Kan AB-styring påvirke antibiotikaresistens?

Bjørn Waagsbø

Overlege RKS Midt

Driving forces of evolving AMR

Some relevant questions

1) Is antimicrobial consumption a driver of AMR?

   At individual level **Yes**

   At country-level **Yes**

   → **Improvement of diagnosis and therapy practices**

2) Is exposure to AMR-pathogens a driver of AMR? **Yes**

3) Is suboptimal diagnostics a driver of AMR? **Yes**

4) Is the lack of research and development for new antibiotics a driver of AMR? **Yes**

5) Is the lack of coordinated global initiatives a driver of AMR? **Yes**

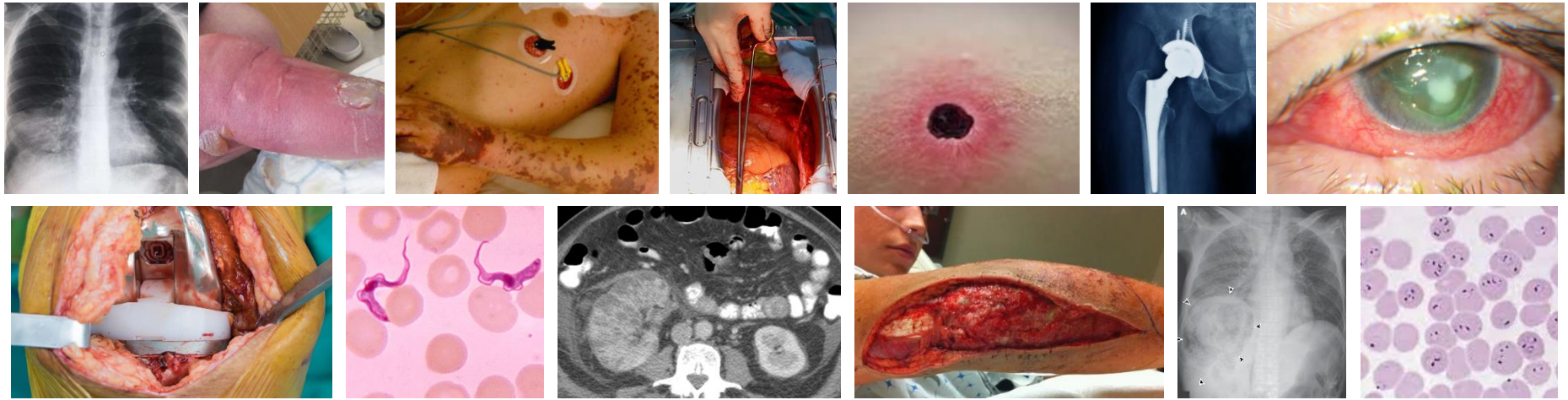
Editors of NEJM 2000

The NEW ENGLAND JOURNAL of MEDICINE

The discovery of antibiotics

What impact did it have?

> The discovery of antimicrobials is doubtless one of the greatest accomplishments of medical science



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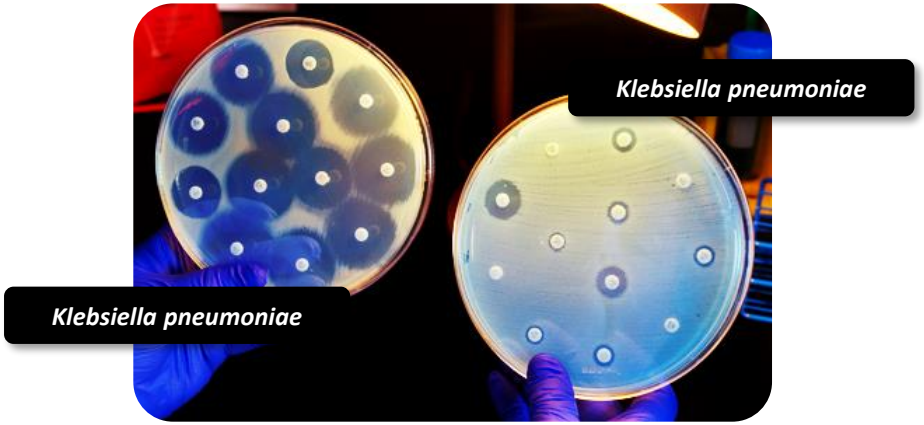
Antimicrobial resistance (AMR)

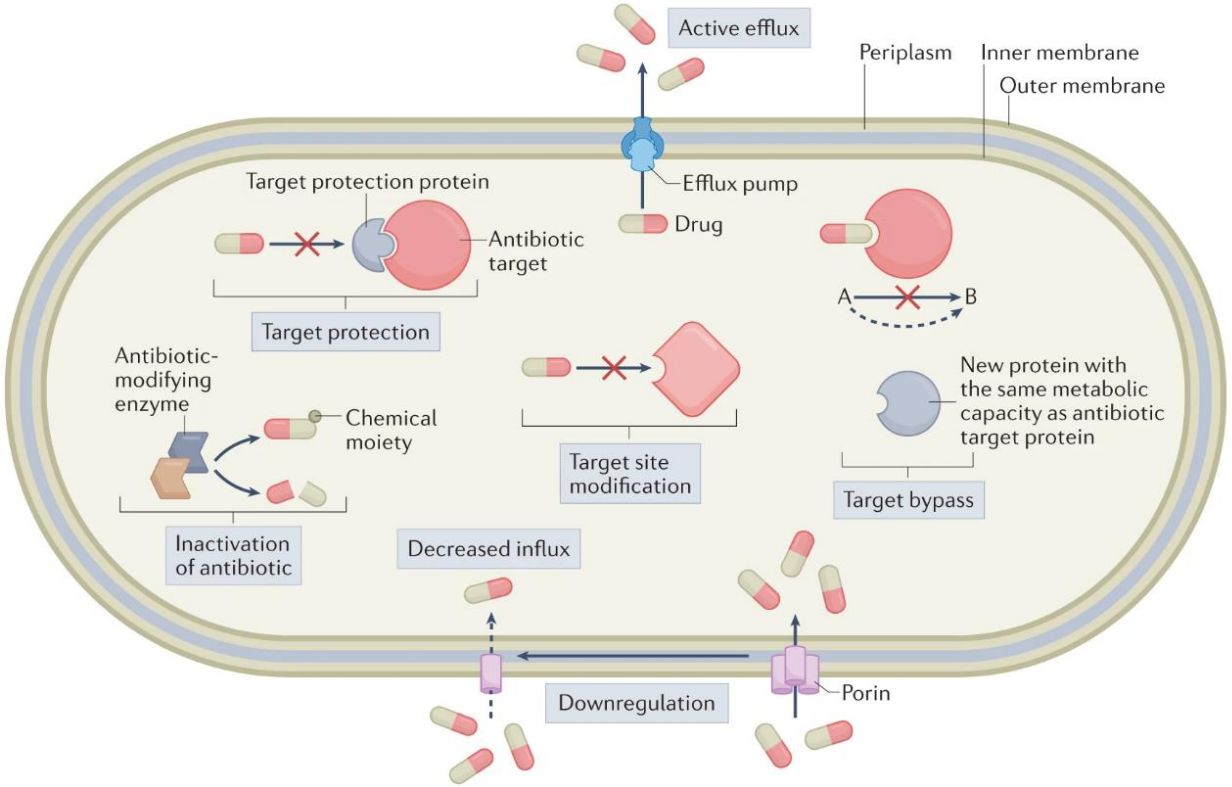
What is it?



> Antimicrobial resistance (AMR) is the ability in bacteria to resist antibiotics

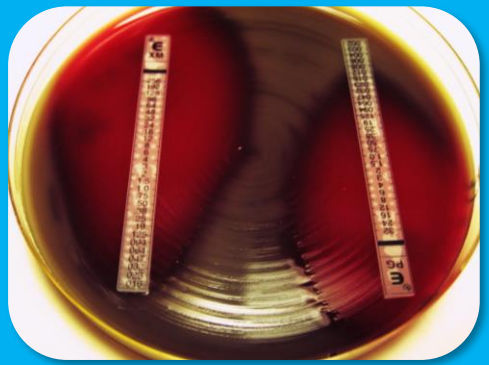
Molecular mechanisms of AMR

Complex mechanisms



Antimicrobial resistance (AMR)

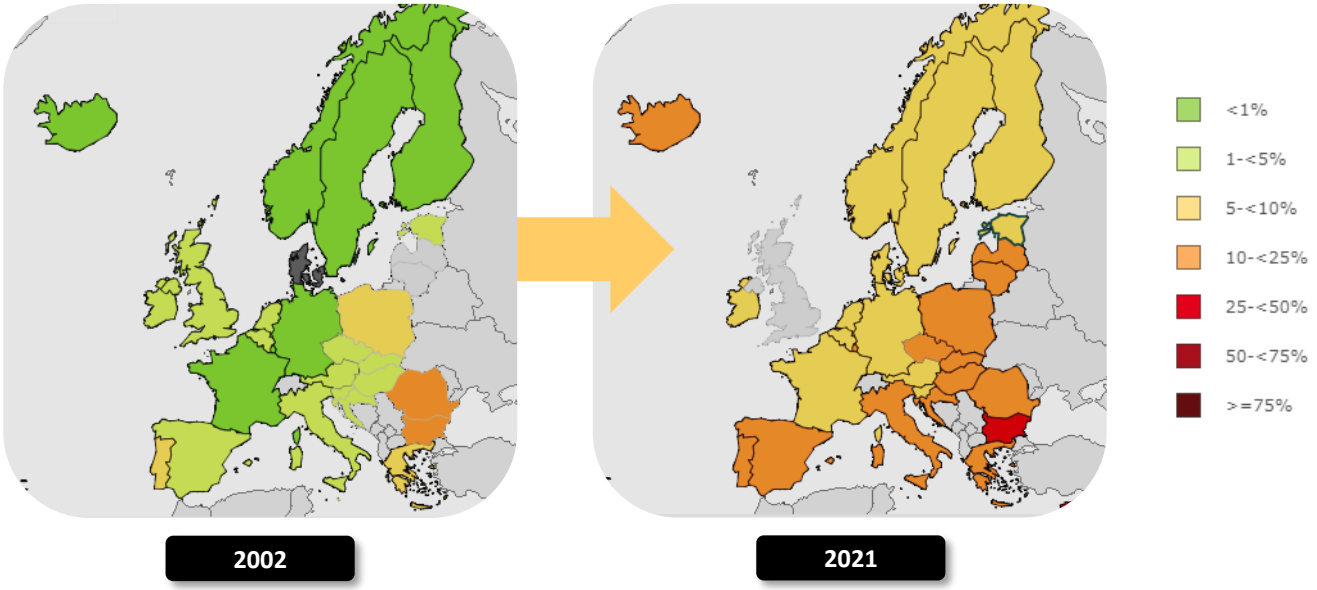
What is the current situation?



ECDC-database 2021

3rd gen. cephalosporin resistance in *E coli*

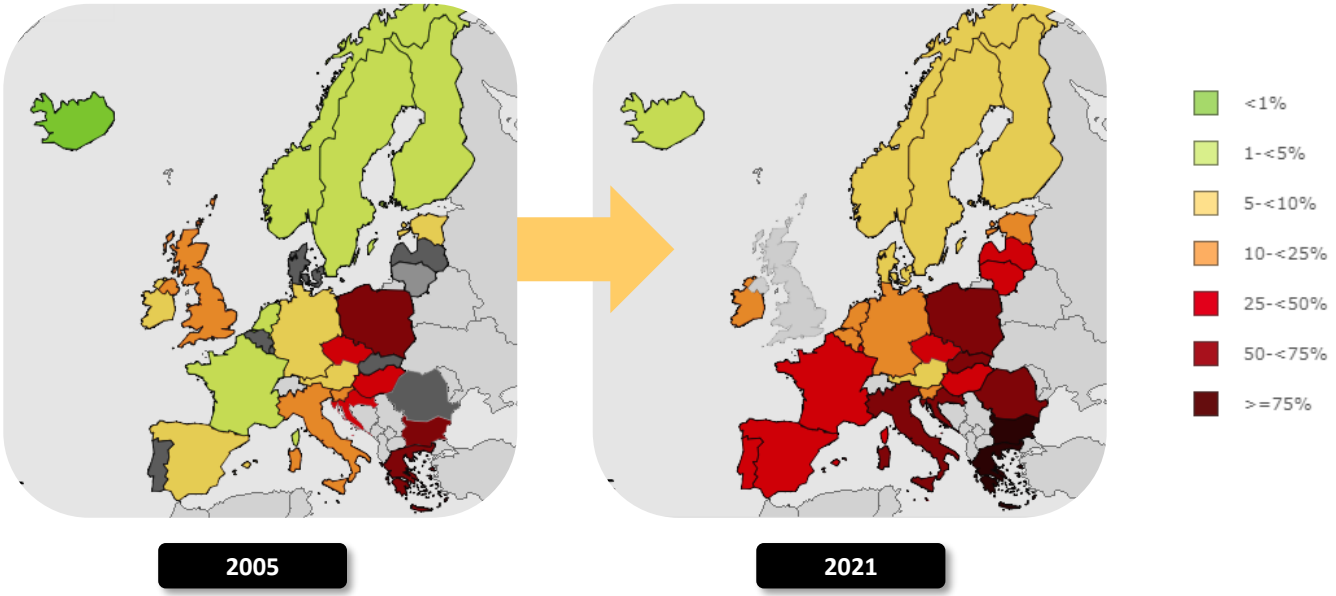
Antimicrobial resistance prevalence in Europe 2021



ECDC-database 2021

3rd gen. cephalosporin resistance in *K pneumoniae*

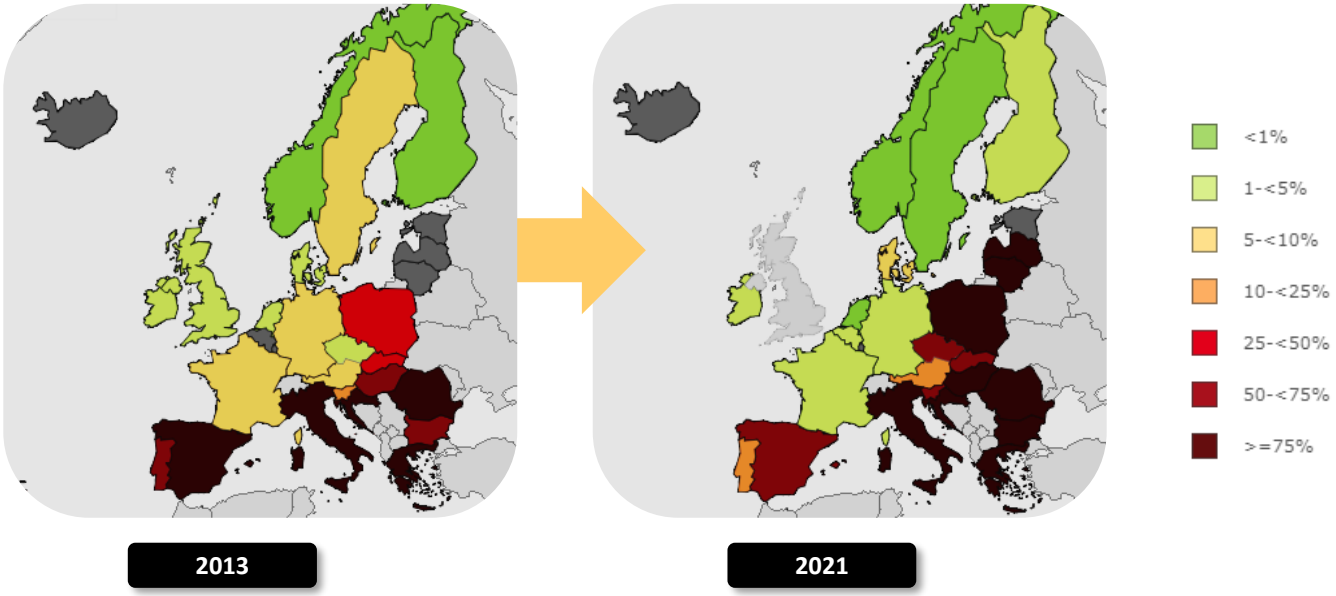
Antimicrobial resistance prevalence in Europe 2021



ECDC-database 2021

Carbapenem resistance in *Acinetobacter* spp

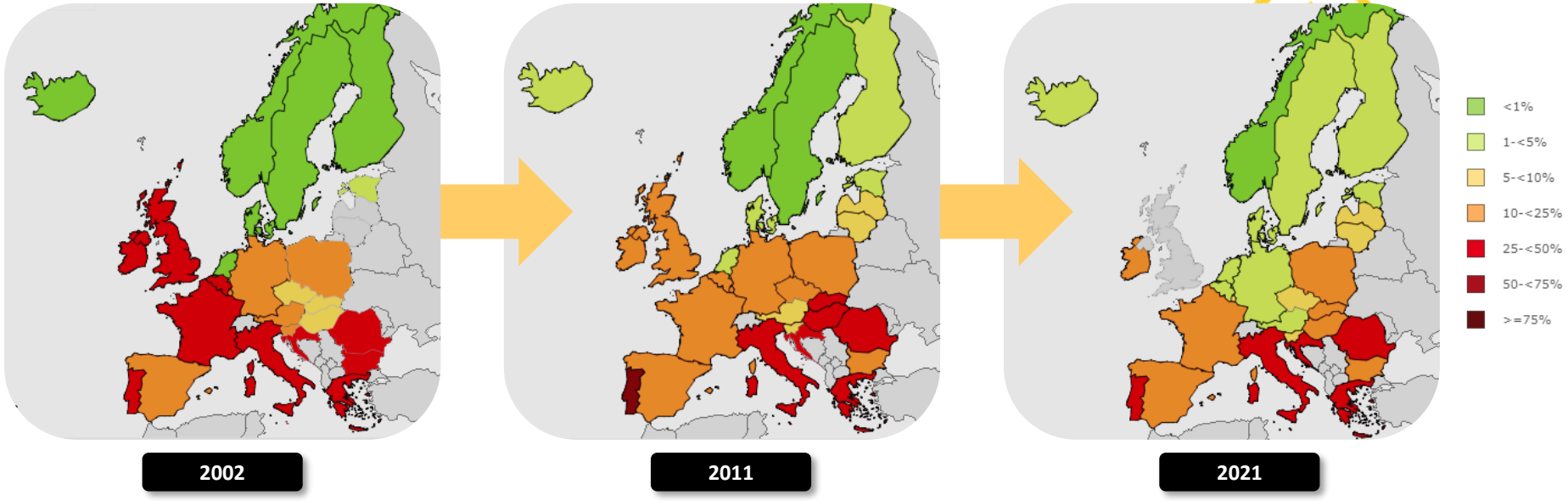
Antimicrobial resistance prevalence in Europe 2021



ECDC-database 2021

Meticillin resistance in *S aureus* (MRSA)

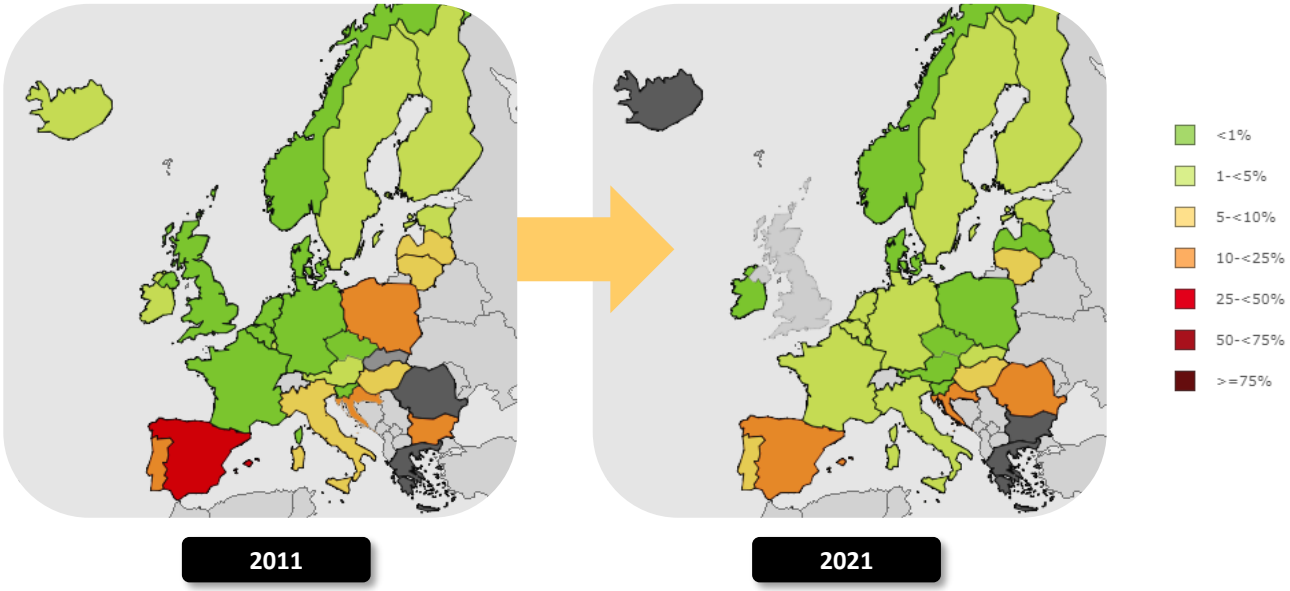
Antimicrobial resistance prevalence in Europe 2021



ECDC-database 2021

Penicillin resistance in *S pneumoniae*

Antimicrobial resistance prevalence in Europe 2021

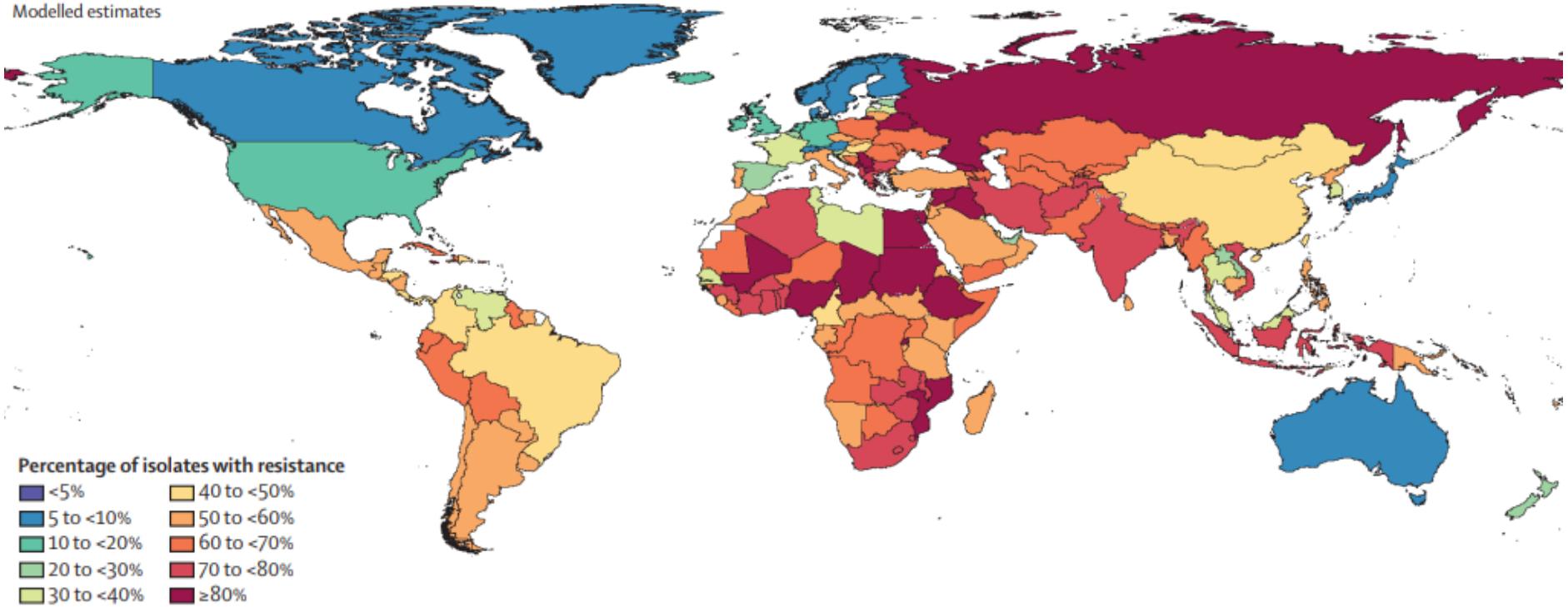


AMR is increasing in Europe

North ▶ south, and a west ▶ east AMR-gradient

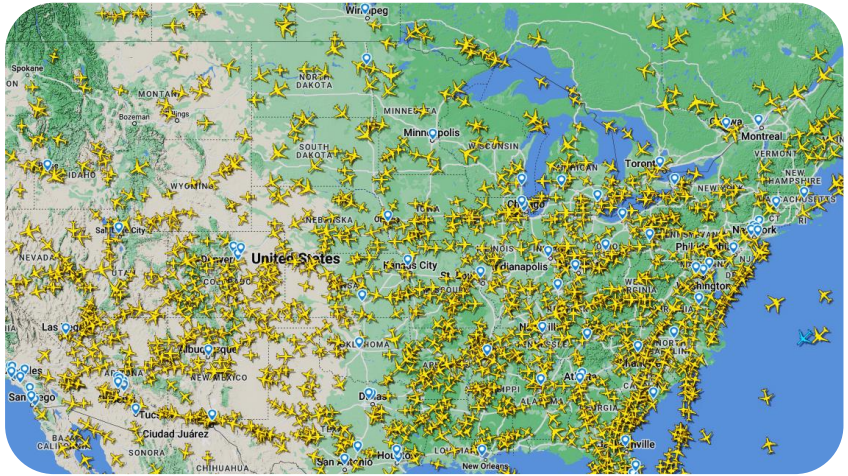
AMR global perspective

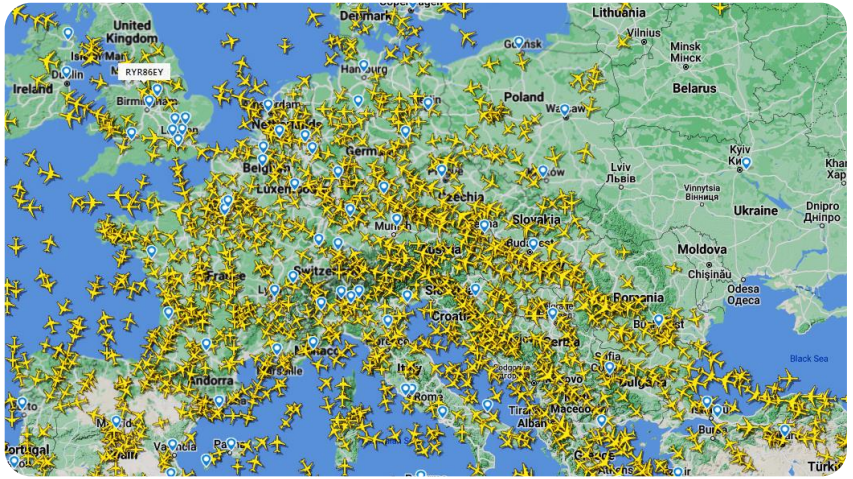
3rd generation cephalosporin-resistant K pneumoniae in 2019



Air travel

Random moment

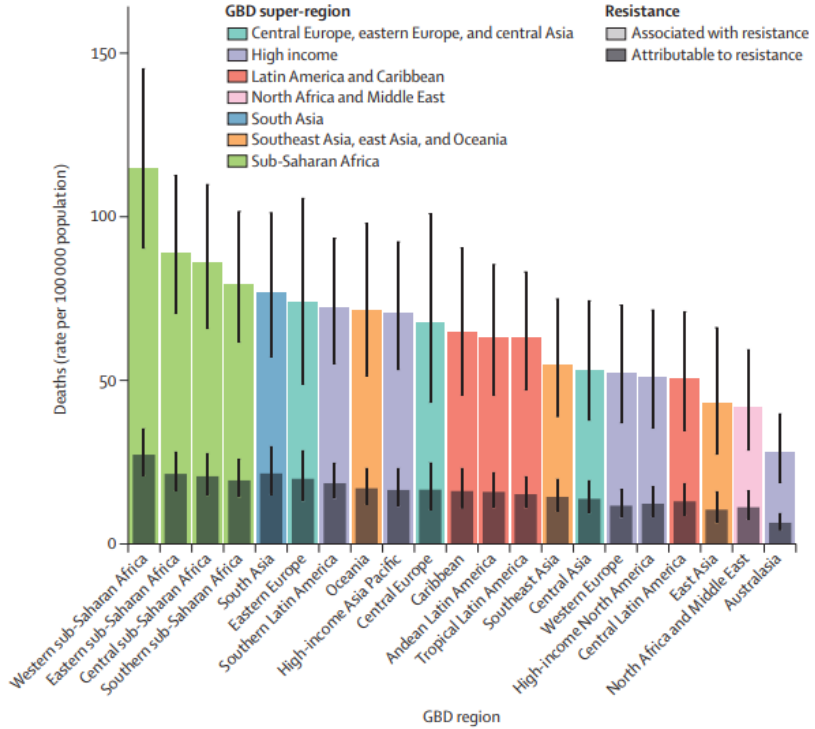




What are consequences of AMR?

AMR deaths

Deaths associated or attributable to AMR in 2019

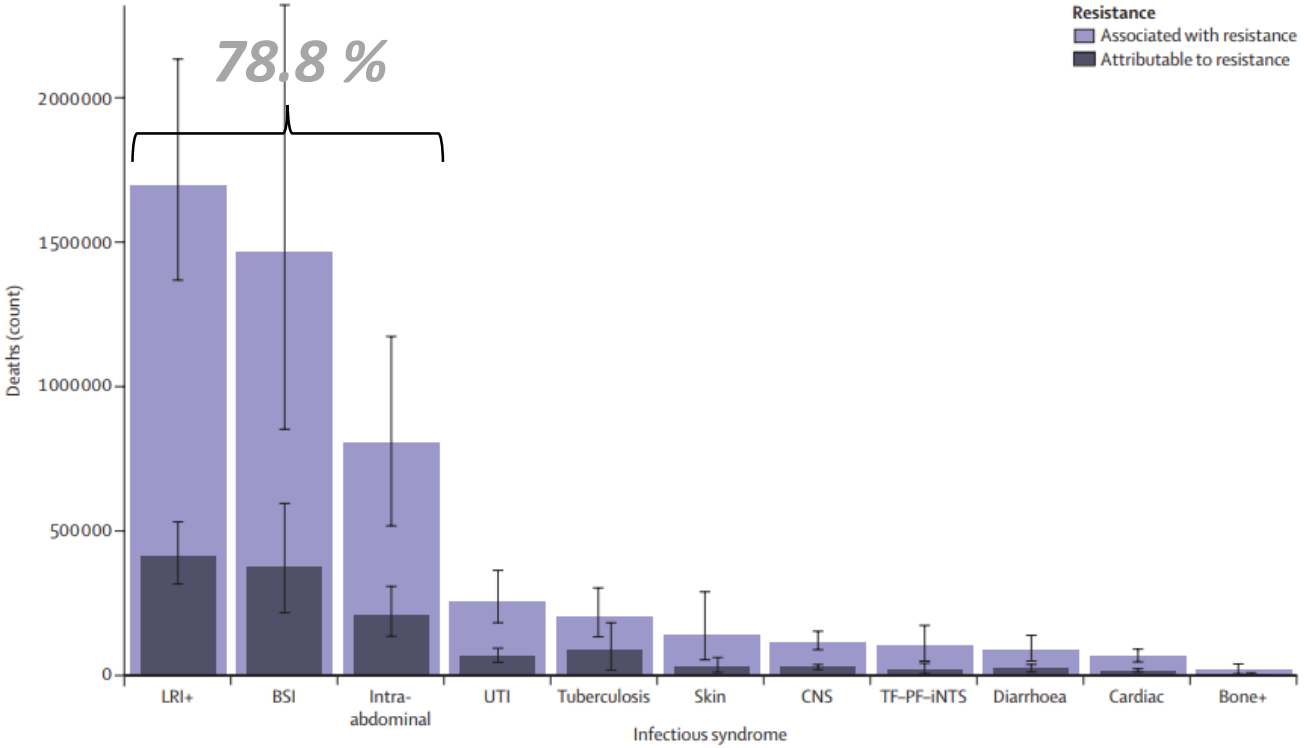


Associated deaths
due to AMR
4.95 mill

Attributable deaths
due to AMR
1.27 mill

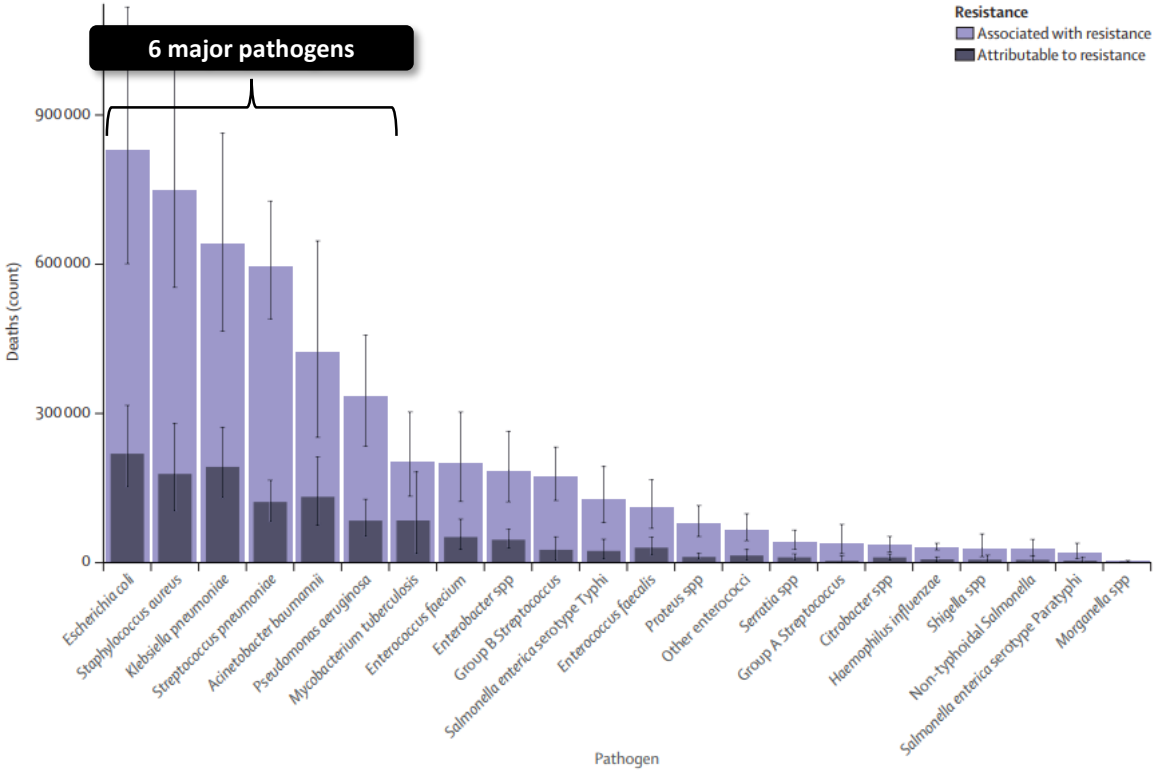
AMR deaths by clinical syndrome

Deaths associated or attributable to AMR in 2019



AMR deaths by pathogen

Deaths associated or attributable to AMR in 2019



WHO list of priority pathogens

Research and development for new antibiotics are urgently needed

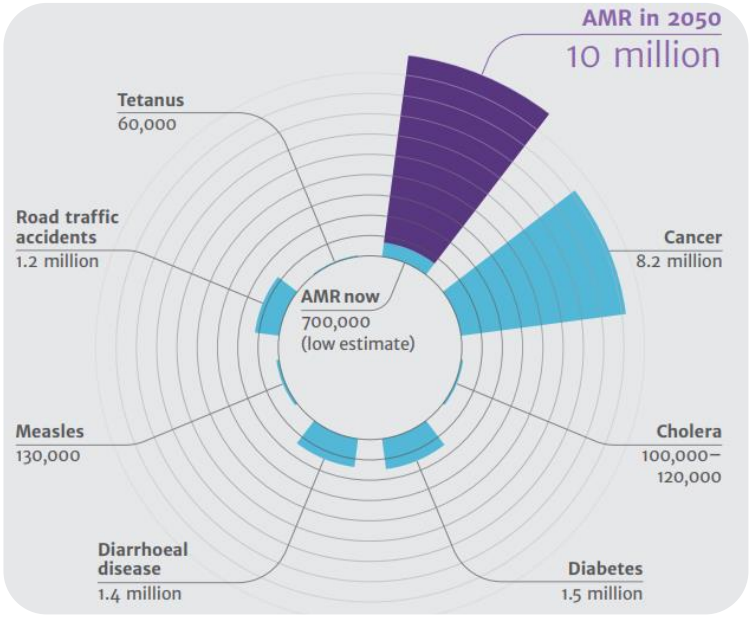
Critical	***Acinetobacter baumannii***	Carbapenem-resistant
	Pseudomonas aeruginosa	Carbapenem-resistant
	Enterobacteraceae	Carbapenem-resistant, ESBL-producing
High	***Enterococcus faecium***	Vancomycin-resistant
	Staphylococcus aureus	MRSA, VIR/VR
	Helicobacter pylori	Clarithromycin-resistant
	***Campylobacter* spp**	Fluoroquinolone-resistant
	Salmonellae	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Cephalosporin/quinolone-resistant
Medium	***Streptococcus pneumoniae***	Penicillin-non-susceptible
	Haemophilus influenza	Ampicillin-resistant
	***Shigella* spp**	Fluoroquinolone-resistant

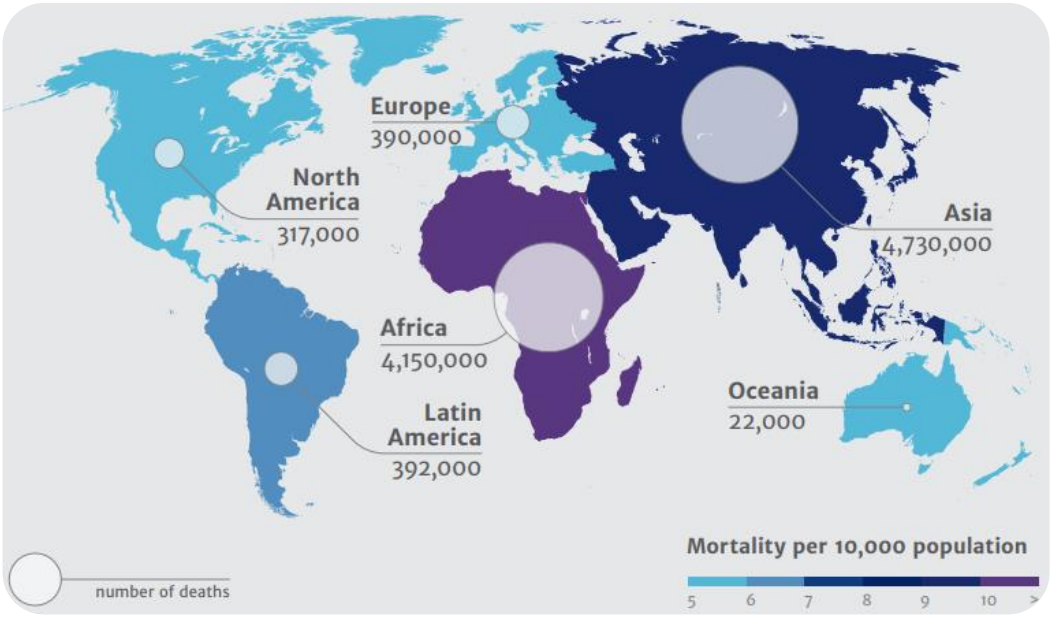
O'Neill et al 2015

Review on Antimicrobial Resistance

Estimated future AMR burden

Estimated annually worldwide deaths attributable to AMR





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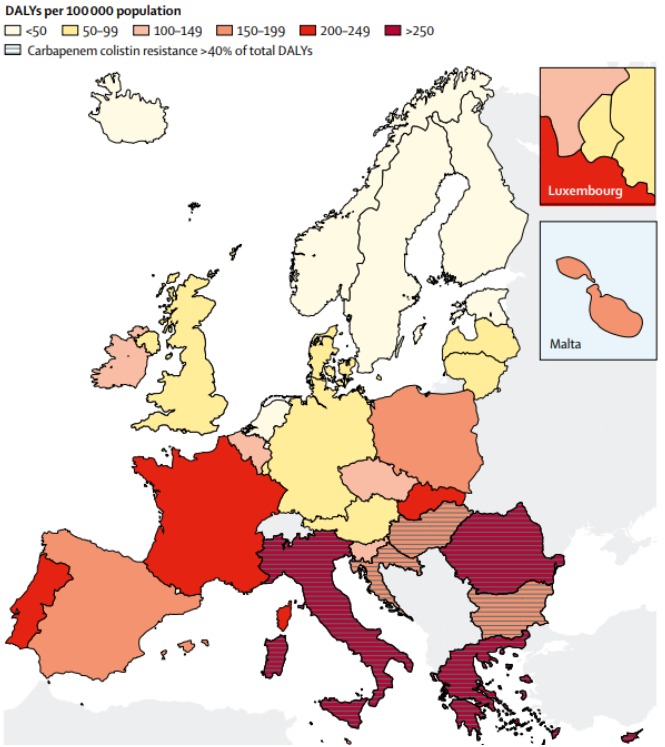
Cassini et al 2019
THE LANCET Infectious Diseases

Disabilty-adjusted life years

Estimated DALYs in AMR situations in Europe using EARS-Net data in 2015

Average DALYs
due to AMR
170 pr 100.000

- **Similar to that of INFLUENZA + TB + HIV (combined)**
- **Similar to that of CANCER**



Driving forces of evolving AMR

Some relevant questions

1) Is antimicrobial consumption a driver of AMR?

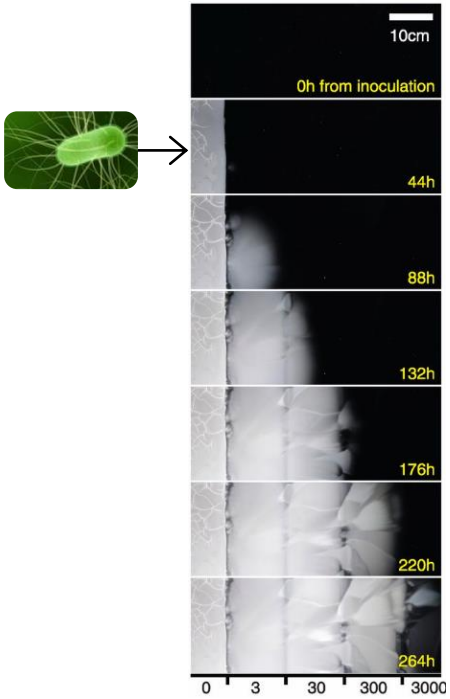
   At an individual level

   At a country-level

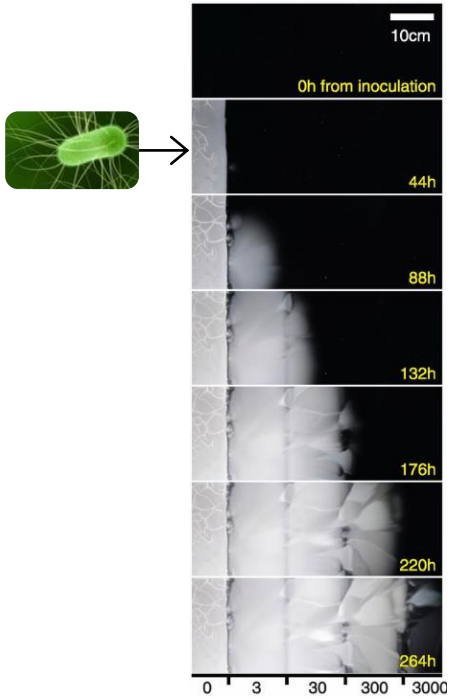
Baym et al 2016 Science

AMR development on antibiotic landscape

Spatiotemporal AMR evolution observed through a microscope on an antibiotic landscape model



Trimethoprim



Ciprofloxacin

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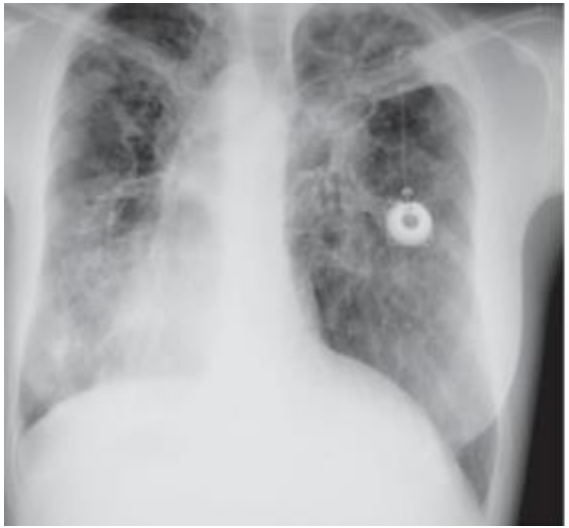
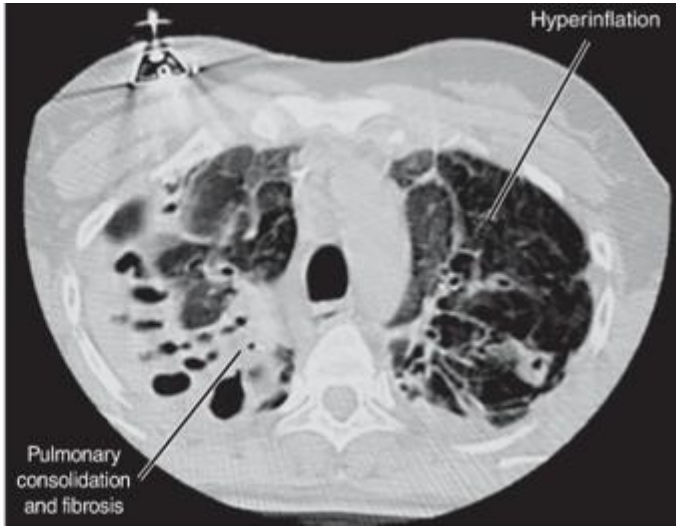
Morita et al 2013

frontiers in Microbiology

Example: *P aeruginosa* in cystic fibrosis

Biological responses in *Pseudomonas aeruginosa*





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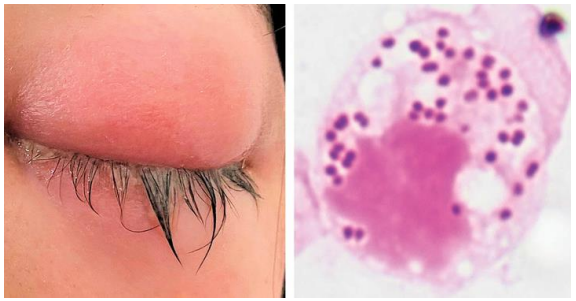
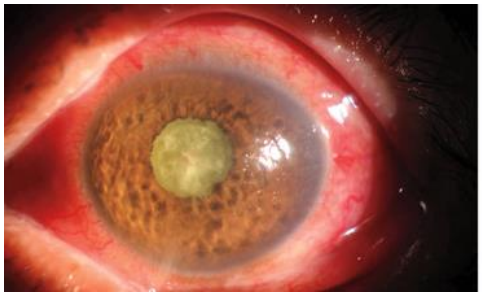
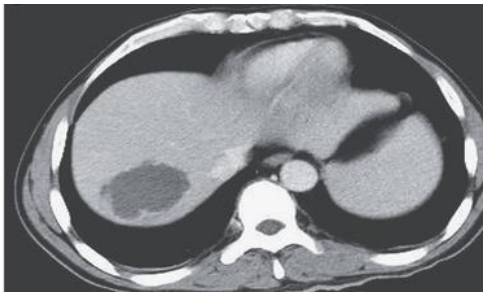
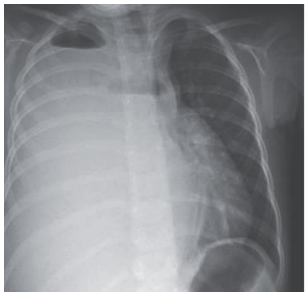
AMR is frequently reported in clinical cases

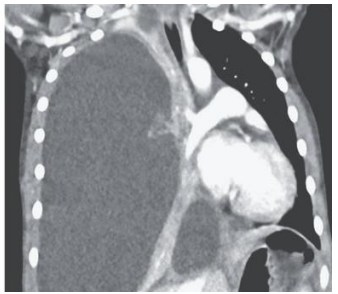
Pre-infection antimicrobial therapy is frequently reported in clinical cases







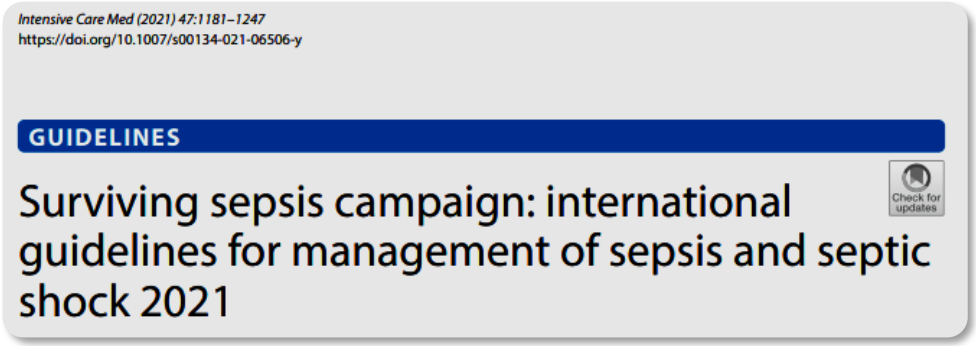




Evans et al 2021

AMR precautions in guidelines

Clinical practice guidelines have incorporated AMR-precautions

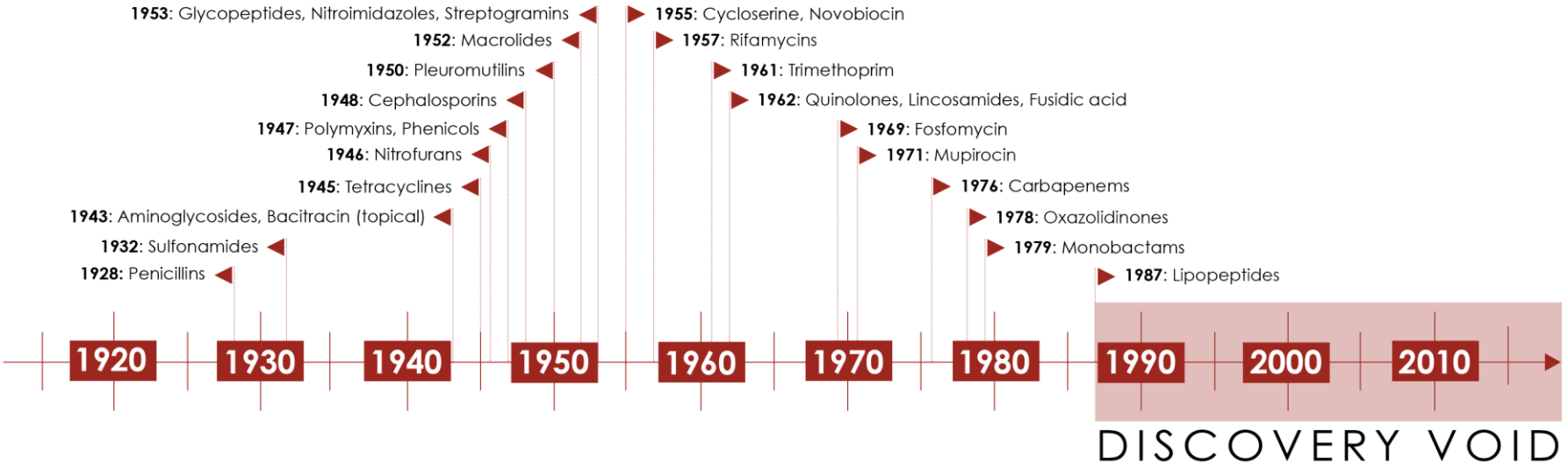


For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.

At an individual level, risk of AMR-emergence is associated with previous antimicrobial therapy

Antimicrobial therapy development

According to ReAct group 2018

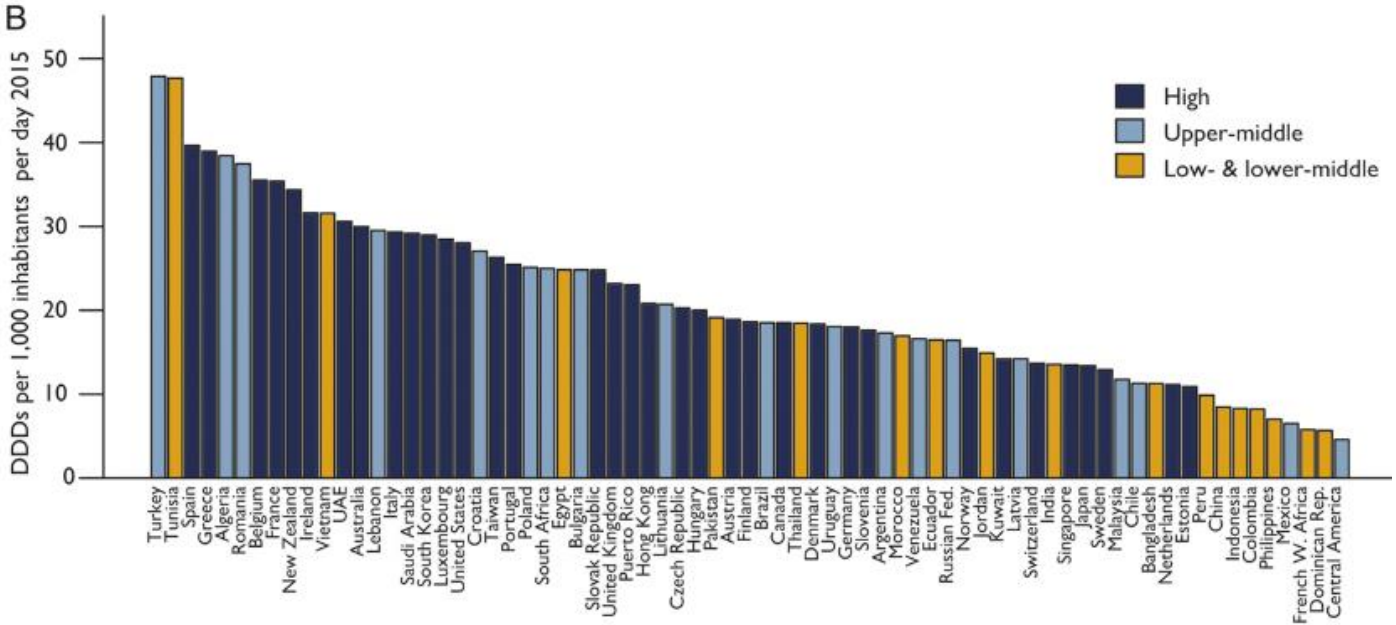


Klein et al; 2018

PNAS

National variations

Consumption rates by country and GDP in 2015 IQVIA



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Klein et al; 2018

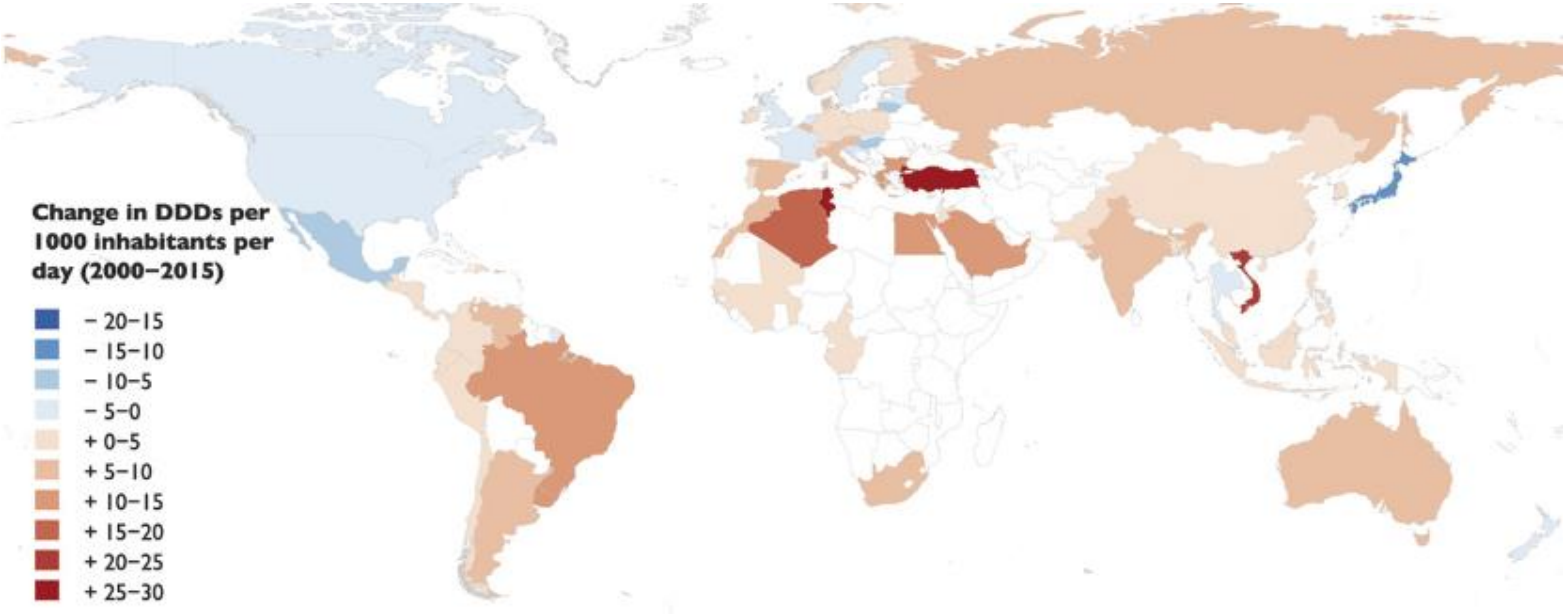
PNAS

Change in DDDs

Variations 2000 - 2015 IQVIA

Global consumption in DDDs: + 65 %

Global consumption in DIDs: + 39 %



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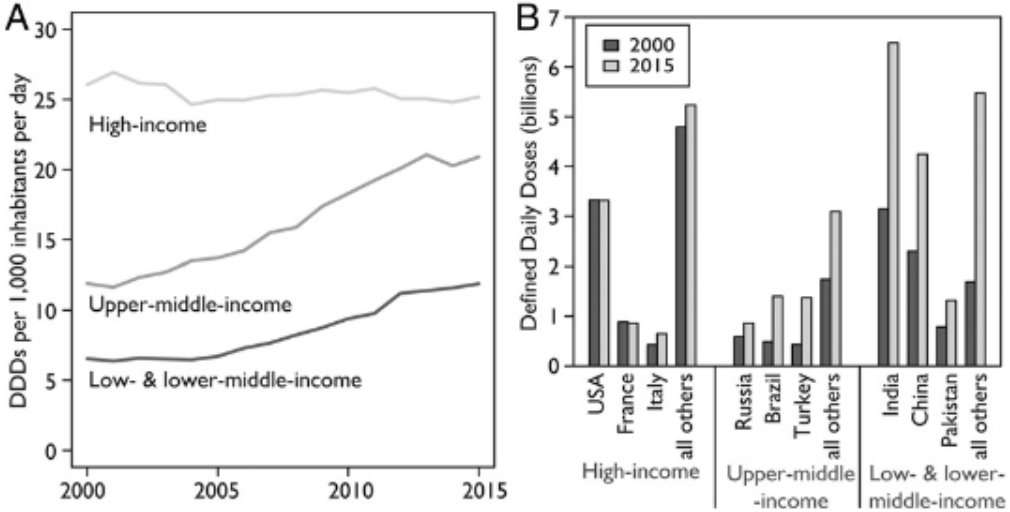
Klein et al; 2018

PNAS

Drivers for increase

Antimicrobial consumption IQVIA

Factor	Low- and middle-income countries	High-income countries
Log(GDP per capita)	3.14 (1.00)[1]	0.56 (0.70)
Percentage of children (12–23 mo) vaccinated for measles	0.04 (0.05)	0.07 (0.06)
Log(Imports as percentage of GDP)	−1.01 (1.01)	−0.20 (1.16)
Physician density per 1,000 population	1.39 (0.73)	0.49 (0.34)
Observations	302	305
Countries	39	32



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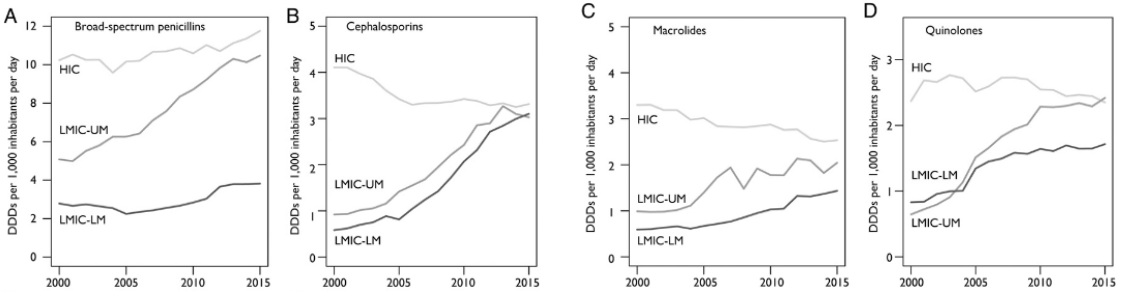
Klein et al; 2018

PNAS

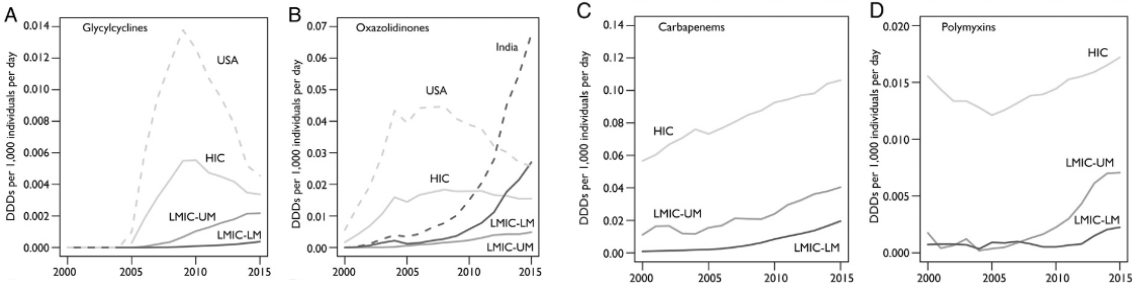
Classes of antibiotics

Antimicrobial consumption IQVIA

4 most used generics



New and last resort generics



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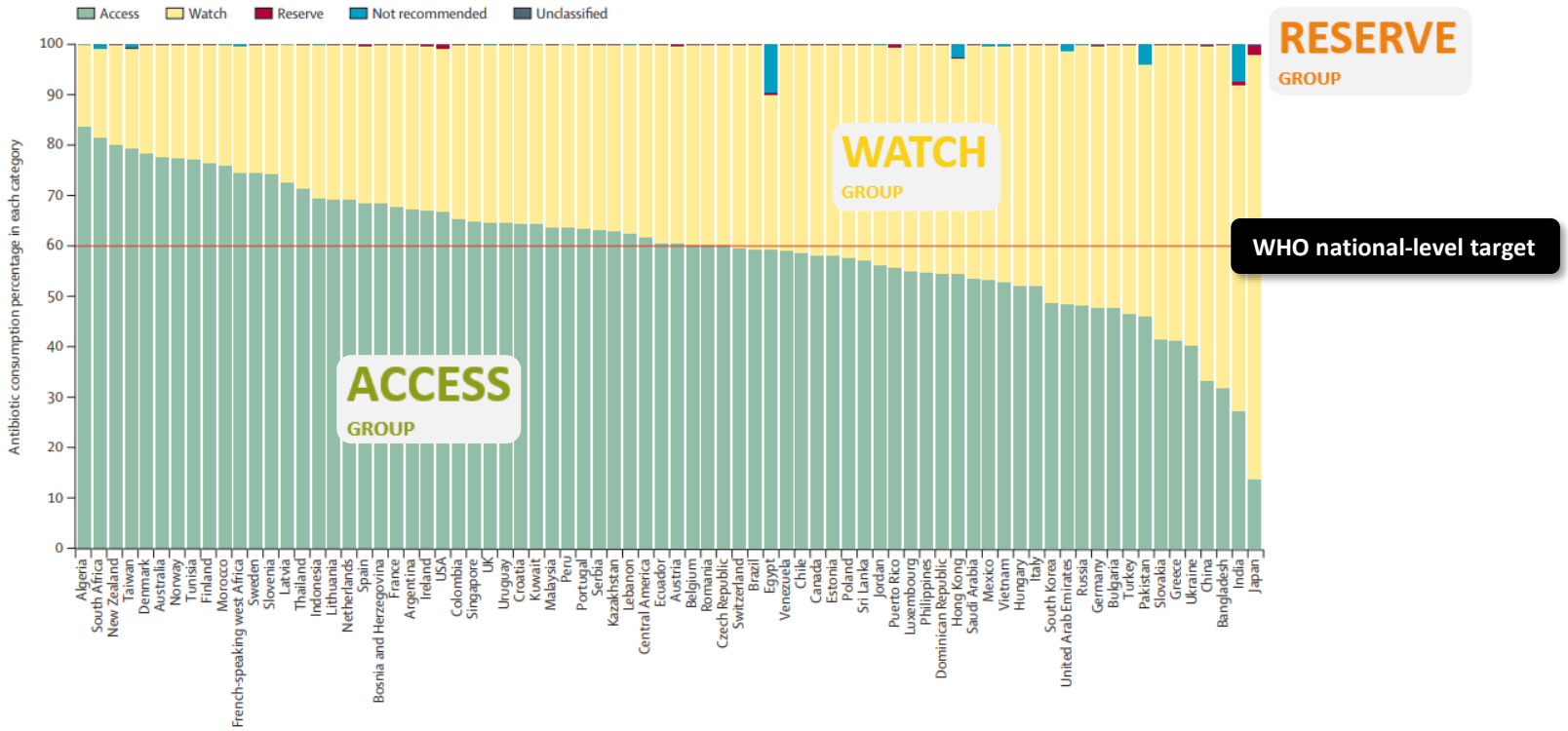
Klein et al; 2021
THE LANCET Infectious Diseases

Antimicrobial consumption

According to AWaRe 2015



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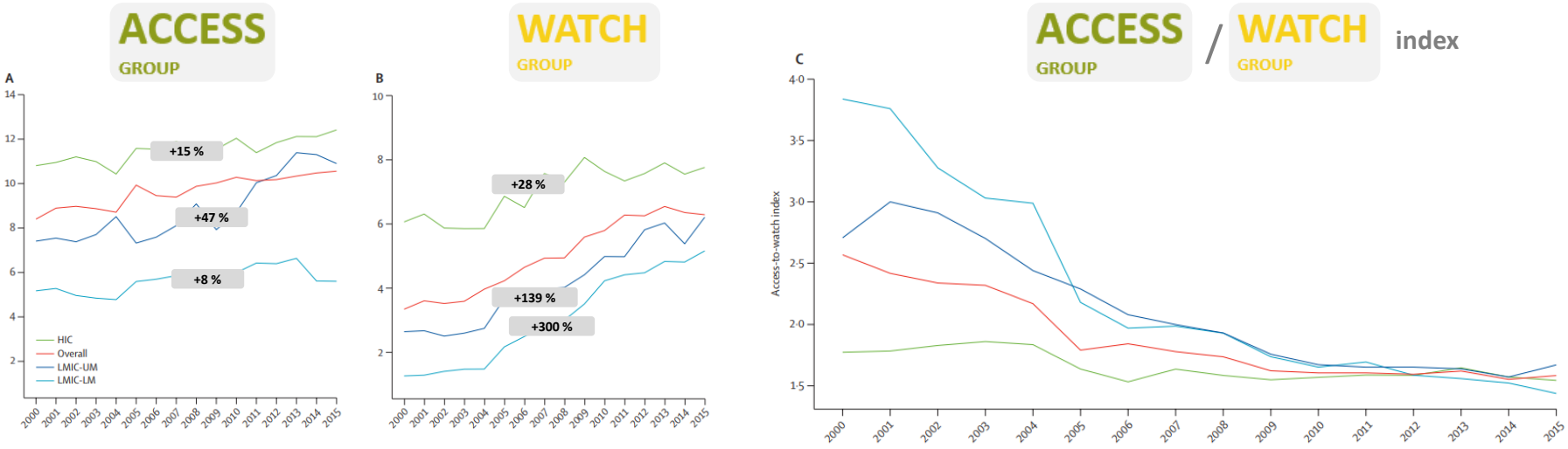
Klein et al; 2021
THE LANCET Infectious Diseases

Correlation with GDP

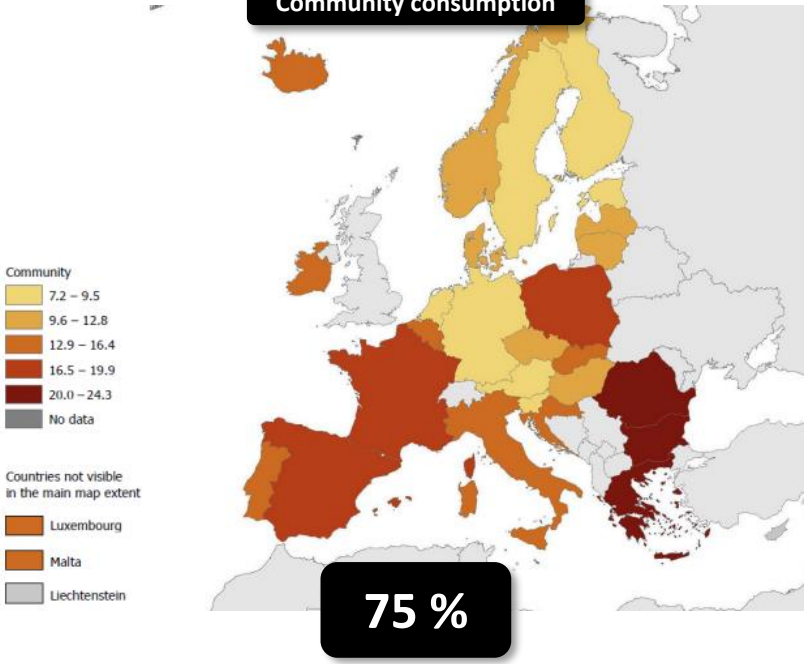
According to AWaRe 2000 – 2015



Antimicrobial consumption

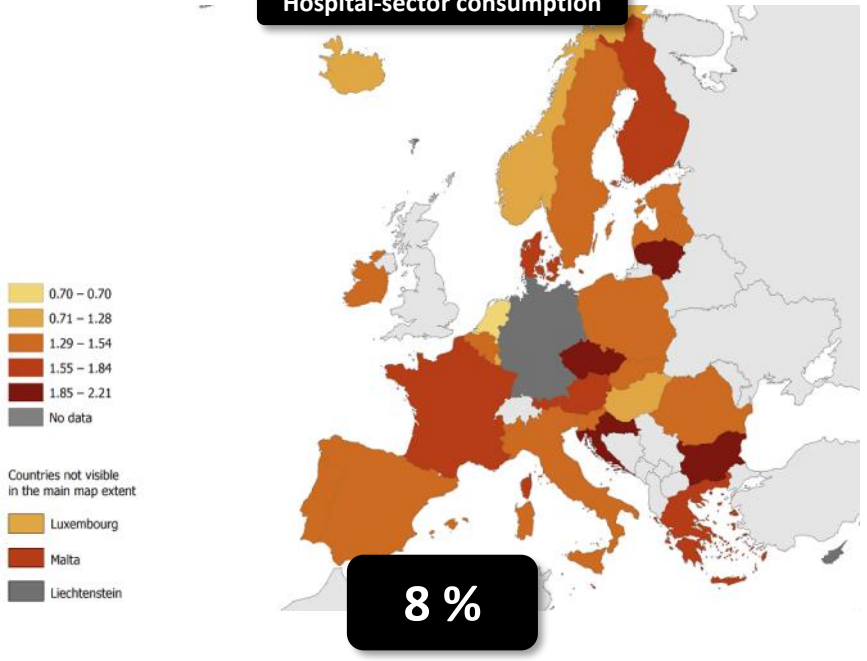
According to ESAC-Net 2021 (ATC: J01)

Community consumption



75 %

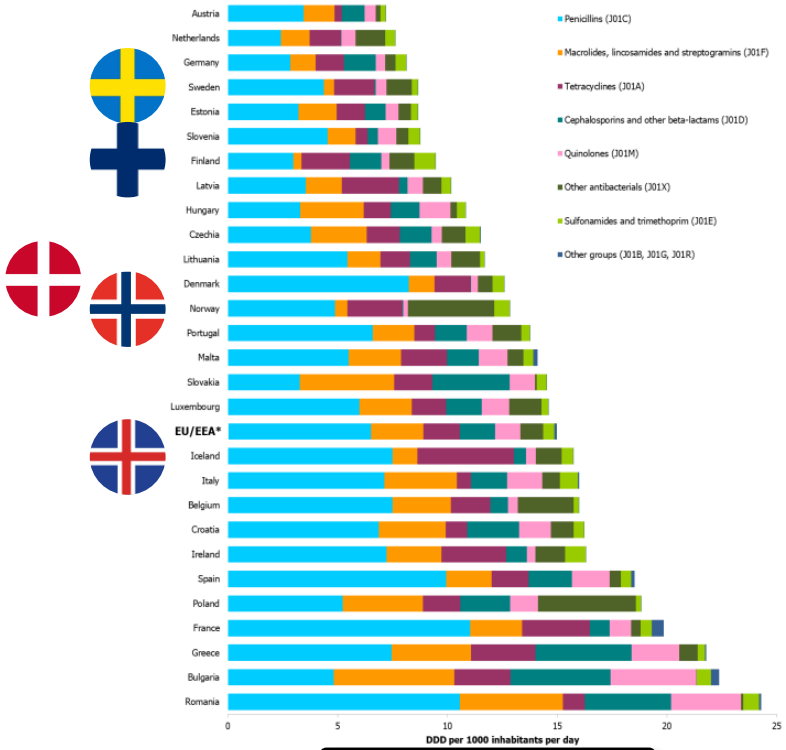
Hospital-sector consumption



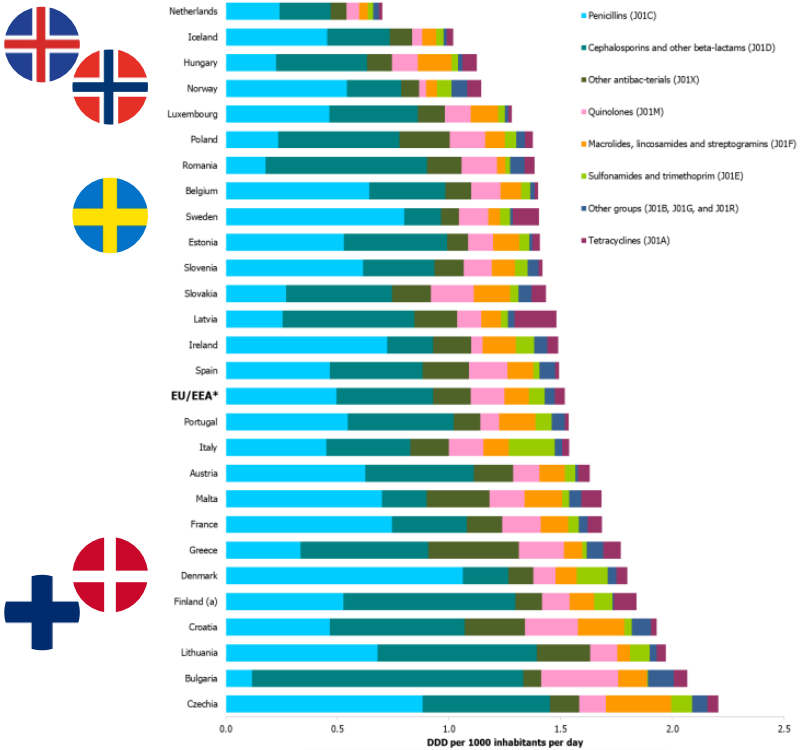
8 %

Antimicrobial consumption

According to ESAC-Net 2021 (ATC: J01)



Community consumption



Hospital-sector consumption

Broad-spectrum per total consumption

According to ESAC-Net 2021 (ATC: J01)

- Glycopeptides
- Third-generation cephalosporins
- Fourth-generation cephalosporins
- Monobactams
- Carbapenems
- Fluoroquinolones
- Polymyxins
- Piperacillin-tazobaktam
- Linezolid and tedizolid
- Daptomycin

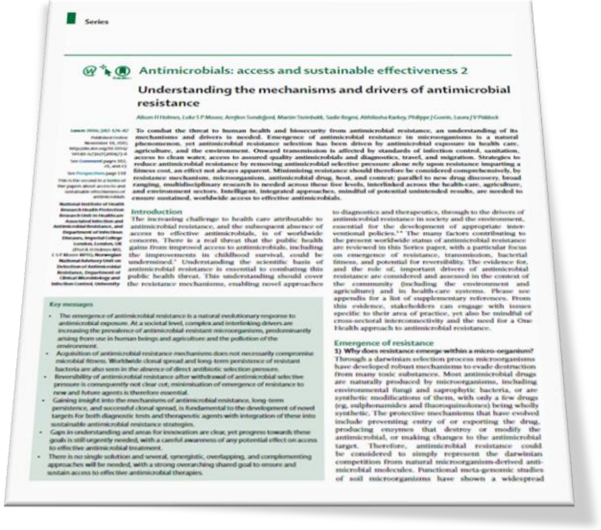
- All antimicrobials in hospital settings

Country	2021	CAGR
Bulgaria	70,9	2.8 %
Romania	64,8	
Greece	59,9	4.7 %
Spain	50,3	
Italy	44,4	0.0 %
Portugal	44,2	0.8 %
Poland	44,1	9.4 %
Hungary	42,4	1.5 %
Latvia	41,9	1.4 %
Malta	41,2	3.9 %
Croatia	39,5	4.5 %
Slovakia	38,6	4.0 %
Luxembourg	37,5	
Austria	36,5	
France	33,4	0.5 %
Slovenia	32,2	-0.1 %
Ireland	31,1	1.9 %
Belgium	30,6	-0.2 %
Sweden	30,4	2.2 %
Netherlands	28,7	1.7 %
Estonia	24,8	0.7 %
Denmark	24,1	1.4 %
Lithuania	21,8	-2.3 %
Norway	21,7	0.1 %
Iceland	21,3	
Finland	19,5	0.3 %
United Kingdom	16,9	

At a country-level, AMR prevalence correlates with antimicrobial consumption

AMR review

Understanding the mechanisms and drivers of AMR


Series

Antimicrobials: access and sustainable effectiveness 2

Understanding the mechanisms and drivers of antimicrobial resistance

To combat the threat to human health and biosecurity from antimicrobial resistance, an understanding of its mechanisms and drivers is needed. Emergence of antimicrobial resistance in microorganisms is a natural phenomenon, yet antimicrobial resistance selection has been driven by antimicrobial exposure in health care, agriculture, and the environment. Onward transmission is affected by standards of infection control, sanitation, access to clean water, access to assured quality antimicrobials and diagnostics, travel, and migration. Strategies to reduce antimicrobial resistance by removing antimicrobial selective pressure alone rely upon resistance imparting a fitness cost, an effect not always apparent. Minimising resistance should therefore be considered comprehensively, by resistance mechanism, microorganism, antimicrobial drug, host, and context; parallel to new drug discovery, broad ranging, multidisciplinary research is needed across these five levels, interlinked across the health-care, agriculture, and environment sectors. Intelligent, integrated approaches, mindful of potential unintended results, are needed to ensure sustained, worldwide access to effective antimicrobials.

Introduction

Key messages

Emergence of resistance

> AMR selection is driven by antimicrobial exposure in health care, agriculture, and the environment

> Onward transmission is affected by standards of infection control, sanitation, access to clean water, access to assured quality antimicrobials and diagnostics, travel, and migration.

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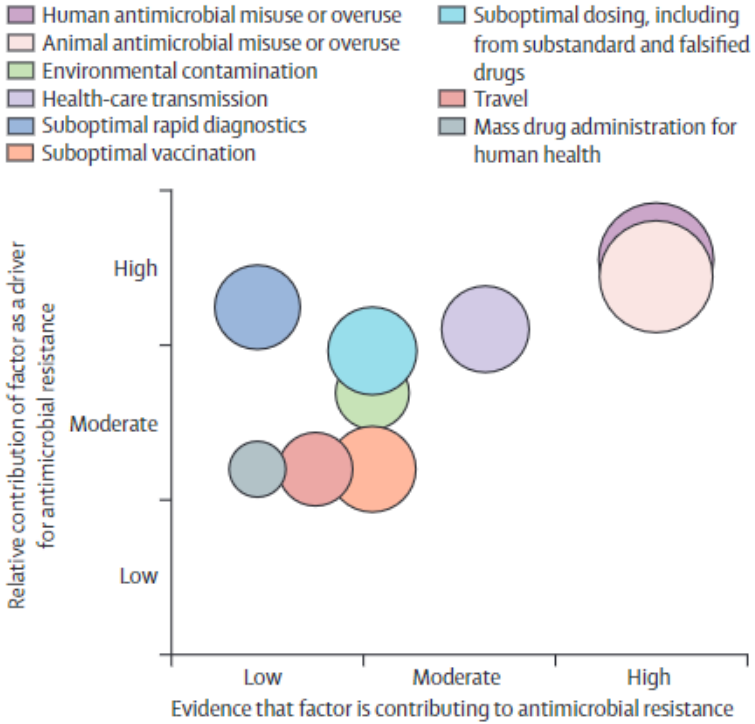
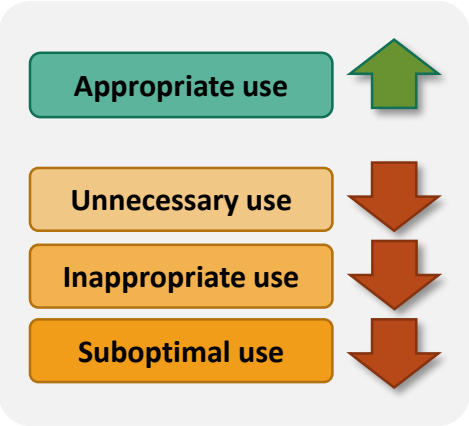
Holmes et al 2016 THE LANCET

Understanding the drivers for AMR

Review





Thank you for your time and your attention