

Stewarding Bugs Not Drugs: Rethinking Antimicrobial Regulation Beyond The Clinic



Claas Kirchhelle
INSERM, U988

Today

1. An Antibiotic Apocalypse?
2. Breaking the Mould: the long history of antimicrobials
3. Narrow Fixes: the rise of stewardship
4. Shifting The Perspective: An Antibiocene
5. Conclusion: Towards Microbial Health

**RESISTANT GONORRHEA
ALERT!**

Penicillinase-producing
Neisseria gonorrhea
(PPNG) and Spectinomycin resistant
Neisseria gonorrhea
(SRNG)

... are antibiotic resistant strains of gonorrhea
which are spreading rapidly throughout
the South and West sides of Chicago!


If you have more than
one sex partner, you are at
great risk of catching
the disease!



Be Smart! Get a
**FREE
GONORRHEA TEST!**

Remember, what you don't know CAN hurt you!

**CHICAGO STD CLINIC
(South)**
Comprehensive Environmental
Public Health Facility
1306 South Michigan Ave.
Telephone: 435-5400
Mon., Tue., Thurs. & Fri.
8:30 a.m. to 4:30 p.m.
Wed. 11:30 a.m. to 7:30 p.m.

**CHICAGO STD CLINIC
(West)**
Bundesen Clinic
100 North Central Park
Telephone: 638-3365
Mon. to Fri.
8:00 a.m. to 4:00 p.m.


CITY OF CHICAGO
Eugene Sawyer, Mayor
DEPARTMENT OF HEALTH
Lonnie C. Edwards
Commissioner

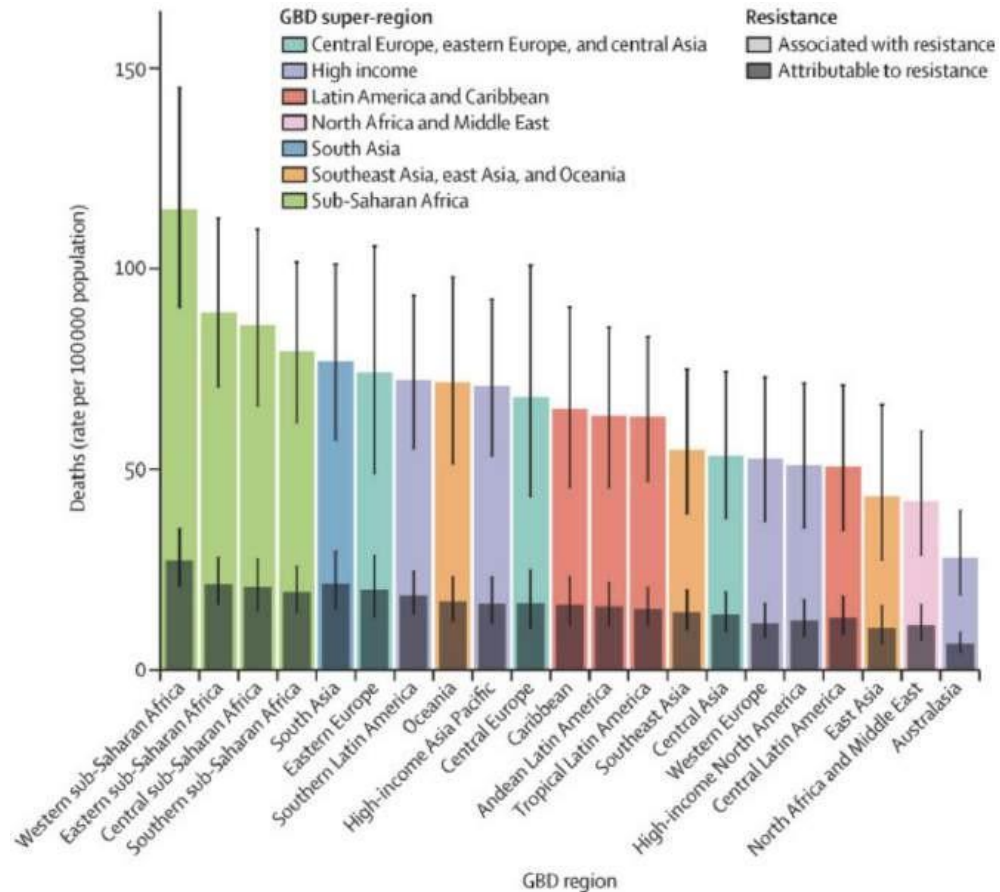
 

1. Apocalypse Now?

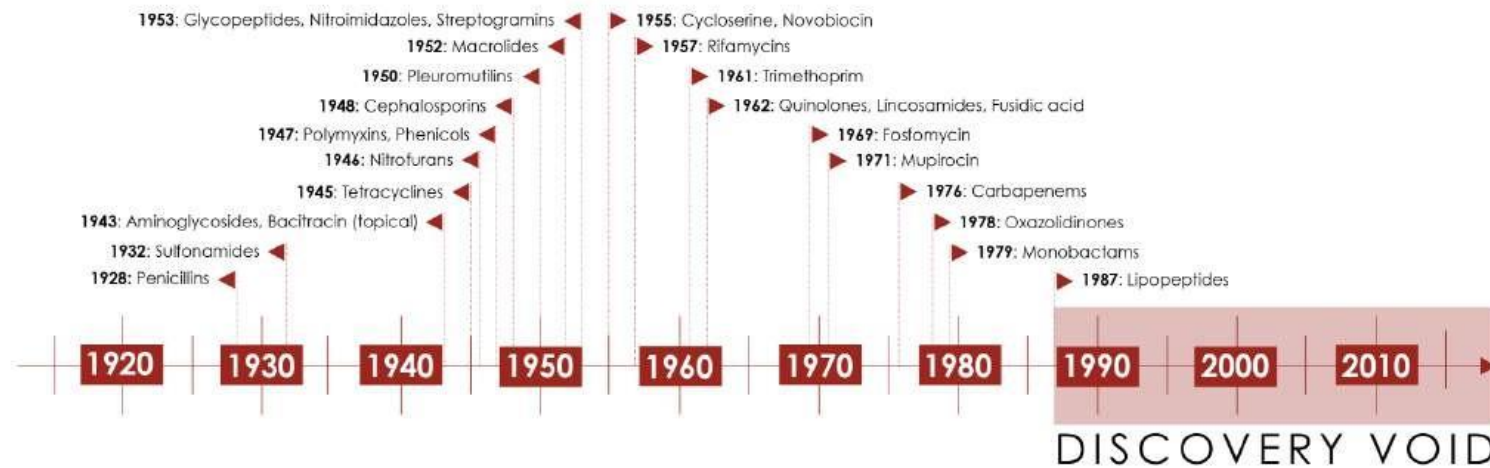
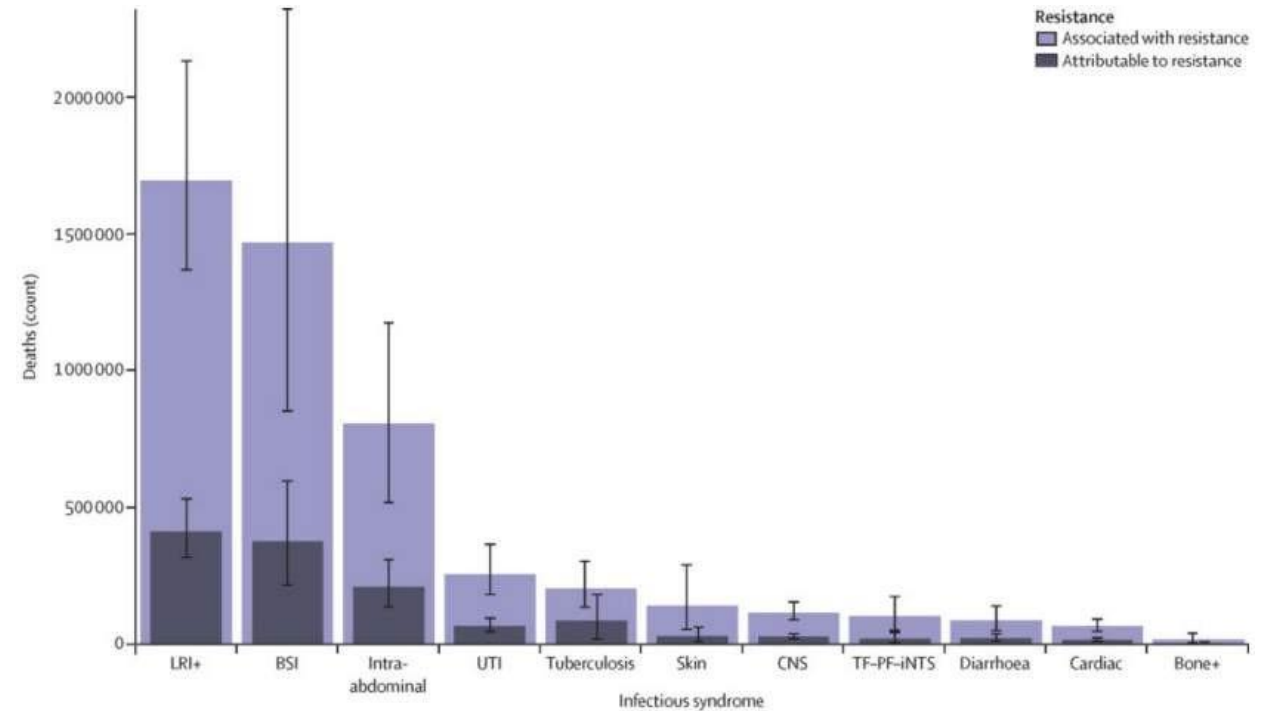


A collage of media content related to antibiotic resistance. At the top left is a photo of Professor Dame Sally C. Davies. To its right is the BBC Future website header with the title 'future' and a navigation bar. Below the BBC header is a large image of hands being washed with the headline 'All you need to know about the 'antibiotic apocalypse''. Below this is a screenshot of a MailOnline article titled 'England's chief medical officer warns of 'antibiotic apocalypse'' by Sarah Boseley, dated Thursday 18 May 2016. The article text states: 'Efficiency of antibiotics falling as deaths in EU and US hit around 50,000 annually from infections drugs can no longer treat'. Below the article is a photo of surgeons in an operating room. To the right of the MailOnline article is a Penguin Specials book cover titled 'THE DRUGS DON'T WORK: A GLOBAL THREAT' by PROFESSOR DAME SALLY C. DAVIES, featuring a penguin logo. At the bottom right is a small penguin logo on a teal background.

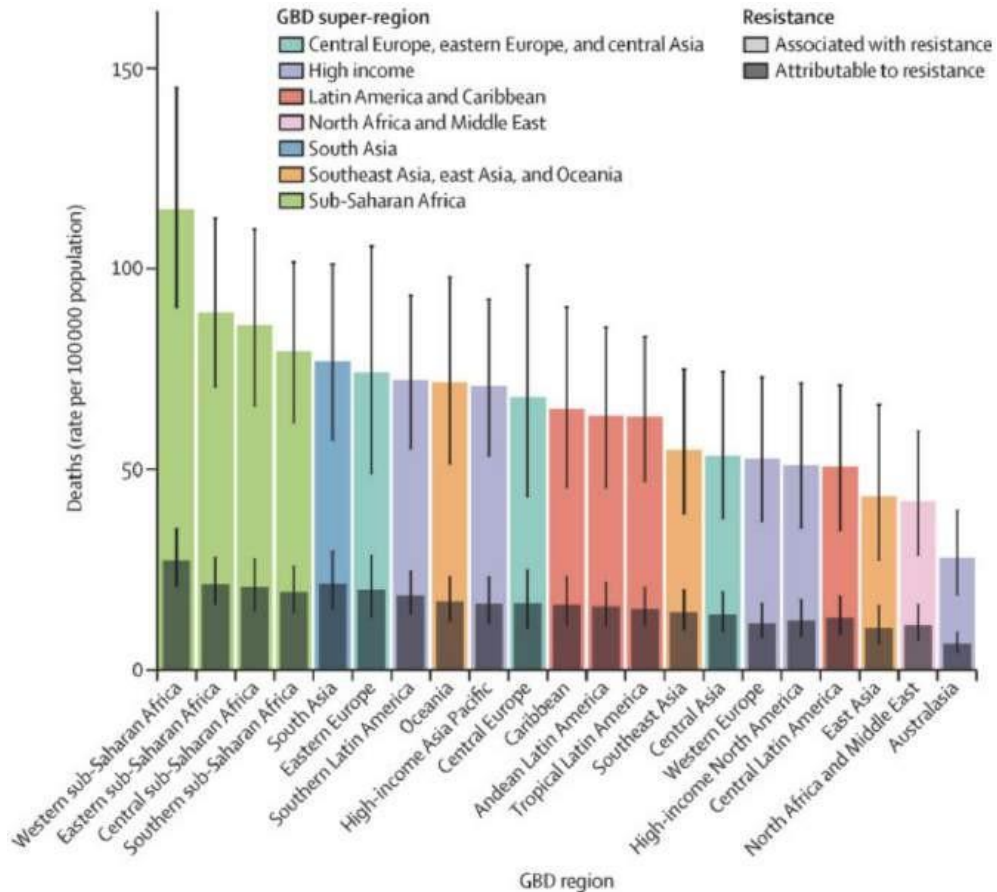
An “Antibiotic Apocalypse?”



Murray et al. *Lancet* 2022



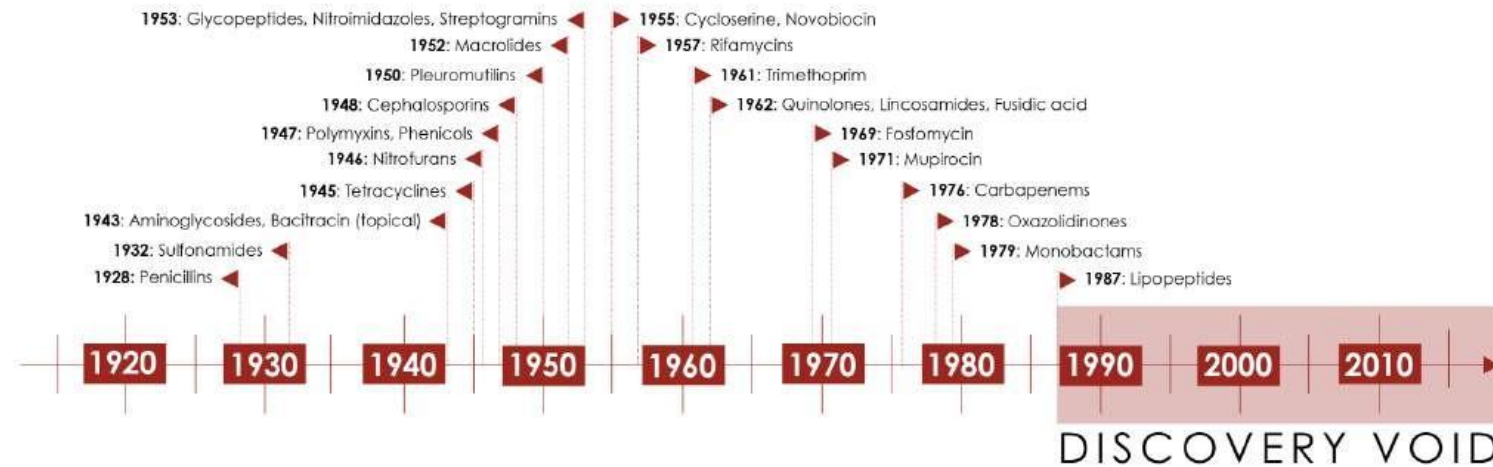
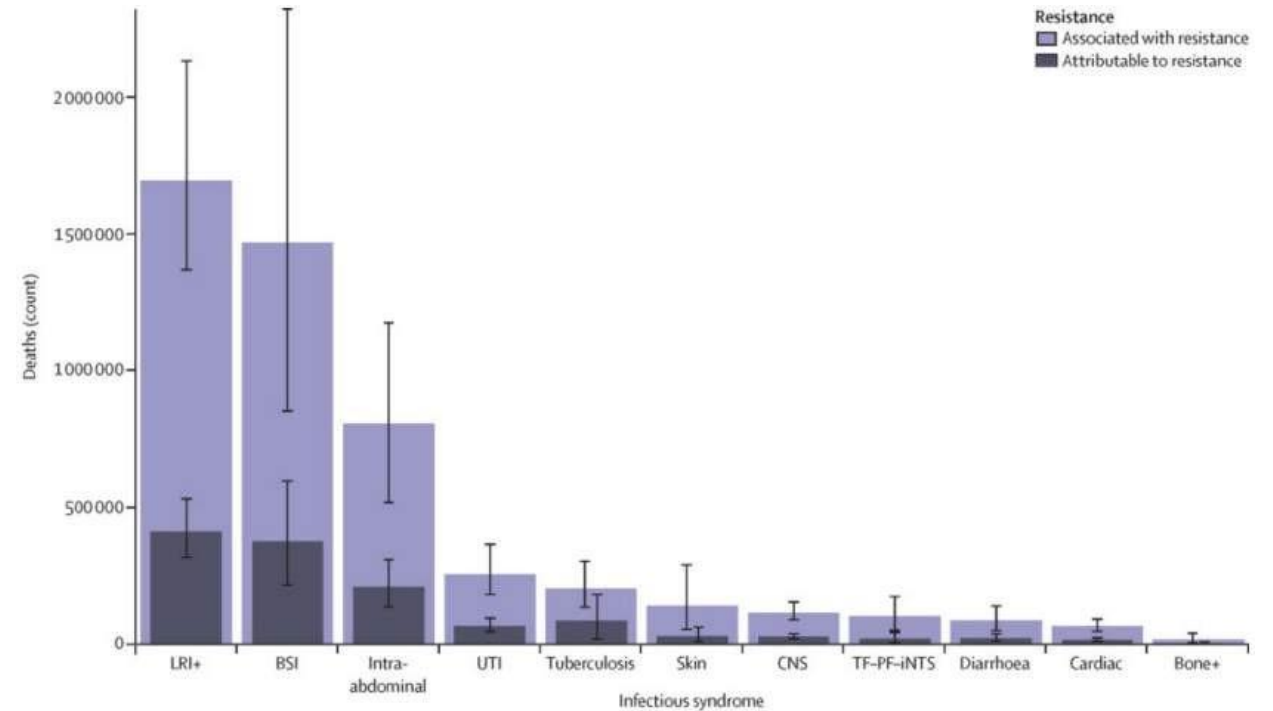
An “Antibiotic Apocalypse?”



Murray et al. *Lancet* 2022

But – no cliff edge:

- Other forms of infection control exist.
- Some drugs will continue to work.



AMR: an infrastructure challenge

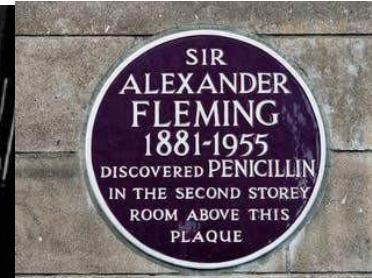
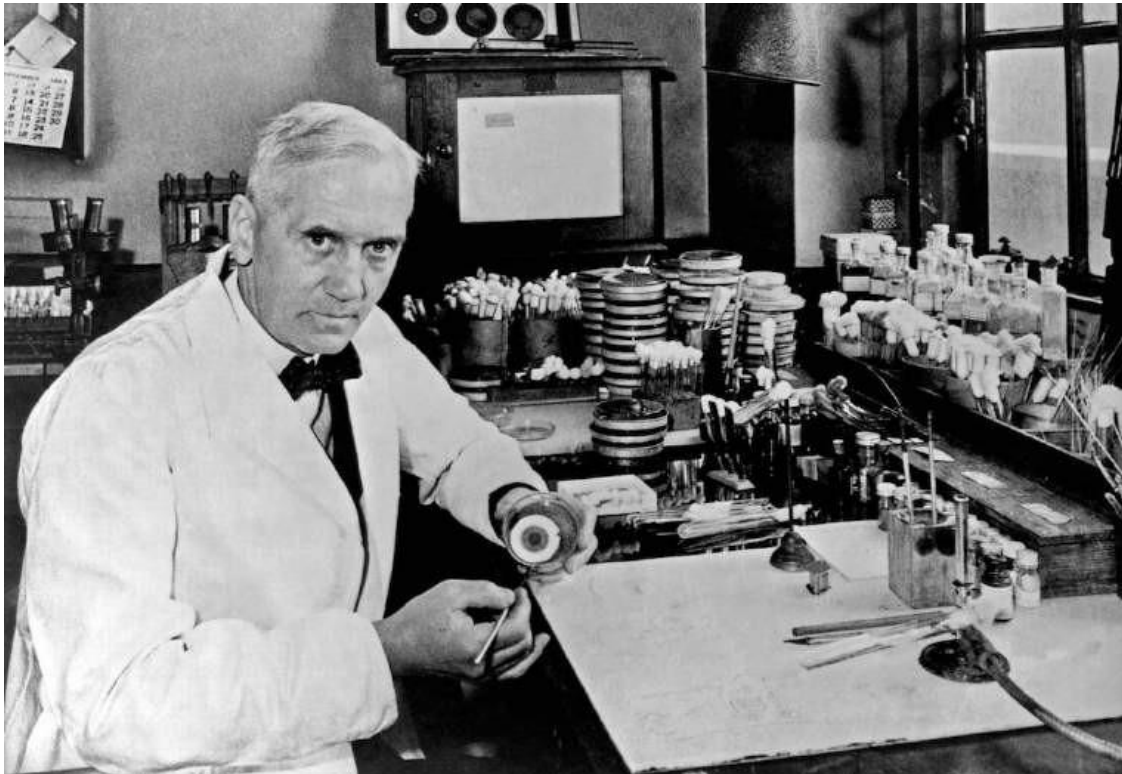


Chandler: AMR as a systems challenge for modern health- and food production infrastructures.

2. Breaking the Mould: the long history of antimicrobials



In the beginning [1928] was ... a lone genius



Exhibition by Fleming
Fleming placed on both in flask. How do. Room lamp (note window)
Equal parts of 10% mixed broth and distilled agar mixed and placed
into tubes in an agar plate. After each mixture placed into
blood agar containing haemolytic streptococci.
After 18 hours.



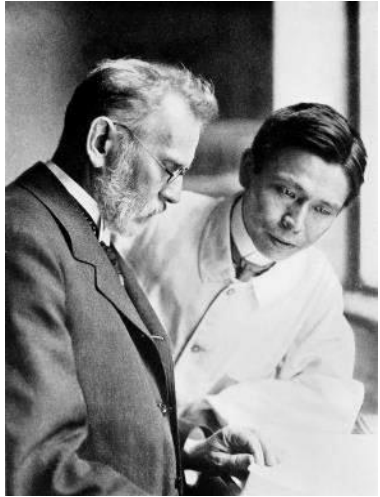
The
**Fleming
Fund**



In the beginning [1928] was ... a lone genius



Demoulding Antimicrobial History



Ehrlich & Hato
1910: Salvarsan



Domagk
1935: Prontosil



Dubos
1939: Tyrocidine
Gramicidin



Waksman
1943: Streptomycin

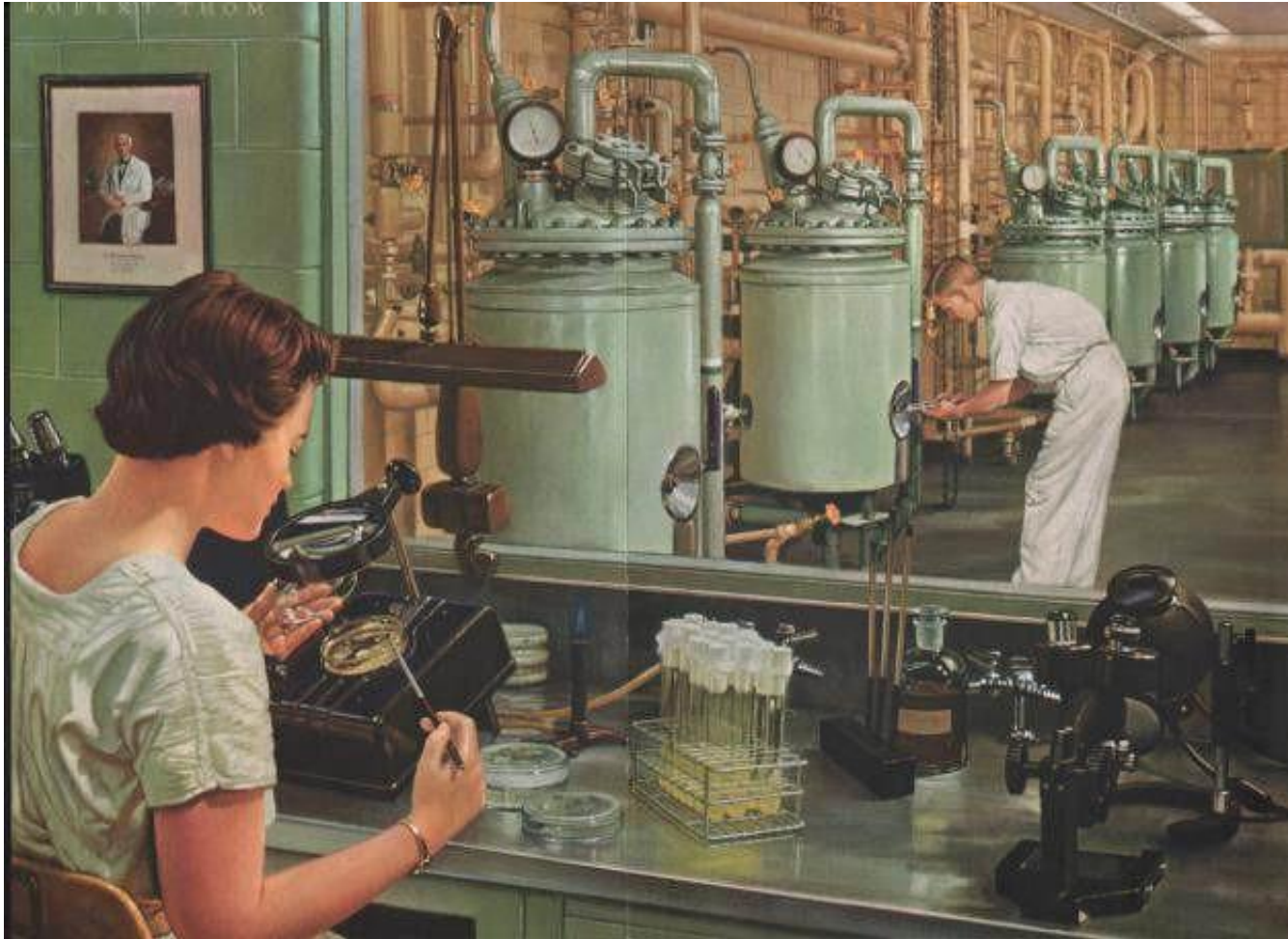


Oxford
1939/40: Penicillin

The Antimicrobial era began around 1900 and took off in the mid-1930s.

- 'Big Science/ Big Industry/ Big States'.
- Antimicrobials as 'miracles' of modern science.

An Era Of Systematised Innovation



“The Era of Antibiotics” - Robert A. Thom (ca. 1952)

1933 Sulfonamidochrysoïdine (Prontosil)

1935 Sulfanilamide

1937 Sulfapyridine (M&B 693)

1939 Gramicidin (toxic)

1941 Penicillin

1944 Streptomycin

1945 Chlortetracycline (Aureomycin)

1945 Oxytetracycline (Terramycin)

1947 Chloramphenicol

1959 Methicillin (Meticillin)

1962 Nalidixic Acid

1964 Cephalothin

New Infrastructures: Medicine

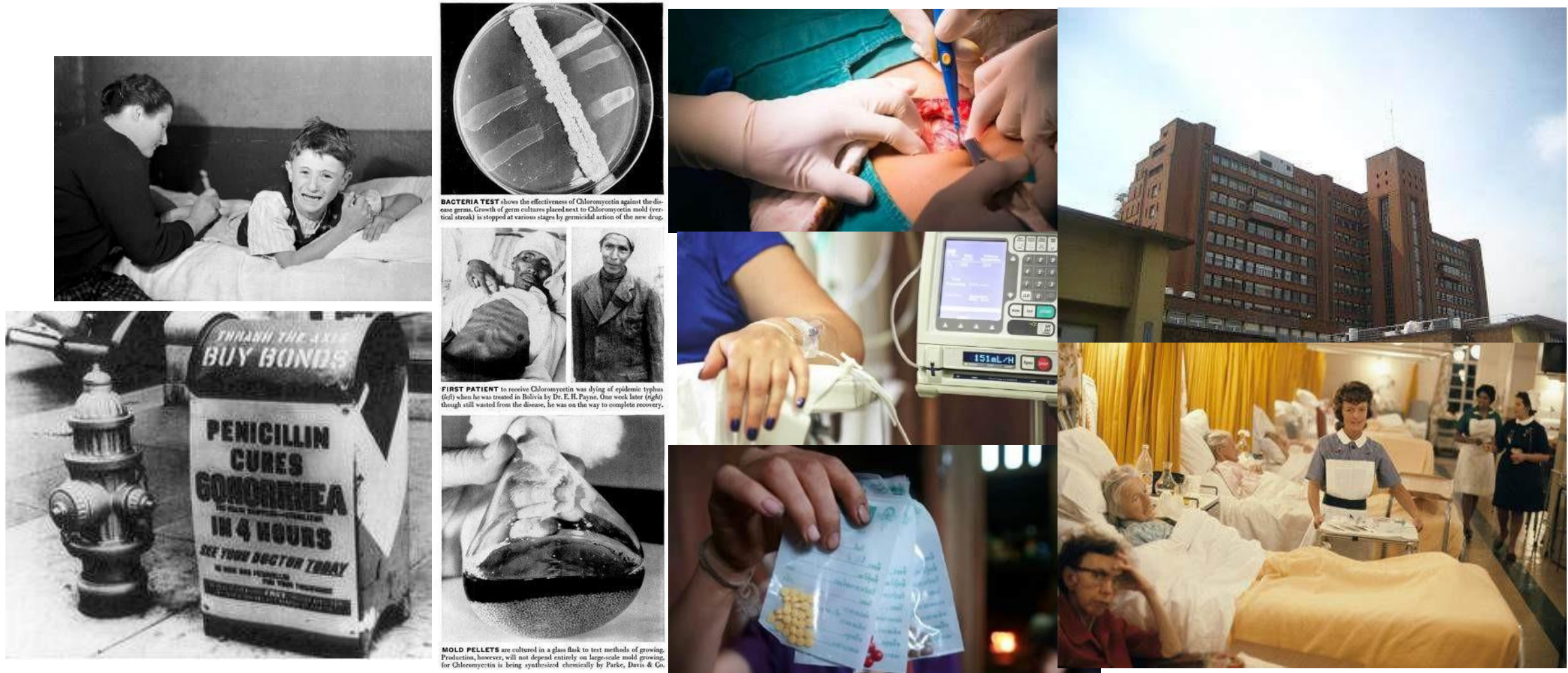


Image Source EScience Commons, PBS, Wikicommons, AMIS, Beaujon Hospital, NHS People's History

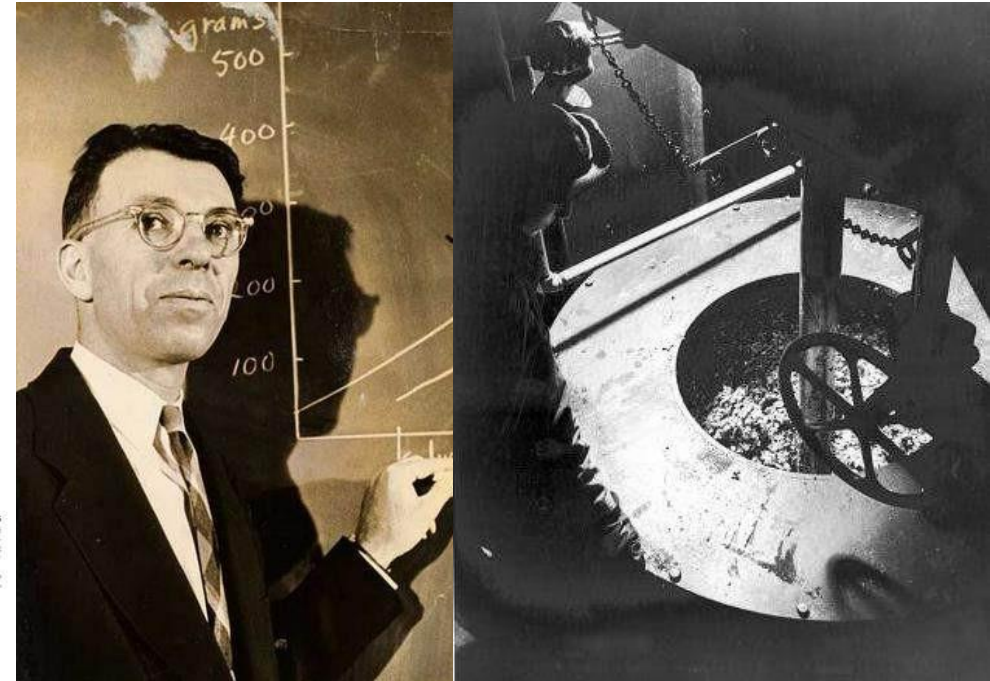
New Infrastructures: Food Production



1940
Sulfapyridine
advert

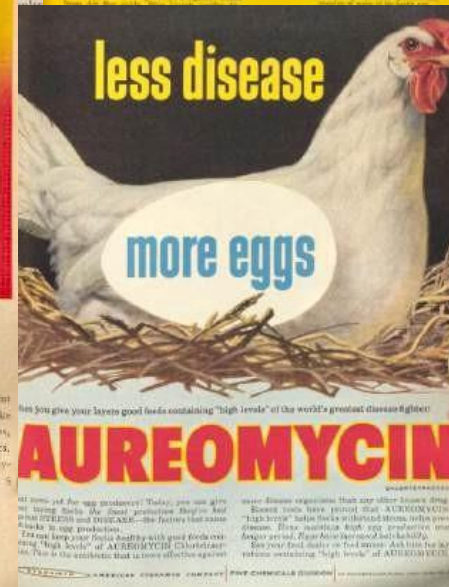
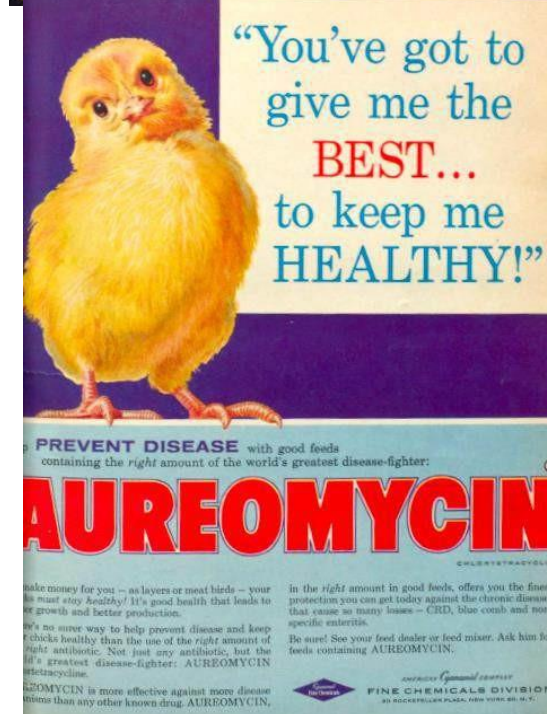


1948
Sulfaquinoxaline
Mass-treatment
and prophylaxis



1949
Non-therapeutic use:
Announcement of the
antibiotic growth effect

Non-therapeutic Use



USA

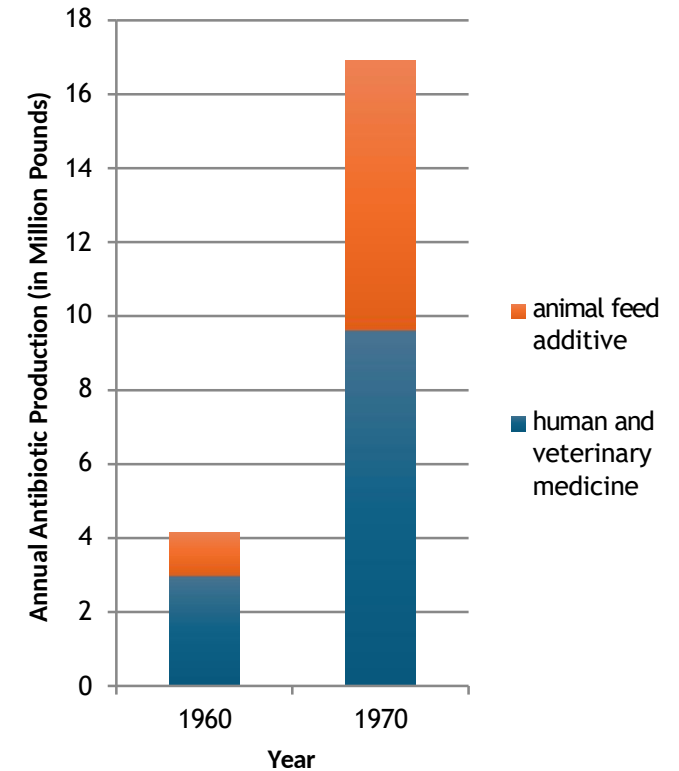


Image Source Farm Journal; Progressive Farmer; Wallaces Farmer



Inserm



New Infrastructures: Plant Production



1950s USDA Spraying



1970s Rice Blast Spraying



Streptomycin Spraying/ Citrus Injections 2000s

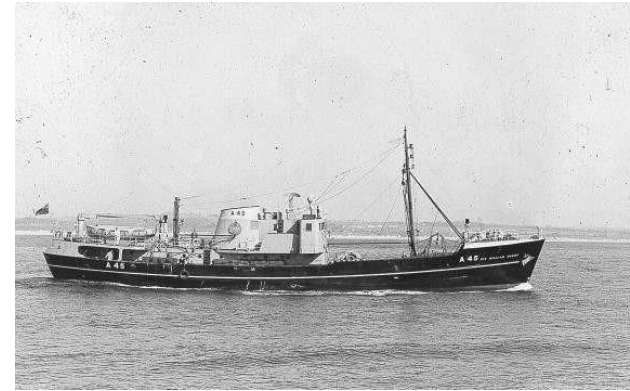


2000s Drone Spraying

New Infrastructures: Food Preservation



Poultry Preservation
(USA 1955/56)



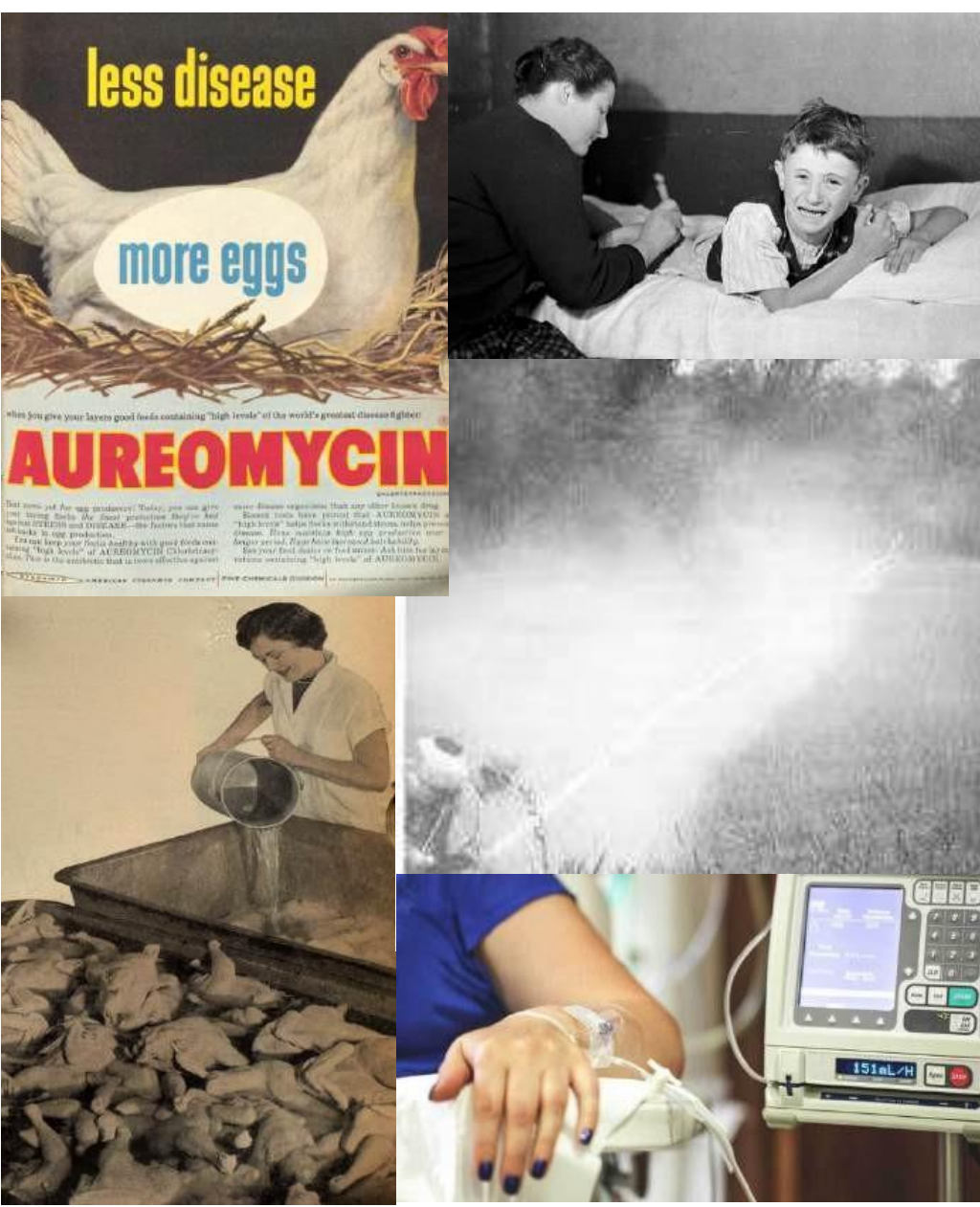
Fish Preservation (USA/UK)



Whaling (Iceland 1953)

Image Source www.aberdeenships.com; Farm Journal 1956; Arizona Republican 1956; Iceland Eyes

Infrastructures of Modernity

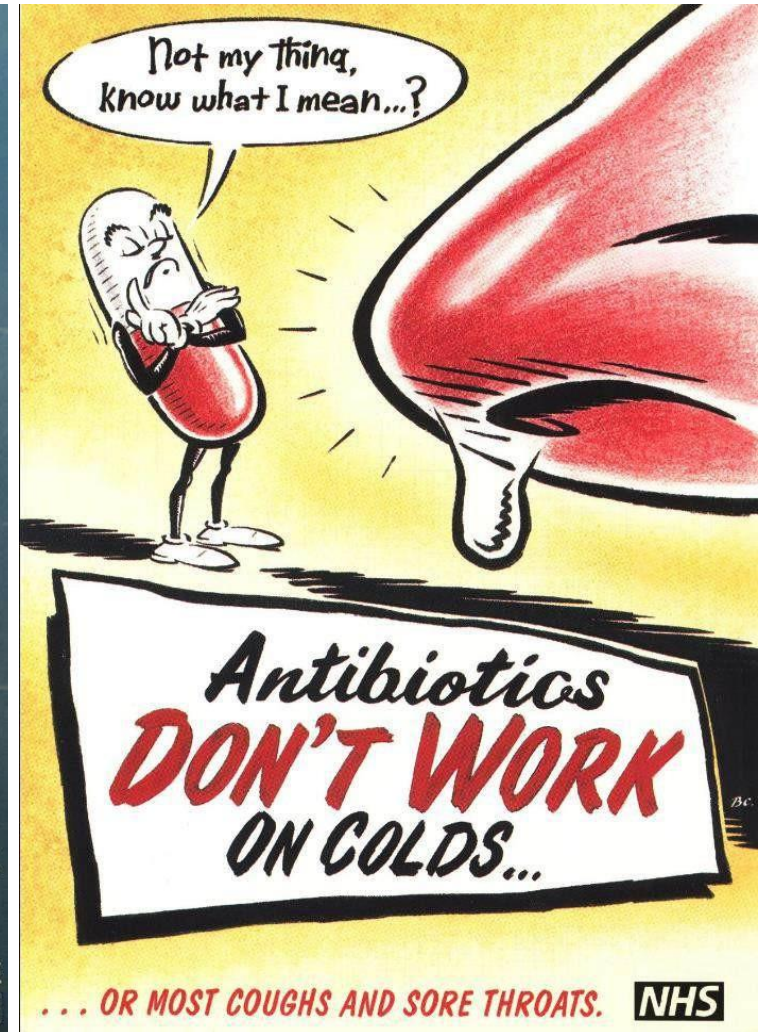


Antimicrobials Enable:

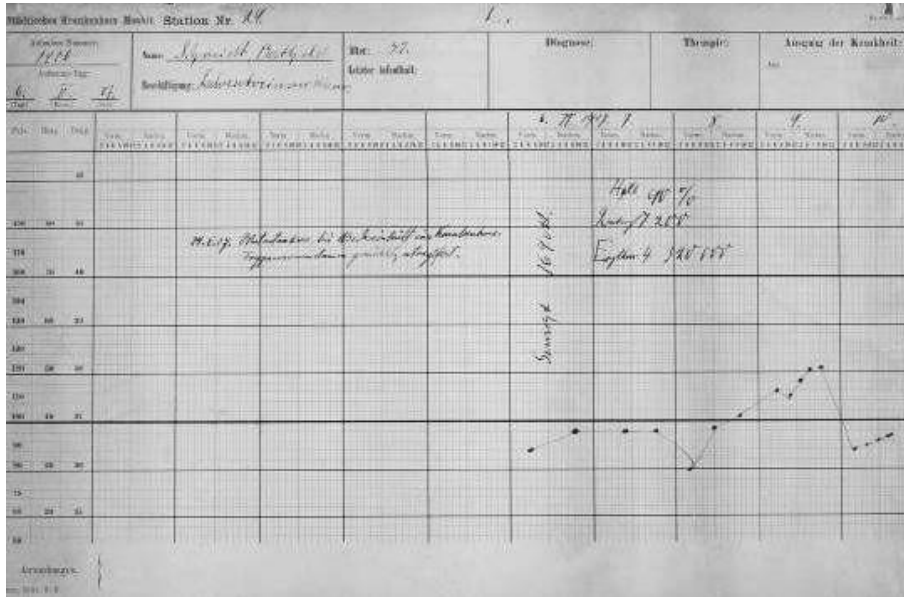
- Dramatic extension of microbial control.
 - Replacement of more expensive forms of care.
 - Efficacy gains for health- and food systems.
-
- Crucial for modernist developmentalism.
 - Win-win-win for states, industry, and the public.

Part Three:

Narrow
Scenarios -
Fixing AMR



Drug Fastness



1907 RKL patient readmission form shows trypanosome strain become resistant to atoxyl (Gradmann 2011)

Table III represents the results of experiments with salvarsan and shows how various *pallidum* strains, and *microdentium* and *refringens*, withstood the action of the drug.

TABLE III.

Salvarsan.

Maximum Doses in Which Abundant Growth Still Occurred on Successive Transplantations.

	Generation in drug media.						
	1	2	3	4	5	6	7
<i>T. pallidum</i> .	mg.	mg.	mg.	mg.	mg.	mg.	mg.
Strain McD.....	0.03	0.05	0.06	0.07	0.07	0.08	0.1
" R.....	0.02	0.03	0.04	0.04	0.05	0.1	0.12
" Z. A.....	0.02	0.04	0.04	0.05	0.08	0.12	Accident
<i>T. microdentium</i>	0.01	0.02	0.04	0.06	0.07	0.07	"
<i>S. refringens</i>	0.02	0.02	0.04	Accident.	0.04	0.04	0.05

Aeinai Akatsu and Hideyo Noguchi, Journal of Experimental Medicine, 1916

- Resistance is well known and under investigation by 1945.

Well-established Concerns

SLEEPING SICKNESS IN THE IKOMA
DISTRICT OF TANGANYIKA TERRITORY;
NOTES ON SOME CASES TREATED BY
PROFESSOR F. K. KLEINE

BY
J. F. CORSON

(Received for publication 3 September, 1928)

INTRODUCTION

THE INHIBITION OF THE BACTERIOSTATIC ACTION OF
SULFONAMIDE DRUGS BY SUBSTANCES OF
ANIMAL AND BACTERIAL ORIGIN*

By COLIN M. MacLEOD, M.D.

(From the Hospital of The Rockefeller Institute for Medical Research)

(Received for publication, June 19, 1940)

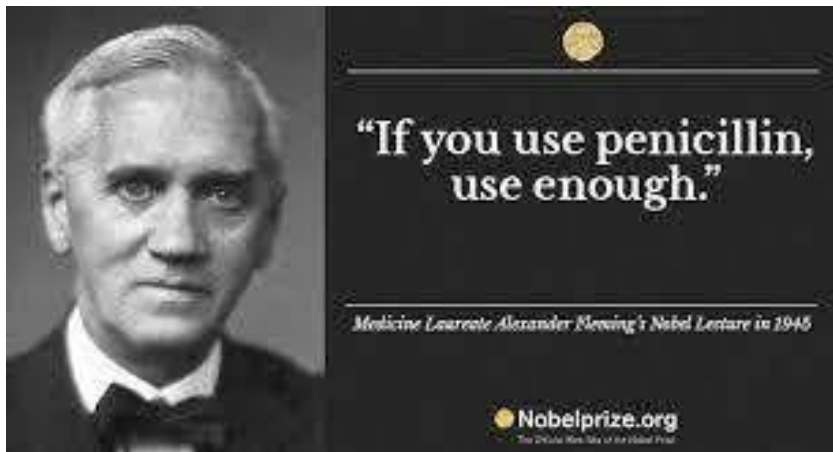
Stewardship from the 1920s onwards:

1920s: concerns about drug-fast trypanosomiasis during colonial/ international sleeping sickness campaigns

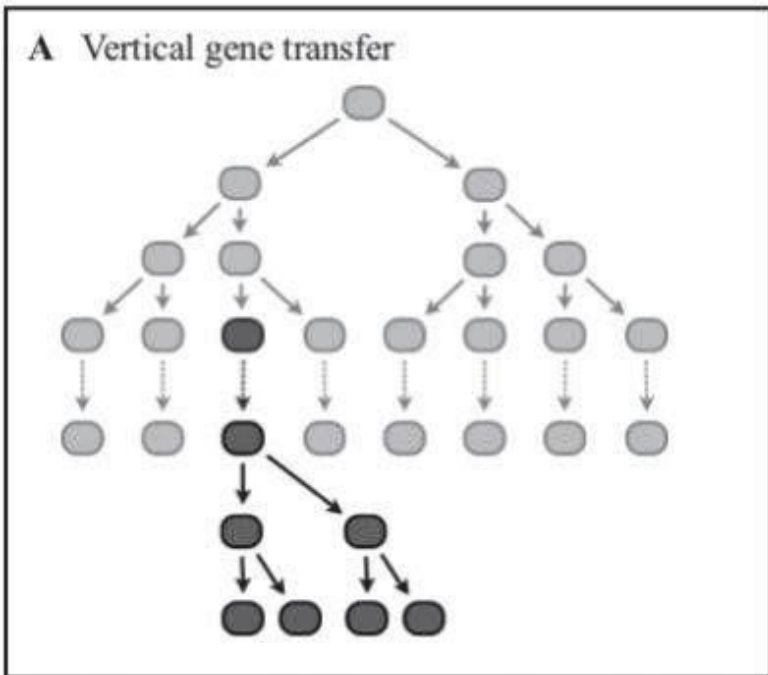
1935-1940: AMR emergence observed against sulfonamide drugs.

1940/1942: first reports penicillin resistance.

1945: There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory (...). **Moral: If you use penicillin, use enough.**



Why was AMR not taken more seriously?

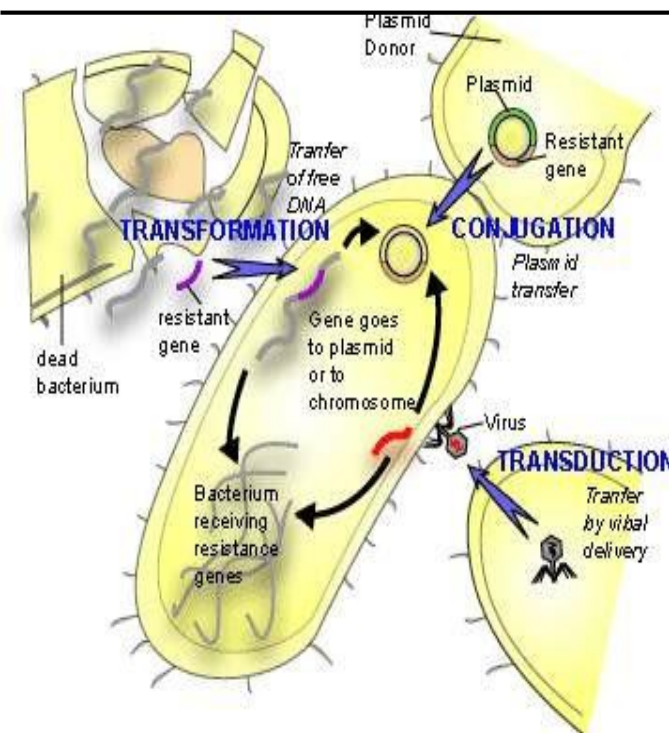


Factors:

1. Confidence in industry's ability to keep ahead of AMR
2. "Vertical" localized scenarios of resistance proliferation
 - Containing organisms rather than resistance as a genetic characteristic.

Result: More and more areas of health systems and food production become antibiotic dependent.

Partial Awareness



Discovery of horizontal gene transfer (HGT) and R-factors around 1960.

1965:

‘Genes have an epidemiology of their own’ (E.S. Anderson)

1966:

NEJM warns of return to ‘preantibiotic Middle Ages’

NYT describes AMR as ‘threat to spaceship earth’.

From mid-1960s:

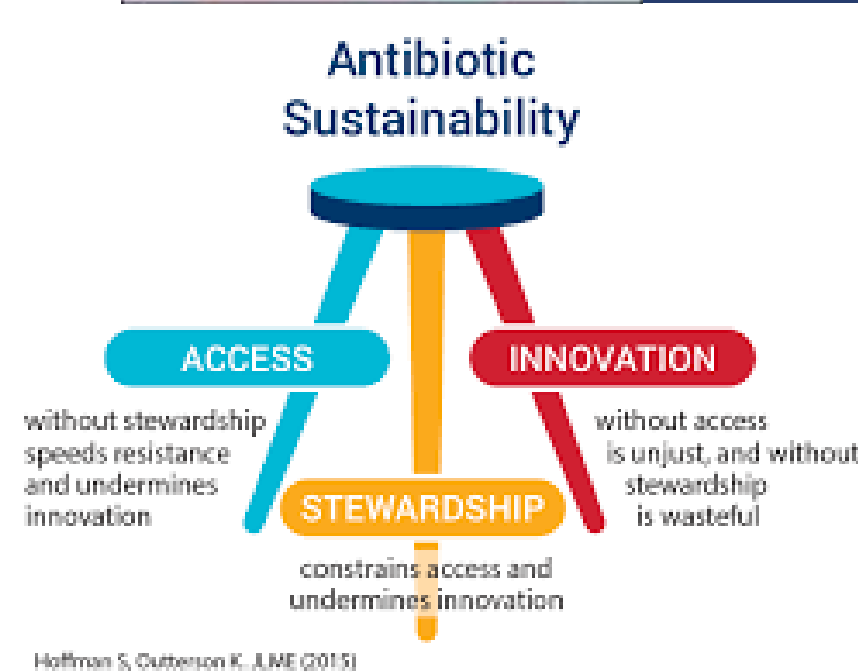
➤ **Regulatory focus on protecting status quo – keeping infrastructures working.**



Firefighting

1. Public Behaviour ('Pushy Patients'/ Farmers)
2. Practitioner Education ('Rational Drug Use')
3. Antibiotic Restriction (AGP bans/ temporary bans)
4. Infection Control (Biosecurity/ hygiene practices)
5. Improved AMR Surveillance
6. Antibiotic Innovation

➤ **Structural drivers of antimicrobial usage remain unaddressed.**

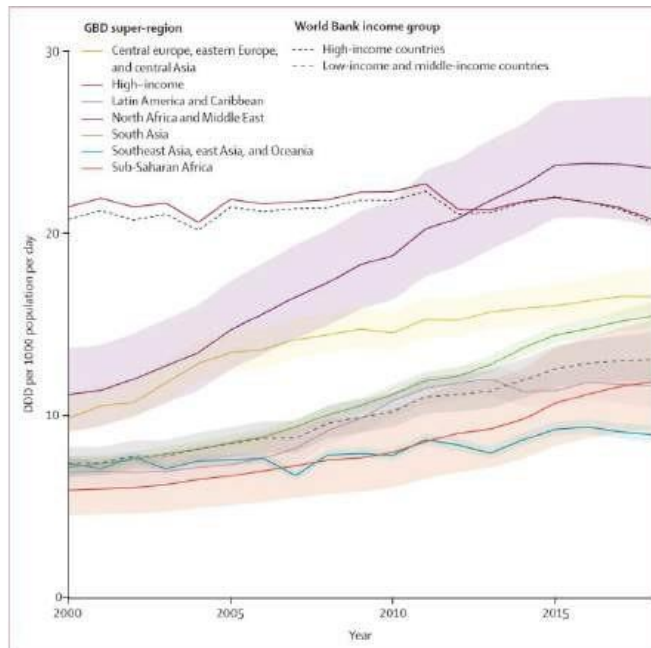


Hoffman S, Outterson K. JME (2015)



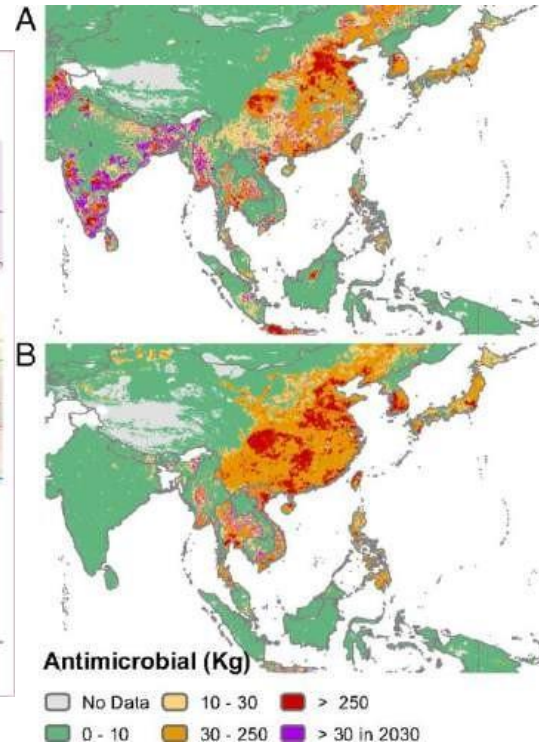
Mission (Yet To Be) Accomplished

AMR (RISING)



Browne et al., *Lancet* 2021.

AMU (RISING)



Van Boeckel, PNAS, 2015

Stewardship (INSUFFICIENT)

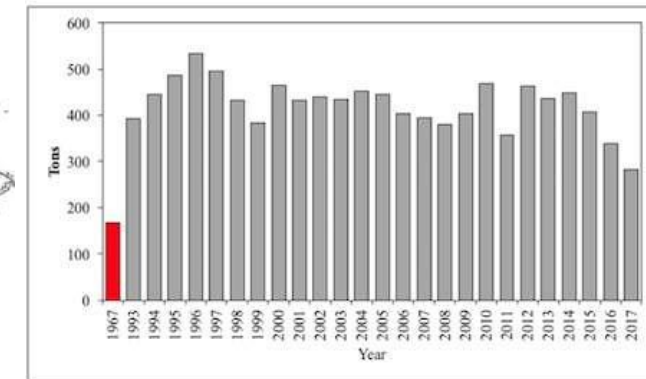


Figure 20: Total Annual Sale of Active Antibiotic Ingredients In The UK
Source: 'Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine' (London: HMSO, 1969). 'UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2017)' (New Haw: VMD, 2018).

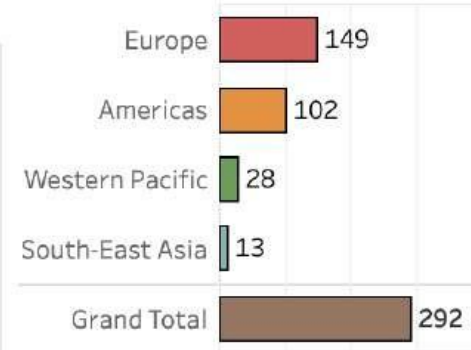
Kirchhelle, 2020

Innovation (STALLED)

Company	Location of headquarters	Current status as of April 2024	Date of first FDA antibiotic approval	FDA-approved product	Accumulated deficit as of first FDA antibiotic approval	Market cap (calculated on April 8, 2024) or acquisition price
Achaogen	USA	Bankrupt on 4/15/2019; has ceased operations	6/25/2018	Plazomicin (Zemdri)	\$420,067,000	n/a
Entasis	USA	Now Innoviva	5/23/2023	Sulbactam/durlobactam (Xacduro)	\$170,046,000	\$113,000,000
Melinta	USA	Bankrupt on 12/27/2019; now a part of Deerfield	6/19/2017	Delafloxacin (Baxdela)	\$459,871,000	n/a
Nabriva	Austria	Ceased operations from 1/6/2023	8/19/2019	Lefamulin (Xenleta)	\$393,978,000	\$n/a
Paratek	USA	Now a part of Novo Holdings	10/2/2018	Omadacycline (Nuzyra)	\$559,677,000	\$462,000,000
Seres	USA	Active, but announced 41% reduction in force on Nov. 2, 2023	4/26/2023	Fecal microbiota spores, live-BRPK (Vowst)	\$935,685,000	\$110,871,000
Tetraphase	USA	Now La Jolla	8/27/2018	Eravacycline (Xerava)	\$493,002,000	\$43,000,000
				Totals	\$3,432,326,000	\$728,871,000
					Net Loss to Date	\$2,703,455,000

McEnany and Outterson, 2024

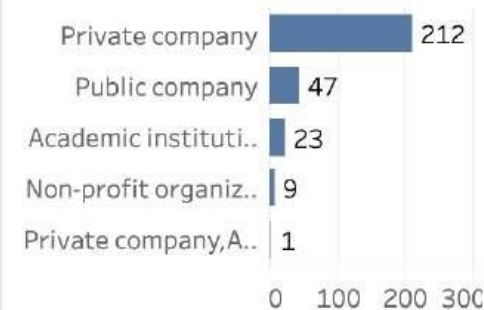
A.1. No. by WHO region



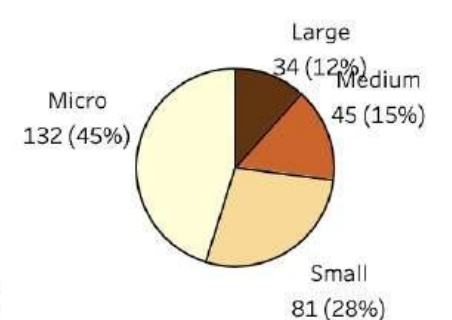
A.2. No. by income group



A.3 No. by type of developer institution



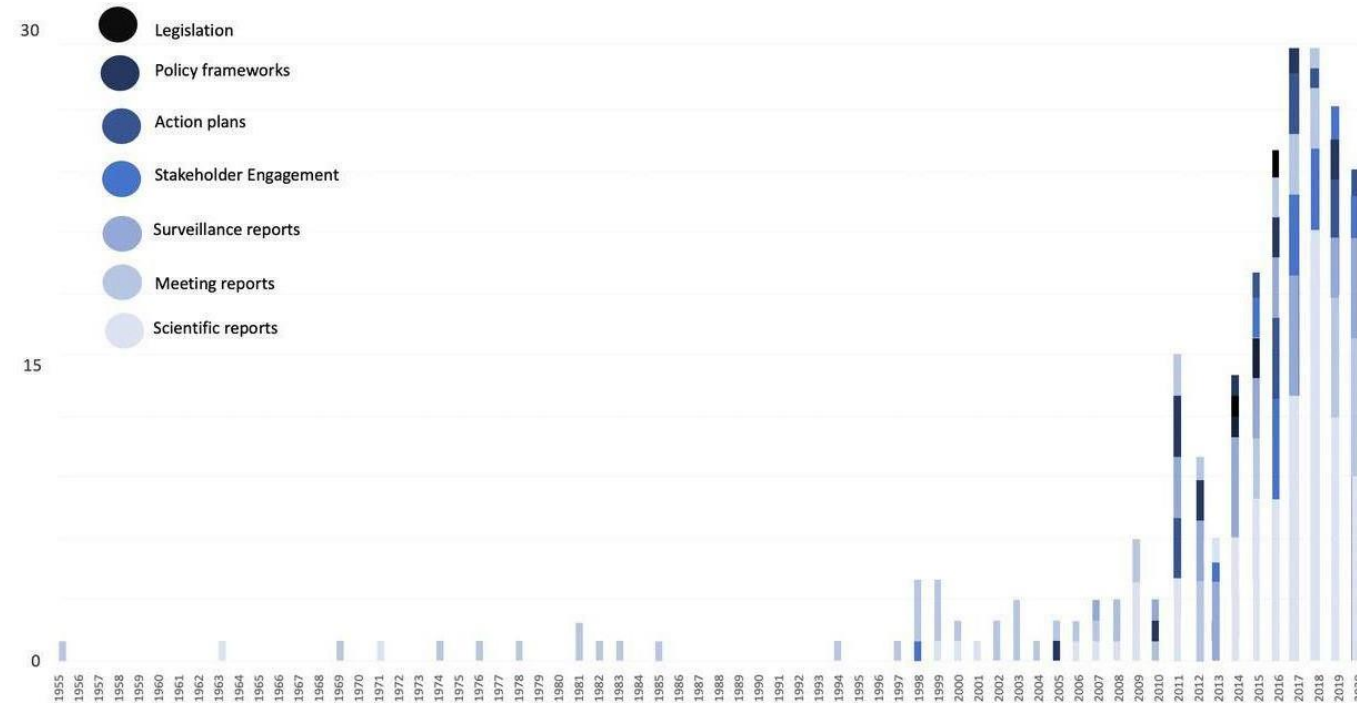
A.4 No. by size of developer institution



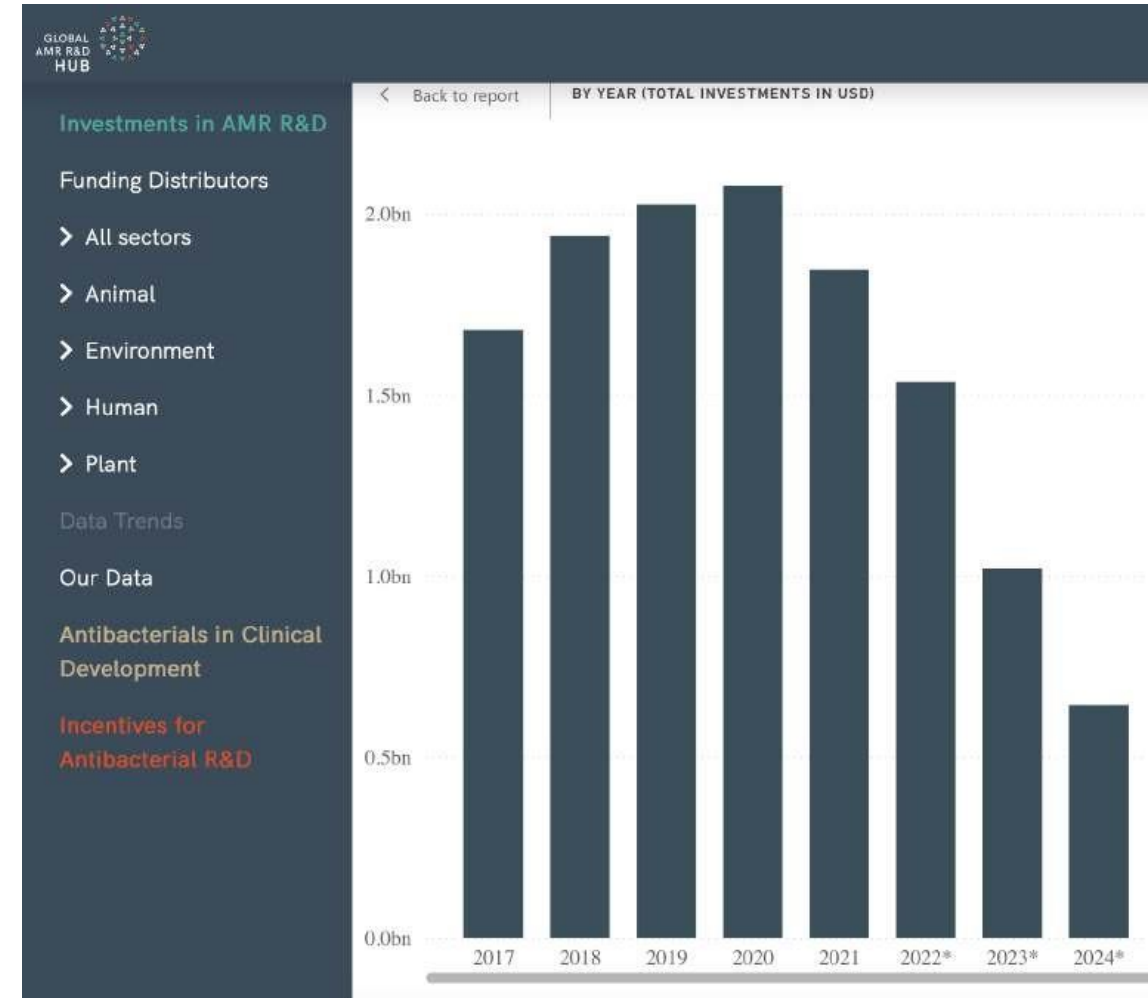
WHO Pipeline Review, 2022

- Since 2010, every SME with market approval has suffered bankruptcy or unfavourable exit.
- Public-Private 'Pipeline' targets Global North.

Post-peak AMR?



International AMR reports published per year
Overton et al. 2021



Global AMR R&D Hub Total Investment, 2024

➤ Attention for and investment in AMR are sinking.

UN General Assembly: 26.09.2024

➤ Harder, Better, Stronger, Faster?



Reduce AMR deaths by 10% by 2030 against 2019 baseline of 4.95 million deaths.

Reaffirmed focus on stewardship, IPC/WASH, Access, and Innovation.

Clinic/ farms at the centre of “One Health” action.

UN General Assembly: 26.09.2024

➤ Harder, Better, Stronger, Faster?



Reduce AMR deaths by 10% by 2030 against 2019 baseline of 4.95 million deaths.

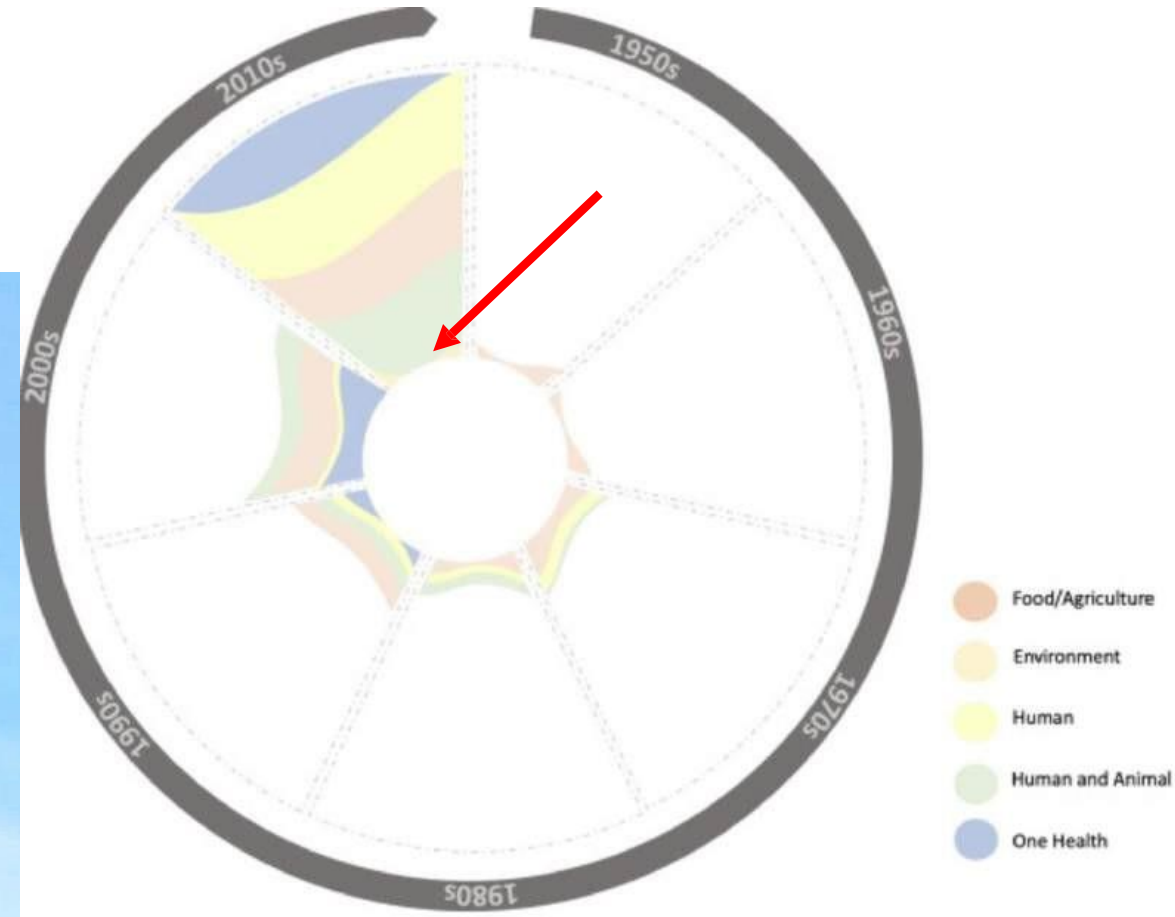
Reaffirmed focus on stewardship, IPC/WASH, Access, and Innovation.

Clinic/ farms at the centre of “One Health” action.

➤ Or are we missing something?

UN General Assembly

Overton et al. 2021



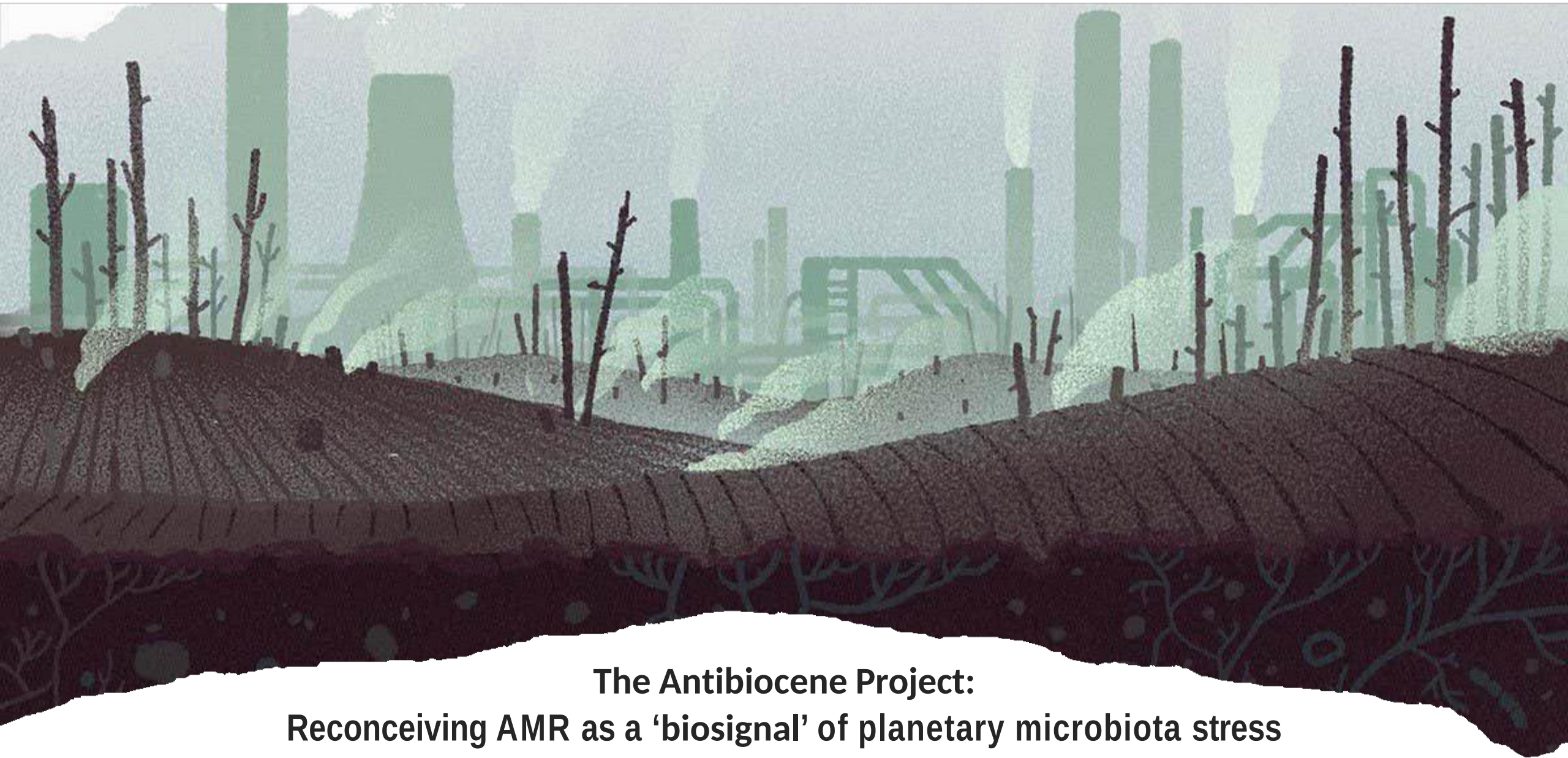
- “Environment” gets 3 of 106 paragraphs, **microbes not mentioned!**
- 2 of 248 international policy documents on AMR since 1945 exclusively target the environment’s role in AMR selection.

Shifting the perspective

What happens if we reframe AMR not as a clinical threat but as an environmental phenomenon?



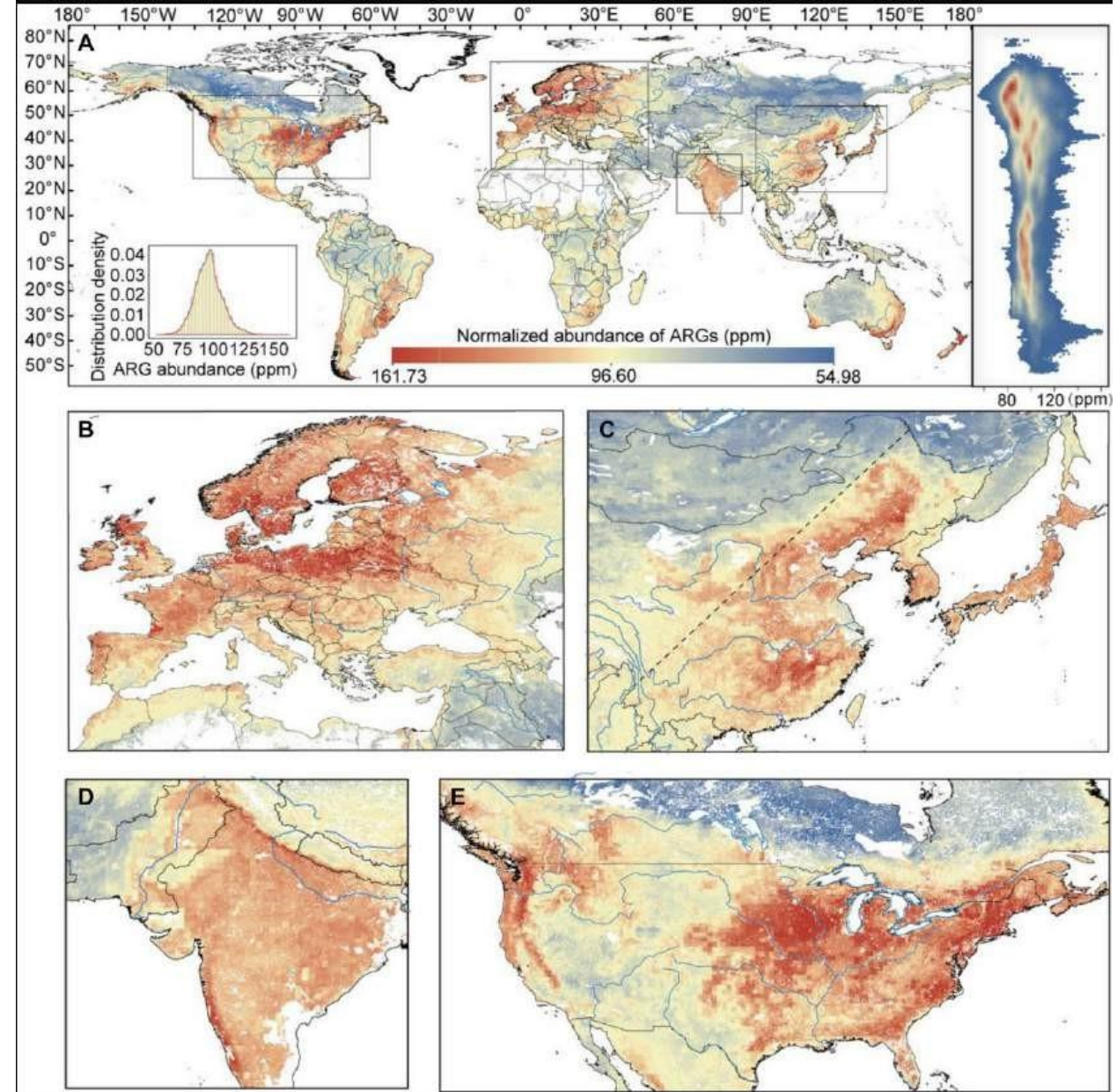
Where there is smoke....



**The Antibiocene Project:
Reconceiving AMR as a 'biosignal' of planetary microbiota stress**

The Antibiocene:

A permanent genetic shift of the global microbial biosphere caused by accelerating pharmaceutical and non-pharmaceutical selection...



Prevalence of Antimicrobial Resistance Genes (ARGs) in Soils

Zheng et al. Science Advances 2022



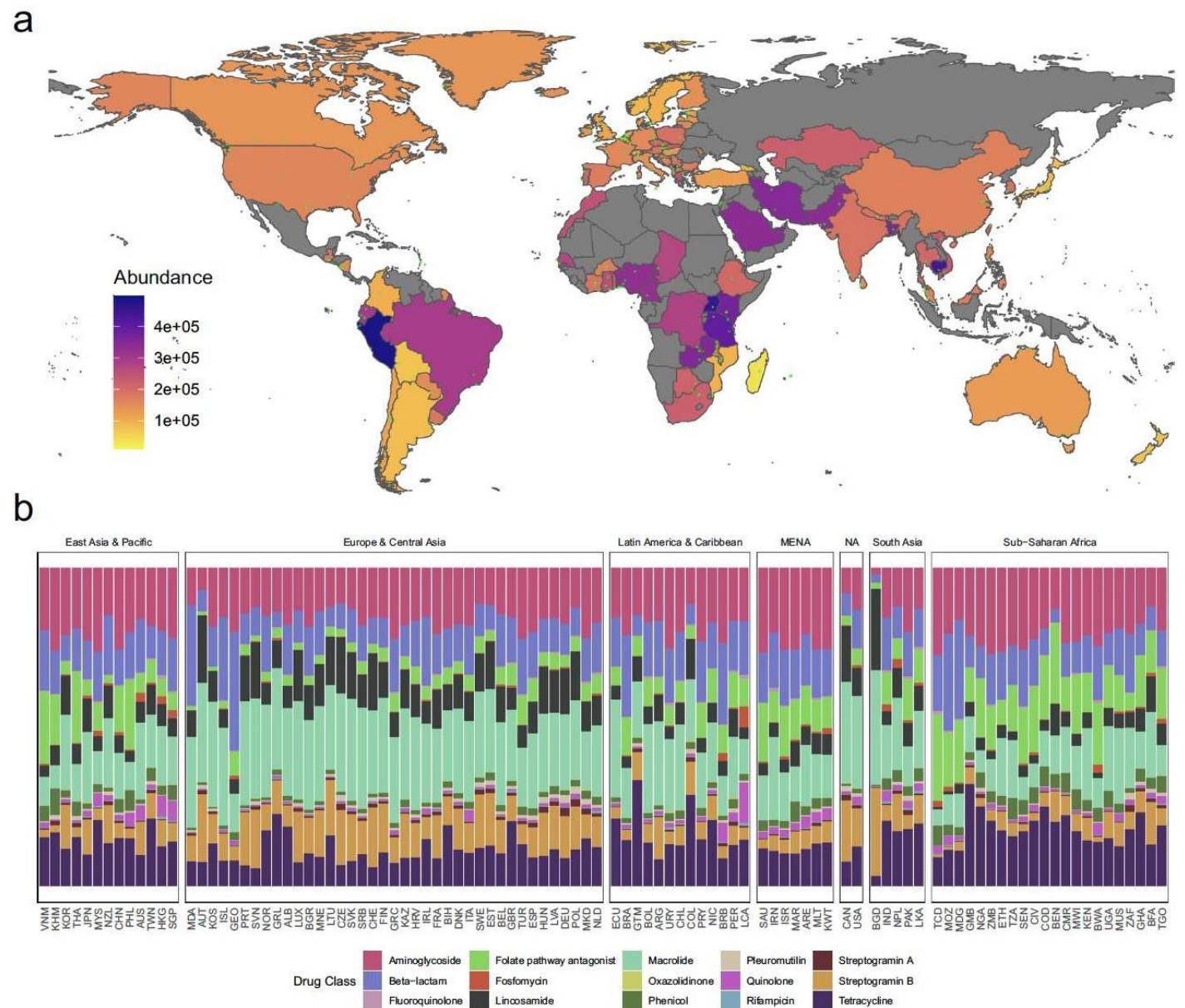
Inserm



The Antibiocene

...with distinct biogeographies and overlaps with other forms of anthropogenic stressors (e.g. climate change, biodiversity loss, etc.)...

Kirchhelle, Nature Hums, 2023



Prevalence of ARGs in Sewage Samples with distinct biogeographies:

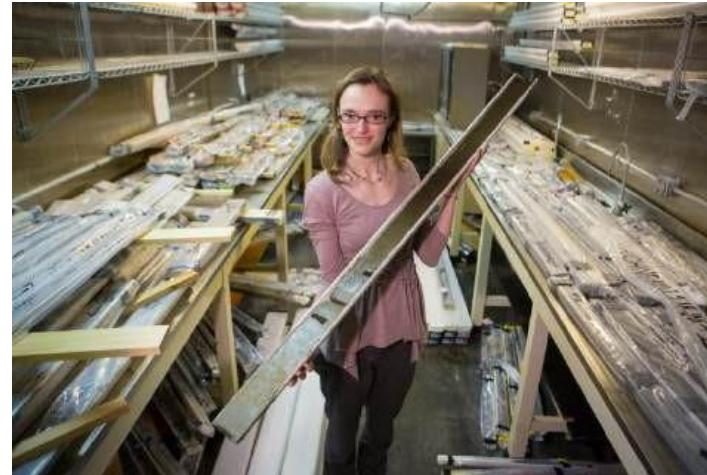
Munk et al. Nature Communications 2022

The Antibiocene

... and measurable spatiotemporal 'golden spikes' of ARGs associated with extreme exposure.



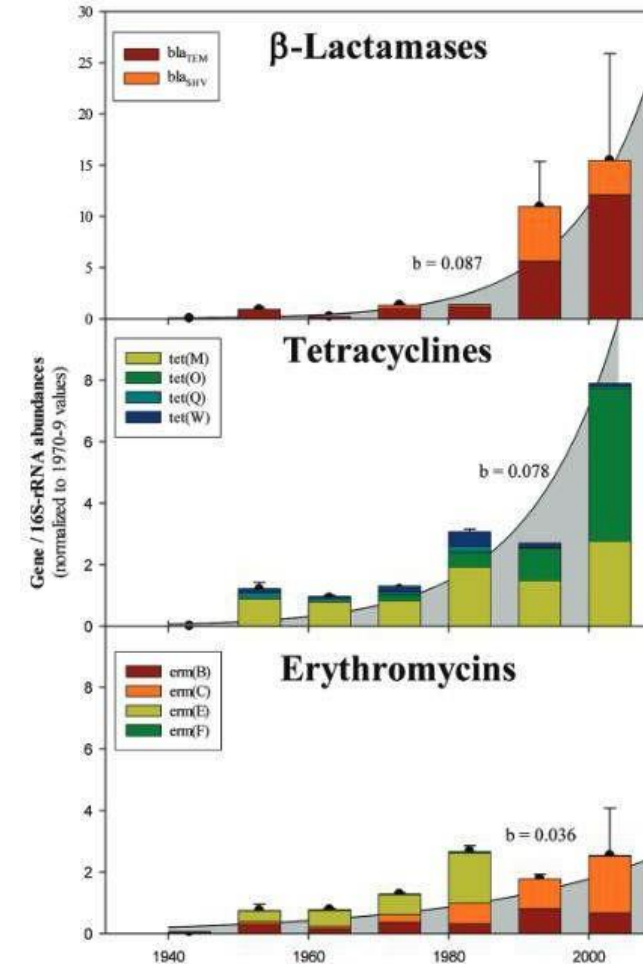
USDA Soil Archive



University of Buffalo Lake Sediments



Musi River, Hyderabad



Knapp et al. 2010

Scales of a Shift:

Studying the microbe as a socio-ecological event.
(Hannah Landecker, 2016/2024)

- AMR as a multiscalar signal of shifting human-microbial relations.

Species Level

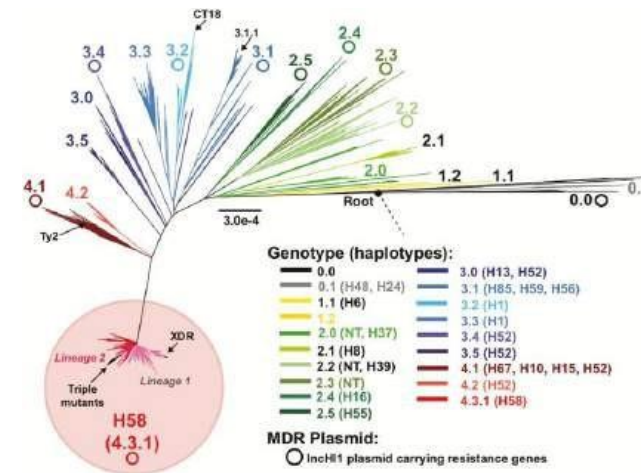
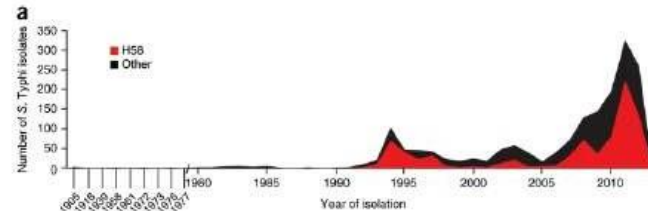
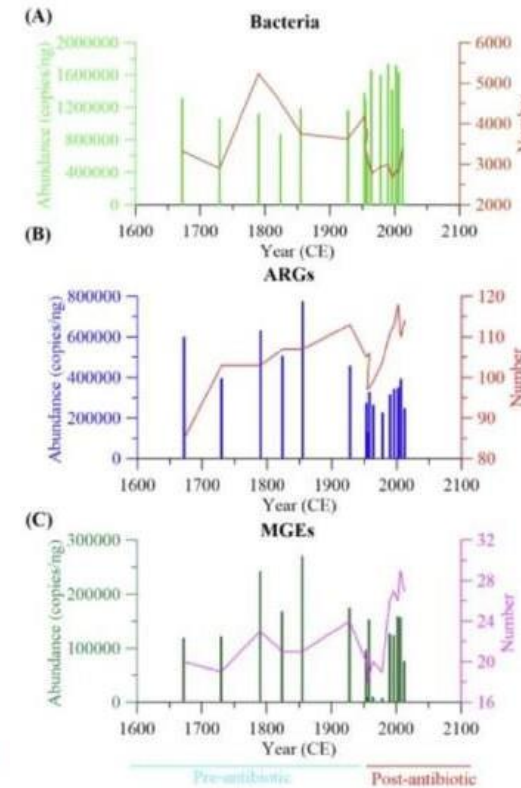


Figure 1: Population structure of the 1,832 *S. Typhi* isolates analyzed in this study.



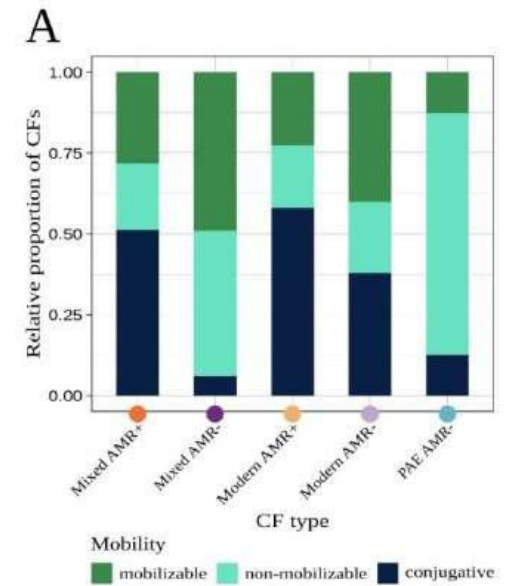
Kirchhelle et al. CID 2019
Wong et al. Nature 2015

Genetic Level



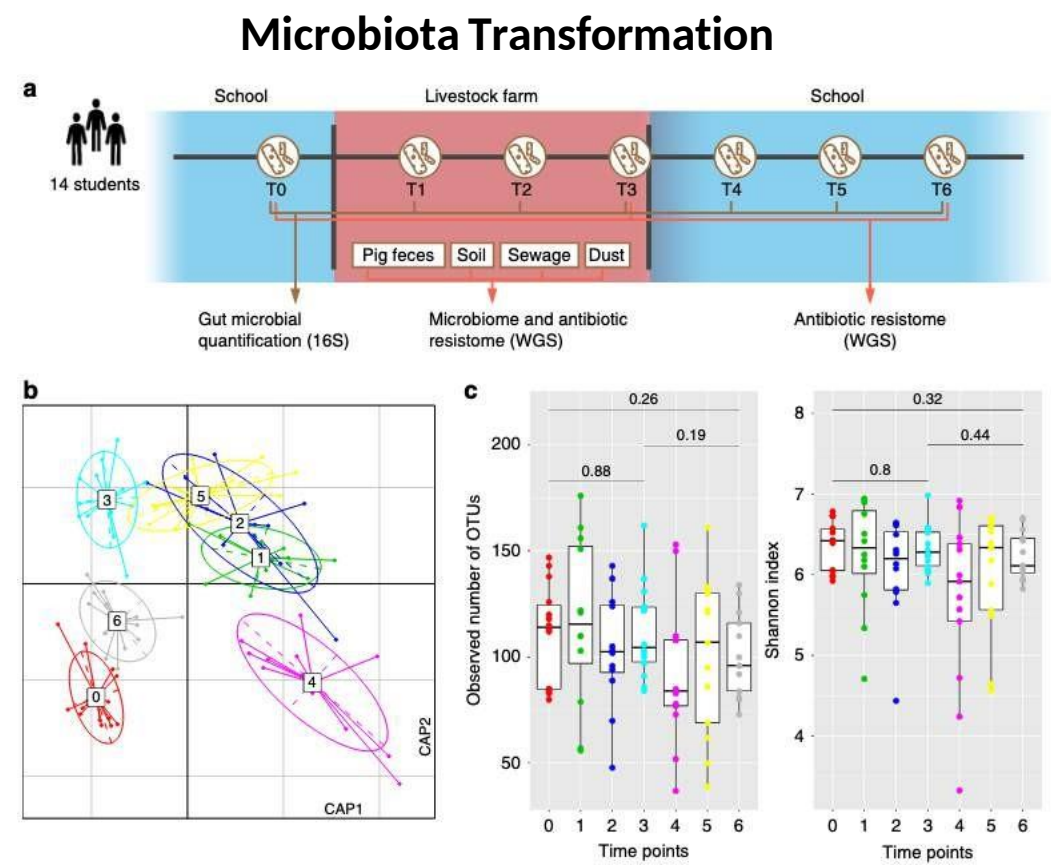
Yan et al.
Environment
International 2024

Mobilome



Cazares et al. 2024
(under review)

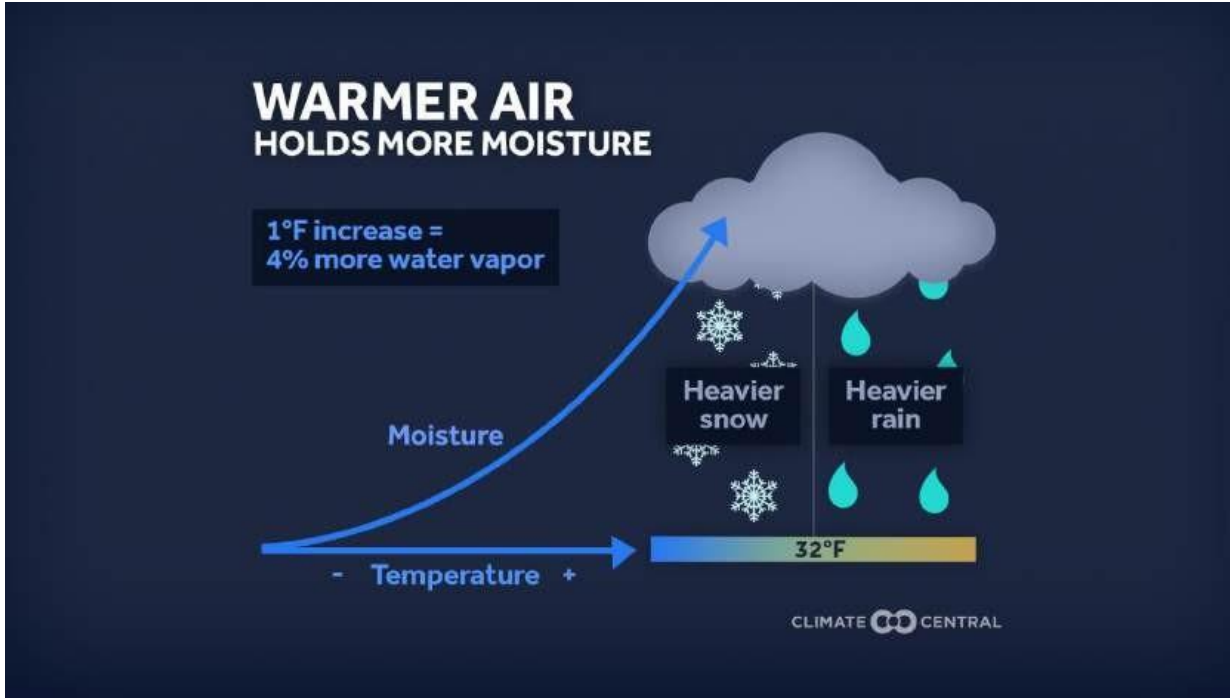
Scales of a Shift:



Change in the human gut microbiota following environmental conversion

Sun et al. Nature Comms 2020

Pressure & Flare Ups



- Therapy failures as 'flare ups' resulting from rising environmental AMR.
- AMR as a microbial signal of the triple planetary crisis (climate change, pollution, diversity loss)

Conclusion: Towards Microbial Health

Antimicrobial infrastructures have and will continue to underpin modern health and food production systems.

➤ Protecting drug efficacy remains important.

Reconceptualizing AMR as an environmental planetary health challenge enables new governance approaches:

Structural: From individual to societal responsibility for antimicrobial pollution.

Ecological: Microbial rather than antimicrobial stewardship.

Social Justice: Antimicrobial exposures reflect and exacerbate social inequalities.

Legal: Antimicrobial pollution as a violation of the human right to a healthy (microbial) environment.

➤ **January 2025 submission to UN Committee on Economic, Social, and Cultural Rights.**



Thank You!

THE LANCET
Microbe

This journal Journals Publish Clinical Global health Multimedia Events About

COMMENT · Volume 3, Issue 11, E806-E807, November 2022 · [Open Access](#)

[Download Full Issue](#)

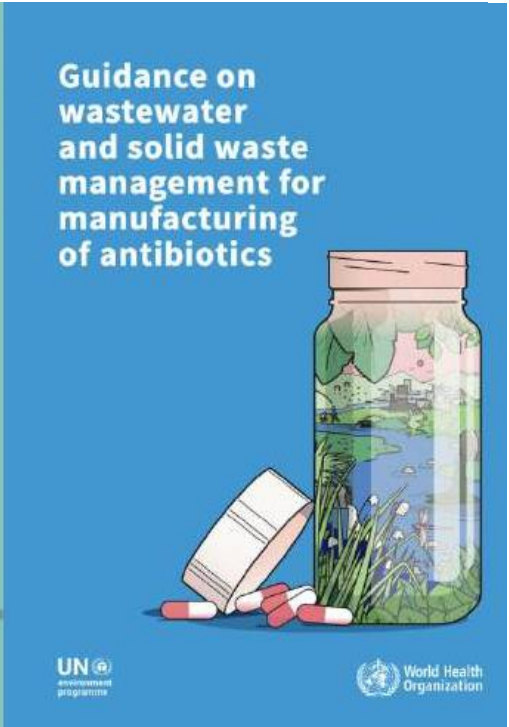
Embracing the monsters: moving from infection control to microbial management

[Claas Kirchhelle](#)^a · [Adam P Roberts](#)^b 

[Affiliations & Notes](#)  [Article Info](#) 



UNEP 2023



UNEP/WHO 2024

Cell

Leading Edge

50 CellPress
OPEN ACCESS

Review

Scientists' call to action: Microbes, planetary health, and the Sustainable Development Goals

Thomas W. Crowther,^{1,2,*} Rino Rappuoli,^{3,*} Cinzia Corinaldesi,^{4,5} Roberto Danovaro,^{5,6} Timothy J. Donohue,⁷ Jef Huisman,⁸ Lisa Y. Stein,⁹ James Kenneth Timmis,^{10,11} Kenneth Timmis,¹² Matthew Z. Anderson,^{13,14} Lars R. Bakken,¹⁵ Matthew Baylis,¹⁶ Michael J. Behrenfeld,¹⁷ Philip W. Boyd,¹⁸ Ian Brettell,¹ Ricardo Cavicchioli,¹⁹ Camille S. Delavaux,¹ Christine M. Foreman,²⁰ Janet K. Jansson,²¹ Britt Koskella,²² Kat Milligan-McClellan,²³ Justin A. North,²⁴ Devin Peterson,²⁵ Mariagrazia Pizza,²⁶ Juan L. Ramos,²⁷ David Reay,²⁸ Justin V. Remais,²⁹ Virginia I. Rich,³⁰ William J. Ripple,³¹ Brajesh K. Singh,³² Gabriel Reuben Smith,¹ Frank J. Stewart,³³ Matthew B. Sullivan,³⁴ Johan van den Hoogen,¹ Madeleine J.H. van Oppen,^{35,36} Nicole S. Webster,^{18,35,37} Constantin M. Zohner,¹ and Laura G. van Galen^{1,38,*}

¹Department of Environmental Systems Science, Institute of Integrative Biology, ETH Zürich (Swiss Federal Institute of Technology), Zürich

Article | [Open access](#) | Published: 28 September 2023

The Antibiocene – towards an eco-social analysis of humanity's antimicrobial footprint

[Claas Kirchhelle](#) 

[Humanities and Social Sciences Communications](#) **10**, Article number: 619 (2023) | [Cite this article](#)



Inserm

