Antimicrobial Resistance Unveiled: From Awareness to Action

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Associate Hospital Epidemiologist
Tufts Medical Center

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No disclosures

The Miracle of Antibiotics

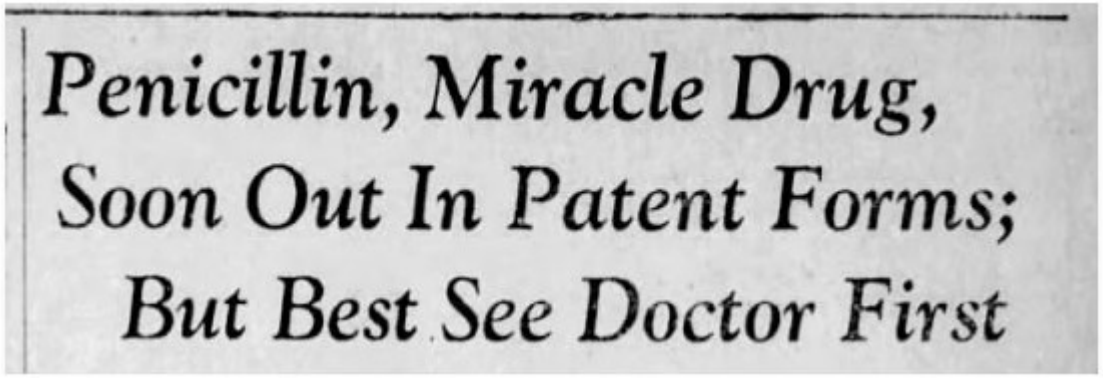
In March 1942, Mrs. Anne Miller of New Haven, Connecticut, was dying of streptococcal bacteremia.

Desperate to save her, doctors administered an experimental drug: **Penicillin**, which Alexander Fleming discovered 14 years earlier.

Next morning her temperature had improved

Within 48 hours she had recovered becoming the first person in the US to be saved by penicillin.

Rather than dying in her thirties, Mrs. Miller lived to be 90 years old.



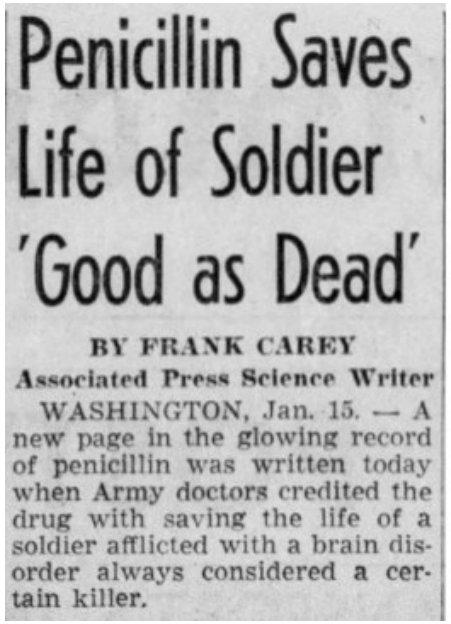
Penicillin, Miracle Drug, Soon Out In Patent Forms; But Best See Doctor First

Anne Miller, 90, First Patient Who Was Saved by Penicillin

Share full article

By Wolfgang Saxon

June 9, 1999



Penicillin Saves Life of Soldier 'Good as Dead'

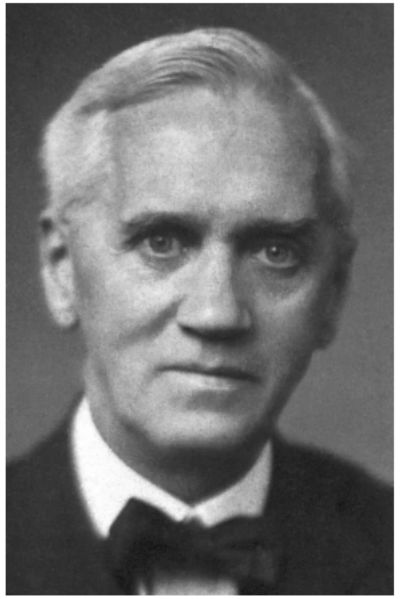
BY FRANK CAREY

Associated Press Science Writer

WASHINGTON, Jan. 15. — A new page in the glowing record of penicillin was written today when Army doctors credited the drug with saving the life of a soldier afflicted with a brain disorder always considered a certain killer.

Sir Alexander Fleming
Facts

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11339718/



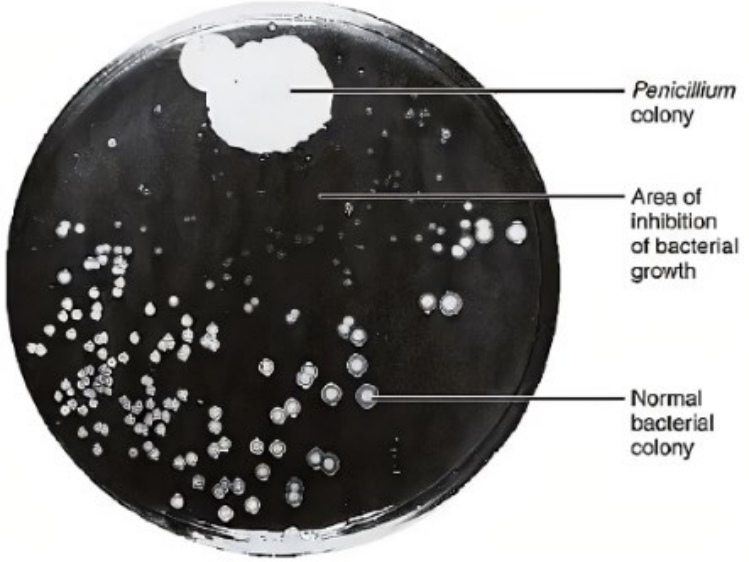
Sir Alexander Fleming
The Nobel Prize in Physiology or Medicine 1945

Born: 6 August 1881, Lochfield, Scotland

Died: 11 March 1955, London, United Kingdom

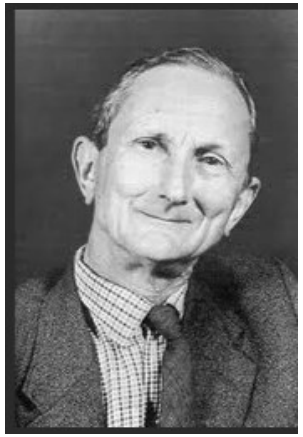
Affiliation at the time of the award: London University, London, United Kingdom

Prize motivation: "for the discovery of penicillin and its curative effect in various infectious diseases"

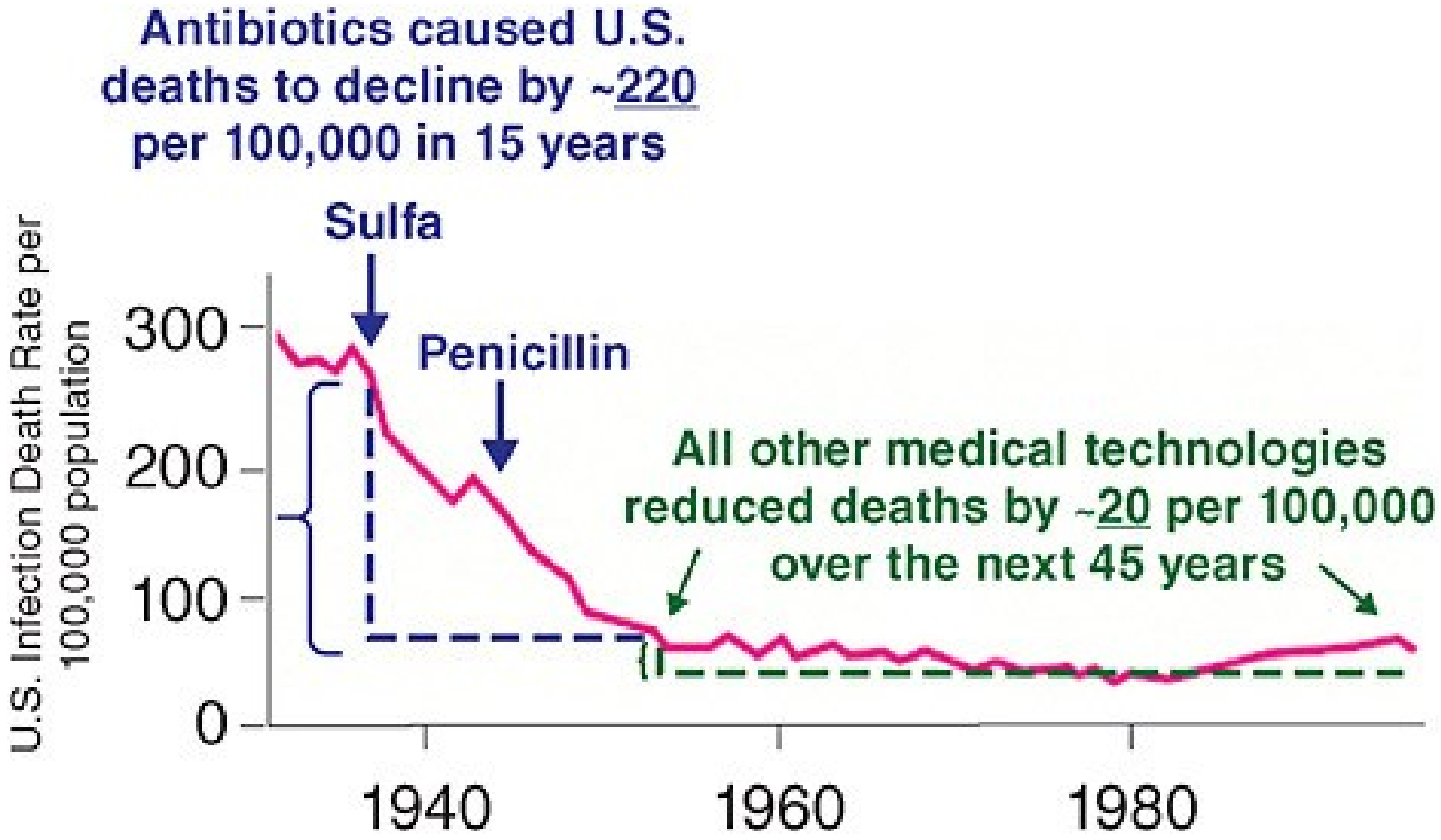


Howard Florey

Ernst Boris Chain



Norman Heatly



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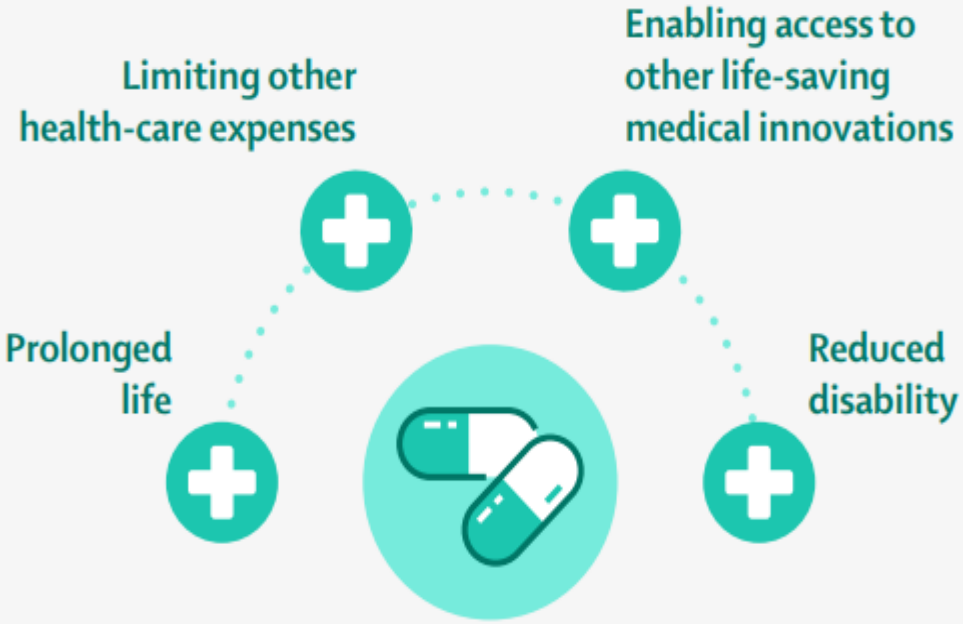
“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

-Alexander Flemming, Nobel Prize Acceptance Speech, 1945

Antibiotics, if used as indicated, can avert many deaths from bacterial infections, and access to second-line antibiotics can even prevent deaths from some drug-resistant infections. However, rising resistance threatens to thwart the benefits antimicrobial use provides, such as:



Everyone is at risk—including those that have never taken an antibiotic. Those most vulnerable include:

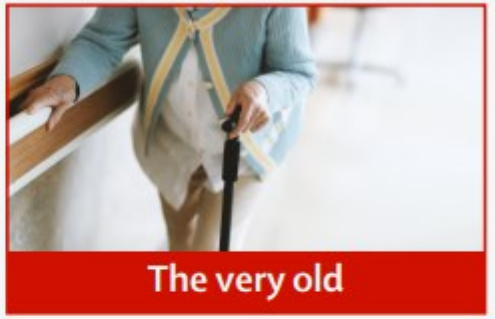


Image credits: Ariel Skelley; RUNSTUDIO; Alexander Grey; Guido Dingemans, De Eindredactie

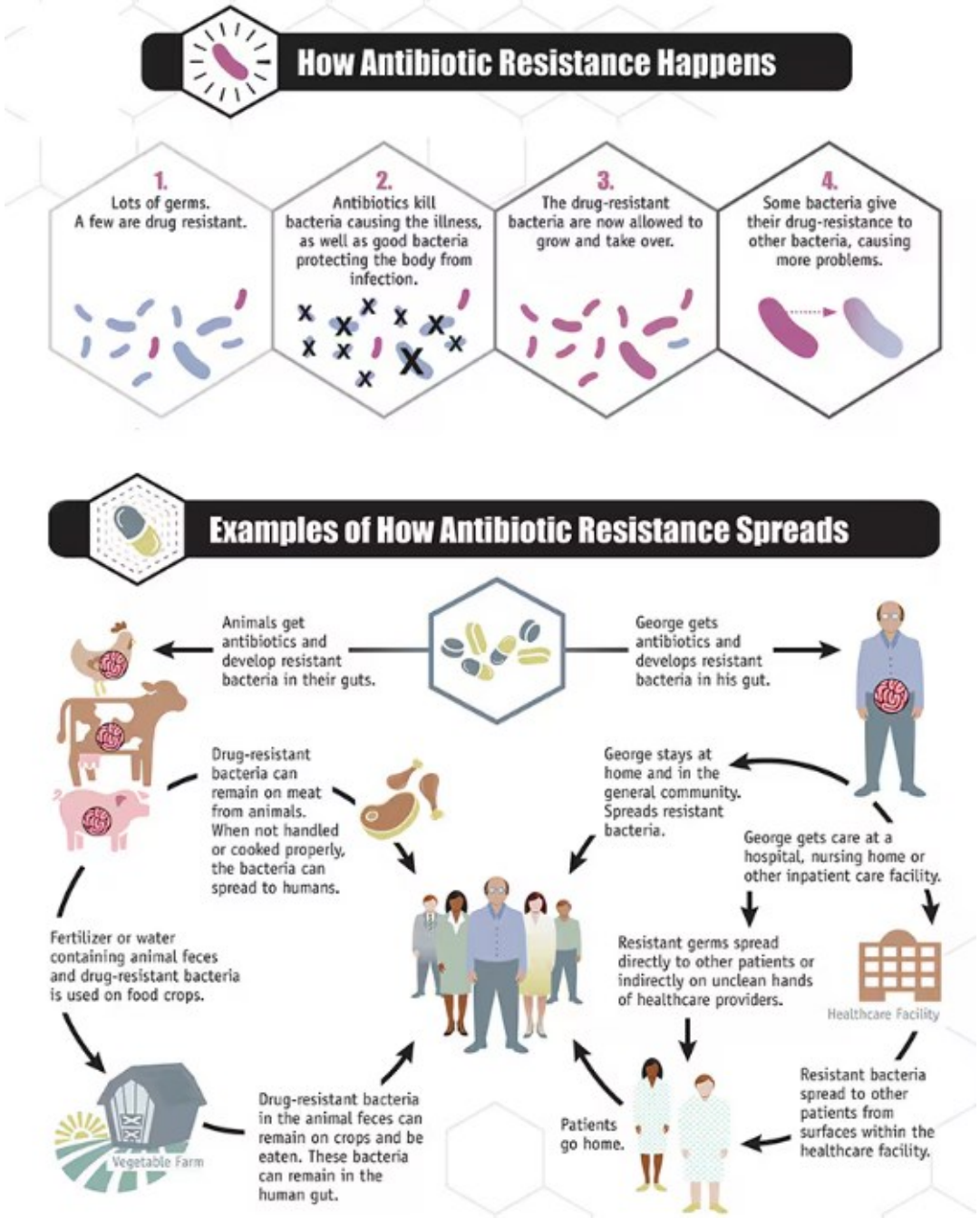
https://www.thelancet.com/series/antibiotic-resistance?dgcid=tlcom_infographic_amr2024_lancet

Germs Develop Antibiotic Resistance

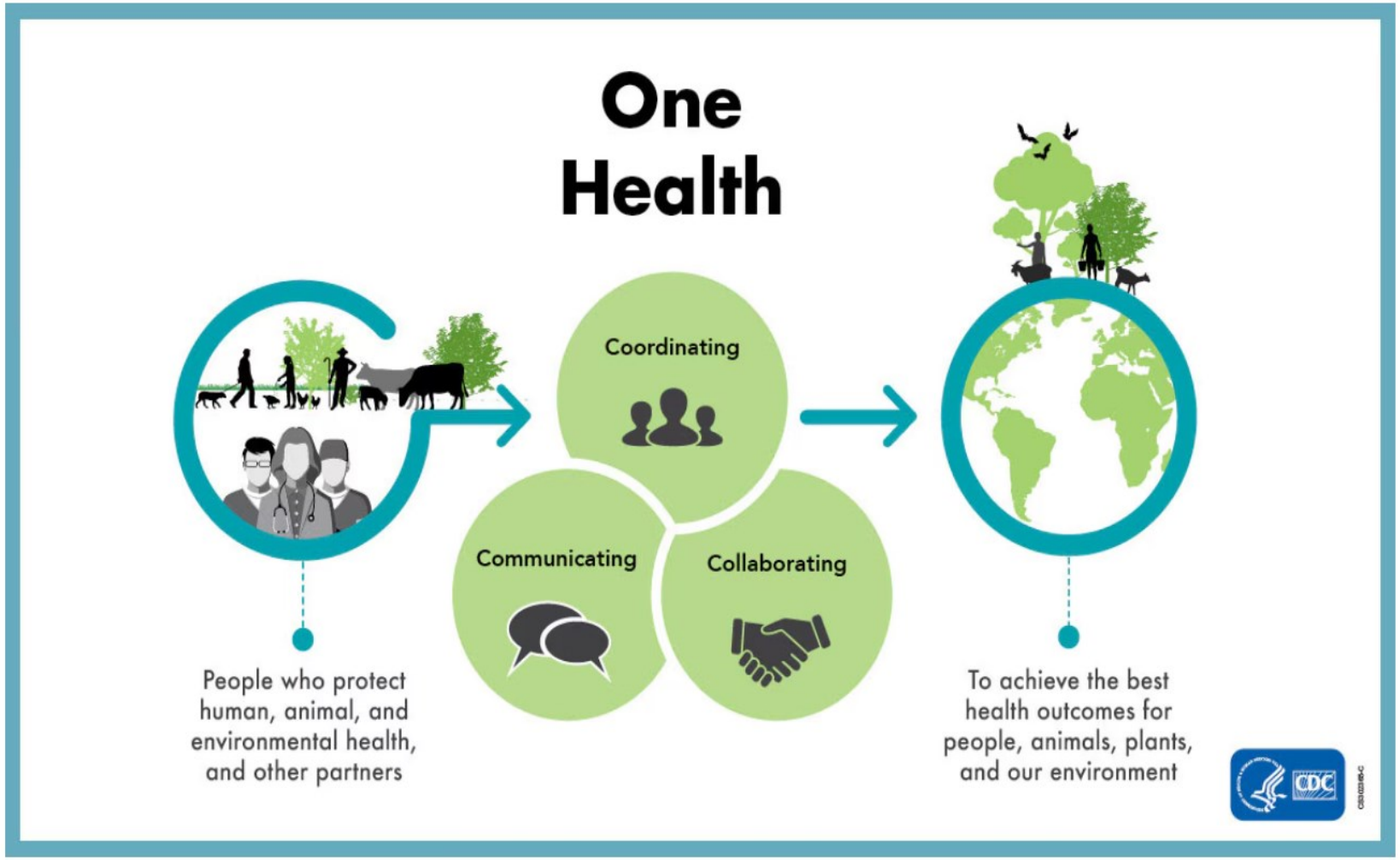
Select Germs Showing Resistance Over Time

Since the discovery of penicillin more than 90 years ago, germs have continued to develop new types of resistance against even our most powerful drugs. While antibiotic development has slowed, antibiotic resistance has not. This table demonstrates how rapidly important types of resistance developed after approval and release of new antibiotics, including antifungals.

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[20, 21]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[9,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015



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

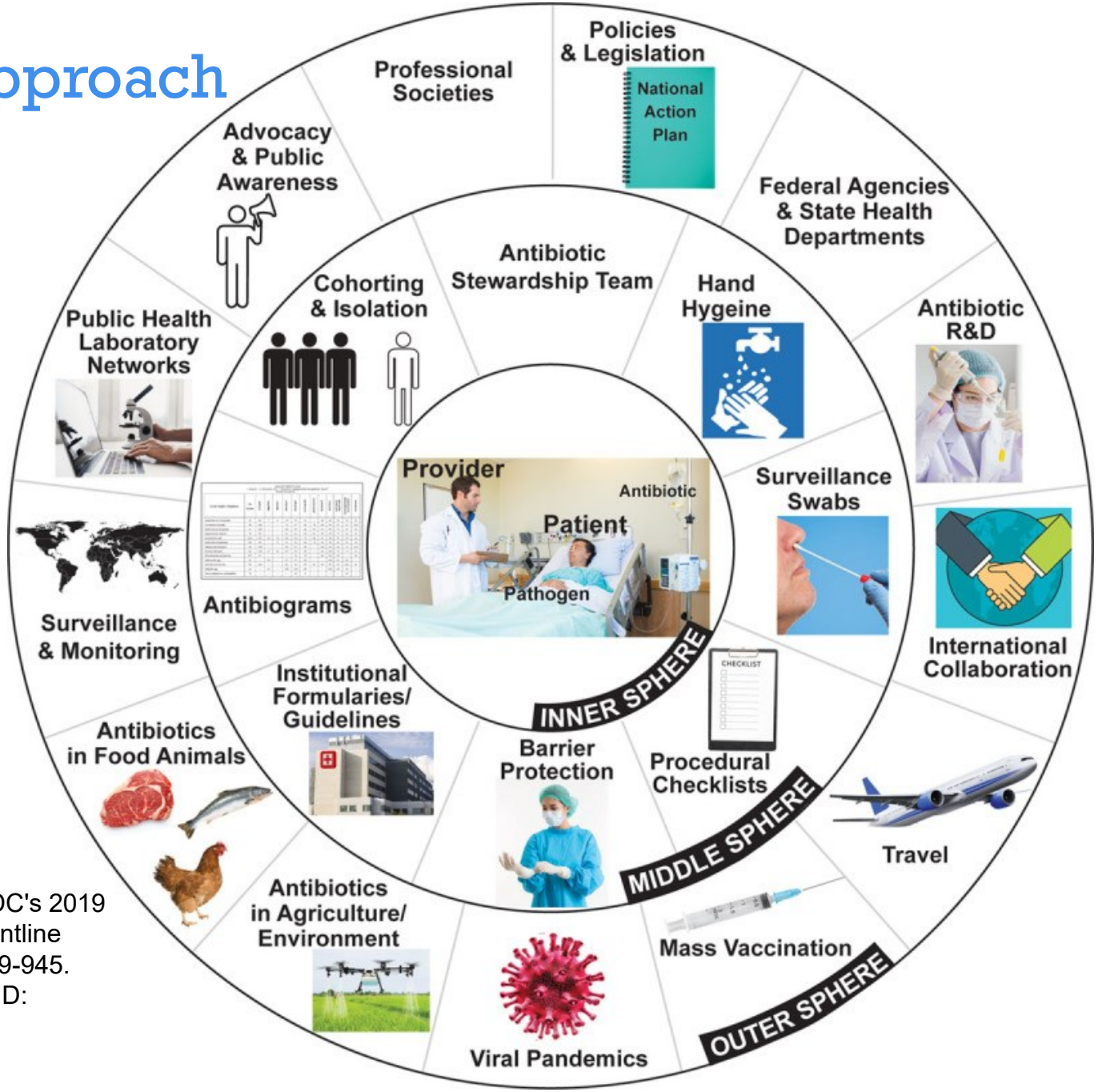


Velazquez-Meza ME, Galarde-López M, Carrillo-Quiróz B, Alpuche-Aranda CM. Antimicrobial resistance: One Health approach. Vet World. 2022 Mar;15(3):743-749. doi: 10.14202/vetworld.2022.743-749. Epub 2022 Mar 28. PMID: 35497962; PMCID: PMC9047147.

Integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems.

It recognizes that the health of humans, animals, and the wider environment are inherently linked and interdependent

One Health Approach



Kadri SS. Key Takeaways From the U.S. CDC's 2019 Antibiotic Resistance Threats Report for Frontline Providers. Crit Care Med. 2020 Jul;48(7):939-945. doi: 10.1097/CCM.0000000000004371. PMID: 32282351; PMCID: PMC7176261.

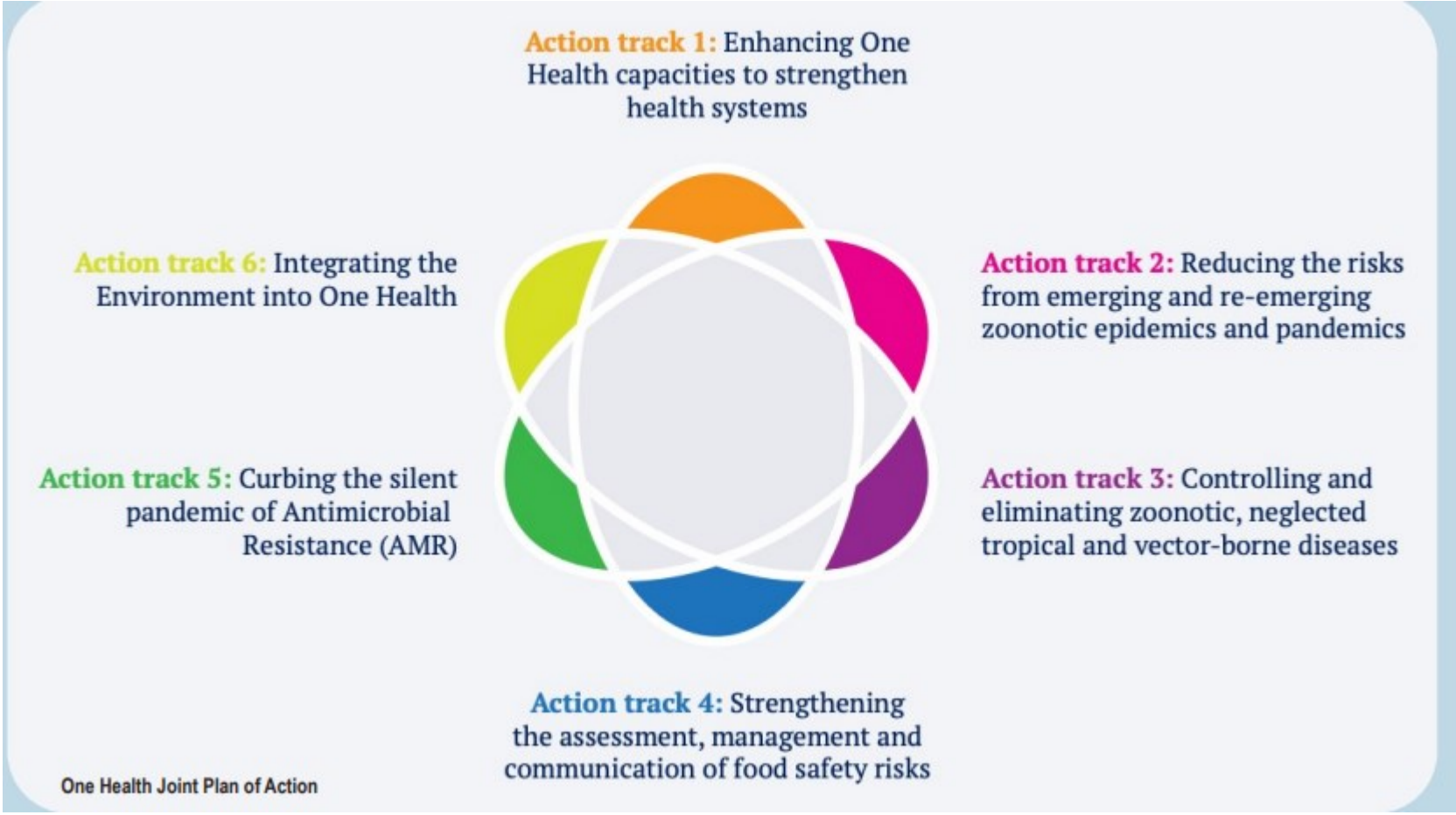
One Health Quadripartite

World Health Organization

Food and Agriculture Organization

World Organisation for Animal Health
Founded as OIE

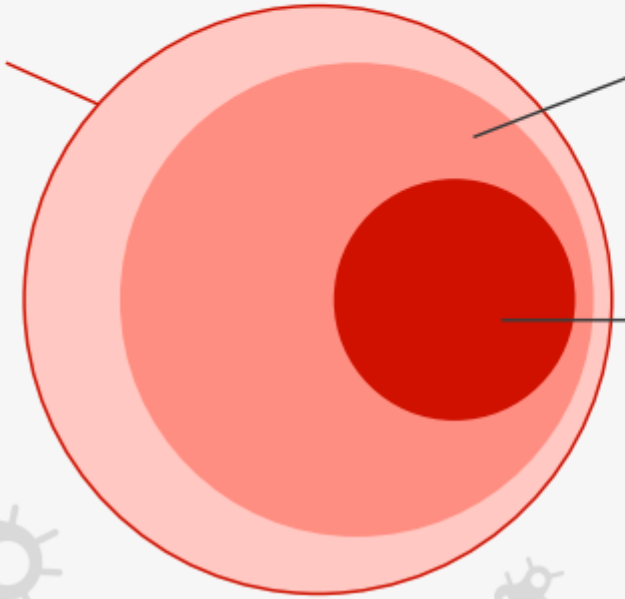
UN environment programme



WHO Reference Number:
WHO/EURO:2024-9510-49282-73655

Antimicrobial resistance: an enormous, growing, and unevenly distributed threat to global health

Each year, an estimated 7·7 million deaths are associated with bacterial infections

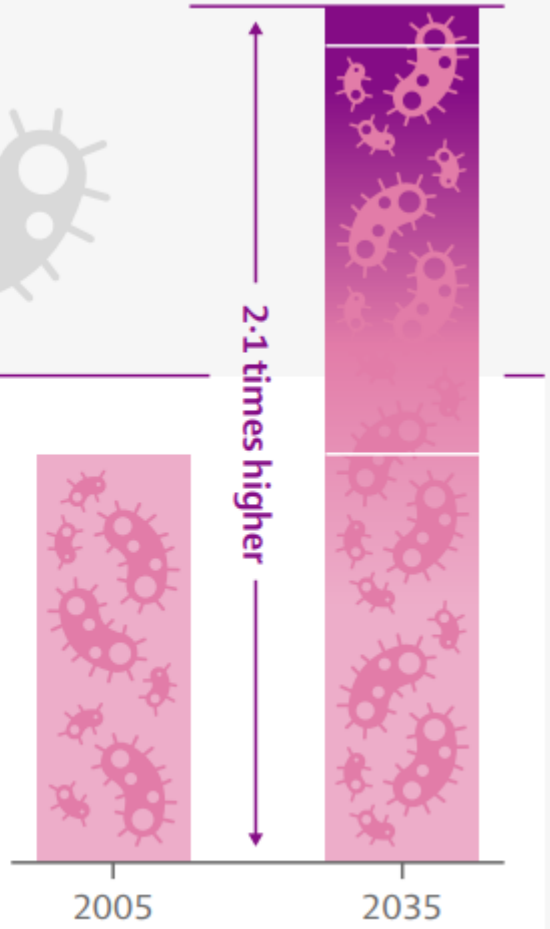


7·7m annual deaths

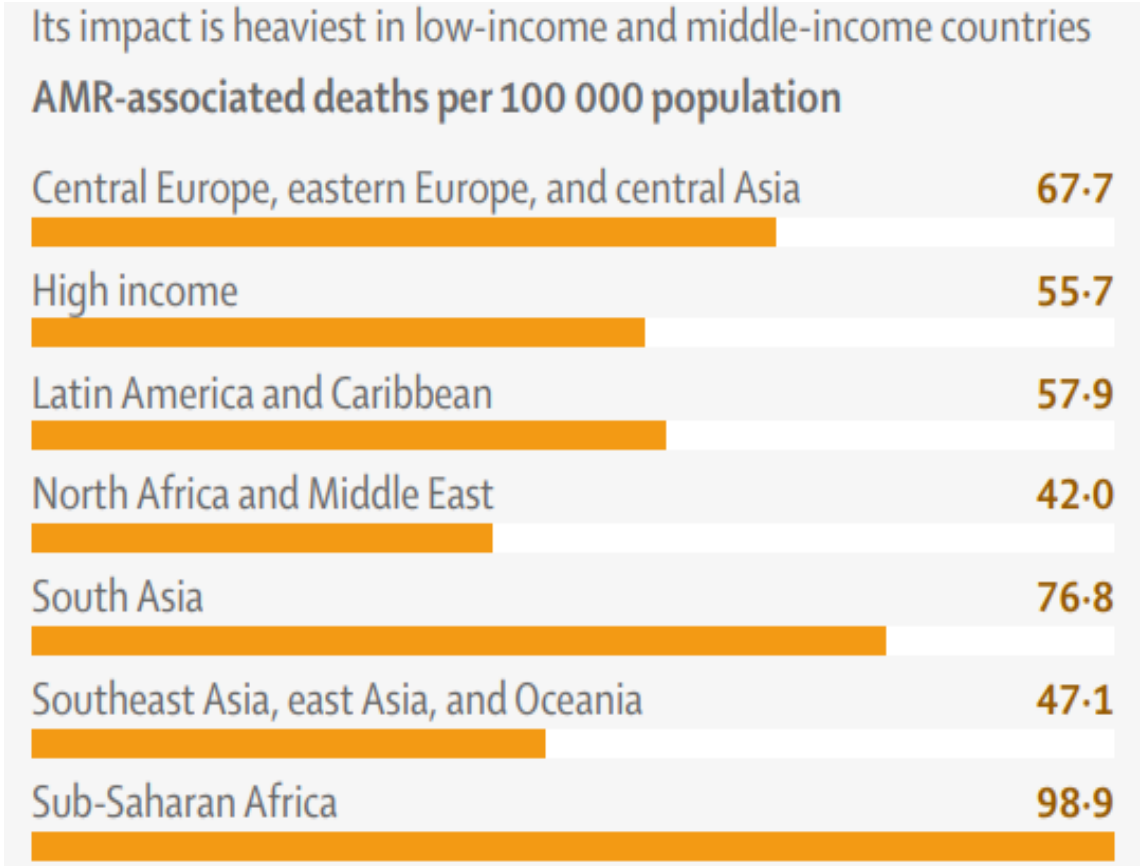
4·95m are associated with antimicrobial resistance (AMR)

1·27m of which are caused by bacterial pathogens resistant to the antibiotics available to treat them

Rising AMR has been documented over the past two decades. Projections from high-income countries predict resistance to third-line antibiotics—the last-resort drugs—could be 2·1 times higher in 2035 compared to 2005



https://www.thelancet.com/series/antibiotic-resistance?dgcid=tlcom_infographic_amr2024_lancet



1 in 8 deaths globally are linked to bacterial infections, the second leading cause of death after ischemic heart disease

https://www.thelancet.com/series/antibiotic-resistance?dgcid=tlcom_infographic_amr2024_lancet

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

*GBD 2021 Antimicrobial Resistance Collaborators**

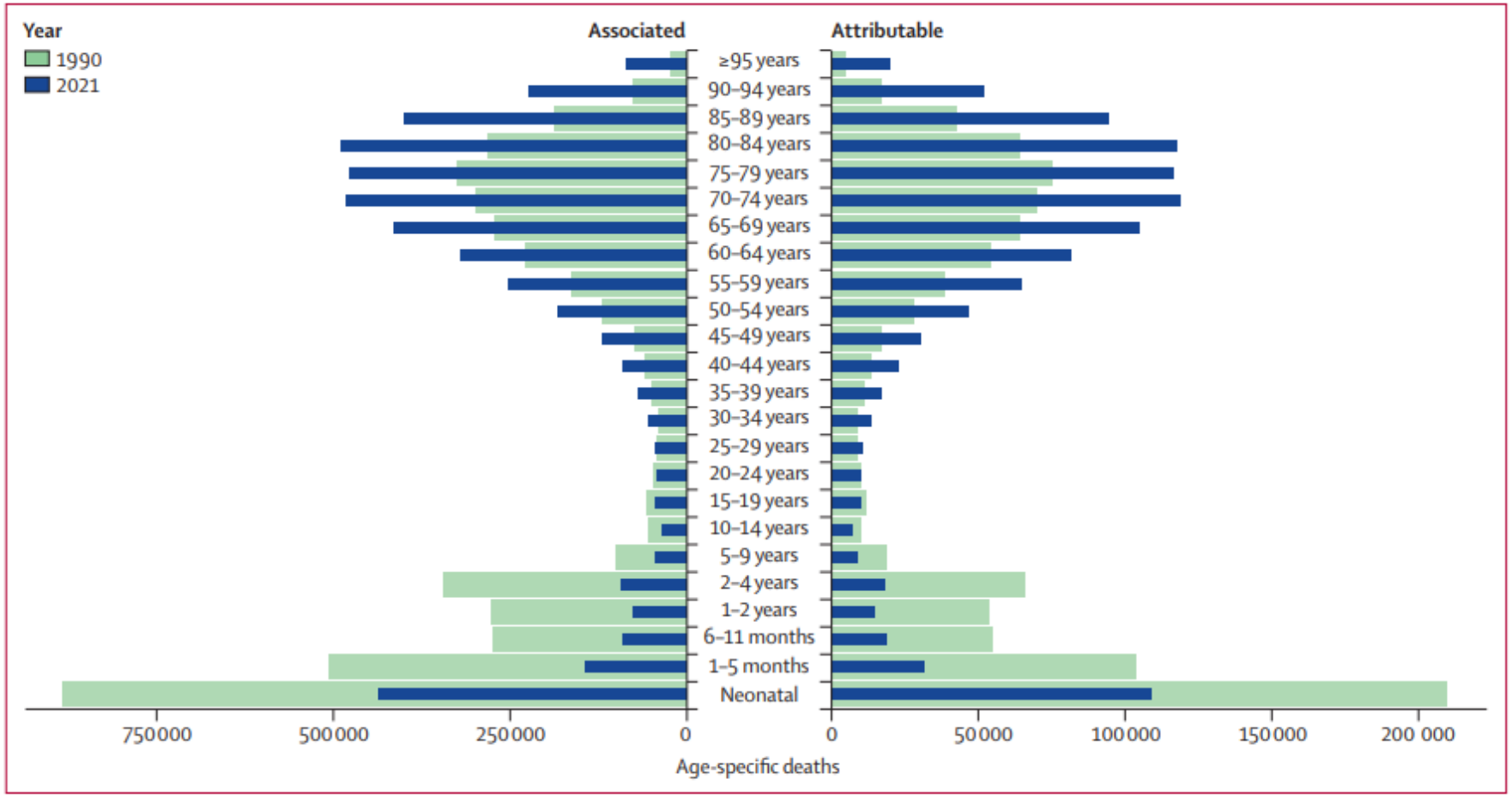
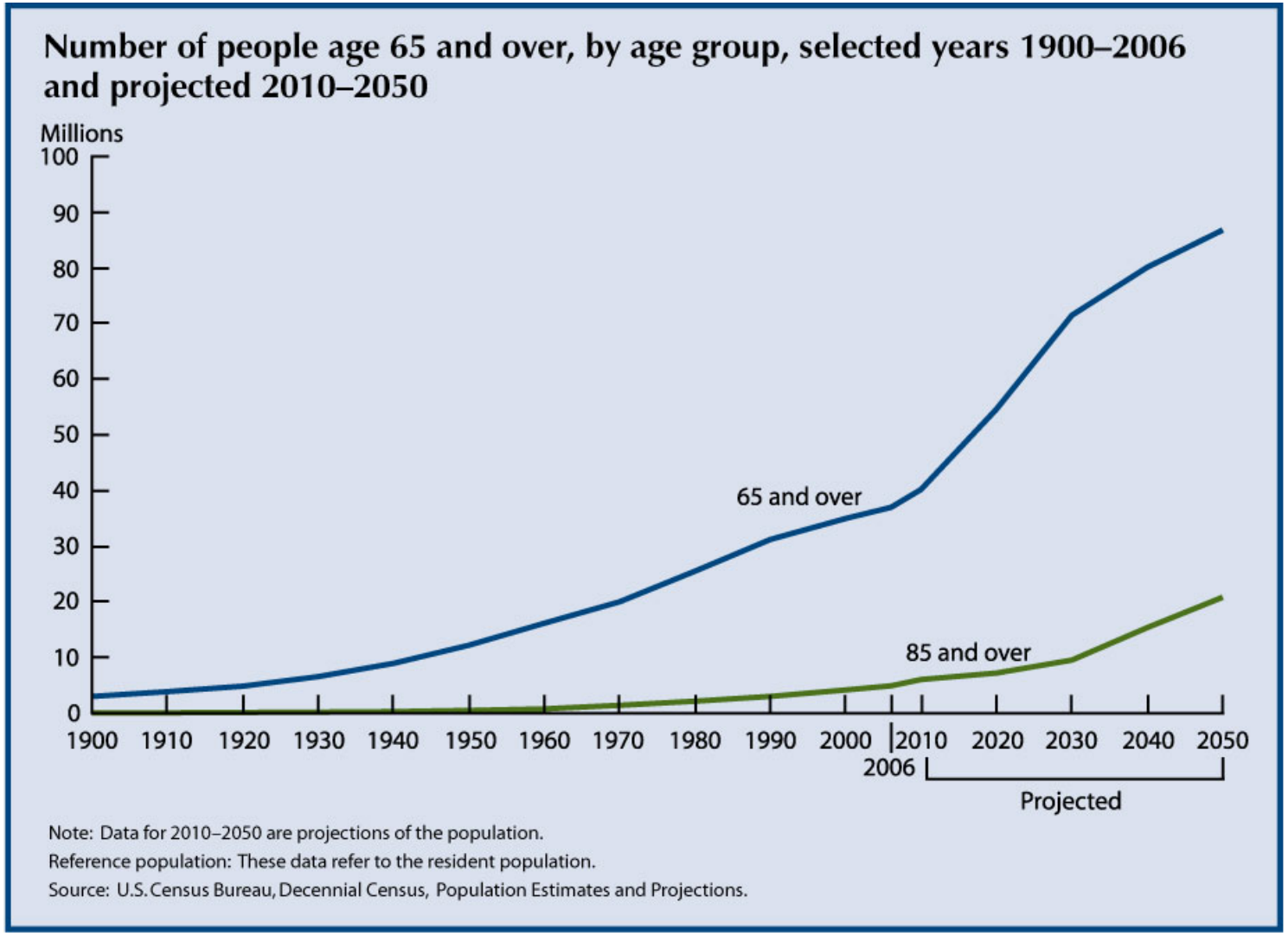


Figure 2: **Deaths attributable and associated with antimicrobial resistance, by detailed age group, for 1990 and 2021**

Meanwhile… the population keeps aging



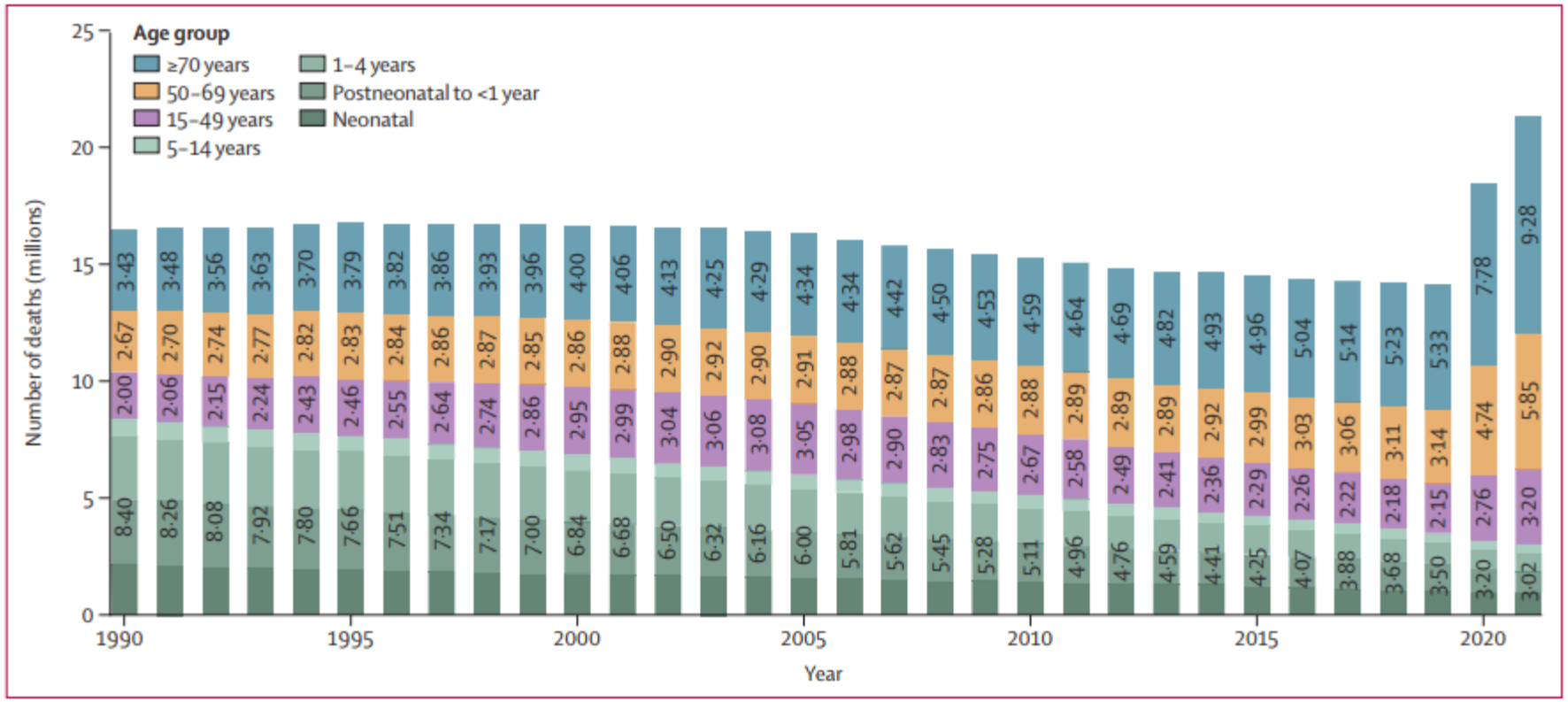
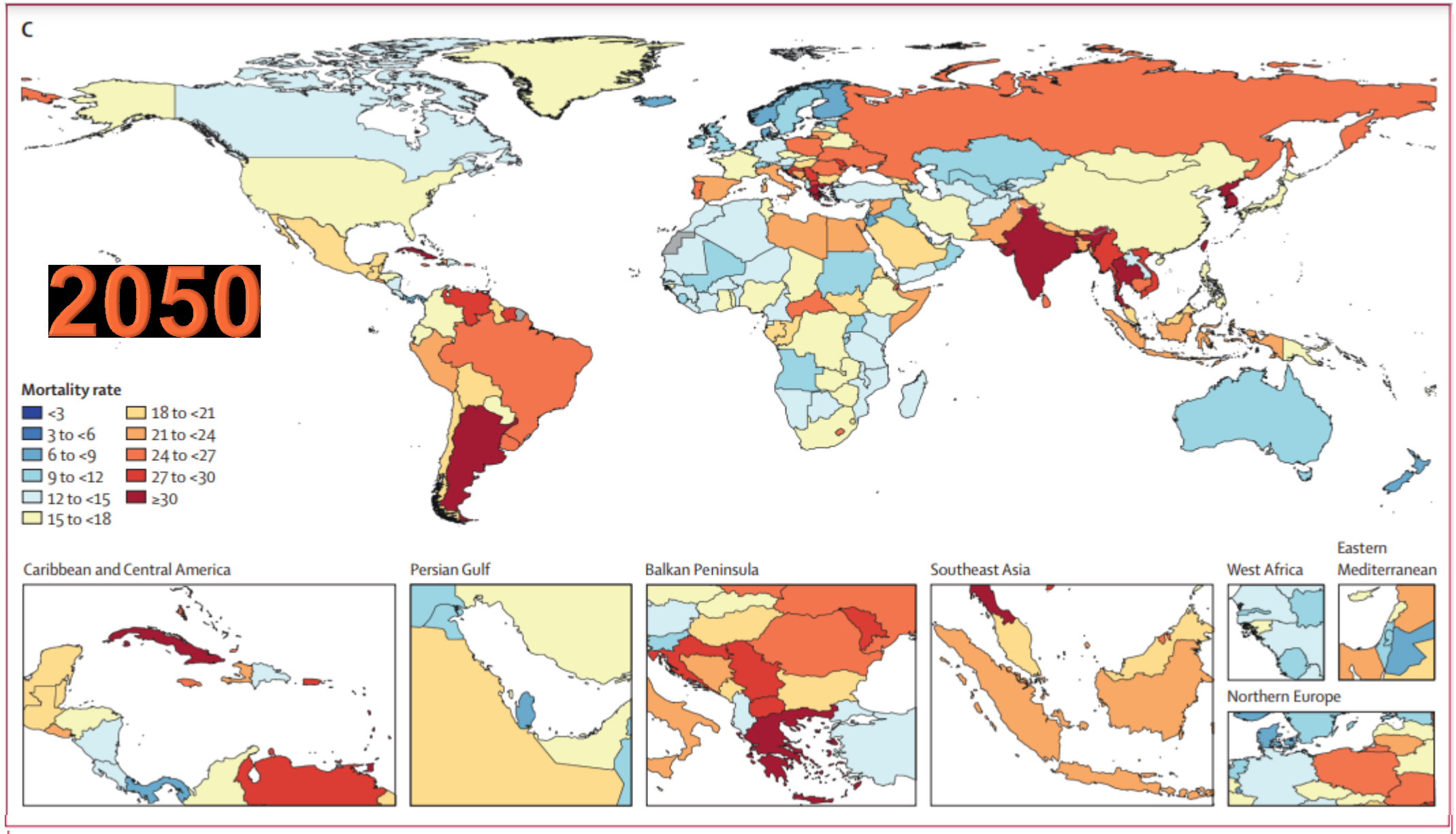


***Figure 1*: Global time trend of sepsis, by age, 1990–2021**

Bar labels represent the number of sepsis deaths in a given year for people aged 0–14 years, 15–49 years, 50–69 years, and ≥70 years. Values for the age group of 0–14 years represent the sum of sepsis deaths among neonates, postneonates to <1 year, 1–4 years, and 5–14 years.

Deaths Attributable to AMR



IF NOT TACKLED, RISING AMR COULD HAVE A DEVASTATING IMPACT

By 2050, the death toll could be a staggering

one person every three seconds

if AMR is not tackled now.

Strengthening surveillance

In all cases, AMR is inadequately documented because laboratory testing is insufficient, and its burden of disease is poorly measured. Strengthening surveillance is essential for stopping AMR and measuring successes in its containment.

Aligning IPC standards

–337 000 *deaths*

Aligning infection prevention and control (IPC) standards in LMIC healthcare settings with those of HICs could prevent up to 337 000 AMR-associated deaths annually

Access to WASH services

–247 800

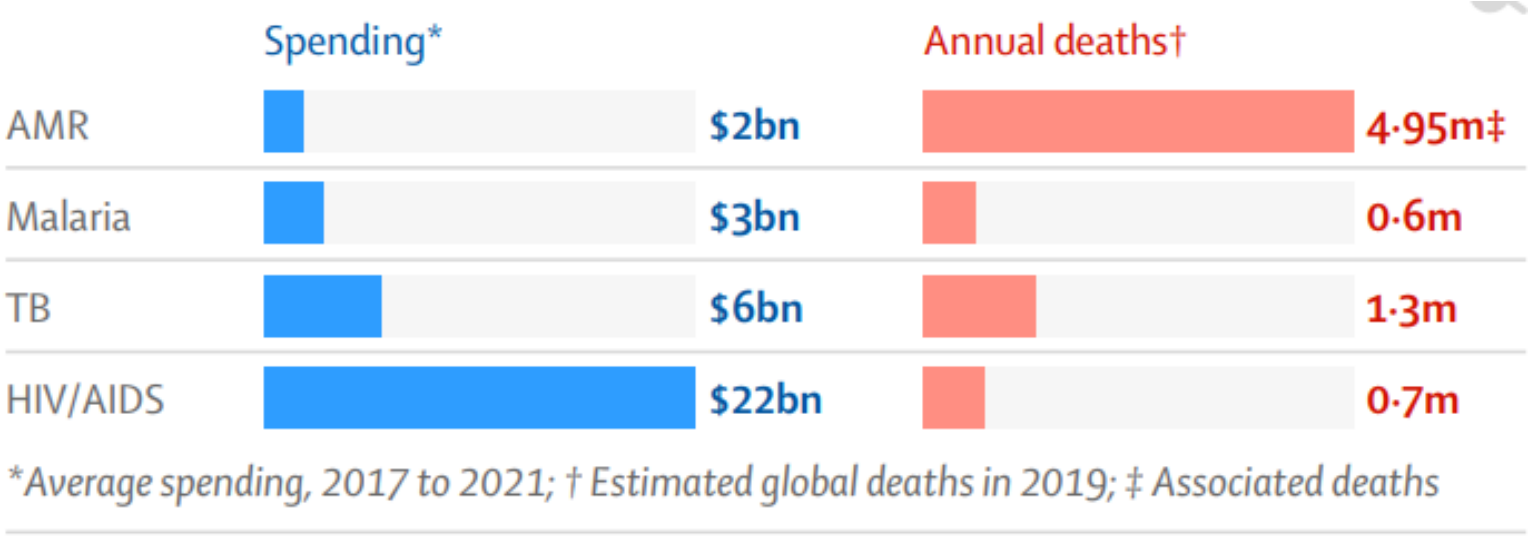
Achieving universal access to water, sanitation, and hygiene (WASH) services could prevent up to 247 800 AMR-associated deaths annually

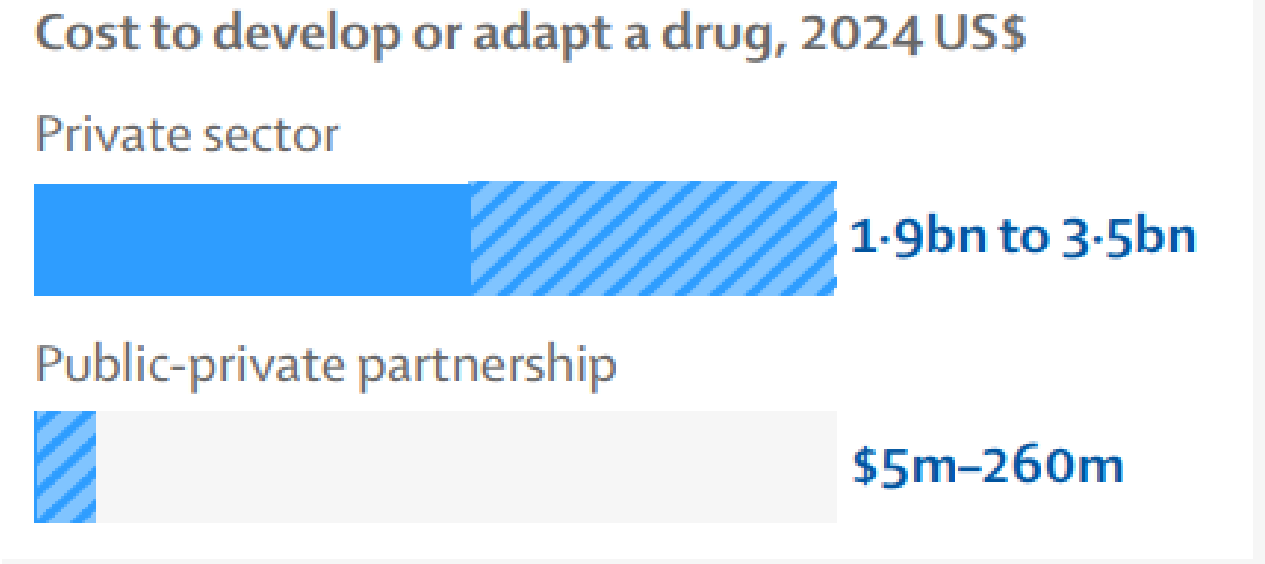
High-priority paediatric vaccines

–181 500

Achieving universal coverage of high-priority paediatric vaccines—such as those against rotavirus, pneumococci, and RSV—could prevent up to 181 500 AMR-associated deaths annually

https://www.thelancet.com/series/antibiotic-resistance?dgcid=tlcom_infographic_amr2024_lancet



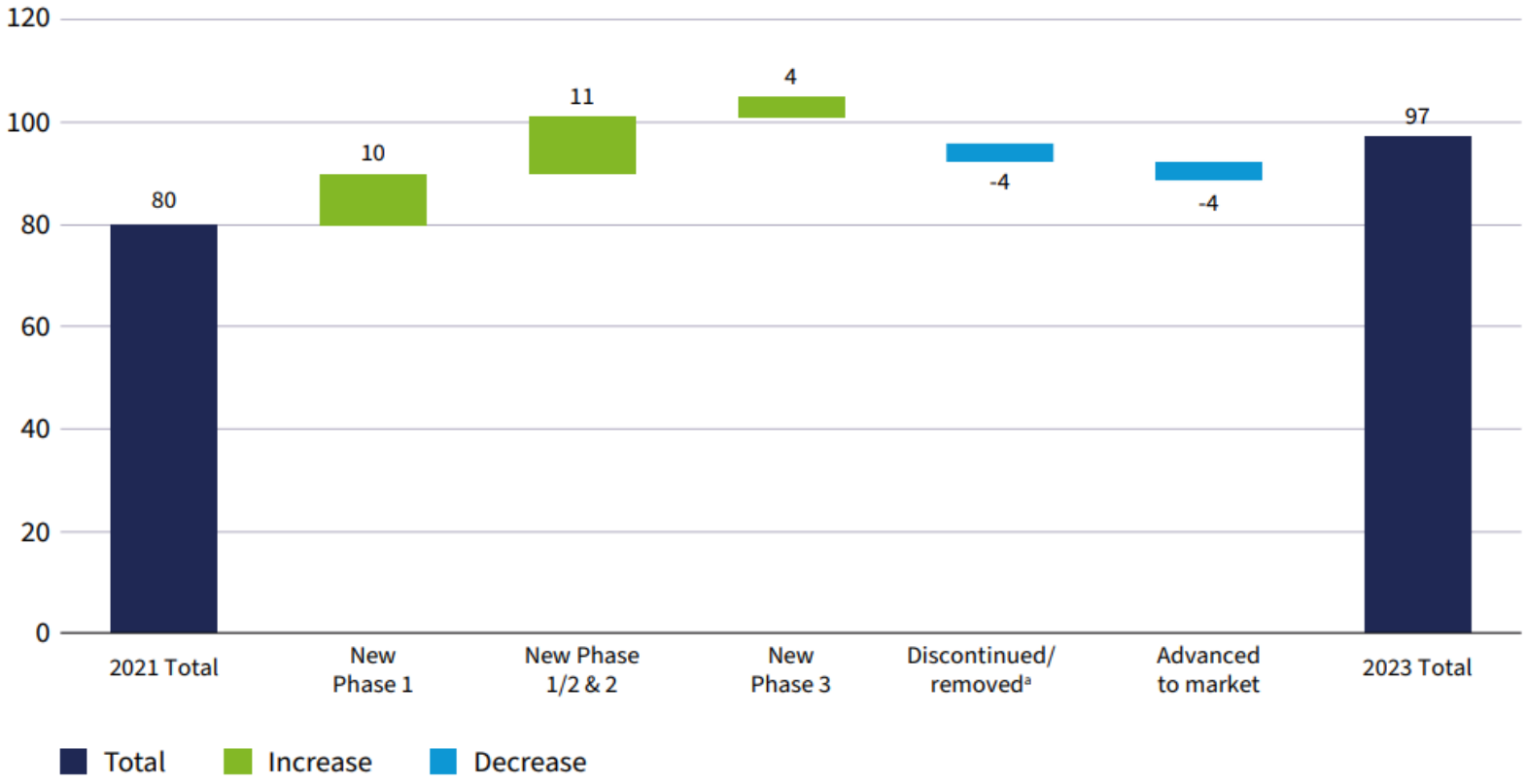


https://www.thelancet.com/series/antibiotic-resistance?dgcid=tlcom_infographic_amr2024_lancet

2023 Antibacterial agents in clinical and preclinical development: an overview and analysis

14 June 2024 | Technical document

Fig. 3. Number of products entering and exiting the pipeline since the 2021 report to 31 December 2023

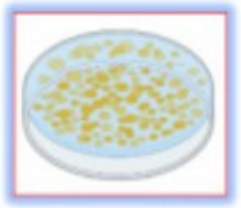


World Health Organization

Antibiotic Discovery Methods

Examples of current approaches

Traditional methods



- Waksman platform (solid or liquid culture-based methods)
- Semi-synthesis of antibiotics from existing molecules

Bacteriophages

- Infection of specific bacterial cells (lytic lifecycle)
- Specificity, safety, practical selection and isolation
- Possibility to combine as cocktails

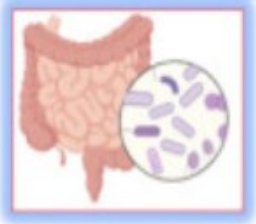
Inhibition of bacterial virulence

- Secretion system inhibitors
- Anti-biofilm molecules/mechanisms
- Siderophore inhibitors
- Exotoxin inhibition
- Adherence inhibition
- Two-component systems inhibition

Genome mining

- Bioinformatics and computing technologies
- Engineering the expression of silent biosynthetic genes to encode novel antibiotics

Microbiome-modulating agents



- Enhancement of beneficial microbiome to stimulate immune response
- Preservation of intestinal microbiota using antibiotic inactivators

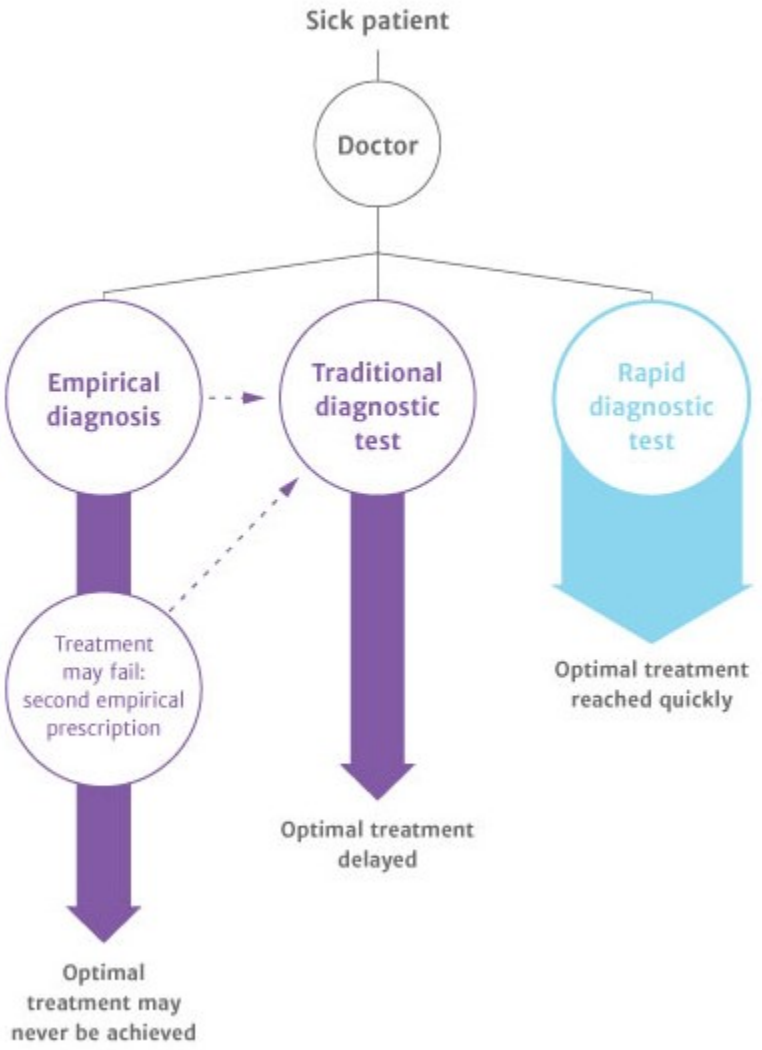
Antibacterial antibodies

- Monoclonal antibodies directed towards bacterial proteins or virulence factors

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8868473/

Diagnostics

Improve quality, speed, and affordability



Vaccines

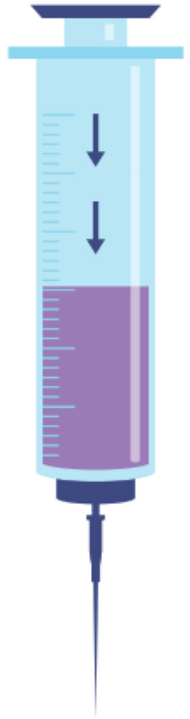
Reduce the number of bacterial infections that need antibiotics

Reduce the number of drug-resistant infections

Reduce the number a of viral infections for which antibiotics are unnecessarily given

INCREASING COVERAGE OF VACCINES CAN REDUCE ANTIBIOTIC USE

Universal coverage by a pneumococcal conjugate vaccine could potentially avert 11.4 million days of antibiotic use per year in children younger than five, roughly a 47% reduction in the amount of antibiotics used for pneumonia cases caused by *S. pneumoniae*.



47%
reduction in antibiotic use

Source: Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K, Davies S, Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness, *Lancet*, 2016, 387: 168–75.

Review on Antimicrobial Resistance

Global Targets Proposed

By 2030, relative to 2019, achieve the following global targets*:

- **A 10% reduction** in mortality from AMR
- **A 20% reduction** in inappropriate human antibiotic use
- **A 30% reduction** in inappropriate animal antibiotic use

*National targets may vary depending on their current situation

- The establishment of **an independent scientific body to expand the evidence base** for policy implementation and to inform new targets
- **Increased funding** for infection prevention mitigation programmes in human and animal health

World Health Organization

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World leaders commit to action to ensure future of modern medicine

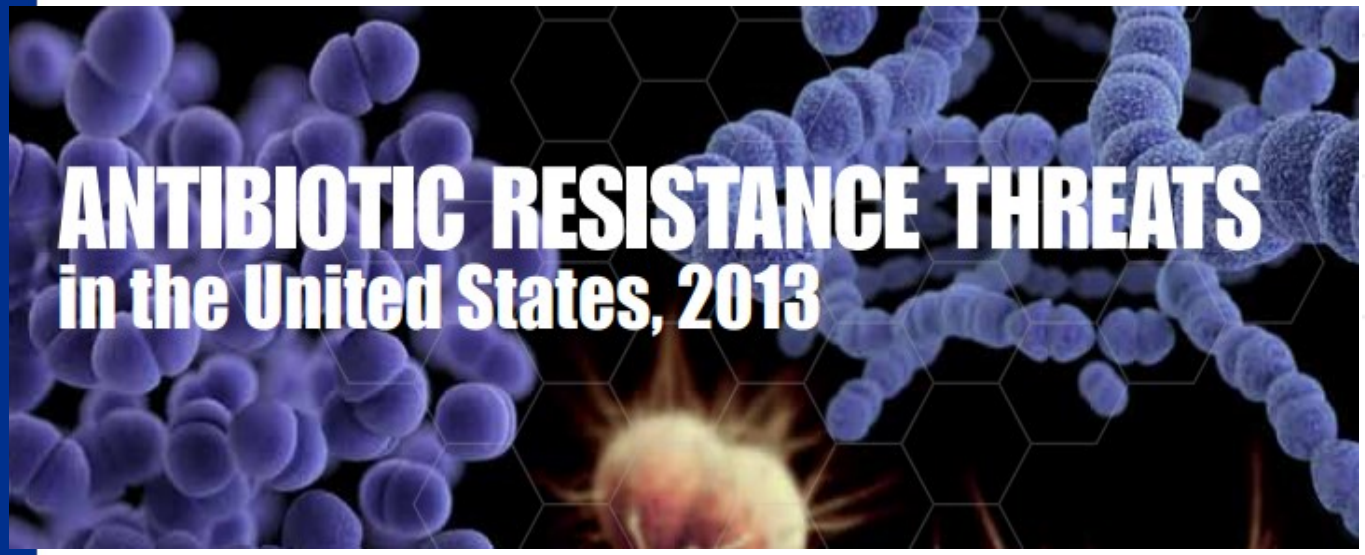
26 September 2024

At the United Nation General Assembly in New York, all countries approved a major new political declaration to radically scale-up efforts to combat antimicrobial resistance (AMR) – a major threat to modern medicine.

Antibiotic Resistance in the US

About the National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025

This Plan describes activities that the U.S. Government will undertake from 2020 through 2025 to reduce the impact of antibiotic and antimicrobial resistance on the nation.[1]



Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

THE WHITE HOUSE
WASHINGTON

TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria
By 2020, the United States will:
For CDC Recognized Urgent Threats:
Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.
Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.
For CDC Recognized Serious Threats:
Reduce by 35% multidrug-resistant *Pseudomonas spp.* infections acquired during hospitalization compared to estimates from 2011.
Reduce by at least 50% overall methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections by 2020 as compared to 2011.*
Reduce by 25% multidrug-resistant non-typhoidal *Salmonella* infections compared to estimates from 2010-2012.
Reduce by 15% the number of multidrug-resistant TB infections.[1]
Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among <5 year-olds compared to estimates from 2008.
Reduce by at least 25%the rate of antibiotic-resistant invasive pneumococcal disease among >65 year-olds compared to estimates from 2008.

Goal 1: slow emergence of resistance bacteria and prevent spread of resistant infections

Goal 2: strengthen national one health surveillance efforts to combat resistance objectives

Goal 3: Advance development and Use of Rapid Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria

Goal 4: Accelerate Research to Develop new antibiotics, other therapeutics, vaccines.

In 2018, CDC proposed five core actions to better prepare the United States for the resistance that will continue to emerge worldwide:

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

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Revised Dec. 2019

CDC's 2019 AR Threats Report:

PREVENTION WORKS.

18% fewer deaths from antibiotic resistance overall since 2013 report

28% fewer deaths from antibiotic resistance in hospitals since 2013 report

AND DECREASES IN INFECTIONS CAUSED BY:

- **41%** Vancomycin-resistant *Enterococcus*
- **33%** Carbapenem-resistant *Acinetobacter*
- **29%** Multidrug-resistant *Pseudomonas aeruginosa*
- **25%** Drug-resistant *Candida*
- **21%** Methicillin-resistant *Staphylococcus aureus* (MRSA)
- **STABLE** Carbapenem-resistant Enterobacteriaceae (CRE) & drug-resistant tuberculosis (TB disease cases)

CDC strategies that work in healthcare:

Preventing device- and procedure-related infections, such as from urinary catheters or central lines

Stopping the spread of resistant germs within and between healthcare facilities

Containing emerging threats through early detection and aggressive response

Tracking and improving appropriate antibiotic use

Infection prevention and control in non-hospital settings, such as long-term care facilities

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)*

COVID-19

U.S. IMPACT ON ANTIMICROBIAL RESISTANCE

2022 SPECIAL REPORT

	Resistant Pathogen	2017 Threat Estimate	2018 Threat Estimate	2019 Threat Estimate	2017-2019 Change	2020 Threat Estimate and 2019-2020 Change
URGENT	Carbapenem-resistant *Acinetobacter*	8,500 cases 700 deaths	6,300 cases 500 deaths	6,000 cases 500 deaths	Stable*	7,500 cases 700 deaths **Overall: 35% increase*** **Hospital-onset: 78% increase***
URGENT	Antifungal-resistant *Candida auris*	171 clinical cases†	329 clinical cases	466 clinical cases	▲ Increase	754 cases **Overall: 60% increase**
URGENT	*Clostridioides difficile*	223,900 infections 12,800 deaths	221,200 infections 12,600 deaths	202,600 infections 11,500 deaths	▼ Decrease	Data delayed due to COVID-19 pandemic
URGENT	Carbapenem-resistant Enterobacterales	13,100 cases 1,100 deaths	10,300 cases 900 deaths	11,900 cases 1,000 deaths	▼ Decrease*	12,700 cases 1,100 deaths Overall: Stable* **Hospital-onset: 35% increase***
URGENT	Drug-resistant *Neisseria gonorrhoeae*	550,000 infections	804,000 infections	942,000 infections	▲ Increase	Data unavailable due to COVID-19 pandemic
SERIOUS	Drug-resistant *Campylobacter*	448,400 infections 70 deaths	630,810 infections	725,210 infections	▲ Increase	Data delayed due to COVID-19 pandemic‡ 26% of infections were resistant, a 10% decrease
SERIOUS	Antifungal-resistant *Candida*	34,800 cases 1,700 deaths	27,000 cases 1,300 deaths	26,600 cases 1,300 deaths	▼ Decrease*	28,100 cases 1,400 deaths **Overall: 12% increase*** **Hospital-onset: 26% increase***
SERIOUS	ESBL-producing Enterobacterales	197,400 cases 9,100 deaths	174,100 cases 8,100 deaths	194,400 cases 9,000 deaths	▲ Increase*	197,500 cases 9,300 deaths **Overall: 10% increase*** **Hospital-onset: 32% increase***
SERIOUS	Vancomycin-resistant Enterococcus	54,500 cases 5,400 deaths	46,800 cases 4,700 deaths	47,000 cases 4,700 deaths	Stable*	50,300 cases 5,000 deaths **Overall: 16% increase*** **Hospital-onset: 14% increase***

CDC

ANTIMICROBIAL RESISTANCE THREATS in the United States, 2021-2022

	Threat	Change in Rates or Number of Infections***			
		2020 vs. 2019	2021 vs. 2020	2022 vs. 2021	2022 vs. 2019
URGENT*	Hospital-onset CRE	▲ Increase	▲ Increase	— Stable	▲ Increase
URGENT*	Hospital-onset Carbapenem-resistant *Acinetobacter*	— Stable	— Stable	— Stable	▲ Increase**
URGENT*	Clinical Cases of *C. auris*	▲ Increase	▲ Increase	▲ Increase	▲ Increase
SERIOUS*	Hospital-onset MRSA	▲ Increase	— Stable	▼ Decrease	— Stable
SERIOUS*	Hospital-onset VRE	▲ Increase	▲ Increase	— Stable	▲ Increase
SERIOUS*	Hospital-onset ESBL-producing Enterobacterales	▲ Increase	— Stable	— Stable	▲ Increase
SERIOUS*	Hospital-onset MDR *Pseudomonas aeruginosa*	▲ Increase	▲ Increase	— Stable	▲ Increase

20% Bacterial antimicrobial-resistant hospital-onset infections caused by the pathogens listed above increased by a combined 20% during the COVID-19 pandemic compared to the pre-pandemic period, peaking in 2021. In 2022, rates for all but one of these pathogens (MRSA) remained above pre-pandemic levels.

5x The number of reported clinical cases of *C. auris* increased nearly five-fold from 2019 to 2022. Clinical cases are identified when specimens collected from patients during routine clinical care test positive for *C. auris*.

USDA Office of the Chief Scientist
U.S. DEPARTMENT OF AGRICULTURE

The Strategy is organized around three Areas of Focus and 10 Priorities for collaborative action by USDA and its public and private partners:

AREA OF FOCUS 1
Reduce disease and pathogen transmission

PRIORITY 1
Improve animal and crop health

PRIORITY 2
Promote biosecurity

PRIORITY 3
Promote food safety

AREA OF FOCUS 2
Improve the scientific knowledge base on AMR risk

PRIORITY 4
Continuously improve data infrastructure using a One Health approach

PRIORITY 5
Support science and research across sectors to inform risk analysis

PRIORITY 6
Improve understanding of drivers of antimicrobial use[2] (AMU)

PRIORITY 7
Enhance feedback loops between (1) monitoring and surveillance; (2) research; and (3) education and outreach

AREA OF FOCUS 3
Improve communication and collaboration within USDA and with national, regional, and global partners to address AMR risk

PRIORITY 8
Enhance partnerships through building trust

PRIORITY 9
Improve knowledge dissemination and include contextual information

PRIORITY 10
Develop and deliver science-based solutions locally and globally

The future of CDC AR threats reporting

Clinician Action

- Antibiotics
- Antivirals
- Antifungals
- Antiparasitics

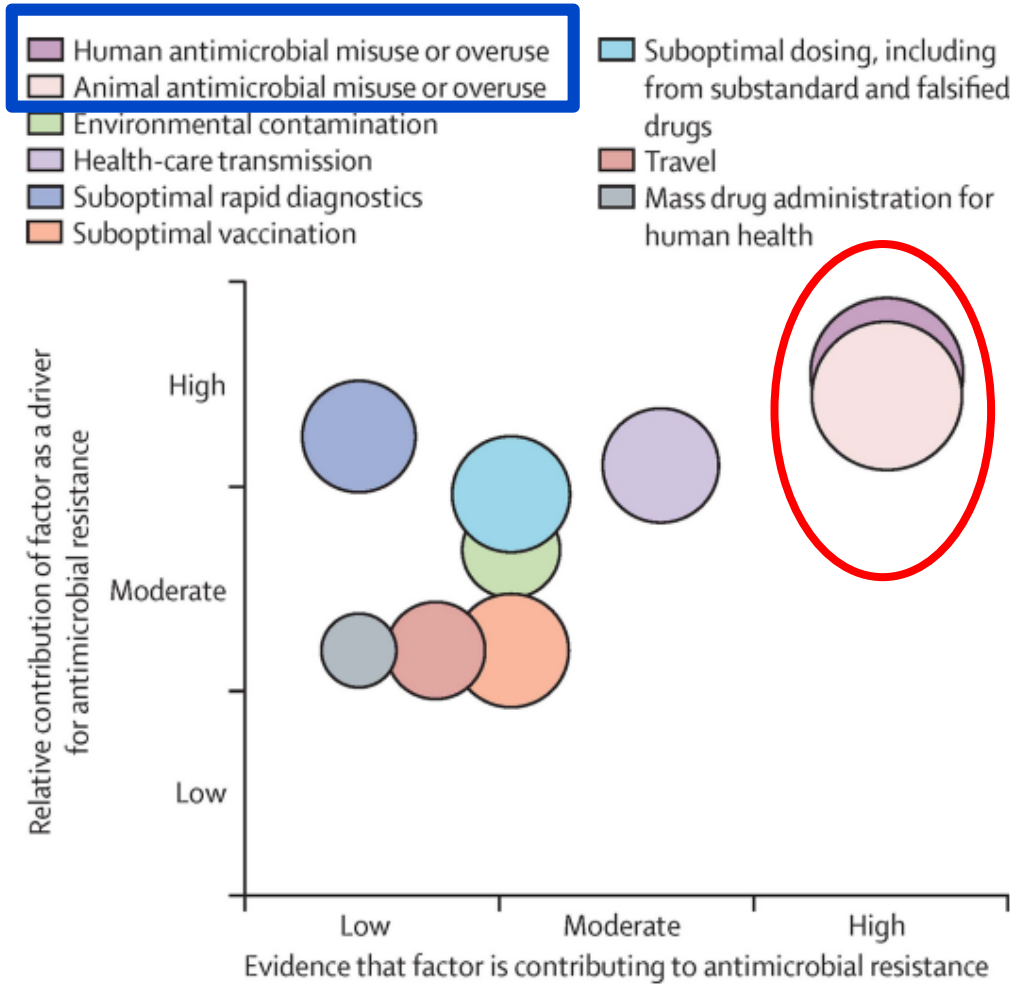
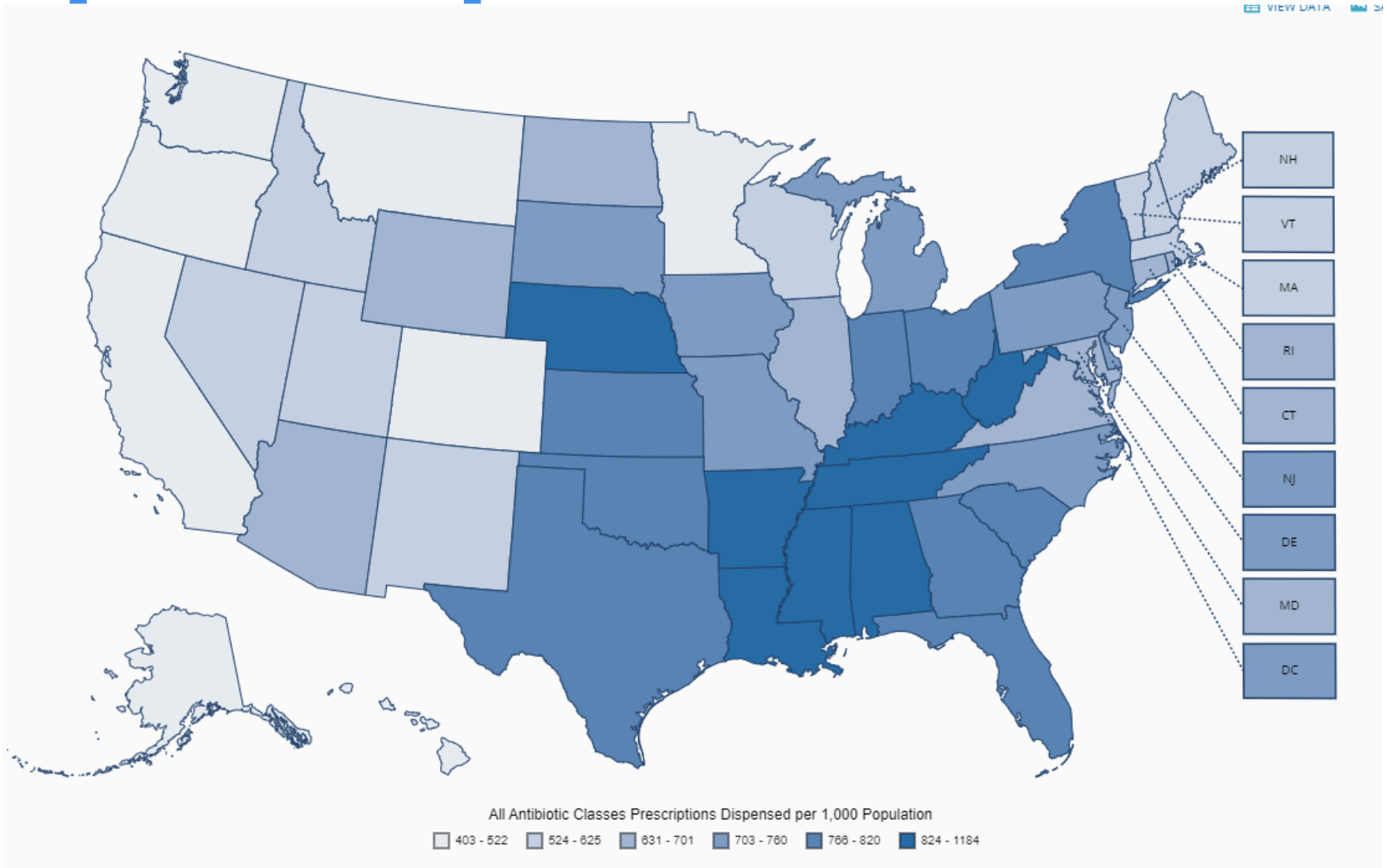


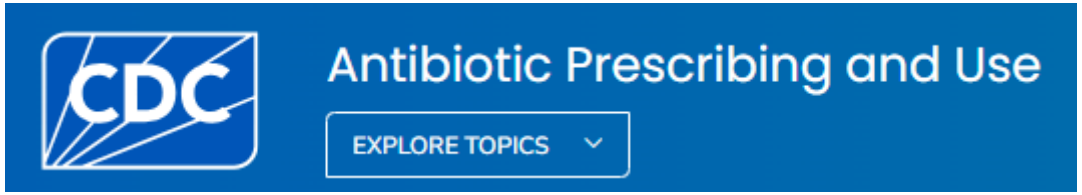
FIGURE 4 Role of modifiable drivers for antimicrobial resistance: a conceptual framework. Reprinted from Lancet (8) with permission of the publisher.

McEwen SA.Collignon PJ.2018.Antimicrobial Resistance: a One Health Perspective. Microbiol Spectr6:10.1128/microbiolspec.arba-0009-2017.https://doi.org/10.1128/microbiolspec.arba-0009-2017

Outpatient prescription rate of ALL antibiotic classes dispensed in US pharmacies



https://arpsp.cdc.gov/profile/antibiotic-use/all-classes?tabsection-27=2



28%

Of prescribed outpatient antibiotics (includes ED) were not needed at all

50%

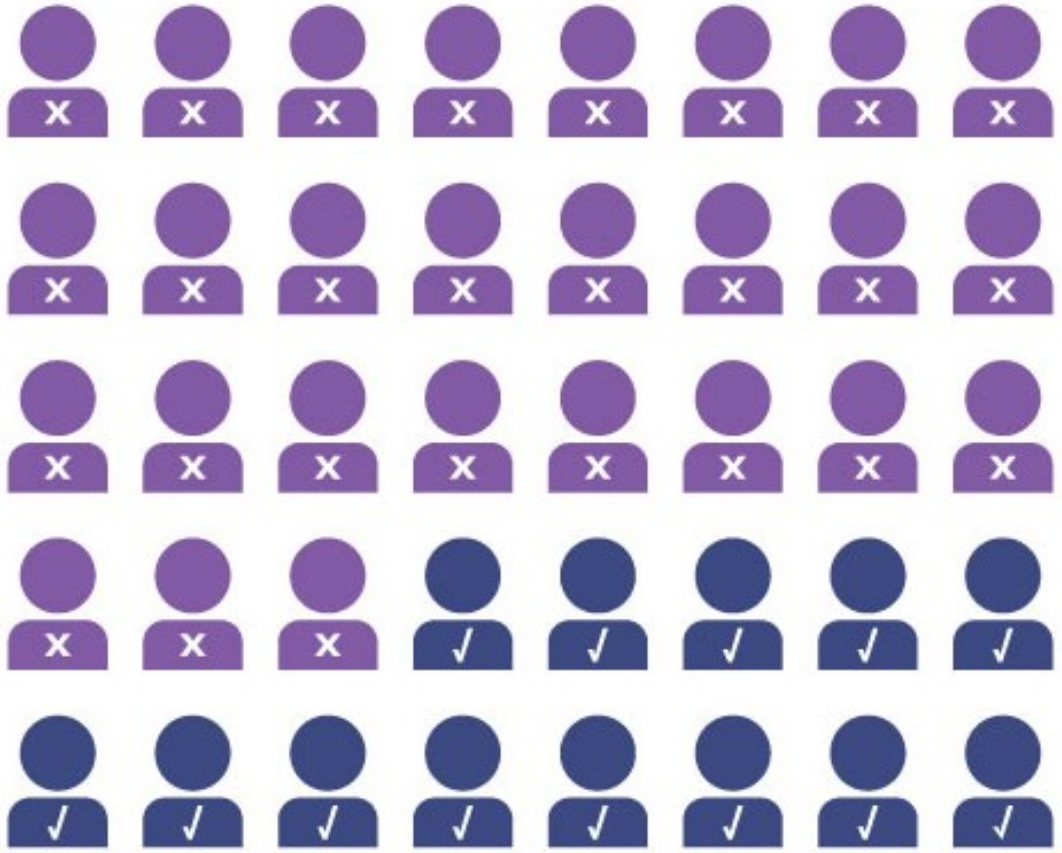
Of all outpatient antibiotic prescriptions were inappropriate due to unnecessary antibiotic use, inappropriate agent, duration or dosing

https://www.cdc.gov/antibiotic-use/hcp/data-research/stewardship-report.html

Out of 40m people who get given antibiotics for respiratory issues, annually in the US:

27m
get antibiotics unnecessarily

13m
who need antibiotics get them



Data extracted from: Shapiro D J, Hicks L A, Pavia A T, Hersh A L. *Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09.* Journal of Antimicrobial Chemotherapy 2013.

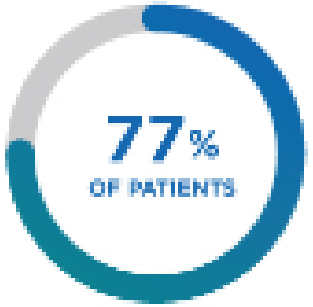
NEW CDC DATA

MORE THAN HALF OF ANTIBIOTIC PRESCRIBING FOR SELECTED EVENTS IN HOSPITALS WAS NOT CONSISTENT WITH RECOMMENDED PRESCRIBING PRACTICES

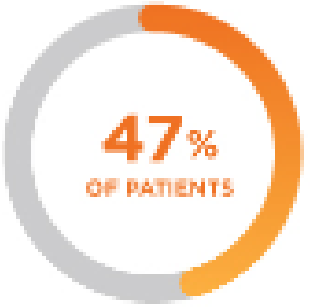
CDC

ANTIBIOTIC PRESCRIBING WAS NOT SUPPORTED IN:

with community-acquired pneumonia



with urinary tract infections



prescribed fluoroquinolone treatment

prescribed intravenous vancomycin antibiotic

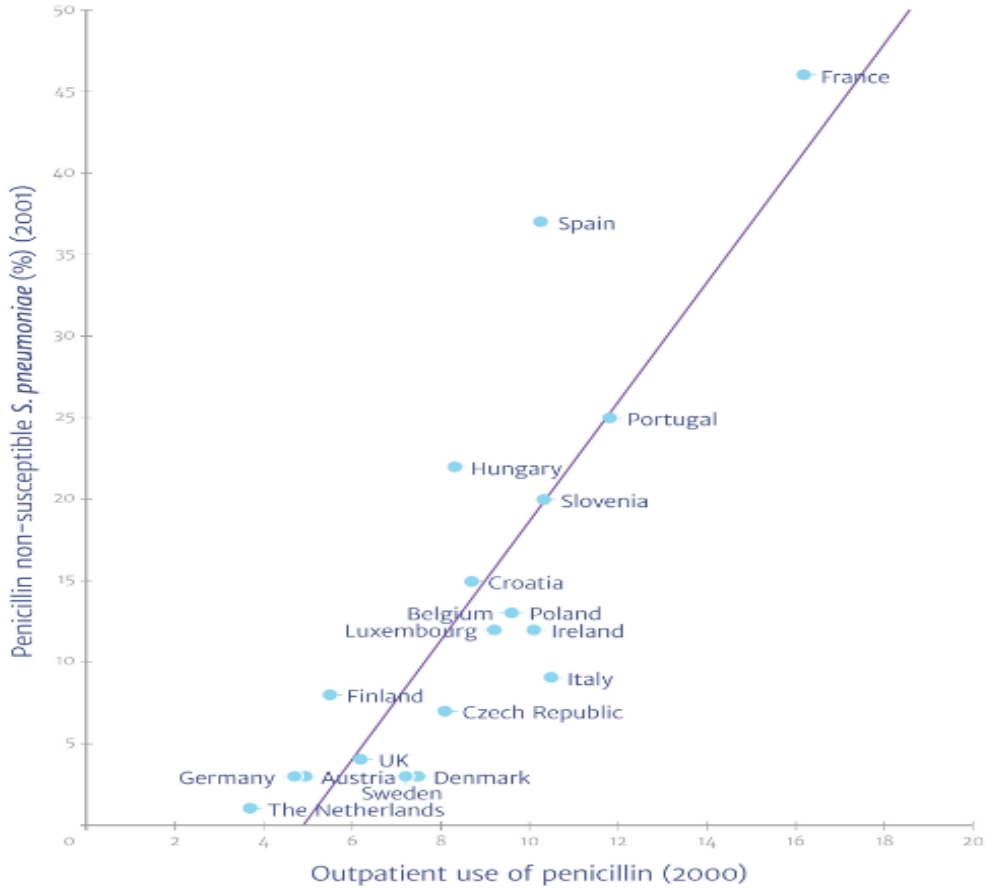
HOSPITAL PRESCRIBERS & PHARMACISTS CAN IMPROVE PRESCRIBING:

- Optimize antibiotic selection
- Re-assess antibiotic treatment when the results of diagnostic testing are available
- Use the shortest effective duration of therapy

FIND RESOURCES ON HOW TO IMPROVE HOSPITAL ANTIBIOTIC USE AND HELP FIGHT ANTIBIOTIC RESISTANCE:

https://bit.ly/HospitalCoreElements

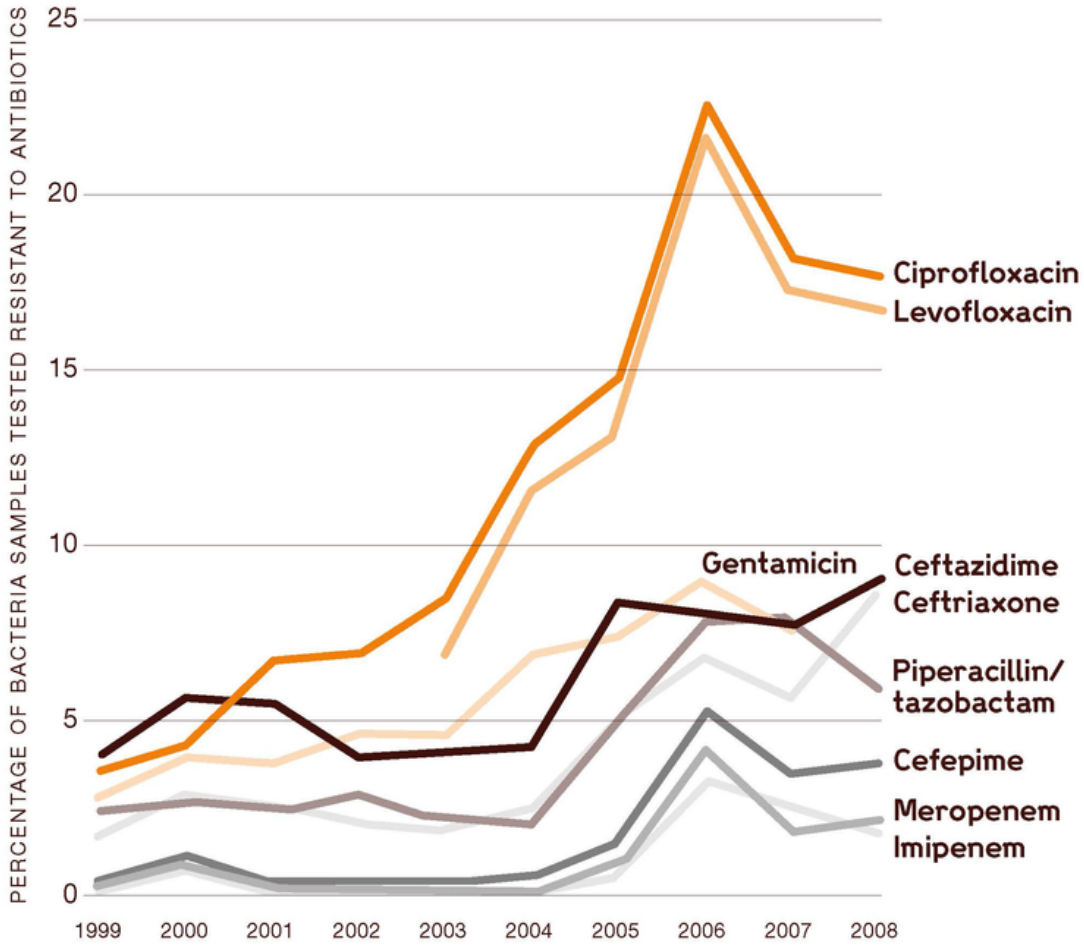
THERE IS A HIGH CORRELATION BETWEEN ANTIBIOTIC USE AND RESISTANCE



Source: Goossens H, Ferech M, Vander Stichele R, et al. *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet 2005; 365(9459): 579–87.

Review on Antimicrobial Resistance

Resistance to many key antibiotics has increased over time



https://www.pnas.org/doi/10.1073/pnas.1717160115

Serious Adverse Events

Antibiotics are responsible for almost **1 out of 5** emergency department visits for adverse drug events.[1]

Antibiotics are **the most common cause** of emergency department visits for adverse drug events in children under 18 years of age.[1]

Anytime antibiotics are prescribed, they can cause adverse events. Only prescribe antibiotics when clinically indicated.

To learn more about antibiotic prescribing and use, visit **www.cdc.gov/antibiotic-use**.

[1]Shehab N, et al. JAMA. 2016 Nov;316(20):2115-25

CS324608-A

Every additional day of excess antibiotic exposure increases risk of ANY adverse event

Hospitalized adults who received course of antibiotics for pneumonia

43 Hospitals; 6481 patients
68% of patients received excess ABX therapy
93% of excess duration was prescribed at discharge

5%

Increased odds of AE per day

Vaughn et al. Annals of IM 2019; 171: 153-163.

Critical Action by Clinicians

The power and potential to tip the resistance scale in either direction even on a population scale is on us!

To stop antibiotic resistance, our nation must:

- **Stop referring to a coming post-antibiotic era—**it's already here. You and I are living in a time when some miracle drugs no longer perform miracles and families are being ripped apart by a microscopic enemy. The time for action is now and we can be part of the solution.
- **Stop playing the blame game.** Each person, industry, and country can affect the development of antibiotic resistance. We each have a role to play and should be held accountable to make meaningful progress against this threat.
- **Stop relying *only* on new antibiotics** that are slow getting to market and that, sadly, these germs will one day render ineffective. We need to adopt aggressive strategies that keep the germs away and infections from occurring in the first place.
- **Stop believing that antibiotic resistance is a problem "over there"** in someone else's hospital, state, or country—and not in our own backyard. Antibiotic resistance has been found in every U.S. state and in every country across the globe. There is no safe place from antibiotic resistance, but everyone can take action against it. Take action where you can, from handwashing to improving antibiotic use.

The problem will get worse if we do not act now, but we can make a difference.

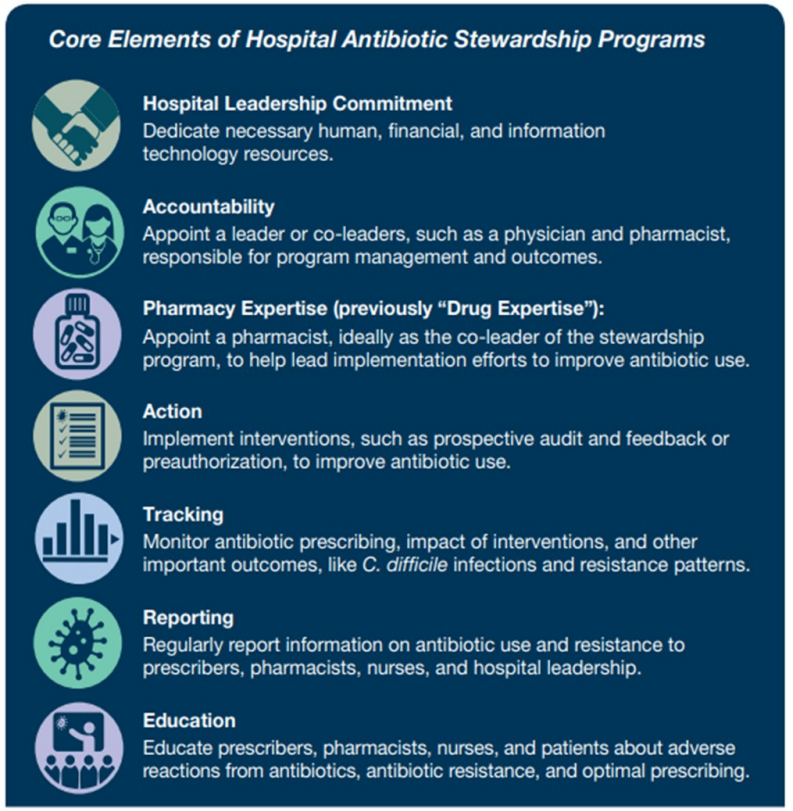
Robert R. Redfield, M.D.
Director, U.S. Centers for Disease Control and Prevention
November 13, 2019

Antimicrobial Stewardship Programs Goals

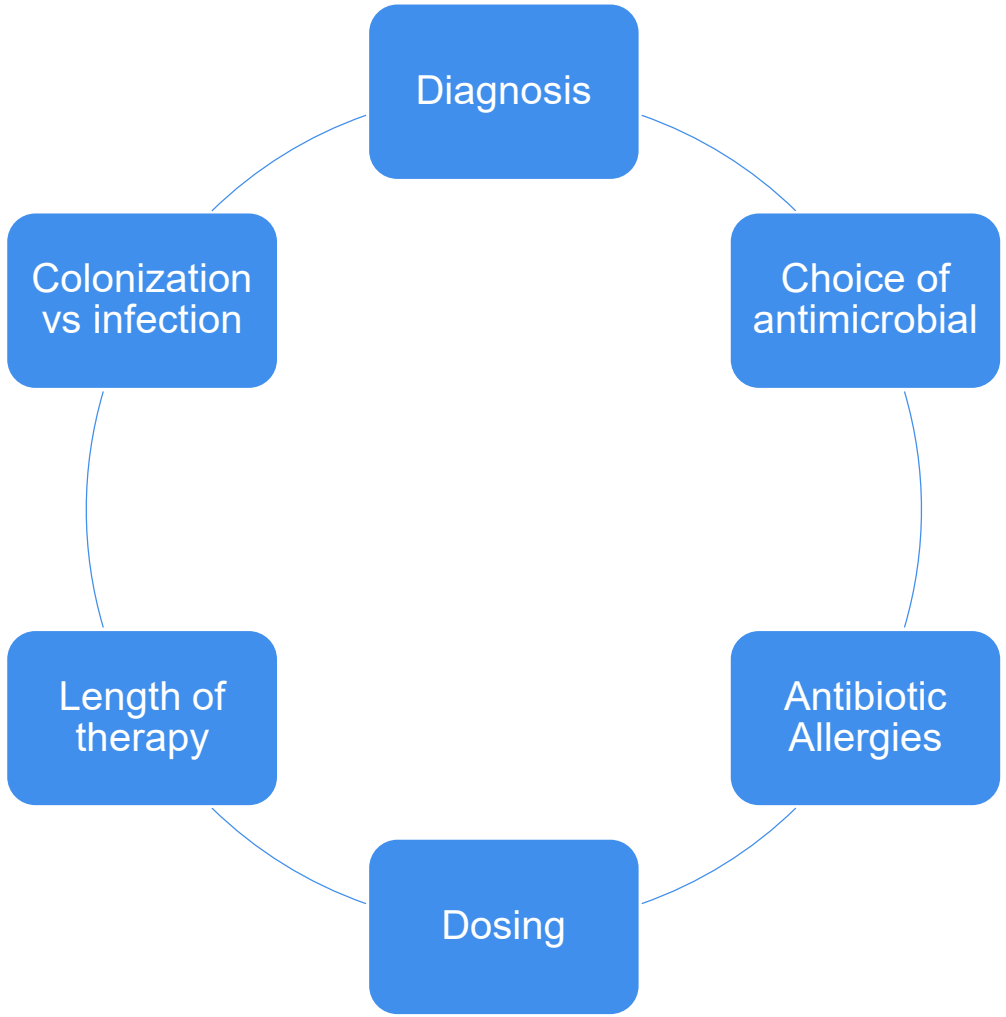
Help optimize antimicrobial therapy, ensuring the best clinical outcome for the patient while lowering the risk of subsequent development of antimicrobial resistance

The 5 “R’s” of Stewardship

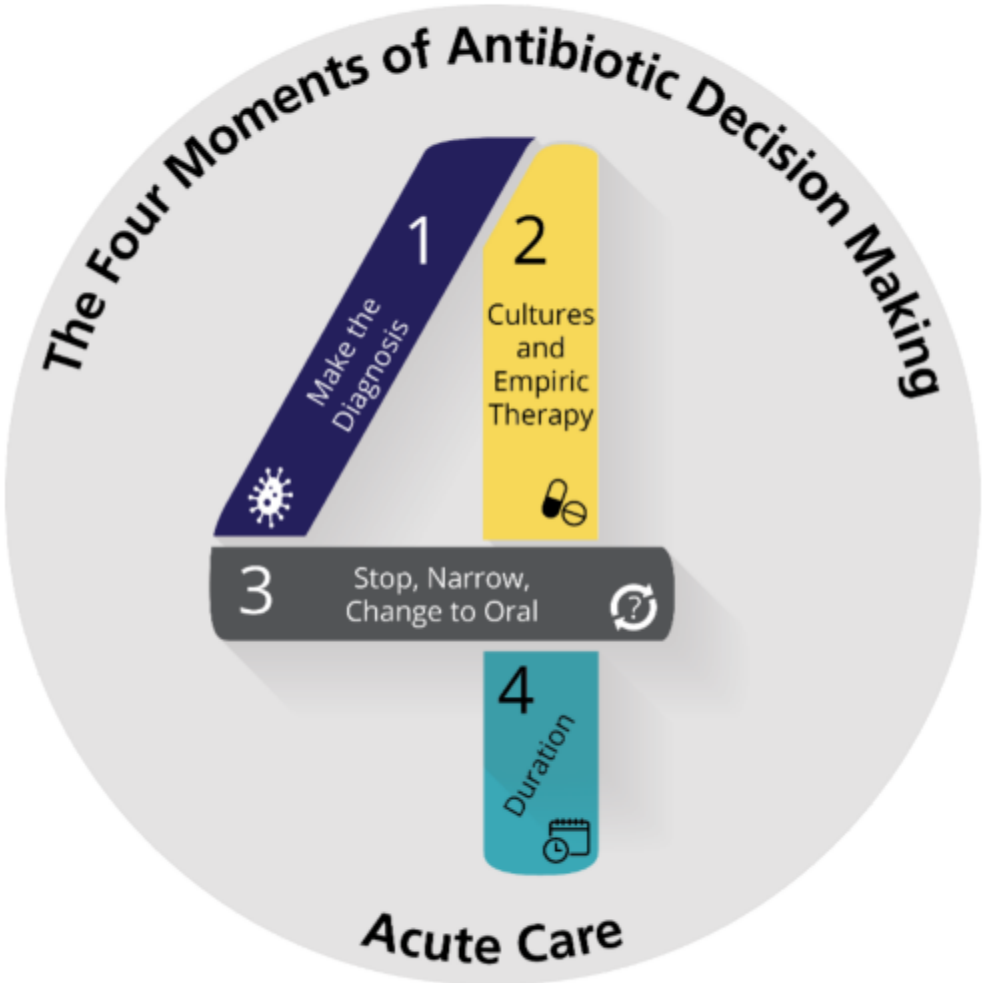
Right drug at the
Right time with the
Right dose for the
Right bug for the
Right duration



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

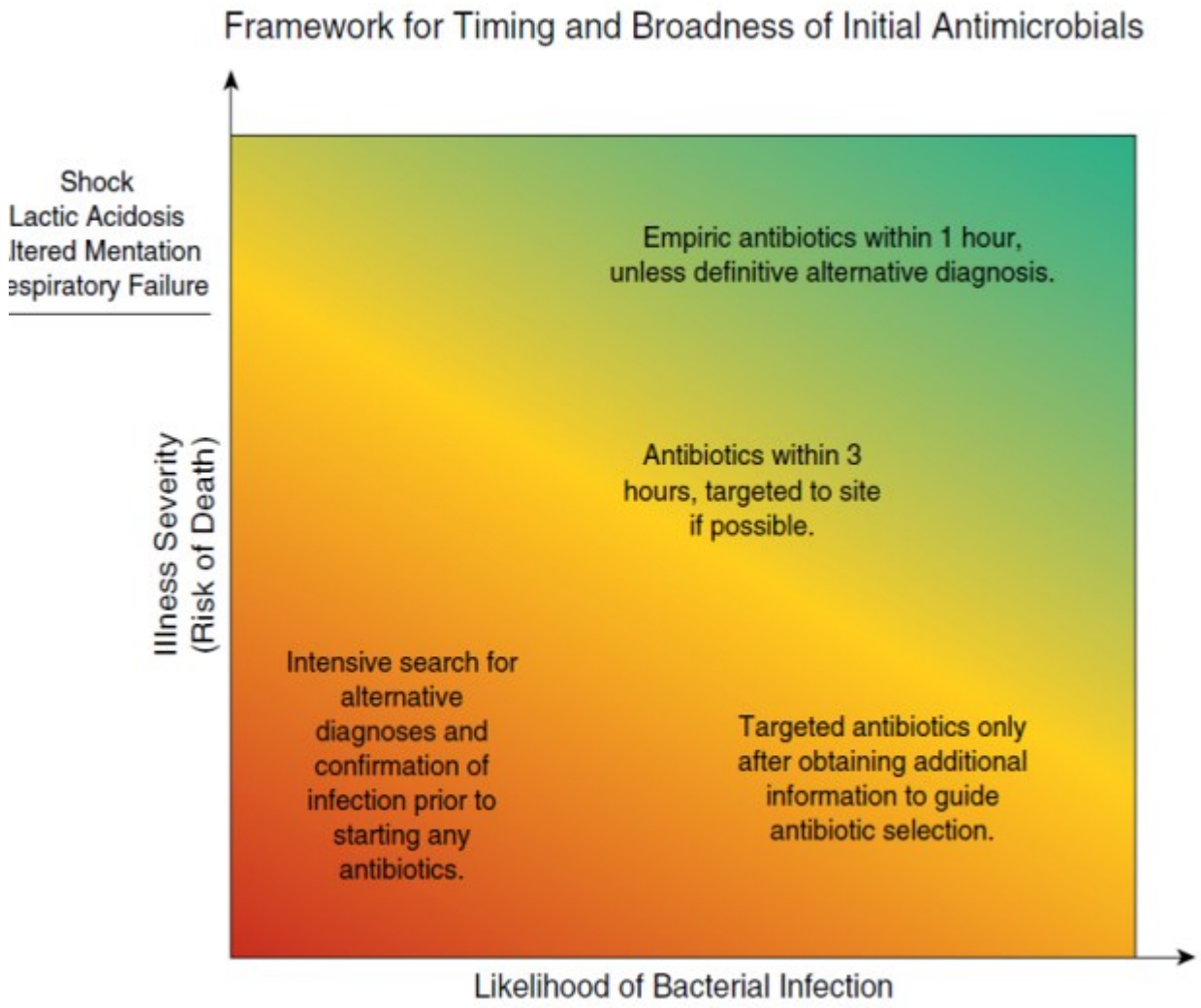

Diagnosis
Choice of antimicrobial
Antibiotic Allergies
Dosing
Length of therapy
Colonization vs infection

Stewarding the Measure



1. Does my patient have an infection that requires antibiotics?
2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?
3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?
4. What duration of antibiotic therapy is needed for my patient's diagnosis?

Tamma PD et al. JAMA. 2019; 32(12):139-140. Tamma PD et al. Ann Am Thorac Soc. 2021; 18: 200-203



Illness severity (risk of death):
Combination of pre-existing risk factors and acute physiological derangements

Likelihood of bacterial infection:
Assess based on signs and symptoms, labs, imaging

Prescott HC and Iwashyna TJ. Ann Am Thorac Soc. 2019; 16(4): 426–429.

Core Elements of Hospital Diagnostic Excellence

Core Element	Description
1. Hospital Leadership Commitment and Accountability	Commitment to the staff and board that improving diagnosis is a priority for the hospital and ensuring the entire organization is accountable for progress. Dedicating the necessary human, financial, technological, and information technology resources.
2. Multidisciplinary Expertise	Creating inclusive and multidisciplinary diagnostic teams that include laboratory and radiology testing experts.
3. Patient, Family, and Caregiver Engagement	Engaging patients, their families, and caregivers as partners in diagnostic excellence, including identifying effective ways to communicate diagnostic test results and other information.
4. Actions	Improving diagnosis through 1) diagnostic stewardship, 2) strengthening systems and processes, and 3) identifying, monitoring, and learning from diagnostic safety events. Improving teamwork and coordination within the hospital and across the continuum of care.
5. Education	Educating healthcare personnel, patients, and family/caregivers about diagnosis and testing.
6. Tracking and Reporting	Monitoring and reporting the activities of the diagnostic excellence program.

CDC September 17,2024

https://www.cdc.gov/patient-safety/hcp/hospital-dx-excellence/index.html#:~:text=Diagnostic%20stewardship%20is%20the%20application,better%20interpretation%20and%20treatment%20decisions.

Diagnostic Stewardship – Optimizing diagnosis by improving the process of ordering, laboratory performance, and reporting of diagnostic test

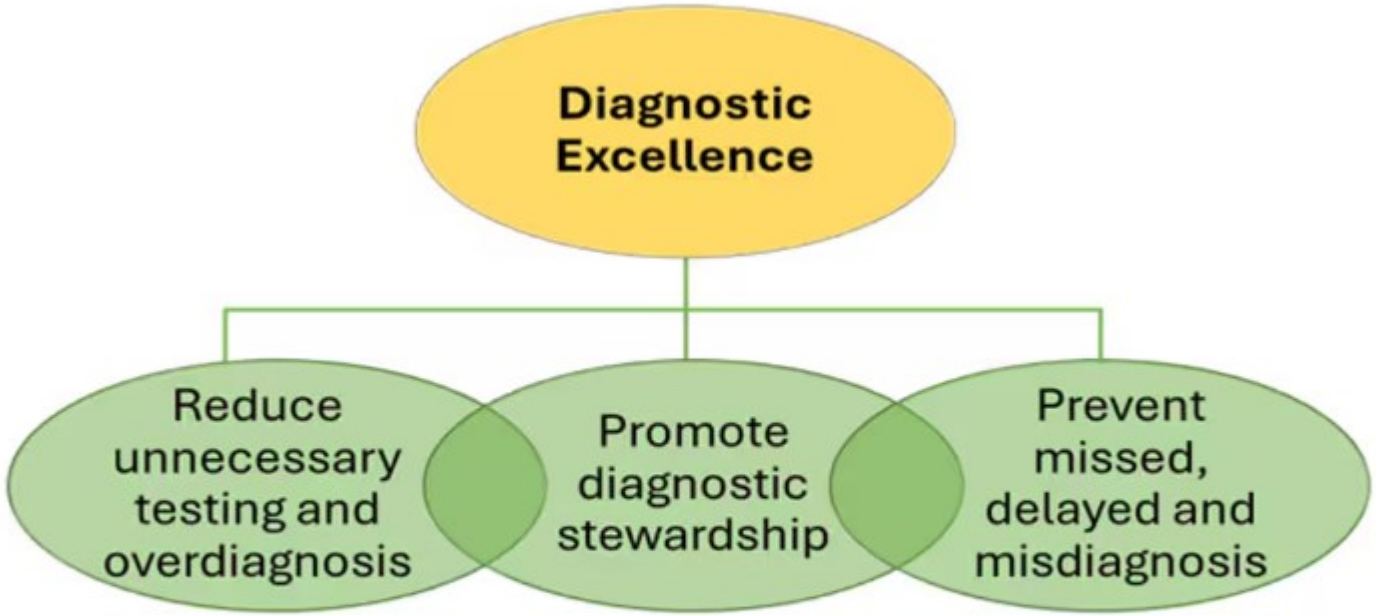


Figure 1: Diagram showing the aspects of diagnosis that are part of diagnostic excellence to be addressed by these Core Elements.

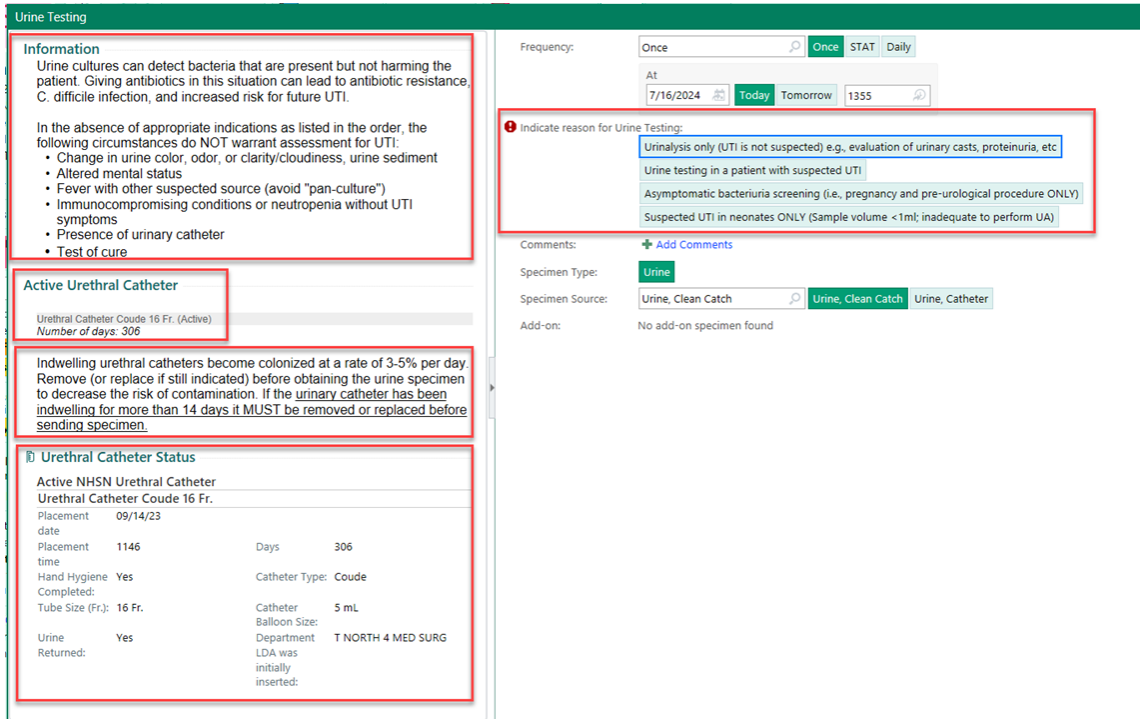
Indication-based Clinical Decision Support for Infectious Diseases Diagnostics has become Best Practice

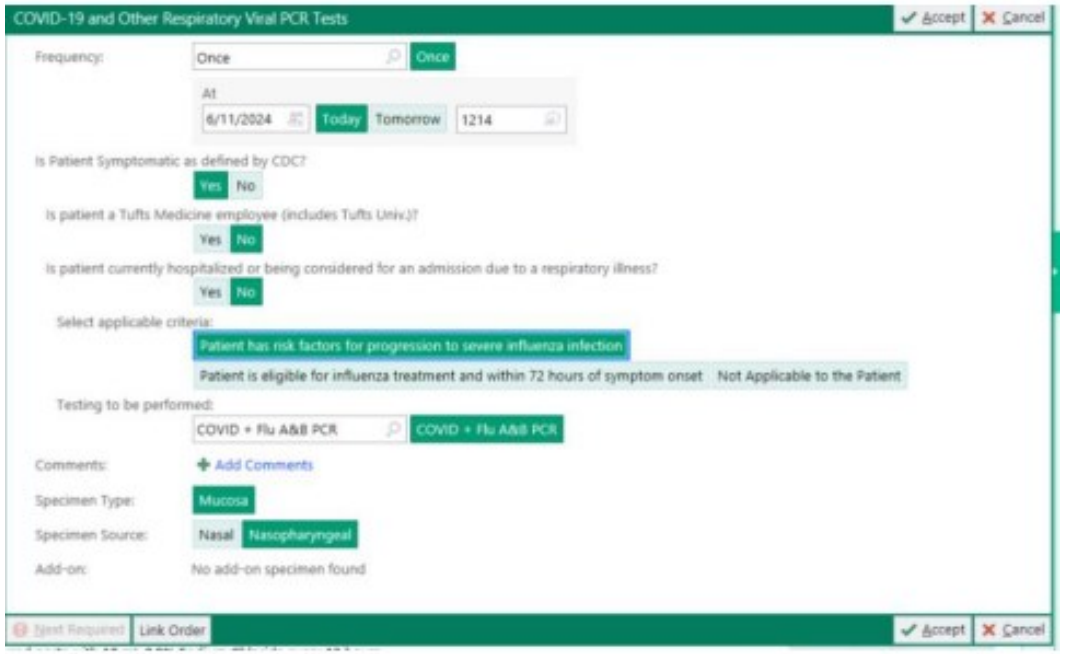
Urine testing

Viral respiratory testing

C diff testing

Blood cultures



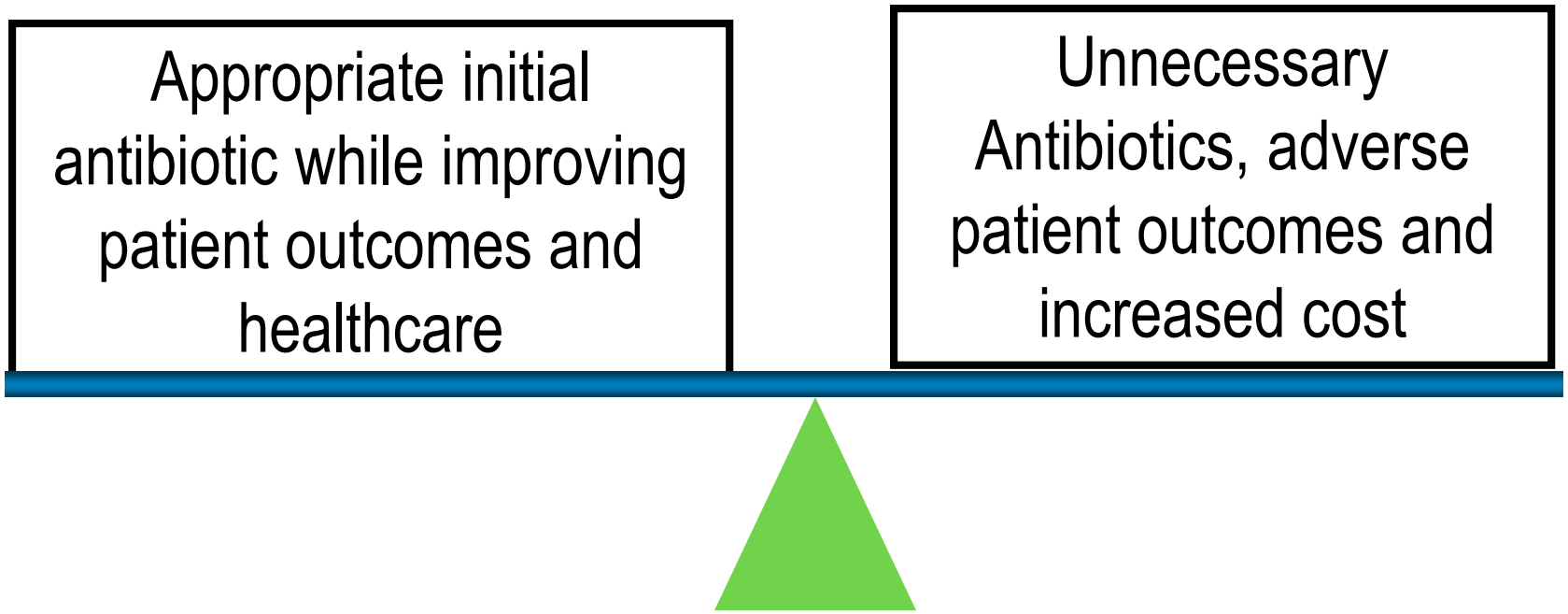


Rapid Diagnostics: Biofire FilmArray® for Blood Culture Identification 2

Aggregate data suggests that BCID2 has 99% sensitivity and 99.8% specificity.

Gram positive	Gram negative	Yeast	Resistance Genes
*Enterococcus faecalis**	*Acinetobacter baumannii complex*	*Candida albicans*	**Carbapenemases**
*Enterococcus faecium**	*Bacteroides fragilis**	*Candida auris*	*KPC*
Listeria monocytogenes	*Enterobacterales*	*Candida glabrata*	*OXA-48 like**
Staphylococcus	*Enterobacter. cloacae complex*	*Candida krusei*	*IMP**
S. aureus	*Escherichia coli*	*Candida parapsilosis*	*NDM**
*S. Epidermidis**	*Klebsiella aerogenes**	*Candida tropicalis*	*VIM**
*S. lugdunensis**	*Klebsiella oxytoca*	*Cryptococcus*	
Streptococcus	*Klebsiella pneumoniae group*	*neoformans/gattii*	**Colistin resistance**
S. agalactiae	*Proteus spp*		*Mcr-1**
S. pyogenes	*Salmonella spp***		
S. pneumoniae	*Serratia marcescens*		**ESBL**
	Haemophilus influenzae		*CTX-M**
	Neisseria meningitidis (encapsulated only)		**Methicillin-R**
	Pseudomonas aeruginosa		*mecA/C*
	Stenotrophomonas maltophili		*MecA/C and MREJ (MRSA)**
			Vancomycin R
			Van A/B

Antimicrobial Therapy



A Balancing Act

Selection and Dosing of Empiric Antimicrobials

Evidenced based practice following:

National guidelines and data

Institutional guidelines by disease state

Antibiogams

Source of infection:

- Coverage is <u>not</u> always needed
  - For MRSA- CAP, intra-abdominal infections, UTIs, non purulent cellulitis.
  - For pseudomonas - CAP, intraabdominal, SSTI, UTIs.

Extended Infusions:

prolonged beta lactam infusions associated with lower mortality

TuftsMedicine
Tufts Medical Center

Tufts Medical Center Antibiogram
Isolates collected 1/1/2023- 12/31/2023

Confidential Information for TMC staff only
Provided by Department of Pharmacy, Hospital Labs, Microbiology Services and Division of Geographic Medicine and Infectious Diseases

All sources, Adult inpatient and emergency department, 1st isolate per site

Pathogen Tested,n % susceptible	Isolates	Penicillins & Beta-lactamas inhibitors: Ampicillin	Ampicillin /sulbactam	Piperacillin /tazobactam	Cephalosporins: Meropenem	Ertapenem	Cefazolin	Cefoxitin	Ceftriaxone	Ceftazidime	Cefepime	Aminoglycosides: Gentamicin	Tobramycin	Quinolone: Amikacin	Ciprofloxacin	UTI Agent: Trimethoprim /Sulfamethoxazole	Nitrofurantoin
Citrobacter spp.[A]	43	-	-	76	97	100	-	50	65	79	93	97	96	100	88	83	87
Enterobacter spp.[A]	90	-	-	65	100	92	-	0	65	70	93	97	96	98	93	85	37
Escherichia coli[B]	703	51	61	93	99	99	83	92	87	91	96	89	89	100	74	73	97
Klebsiella pneumoniae[B]	252	-	69	80	97	97	83	93	82	85	95	92	90	99	86	82	19
Klebsiella oxytoca[B]	45	-	47	80	100	100	-	95	73	91	93	91	91	100	89	91	85
Proteus mirablis	103	76	87	100	100	94	-	97	95	98	98	89	91	100	84	82	0
Serratia marcescens	52	0	0	83	98	98	-	-	80	98	100	96	82	100	98	98	0
Pseudomonas aeruginosa	215	-	-	80	88	-	-	-	-	84	86	-	96	95	86	-	-
Stenotrophomonas maltophilia[C]	40	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100	-
Acinetobacter spp.[C]	27	-	100	66	88	-	-	-	23	88	88	100	100	100	88	88	-
Outpatient urine isolates Enterobacterales	368	46	66	95	100	100	88	90	92	95	98	90	90	99	77	78	79
ED Urine Isolates Enterobacterales	540	43	66	94	99	99	84	89	90	94	97	89	90	97	82	78	73

(-) drug not tested or not indicated

Scenario	Action
An alternative, nonbacterial etiology is identified (e.g., pulmonary embolism)	Stop antibiotics
A bacterial infection is identified and culture data are available	Narrow or broaden therapy as appropriate
A bacterial infection is identified but culture data are not available (e.g., HAP, non-purulent cellulitis)	Antibiotic regimen based on likely pathogens informed by local susceptibility data and other available data (e.g., MRSA nasal swab results)
Neither a bacterial or a non-bacterial etiology is identified and the patient is better	Stop antibiotics and monitor (avoid pre-determined courses of antibiotics)
Neither a bacterial or a non-bacterial etiology is identified and the patient is not better	• Additional work up for infectious disease processes • Additional workup for non-infectious causes • 7 day antibiotic course for most

The New Antibiotic Mantra: Shorter is Better

CLINICAL GUIDELINE

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Appropriate Use of Short-Course Antibiotics in Common Infections: Best Practice Advice From the American College of Physicians

Rachael A. Lee, MD, MSPH; Robert M. Centor, MD; Linda L. Humphrey, MD, MPH; Janet A. Jokela, MD, MPH; Rebecca Andrews, MS, MD; and Amir Qaseem, MD, PhD, MHA; for the Scientific Medical Policy Committee of the American College of Physicians*

Lee RA. Ann Intern Med. 2021

Duration of Antimicrobials for Common Infectious Diseases

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	5-8	10-15	Equal	3
Empyema	14-21	21-42	Equal	2
Cystic Fibrosis Excerbation	10-14	14-21	Equal	1
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	11**
Intra-abd Infection	4	8-10	Equal	3
Complex Appendicitis	1-2	5-6	Equal	2
GNB Bacteremia	7	14	Equal	3†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2Φ
Septic Arthritis	14	28	Equal	1
Bacterial Meningitis (peds)	4-7	7-14	Equal	6
AECB & Sinusitis	≤5	≥7	Equal	>25
Variceal Bleeding	2-3	5-7	Equal	2
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	55Ψ
Erythema Migrans (Lyme)	7-10	14-20	Equal	3
P. vivax Malaria	7	14	Equal	1

Total: 22 Conditions >130 RCTs

https://www.bradspellberg.com/shorter-is-better

Tufts and Massachusetts DPH

SHORTER IS SMARTER

SUMMARY OF APPROPRIATE USE OF SHORT-COURSE ANTIBIOTICS IN COMMON INFECTIONS

Condition	Short duration	Available evidence	Mortality	Length of stay	Clinical success rate	Relapse rate	Adverse events	Tufts Medical Center Antimicrobial Stewardship Team Advice
Acute exacerbation of chronic bronchitis (AECB) or chronic pulmonary obstructive disease (COPD)	5 days	GOLD guideline[1] >20 RCTs (N=11,008)[24,25]	No difference in mortality between groups[2]	*Limited/ insufficient data*	No difference in clinical improvement between groups[1]	No difference in one-year exacerbation rate between groups[2]	No difference in adverse events between groups[2]	Clinicians should limit antibiotic treatment duration to 5 days when managing patients with COPD exacerbations and acute uncomplicated bronchitis who have clinical signs of bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume).*[1]
Community-acquired pneumonia (CAP)	3-5 days	IDSA/ATS guideline[1] 14 RCTs (N=8,732)[1]	Lower mortality in short-course group[1]	No difference in length of ICU stay between groups[3]	No difference in clinical improvement between groups[1]	No difference in relapse rates between groups[4,5]	Fewer adverse events in short-course group[1]	Clinicians should prescribe antibiotics for CAP for a minimum of 5 days. Extension of therapy after 5 days of antibiotics should be guided by validated measures of clinical stability, which include resolution of vital sign abnormalities, ability to eat, and normal mentation.*[1]
Urinary Tract infection (UTI): bacterial cystitis	3-5 days or single-dose, depending on antibiotic selected	IDSA/ESCMID guideline[1] 3 recent RCTs[1]	*Limited/ insufficient data*	*Limited/ insufficient data*	No difference in clinical improvement between groups except in patients with complicated UTI[1]	No difference in rate of recurrent UTI within 30 days[1]	No difference in adverse events between groups[6,7]	In women with uncomplicated bacterial cystitis, clinicians should prescribe short-course antibiotics with either nitrofurantoin for 5 days, trimethoprim-sulfamethoxazole (TMP-SMZ) for 3 days, or fosfomycin as a single dose.*[1]
Urinary tract infection (UTI): pyelonephritis or febrile UTI	5-7 days or 10-14 days depending on antibiotic selected	IDSA/ESCMID guideline[1] 9 RCTs (N=1,814)[1]	*Limited/ insufficient data*	*Limited/ insufficient data*	No difference in clinical improvement between groups except in patients with complicated UTI[1,6,8]	No difference in rate of recurrent pyelonephritis within 30 days[1]	No difference in adverse events between groups[9,10]	For pyelonephritis or febrile UTI in both males and females, duration of therapy will vary based upon agent and antibiotic susceptibilities. Give fluoroquinolones for 5-7 days, TMP-SMZ for 14 days, or beta-lactams (e.g. cephalexin) for 10-14 days.[9,10,11]
Nonpurulent cellulitis	5-6 days	IDSA guideline[1] NICE guideline[1] 4 RCTs (N=1,412)[1]	*Limited/ insufficient data*	*Limited/ insufficient data*	No difference in clinical improvement between groups[1]	*Limited/ insufficient data*	Gastrointestinal adverse events were less frequent or similar with 6-day tedizolid than 10-day linezolid[11]	In patients with nonpurulent cellulitis, clinicians should use a 5- to 6-day course of antibiotics active against streptococci, particularly for patients able to self-monitor and who have close follow-up with primary care.*[1]
Debrided diabetic osteomyelitis	21 days	1 RCT (N=93)[33]	*Limited/ insufficient data*	*Limited/ insufficient data*	No difference in clinical improvements in between groups	*Limited/ insufficient data*	No difference in adverse events	In a randomized controlled pilot trial, a postdebridement systemic antibiotic therapy course for diabetic foot osteomyelitis of 3 weeks gave similar (and statistically noninferior) incidences of remission and adverse events to a course of 6 weeks[33]

Compiled from ACP and other literature

RCT: Randomized Clinical Trial
*Direct recommendation from ACP Guidelines
**Direct recommendation from the IDSA

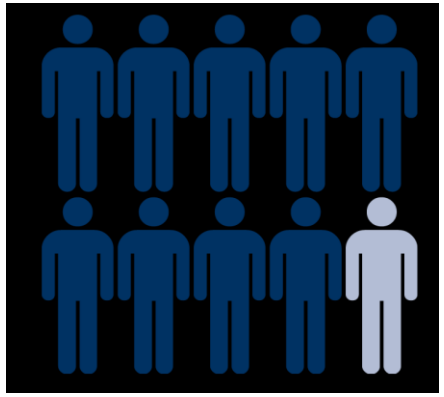
February 2024

Tufts Medical Center

https://infectioncontrolma.org/docs/Shorter-is-Smarter-2024.pdf

Prevalence of Antibiotic Allergy

- Penicillin is the most commonly reported antibiotic allergy
  - 1 in 10 US population reported allergy to penicillin



  - But only <1% of the population has true penicillin allergy
  - 95% of these individuals tolerate beta-lactam antibiotics
    - IgE mediated penicillin allergy wanes over time, 80% tolerate penicillin after 10 years
    - Reported allergy was not a true allergy

Zhou L et al. Allergy. 2016 Sep;71(9):1305-13
Sacco KA et al. Allergy. 2017 Sep;72(9):1288-96
Shenoy ES et al. JAMA. 2019 Jan 15;321(2):188-99
Khan DA et al. J Allergy Clin Immunol. 2022 Dec;150(6):1333-93

Why Mislabeling of Antibiotic Allergy Matters

Personal Health Implications

- Fewer efficacious antibiotic options
- More adverse drug reactions associated with alternative antibiotic
- Sub-optimal clinical outcomes or treatment failure
- Use of unnecessarily broader-spectrum antibiotics
- Increased risk for post-operative surgical site infection (50%)

Public Health Implications

- Antibiotic resistance
- Increased risks for *Clostridioides difficile* infection
- Increased risks for MRSA and VRE infections
- Use of more costly antibiotics
- Increased length of hospital stay

Castells M et al. N Engl J Med. 2019 Dec 12;381(24):2338-51

Macy et al. J Allergy Clin Immunol. 2014 Mar;133(3):790-6

Blumenthal KG et al. Clin Infect Dis. 2015 Sep 1;61(5):741-9

Blumenthal KG et al. Ann Allergy Asthma Immunol. 2015 Oct;115(4):294-300

MacFadden DR et al. Clin Infect Dis. 2016 Oct 1;63(7):904-10

Blumenthal KG et al. BMJ. 2018 Jun 27;361:k2400

Blumenthal KG et al. Clin Infect Dis. 2018 Jan 18;66(3):329-36

Mattingly TJ 2nd et al. J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1649-1654.e4

Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use: technical report

10 October 2024 | Technical document

> **“The best infection is the one that doesn't occur...When we vaccinate people, then they don't develop infections and they don't require antibiotics.”**

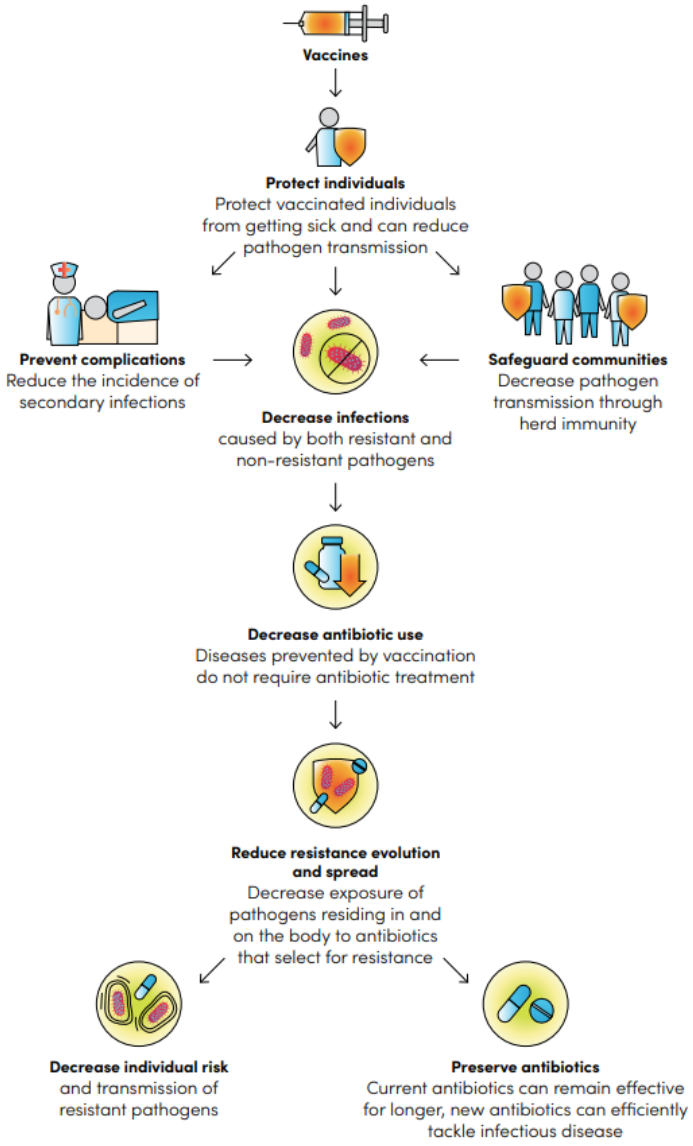
Introduction and deployment of 44 vaccines against 24 pathogens could:

Avert more than half a million deaths from drug-resistant infections annually

Cut AMR-related healthcare costs and productivity losses by billions of dollars

Reduce the number of antibiotics needed to treat infections by 2.5 billion doses annually

Fig. 1.2. Impact of vaccines on AMR in humans: a schematic pathway



AMR: *antimicrobial resistance.*

Source: Reproduced with permission from Frost et al. 2022 (22).

World Health Organization

Hand Washing & Environment of Care

A systematic review found that on average, adherence to handwashing practices by healthcare workers is only 40% – although self-reported rates are frequently near 100%.

Source: Eramus V, Daha TJ, Brug H, et al., Systematic review of studies on compliance with hand hygiene guidelines in hospital care, *Infection Control and Hospital Epidemiology*, 2010, 31(3), 283-294.

Levels of hand hygiene compliance in healthcare facilities for high-income countries rarely exceed 70%

Handwashing education in the community can prevent about:

- 30% of diarrhea-related sicknesses
- 20% of respiratory infections.

Take Away

We are living in the Era of Antimicrobial Resistance

Reflect on our own clinical practice and potential contributions to AMR

PAUSE every time we prescribe an antibiotic

Think about spectrum, duration, optimal dosing

Broader is not always better or safer

Human colonization with microorganisms is common

Positive culture is NOT equal to infection

Reassess whether a diagnostic testing is necessary/indicated.

Address antibiotic allergies

WASH your hands!

Vaccinate!

CDC

Fighting Antimicrobial Resistance

TAKES ALL OF US

November 18-24, 2024

Thank You

Tufts Medicine

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