



## Access to antibiotics

12<sup>th</sup> June 2024





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# Penicillin developed in Oxford, saved tens of millions of lives...



From the OxSciBlog Archives... [2008-2013]





#### Penicillin: the Oxford story

SHARE THIS

Jonathan Wood | 16 Jul 2010

- When Howard Florey came to Oxford in 1935 as the newly appointed Professor of Pathology, he arrived to state of the art but largely empty labs in the new
- Sir William Dunn School.

Antimicrobial drugs have added about 20 years to life expectancy...

## But...

<u></u>Ξ Q

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



## 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

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 in

 ♫

 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



#### No or inappropriate access leads to FINANCIAL TIMES AMR COMPANIES TECH MARKETS CLIMATE ODINION WORK CAREERS LIEED ARTS WITH



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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# 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



ReAct

# AMR burden from bloodstream infections by deprivation in UK



IMD = Indices of Multiple Deprivation

## Key drivers of resistance





## 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.



# 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

GOPEN ACCESS DEPER-REVIEWED

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

Cecilia Kållberg 📴, Christine Årdal, Hege Salvesen Blix, Elli 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	Abstract										
Introduction	Background										
Material and methods											
Results	Despite the urgent need for new, effective antibiotics, few antibiotics of value have enterer 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										
Discussion											
Conclusion	approved antibio availability and m	tics needs to be better und narket introduction of antibi	needs to be better understood. In this study, we analyze geographic tet 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

1 (1100 11 11

#### NCE Year Year High Upper Countries Total Span Code Middle Middle number of after Income with MA first Countries Income Income registered countries MA Countries Countries sales with registered sales MOXIFLOXACIN 75 1999 3 67% 26% 39 0-10 5 65% 29% 49 11-20 10 59% 27% 13% 70 21-30 LINEZOLID 70 31-2000 3 81% 36 40 5 72% 2.3% 43 41-50 10 58% 27% 14% 59 51-60 ERTAPENEM 2002 3 63% 31% 32 65 61-70 29% 5 65% 48 71-80 10 53% 33% 13% 64 81-90 TIGECYCLINE 2005 69% 25% 36 65 91-3 100 50 5 64% 26% 10 55% 29% 65 DAPTOMYCIN 100% 2003 3 1 47 19 5 95% 10 62% 29% 42 DORIPENEM 2005 3 3 44 70% 22% 27 5 10 26 50% 27% TELITHROMYCIN 2001 72% 18 43 3 28% 61% 34% 38 5 10 22 82% 14% CEFTAROLINE 2010 3 78% 23 31 GATIFLOXACIN 1999 3 45% 45% 11 30 15 5 47% 40% 10 21% 29% 43% 14 GEMIFLOXACIN 2003 4 28 3 75% 25% 40% 15 40% 5 10 35% 23 35% 30% DALFOPRISTIN/ 1999 100% 21 3 15 QUINUPRISTIN 5 100% 14 10 100% 3 PRULIFLOXACIN 2002 3 100% 0% 2 14 2 10 67% 22% 9

Lower

Table 2. Spread of NCEs between country income classes

#### 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/	1999	3	20%	60%	0%	13%	7%	0%	0%	15	21
QUINUPRISTIN											
		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:  $\beta$ -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





INEOS OXFORD MUNICIPALITY OF OXFORD MULTIPLE ALL THE ALL THE STRATEGY GROUP FOR

ANTIMICROBIAL RESISTANCE

#### AMR IN THE COMMUNITY **WORKSHOP**



Save The Date **Wed, 16 March, 2022** 10.00 - 13.00 CET (9.00 - 12.00 GMT) | Online Meet

JOIN US ZOOM LINK: <u>https://itu.zoom.us/j/92745514230</u>

Organised jointly by the Global Health Strategy Group for Antimicrobial Resistance, an initiative of the University of Oxford, and the Working Group for Collaborations and Outreach of the ITU-WHO Focus Group for AI for Health in partnership with:



## **Toolkit of access strategies**



#### SECURE INTERIM REPORT

4: SECURE Pricing and Payment models
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## **Access Thinking**

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

2024 report

## Testing, treatment, and stewardship

			Afi	rica				LA TAM				MEA		Eur	ope
		ZA	KE	EG	NG	МХ	BR	со	GT	PA	IN	JO	РК	GE	RS
ASPs	<b>Presence of an active ASP plan</b> (Widespread implementation / moderate level implementation / in writing)							/							
Treatment	Presence of treatment guidelines (National level / local or hospital level implementation of international guidelines / no guidelines)														
guidelines	<b>Compliance to guidelines</b> (Full compliance across hospitals / moderate compliance / low or no compliance)														
Testing	Level of diagnostic and sensitivity testing performed (Widespread testing in most hospitals / moderate level of testing/ no testing )														
	<b>Testing resources available</b> (Automated testing widely available / mainly manual testing available / no testing in any hospitals)														
		Private													

Public

## Testing, treatment, and stewardship

			Africa					LATAM				MEA	Europe		
		ZA	KE	EG	NG	МХ	BR	СО	GT	РА	IN	JO	РК	GE	RS
ASPs	<b>Presence of an active ASP plan</b> (Widespread implementation / moderate level implementation / in writing)														
Treatment	<b>Presence of treatment guidelines</b> (National level / local or hospital level implementation of international guidelines / no guidelines)														
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Tostina	Level of diagnostic and sensitivity testing performed (Widespread testing in most hospitals / moderate level of testing/ no testing )														
Testing	Testing resources available (Automated testing widely available / mainly manual testing available / no testing in any hospitals)														
		Others	rtiary											24	

## Unmet needs: Public v Private Sector

		Afi	rica		LATAM			MEA			Europe			
	ZA	KE	EG	NG	МХ	BR	со	GT	PA	IN	JO	РК	GE	RS
	T1	T1	T1	T2	T1	T1	T2	T2	T2	T1	T1	T2	T2	T2
Stable supply of essential antibiotics														
New products that better manage carbapenem- resistant infections														
Improved efficacy and response to currently available treatments														
Convenient frequency of administration														
Better price / affordability														
Improved safety / toxicity														
Accurate early diagnosis of bacterial infection														
Testing for carbapenem resistance														
Guarantee of product quality														
	Private													

Public

## 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

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,

#### **One Health**



## **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 27<sup>th</sup> and Friday 28<sup>th</sup> 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

# <figure>

 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 o1, Yu Wango1, Marius Glibert<sup>2,3</sup>, Thomas P. Van Boeckel o<sup>1,4</sup>\*

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

artend 2. Spatial Epidemiology Lab. a de la Rehenciro Stanflans, Brussels, y, New Dehl, 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%.</li>
  - three quarters given by injection.

## Per kilo of livestock (more variability)

#### Antibiotic usage in livestock, 2020



Milligrams of total antibiotic use per kilogram of livestock. This is adjusted for differences in livestock numbers and species by standardizing to a population-corrected unit (PCU). A suggested global cap of antibiotic use in livestock is set at 50mg/PCU.



## 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 crossdisciplinary 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)

#### ≡ Q

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

This report examines the causes and effects of an increasing global resistance to antibiotics: from the pressures doctors are under to prescribe them even for viral infections, to what new treatments are currently in the pipeline, as well as what role can the consumer play in reducing antibiotic use in the food chain



## State of development of NAPs

#### A snapshot of AMR self-assessment

Country progress with development of a national action plan on AMR

- A No national action plan or plan under development
- B National action plan developed
- C National action plan approved by government and being implemented
- D National action plan has operational plan and monitoring mechanism in place
- E Financial provision for the national action plan implementation included in national plans and budgets



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## State of development of NAPs

Nearly fifty countries still have no national system for monitoring the use of antimicrobials in human health

- A No national plan or system for monitoring use of antimicrobials
- B System designed for surveillance of antimicrobial use, includes monitoring national sales or consumption of antibiotics in health services
- C Total sales of antimicrobials are monitored at national level and/or some monitoring of antibiotic use at sub-national level
- D Prescribing practices and appropriate antibiotic use are monitored in a national sample of healthcare settings
- E Regular data reported on antimicrobial sales/consumption for human use and antibiotic prescribing and appropriate/rational use



#### Number of countries

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## The implementation gap



#### Governance scores

Governance score from 0 (worst) to 100 (best), as assessed by a study of 114 countries' data and national action plans in 2021-22



## Highly variable performance

• Country with below-average governance and above-average resistance



AMR governance scores

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Source: Patel et al, 2023, IHME

#### Country legislation on antimicrobial use

Presence of laws or regulations covering:



#### Country legislation on antimicrobial use

Presence of laws or regulations covering:

Prescription and sale of antimicrobials for terrestrial animal use



FINANCIAL TIMES Source: <u>WHO Country Self-assessment Survey (TrACSS)</u>, October 2022 • \*For terrestrial and/or aquatic animals

#### Country legislation on antimicrobial use

Presence of laws or regulations covering:

Yes No

Q

Prescription and sale of antimicrobials for aquatic animals

FINANCIAL TIMES Source: WHO Country Self-assessment Survey (TrACSS), October 2022 • \*For terrestrial and/or aquatic animals

#### Country legislation on antimicrobial use

Presence of laws or regulations covering:



#### Legal protection for the environment is patchy

Legislation and/or regulations in place:

Yes

Q

Prevent contamination of the environment with antimicrobials



#### Legal protection for the environment is patchy

Legislation and/or regulations in place:



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#### Legal protection for the environment is patchy

Legislation and/or regulations in place:

...wastewater discharges from health facilities for disposal in the environment



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Yes

#### Legal protection for the environment is patchy

Legislation and/or regulations in place:

...management of solid clinical waste from health facilities to be destroyed by incineration



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Yes

#### Legal protection for the environment is patchy

Legislation and/or regulations in place:

...disposal of medicines, antimicrobial agents for human use



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#### Legal protection for the environment is patchy

Legislation and/or regulations in place:

Yes No

Q

...disposal of medicines, antimicrobial agents for animal use]

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## Is this like tackling global heating?



## Who uses lots of antibiotics?

#### A



## 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

