AMR

When the drugs don’t work
The rise of antibiotic resistance
Biology

The Evolution of Bacteria on a "Mega-Plate" Petri Dish (Kishony Lab)

https://www.youtube.com/watch?v=plVk4NVIUh8
History of antibiotic discovery and concomitant development of antibiotic resistance.

Events in the Age of Antibiotics

- Penicillinase discovery
- Antibiotic resistance plasmids
- Transmissible fluoroquinolone resistance

The Dark Ages (Semmelweis)

Golden Pharmacologic Biochemical Target Genomic HTS
FDA Office of New Drugs

THE LEAN YEARS

Disenchantment (Semmelweis) (again!)

ANTIBIOTIC RESISTANCE
HOW IT SPREADS

Antibiotics are given to food producing animals and crops

Animals develop drug-resistant bacteria in their gut

Drug-resistant bacteria reaches humans through food, the environment (water, soil, air) or by direct human-animal contact

Antibiotics are given to patients, which can result in drug-resistant bacteria developing in the gut

Patient attends hospital or clinic

Drug-resistant bacteria spreads to other patients through poor hygiene and unclean facilities

Drug-resistant bacteria spreads to the general public

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

www.who.int/drugresistance

#AntibioticResistance
Bad Bugs, Few Drugs

Few New Classes in 50+ years

- Sulfonamides
- Chloramphenicol
- Tetracyclines
- Macrolides
- Glycopeptides
- Aminoglycosides
- Beta-lactams
- Streptogramins
- Quinolones
- Lincosamides
- Trimethoprim
- Cyclic lipopeptides
- Oxazolidinones

Adapted from Monnet DL, 2004

Slide courtesy: Payal Patel
Drug companies aren’t making new antibiotics. Is there an economic cure?

Aug 4, 2017 8:30 pm EDT

AMR is now getting a lot of attention
HOW BIG IS THE PROBLEM?
We estimate that by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug-resistant infections if we do not find proactive solutions now to slow down the rise of drug resistance. Even today, 700,000 people die of resistant infections every year.
WHO PRIORITY PATHOGENS LIST
FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

*Acinetobacter baumannii*, carbapenem-resistant
*Pseudomonas aeruginosa*, carbapenem-resistant
*Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

*Enterococcus faecium*, vancomycin-resistant
*Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
*Helicobacter pylori*, clarithromycin-resistant
*Campylobacter*, fluoroquinolone-resistant
*Salmonella spp.*, fluoroquinolone-resistant
*Neisseria gonorrhoeae*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

*Streptococcus pneumoniae*, penicillin-non-susceptible
*Haemophilus influenzae*, ampicillin-resistant
*Shigella spp.*, fluoroquinolone-resistant

# Mycobacteria (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), was not subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.
Antibiotic resistance prevalence and national per-capita income

Gandra S et al. *IJD*, October 2016

![Graph showing the relationship between resistance rate and national income](image)

Lines represent predicted values with shaded regions showing 95% confidence intervals according to a linear regression model.
Antibiotic resistance prevalence and national per-capita income

Gandra S et al. *IJID*, October 2016
CAUSES OF ANTIBIOTIC RESISTANCE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

- Over-prescribing of antibiotics
- Patients not finishing their treatment
- Over-use of antibiotics in livestock and fish farming
- Poor infection control in hospitals and clinics
- Lack of hygiene and poor sanitation
- Lack of new antibiotics being developed

www.who.int/drugresistance
#AntibioticResistance
ANTIBIOTIC USE IN HUMANS
The greater the volume of antibiotics used, the greater the chances that antibiotic-resistant populations of bacteria will prevail in the contest for survival of the fittest at the bacterial level.

Evidence from around the world indicates an overall decline in the total stock of antibiotic effectiveness: resistance to all first-line and last-resort antibiotics is rising.

A) Defined Daily Doses (DDDs) per 1,000 inhabitants per day

- High-income
- Upper-middle-income
- Low- & lower-middle-income

B) Defined Daily Doses (billions)

- USA
- France
- Italy
- all others
- Russia
- Brazil
- Turkey
- all others
- India
- China
- Pakistan
- all others

Klein EY et al. under review
ANTIBIOTIC USE IN ANIMALS
Global Antimicrobial Consumption in Food Animals

Some Hot spots:
Southeast coast China
South coast of India, Mumbai, Delhi

Van Boeckel et al PNAS- 2015
Countries with Highest Antimicrobial consumption in Food Animals

2010

2030

Van Boeckel et al PNAS. 2015.
WHAT ARE THE DRIVERS OF AMR?
EXAMPLE OF INDIA
Social Aspects in India

• Reasons for prescribing antibiotics:

**Private Sector**
- patient demand
- fear of clinical failure
- fear of losing patients
- economic incentives
- varying knowledge on antibiotics and antibiotic resistance

**Public Sector**
- Huge workload
- Lack of diagnostic facilities
- Pressure to use short-dated medicines

Social Aspects in India

General Public:

- self-medication
- access to antibiotics without prescription
- Utilizing pharmacies as source of healthcare
- lack of awareness of antibiotic resistance

Poor Environmental Sanitation

Population without access to improved sanitation facilities, 2015

World Bank 2016
Perfect conditions for emergence of Superbugs

HUMAN SECTOR

ANIMAL/AGRI SECTOR

PHARMA SECTOR

Inadequate waste management from human, agriculture, and pharma sector
DRUG-RESISTANT TB AS A CASE STUDY
DRUG-RESISTANT TUBERCULOSIS REMAINS A PUBLIC HEALTH CRISIS

IN 2018

ABOUT 0.5 MILLION PEOPLE FELL ILL WITH DRUG-RESISTANT TB *

ONLY ONE IN THREE PEOPLE ACCESSED TREATMENT

OF THOSE TREATED, ONLY 56% WERE TREATED SUCCESSFULLY

*The 95% uncertainty interval for the incidence of rifampicin-resistant TB is 420,000 - 560,000. About 80% of these cases had multidrug-resistant TB.
Drug-resistant TB: hard to treat with low cure rates

A patient with MDR-TB must take 14,600 pills in two years.

If you stack that many pills end-to-end, the line would be as tall as a 30-story building.
TB treatments costs rise dramatically due to AMR

Treatment costs are much higher in HICs than in LMICs (e.g., 80x higher for TB—and 20x higher for MDR-TB—in the U.S. than in India).

**Drug-resistant pathogens know no borders**


- **US (left axis)**
- **India (right axis)**

**TB** = Tuberculosis (infectious disease caused by bacteria)

**MDR** = Multidrug-resistant

**XDR** = Extensively drug-resistant; TB caused by bacteria that are resistant to some of the most effective anti-TB drugs.
SOLUTIONS & STRATEGIES
Tackling Antimicrobial Resistance on Ten Fronts

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Surveillance
- Rapid diagnostics
- Human capital
- Drugs
- Global Innovation Fund
- International coalition for action
The Longitude Prize is a £10m prize fund, with an £8m payout, that will reward a team of researchers who develop a point-of-care diagnostic test that will conserve antibiotics for future generations and revolutionise the delivery of global healthcare.

CARB-X is investing more than $500 million between 2016 and 2021 into the research and development of new antibiotics, vaccines, rapid diagnostics and other life-saving products to tackle the global threat of drug-resistant bacteria.

https://longitudeprize.org

https://carb-x.org/
Pandemics
A recent outbreak exercise held by the Johns Hopkins Center for Health Security revealed vulnerabilities that are hardwired into the American system.
Pandemic: “epidemic … over a very wide area and usually affecting a large proportion of the population”

https://academic.oup.com/jid/article/200/7/1018/903237
Famous, historic pandemics

• 1347 to 1351 Black Death: remade the landscape of Europe; in a time when the global population was an estimated 450 million, at least 75 million are believed to have perished throughout the pandemic

• 1918 Spanish flu: mortality rate as high as one in five and an estimated one-third of the world population afflicted, as many as 50 million people are believed to have died.
Famous ‘modern’ plagues

- HIV: originated from non-human primates in the 1920s, recognized in humans in 1980s, and killed >35 million people
- Swine flu: One of the new strains was the H1N1 "swine flu" virus that originated in Mexico in 2009. The strain went on to kill more than 18,000 people around the world.
Seven reasons we're at more risk than ever of a global pandemic

By Meera Senthilingam, CNN
③ Updated 2:21 PM ET, Mon April 10, 2017
1. Growing populations and urbanization
2. Encroaching into new environments
3. Climate change
4. Global travel
5. Civil conflict
6. Fewer doctors and nurses in outbreak regions
7. Faster information
“the global response to the rise of new pathogens has continued to be limited, uncoordinated, and dysfunctional. From SARS to MERS, H5N1 to H1N1 to H7N9, the story has been similar. Poor nations are unable to detect new diseases quickly and bring them swiftly under control. Rich nations generally show only marginal interest in outbreaks until the microbes seem to directly threaten their citizens, at which point they hysterically overreact. Governments look after their own interests, cover up outbreaks, hoard scarce pharmaceutical supplies, prevent exports of life-saving medicines, shut borders, and bar travel.”
Lessons from the Ebola Outbreak in West Africa

POLICY FORUM

Toward a Common Secure Future: Four Global Commissions in the Wake of Ebola

Lawrence O. Gostin¹*, Oyewale Tomori², Suwit Wibulpolprasert³, Ashish K. Jha⁴, Julio Frenk⁵, Suerie Moon⁶, Joy Phumaphi⁷, Peter Piot⁸, Barbara Stocking⁹, Victor J. Dzau¹⁰, Gabriel M. Leung¹¹

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Summary Points

- Four global commissions reviewing the recent Ebola virus disease epidemic response consistently recommended strengthening national health systems, consolidating and strengthening World Health Organization (WHO) emergency and outbreak response activities, and enhancing research and development.

- System-wide accountability is vital to effectively prevent, detect, and respond to future global health emergencies.

- Global leaders (e.g., United Nations, World Health Assembly, G7, and G20) should maintain continuous oversight of global health preparedness, and ensure effective implementation of the Ebola commissions’ key recommendations, including sustainable and scalable financing.
Global epidemics: how well can we cope?

Although numerous initiatives have been launched to improve global capacity to respond to major outbreaks of disease, worrying gaps remain, report Jennifer Leigh and colleagues

Jennifer Leigh DrPH candidate¹, Gabrielle Fitzgerald chief executive officer², Elvis Garcia DrPH candidate¹, Suerie Moon director of research³

¹Harvard T H Chan School of Public Health, Boston, MA, USA; ²Panorama Global, Seattle, Washington, USA; ³Global Health Centre, Graduate Institute of Geneva, Switzerland
Summary points

The west Africa Ebola outbreak in 2014-5 highlighted deficiencies in global capacity to respond.

This year’s Ebola outbreak in the Democratic Republic of Congo showed that some of those deficiencies have been addressed.

However, more progress needs to be made related to preparedness, monitoring, and knowledge sharing.

Overall leadership is lacking, leading to numerous unlinked initiatives rather than a functional global response.

Stewardship beyond WHO is needed.

Many funding promises have not been met as epidemics have fallen down the political agenda.
Ring the alarm

The next epidemic is coming. Here’s how we can make sure we’re ready.

By Bill Gates | April 27, 2018
“The 2014 Ebola outbreak was a stark reminder of how vulnerable our society is to epidemics of infectious diseases. We weren’t ready then, and we’re still not ready now—but we can be. We don’t know when the next epidemic will strike, but I believe we can protect ourselves if we invest in better tools, a more effective early detection system, and a more robust global response system.”
Post Ebola, the world responded

- New tools (e.g. Ebola vaccine, diagnostics)
- Global Health Security Agenda
- CEPI
- Pandemic Emergency Financing Facility
New tools for Ebola

Xpert Ebola on GeneXpert platform
100% sensitivity & 96% specificity

Corgenix ReEBOV Antigen Rapid Test Kit
100% sensitivity and 92% specificity

Semper et al, PLoS Medicine, 2016
Broadhurst et al, Lancet 2015
The Global Health Security Agenda (GHSA) was launched in February 2014 and is a growing partnership of over 64 nations, international organizations, and non-governmental stakeholders to help build countries’ capacity to help create a world safe and secure from infectious disease threats and elevate global health security as a national and global priority.

https://www.ghsagenda.org/home
New vaccines for a safer world

CEPI is a global alliance financing and coordinating the development of vaccines against infectious diseases.

http://cepi.net/
The World Bank Group, with the support of Japan, Germany and the World Health Organization, has developed the Pandemic Emergency Financing Facility (PEF), a quick-disbursing financing mechanism that provides a surge of funds to enable a rapid and effective response to a large-scale disease outbreak. Eligible countries can receive timely, predictable, and coordinated surge financing if affected by an outbreak that meets PEF's activation criteria. The PEF breaks new ground by providing the first-ever insurance for pandemic risk, offering coverage to all low-income countries eligible for financing under IDA.
From Ebola to Zika: international emergencies and the securitization of global health

viewing the response to international emergencies only through the limited prism of security would condemn global health to an infinite succession of periods of “war” interspersed with “truces” focused on surveillance systems, rather than confronting the causes of the epidemics, rooted in the social determinants of health. If the immediate responses are not accompanied by structural changes capable of promoting a radical reduction in inequalities, the question remains: who will truly be safe at the end of each “war”? 


Deisy Ventura
1. Rising tide of isolationism and xenophobia — a turn inward — in many high-income nations, particularly the United States and European countries.

2. Growing tide of antiscientific thinking and resistance to Evidence-based medicine — often associated with surging populism and manifesting in the rise of the antivaccination movement.

3. Disease-related danger from change
If there really was a new pandemic, is the world unified enough to fight it??