Antimicrobial resistance

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Why is antimicrobial resistance a global concern?

- **New resistance mechanisms** are **emerging** and **spreading globally**
- Without effective antimicrobials for prevention and treatment of infections, medical procedures such as **organ transplantation**, **cancer chemotherapy**, **diabetes management** and **major surgery** **become very high risk**.
- Cost
- Prolonged illness
- Lengthier stays in hospitals
- Mortality

Antibiotic resistance

- "BBC News 2013" — Antibiotics resistance **as big a risk as terrorism** on a list of threats to the nation.

Professor Dame Sally Davies

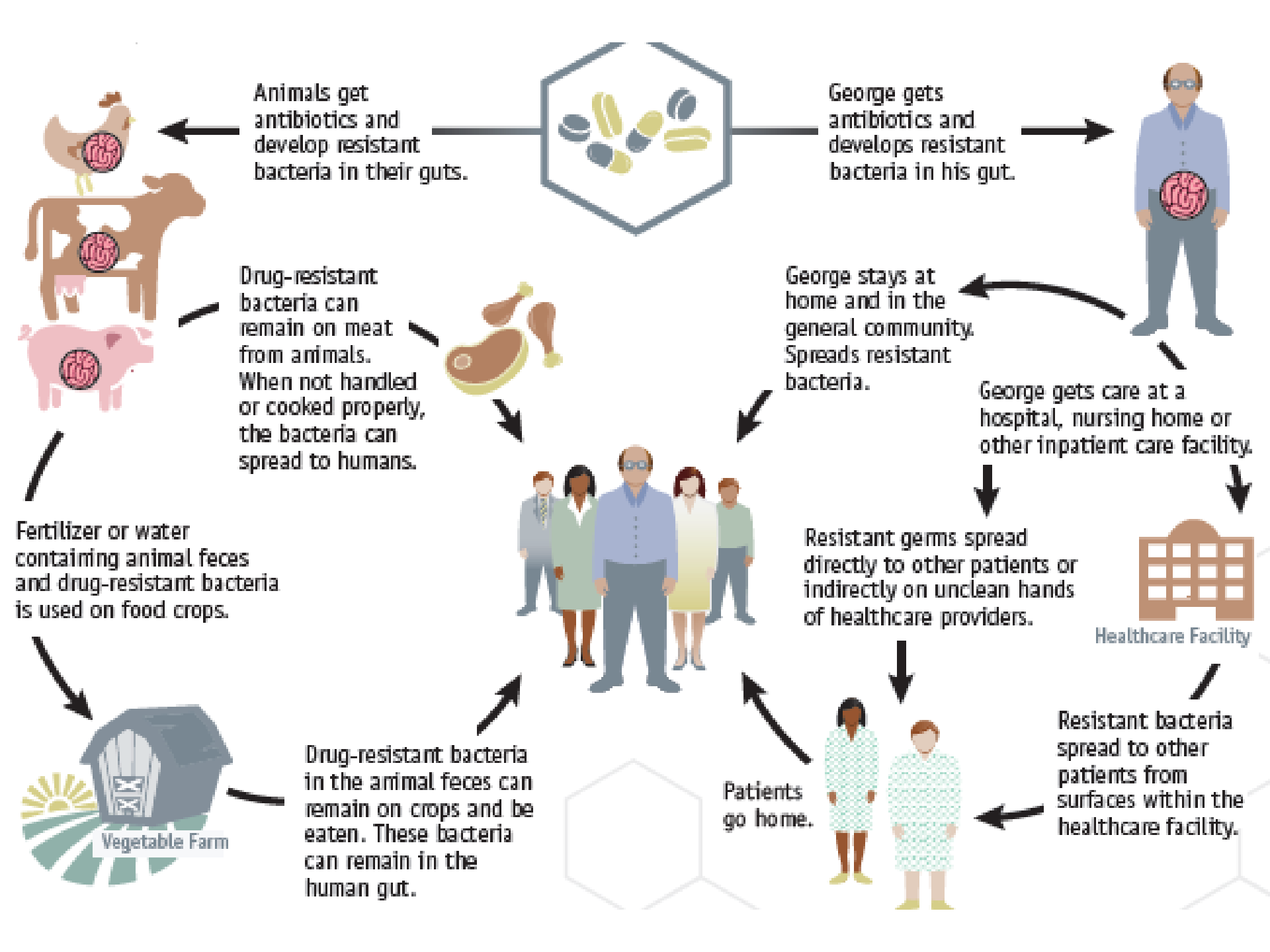
Hematologist

https://www.bbc.co.uk/news/health-21737844

What accelerates the emergence and spread of antimicrobial resistance?

- Antimicrobial resistance occurs **naturally over time**, usually through genetic changes.

- However, the **misuse** and **overuse** of antimicrobials is accelerating this process.


Animals get antibiotics and develop resistant bacteria in their guts.
George gets antibiotics and develops resistant bacteria in his gut.
Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.
George stays at home and in the general community. Spreads resistant bacteria.
George gets care at a hospital, nursing home or other inpatient care facility.
Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.
Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.
Healthcare Facility
Vegetable Farm
Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.
Patients go home.
Resistant bacteria spread to other patients from surfaces within the healthcare facility.

History of Antibiotics

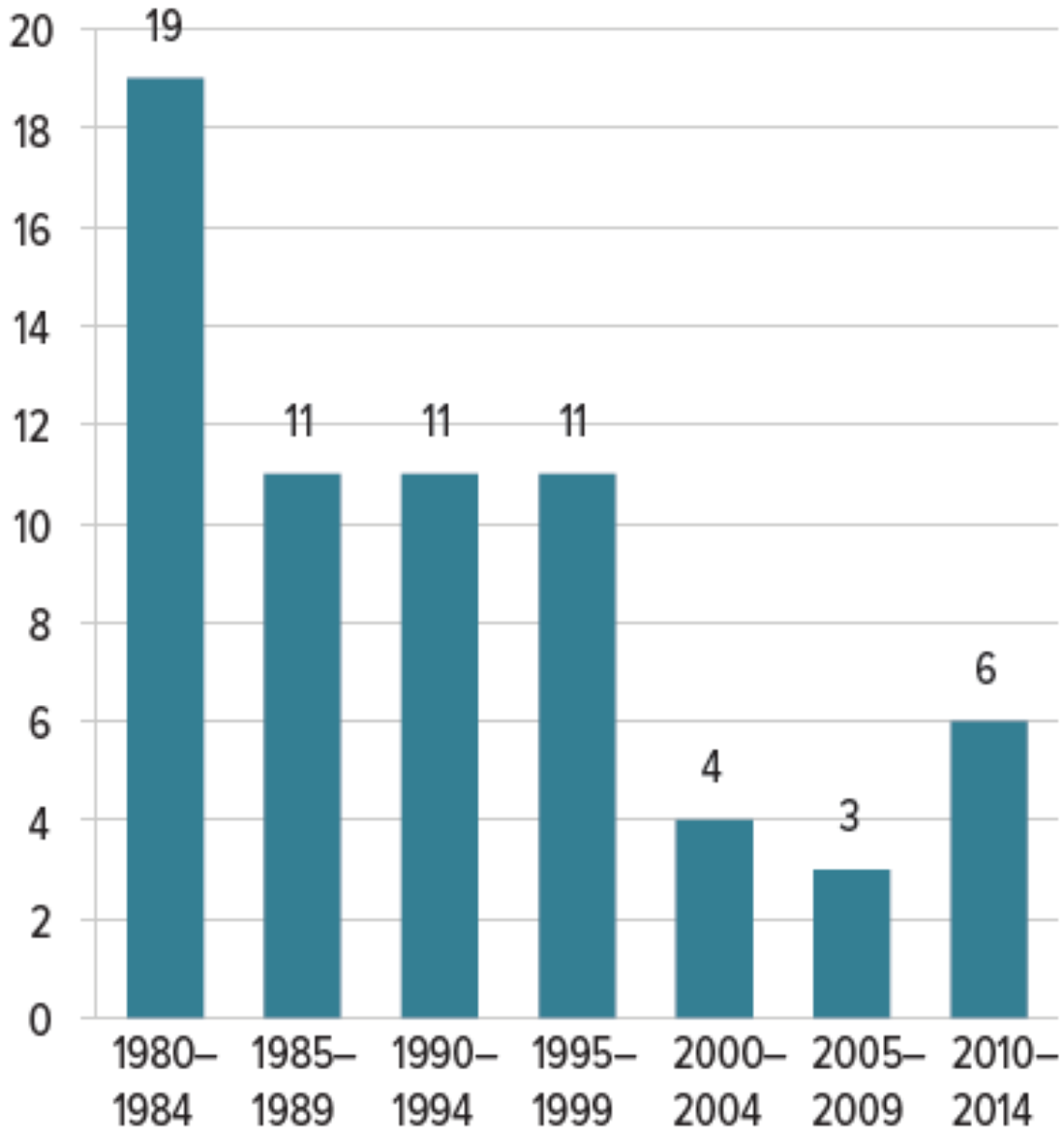
- When Fleming won the Nobel Prize for his discovery, he warned of bacteria becoming resistant to penicillin in his acceptance speech (1945).

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant **Staphylococcus aureus**	1942
		Penicillin-resistant **Streptococcus pneumoniae**	1967
		Penicillinase-producing **Neisseria gonorrhoeae**	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant **Enterococcus faecium**	1988
		Vancomycin-resistant **Staphylococcus aureus**	2002
Amphotericin B	1959	Amphotericin B-resistant **Candida** auris	2016

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Methicillin	1960	Methicillin-resistant **Staphylococcus aureus**	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase-producing Escherichia coli	1983
Azithromycin	1980	Azithromycin-resistant **Neisseria gonorrhoeae**	2011
Imipenem	1985	**KPC**	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant **Neisseria gonorrhoeae**	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant **Candida**	1988

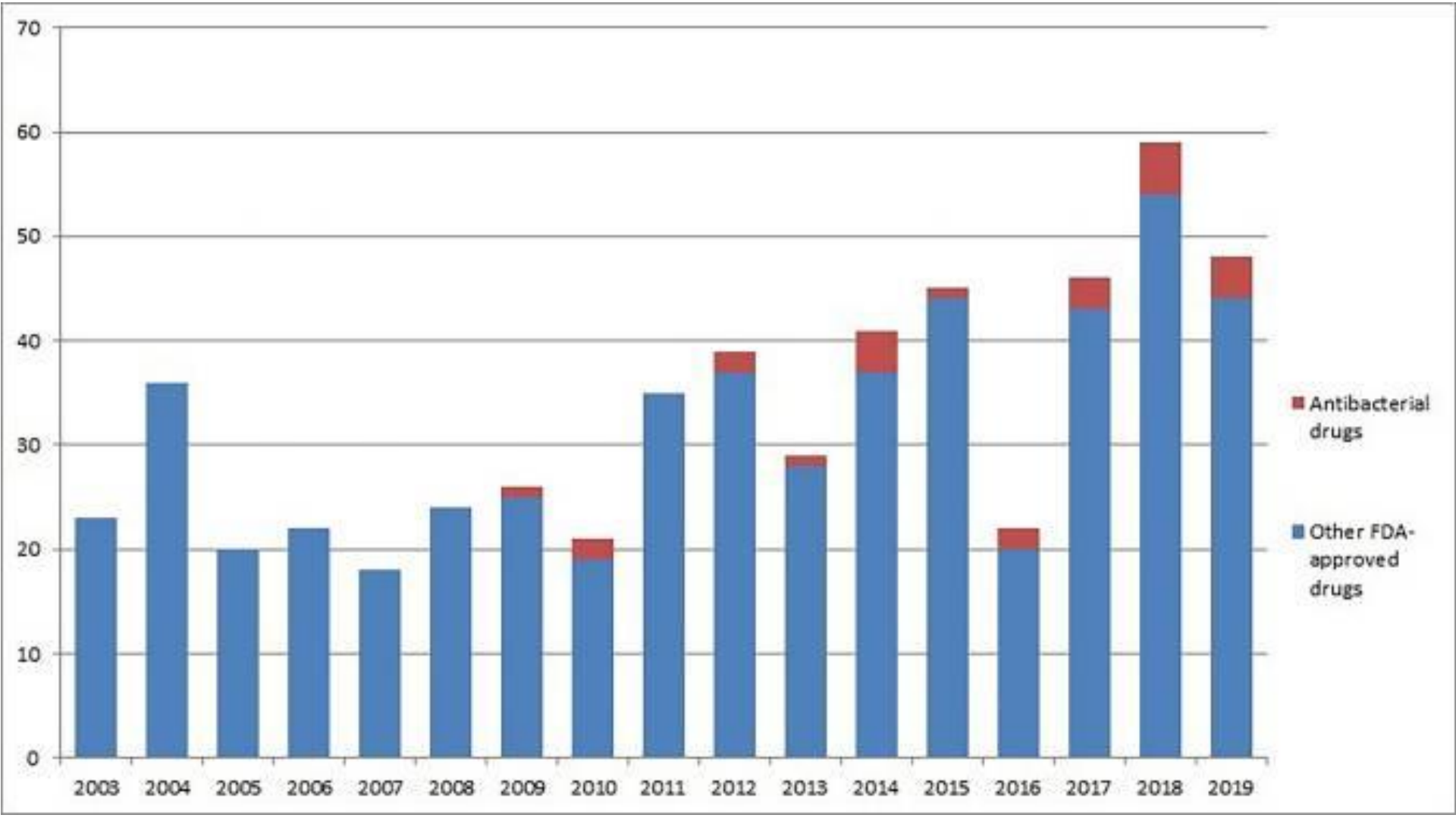
Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Caspofungin	2001	Caspofungin-resistant **Candida**	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant **Staphylococcus aureus**	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing **Klebsiella pneumoniae**	2015

Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



2015-2019
15 new antibacterial Agents approved

Novel FDA-approved antibacterial and non-bacterial drugs by year



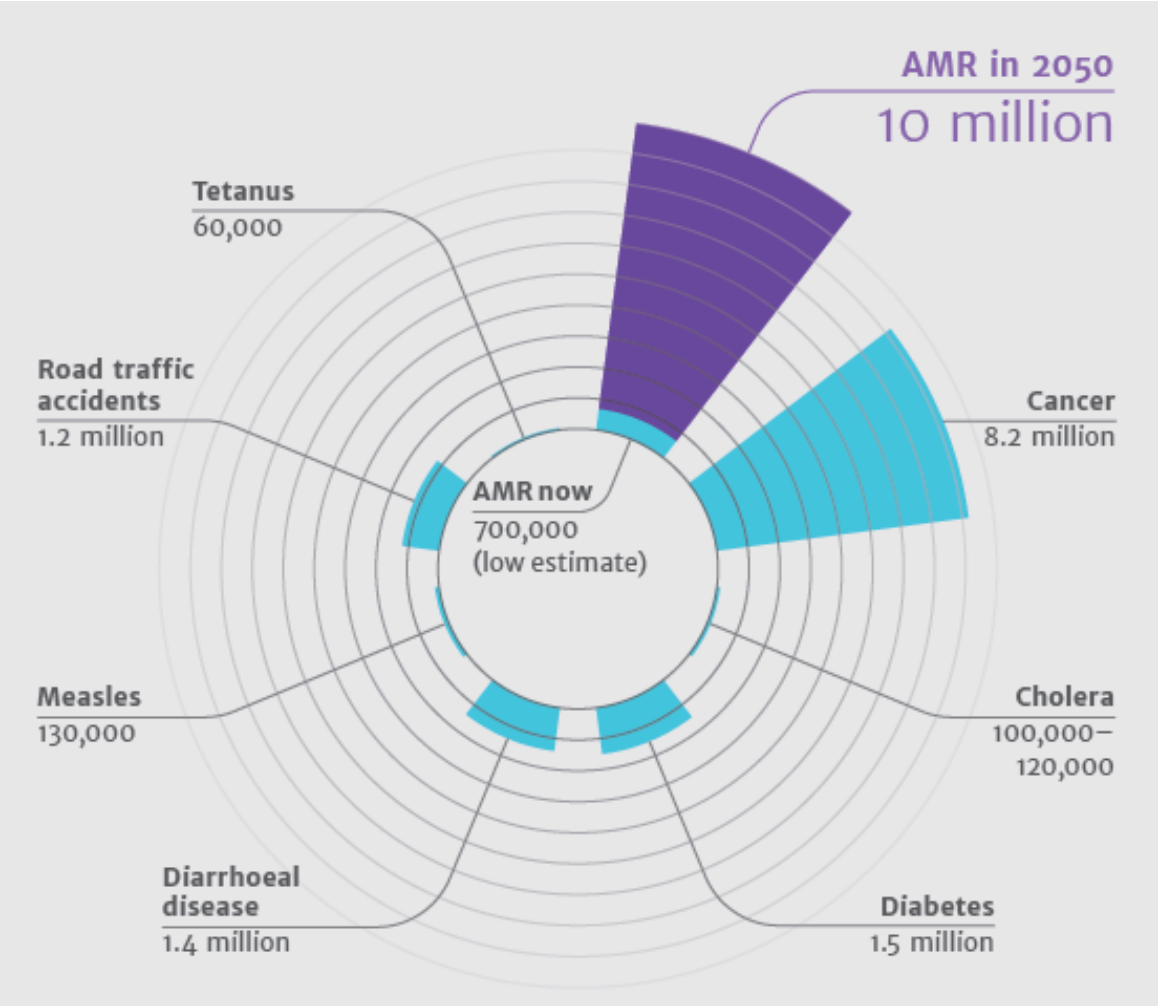

NATIONAL
SUMMARY DATA
Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:
At least 2,049,442 illnesses,
23,000 deaths
*bacteria and fungus included in this report

Mortality Rates by 2050 by Condition

Cancer	8.2 Million
Cholera	100000 - 120000
Diabetes	1.5 Million
Diarrheal Disease	1.4 Million
Measles	130000
Road Traffic Accidents	1.2 Million
Tetanus	60000
Antimicrobial Resistance	10 Million

Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014. Available from: https://amr-review.org/sites/default/files/AMR Review Paper - Tackling a crisis for the health and wealth of nations_1.pdf. Accessed September17, 2019.

Deaths attributable to AMR every year compared to other major causes of death



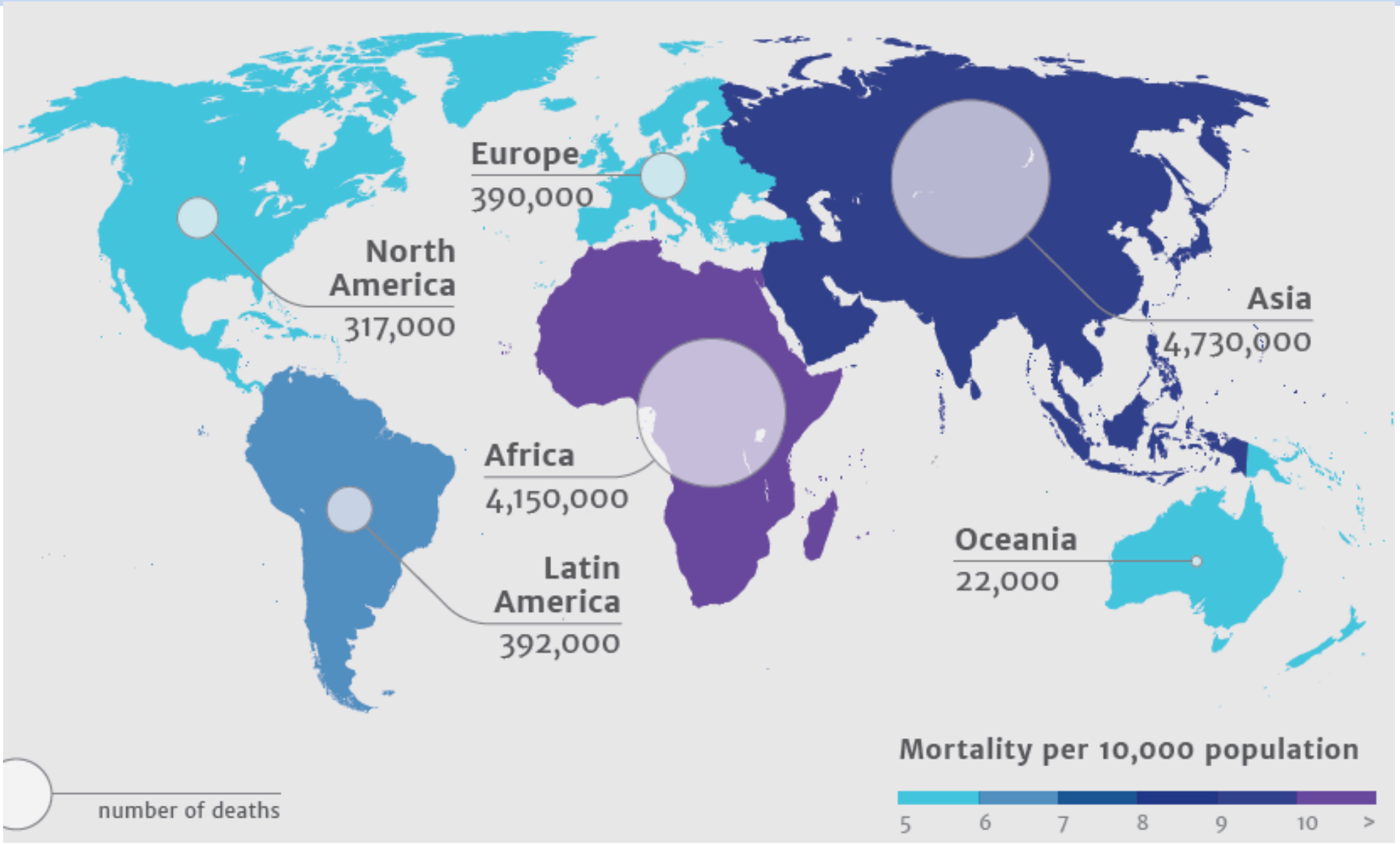
O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014.

Mortality Rates by 2050 Due to AMR in Different Regions

Asia	۴’۷۳۰’۰۰۰
Africa	۴’۱۵۰’۰۰۰
Europe	۳۹۰’۰۰۰
Latin America	۳۹۲’۰۰۰
North America	۳۱۷’۰۰۰
Oceania	۲۲’۰۰۰

Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014. Available from: https://amr-review.org/sites/default/files/AMR Review Paper - Tackling a crisis for the health and wealth of nations_1.pdf. Accessed September17, 2019.

Deaths attributable to AMR every year by 2050



O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014.

Cost

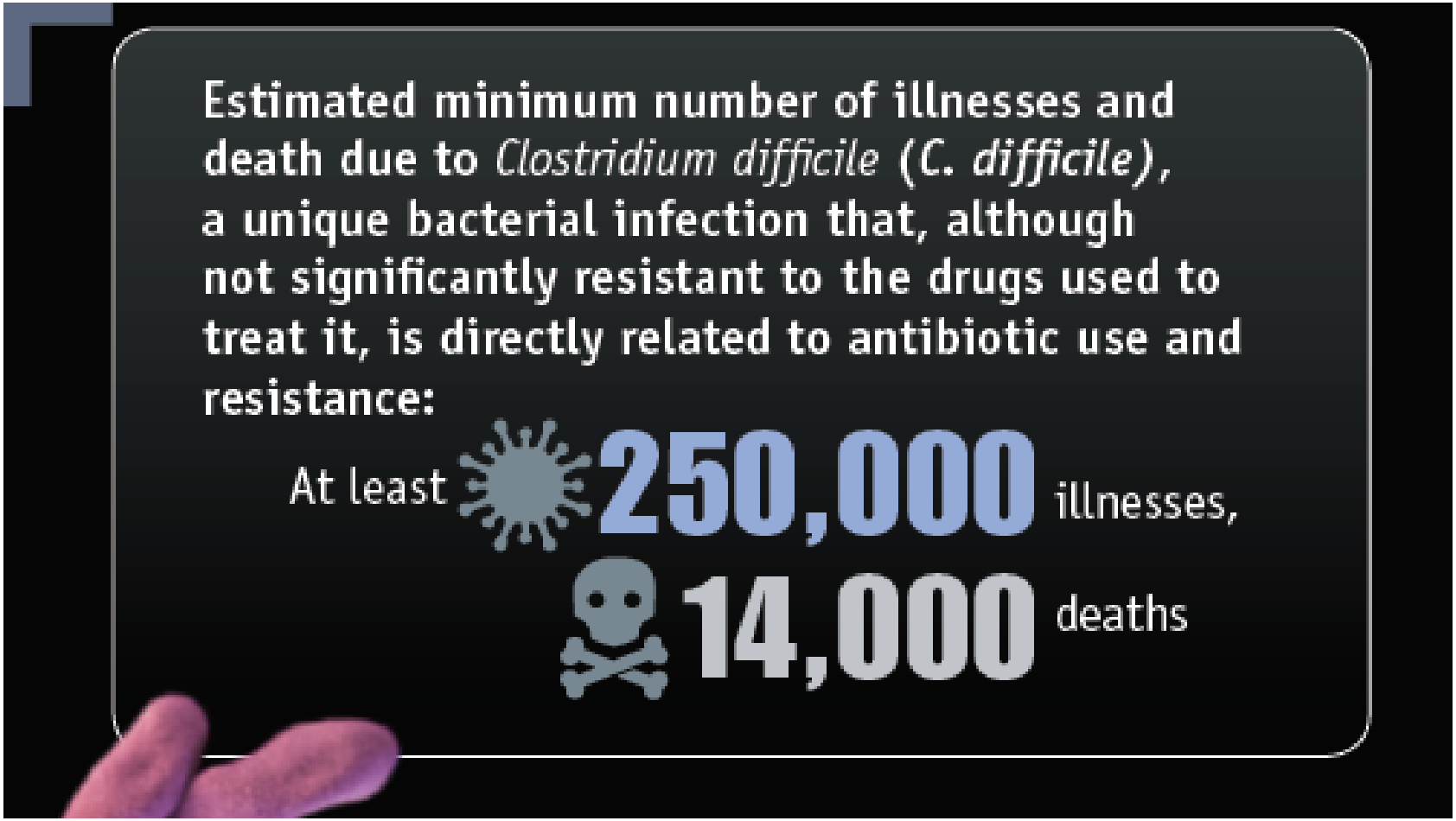
- The estimated national cost to treat infections caused by multidrug-resistant germs identified in the report and frequently found in health care can be substantial—more than **$4.6 billion annually**.

Cost

- According to different studies, it is projected that AMR could cost from **$300 billion** to more than **$1 trillion annually by 2050 worldwide**.

- The CDC estimated that the cost of antimicrobial resistance is **$55 billion every year in the United States**, **$20 billion for health care** and about **$35 billion for loss of productivity**.

Dadgostar P. Antimicrobial resistance: implications and costs. Infection and drug resistance. 2019;12:3903.


Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:
At least 250,000 illnesses,
14,000 deaths

Four Core Actions to Fight Resistance

1 PREVENTING INFECTIONS, PREVENTING THE SPREAD OF RESISTANCE

Avoiding infections in the first place reduces the amount of antibiotics that have to be used and reduces the likelihood that resistance will develop during therapy. There are many ways that drug-resistant infections can be prevented: immunization, safe food preparation, handwashing, and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.

Four Core Actions to Fight Resistance

2 TRACKING

CDC gathers data on antibiotic-resistant infections, causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

Four Core Actions to Fight Resistance

3 IMPROVING ANTIBIOTIC PRESCRIBING/STEWARDSHIP

Perhaps the single most important action needed to greatly slow down the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe. Stopping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria. This commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease, and to choose the right antibiotics and to administer them in the right way in every case—is known as antibiotic stewardship.

Four Core Actions to Fight Resistance

4 DEVELOPING NEW DRUGS AND DIAGNOSTIC TESTS

Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not stopped. Therefore, we will always need new antibiotics to keep up with resistant bacteria as well as new diagnostic tests to track the development of resistance.

Awareness and Education

- **Raising awareness** about the threat of resistance and the need to improve use is critical to tackling the issue.

- Almost two thirds (**64%**) of some **10,000 people** surveyed by the World Health Organization (WHO) across **12 countries** say they know **antibiotic resistance** is an issue that could affect them and their families, but **how it affects** them and **what they can do** to address it are not well understood.

- For example, **64%** of respondents believe **antibiotics can be used to treat colds and flu**, despite the fact that antibiotics have no impact on viruses.

Urgent Threats	Serious Threats	Concerning Threats
Carbapenem-resistant Acinetobacter	Drug-resistant Campylobacter	Erythromycin-Resistant Group A Streptococcus
Candida auris	Drug-resistant Candida	Clindamycin-resistant Group B Streptococcus
Clostridioides difficile	ESBL-producing Enterobacterales	
Carbapenem-resistant Enterobacterales	VRE	
Drug-resistant Neisseria gonorrhoeae	Multidrug-resistant Pseudomonas aeruginosa	
	Drug-resistant nontyphoidal Salmonella	
	Drug-resistant Salmonella serotype Typhi	
	Drug-resistant Shigella	
	MRSA	
	Drug-resistant Streptococcus pneumoniae	
	Drug-resistant Tuberculosis	

Resistant bacteria

- The World Health Organization (WHO) reported **more than 50%** of strains of ***Escherichia coli*** and ***Klebsiella pneumoniae*** were resistant to **third generation cephalosporins** and **quinolones** in many areas worldwide.

World Health Organization. Antimicrobial resistance global report on surveillance. 2014. Available at http://www.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf. Accessed 13 Nov 2018.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Impact on Morbidity, Mortality, and Length of Stay of Hospital-Acquired Infections by Resistant Microorganisms

J. Ignacio Barrasa-Villar,[1,3] Carlos Aibar-Remón,[1,2,3] Purificación Prieto-Andrés,[1,3] Rosa Mareca-Doñate,[1] and Javier Moliner-Lahoz[1,3]

[1]Preventive Medicine and Public Health Unit, Clinical University Hospital of Zaragoza and [2]Public Health Department, University of Zaragoza, and [3]Research Group on Health Services-Instituto de Investigación Sanitaria, Aragón, Spain

- **Patients with resistant infections** have a **mortality rate** and **financial burden two times higher** than that of patients with susceptible infections.

The best antimicrobial therapy

- The best antimicrobial therapy was defined by Joseph and Rodvold as the four **Ds**:

- "right **d**rug, right **d**ose, **d**e-escalation and right **d**uration"

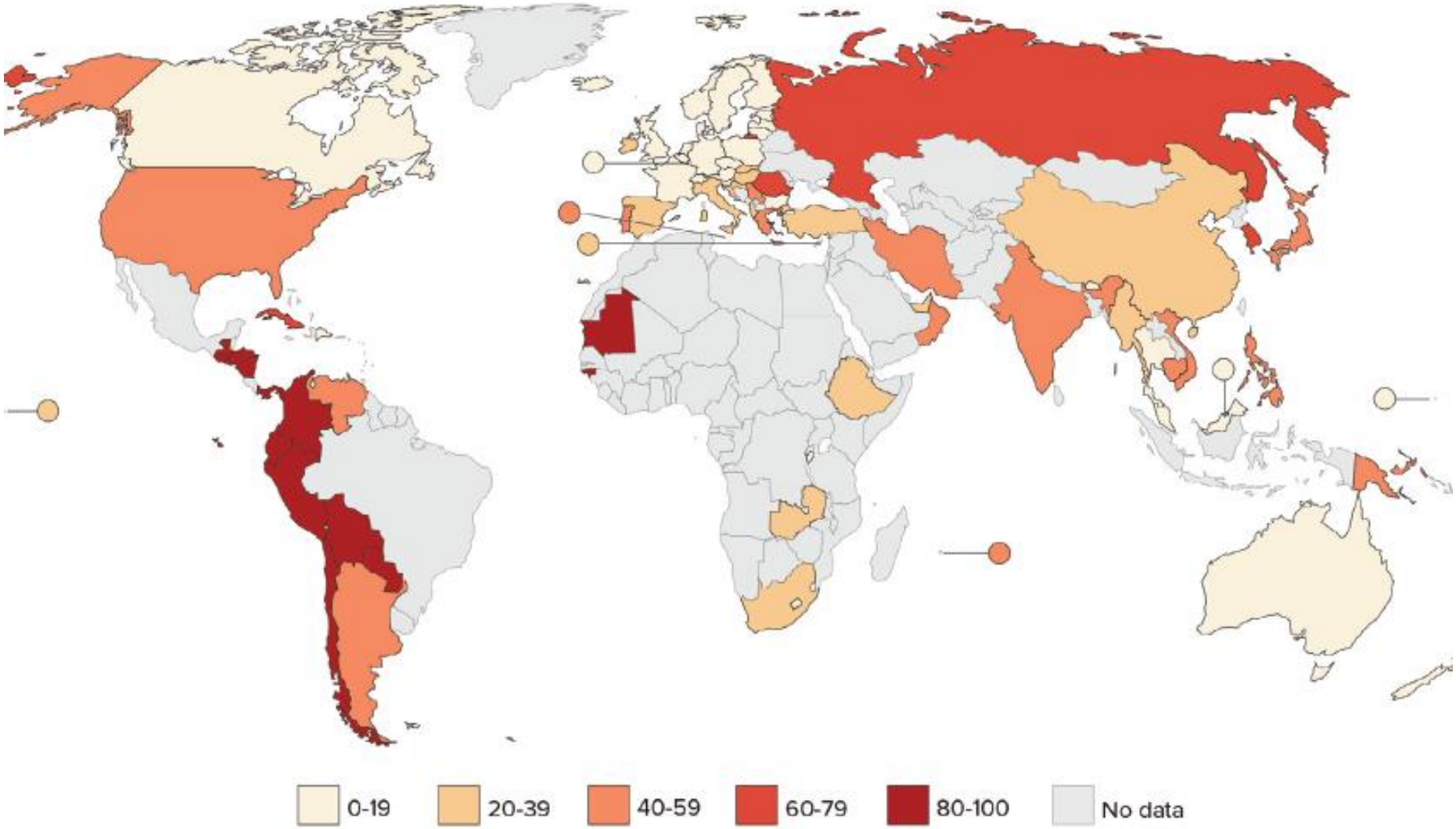
Joseph J, Rodvold KA. The role of carbapenems in the treatment of severe nosocomial respiratory tract infections. Expert Opin Pharmacother. 2008;9:561–75.

Resistance Mechanisms in Staphylococcus aureus

- ***SA*** → beta-lactamase → Penicillin, amoxicillin and ampicillin

- ***MRSA*** → modification of a PBP → resistant to all beta-lactams (penicillins, beta-lactamases inhibitors, cephalosporins, and carbapenems) with the exception of ceftaroline—a cephalosporin that binds to PBP2a.

MRSA



MRSA

- Healthcare-associated MRSA infection
- Community-associated MRSA infection

- MRSA infection that occurs **>48 hours** following hospitalization

- MRSA infection that occurs outside of the hospital **within 12 months of exposure to healthcare** (eg, history of surgery, hospitalization, dialysis, or residence in a long-term care facility

Risk factors for HA-MRSA infection

- Antibiotic use
- Prolonged hospitalization
- Intensive care
- Hemodialysis

- HIV infection
- Long-term care facilities
- IDU

Risk factors associated with post-discharge MRSA infection

- MRSA colonization
- Discharge to a nursing home
- Presence of a chronic wound
- Discharge with a central venous catheter or other invasive device

Antibiotic use

- Antibiotic use (particularly **cephalosporin** and **fluoroquinolone** use) strongly correlates with the risk for MRSA colonization and infection.

MRSA Complication

- Higher mortality
- Longer hospital stays
- Higher healthcare costs

Patients with BSI due to MRSA were 1.5- to 2.0-fold more likely to die than patients with BSI due to MSSA

Patients with infection due to MRSA also have **higher rates of acute renal failure**, **hemodynamic instability**, and **prolonged ventilator dependency than patients with infection due to MSSA**

Resistance Mechanisms in Staphylococcus aureus

- ***VRSA*** → is very rare and is mediated by the vanA gene.

- ***VISA*** → thickening of the bacterial cell wall → decreases the capacity of penetration.

- ***Resistance to daptomycin →*** has been described recently and is related to changes in the homeostasis of the bacterial cellular membrane.

Resistance Mechanisms in Staphylococcus aureus

- **Resistance to linezolid** is still infrequent (less than 1% worldwide) → modification of ribosomal portion.

Resistance to Vancomycin of Enterococcus faecium

- First-line antibiotics against Enterococcus species are **ampicillin**; over time, Enterococcus resistant due to the **hyperexpression of a PBP 5** that has low affinity to penicillin and carbapenems.

- **VRE** → is mediated by the **vanA gene** mainly that produces a modification of the target site in the **peptidoglycan** at the level of the **termination d-ala-d-ala** → **d-ala-d-lac decreases** the affinity to **vancomycin**.

VRE

- Is mediated by the vanA gene → Replacement of **D-Ala-D-Ala**– ending peptidoglycan precursors with D-alanyl-D-lactate termini
- Vancomycin binds with significantly lower **affinity**
- 1980
- Vancomycin resistance had increased to **33 percent** among enterococci that caused healthcare-associated infections in 2006 and 2007

VRE RISK FACTORS

- Previous antimicrobial therapy
- Hospitalization longer than 72 hours
- Exposure to contaminated surfaces
- Residence in long-term care facilities

Previous antimicrobial therapy

- The most consistently observed risk factor for hospital acquisition of VRE is previous treatment with antimicrobials, particularly **vancomycin** and **cephalosporins**.

- **Carbapenems**
- **Metronidazole, Piperacillin-tazobactam, and Quinolones**

ESBL

- ***beta-lactamases*** → possess a serine in their catalytic site → **hydrolyze all the cephalosporins** in larger or lesser extent except for the cephamycins and are inhibited by **beta-lactamases inhibitors, especially clavulanic acid**

AmpC

❑ AmpC-type cephalosporinases

- These enzymes are **chromosomal**
- These enzymes have the capacity to hydrolyze all **penicillins** including **beta-lactamases inhibitors**; **first-, second-, and third-generation cephalosporins**; and **cephamycins** and conserve susceptibility to **cefepime**.
- **However**, there can be resistance to fourth-generation cephalosporins due to a **hyperproduction of AmpC**.

AmpC

- It is very important to keep in mind that **unlike ESBL**, bacteria with **chromosomally encoded** AmpC may not express the enzyme, and thus the antibiogram will show **susceptibility to beta-lactam inhibitors and cephalosporins**. But this type of antibiotics should not be used.

- Traditionally it has been considered that the main treatment options for bacteria with this type of resistance are ***cefepime*** and ***carbapenems***.

Carbapenemases

- **Hydrolyzing carbapenems**

- Classified into **two groups** according to the substrate they have in the catalytic center:
- **Serine-type** carbapenemases
- **Metallocarbapenemases**

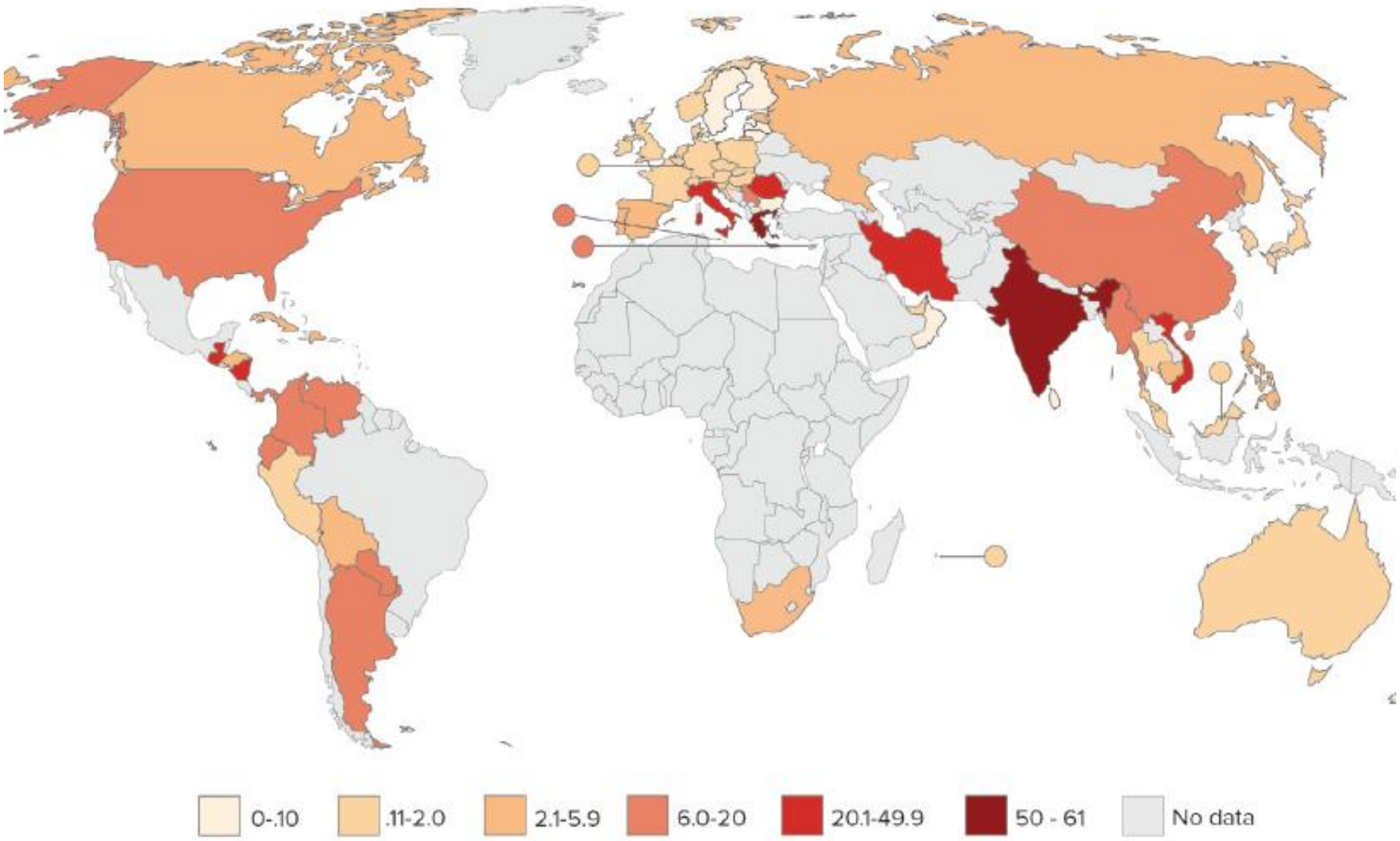
- Along with the production of carbapenemases, other genes that confer resistance to other families of antibiotics are expressed, such as **tigecycline**, **fluoroquinolones**, or **aminoglycosides**.

Carbapenemases

- **Serine-type carbapenemases** such as GES, KPC, SME, or IMI are capable of hydrolyzing all **penicillins**, **cephalosporins**, **aztreonam**, and **carbapenems.**

- **Metallo-carbapenemases** like VIM, IMP, and NDM do **not hydrolyze aztreonam**.

KPC



KPC

Resistance	Sensitive
Ceftriaxone Cefotaxime Ceftazidime Gentamycin Meropenem Piperacillin-tazobactam	Amikacin

Previous antimicrobial therapy

- **Glycopeptides**
- **Fluoroquinolones**
- **Cephalosporins**

Resistance Mechanisms in Non-fermented Gram-Negative Bacillus

- ***Pseudomonas aeruginosa***
- ***Acinetobacter baumannii***

❑ ***Resistance mechanisms:***

- ***Production of carbapenemases (OXA &*** **metallo-carbapenemases)**
- ***Activation of efflux pumps***
- ***Porin downregulation***
- ***Modification of PBPs.***

Thanks