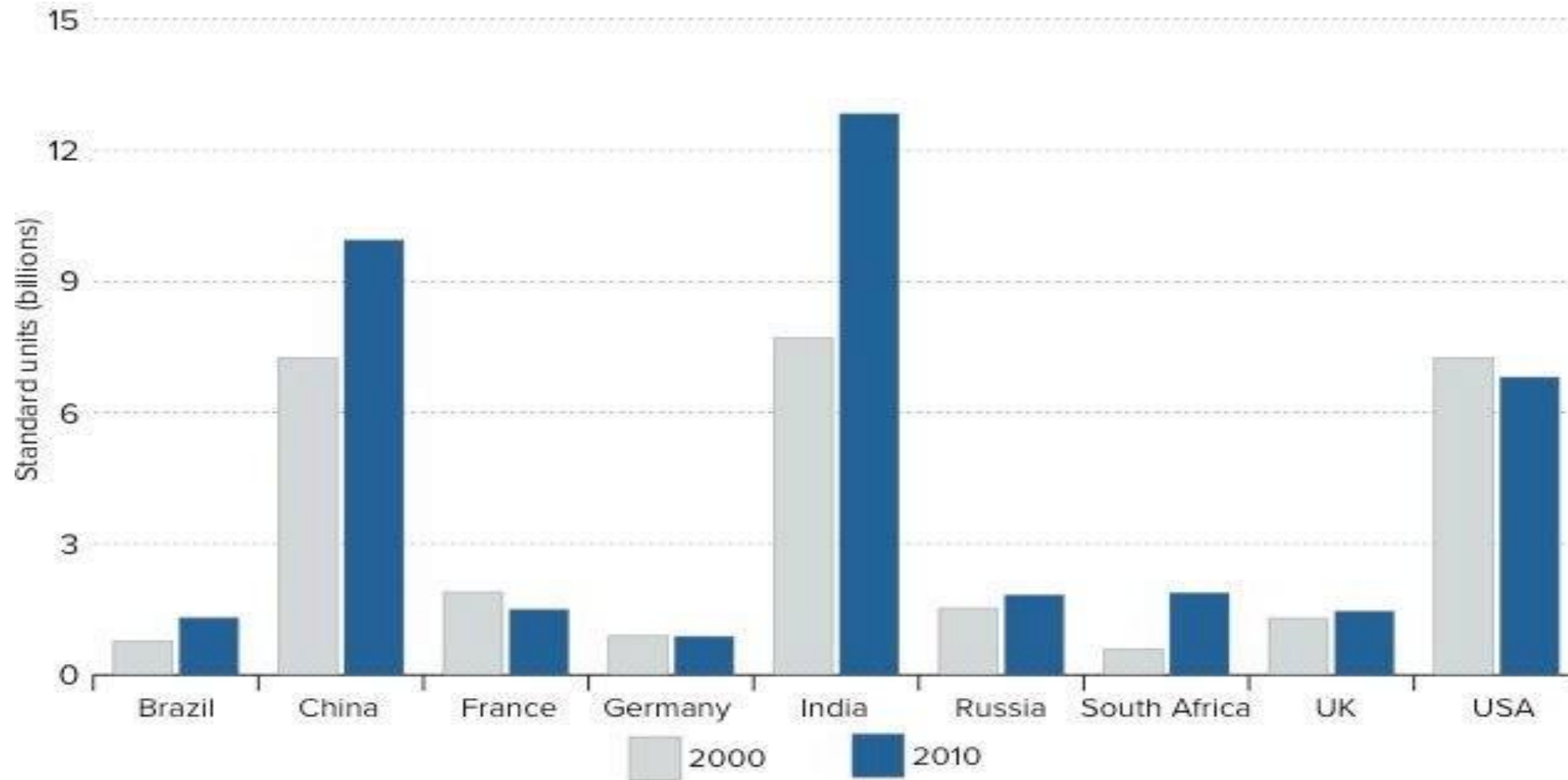
Environment and sanitation: Keep antibiotics and antibiotic-resistant threats from entering the environment through actions like improving sanitation and improving access to safe water



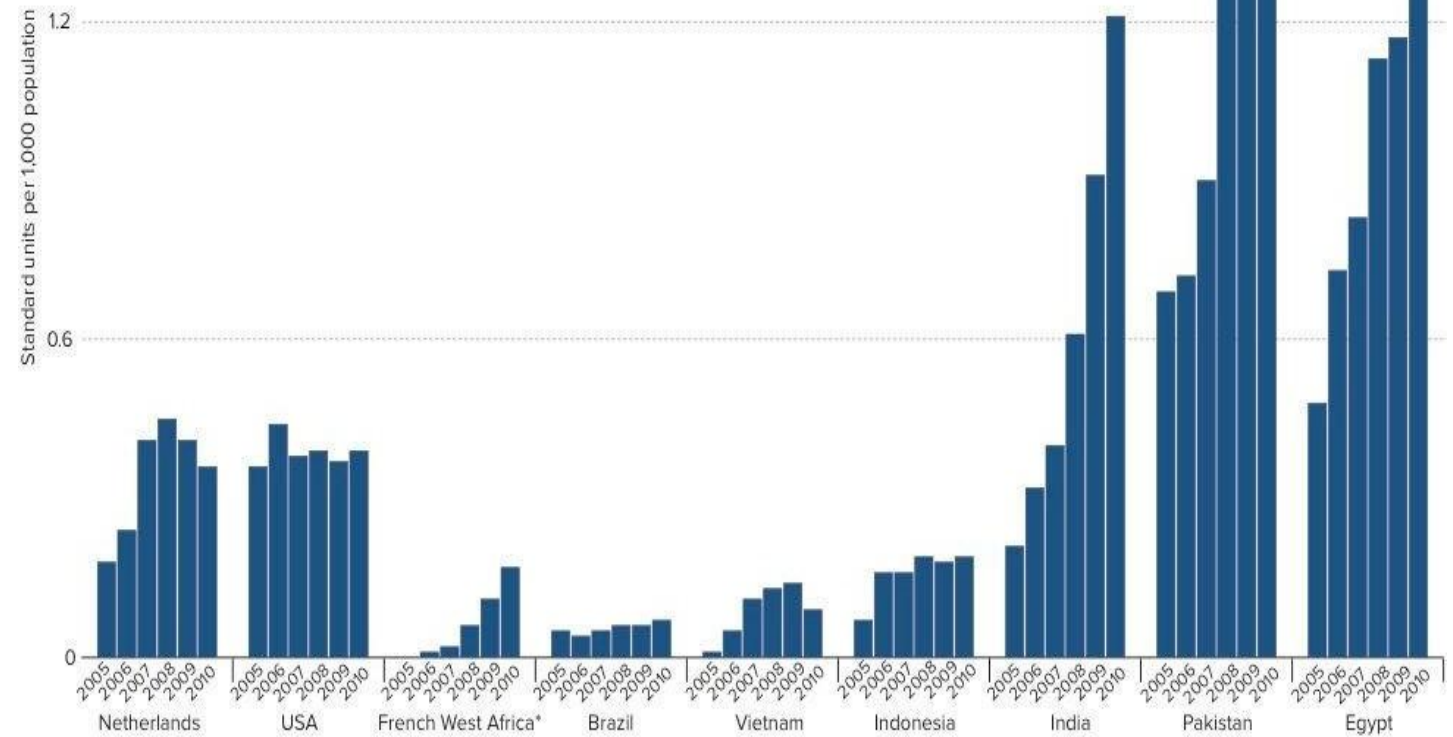
Per capita total antibiotic use, retail sector, 2005-2010

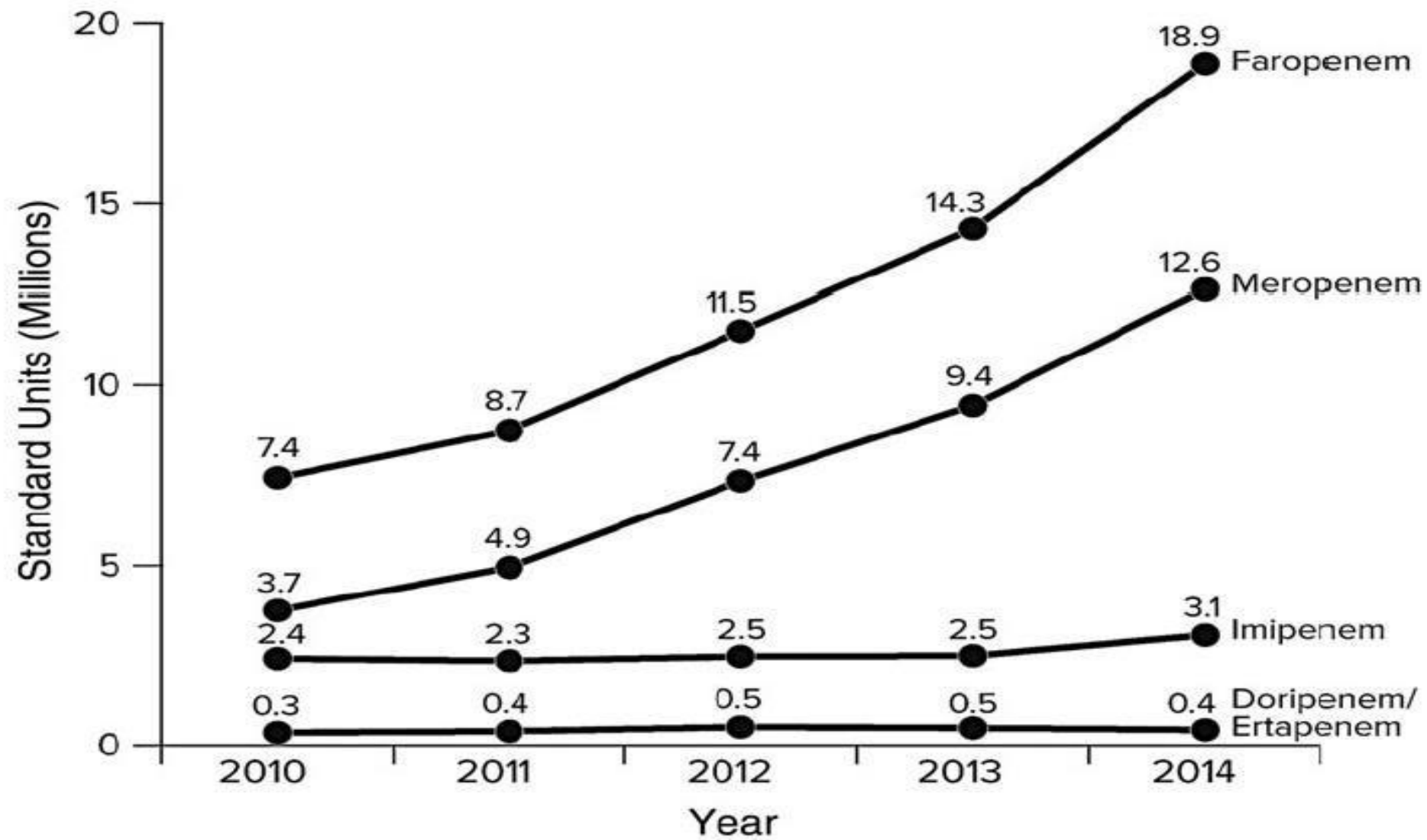


Total antibiotic consumption in selected countries, 2000 and 2010



Carbapenem retail sales in selected countries, 2005–2010 (per 1,000 population)

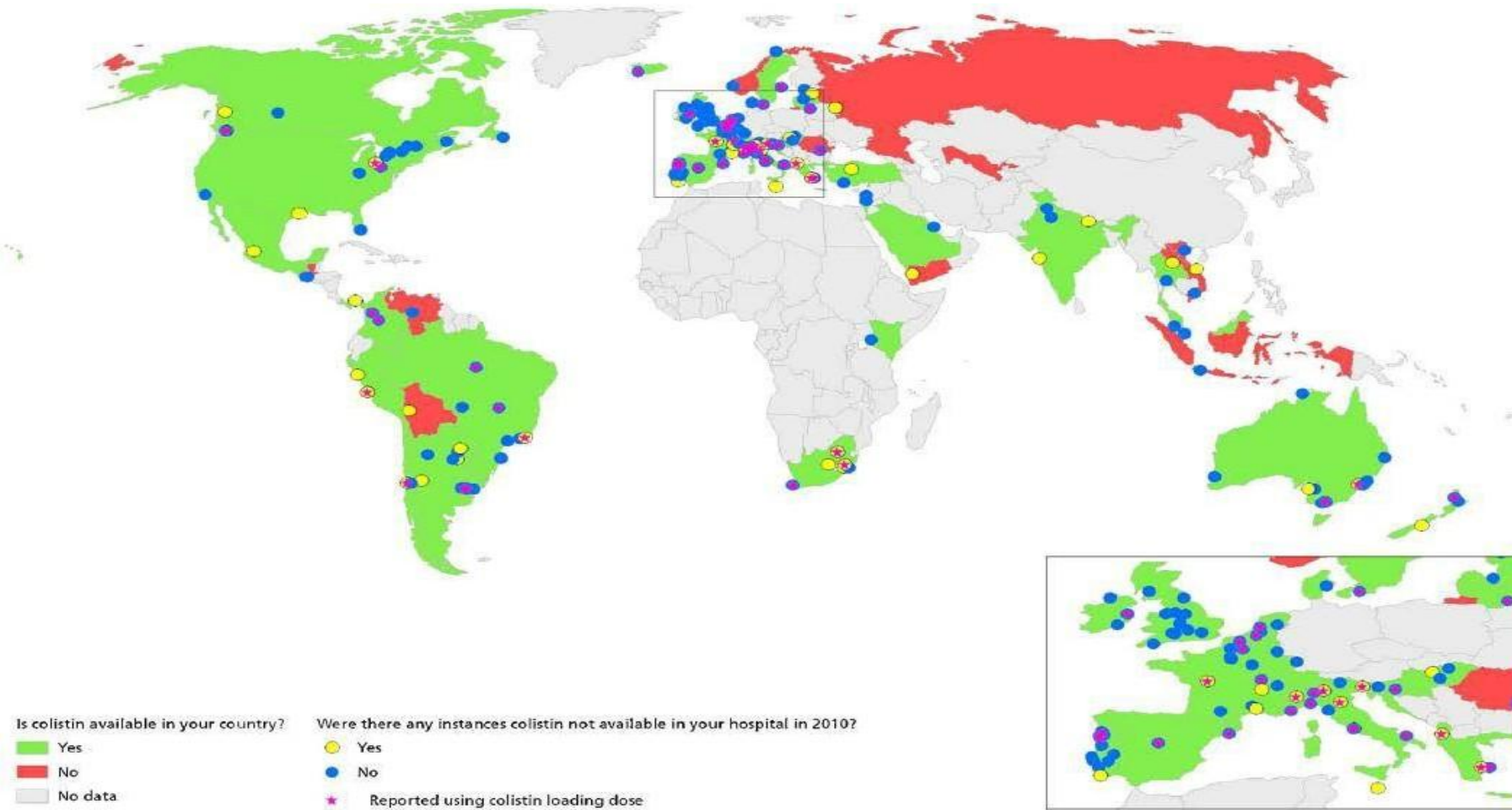




But epidemiology can be local!

- Resistance trends are often local
- Resistance can vary by
 - Country and region
 - Hospital unit
 - Pathogen

Global availability of colistin



Wertheim et al, JGAR 2013

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study



Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Lancet Infect Dis 2015

Published Online

November 18, 2015

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1473-3099(15)00424-7)

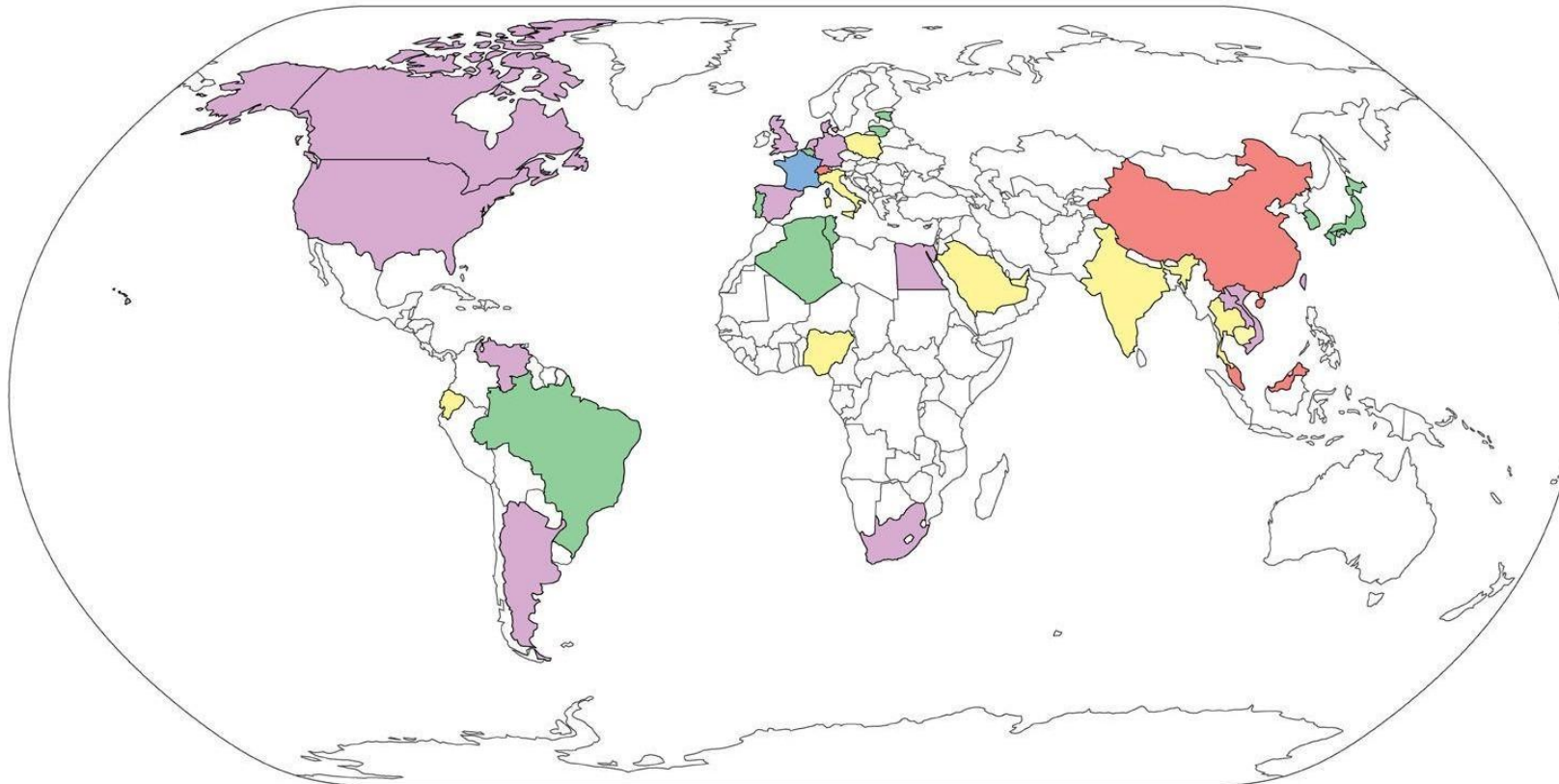
[S1473-3099\(15\)00424-7](http://dx.doi.org/10.1016/S1473-3099(15)00424-7)

See Online/Articles

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1473-3099(15)00462-6)

[S1473-3099\(15\)00462-6](http://dx.doi.org/10.1016/S1473-3099(15)00462-6)

Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*



Isolate source(s):

Animals

Humans

Animals and humans

Animals and environment

Animals, humans
and environment

Data source: Al-Tawfiq, J. A., Laxminarayan, R. & Mendelson, M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? *Int. J. Infect. Dis.* (2016). doi:10.1016/j.ijid.2016.11.415

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.



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

Preventive strategies

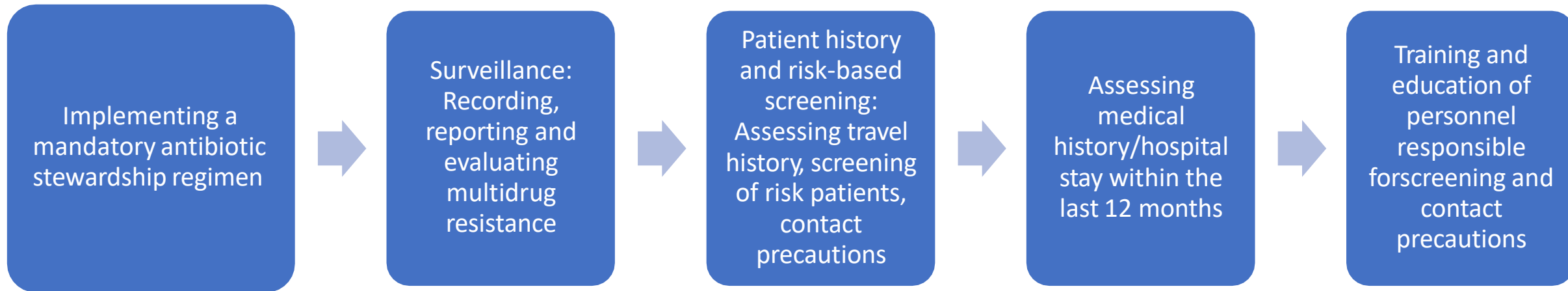
Curtail production, prescription and consumption of antibiotics both in human & veterinary medicine

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

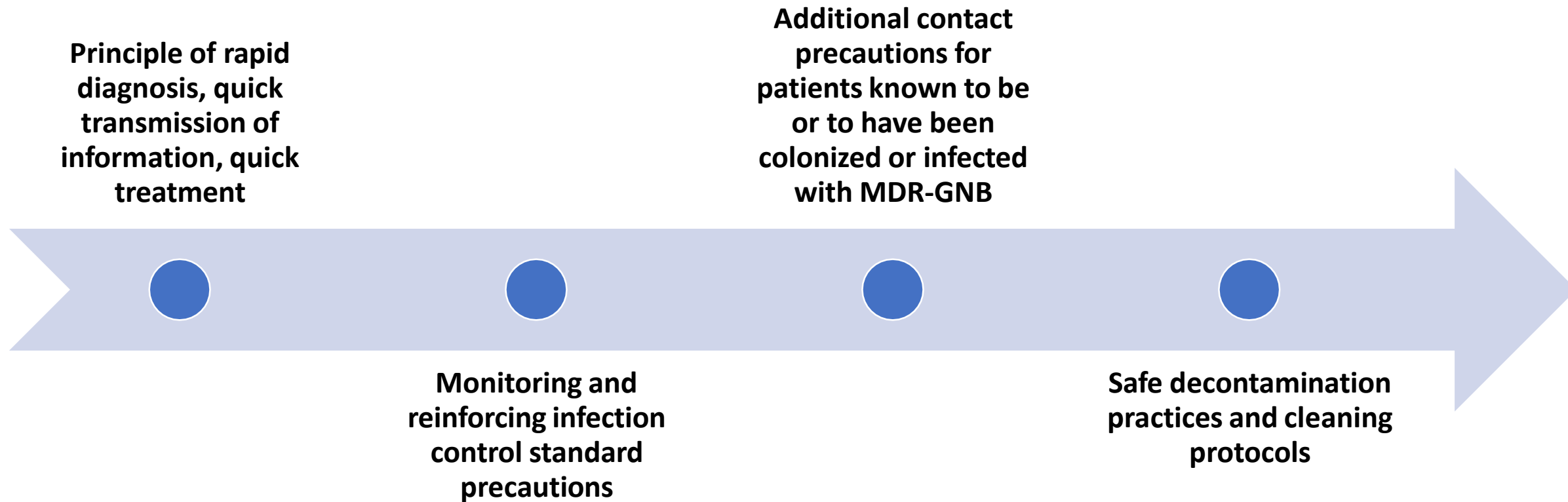
Offering access to clean, affordable water and sanitation to all people

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

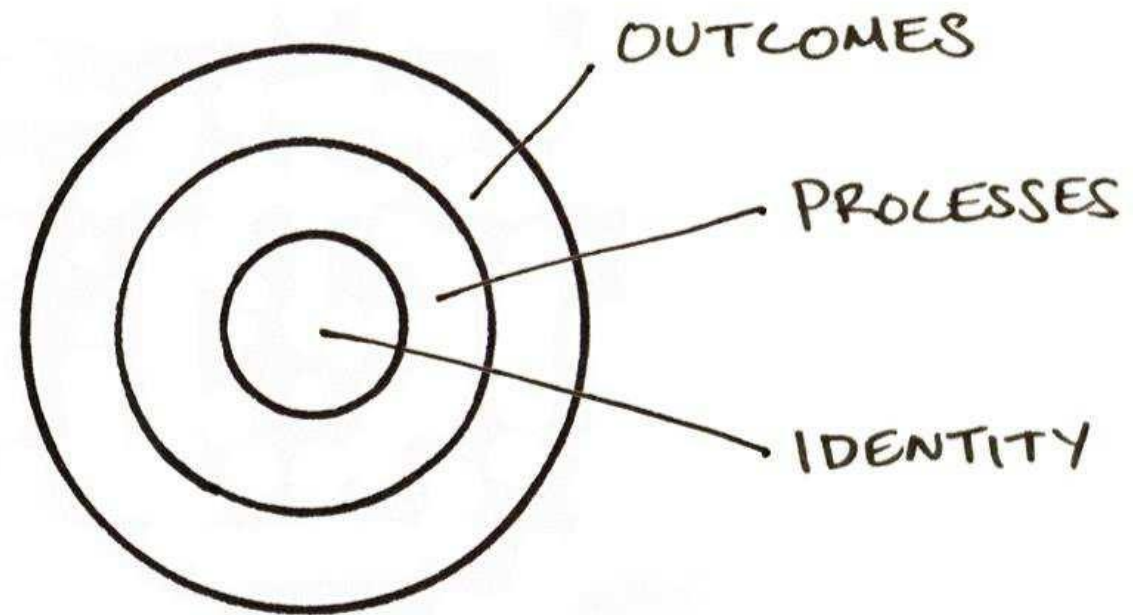
Reservoir- and transmission-based prevention strategies in healthcare & long-term care facilities



Reservoir- and transmission-based prevention strategies in healthcare & long-term care facilities



THREE LAYERS OF BEHAVIOR CHANGE



SPREAD AWARENESS STOP RESISTANCE

Always get advice from a health worker when taking antimicrobial medicines such as antibiotics, antivirals, antifungals and antiparasitics.



**World Health
Organization**



**Antibiotics
Antivirals
Antifungals
Antiparasitics**

SPREAD AWARENESS STOP RESISTANCE

Drug resistance is increasing in post-operative infections, making surgeries including caesarean sections, organ transplants, and joint replacements riskier.



**World Health
Organization**



Antibiotics
Antivirals
Antifungals
Antiparasitics

SPREAD AWARENESS STOP RESISTANCE

Antimicrobial resistance leads to longer hospital stays,
higher medical costs and increased mortality.

Good hand hygiene can help limit the spread of infections.



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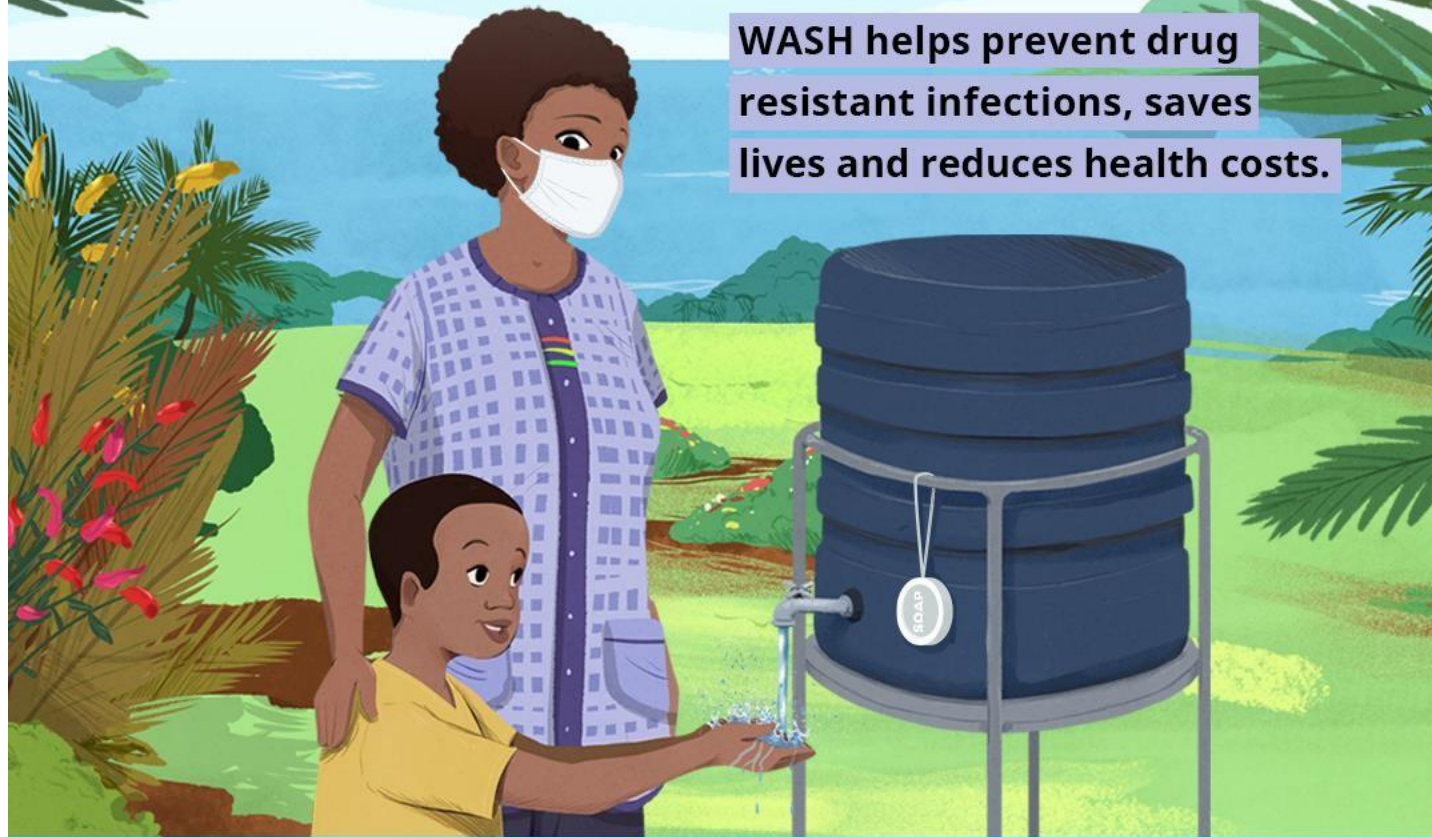


Antibiotics
Antivirals
Antifungals
Antiparasitics

SPREAD AWARENESS STOP RESISTANCE

Access to safe water, sanitation and hygiene (WASH) in homes and health facilities can reduce antibiotic use to treat diarrhoea by up to 60%.

WASH helps prevent drug resistant infections, saves lives and reduces health costs.



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Organization

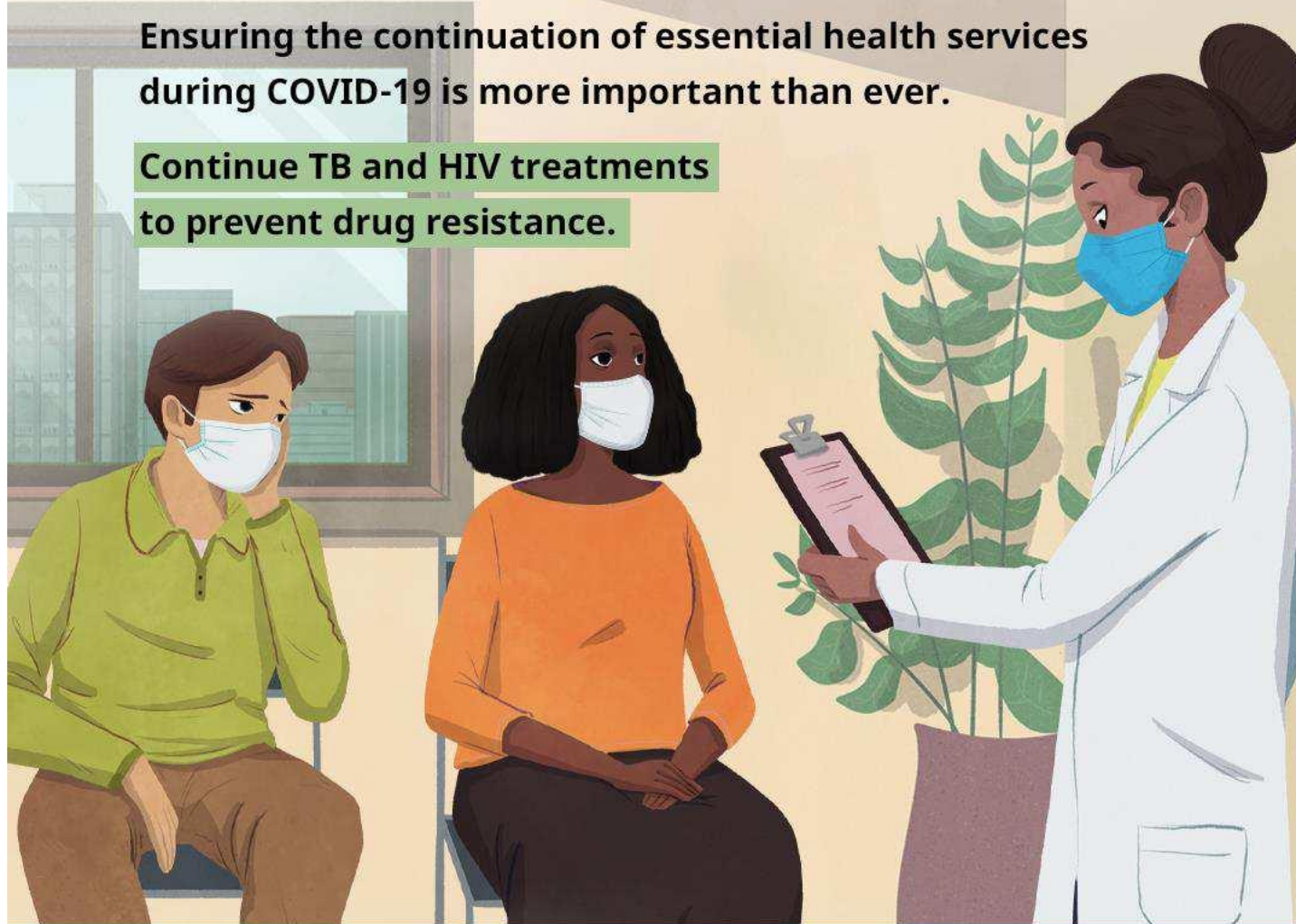


Antibiotics
Antivirals
Antifungals
Antiparasitics

SPREAD AWARENESS STOP RESISTANCE

Ensuring the continuation of essential health services during COVID-19 is more important than ever.

Continue TB and HIV treatments to prevent drug resistance.



World Health
Organization



Antibiotics
Antivirals
Antifungals
Antiparasitics

THANK YOU

ANTIBIOTICS USE-RESPONSIBLY



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

