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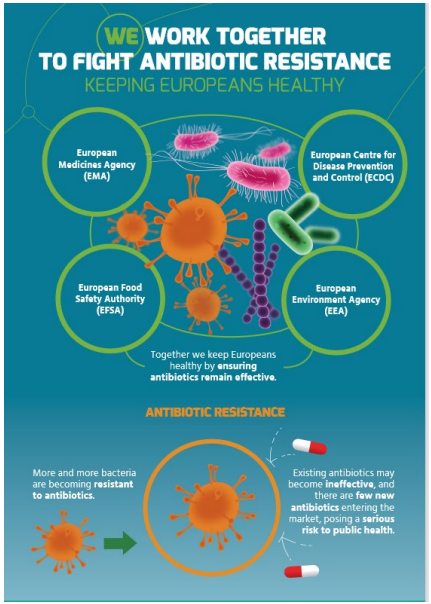
SCIENCE MEDICINES HEALTH

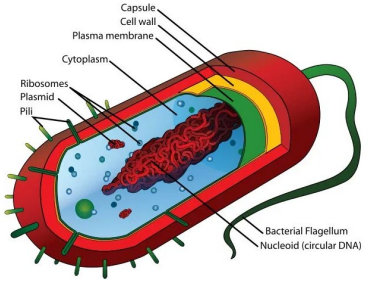
ANTIMICROBIAL RESISTANCE

OVERVIEW OF EMA ACTIVITIES



Presented by Dr. Radu Botgros
Senior Scientific Officer, Health Threats and Vaccines Strategy
European Medicines Agency

DEFINITIONS (for completeness)

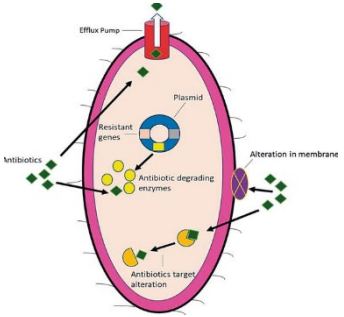


Antimicrobial=antibiotic/antiviral/antifungal/antiprotozoal

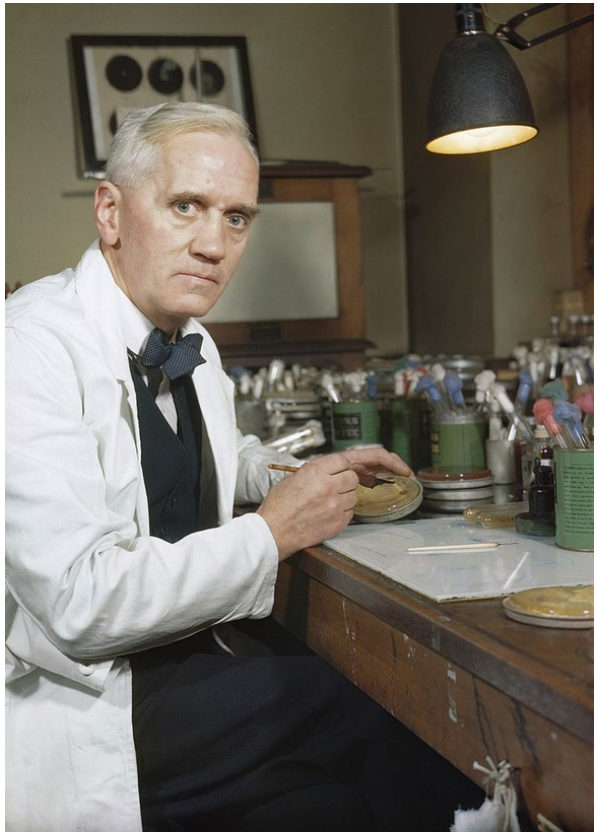
- Active substances of natural or synthetic origin that kill or inhibit the growth of microorganisms.

Antimicrobial resistance (AMR)= the ability of microorganisms of becoming increasingly resistant to an antimicrobial (to which they were previously susceptible)

- A consequence of natural selection, therefore unavoidable when using the drug
  - Exacerbated by human factors: inappropriate use in humans and animals, inadequate practices in the food chain and in health care settings etc.
- Genetic mutations conferring resistance (some that can be passed between the microorganisms)



AMR was foreseen by the discoverer of penicillin…



Sir Alexander Fleming FRS FRSE FRCS (1881–1955)

ALEXANDER FLEMING

Penicillin

Nobel Lecture, December 11, 1945

"…But I would like to sound one note of warning. […] It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

…and has become a global One Health threat

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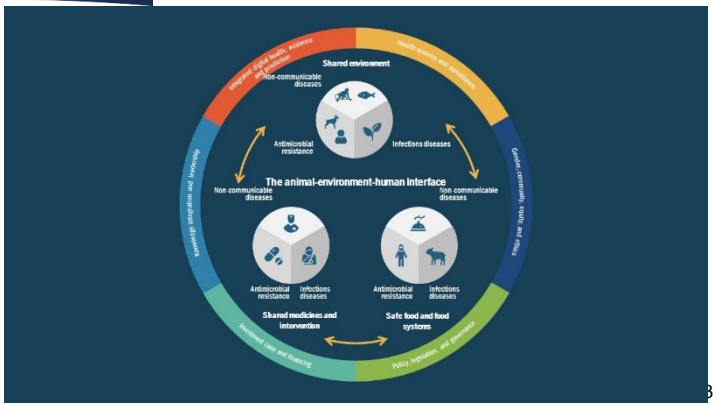
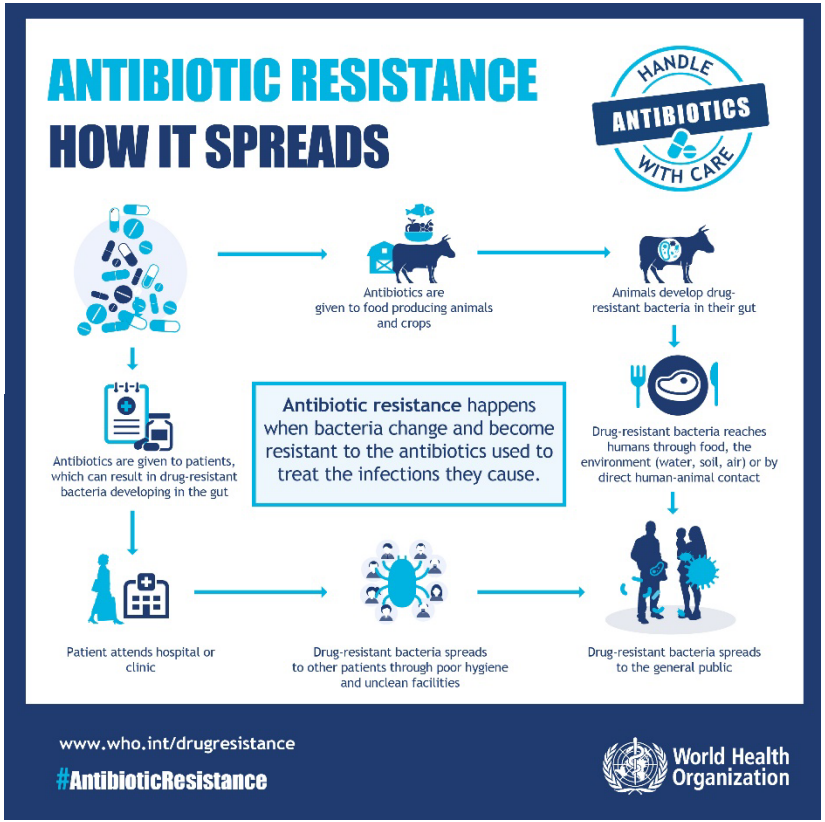
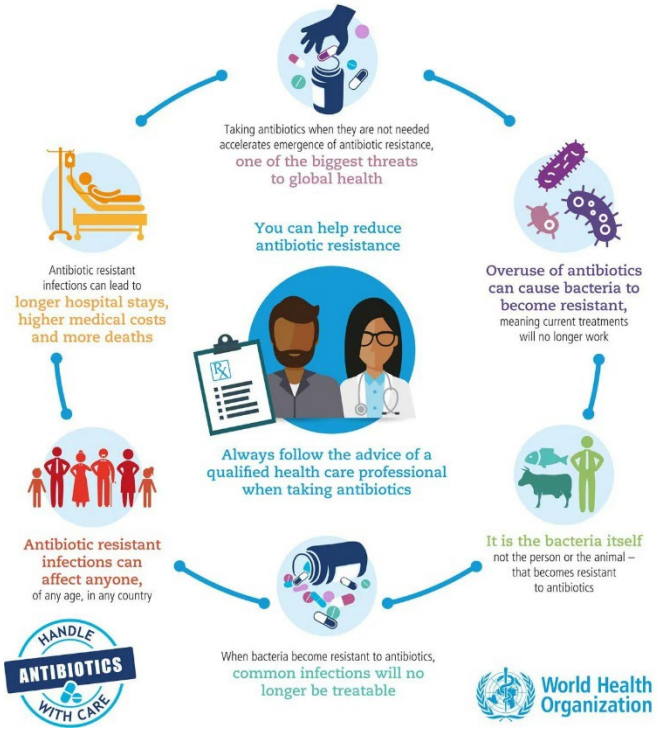




AMR as perceived by the general public a short while ago



- Three quarters (76%) of respondents think that antibiotic resistance happens when the body becomes resistant to antibiotics. In fact bacteria—not humans or animals—become resistant to antibiotics and their spread causes hard-to-treat infections.
- Two thirds (66%) of respondents believe that individuals are not at risk of a drug-resistant infection if they personally take their antibiotics as prescribed. Nearly half (44%) of people surveyed think antibiotic resistance is only a problem for people who take antibiotics regularly. In fact, anyone, of any age, in any country can get an antibiotic-resistant infection.
- More than half (57%) of respondents feel there is not much they can do to stop antibiotic resistance, while nearly two thirds (64%) believe medical experts will solve the problem before it becomes too serious.

AMR: today's figures

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33000 people die every year due to infections with antibiotic-resistant bacteria

News story

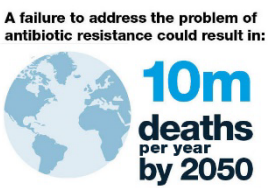
6 Nov 2018

An ECDC study estimates the burden of five types of infections caused by antibiotic-resistant bacteria of public health concern in the European Union and in the European Economic Area (EU/EEA).

Deaths reported by the CDC, WHO and GRAM Paper

https://bit.ly/3GMzVO5 https://bit.ly/3Kw58Hu https://bit.ly/3AfXywb

If no effective action is put in place, AMR to second-line antibiotics will be 72% higher in 2030 compared to 2005 in the EU/EEA. In the same period, AMR to last-line treatments will more than double.



Antimicrobial resistance now a leading cause of death worldwide, study finds

Lancet analysis highlights need for urgent action to address antibiotic-resistant bacterial infections

A researcher holds up two culture plates growing bacteria in the presence of discs containing various antibiotics. The one on the right has a strain that is resistant to all antibiotics tested. Photograph: Science History Images/Alamy

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators*

Summary

Background Antimicrobial resistance (AMR) poses a major threat to human health around the world. Previous publications have estimated the effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen–drug combinations in select locations. To our knowledge, this study presents the most comprehensive estimates of AMR burden to date.

Methods We estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019. We obtained data from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7585 study-location-years. We used predictive statistical modelling to produce estimates of AMR burden for all locations, including for locations with no data. Our approach can be divided into five broad components: number of deaths where infection played a role, proportion of infectious deaths attributable to a given infectious syndrome, proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of a given pathogen resistant to an antibiotic of interest, and the excess risk of death or duration of an infection associated with this resistance. Using these components, we estimated disease burden based on two counterfactuals: deaths attributable to AMR (based on an alternative scenario in which all drug-resistant infections were replaced by drug-susceptible infections), and deaths associated with AMR (based on an alternative scenario in which all drug-resistant infections were replaced by no infection). We generated 95% uncertainty intervals (UIs) for final estimates as the 25th and 975th ordered values across 1000 posterior draws, and models were cross-validated for out-of-sample predictive validity. We present final estimates aggregated to the global and regional level.

Published Online January 20, 2022 https://doi.org/10.1016/S0140-6736(21)02724-0

See Online/Comment https://doi.org/10.1016/S0140-6736(22)00087-3

*Collaborators are listed at the end of the paper

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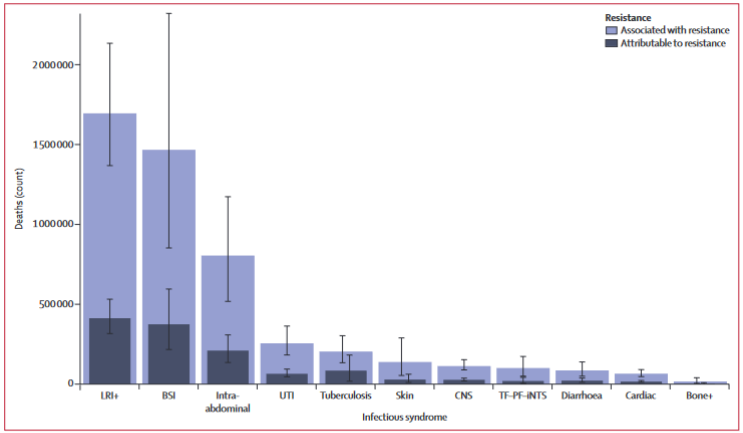

Figure 3: **Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019**

Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals. Does not include gonorrhoea and chlamydia because we did not estimate the fatal burden of this infectious syndrome. Bone+=infections of bones, joints, and related organs. BSI=bloodstream infections. Cardiac=endocarditis and other cardiac infections. CNS=meningitis and other bacterial CNS infections. Intra-abdominal=peritoneal and intra-abdominal infections. LRI+=lower respiratory infections and all related infections in the thorax. Skin=bacterial infections of the skin and subcutaneous systems. TF-PF-iNTS= typhoid fever, paratyphoid fever, and invasive non-typhoidal *Salmonella* spp. UTI=urinary tract infections and pyelonephritis.

AMR: grim forecast for the future

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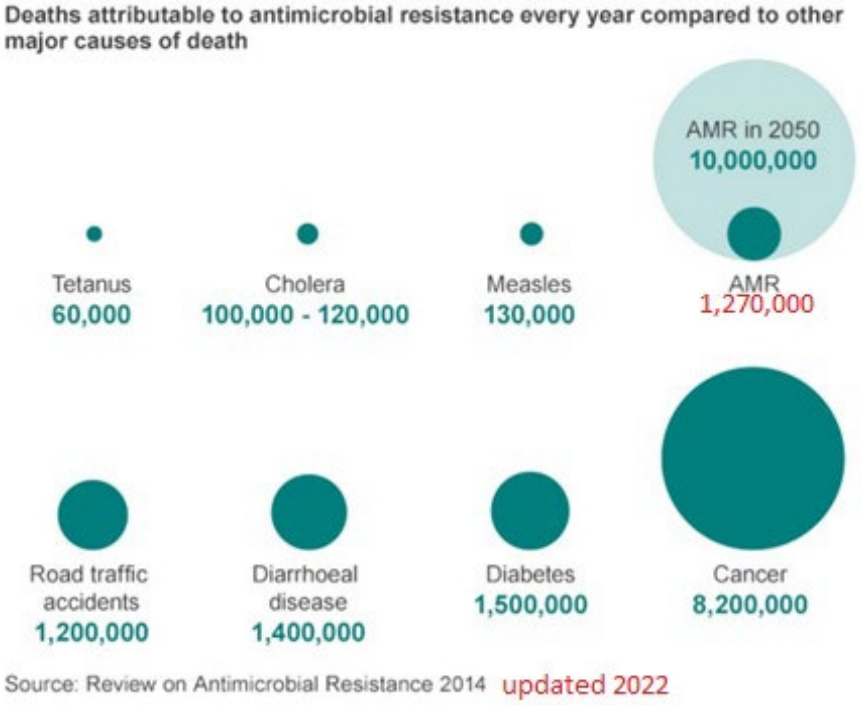
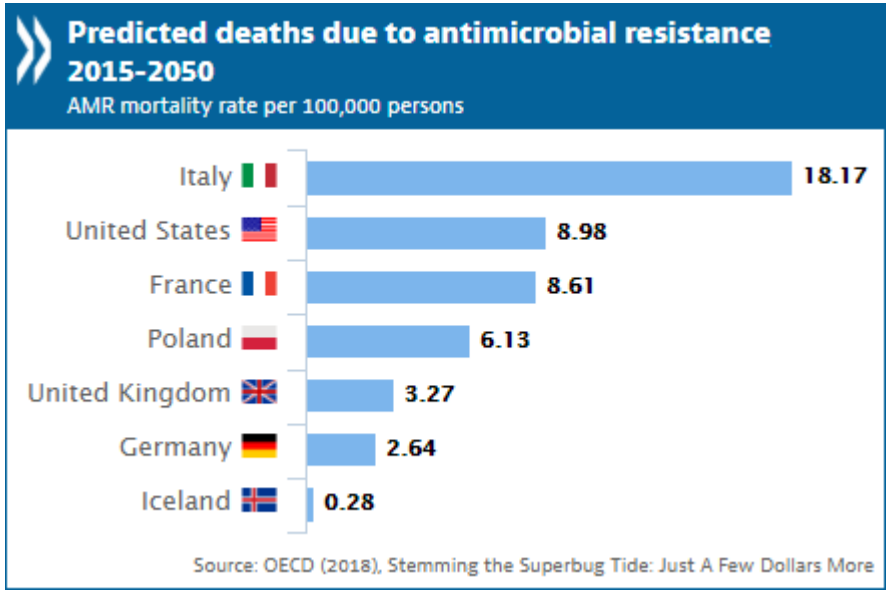


← Tweet

Prof. Dame Sally Davies
@UKAMREnvoy

The 'silent pandemic' is not silent anymore.



On the upside: AMR has made it to the political Agenda…

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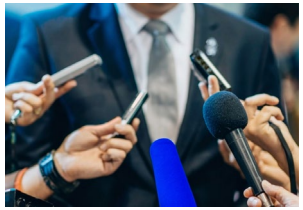

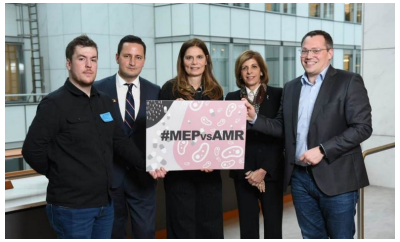

G20 leaders make historic commitment to combat AMR and TB in Declaration

10 July 2017 | Departmental news | Geneva | Reading time: 1 min (315 words)

G7 GERMANY

the core multilateral initiative, is an important component to this end. In this regard, we want to continue to support vaccination rollouts and **local vaccination production in developing countries**. Moreover, we want to step up our efforts to **tackle antimicrobial resistance (AMR)** – the "silent pandemic" that is already under way – and to develop appropriate medical countermeasures.

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2022

Policy Priorities for Germany's G7 Presidency in 2022

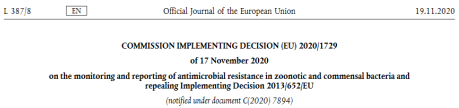
…including in the EU

Flagship initiatives related to antimicrobial resistance

- Pilot innovative approaches to EU R&D and public procurement for antimicrobials and their alternatives aiming to provide pull incentives for novel antimicrobials – target date 2021.
- Promote investment and coordinate research, development, manufacturing, deployment and use for novel antibiotics as part of the new EU Health Emergency Response Authority, prior to the start of the authority's operations preparatory action on AMR – 2021.
- Consider in the review of the pharmaceutical legislation[1] to introduce measures to restrict and optimise the use of antimicrobial medicines. Explore new types of incentives for innovative antimicrobials – 2022.

Other action

- Propose non-legislative measures and optimise the use of existing regulatory tools to combat antimicrobial resistance, including harmonisation of product information, draft evidence-based guidance on existing and new diagnostics; promote the prudent use of antibiotics and communication to healthcare professionals and patients – 2021.


L 387/8 EN Official Journal of the European Union 19.11.2020

COMMISSION IMPLEMENTING DECISION (EU) 2020/1729
of 17 November 2020
on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria and repealing Implementing Decision 2013/652/EU
(notified under document C(2020) 7894)
(Only the English version is authentic)
(Text with EEA relevance)

1. References to the 'pharmaceutical legislation' are to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67) and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

AMR goals in the EU Medicines Agencies Network strategy

HMA
Heads of Medicines Agencies

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3 July 2020
EMA/321483/2020

European medicines agencies network strategy to 2025
Protecting public health at a time of rapid change

3.4. Antimicrobial resistance and other emerging health threats

Strategic goals

Based on its environmental analysis of the strategic area and the identified challenges, the Network has laid down six main goals to be achieved within the strategy period:

1) **Provide high quality information on antimicrobial consumption and surveillance data on antimicrobial resistance in animals and humans in support of policy development.**
2) **Contribute to responsible use of antibacterial agents and effective regulatory antimicrobial stewardship in human and veterinary sectors by putting in place strategies to improve their use by patients, healthcare professionals and national authorities**
3) **Ensure regulatory tools are available that guarantee therapeutic options (with a focus on veterinary medicines) while minimising impact of antimicrobial resistance on public health and the environment**
4) **Define pull incentives for new and old antibacterial agents, including investigating support for new business models and not-for-profit development**
5) **Foster dialogue with developers of new antibacterial agents and alternatives to traditional antimicrobials, to streamline their development and provide adequate guidance in both human and veterinary medicine**
6) **Improve regulatory preparedness for emerging health threats**

Main EMA (h) activities to combat antimicrobial resistance

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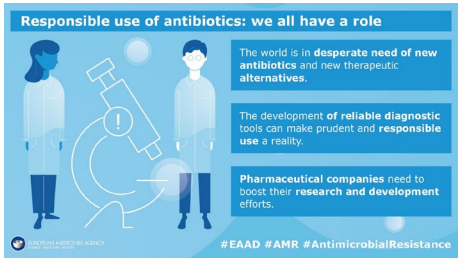

01	Update guidance to developers
02	Interact with international regulators
03	Focus on alternative therapies (other than antibiotics);
04	Role in prudent use of approved antibacterials
05	Make best use of regulatory tools to speed up approval for medicines addressing an unmet medical need
06	Early engagement with developers of medicines that tackle AMR

New antibiotics pipeline

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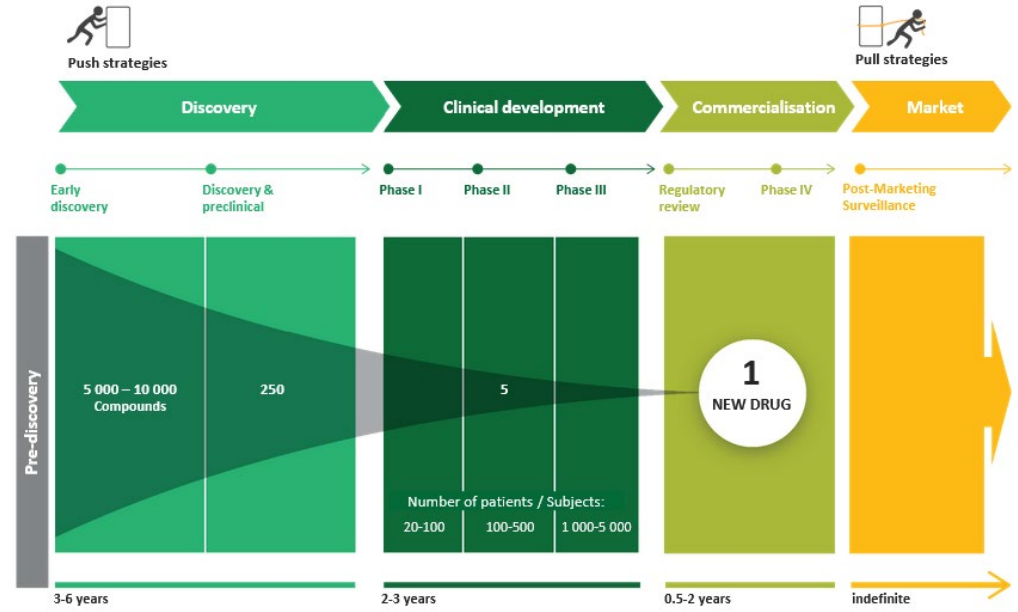
Stages in bringing new antimicrobials to market

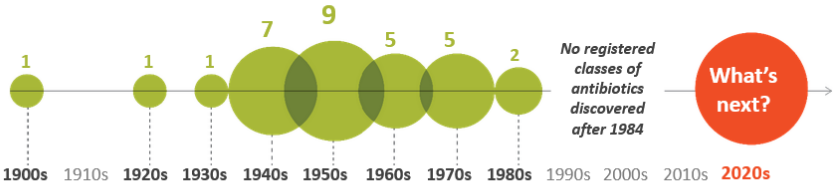


Source: ECA adopted from COMBACTE managing entity (University Medical Centre Utrecht).

Discovery of new antibiotics

More than 30-Year Void in Discovery of New Types of Antibiotics

(Number of antibiotic classes discovered or patented)



Source: ECA based on "A sustained and robust pipeline of new antibacterial drugs and therapies is critical to preserve public health", Pew Charitable Trusts, May 2016.

1. EMA updates guidance to developers

- **EMA/CHMP/351889/2013** Addendum to the guideline on the evaluation

of medicinal products indicated for treatment of bacterial infections

- **EMA/CHMP/594085/2015** Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products
- **EMA/CHMP/187859/2017** Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements.
- **EMA/CPMP/EWP/559/95 Rev 3 / 2019** Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

  ✓ ***Several Scientific Advice Procedures over the last 7 years: more than in the previous 19 years***

2. EMA interacts with international regulators

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EMA-FDA parallel SA

- ***EMA/FDA Consultative Advice option*** allows sponsors to request scientific advice from one regulatory agency and concurrently notify the other regulatory agency of the request

Independently from the above options, new development plans are mutually discussed between FDA, PMDA, HC and EMA on a monthly basis

Tripartite PMDA-FDA-EMA meetings 2016-2019 and further ones to be foreseen

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Examples of agreement - cUTI

	FDA	EMA
Primary endpoint	**Combined clinical and microbiologic response (<1x10⁴CFU/mL)** at TOC at least 5 days post completion of therapy; OR co-primary 5 days post-randomisation before PO switch and 7 days post-completion of therapy	**Microbiological response (<1x10³ CFU/mL)** at TOC 7 days post-completion of therapy, regardless of whether there was an IV/PO switch (based on requirement for **≥10⁵ CFU/mL** at baseline)

Agreed proposal for convergence: Clinical response and Microbiological response with a microbiological reduction cut-off at $1x10^3$ CFU/mL

	FDA	EMA
Population	At least 30% patients with pyelonephritis (for an indication including pyelonephritis)	Separate trials in cUTI and pyelonephritis OR limit % with pyelonephritis and stratify

Agreed proposal for convergence: instead of conducting separate trials in cUTI and pyelonephritis, include both with at least 30% cUTI patients and at least 30% pyelonephritis patients

3. EMA focuses on alternative therapies

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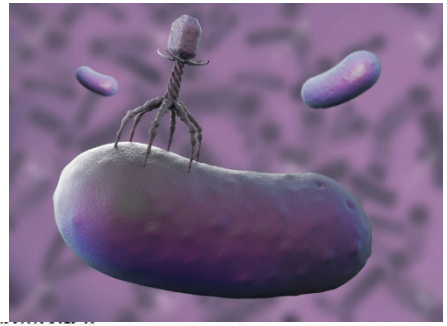
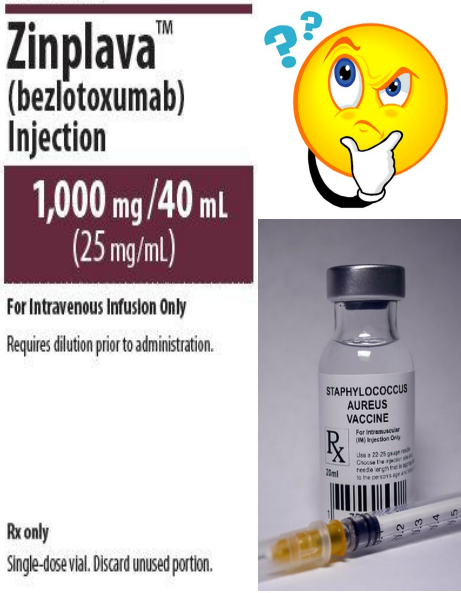


Bacteriophages

- Regulatory issues related to the need of changing the composition of the medicinal product over time. Lack of solid clinical data.

Monoclonal antibodies

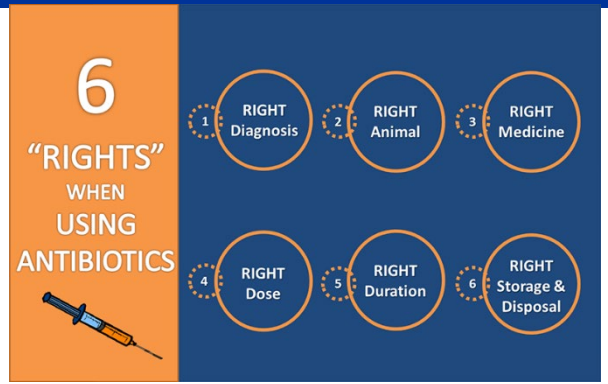
- Variety of targets. Important to have proof of concept for specific activities. Zinplava approved in the EU for prevention of C.diff. Obiltoxaximab SFL approved in the EU for the treatment and post-exposure prophylaxis of anthrax



Vaccines for healthcare associated infections

- Scientific difficulties acknowledged. Target of future interactions with FDA. High potential impact in case of success.

4. EMA role on prudent use of antibiotics in humans



- Old and new antibacterial agents need to be preserved and used rationally, but regulators should not dictate criteria for clinical practice, e.g. by defining line of use for reasons other than benefit-risk
- Rapid diagnostics are a key area, however a pragmatic approach towards rapid diagnostics in the context of product information needs to be retained at this stage
- Modernisation of SmPCs of "old antibiotics" is the most valuable contribution to rational use, i.e. ensuring that updated Product information on indications of use, posology, is provided in a harmonised way for all EU healthcare professionals

5. EMA uses regulatory tools for medicines addressing unmet need

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Tools in legislation

Conditional Marketing authorisation

- Based on less comprehensive data and with obligation to generate these data post-authorisation

Marketing authorisation under exceptional circumstances

- When comprehensive data can not be general at all, subject to specific obligations

Accelerated assessment

- Reduced assessment time for products of major public health interest

Compassionate use

- Products made available to patients prior granting of marketing authorisation

Other tools and initiatives

PRIME

- Support scheme with early and enhanced scientific dialogue

Adaptive pathways

- Scientific concept of medicines development and data generation

Innovation task force

- Forum for informal early dialogue

Early dialogue with EMA

- Other tools and initiatives

6. EMA engages early with developers to combat AMR

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EMA facilitates early engagement with medicine developers to combat antimicrobial resistance

Share

News 24/05/2019

As of today, EMA is opening up the early dialogue available through its Innovation Task Force (ITF) to all medicine developers who work on therapeutic approaches for the treatment or prevention of bacterial and fungal infections. ITF is a forum for dialogue between regulators and developers of innovative emerging therapies, methods and technologies, in the early stages of research and development. ITF is usually reserved for innovative medicines. Given the growing threat to public health caused by antimicrobial resistance and the need for new treatments, EMA is inviting all developers working on medicines for the treatment or prevention of life-threatening microbial infections to enter into early dialogue with the Agency to help strengthen the drug development pipeline for new antimicrobials.

Support **innovative** drug development

Early informal dialogue with opinion leaders on

- **Scientific, legal and regulatory** issues
- Products, **methodologies and technologies**

Free of charge

Brainstorming "style" on innovation in areas without existing guidance

First step to engage is submit completed 3-page template

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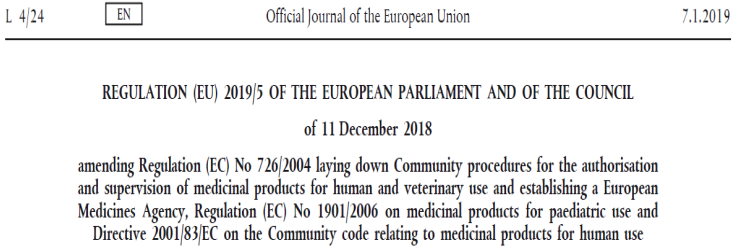
New Veterinary Legislation: new tools to fight AMR

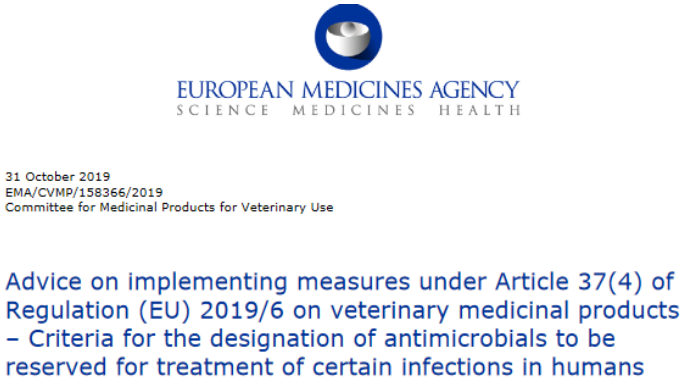


L 4/24 EN Official Journal of the European Union 7.1.2019

REGULATION (EU) 2019/5 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 11 December 2018

amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Directive 2001/83/EC on the Community code relating to medicinal products for human use



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31 October 2019
EMA/CVMP/158366/2019
Committee for Medicinal Products for Veterinary Use

Advice on implementing measures under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products – Criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans

Of relevance for HCPs:

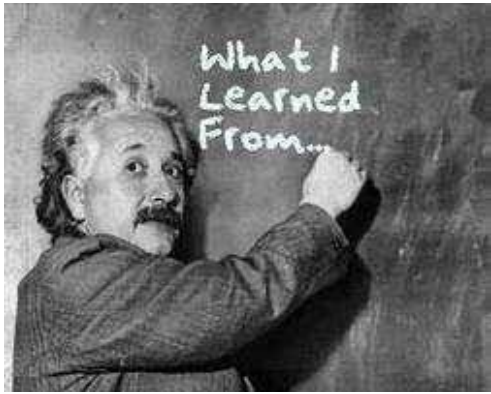
EMA/CVMP advice:

- Criteria for the designation of antimicrobials to be reserved for human medicine

Many other important activities to tackle AMR (remember OneHealth!)

Take home messages

- AMR is a major growing public One Health threat
- Needs to be tackled immediately or we risk to going back to the pre-antibiotic era!
- Increased public and political awareness over the last decade
- Global and EU cooperation and coordination of measures is key
- EMA as the EU Regulator for Medicinal products fights AMR by:
  - Updating guidance to developers;
  - Interacting with international regulators;
  - Focusing on alternative therapies;
  - Promoting prudent use of approved antibacterials;
  - Making best use of regulatory tools to speed up approval for medicines addressing an unmet medical need;
  - Engaging with developers of medicines that tackle AMR;
  - Engaging with all relevant stakeholders



Any questions?

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Send a question via our website www.ema.europa.eu/contact

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Proposal for an EMA multistakeholder workshop on AMR

Scope

- One Health approach
- Focus on antibiotics Vs full range of antimicrobial resistance including antibiotics, antivirals, antifungals and antiparasitics
- Focus on what EMA has done/is doing; with participation of other EMA partners (e.g. EC, HERA, ECDC, EFSA, WHO)
- Stakeholder discussion on what can be done, gather feedback on Agency's direction and identify actions to be taken by other actors

Format

- One-day F2F meeting; by invitation only
- Live broadcast and recorded

Audience

- Human and Veterinary stakeholders
  - Representatives of patients, consumers and healthcare professional organisations, academia, pharmaceutical industry associations, HTA bodies, EMA and National Medicines Agencies, and international partners

Date

- 14 November 2023
- Followed by the PCWP/HCPWP annual meeting with all eligible organisations on 15 November 2023

Topics for discussion

- Comments on proposed scope
- Priorities to consider when drafting the agenda - identification of potential objectives
- Expectations from patients and healthcare professionals
- Potential contributions