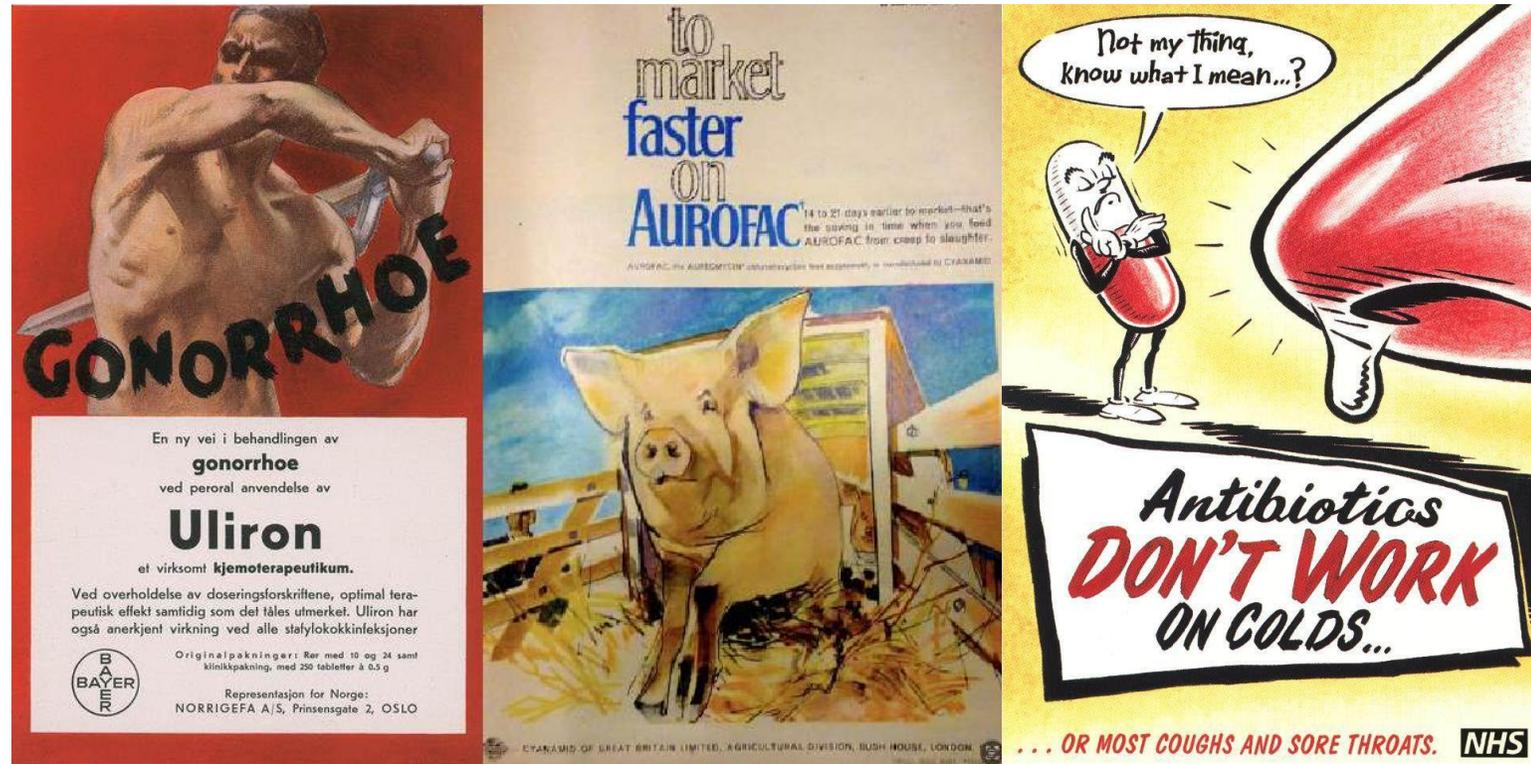


# Stewarding Bugs Not Drugs: Rethinking Antimicrobial Regulation Beyond The Clinic



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 gonorrhoea  
(PPNG) and Spectinomycin resistant  
Neisseria gonorrhoea  
(SRNG)

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

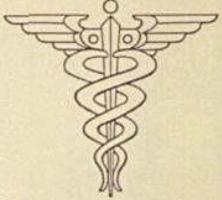
If you have more than  
one sex partner, you are at  
great risk of catching  
the disease!

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.

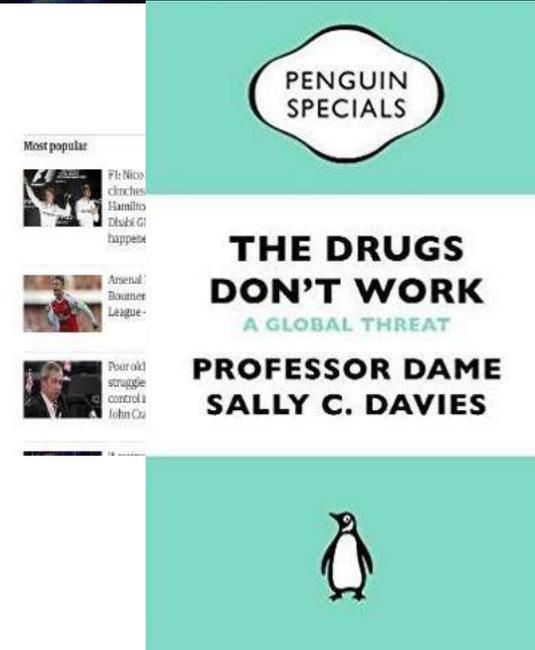


CITY OF CHICAGO  
Eugene Sawyer, Mayor

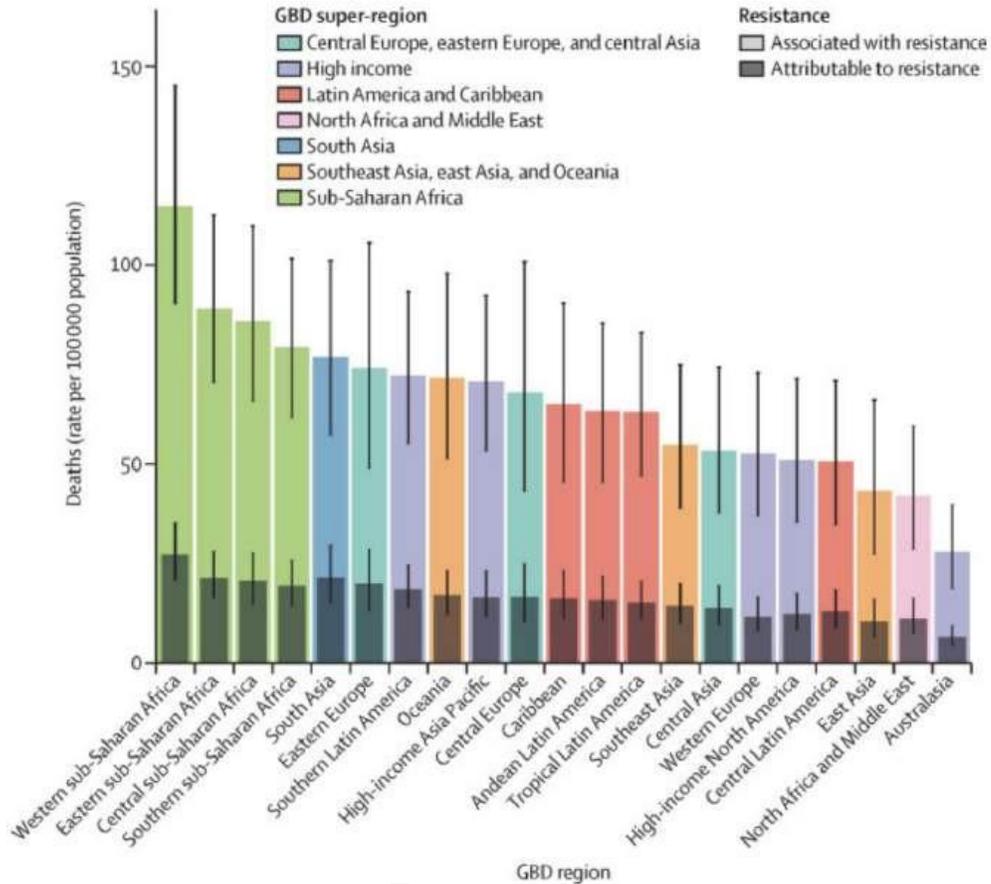


DEPARTMENT OF HEALTH  
Lonnie C. Edwards  
Commissioner

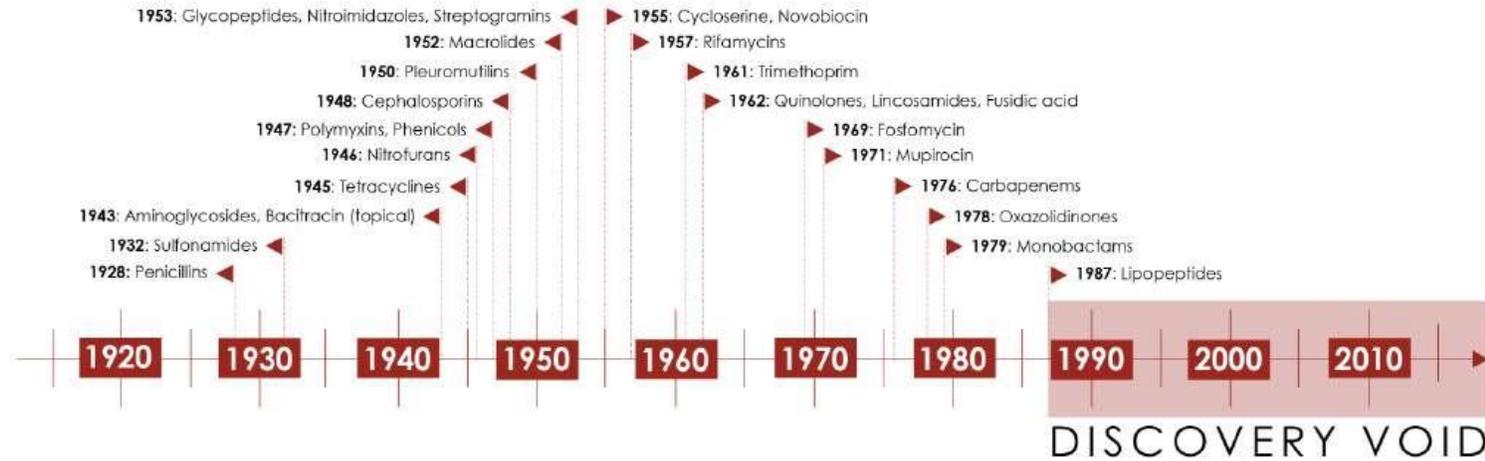
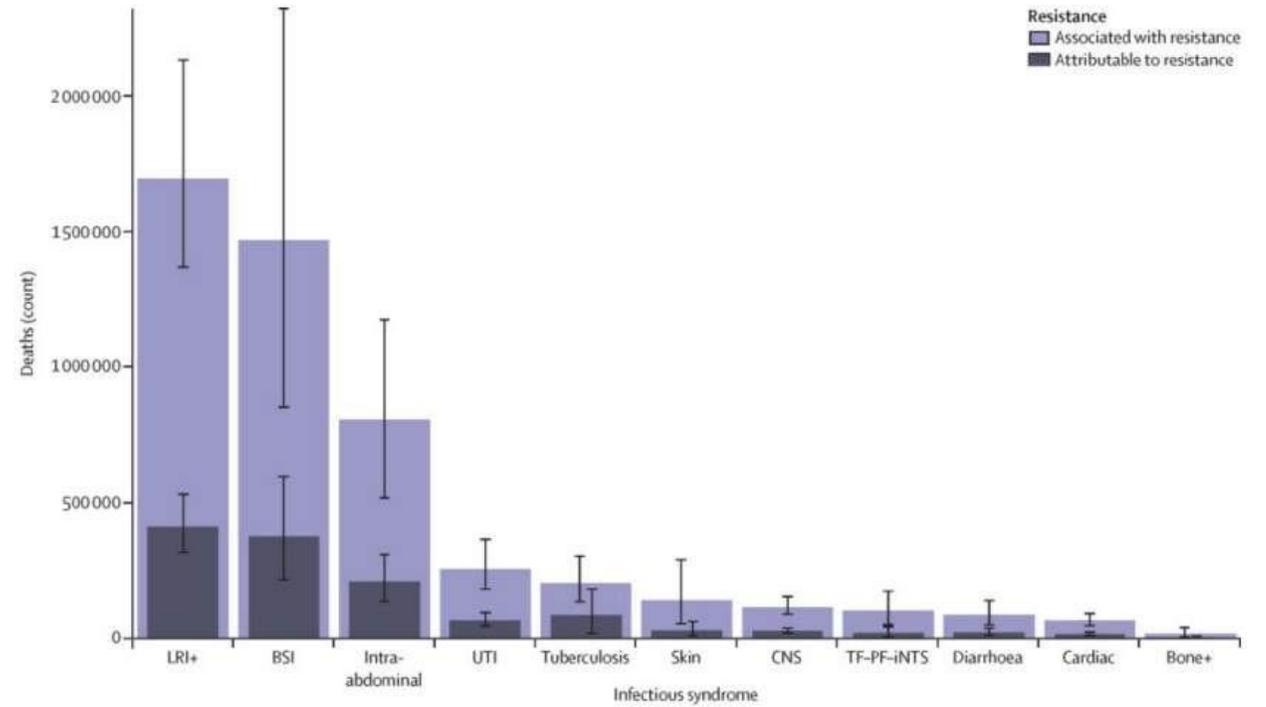
# 1. Apocalypse Now?



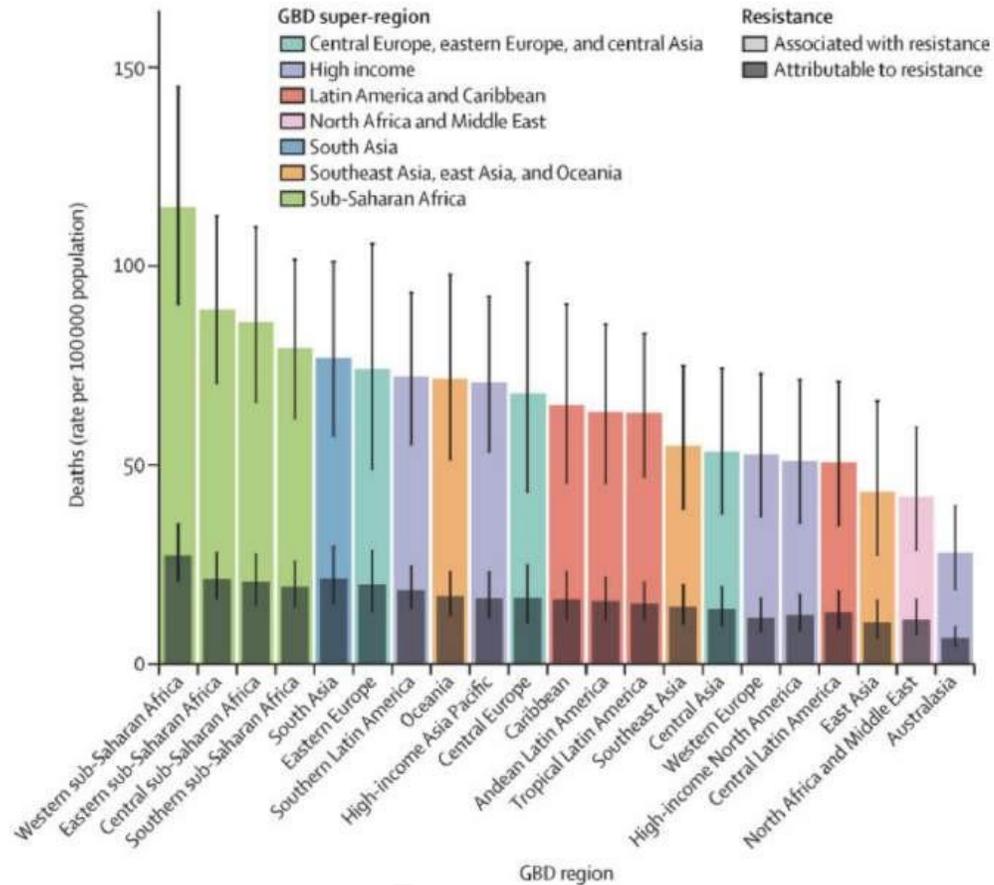
# An "Antibiotic Apocalypse?"



Murray et al. *Lancet* 2022



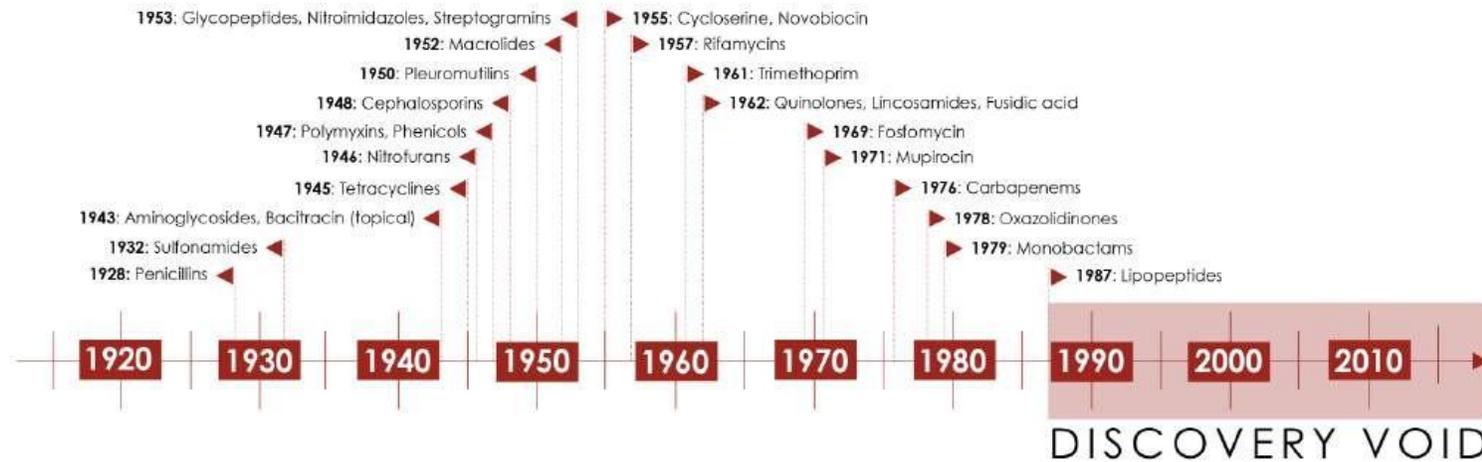
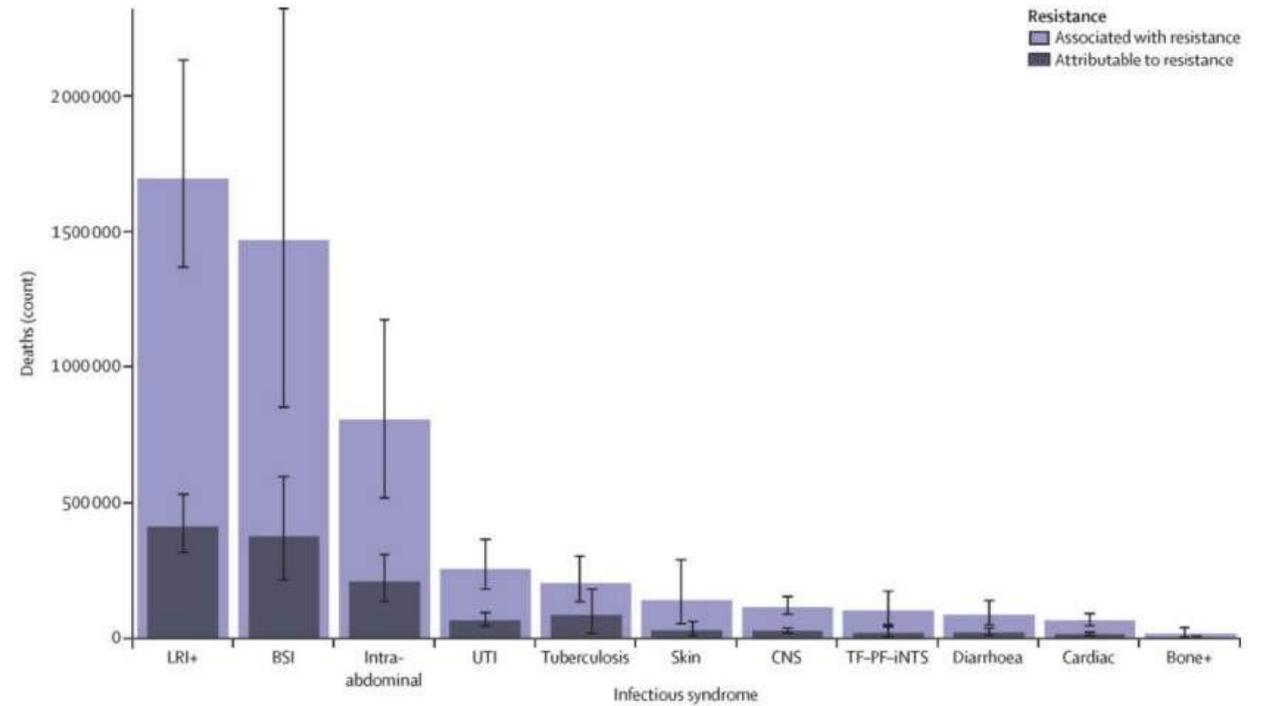
# An “Antibiotic Apocalypse?”



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

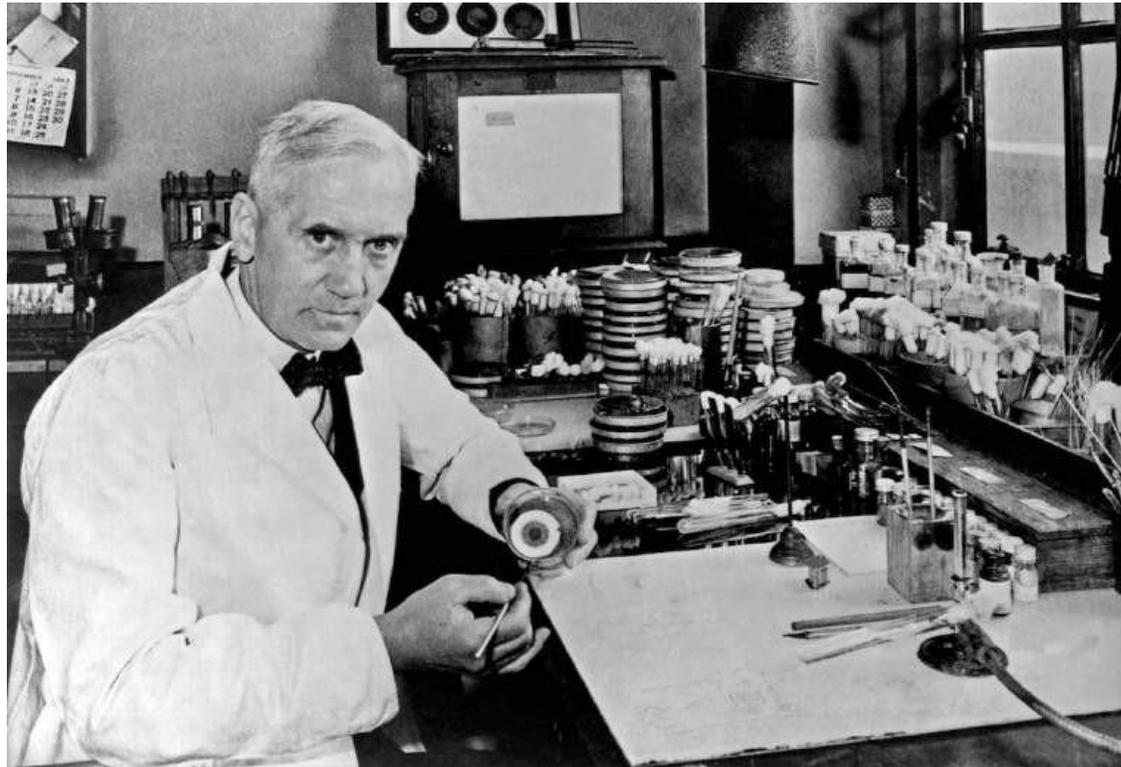


**Chandler: AMR as a systems challenge for modern health- and food production infrastructures.**

## 2. Breaking the Mould: the long history of antimicrobials



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



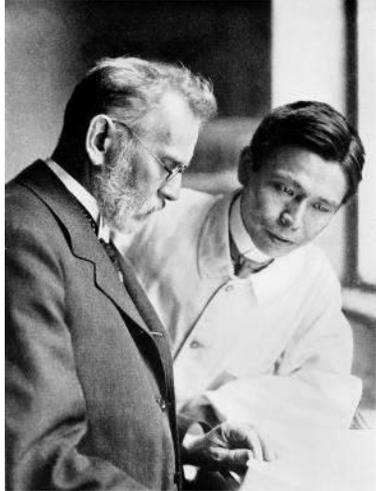
Dec 11. 28  
*Inhibition by moulds.*  
Moulds placed on both in flask & test tube. Room temp. (winter)  
Equal parts of 10% mixed broth and loamy agar mixed and filtered  
into tubes in an agar plate. After each on glass plates with  
blood agar containing haemolytic streptococci.  
After 11 hours.



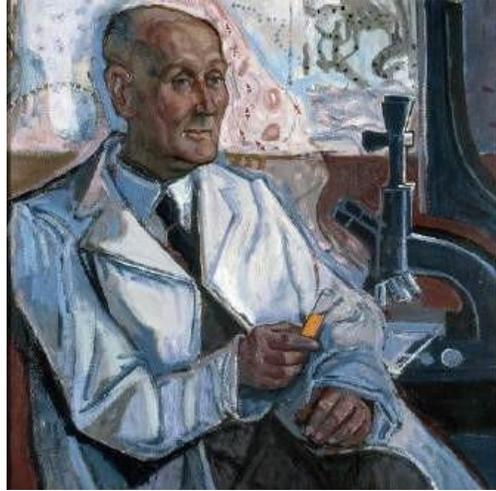
In the beginning [1928] was ... a lone genius



# Demoulding Antimicrobial History



Ehrlich & Hata  
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)

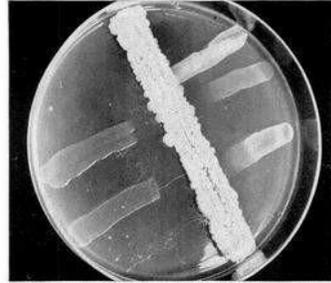
1947 Chloramphenicol

1959 Methicillin (Meticillin)

1962 Nalidixic Acid

1964 Cephalothin

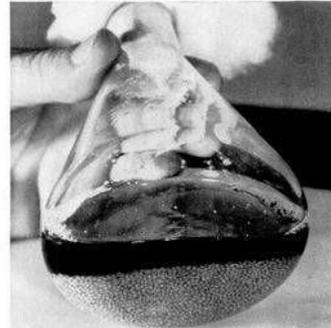
# New Infrastructures: Medicine



**BACTERIA TEST** shows the effectiveness of Chloromycetin against the disease germs. Growth of germ cultures placed next to Chloromycetin mold (vertical streak) is stopped at various stages by germicidal action of the new drug.



**FIRST PATIENT** to receive Chloromycetin was dying of epidemic typhus (left) when he was treated in Bolivia by Dr. E. H. Payne. One week later (right) though still wasted from the disease, he was on the way to complete recovery.



**MOLD PELLETS** are cultured in a glass flask to test methods of growing. Production, however, will not depend entirely on large-scale mold growing, for Chloromycetin is being synthesized chemically by Parke, Davis & Co.



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

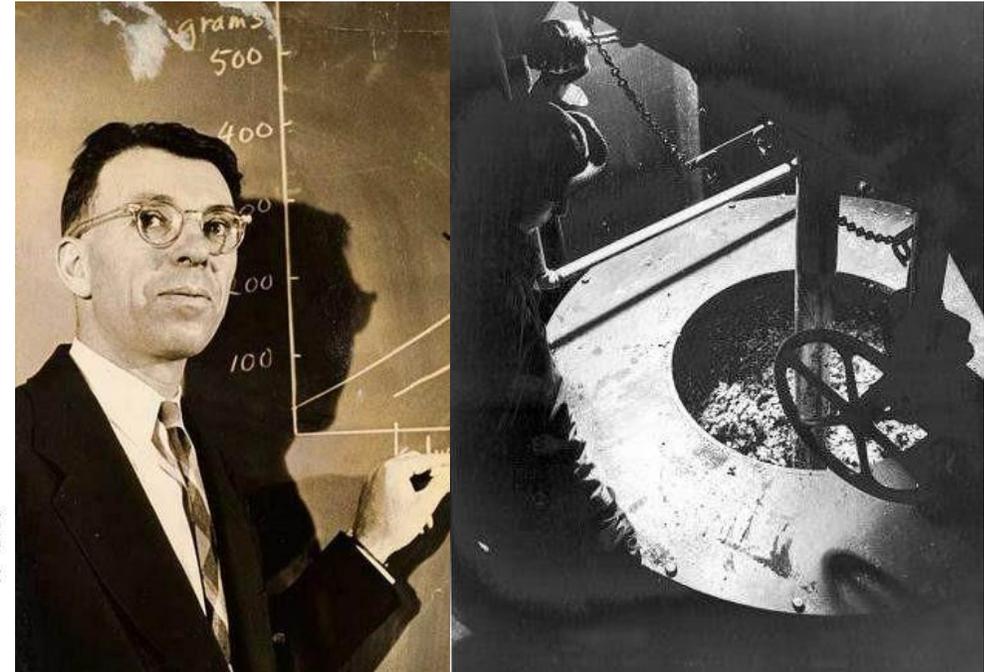
# New Infrastructures: Food Production



1940  
Sulfapyridine  
advert



1948  
Sulfaquinoxaline  
Mass-treatment  
and prophylaxis



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

Image Source Journal of Parasitology, Peoria Historical Society; Yellapragada SubbaRow Archives

# Non-therapeutic Use

**STOP "SCOURS" IN CALVES AND PIGS**

**AUREOMYCIN**  
SOLUBLE

AUREOMYCIN SOLUBLE is your best answer to the problem of "scours" in calves and pigs. With this powerful but gentle antibiotic, you can attack the disease immediately. It dissolves quickly and completely in water, milk or milk replacer.

MYCIN SOLUBLE on hand ready for instant use for individual doses. AUREOMYCIN TABLETS economical, handy and effective. See your veterinarian druggist or feed dealer. Write for free literature.

LEDERLE LABORATORIES DIVISION

**SCIENCE COMES TO THE FARM IN A FEED BAG**

When do they need a High Level feed?

**Terramycin** at high levels  
Pfizer

Usually the best and sometimes the only sign of infection in a laying hen is a swollen, inflamed ovary in egg production. Terramycin, a powerful antibiotic which can control disease-causing bacteria in the body, is effective in preventing such infections.

High levels of Terramycin, available in a special high level feed, keep down the bacteria that can cause your flock to lay fewer eggs. High levels of Terramycin, available in a special high level feed, keep down the bacteria that can cause your flock to lay fewer eggs.

**"You've got to give me the BEST... to keep me HEALTHY!"**

**AUREOMYCIN**

PREVENT DISEASE with good feeds containing the right amount of the world's greatest disease-fighter:

make money for you - as layers or meat birds - your birds must stay healthy! It's good health that leads to growth and better production.

It's no surer way to help prevent disease and keep birds healthy than the use of the right amount of right antibiotic. Not just any antibiotic, but the world's greatest disease-fighter: AUREOMYCIN tetracycline.

AUREOMYCIN is more effective against more disease than any other known drug. AUREOMYCIN.

in the right amount in good feeds, offers you the finest protection you can get today against the chronic diseases that cause so many losses - CRD, blue comb and non-specific enteritis.

Be sure! See your feed dealer or feed mixer. Ask him for feeds containing AUREOMYCIN.

Science comes to the farm in a feed bag.

**Pfizer**

What next from Pfizer and the feed industry?

**LOOK HOW THE RUNTS ARE CATCHING UP WITH THEIR BROTHERS**

The high rate on runts averages out to about 1% to every four farrowed, or upwards of 20,000,000 a year. A lot of potential pork, but up till lately most farmers figured it didn't pay to save runts—even if they could be saved.

Then Ag scientists showed how Terramycin\* in the ration with the Surger of the runts' appetites, put them on their feet and a start in their tails. Within a month feed manufacturers were putting some Terramycin in creep feeds and pig starters. Now they're catching up with their brothers (who were getting some new low-growth good growth themselves), and soon, the source of the big fat, all but disappeared from thousands of farms.

This is just one example of how science, coming to the farm in a feed bag, is helping farmers to produce more meat, milk and eggs at lower feed cost and with low risk than ever before.

Pfizer's Agricultural Research and Development Dept. in Indiana has helped to prove that and make practical many other uses of antibiotics, hormones, vitamins and new sources of extra-growth factors.

What next from Pfizer and your feed man? Maybe it will make any pig that takes more than 8 months to reach 200 pounds look like a runt.

Science comes to the farm in a feed bag.

**Pfizer**

**less disease**

**more eggs**

**AUREOMYCIN**

Does your give your layers good feeds containing "high levels" of the world's greatest disease fighter?

At some of the egg producers' Today, you can give your layers the best protection they can get with **LESS DISEASE AND DISCASTLE**—the factors that cause a lack in egg production.

Let our help your birds healthy with your feeds containing "high levels" of AUREOMYCIN. Call your feed man. This is the antibiotic that is most effective against

several disease organisms that are other layers' drug. These birds have proved that AUREOMYCIN is a "high level" antibiotic in their feeds. In the presence of disease, they produce high egg production longer period. They also have proved that healthy.

See your feed dealer or feed mixer. Ask him for feeds containing "high levels" of AUREOMYCIN.

USA

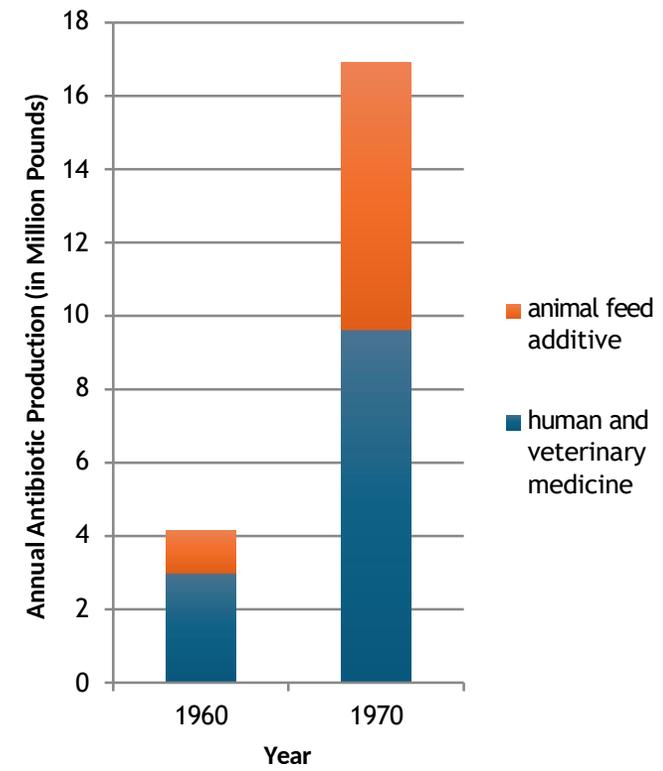


Image Source Farm Journal; Progressive Farmer; Wallaces Farmer

# New Infrastructures: Plant Production



1950s USDA Spraying



1970s Rice Blast Spraying



Streptomycin Spraying/ Citrus Injections 2000s

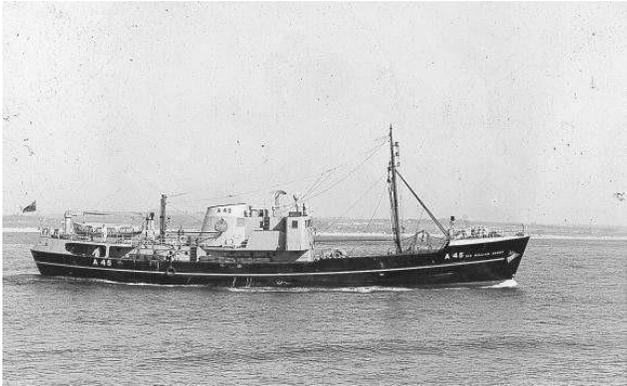


2000s Drone Spraying

# New Infrastructures: Food Preservation



Poultry Preservation (USA 1955/56)



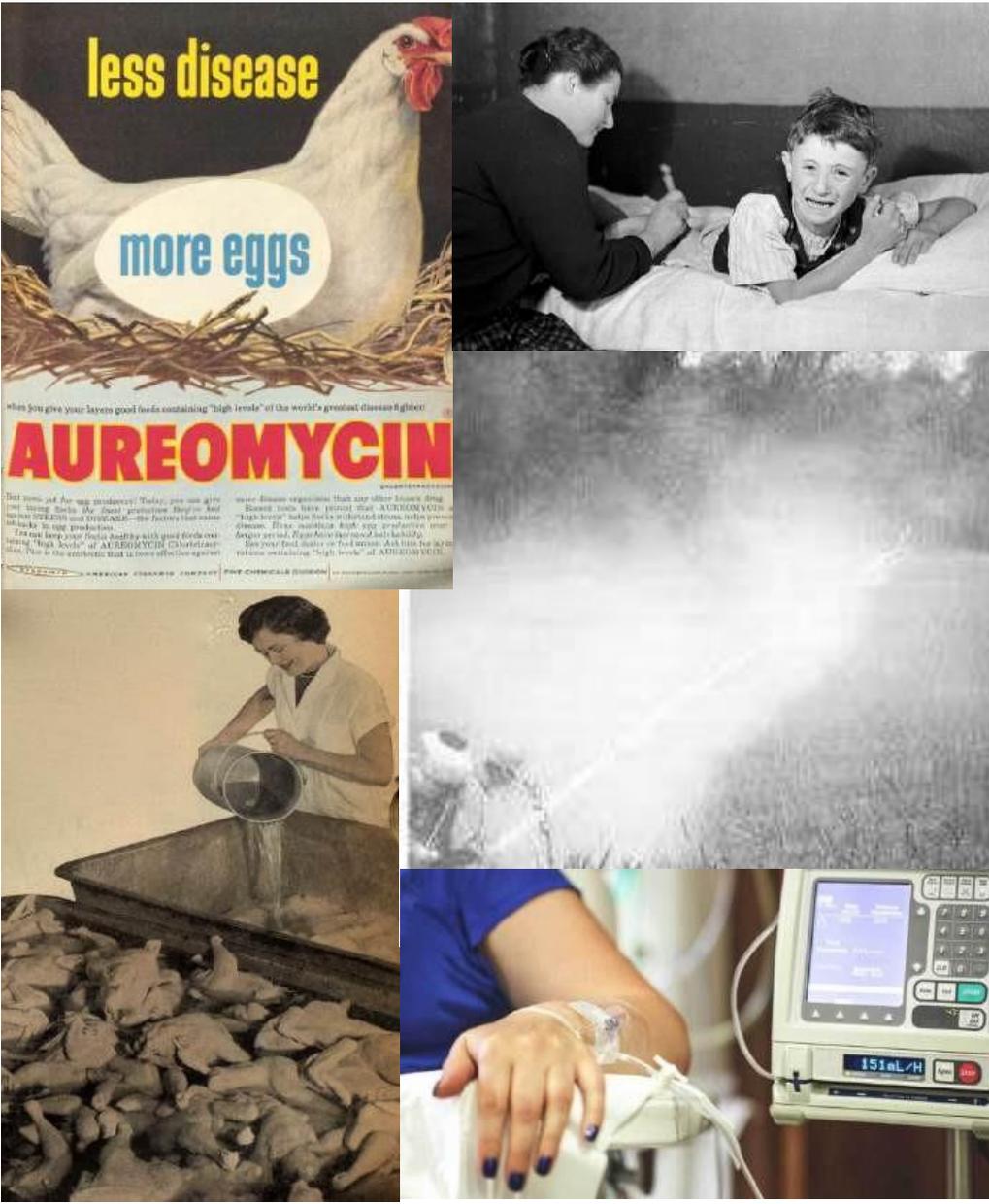
Fish Preservation (USA/UK)



Whaling (Iceland 1953)

Image Source [www.aberdeenships.com](http://www.aberdeenships.com); Farm Journal 1956; Arizona Republican 1956; Iceland Eyes

# Infrastructures of Modernity

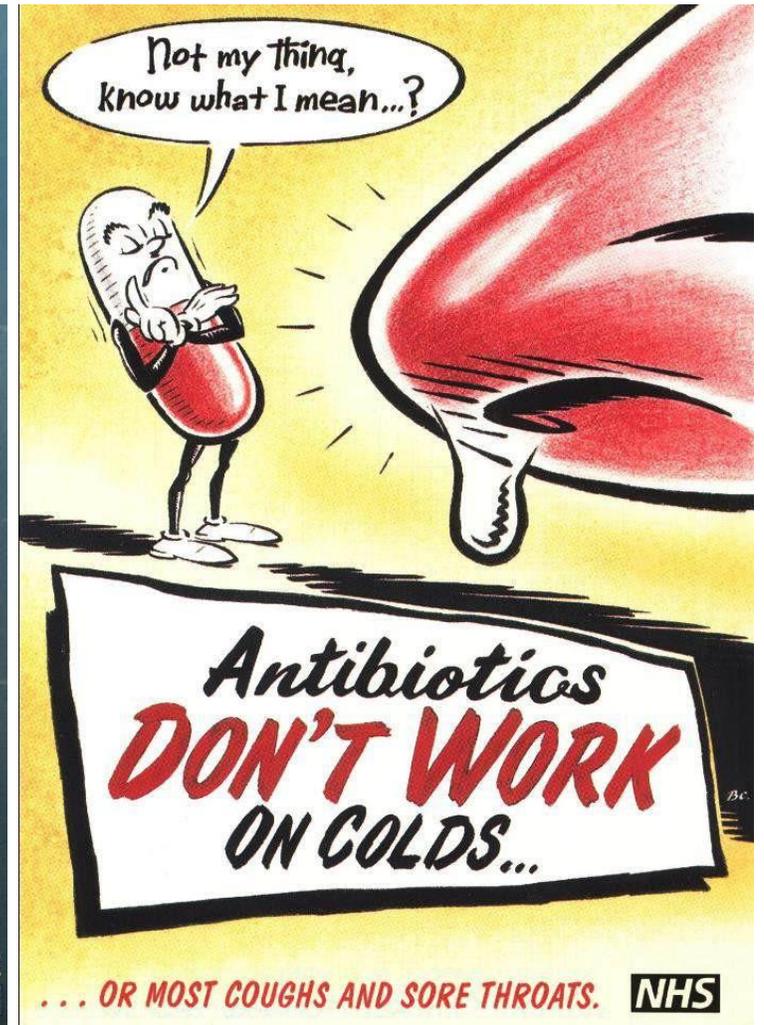


## Antimicrobials Enable:

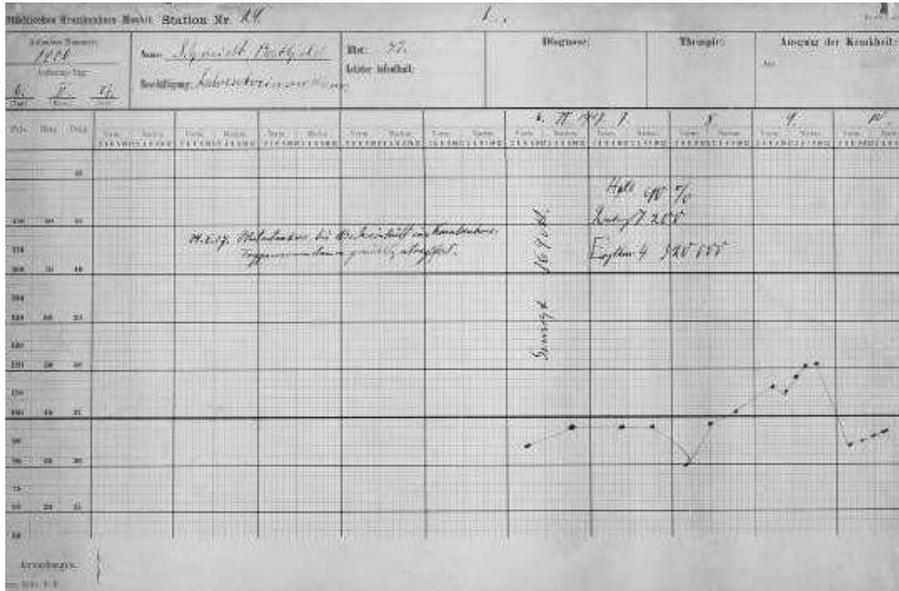
- Dramatic extension of microbial control.
  - Replacement of more expensive forms of care.
  - Efficacy gains for health- and food systems.
- 
- Crucial for modernist developmentalism.
  - Win-win-win for states, industry, and the public.

Part Three:

Narrow  
Scenarios -  
Fixing AMR



# Drug Fastness



1907 RKI 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)*

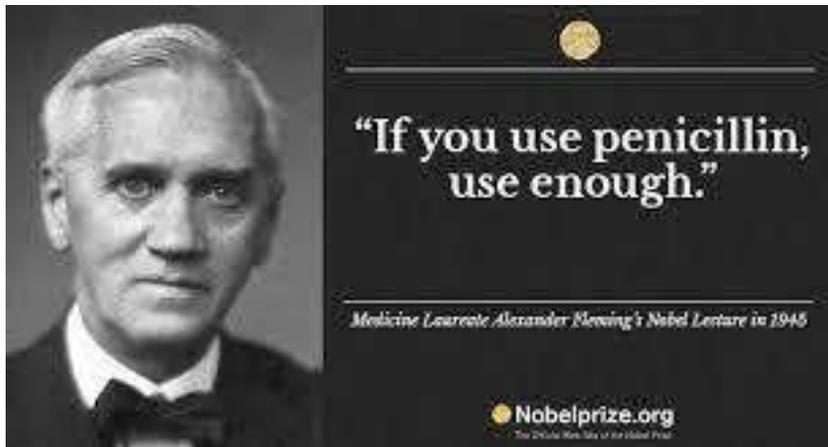
## Stewardship from the 1920s onwards:

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

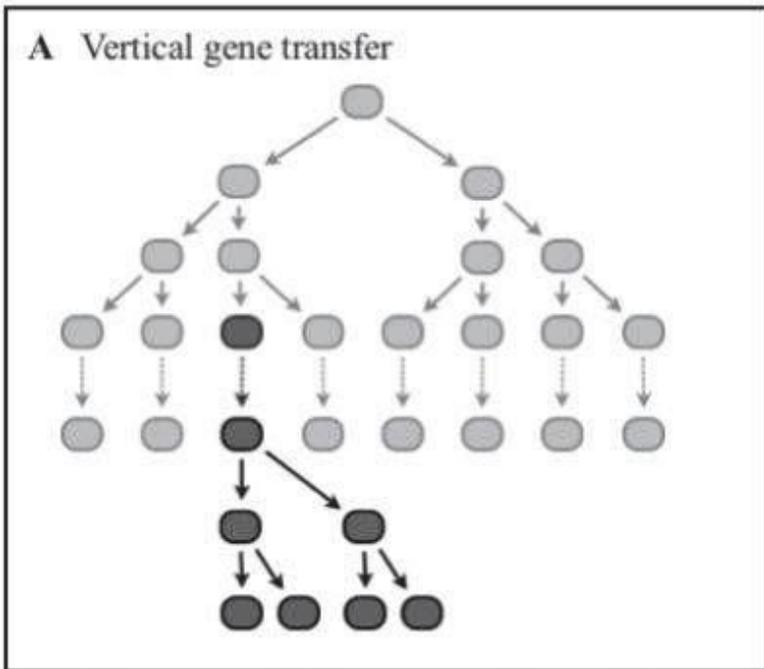
1935-1940: AMR emergence observed against sulfonamide drugs.

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?

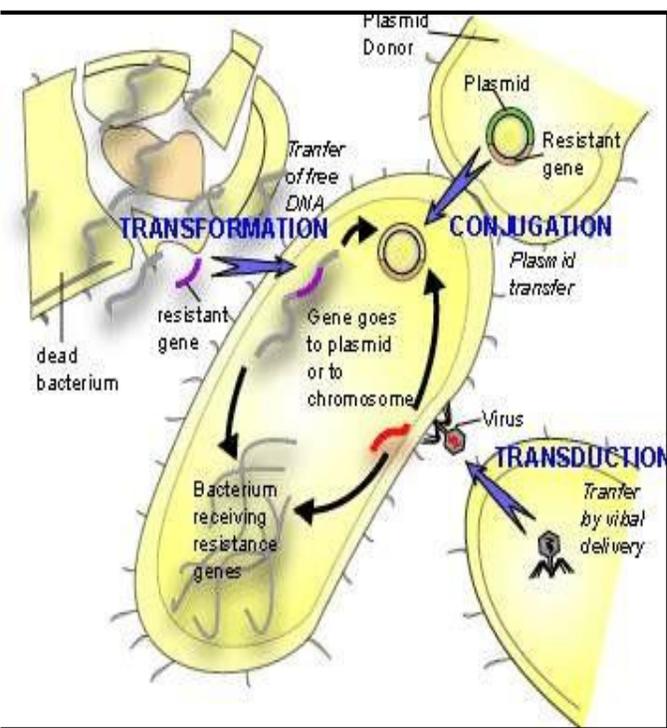


## Factors:

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.**



## LES CAUSES DE LA RÉSISTANCE AUX ANTIBIOTIQUES



L'antibiorésistance est un phénomène qui apparaît lorsqu'une bactérie évolue et devient résistante aux antibiotiques utilisés pour traiter les infections dont elle est responsable.



Une prescription excessive d'antibiotiques



Des patients qui ne terminent pas leur traitement



Un usage excessif des antibiotiques dans l'élevage et la pisciculture



Des pratiques inadéquates de lutte contre les infections dans les établissements de santé



Un manque d'hygiène et une insuffisance de l'assainissement

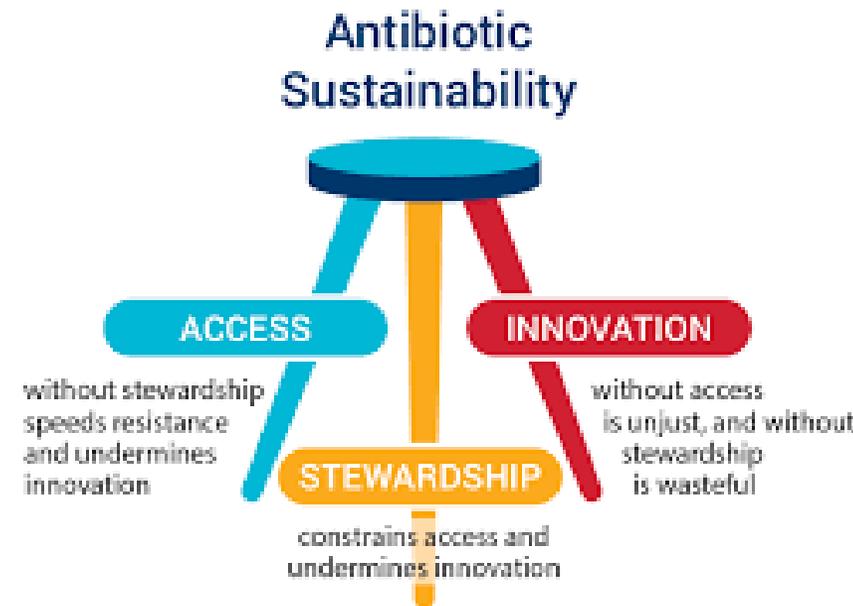


L'absence de nouveaux antibiotiques en cours de développement

[www.who.int/drugresistance/fr](http://www.who.int/drugresistance/fr)

#AntibioticResistance

Organisation mondiale de la Santé

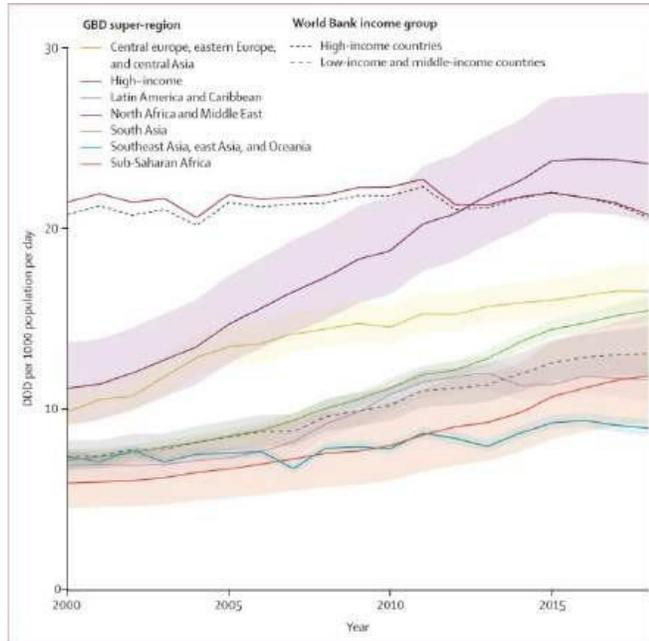


Hoffman S, Outerson K. JAMA (2015)



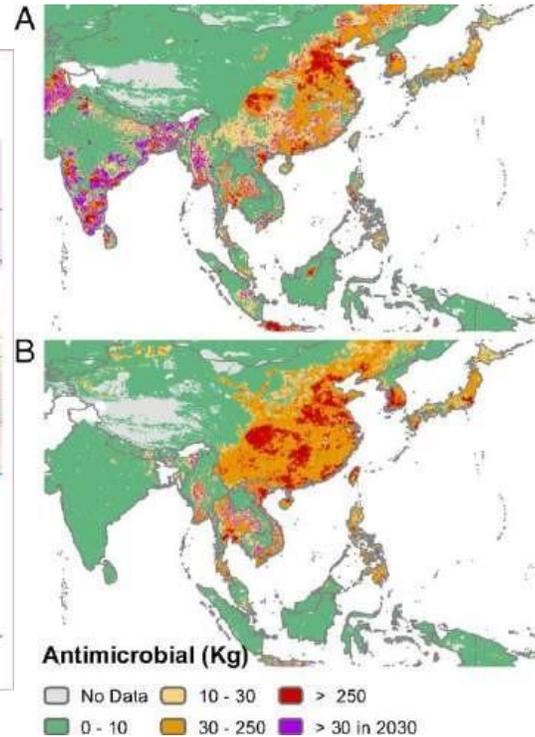
# Mission (Yet To Be) Accomplished

**AMR (RISING)**



Browne et al., *Lancet* 2021.

**AMU (RISING)**



Van Boeckel, *PNAS*, 2015

**Stewardship (INSUFFICIENT)**

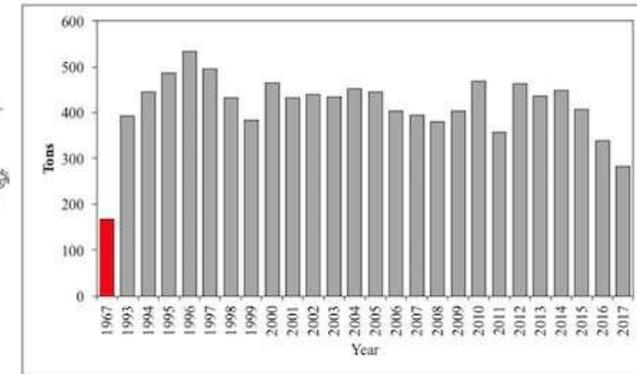


Figure 20: Total Annual Sale of Active Antibiotic Ingredients In The UK  
Source: 'Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine' (London: HMSO, 1969). 'UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2017)' (New Haw: VMD, 2018).

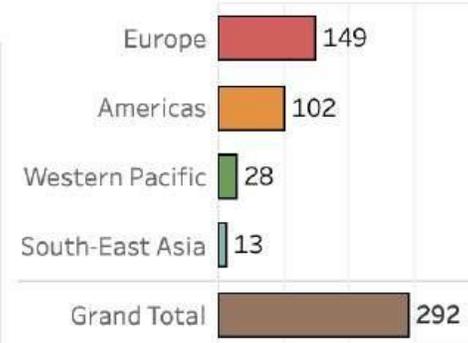
Kirchhelle, 2020

# 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

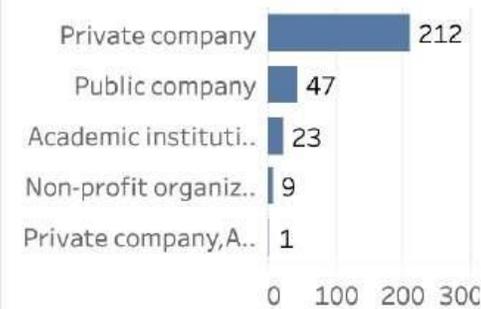
A.1. No. by WHO region



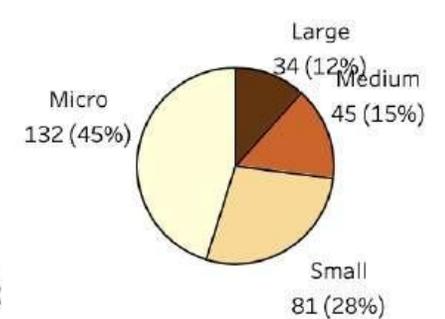
A.2. No. by income group



A.3 No. by type of developer institution



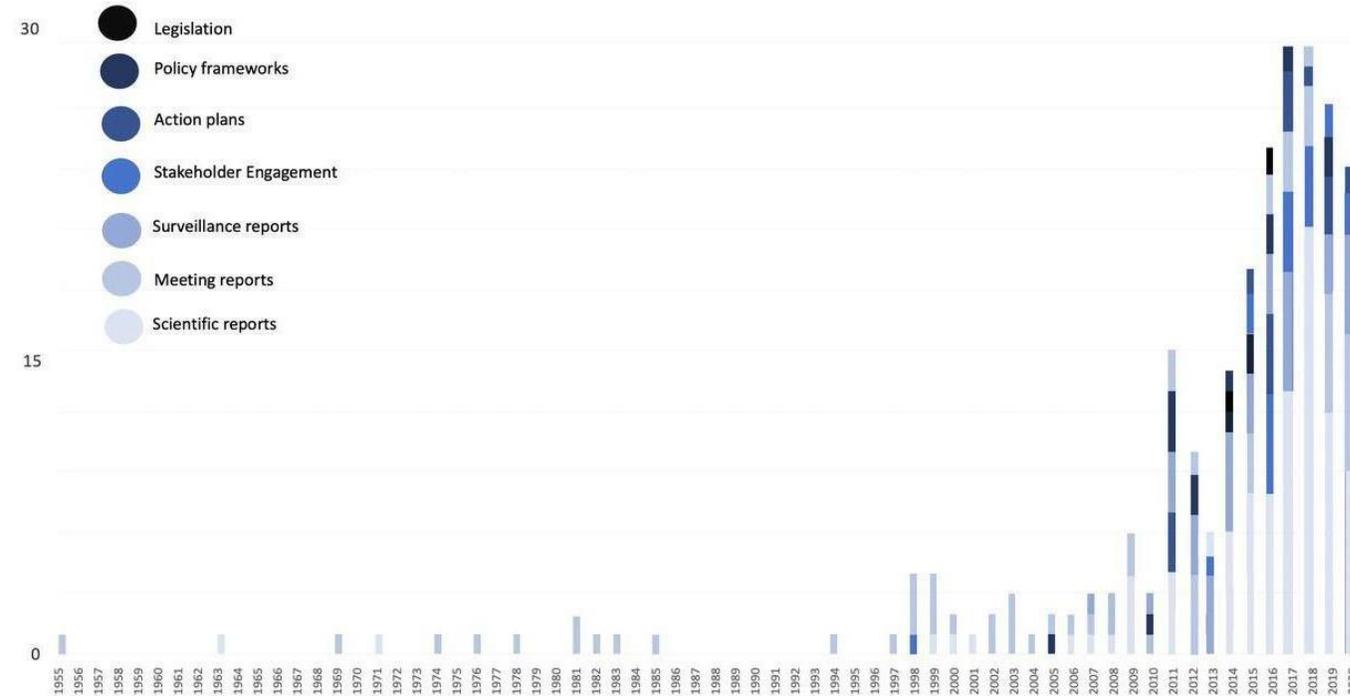
A.4 No. by size of developer institution



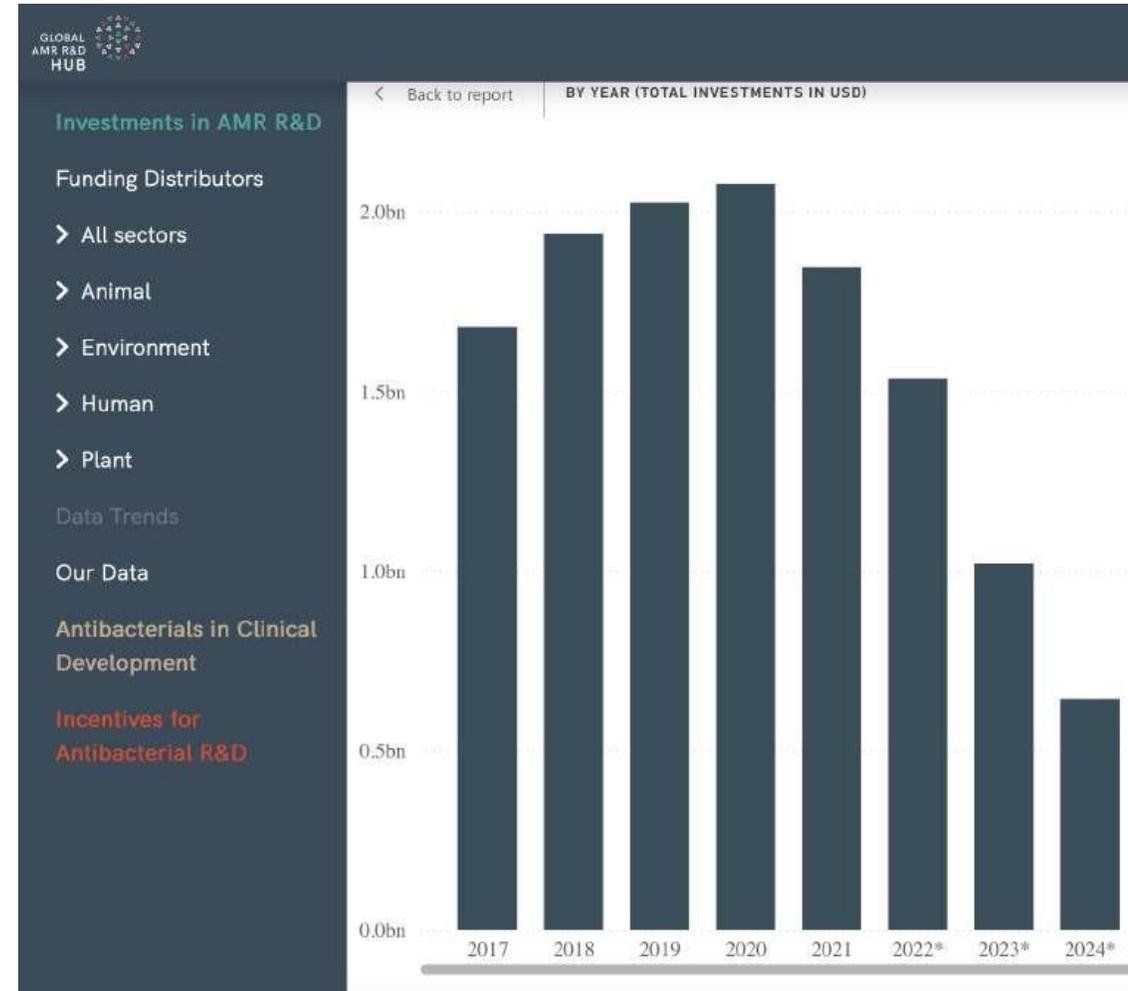
WHO Pipeline Review, 2022

- 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.

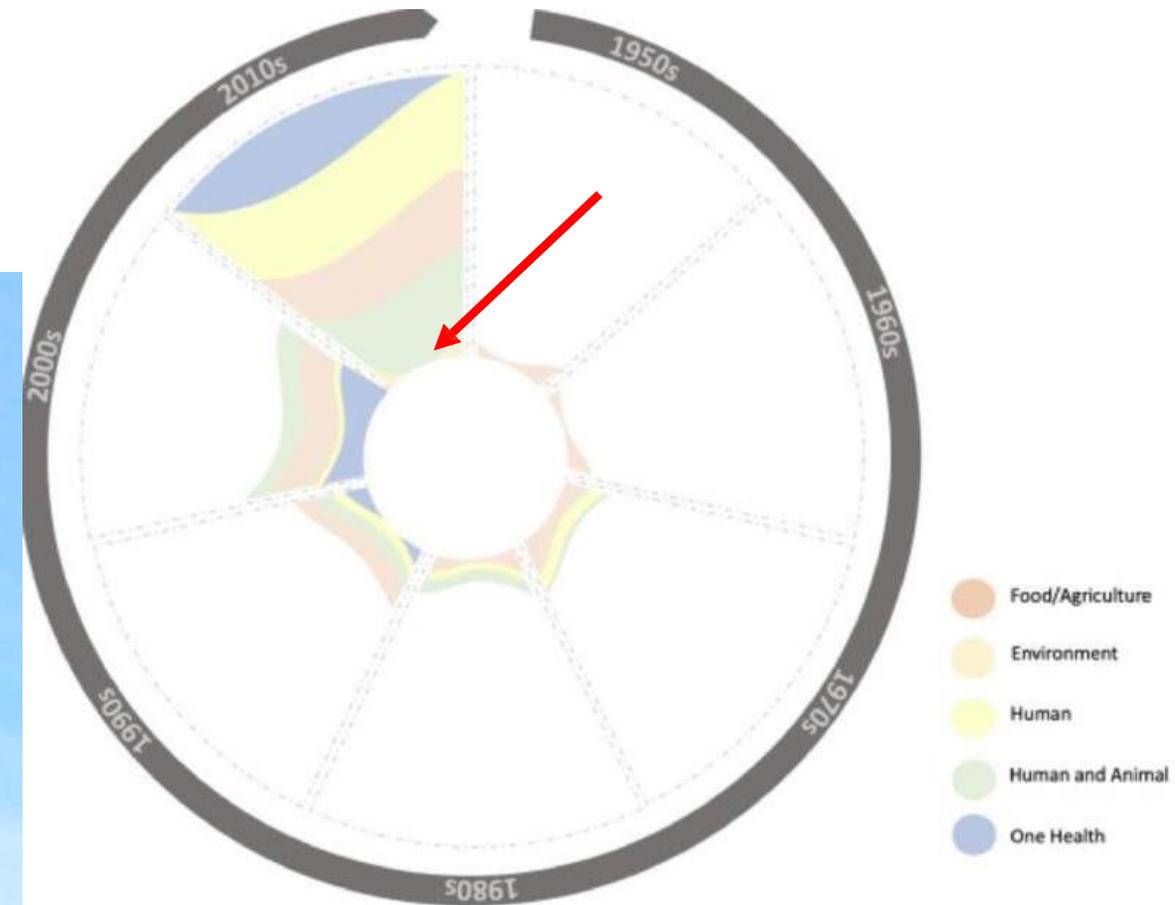
Reaffirmed focus on stewardship, IPC/WASH, Access, and Innovation.

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

## ➤ Or are we missing something?

# UN General Assembly

Overton et al. 2021



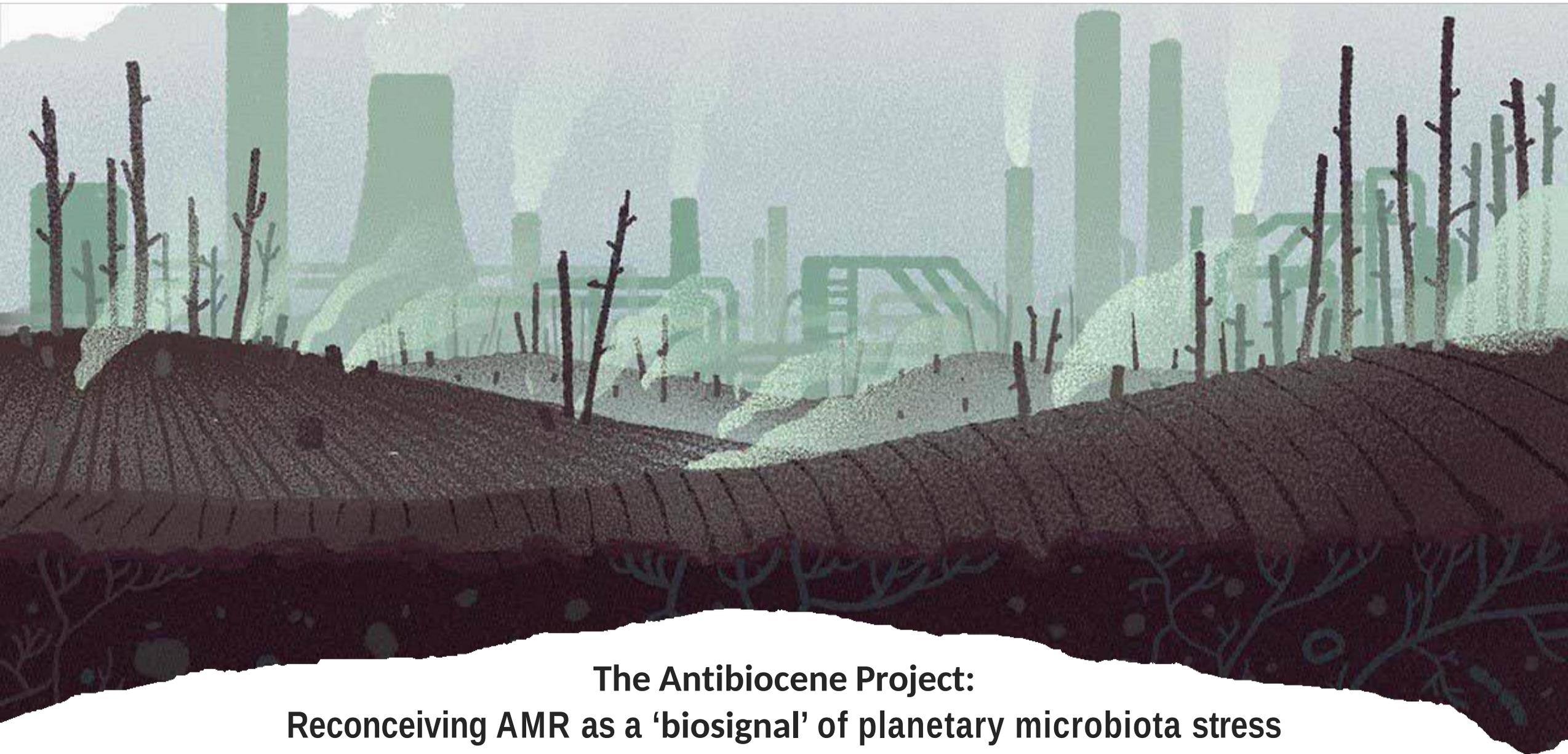
- “Environment” gets 3 of 106 paragraphs, **microbes not mentioned!**
- 2 of 248 international policy documents on AMR since 1945 exclusively target the environment’s role in AMR selection.

# Shifting the perspective

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



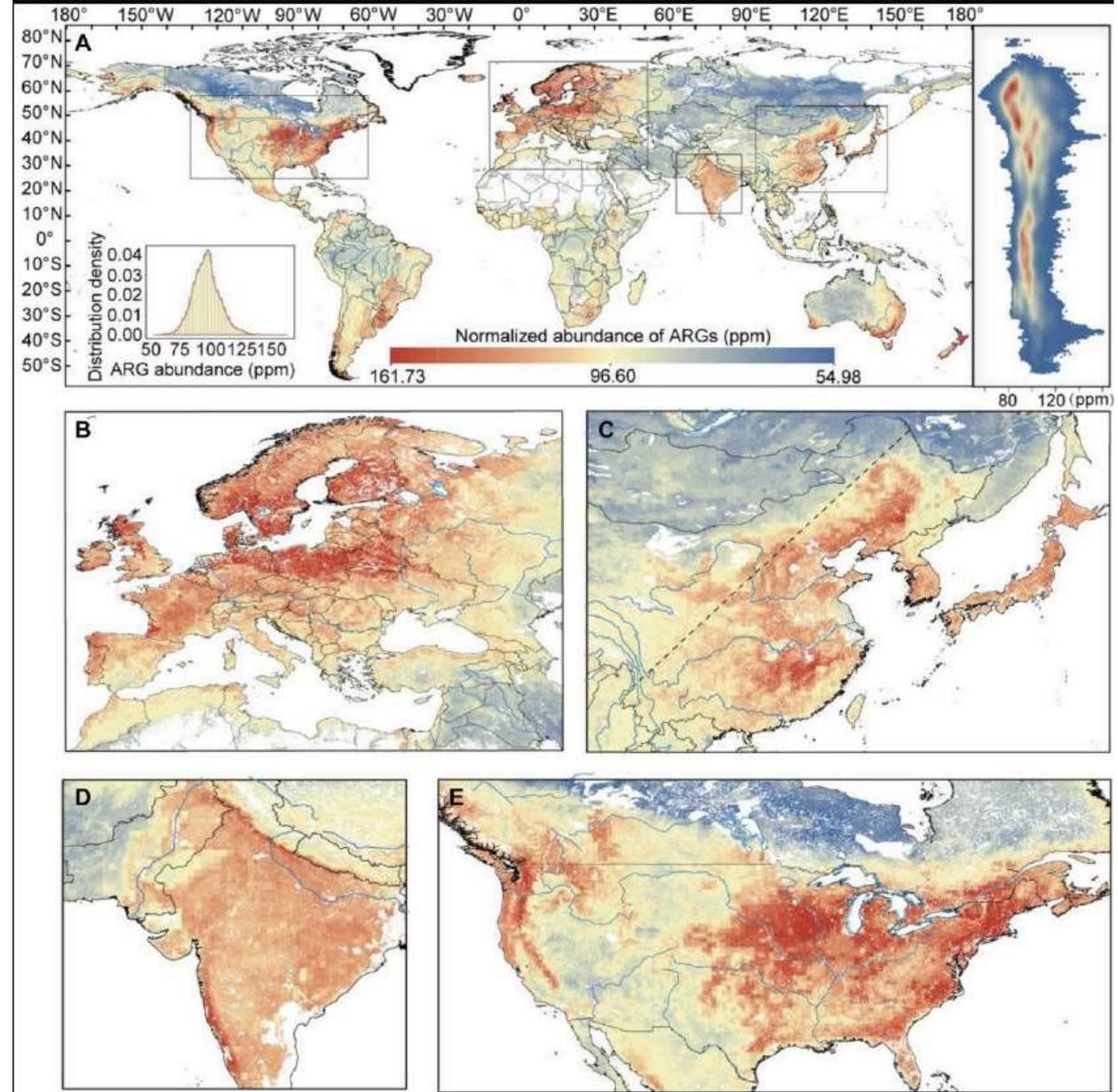
Where there is smoke....



**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...



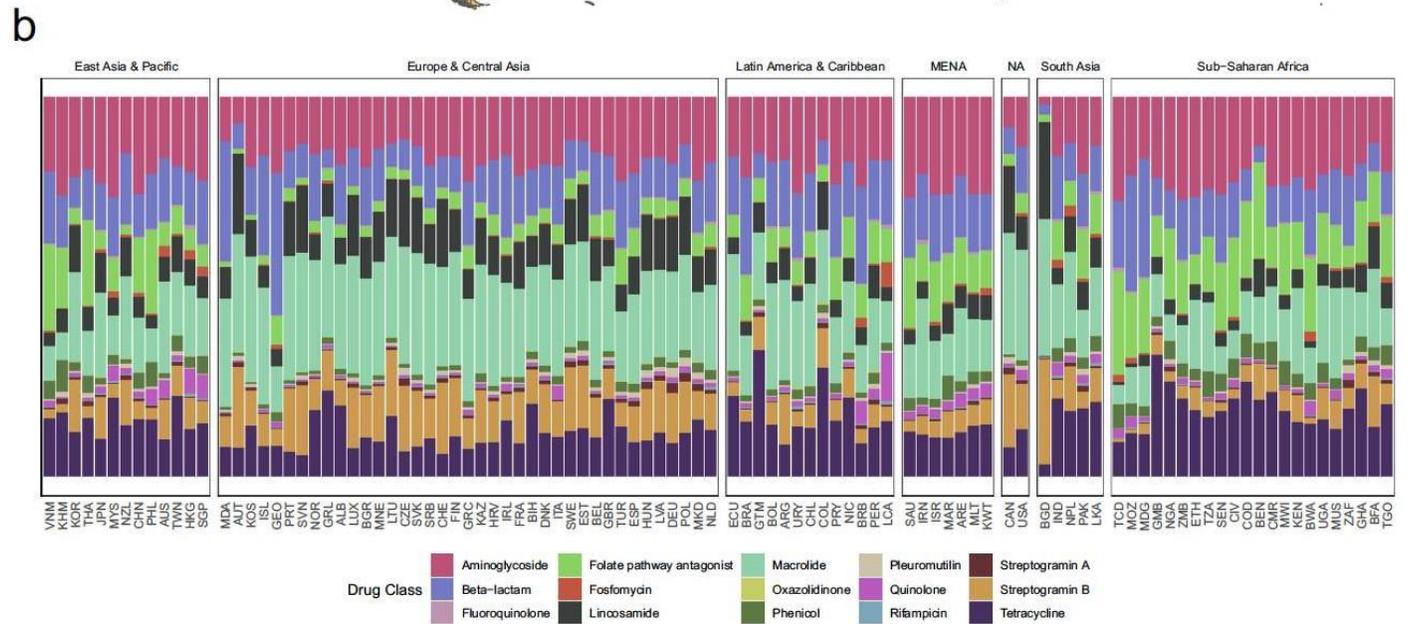
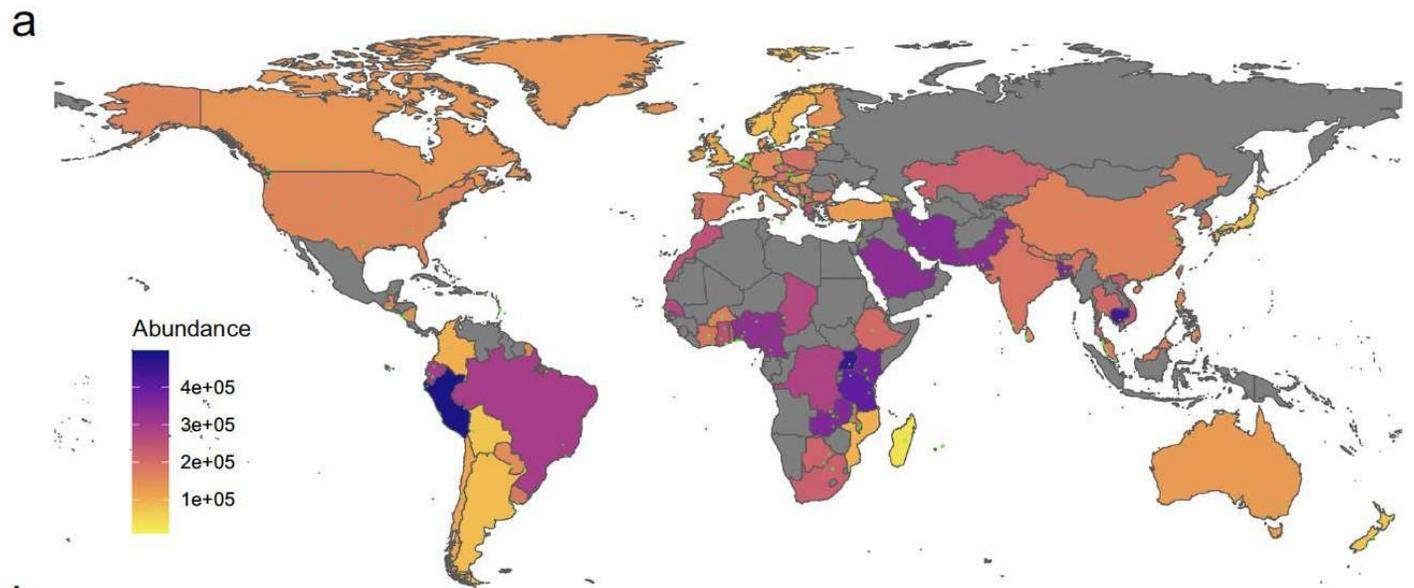
Prevalence of Antimicrobial Resistance Genes (ARGs) in Soils

Zheng et al. Science Advances 2022

# 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

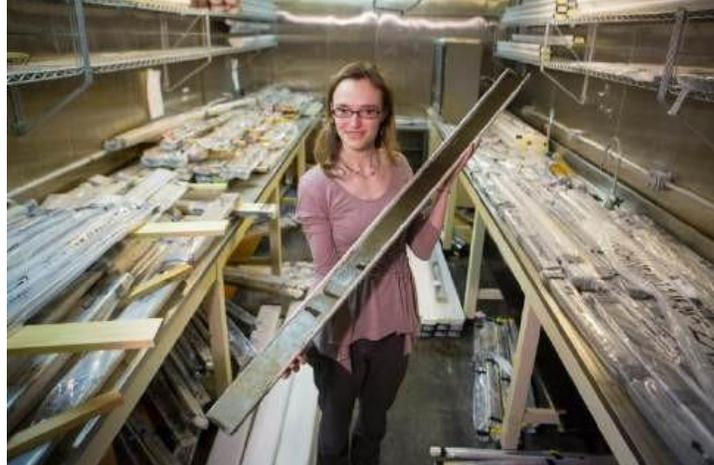


# The Antibiocene

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



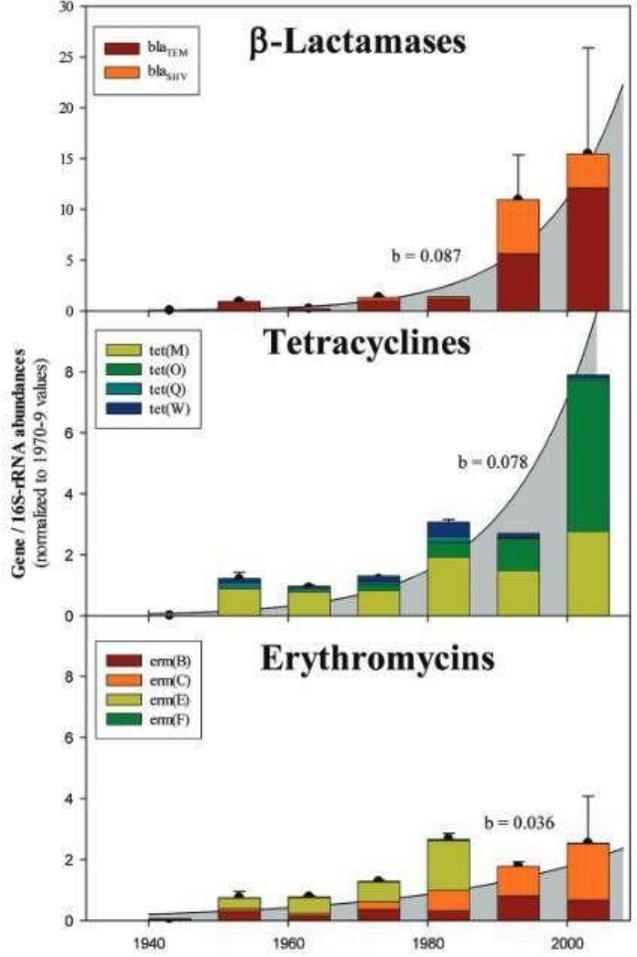
USDA Soil Archive



University of Buffalo Lake Sediments



Musi River, Hyderabad



Knapp et al. 2010

# Scales of a Shift:

## Species Level

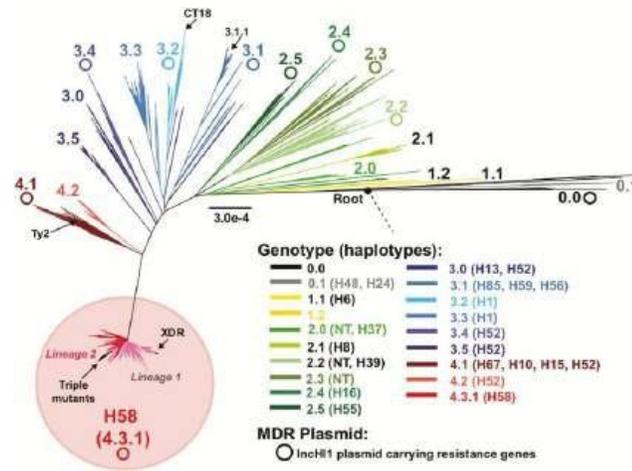
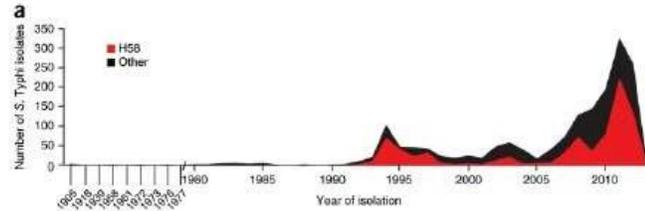
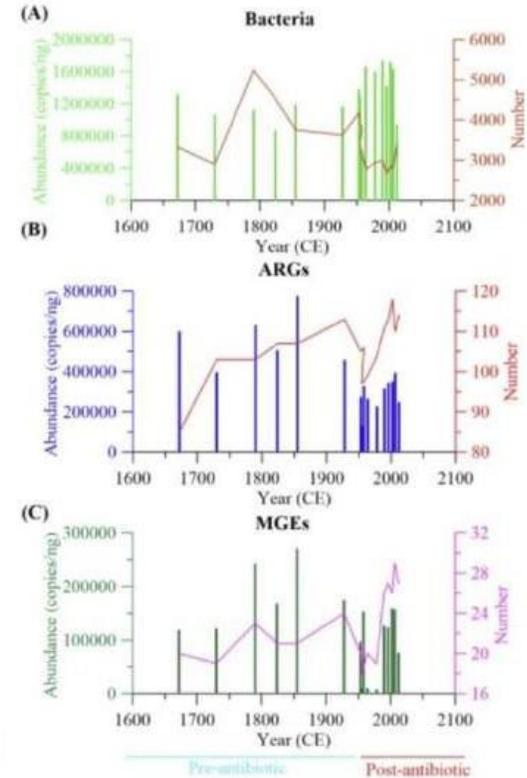


Figure 1: Population structure of the 1,832 *S. Typhi* isolates analyzed in this study.



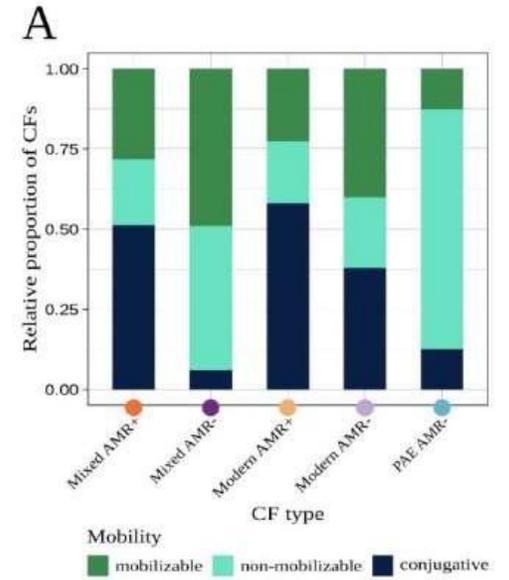
Kirchhelle et al. CID 2019  
Wong et al. Nature 2015

## Genetic Level



Yan et al.  
Environment  
International 2024

## Mobilome

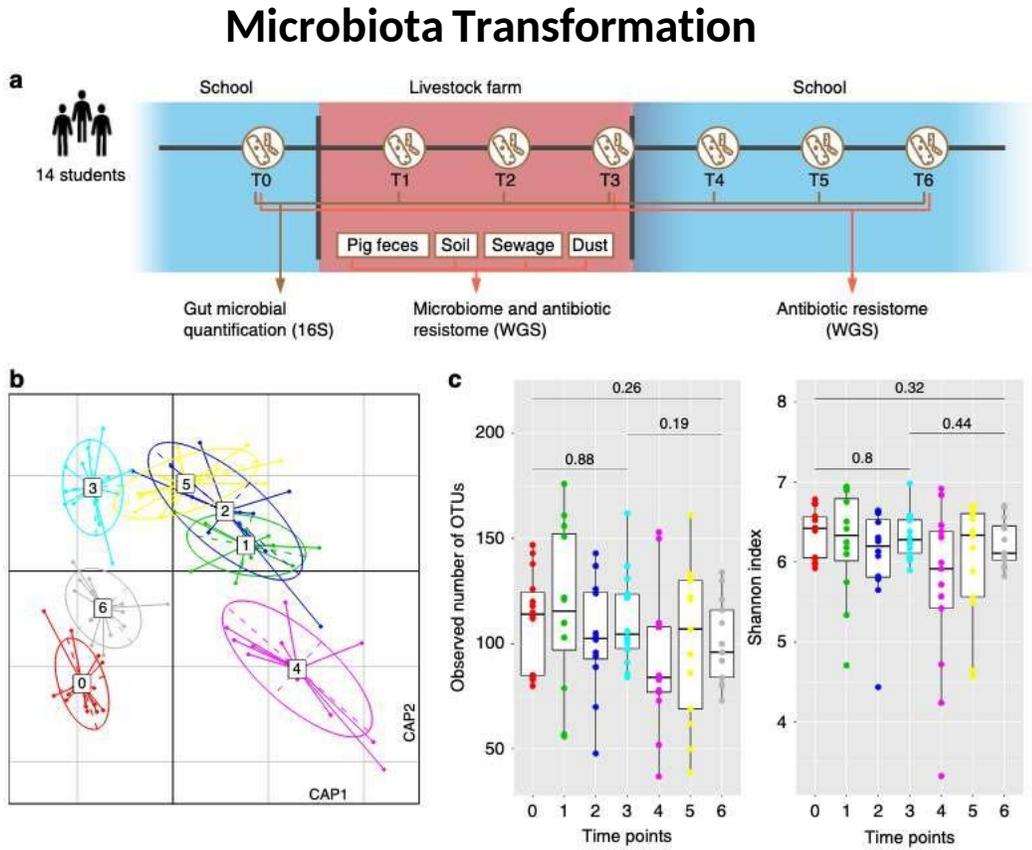


Cazares et al. 2024  
(under review)

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

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

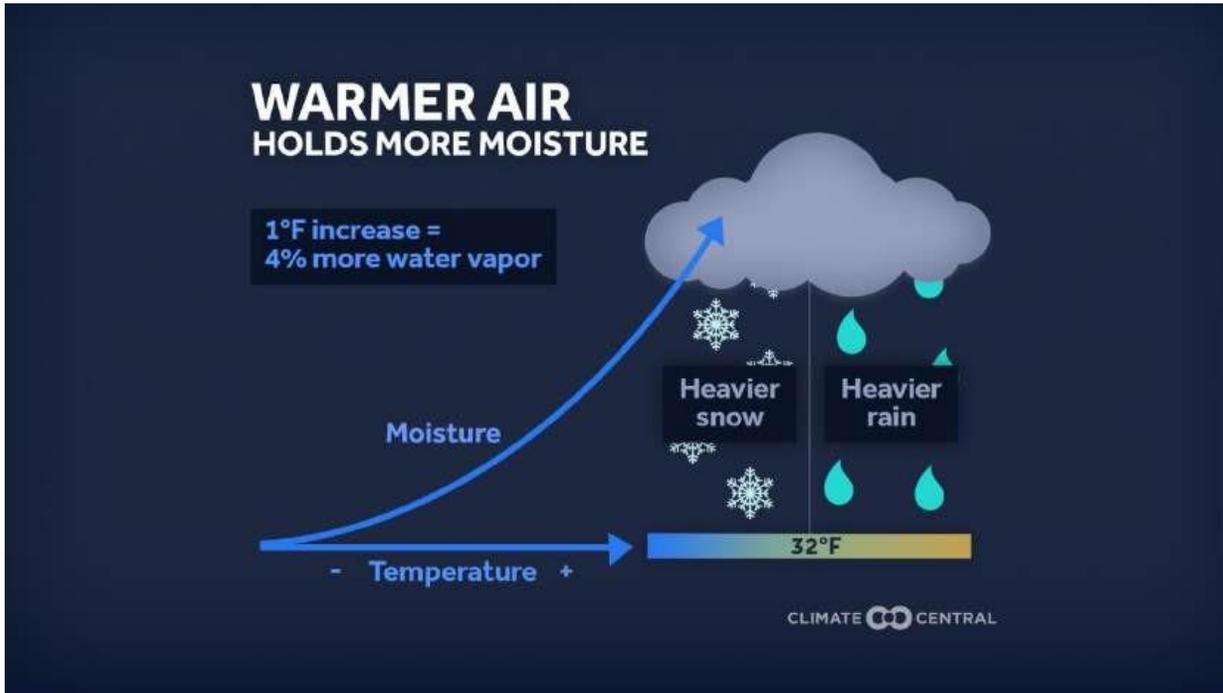
# Scales of a Shift:



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!

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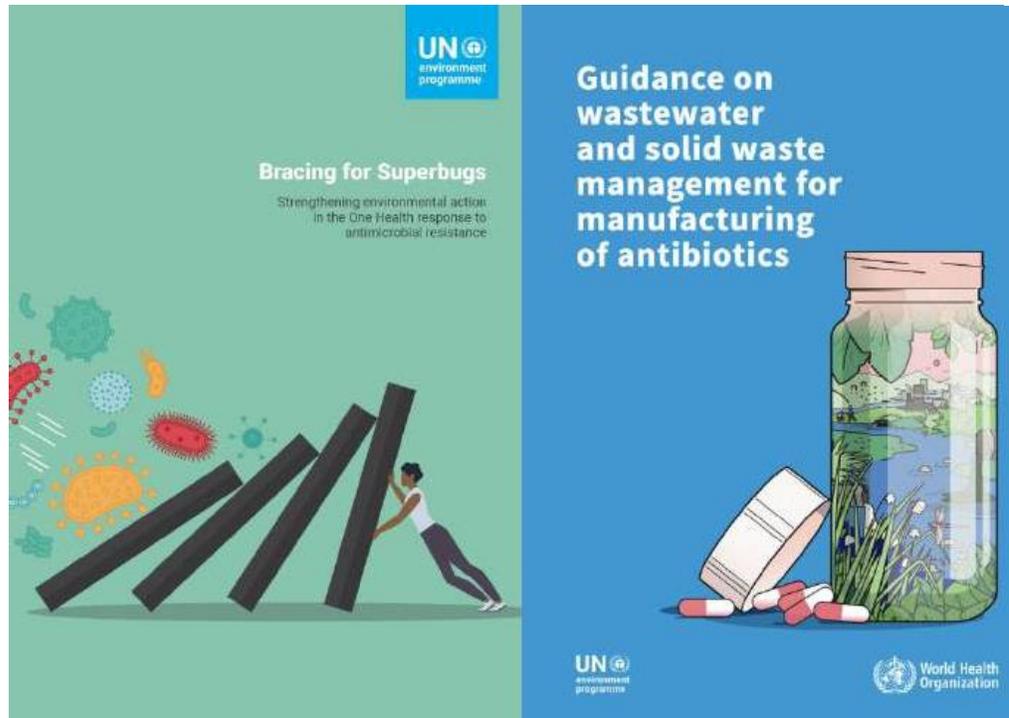
COMMENT · Volume 3, Issue 11, E806-E807, November 2022 · [Open Access](#)

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## Embracing the monsters: moving from infection control to microbial management

Claas Kirchhelle <sup>a</sup> · Adam P Roberts <sup>b</sup> [✉](#)

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Review

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

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

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

Claas Kirchhelle [✉](#)

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