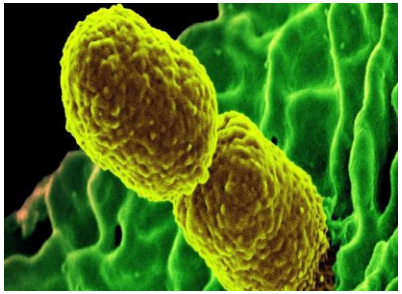
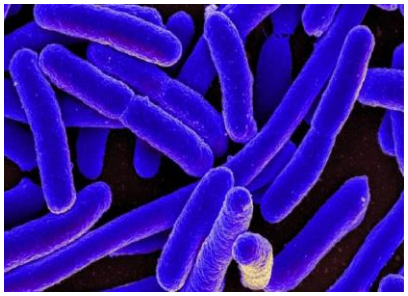




Access to antibiotics

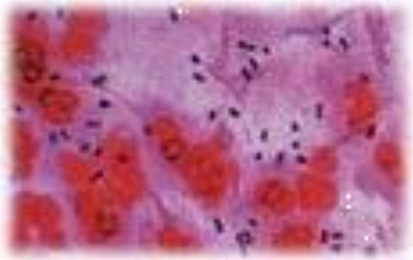
12th June 2024

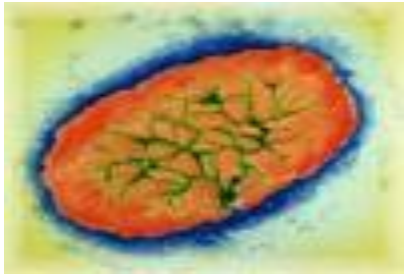


Andrew Farlow

University of Oxford,
Senior Research Fellow
Centre for
Tropical Medicine and Global Health
Nuffield Department of Medicine

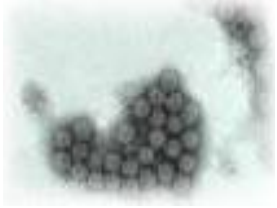
(some slides removed before public posting)












© Andrew Farlow 2024. Not for sharing.

Penicillin developed in Oxford, saved tens of millions of lives…

Antimicrobial drugs have added about 20 years to life expectancy…

But…

FINANCIAL TIMES

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Special Report **FT Health: Future of Antibiotics**

Antibiotic resistance + Add to myFT

Antibiotic resistance raises prospect of untreatable gonorrhoea

Just one drug remains effective for the sexually transmitted disease but soon the bacteria may be able to evade it

Save

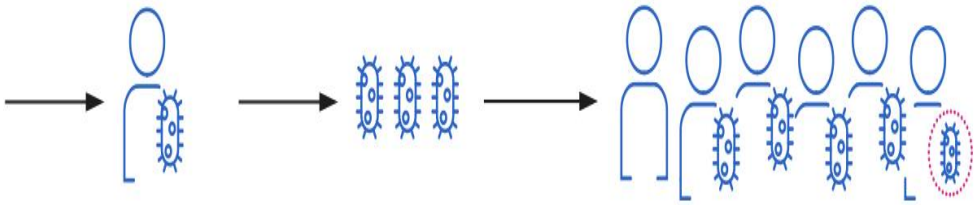
- Gonorrhoea the second most common bacterial STI in the UK
  - over 82,000 cases reported in 2022
  - 50.3% (54,961) increase on 2021
  - Might become untreatable in the future due to the rapid rise of AMR

- Not just common STIs already resistant to antibiotics.
- 92% of bacteria that cause urinary tract infections (UTIs) are resistant to at least one common antibiotic; 80% are resistant to two

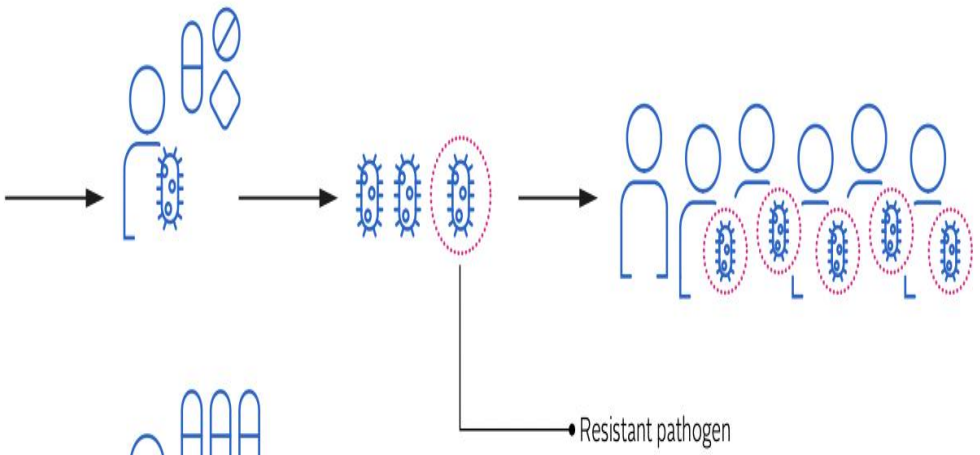
#NotInOurLifetime

No or inappropriate access leads to AMR

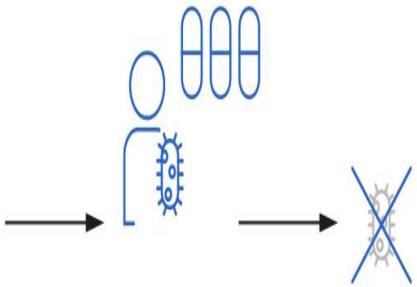
1. **No access to antibiotics:** the infection can spread unchecked among a population and may develop resistance due to natural selection, despite the absence of antibiotics.

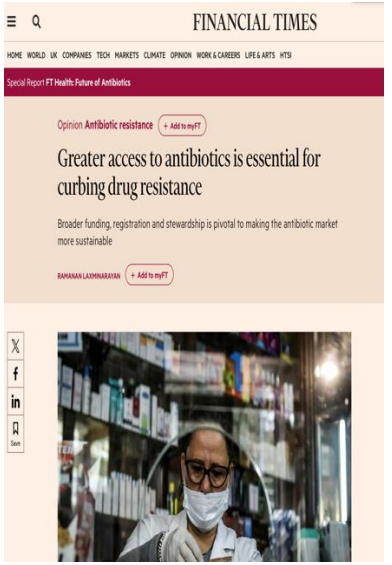


2. **Lack of access to the right antibiotic:** the wrong antibiotic kills only some susceptible pathogens and allows for pathogens with resistant genes to survive and spread unchecked. This is the highest driver of resistance.



3. **Access to the right antibiotic:** the right antibiotic is the most likely to cure the infection and stop further spread of AMR.





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Special Report FT Health: Future of Antibiotics

Opinion Antibiotic resistance + Add to myFT

Greater access to antibiotics is essential for curbing drug resistance

Broader funding, registration and stewardship is pivotal to making the antibiotic market more sustainable

RAMANAN LAXMINARAYAN + Add to myFT

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Report FT Health: Future of Antibiotics

Pharmaceuticals sector + Add to myFT

Limited access to antibiotics is driving resistance, warns watchdog

Failure to ensure they reach world's poorest increases health risks, says pharma body

Antimicrobial resistance poses one of the greatest threats to public health in the 21st century, according to experts © Daniel Berehulak/Getty Images

Andrew Jack in London NOVEMBER 18 2021

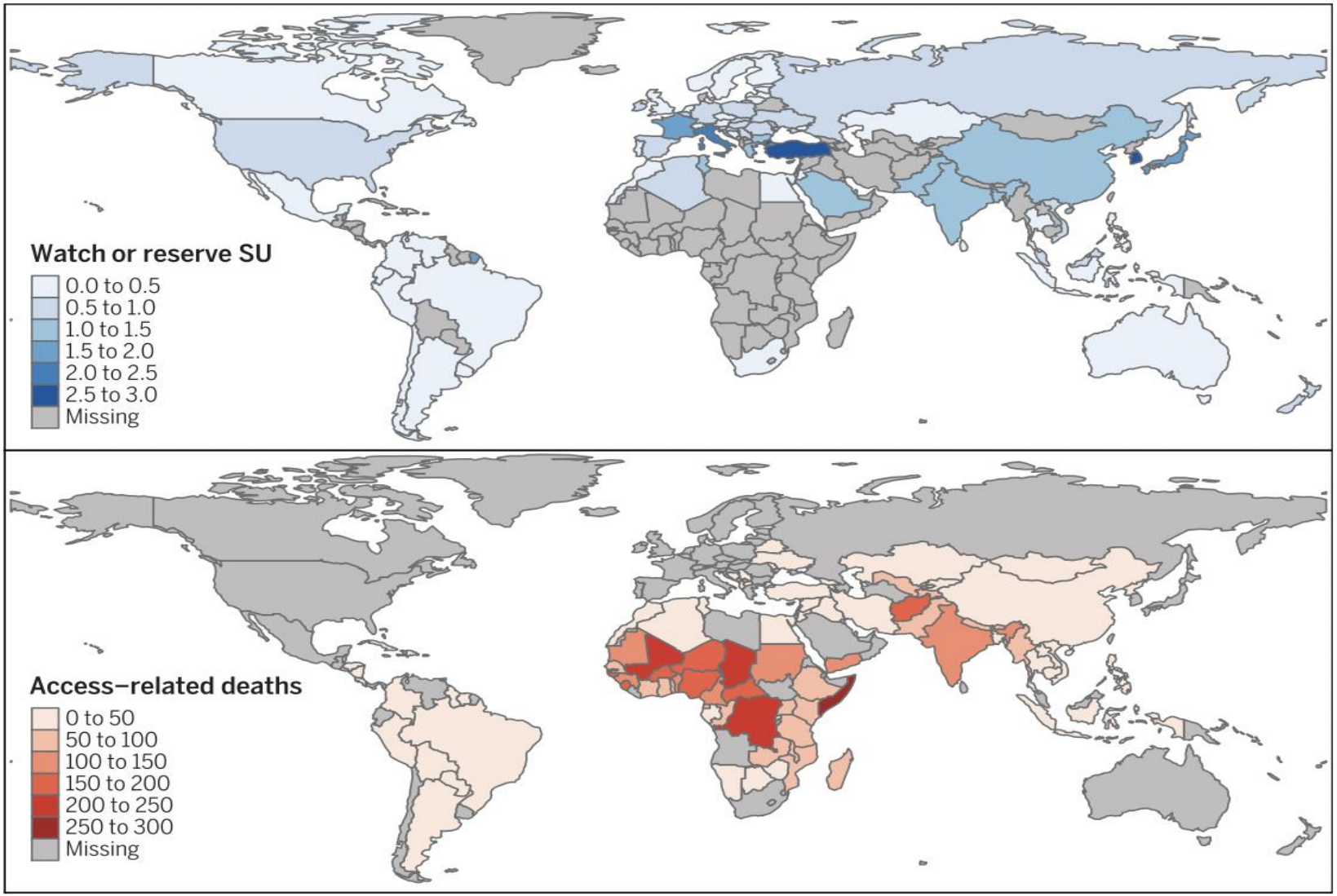
WHO AWaRe Strategy for antibiotic stewardship

which indicates the antibiotic of choice for each of the 25 most common infections. These antibiotics should be available at all times, affordable and quality-assured

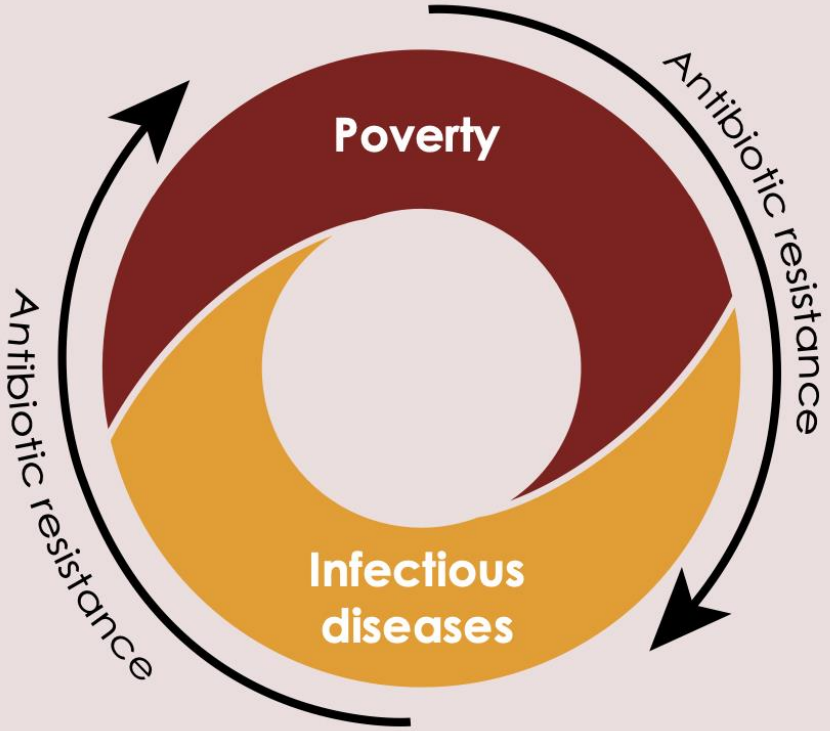
which includes most of the "highest-priority critically important antimicrobials" for human medicine and veterinary use. These antibiotics are recommended only for specific, limited indications

antibiotics that should only be used as a last resort when all other antibiotics have failed

Overuse in some places while lack of access in other places



Vicious circle



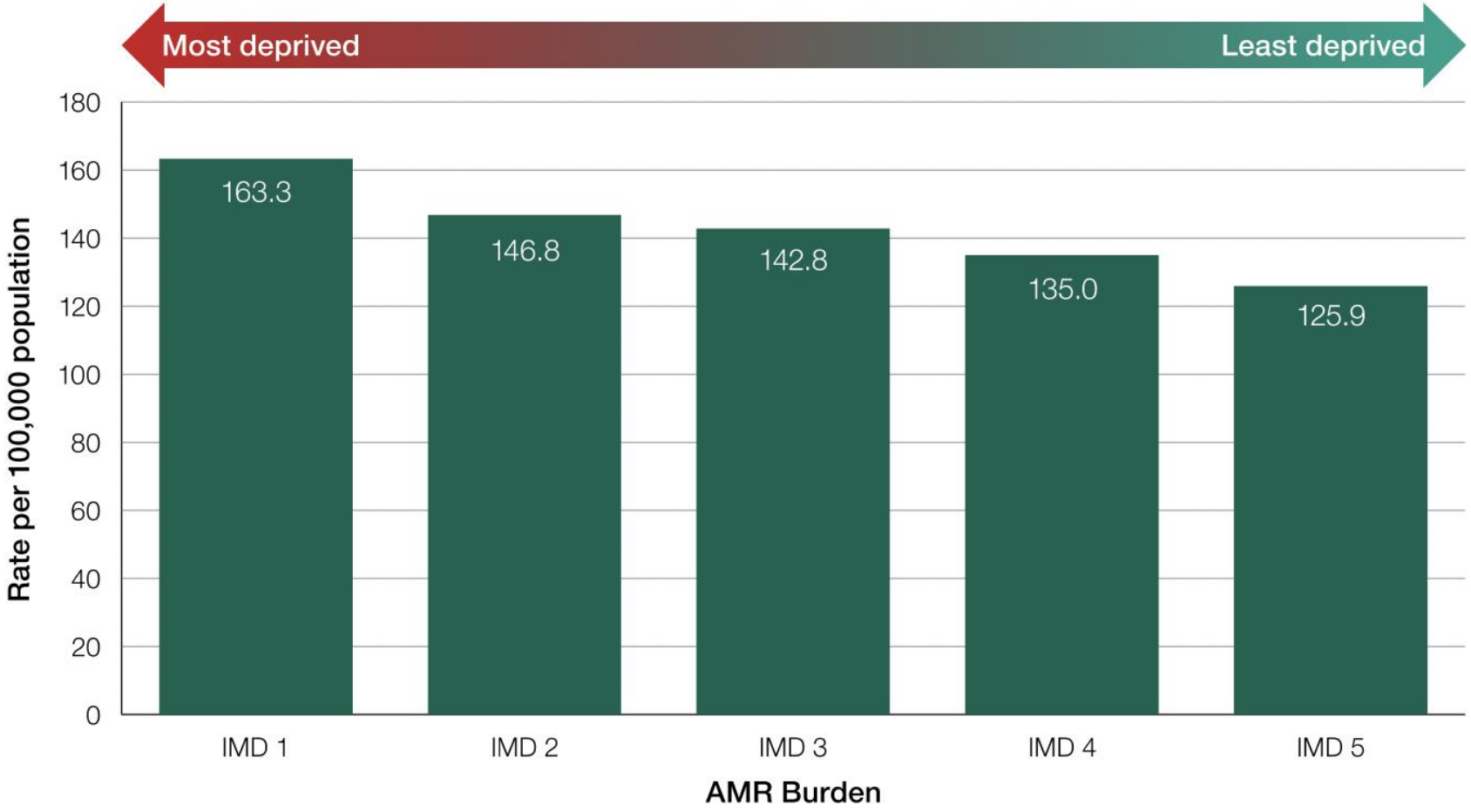
People living in poverty are more prone to infectious diseases

→ Circumstances of poverty increase the spread of antibiotic resistance

The cost of having an infectious disease drives people into poverty

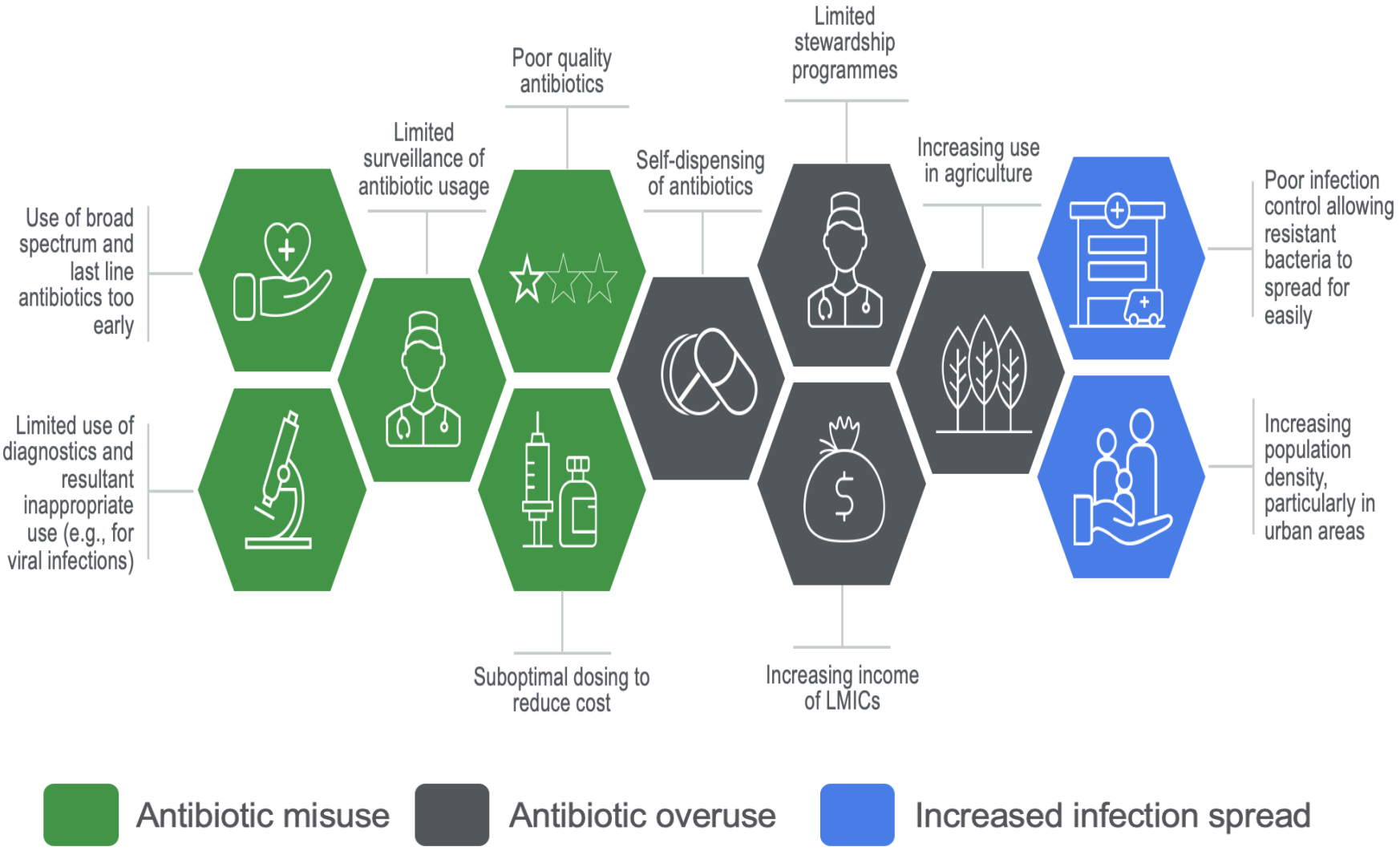
→ Antibiotic resistance significantly increases cost of treatment driving people into poverty or making treatment inaccessible

AMR burden from bloodstream infections by deprivation in UK



IMD = Indices of Multiple Deprivation

Key drivers of resistance



Need to balance access, innovation, stewardship

Supply-Side Access Solutions

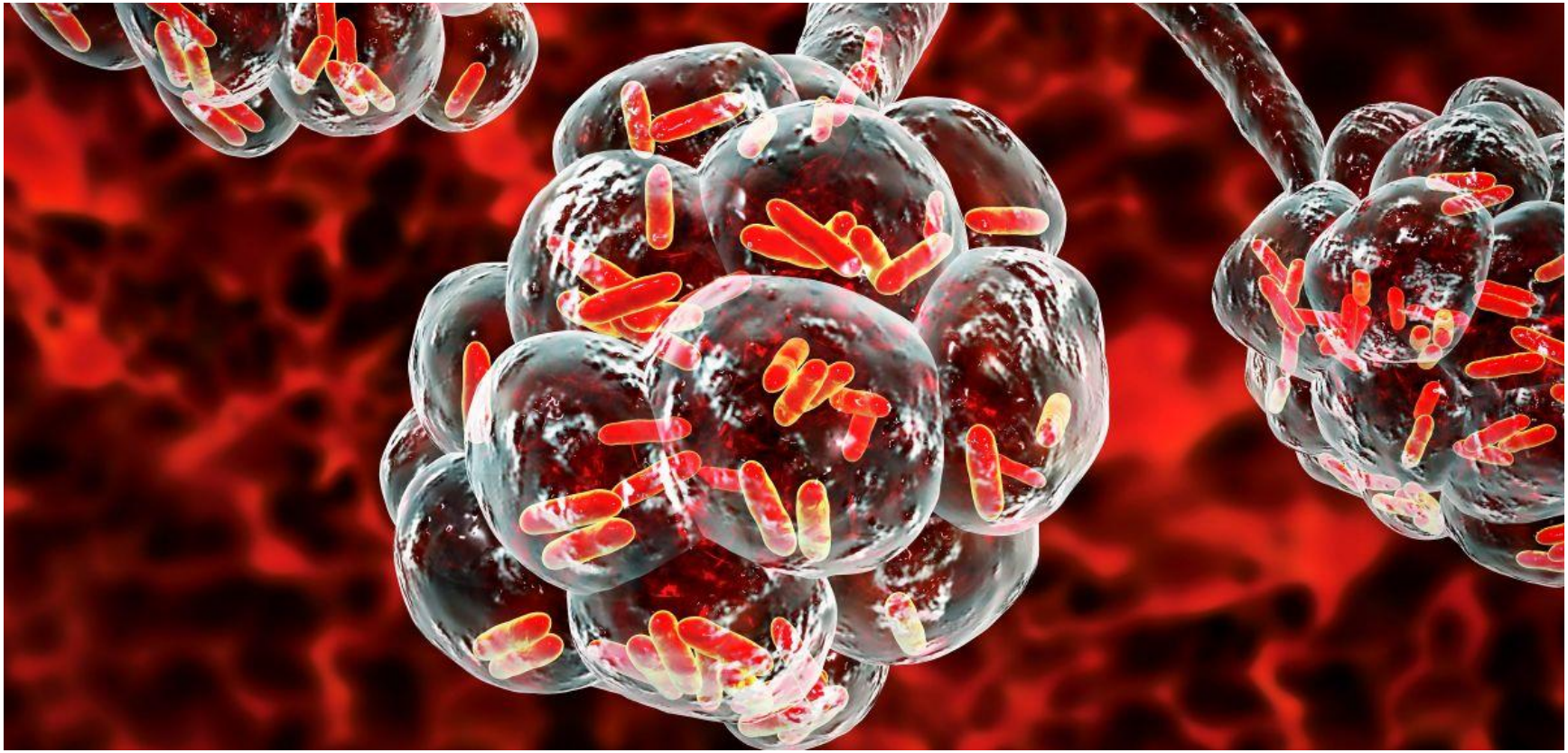
- Product Development Partnerships
- Prize funds
- Longer patent lives of new classes of antimicrobial drugs
- New procurement models (Netflix fee to use, insurance, etc.)
- International agreement (like WHO Framework Convention on Tobacco Control) to control use of antimicrobials, including:
  - technical and financial assistance to poor and low-income countries to balance access to essential drugs with action to curb resistance;
  - Monitoring emergence of drug-resistant microbes;
  - systems to ensure compliance with the agreement

Demand-Side Access Solutions

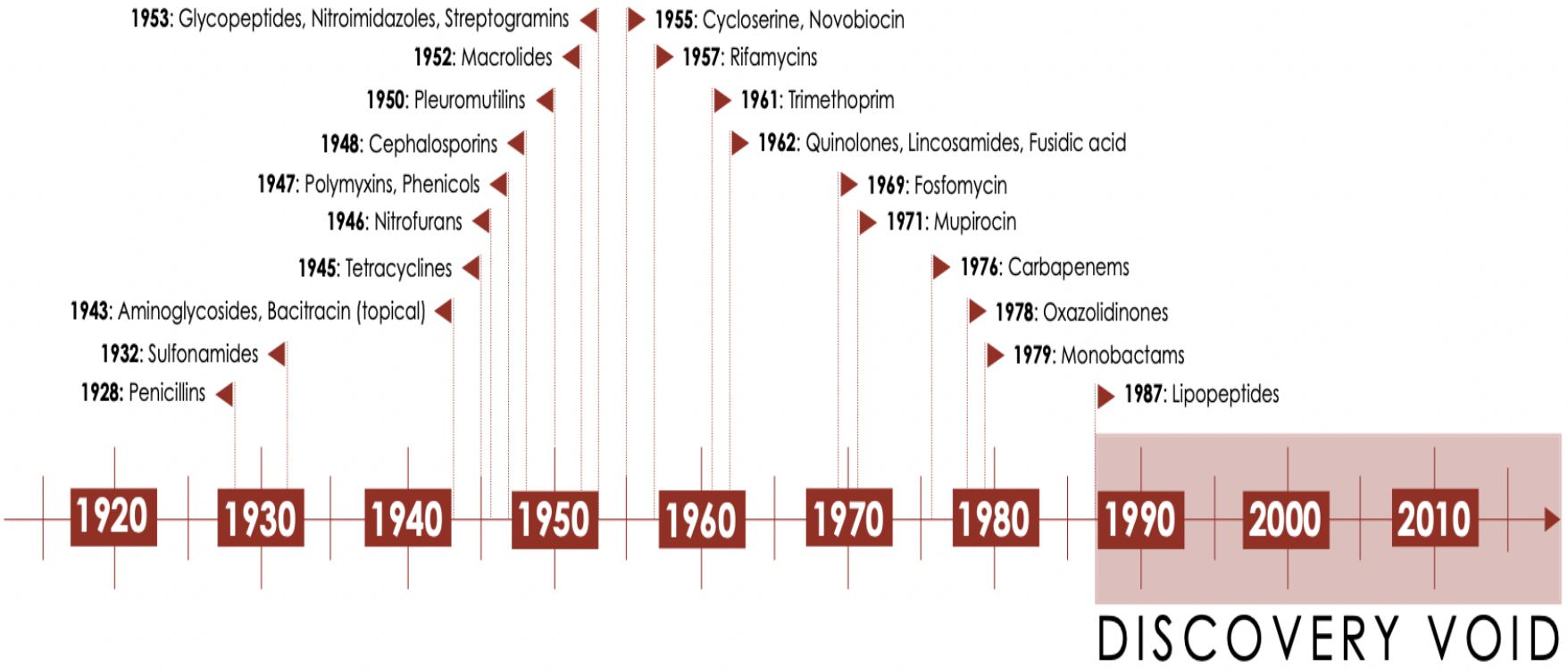
- Alternative treatment options (where possible)
- Increase immunity (health and non-health ways)
- Education of health professionals and patients:
  - Most patients think antibacterial drugs are effective against common cold and influenza, and demand them when they have viral infection. Doctors oblige.
- Infection control measures (e.g., hand washing, screening and isolation)
  - 2-10 million bacteria between our fingertips and our elbows
  - Few people wash their hands long enough to kill off all infectious bugs after going to the toilet.

- Policies of stewardship and regulations

Need to develop new effective vaccines, medicines, and treatments



Discovery void



- No new class of antibacterial drug developed since 1987
- Any new class of drugs will be restricted to prevent resistance, reducing R&D returns
- Higher returns from chronic diseases, such as diabetes (longer use of drugs)

New antibiotics do not go to those who need them


PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Introduction and geographic availability of new antibiotics approved between 1999 and 2014

Cecilia Kållberg, Christine Årdal, Hege Salvesen Blix, Eili Klein, Elena M. Martinez, Morten Lindbæk, Kevin Outterson, John-Arne Røttingen, Ramanan Laxminarayan

Published: October 16, 2018 • https://doi.org/10.1371/journal.pone.0205166

Article | Authors | Metrics | Comments | Media Coverage

Abstract
Introduction
Material and methods
Results
Discussion
Conclusion

Abstract

Background

Despite the urgent need for new, effective antibiotics, few antibiotics of value have entered the market during the past decades. Therefore, incentives have been developed to stimulate antibiotic R&D. For these incentives to be effective, geographic availability for recently approved antibiotics needs to be better understood. In this study, we analyze geographic availability and market introduction of antibiotics approved between 1999 and 2014.

- Nearly 40 per cent of new antibiotics launched between 1999 and 2014 were registered for sale in fewer than 10 countries.
- In 185 countries the drugs were not made available.
  - Undermines immediate health needs
  - Harms long-term effort to curb drug-resistant infections

Of 25 NCEs, only 12 had registered sales in more than 10 countries

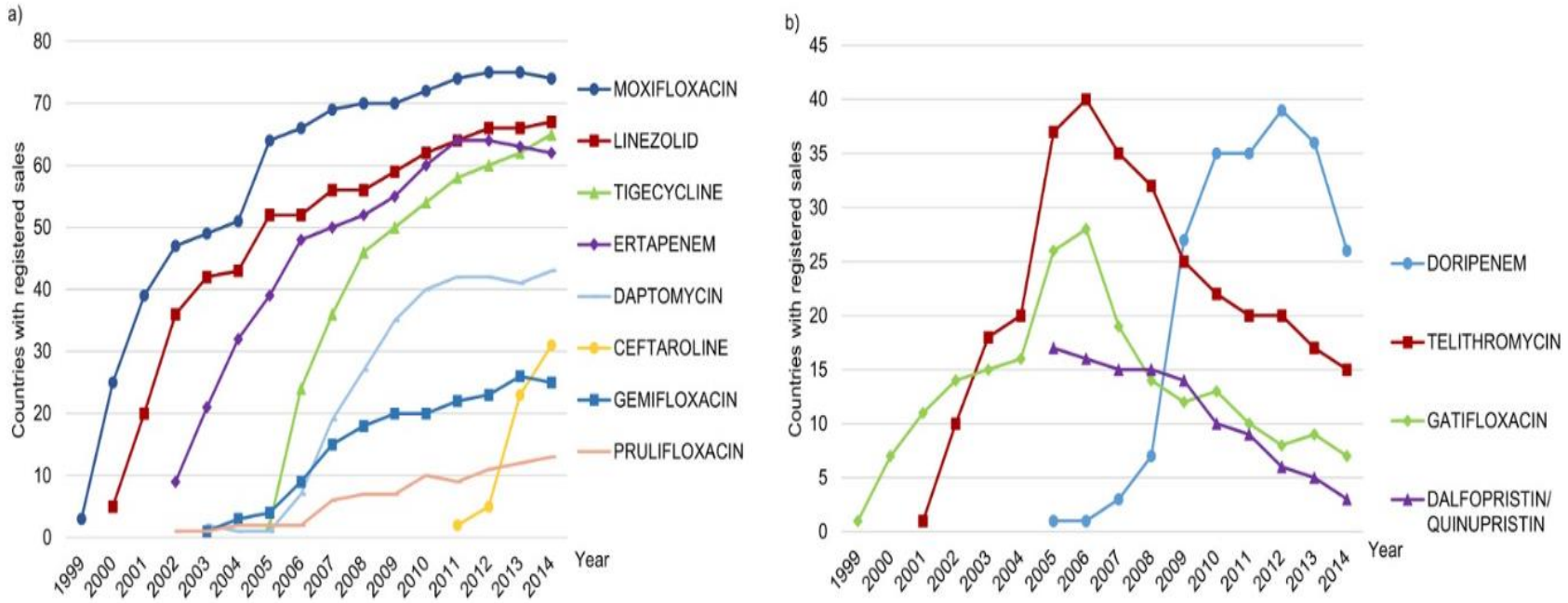


Fig 1. Number of countries with registered sales of the NCEs reaching more than 10 countries. (a) The 8 NCEs experiencing a continuous increase in number of countries with registered sales per year. (b) The 4 NCEs experiencing an increase followed by a decrease in number of countries with registered sales per year.

https://doi.org/10.1371/journal.pone.0205166.g001

Heavily skewed by income class of country

Table 2. Spread of NCEs between country income classes.

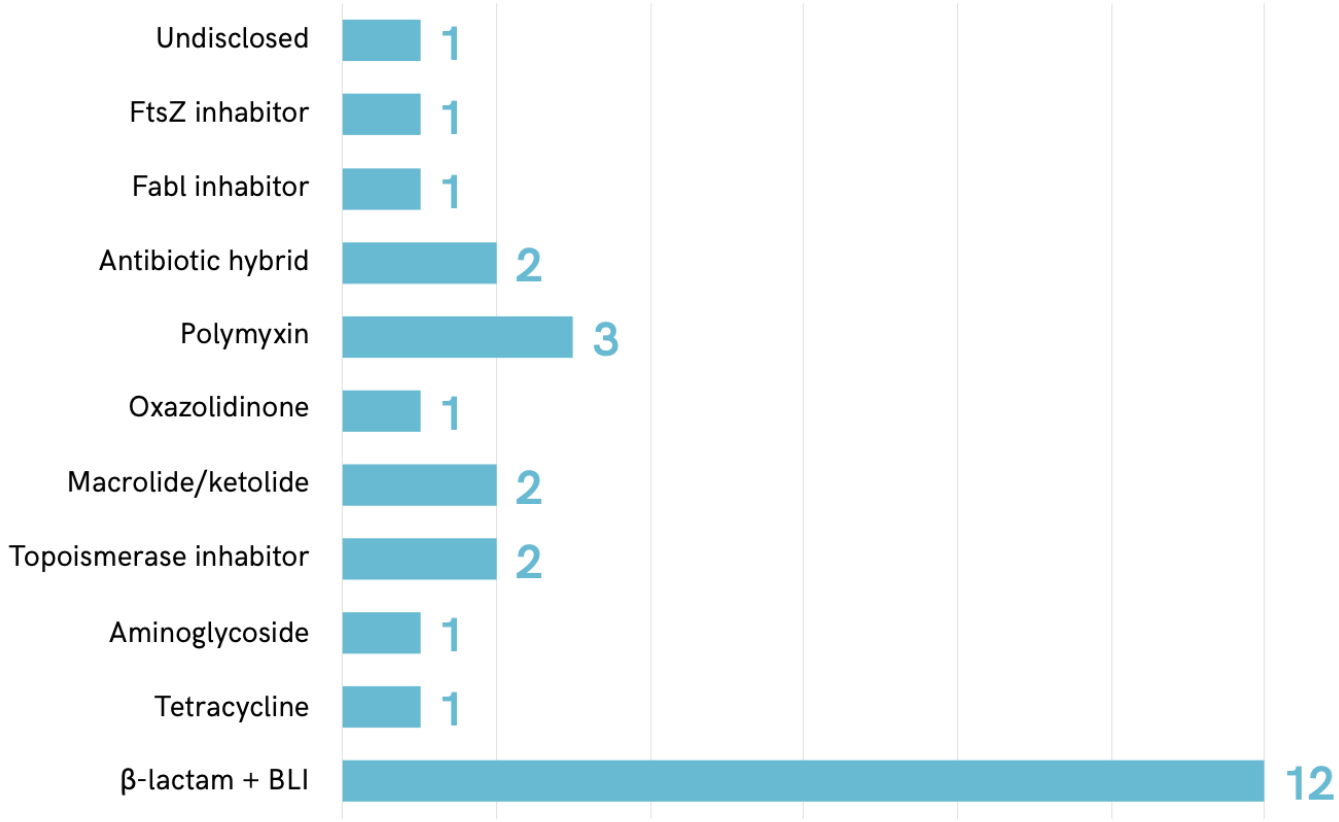
NCE	Year of MA	Year after first MA	High Income Countries	Upper Middle Income Countries	Lower Middle Income Countries	Countries with registered sales	Total number of countries with registered sales	Span	Code
MOXIFLOXACIN	1999	3	67%	26%	5%	39	75	0–10	
		5	65%	29%	4%	49		11–20	
		10	59%	27%	13%	70		21–30	
LINEZOLID	2000	3	81%	17%	3%	36	70	31–40	
		5	72%	23%	5%	43		41–50	
		10	58%	27%	14%	59		51–60	
ERTAPENEM	2002	3	63%	31%	3%	32	65	61–70	
		5	65%	29%	4%	48		71–80	
		10	53%	33%	13%	64		81–90	
TIGECYCLINE	2005	3	69%	25%	6%	36	65	91–100	
		5	64%	26%	8%	50			
		10	55%	29%	14%	65			
DAPTOMYCIN	2003	3	100%	0%	0%	1	47		
		5	95%	5%	0%	19			
		10	62%	29%	10%	42			
DORIPENEM	2005	3	100%	0%	0%	3	44		
		5	70%	22%	7%	27			
		10	50%	27%	19%	26			
TELITHROMYCIN	2001	3	72%	28%	0%	18	43		
		5	61%	34%	3%	38			
		10	82%	14%	0%	22			
CEFTAROLINE	2010	3	78%	17%	4%	23	31		
GATIFLOXACIN	1999	3	45%	45%	9%	11	30		
		5	47%	40%	13%	15			
		10	21%	29%	43%	14			
GEMIFLOXACIN	2003	3	75%	25%	0%	4	28		
		5	40%	40%	20%	15			
		10	35%	30%	35%	23			
DALFOPRISTIN/ QUINUPRISTIN	1999	3	100%	0%	0%	15	21		
		5	100%	0%	0%	14			
		10	100%	0%	0%	3			
PRULIFLOXACIN	2002	3	100%	0%	0%	2	14		
		5	100%	0%	0%	2			
		10	67%	22%	11%	9			

Table 3. Spread of NCEs between geographic regions.

NCE	Year of MA	Year after first MA	East Asia & Pacific	Europe & Central Asia	MENA	North America	Latin America & Caribbean	South Asia	Sub-Saharan Africa	Countries with registered sales	Total number of countries with registered sales
MOXIFLOXACIN	1999	3	21%	41%	8%	5%	23%	0%	3%	39	75
		5	20%	43%	8%	4%	22%	0%	2%	49	
		10	19%	44%	10%	3%	17%	4%	3%	70	
LINEZOLID	2000	3	22%	50%	0%	6%	17%	3%	3%	36	70
		5	23%	51%	0%	5%	16%	2%	2%	43	
		10	22%	46%	2%	3%	19%	7%	2%	59	
ERTAPENEM	2002	3	25%	38%	0%	6%	28%	0%	3%	32	65
		5	23%	46%	2%	4%	23%	0%	2%	48	
		10	19%	48%	6%	3%	19%	3%	2%	64	
TIGECYCLINE	2005	3	19%	44%	6%	6%	22%	3%	0%	36	65
		5	20%	46%	4%	4%	20%	4%	2%	50	
		10	20%	46%	8%	3%	17%	5%	2%	65	
DAPTOMYCIN	2003	3	0%	0%	0%	100%	0%	0%	0%	1	47
		5	0%	84%	0%	5%	11%	0%	0%	19	
		10	26%	52%	0%	5%	14%	2%	0%	42	
DORIPENEM	2005	3	33%	0%	0%	33%	33%	0%	0%	3	44
		5	26%	59%	0%	4%	7%	4%	0%	27	
		10	35%	38%	0%	4%	15%	4%	4%	26	
TELITHROMYCIN	2001	3	6%	61%	17%	0%	11%	0%	6%	18	43
		5	11%	39%	13%	5%	29%	0%	3%	38	
		10	5%	68%	0%	9%	9%	0%	9%	22	
CEFTAROLINE	2010	3	17%	74%	0%	4%	4%	0%	0%	23	31
GATIFLOXACIN	1999	3	36%	0%	0%	18%	36%	0%	9%	11	30
		5	47%	0%	0%	13%	27%	7%	7%	15	
		10	36%	7%	7%	7%	21%	21%	0%	14	
GEMIFLOXACIN	2003	3	25%	0%	0%	25%	25%	0%	25%	4	28
		5	20%	7%	20%	13%	20%	13%	7%	15	
		10	13%	13%	35%	4%	17%	13%	4%	23	
DALFOPRISTIN/ QUINUPRISTIN	1999	3	20%	60%	0%	13%	7%	0%	0%	15	21
		5	21%	64%	0%	7%	7%	0%	0%	14	
		10	33%	33%	0%	33%	0%	0%	0%	3	
PRULIFLOXACIN	2002	3	50%	50%	0%	0%	0%	0%	0%	2	14
		5	50%	50%	0%	0%	0%	0%	0%	2	
		10	33%	56%	0%	0%	0%	11%	0%	9	

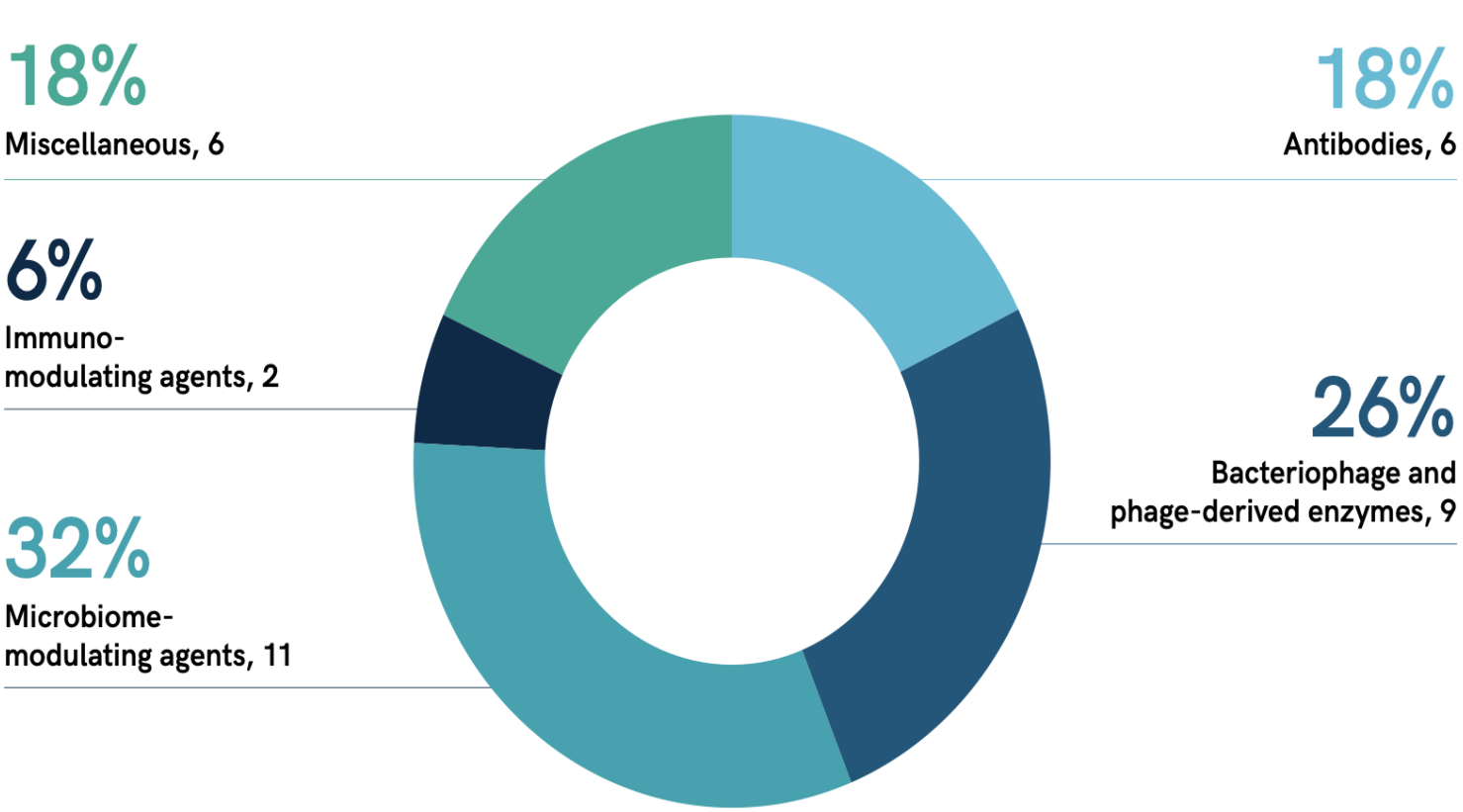
Antibiotics in the clinical pipeline targeting WHO priority pathogens

still insufficient against priority pathogens



BLI: β-lactamase inhibitor; FabI: enoyl-acyl carrier protein reductase; FtsZ: filamenting temperature-sensitive Z; WHO: World Health Organization.

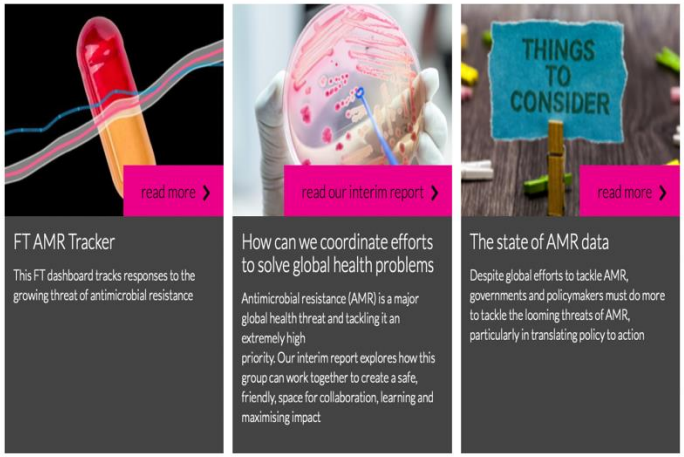
Diversity of non-traditional approaches

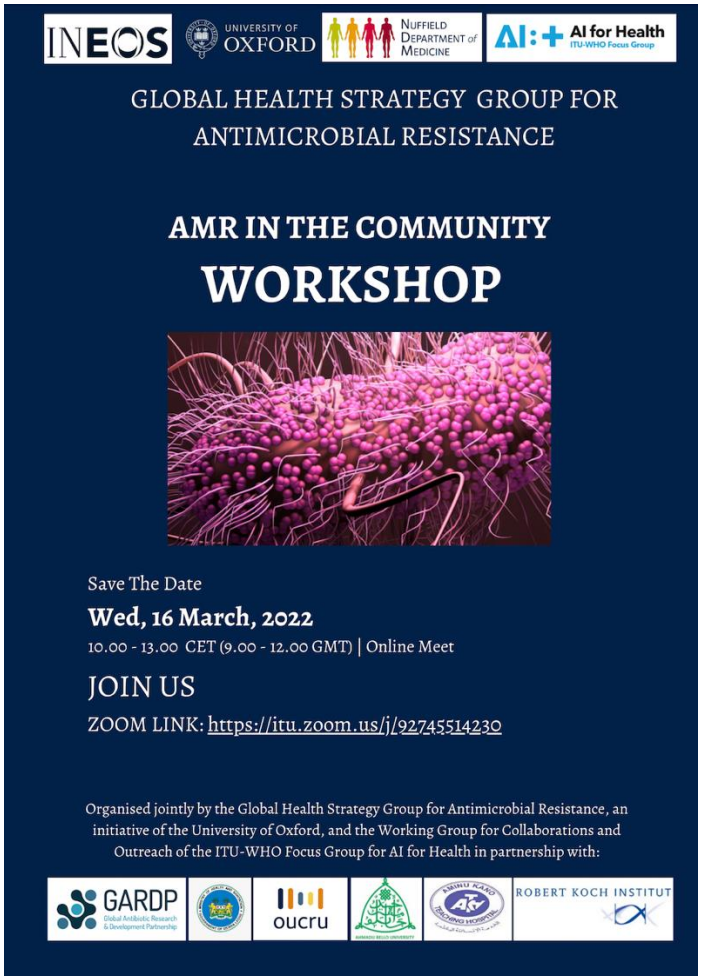


BUT: over **90% (*n* = 30) of the non-traditional agents are pathogen-specific**, most of which target *S. aureus* (*n* = 7) and *C. difficile* (*n* = 12). This **selectivity** confirms a trend also observed in the preclinical space and **requires significant diagnostic availability for optimal use**, often **not available** outside of specialized health-care facilities in **low-resource settings**

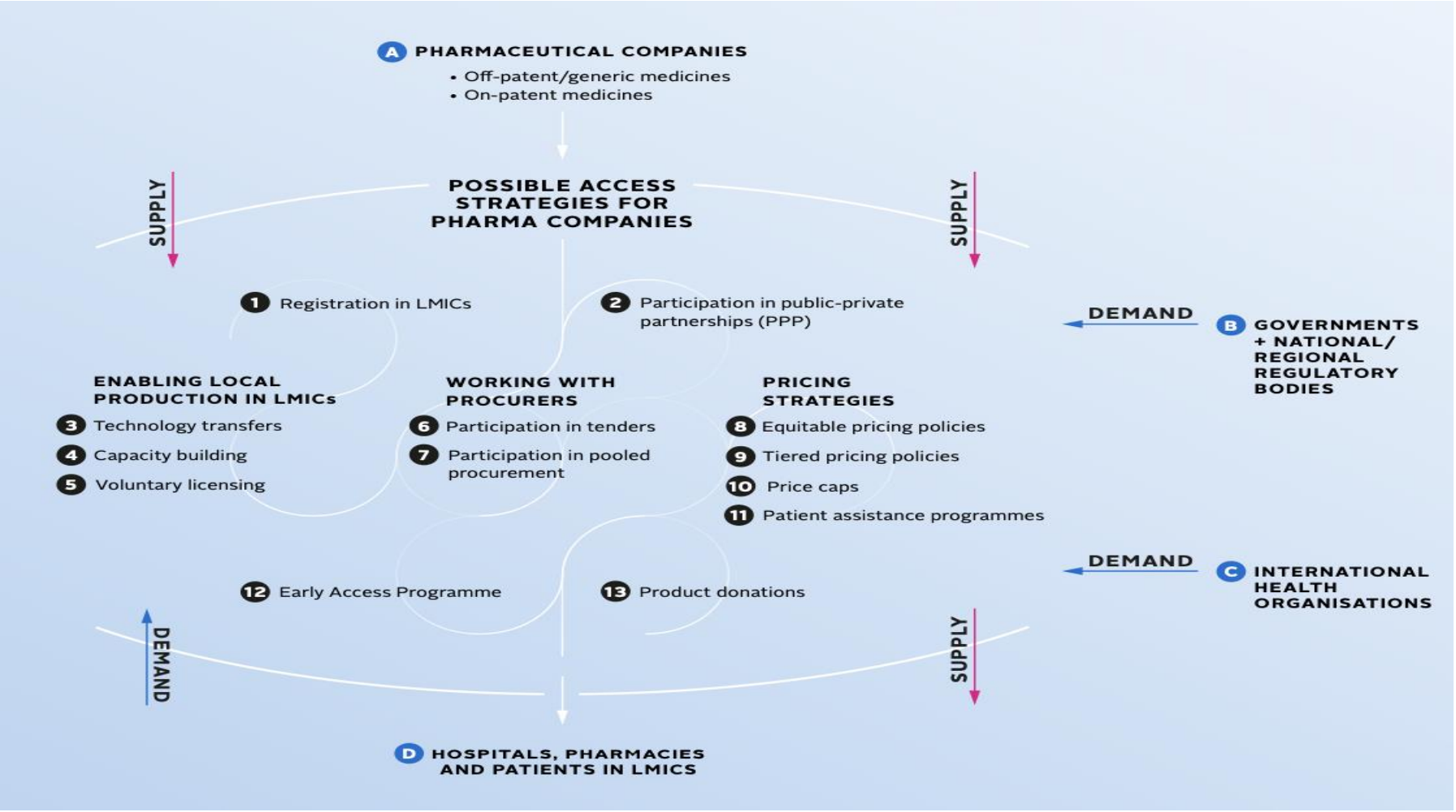
Some recent AMR activities (including access)

Antimicrobial resistance





Toolkit of access strategies



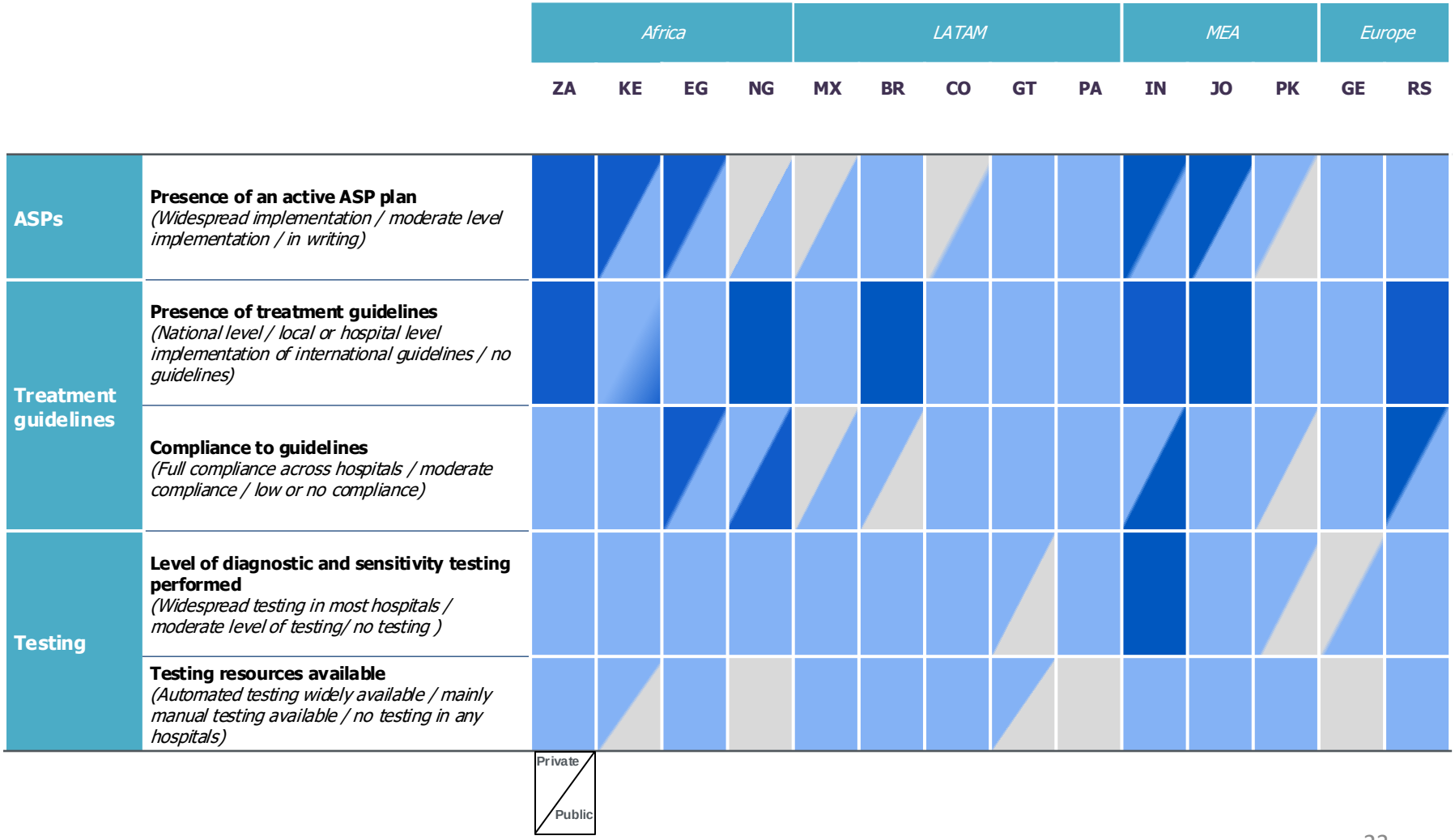
SECURE INTERIM REPORT

Access Thinking

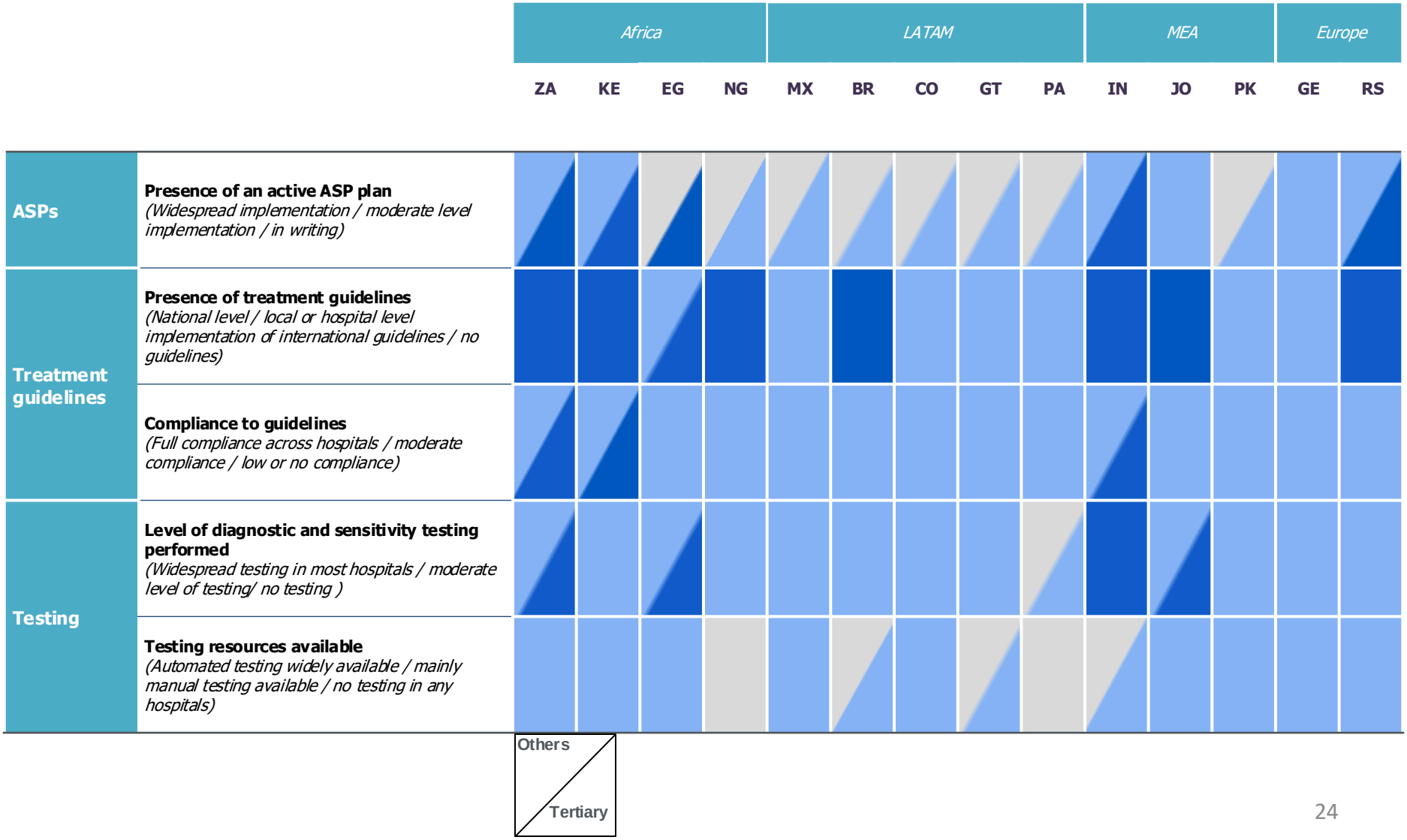
(especially with Fred McElwee, Jean-Christophe Spiliotis-Saquet, and Humayra Bashir)

2024 report

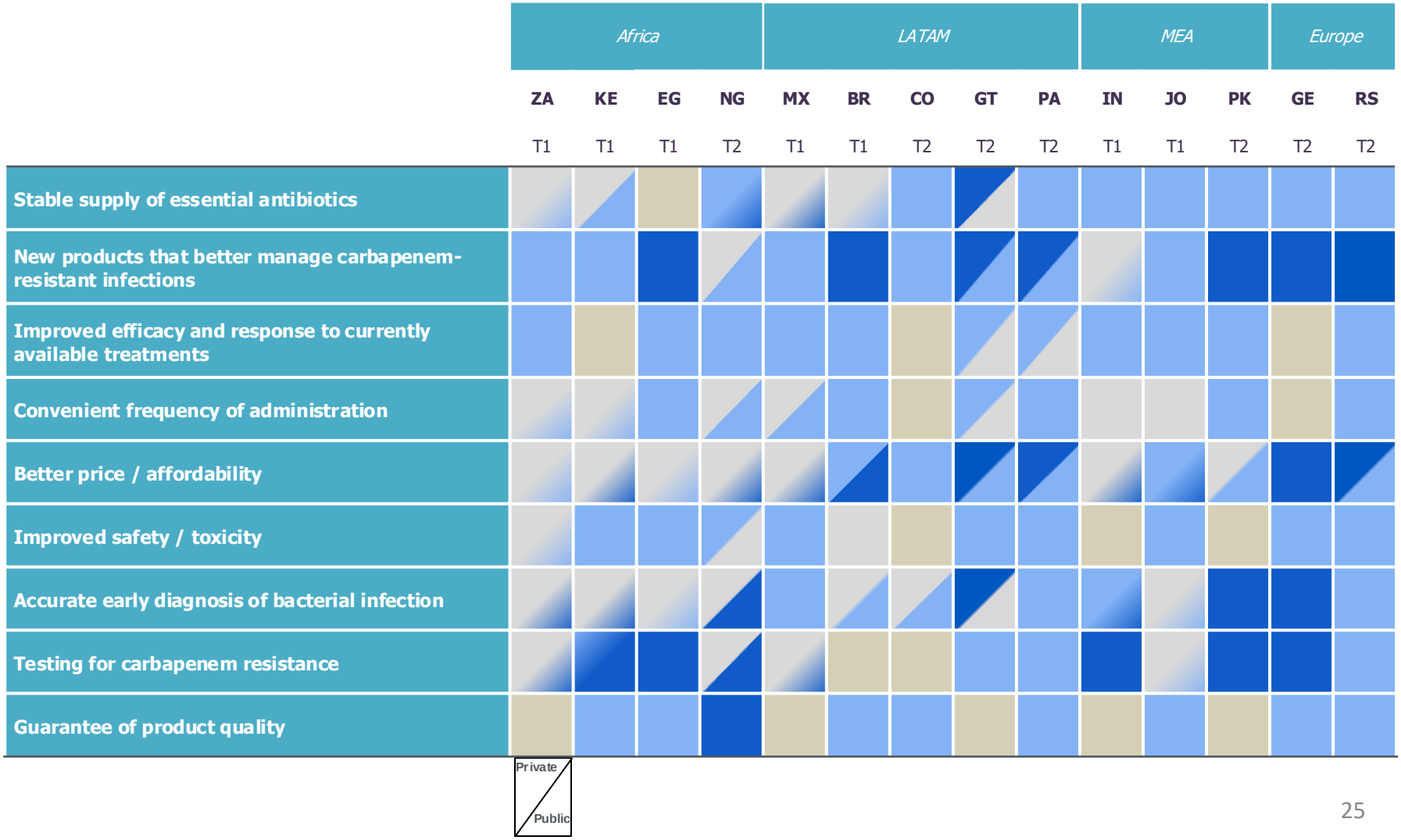
Testing, treatment, and stewardship



Testing, treatment, and stewardship



Unmet needs: Public v Private Sector



Not short of groups engaged
What are we short of?

Alternative thinking?

Final Report of a Scoping and Brainstorming Exercise to explore:

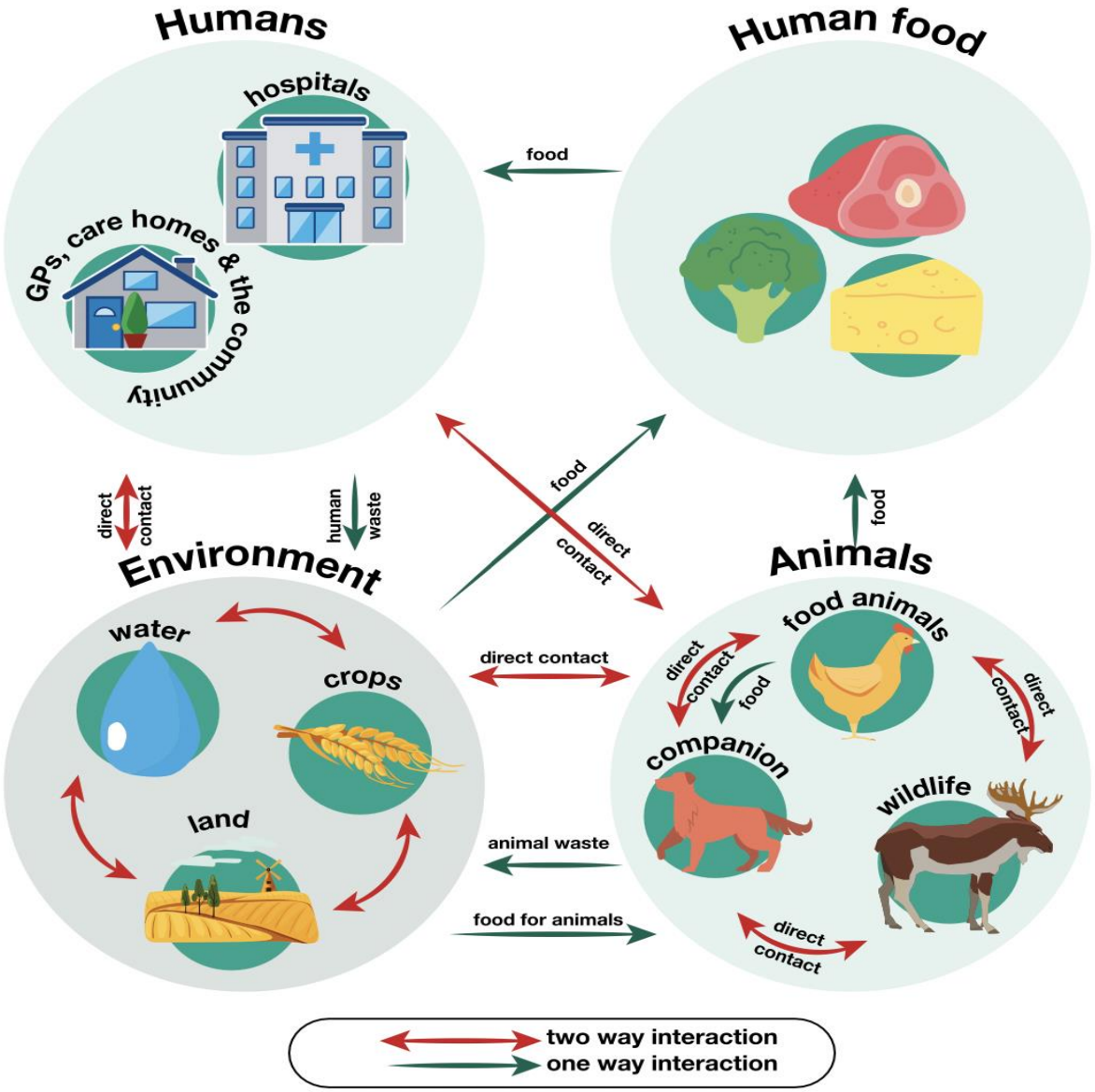
Possible core components of SECURE based on economics principles

Andrew Farlow
University of Oxford
September 2023

1

2

One Health


Humans
hospitals
GPs, care homes & the community
Human food
food
direct contact
human waste
food
direct contact
food
Environment
Animals
water
crops
land
direct contact
food animals
direct contact
food
direct contact
companion
wildlife
animal waste
food for animals
direct contact
two way interaction
one way interaction

Evolving UK/Germany/Africa Food and AMR network

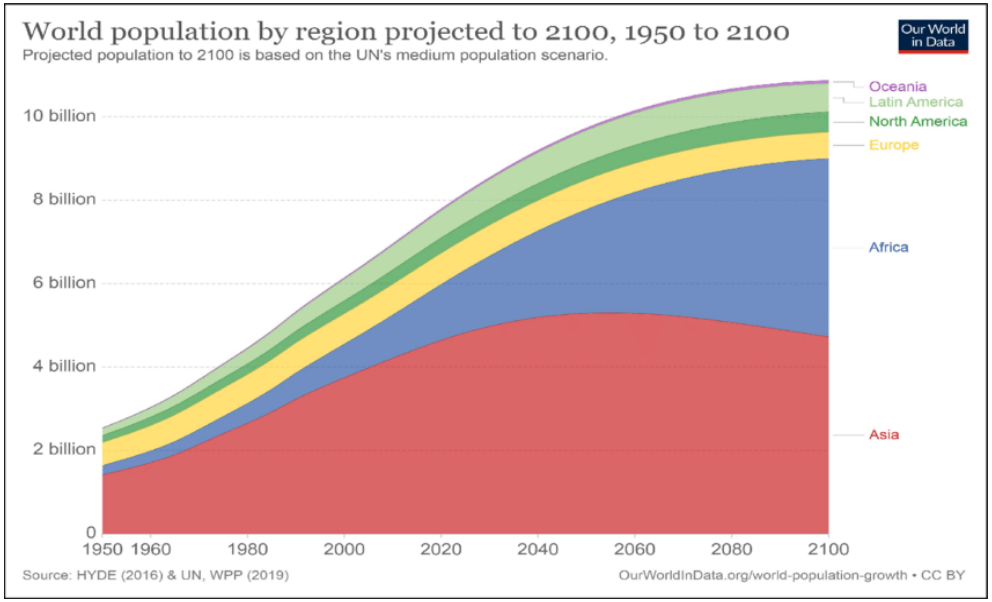
(especially with Sam Shepard, Harriet Bartlett, Chioma Achi, Humayra Bashir)

Food Systems and Antimicrobial Resistance:

Making food systems more robust to reduce AMR risk globally

Thursday 27th and Friday 28th June 2024

Max Liebermann Haus, Berlin and online



- Global population growth.
- Life-style aspirations lead to greater meat consumption and pressure on farmers to deliver low-cost animal protein even if AMR risk.
- Global meat production grew 45% between 2000 and 2020.
- Many food production systems rely on antimicrobials as a less costly substitute for infection prevention.
- AMR risk.
- Green-house gas and climate change risks too.

Volumes of antimicrobial use in food producing animals

PLOS GLOBAL PUBLIC HEALTH

Global trends in antimicrobial use in animals in 2020 and 2030

Fig 2. Antimicrobial consumption per country in 2020 and 2030. Circles are proportional to quantity of antimicrobials used. Red circles correspond to the quantity used in 2020, and outer dark red ring corresponds to the projected increase in consumption in 2030. Country boundaries were obtained from GADM (https://gadm.org/download_world40.html).

Global trends in antimicrobial use in food-producing animals: 2020 to 2030

Ranya Mulchandani[1], Yu Wang[1], Marius Gilbert[2,3], Thomas P. Van Boeckel[1,4]*

1 Health Geography and Policy Group, ETH Zürich, Zurich, Switzerland, 2 Spatial Epidemiology Lab, Université Libre de Bruxelles, Brussels, Belgium, 3 Fonds National de la Recherche Scientifique, Brussels, Belgium, 4 Center for Diseases Dynamics, Economics, and Policy, New Delhi, India

- By volume, the largest contributor to antimicrobial consumption.
- About 70-75% of all antimicrobials worldwide.
- 99,502 tonnes (95% CI 68,535–198,052) in 2020.
- Based on current trends, increase 8.0% to 107,472 tonnes (95% CI: 75,927–202,661) by 2030.
- Hotspots overwhelmingly in Asia (67%).
- <1% were in Africa.

Hotspots of veterinary antimicrobial consumption

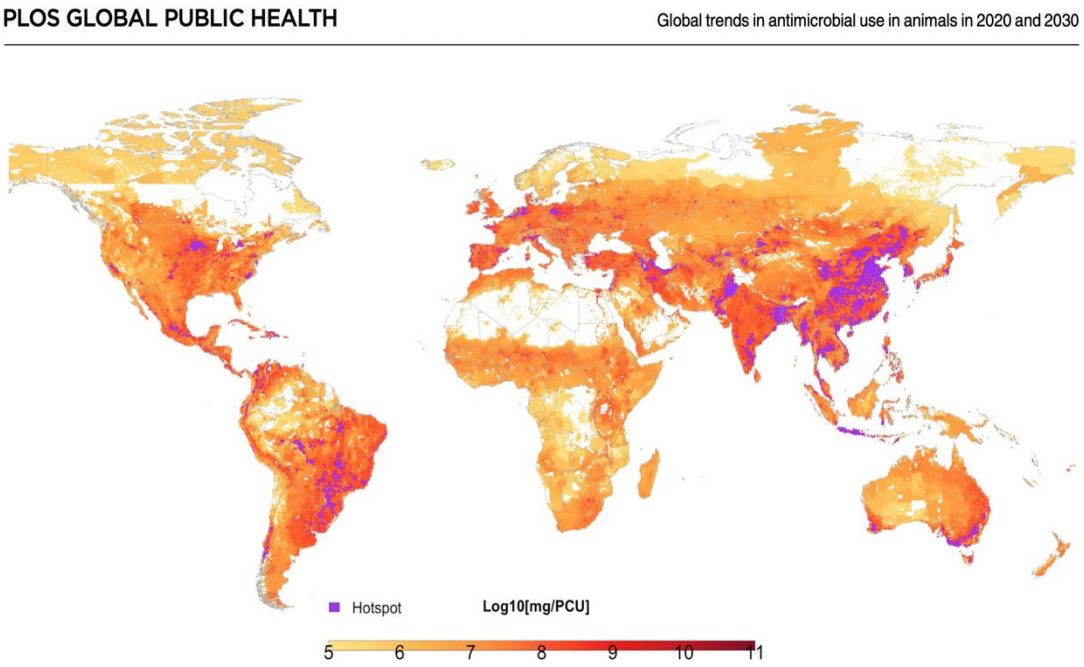
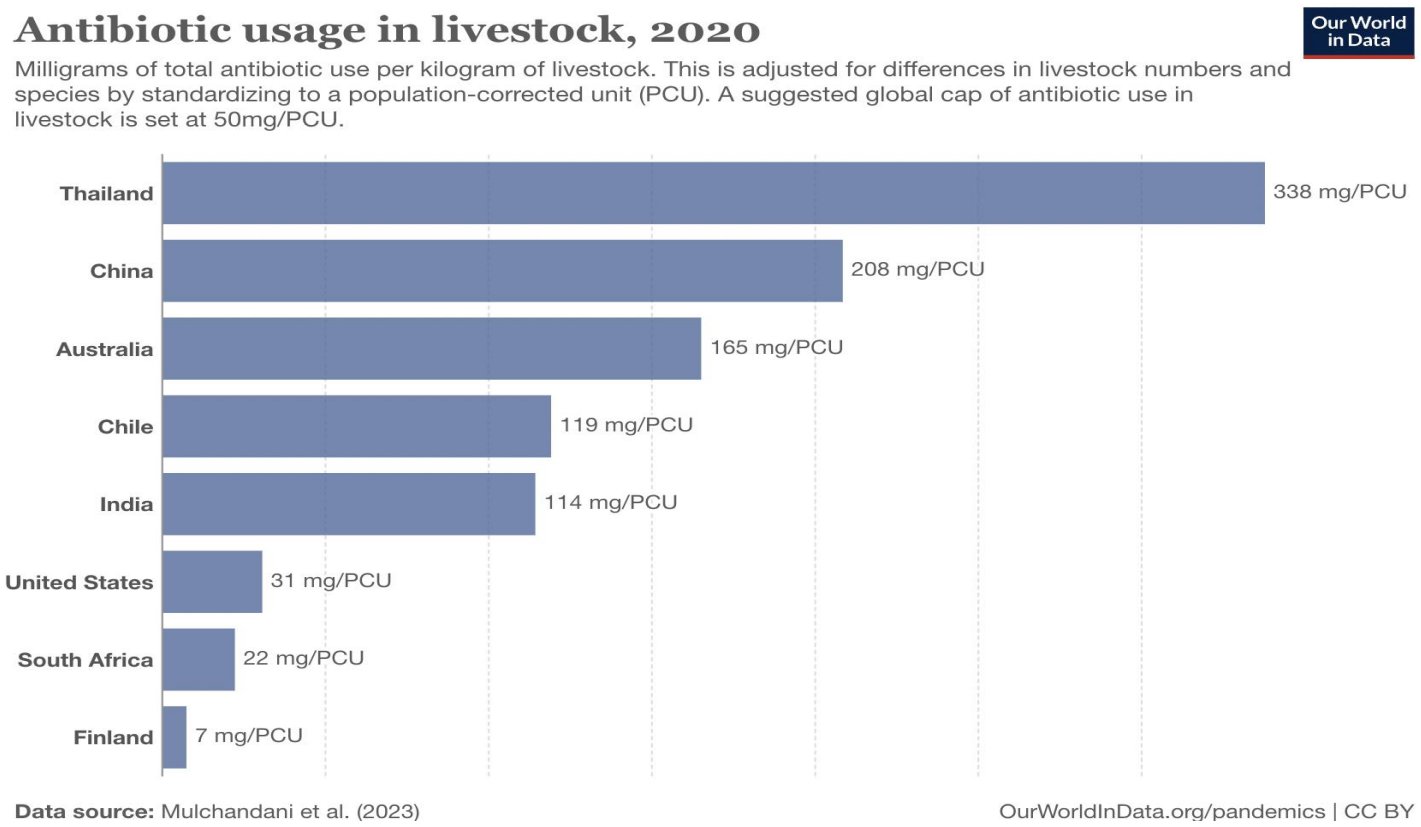


Fig 3. Global distribution of veterinary antimicrobial consumption at 10 x 10 kilometers resolution expressed in milligrams per biomass (population correction units). Purple indicates hotspot areas (top 95% percentile). Country boundaries were obtained from GADM (https://gadm.org/download_world40.html).

- Variability:
  - UK: 75% of farm antibiotics used in feed or water.
  - **Less than a quarter** given by **injections**, to treat individual animals.
  - **Sweden: less than half the farm antibiotics administered in the UK.**
  - proportion of antibiotics given via **feed or drinking** <10%.
  - **three quarters given by injection.**

Per kilo of livestock (more variability)



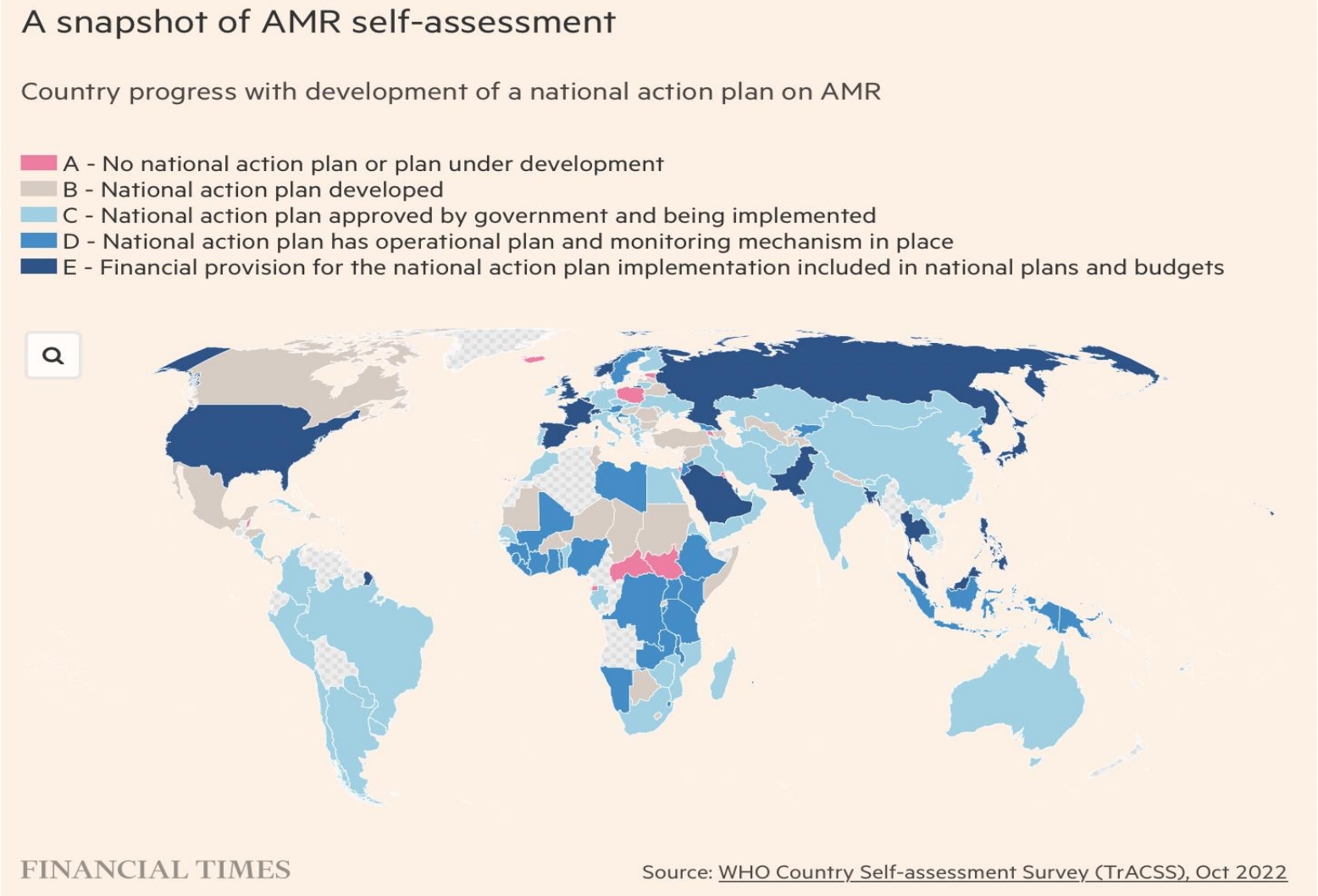
Big evidence gaps

- AMU in animals highly variable geographically, by type of antimicrobial, over time.
- **Relative contribution of animal AMU versus human AMU in driving AMR unknown.**
- Need evidence on drug-pathogens combinations in animals that pose the most serious threat to human health from AMR.
- Poor understanding of constraints/incentives that shape choices, especially pressure farmers face to use antibiotics, actual and perceived risks, how to mitigate those risks, and pressures inside food supply chain.
- Socioeconomics: resistance rates and effect on health differ with countries' socioeconomics, health-care systems, patient populations, and antibiotic consumption.
- Most outcomes the result of the systems, needs multi-sectoral and cross-disciplinary systems thinking.
- Implement challenge. Just having good evidence is not enough to change behaviour.

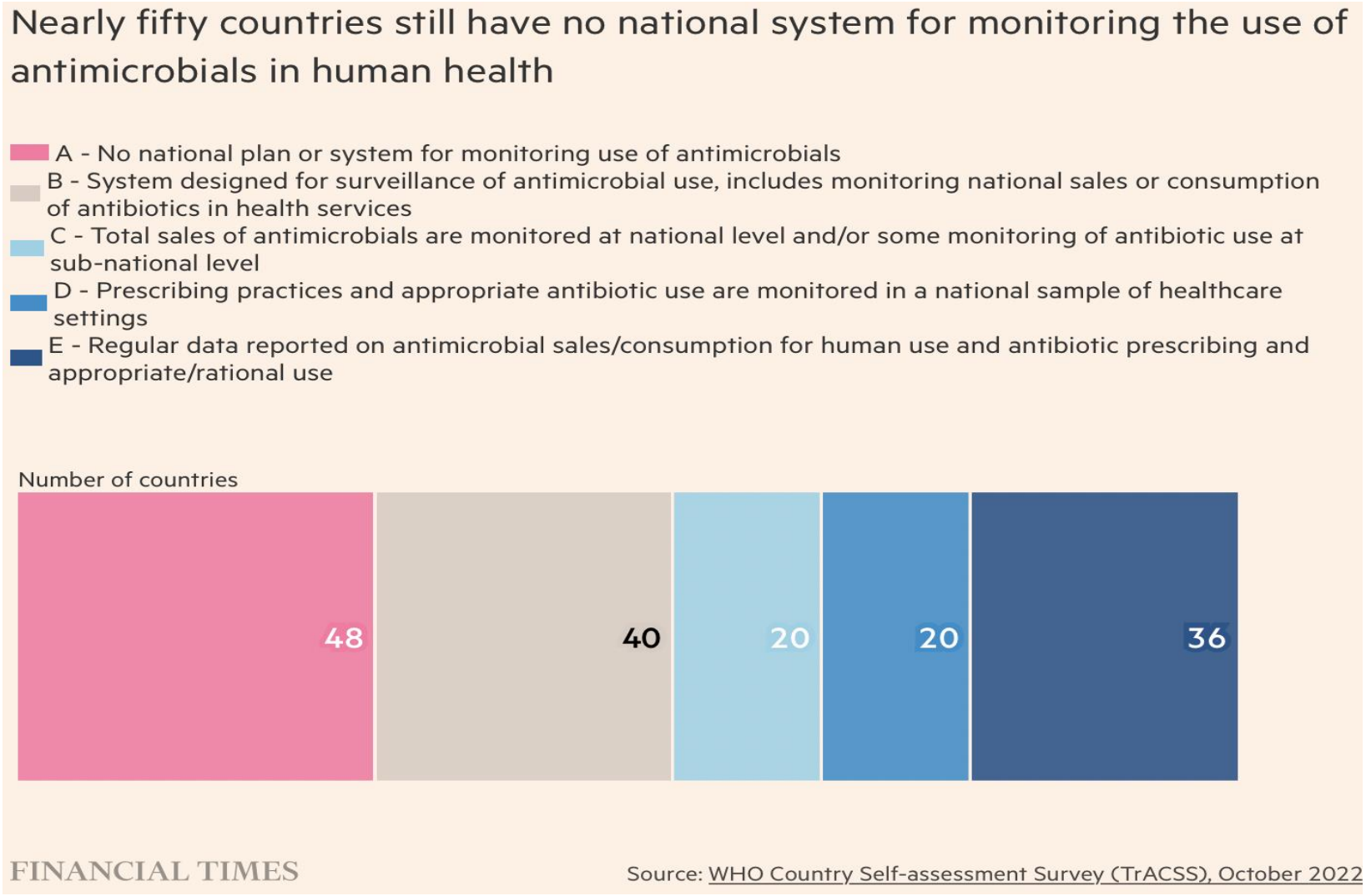
National Action Plans

(especially with Yuzana Khine Zaw and Numyra Bashir)

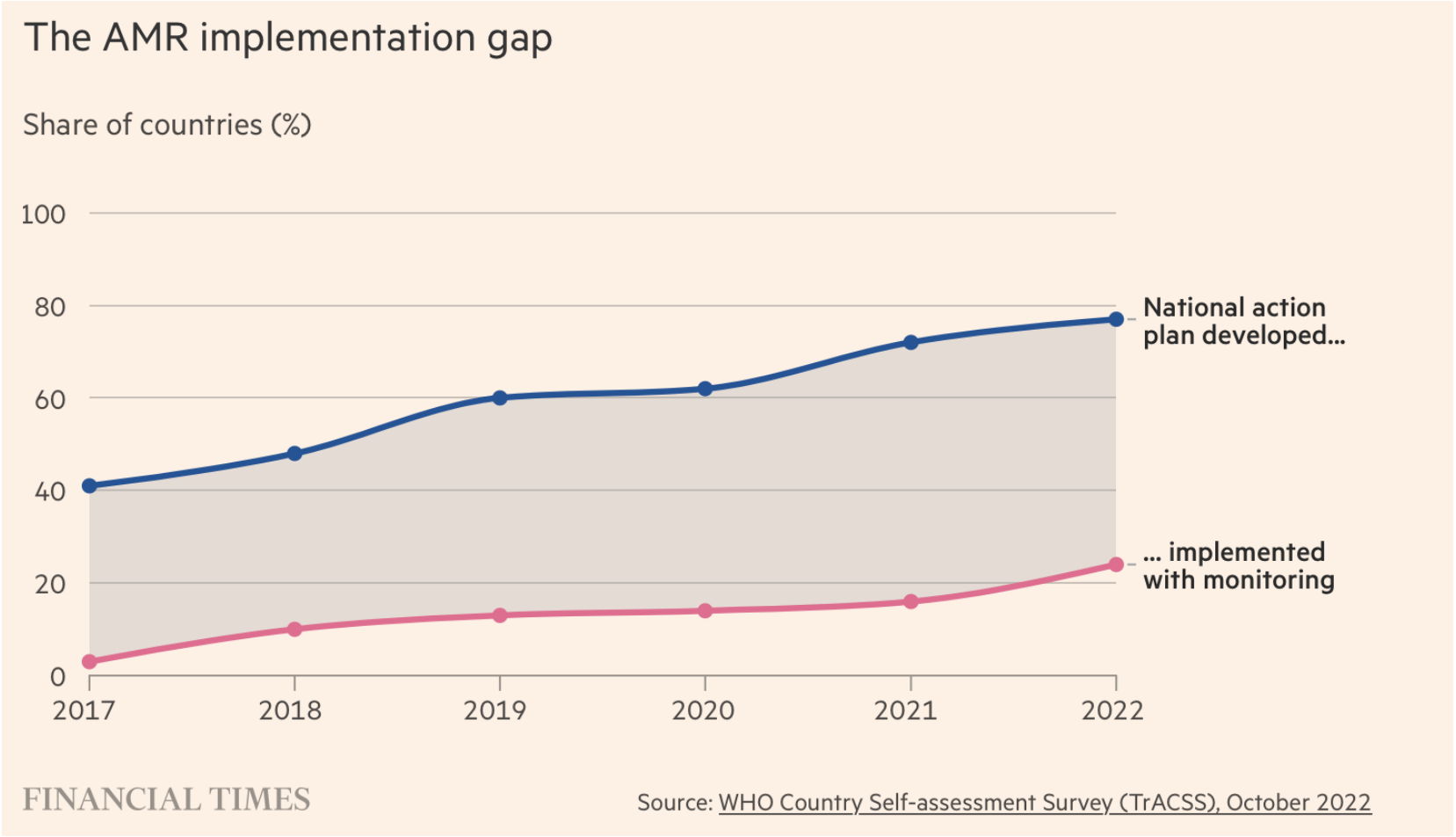
State of development of NAPs



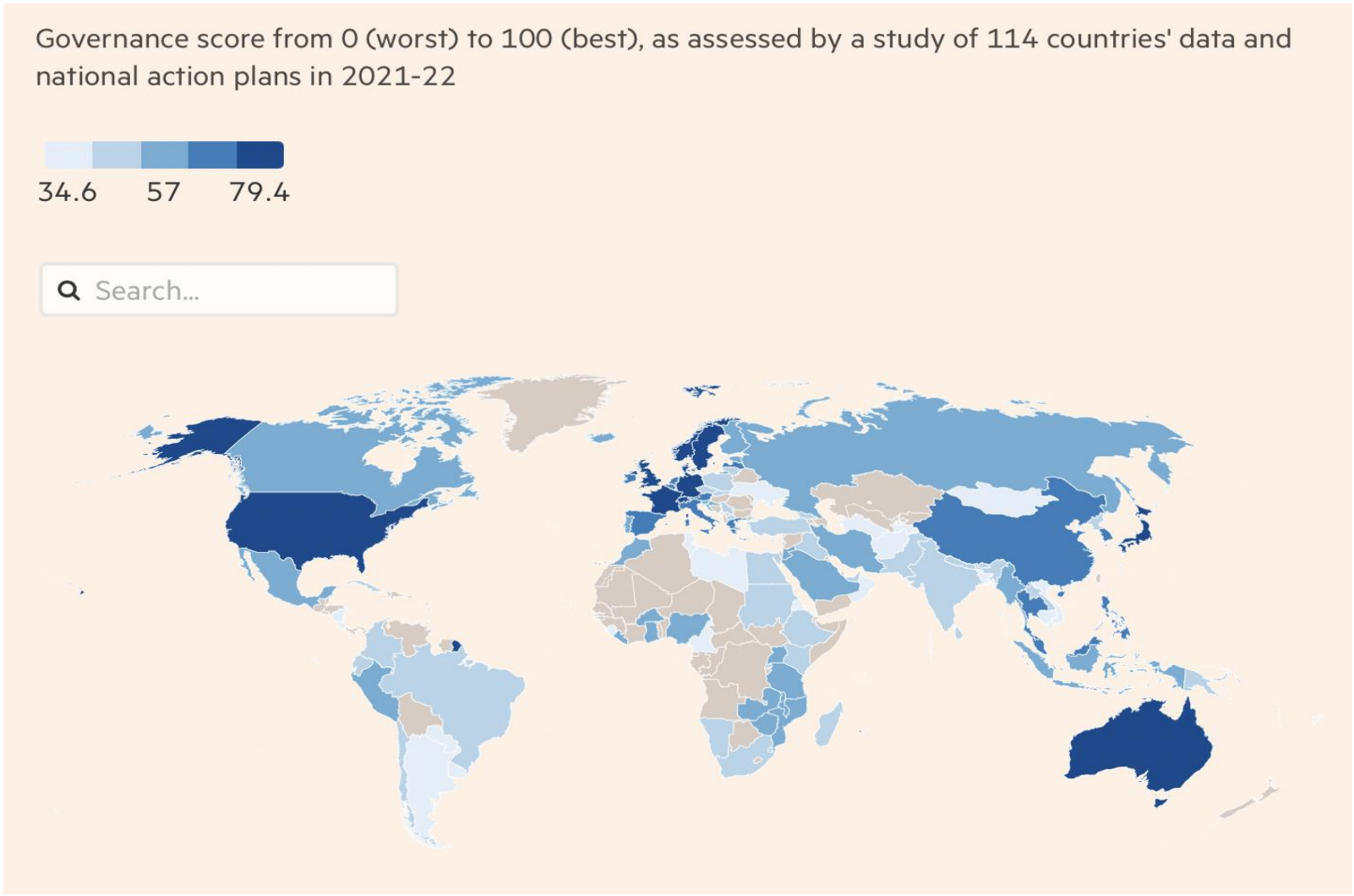
State of development of NAPs



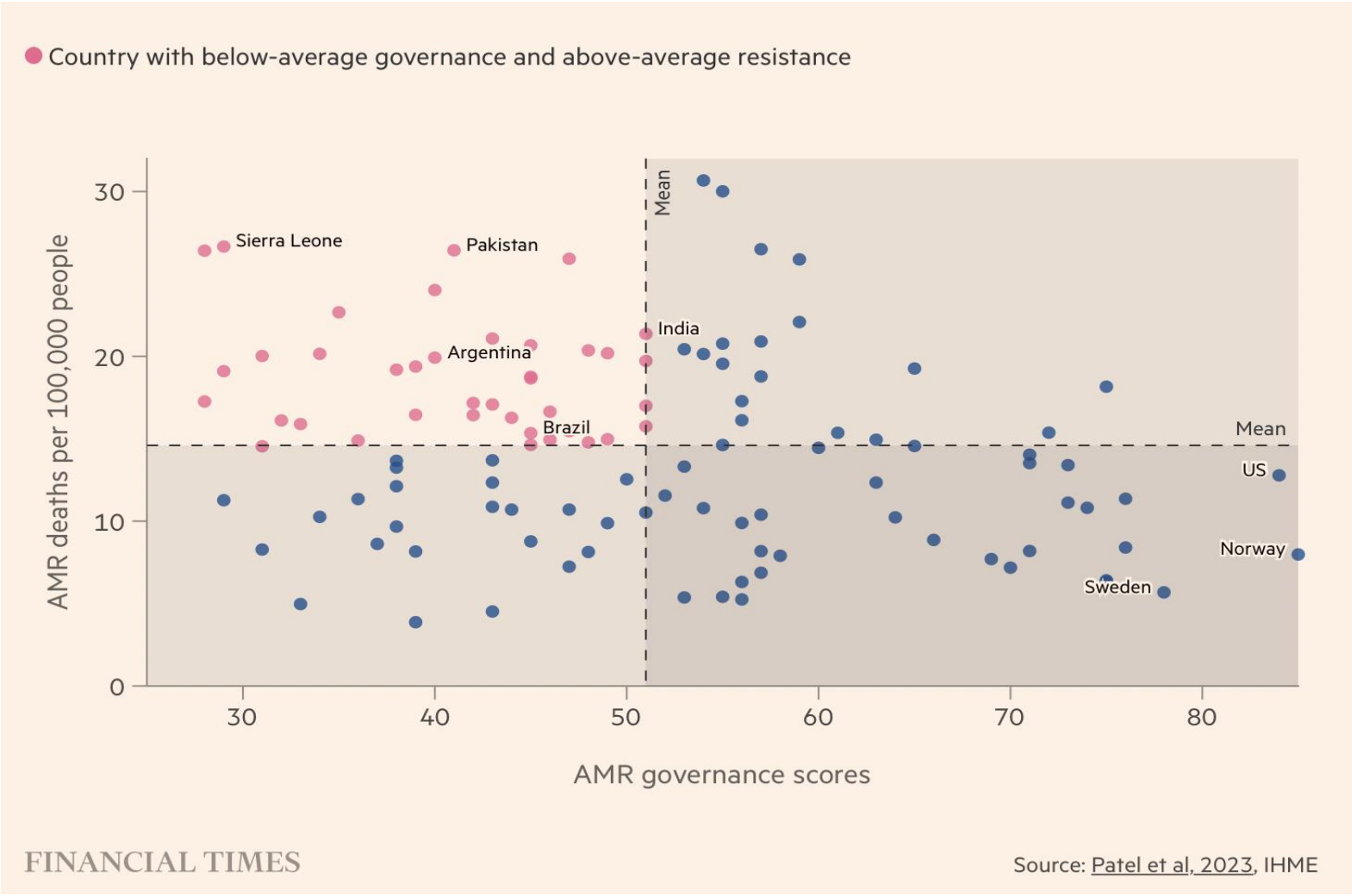
The implementation gap



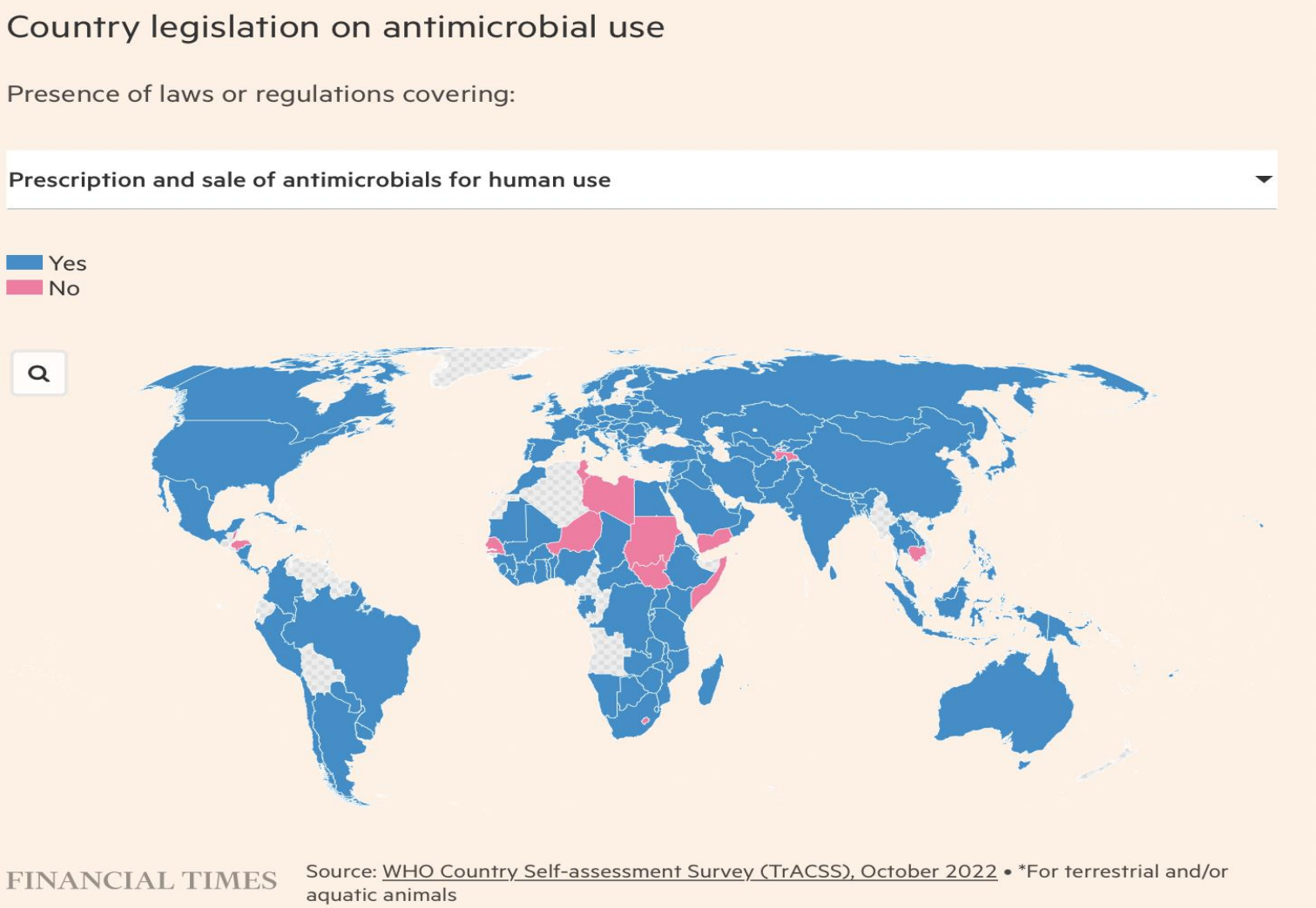
Governance scores



Highly variable performance



Legislation



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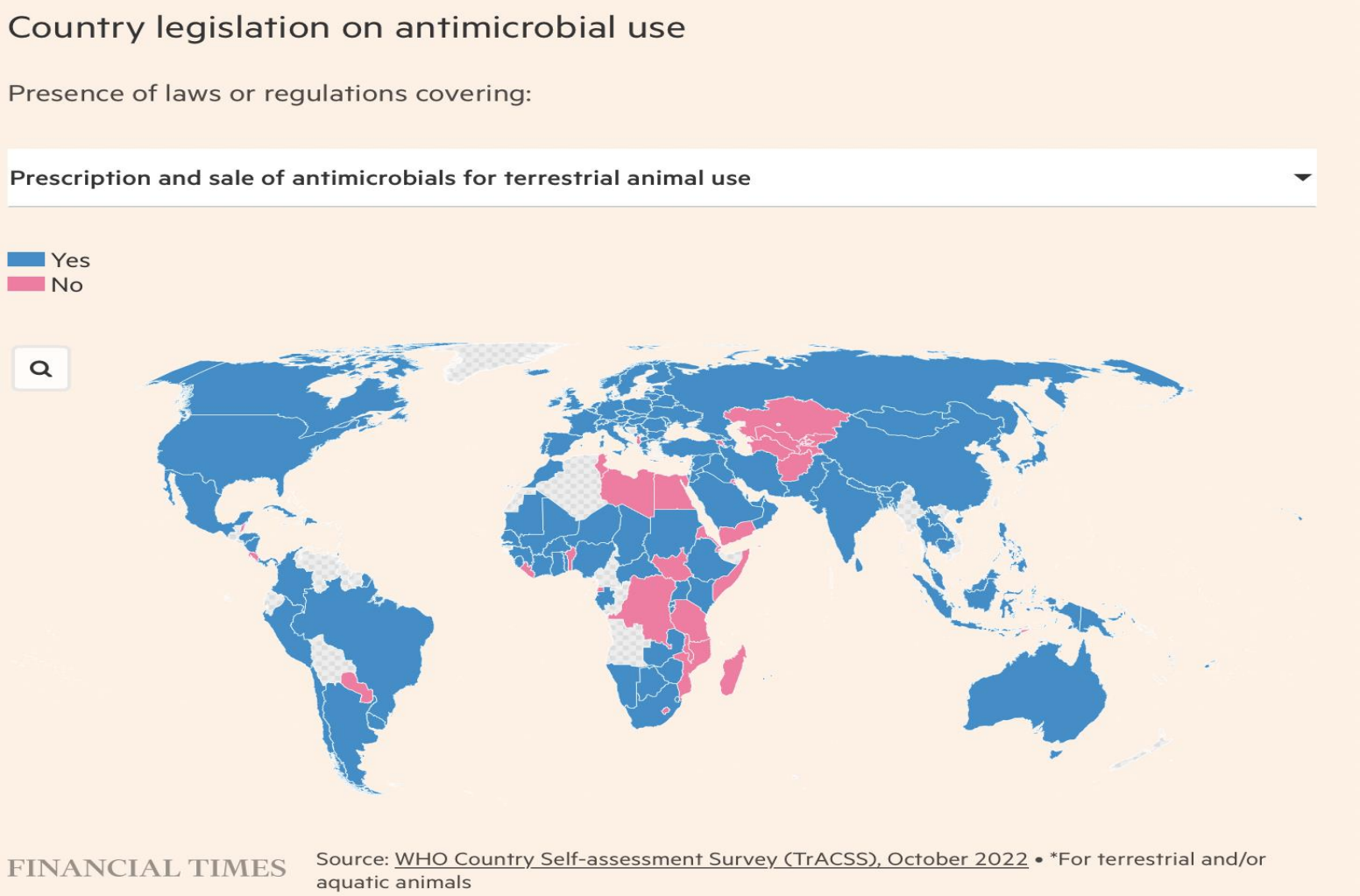

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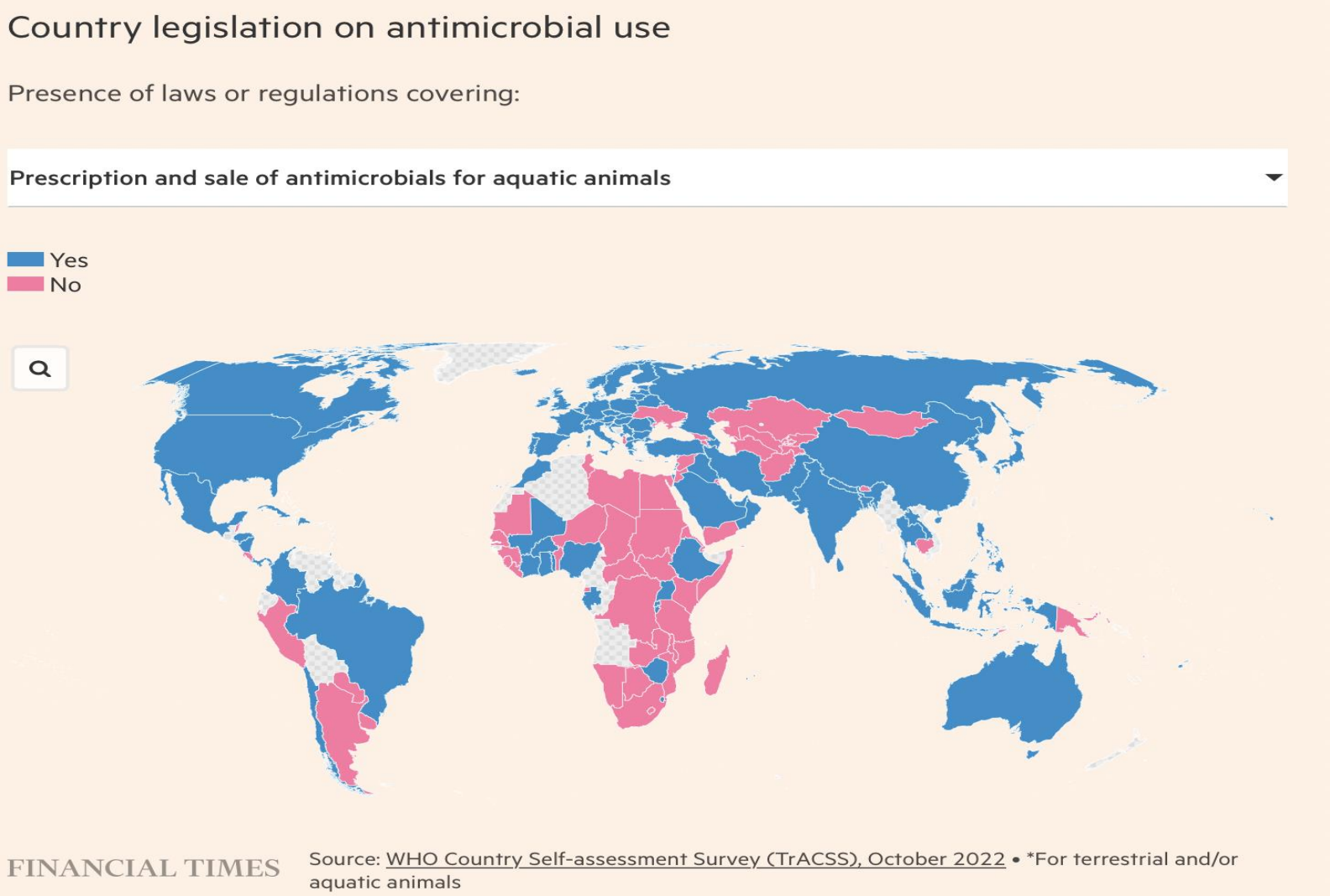

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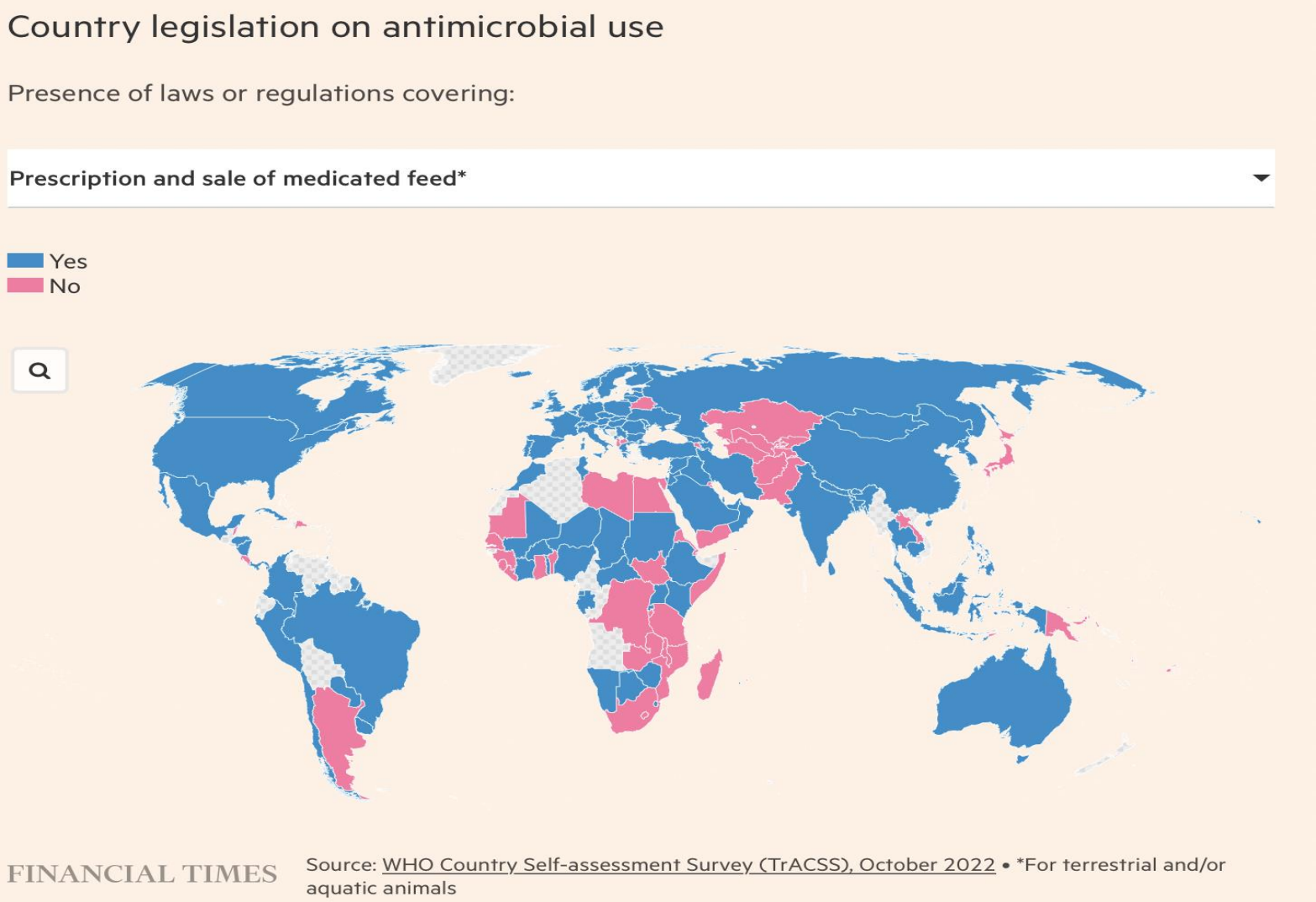
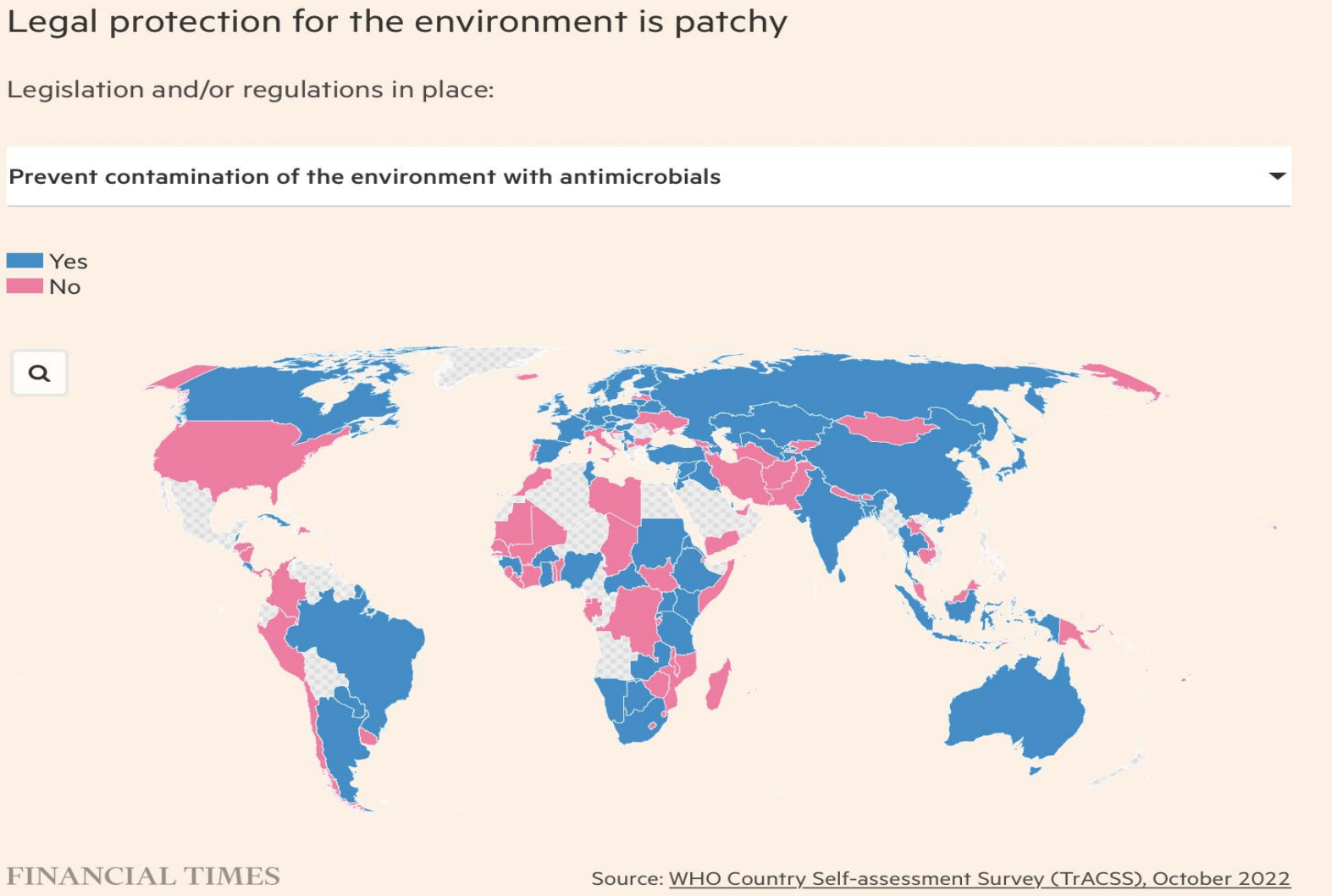


Environmental protection



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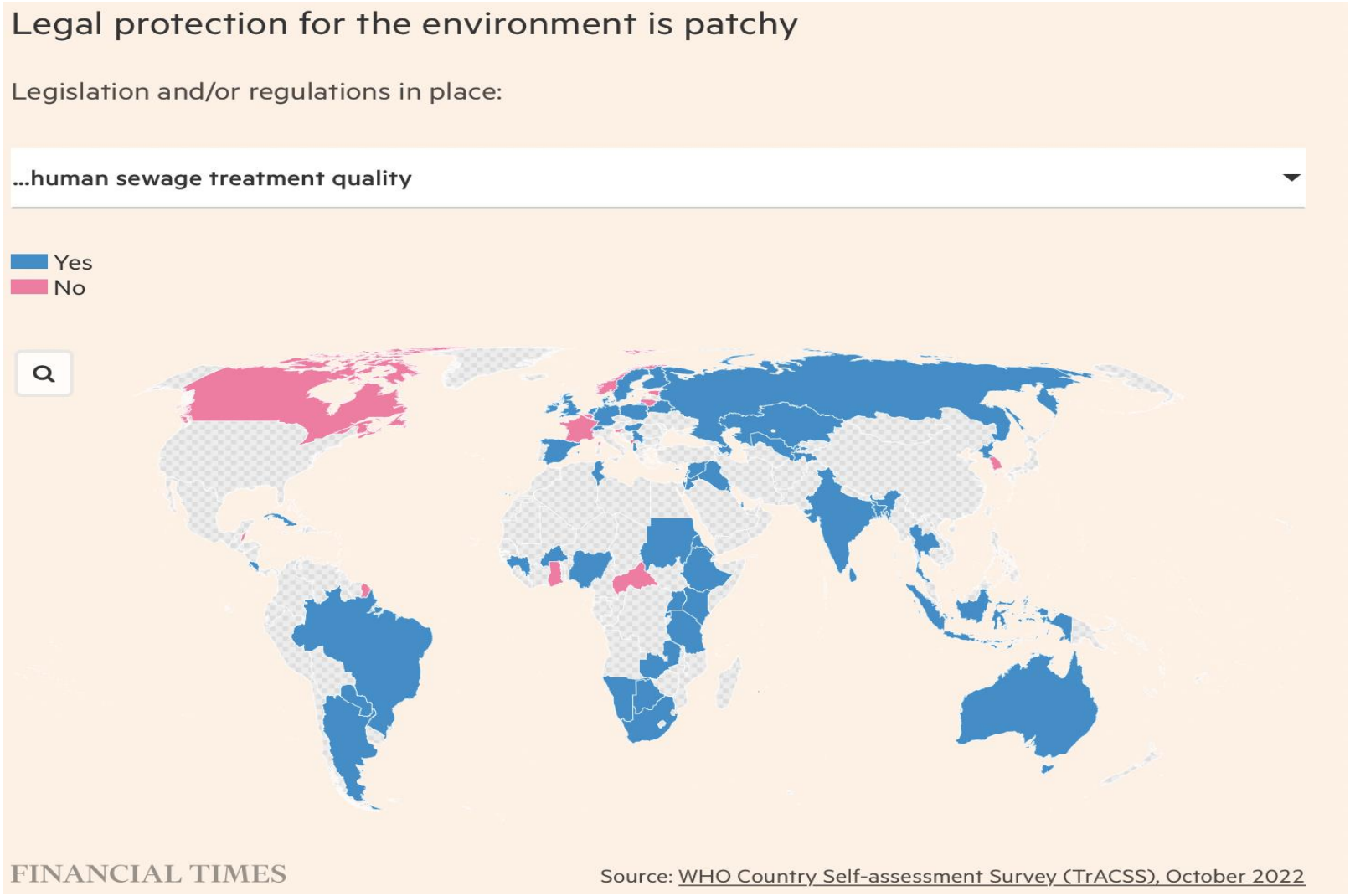

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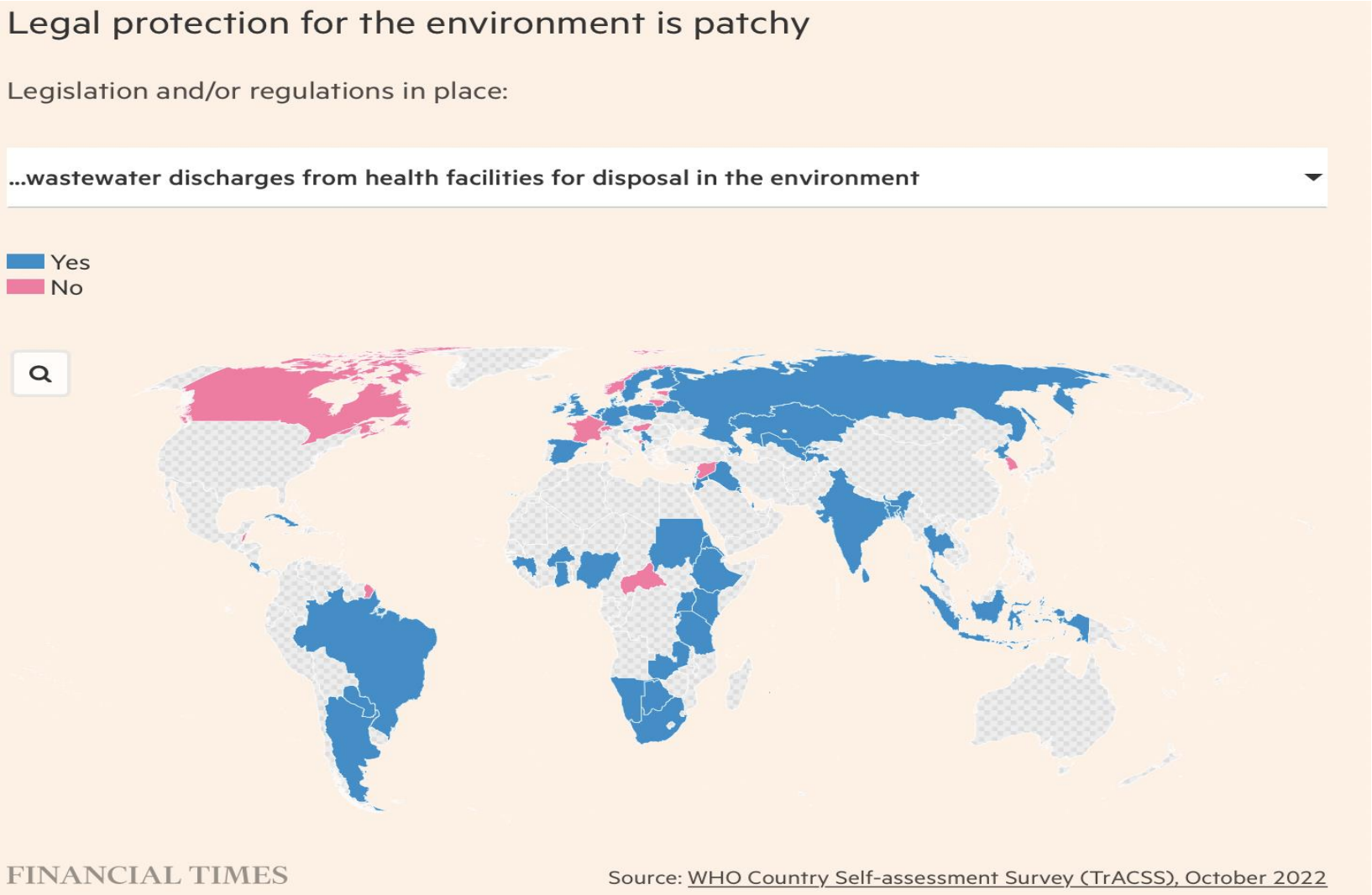

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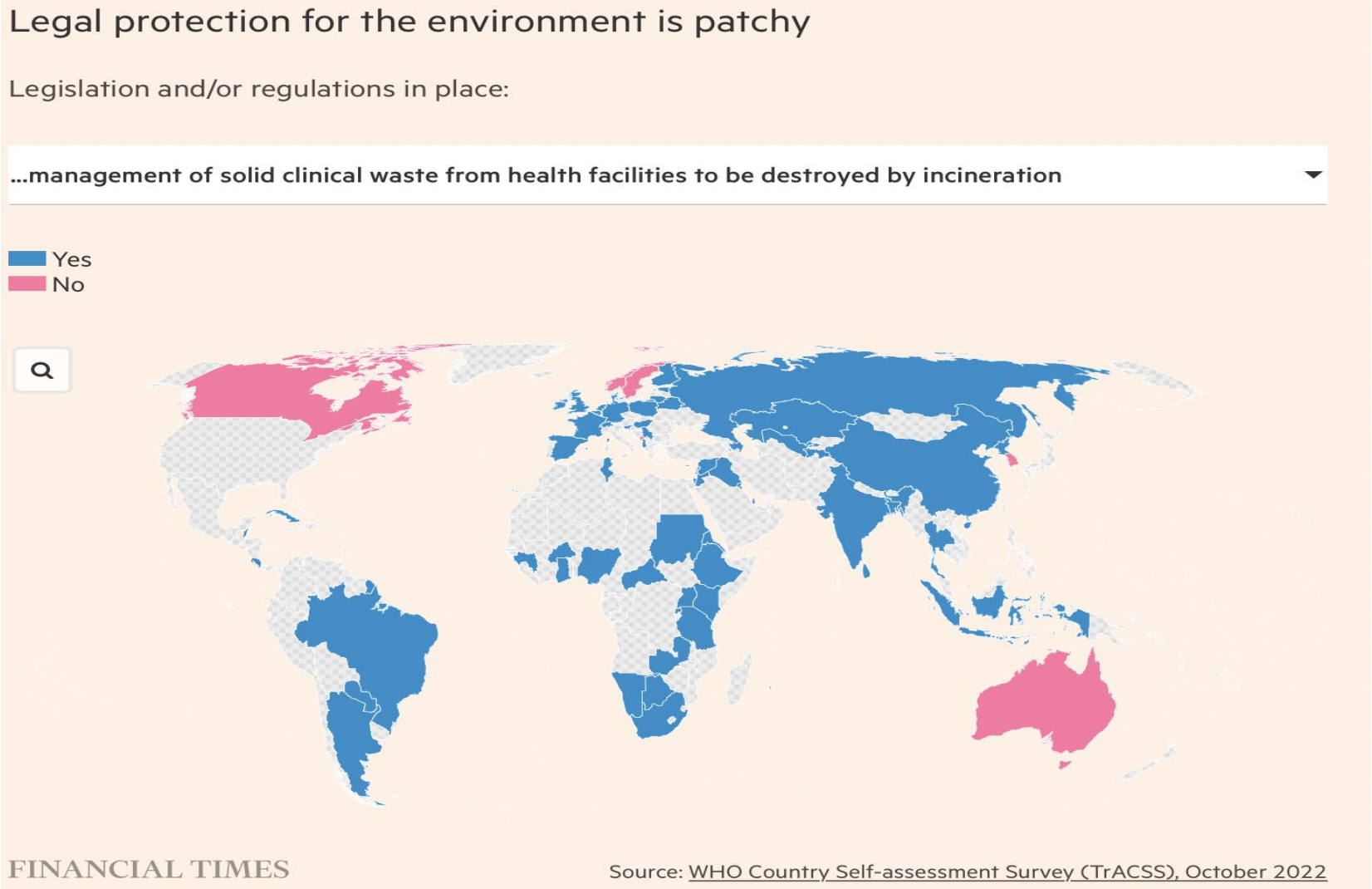
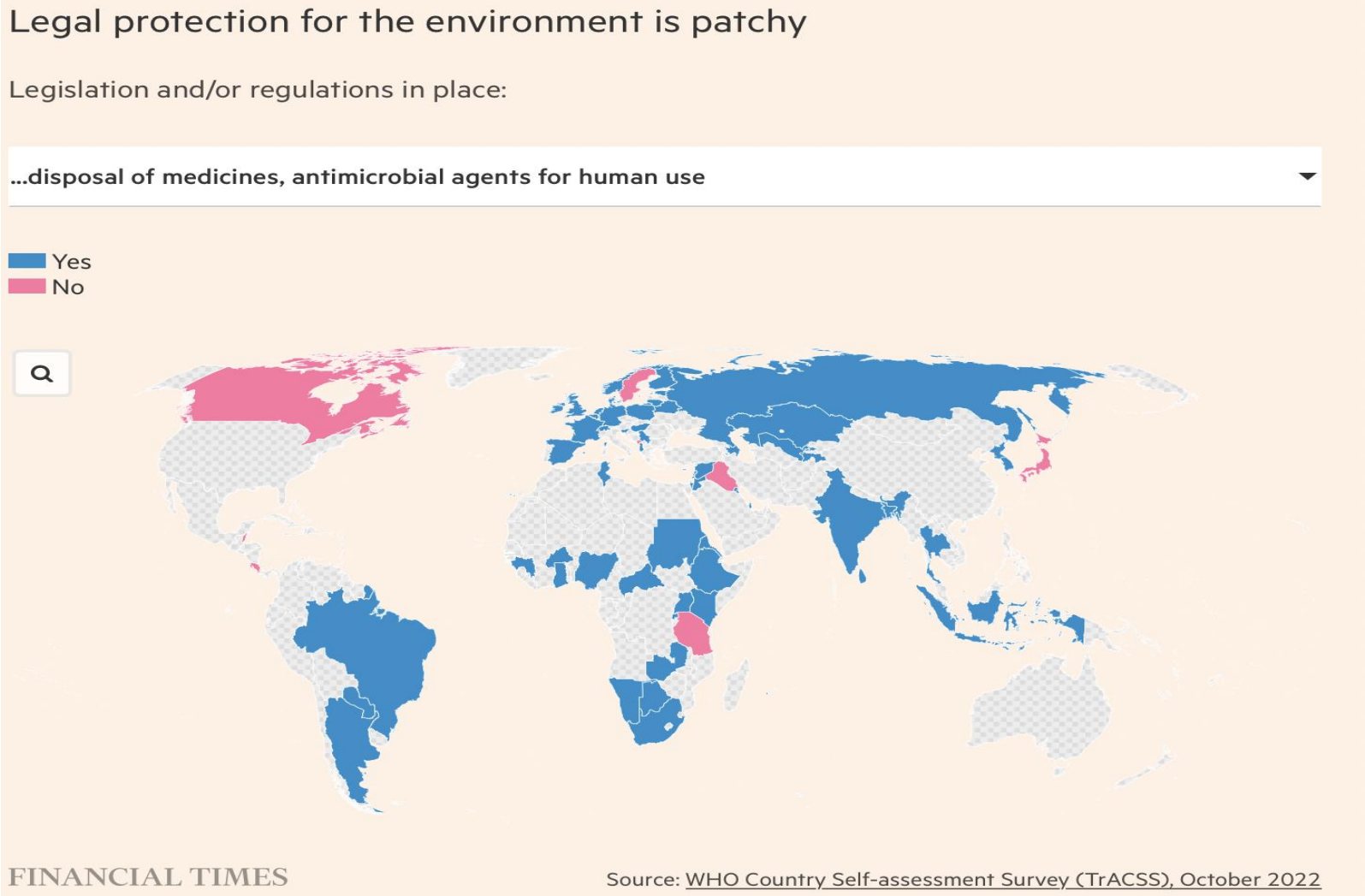
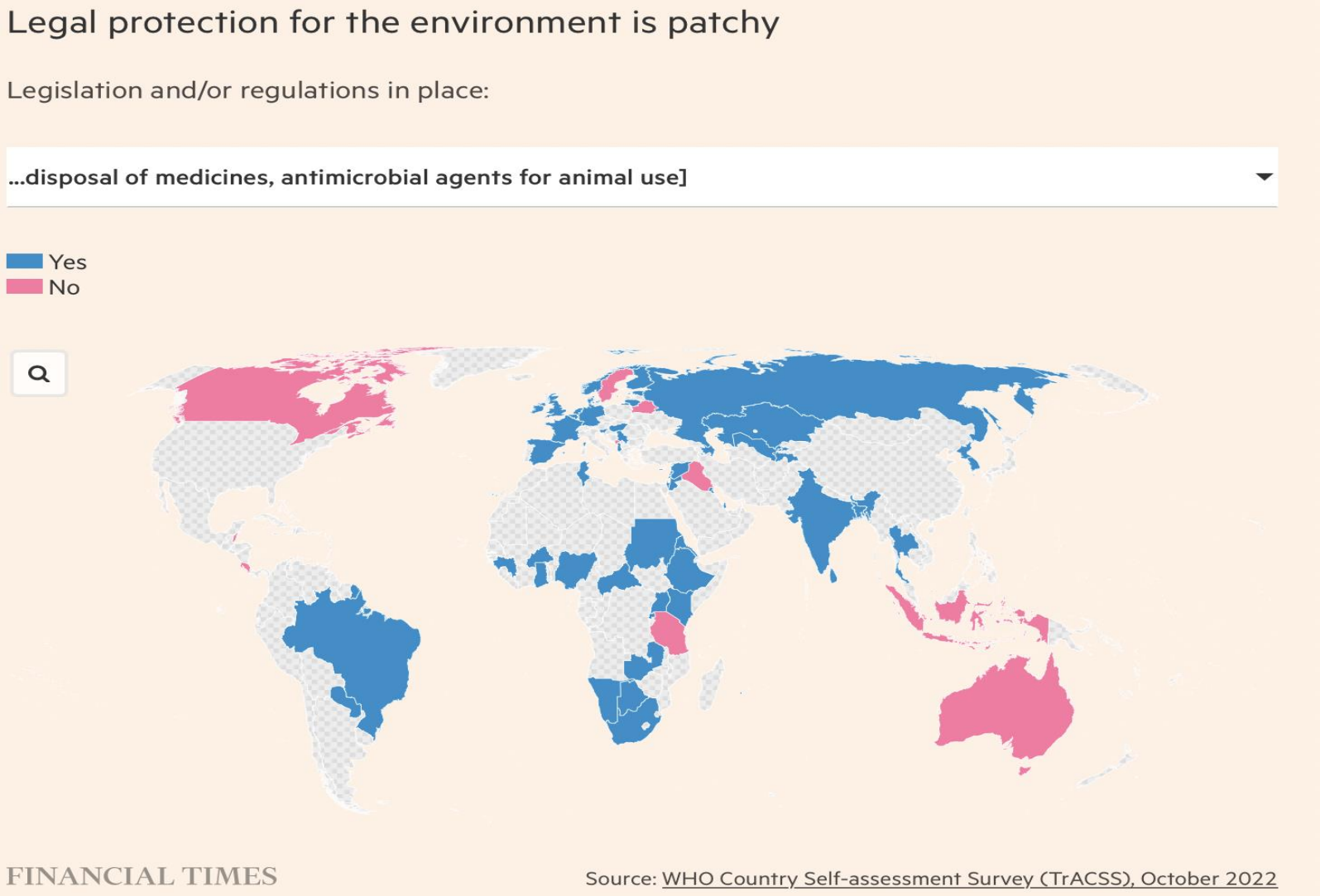


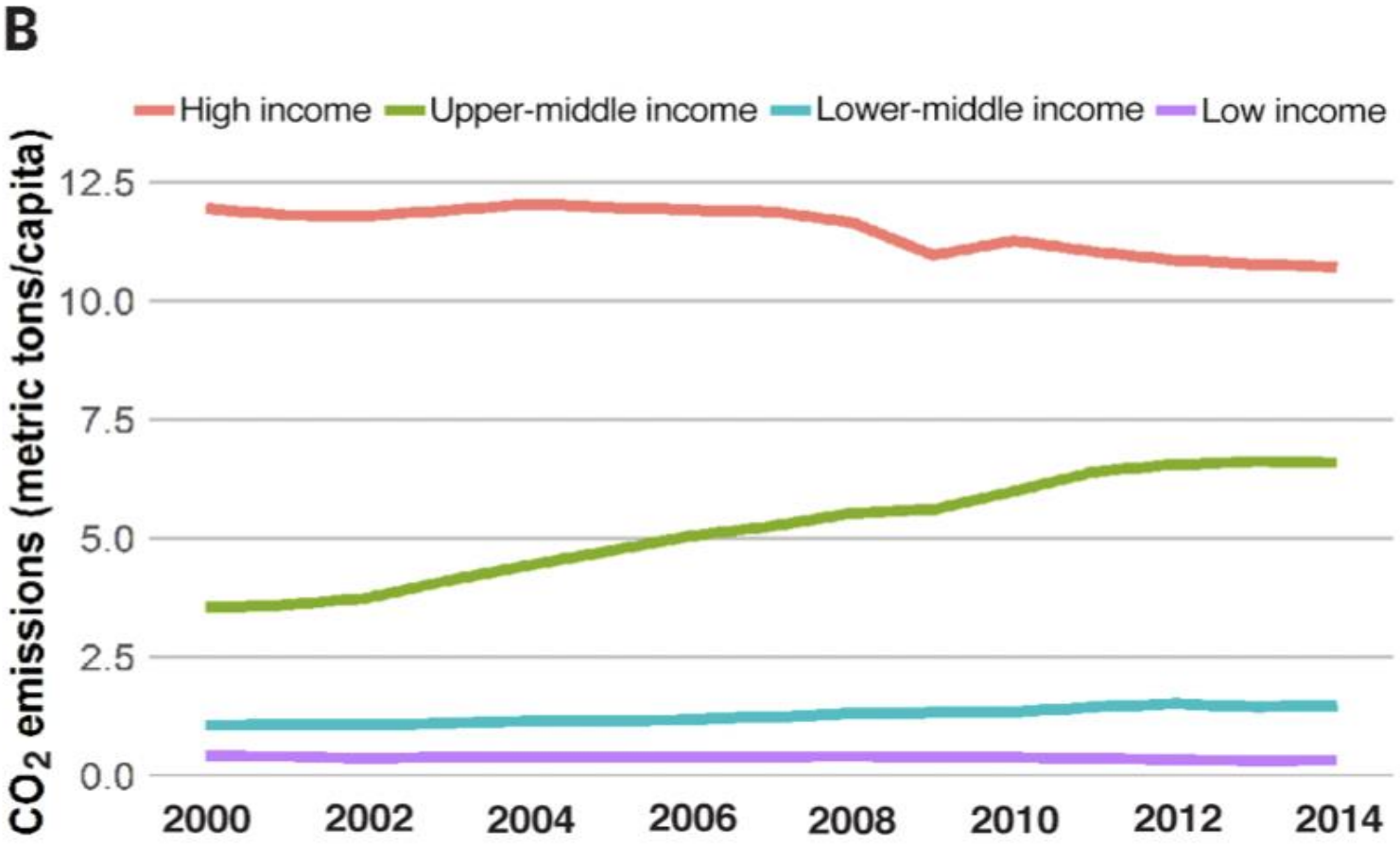
Environmental protection



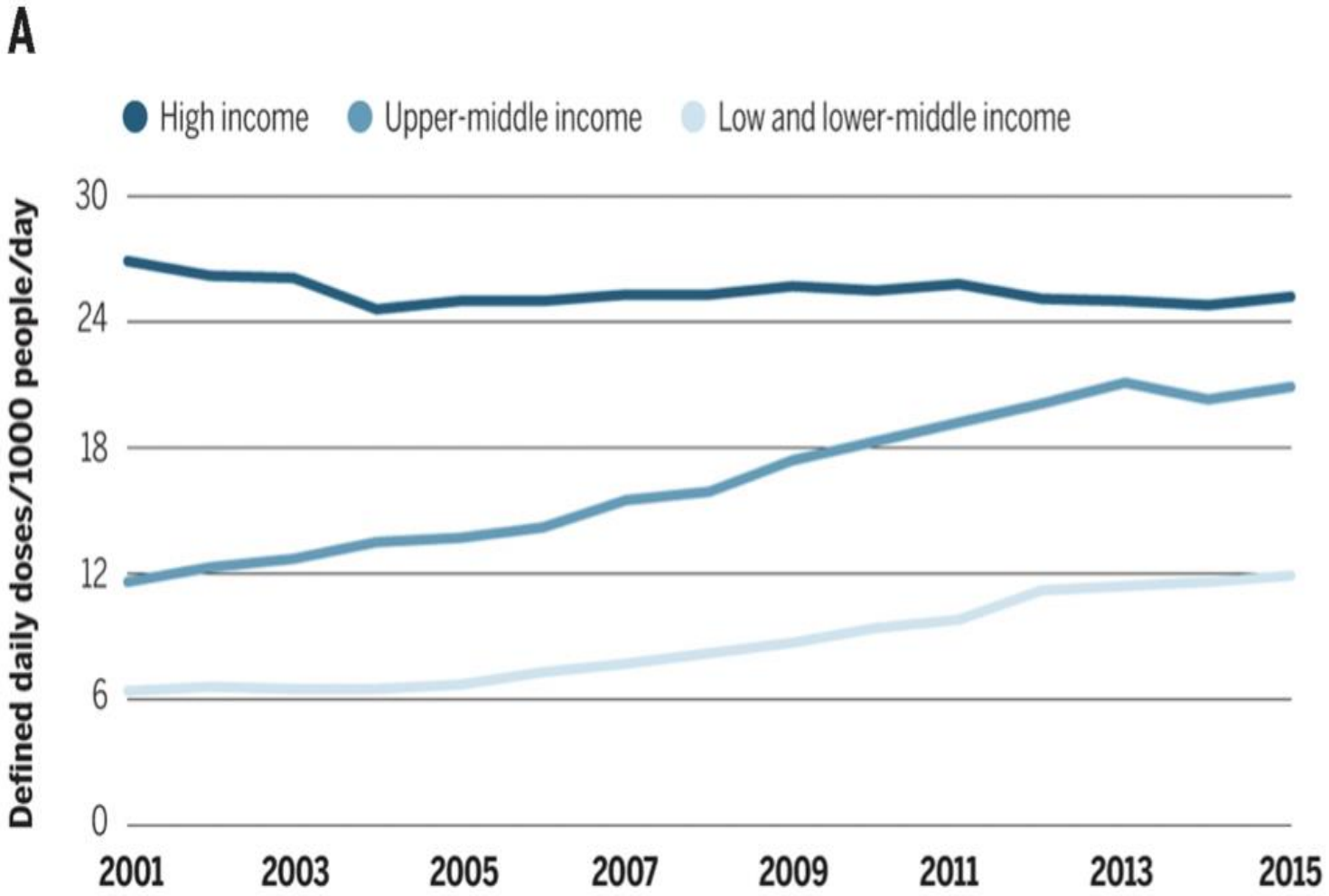
Environmental protection



Is this like tackling global heating?



Who uses lots of antibiotics?



Similarities with climate change

- Both are global **"tragedy of the commons,"**
- Both driven by consumption generating short-term benefits but **long-term costs**
- Individuals have little incentive to forego short-term benefits:
  - costs are highly uncertain
  - harmful events may happen far in the future which they discount
- The costs are unlikely to be avoided **unless many other people also** decide to reduce their carbon and antibiotic consumption.
- **Costs and benefits are not distributed unequally**
- **intergenerational equity**
- **Equitable and optimal antibiotics access critical to overcoming tragedy of the commons**


THANK YOU