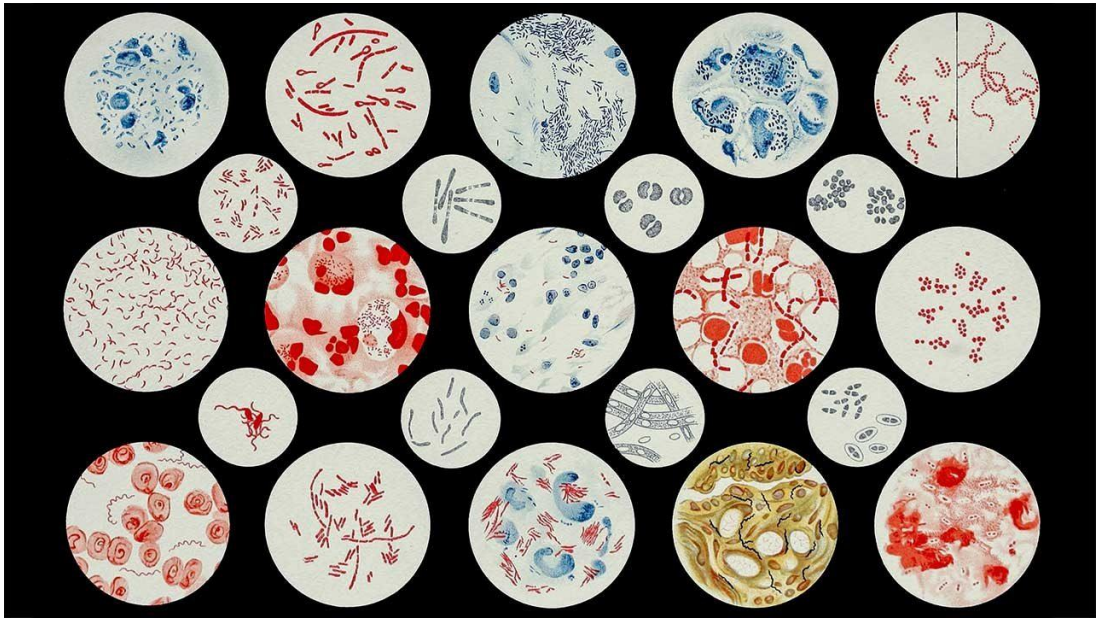
# Challenges in the treatment of bacterial infections
## *-A global view-*

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Professor of Medicine,
University of Bern, Switzerland
**Secretary General,**
**International Society of Internal Medicine (ISIM)**

# Topics

## Antimicrobial resistance (AMR)

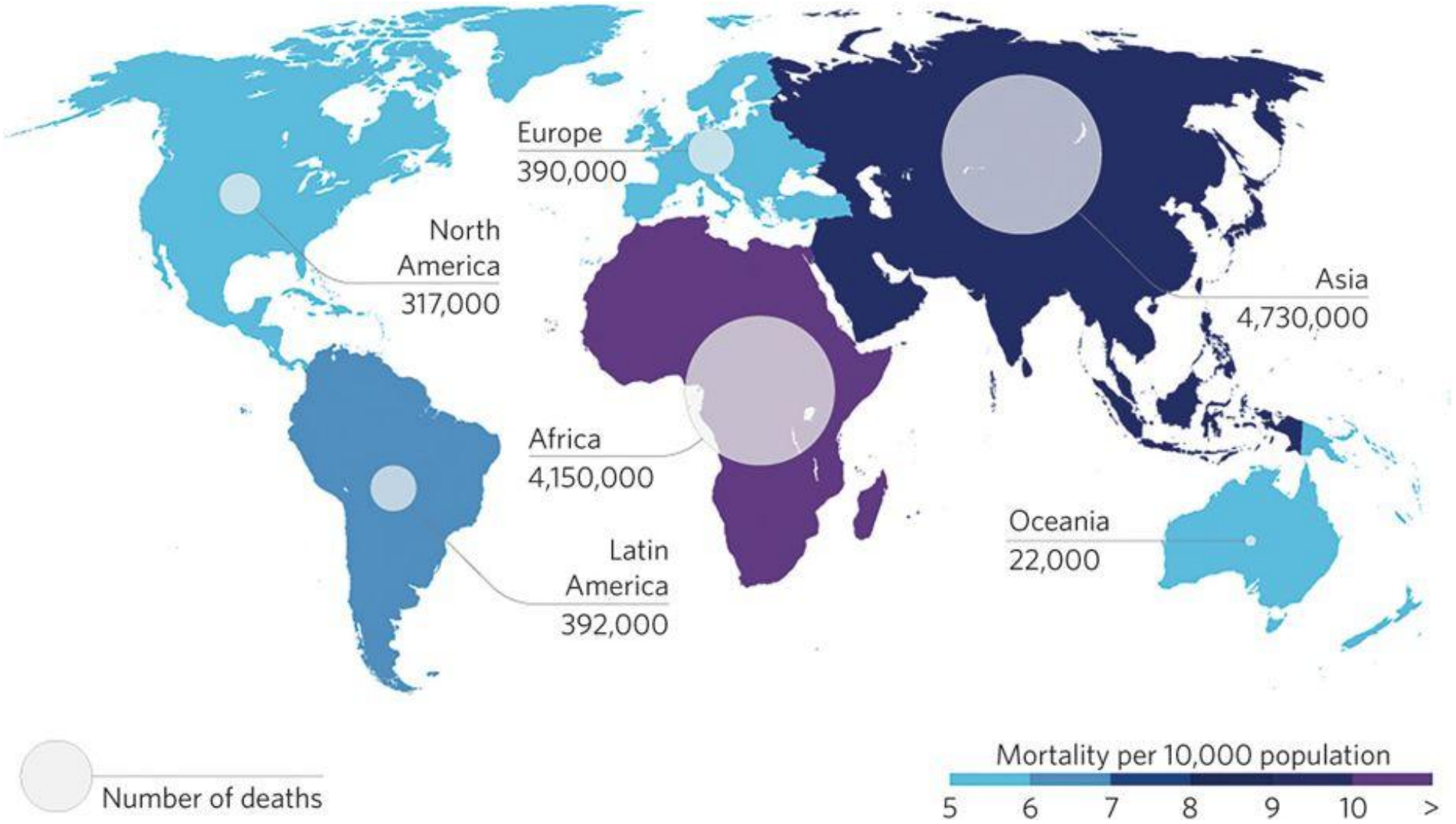
-Mechanism of drug resistance

-Use of antibiotics in food producing animals

-Non-prescription use of antimicrobials

-Speeding up diagnostics and antimicrobial susceptibility testing (AST)

# Death toll of antimicrobial resistance by 2050



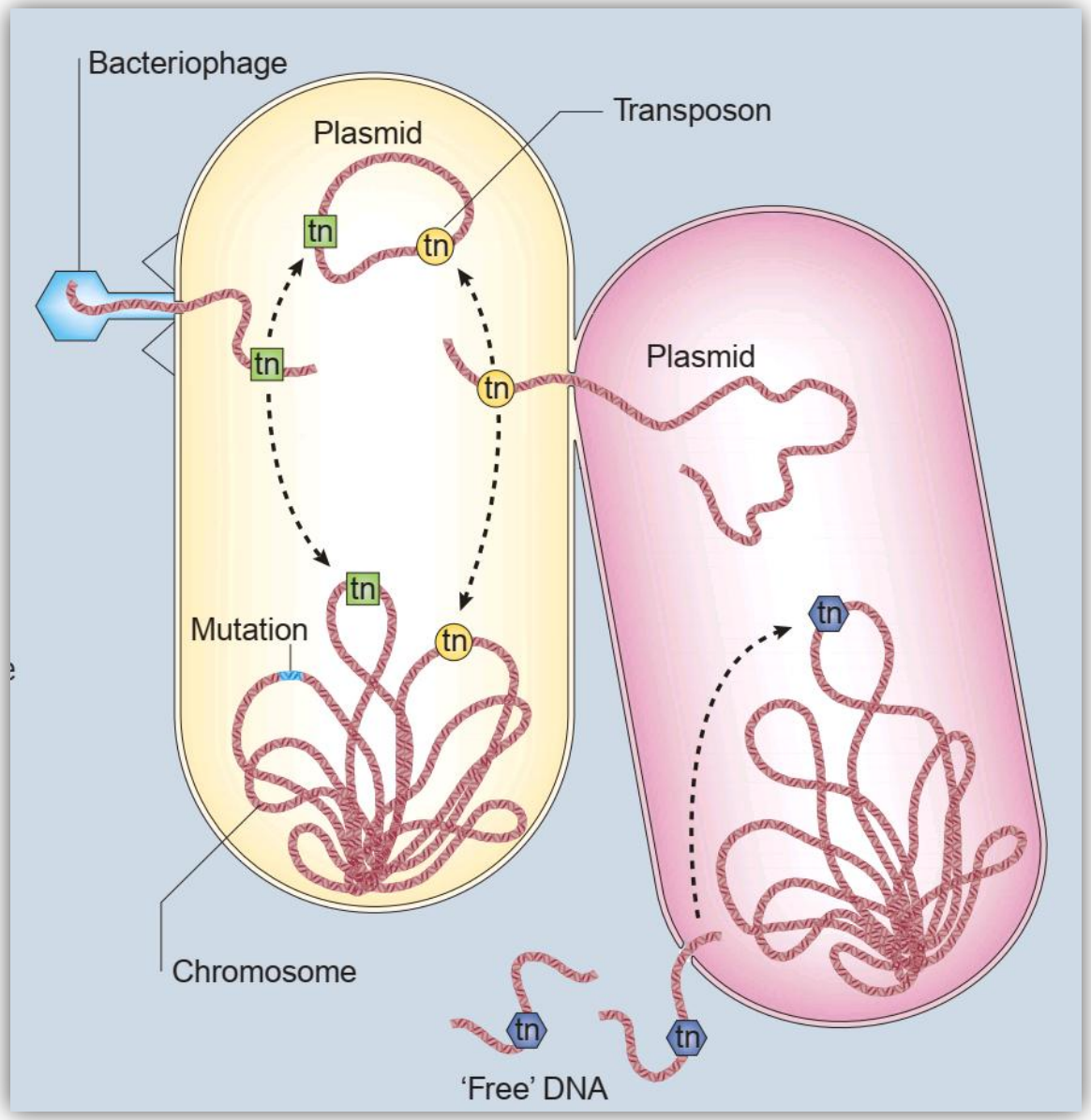

Nature Microbiology volume 1, Article number: 16187 (2016)

# Antibiotic families – mechanisms of action

**Table 1 Major antibiotic families and their mechanisms of action**

| Mechanism of action | Antibiotic families |
|---|---|
| Inhibition of cell wall synthesis | Penicillins; cephalosporins; carbapenems; daptomycin; monobactams; glycopeptides |
| Inhibition of protein synthesis | Tetracyclines; aminoglycosides; oxazolidonones; streptogramins; ketolides; macrolides; lincosamides |
| Inhibition of DNA synthesis | Fluoroquinolones |
| Competitive inhibition of folic acid synthesis | Sulfonamides; trimethoprim |
| Inhibition of RNA synthesis | Rifampin |
| Other | Metronidazole |

# Spread of drug resistance




**<u>Various mechanisms</u>:**

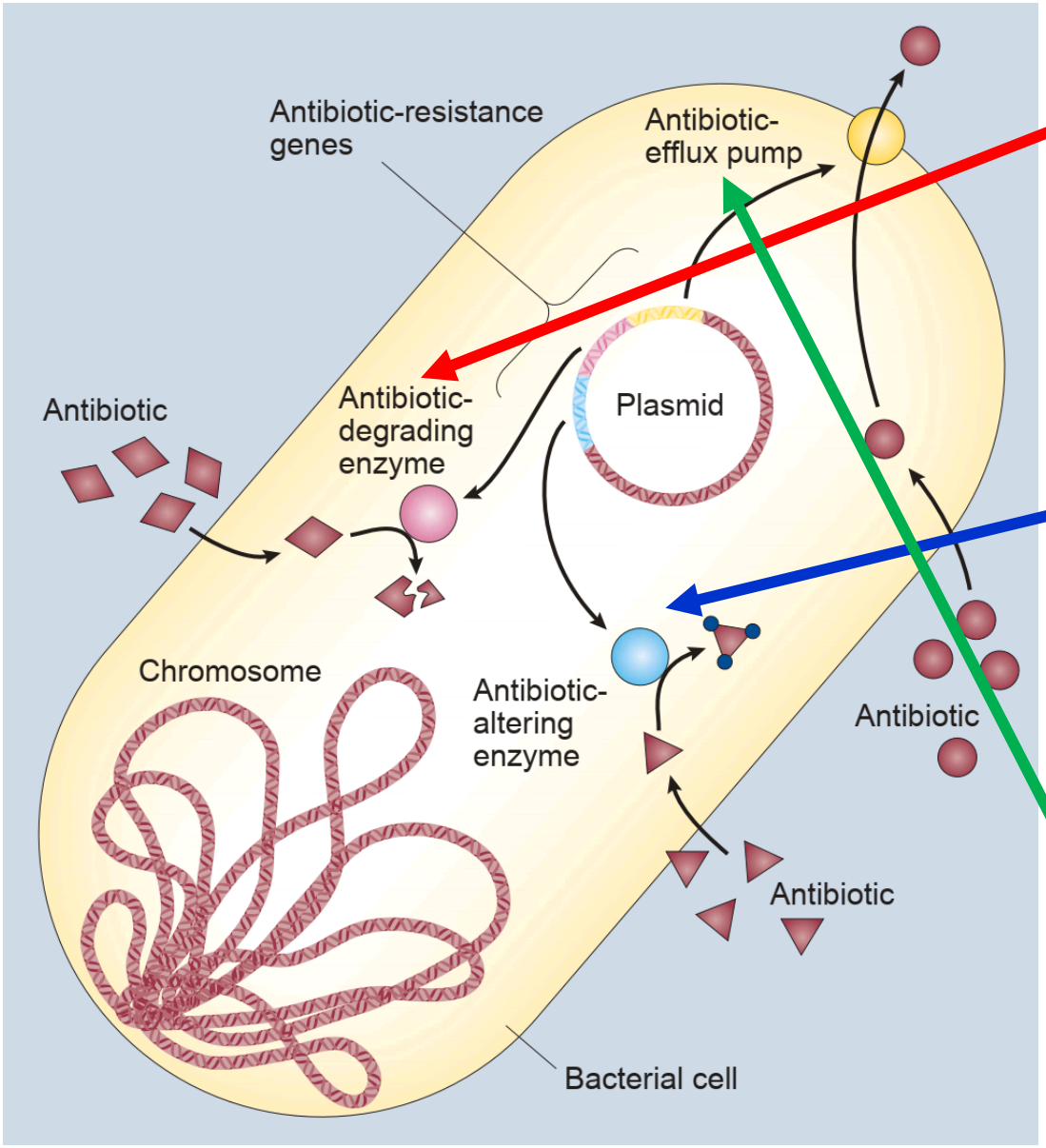
-Plasmids

-Bacteriophages

-Naked DNA

-Transposons

# Biological mechanisms of resistance




**Enzymes:**
β-lactamases destroy penicillins and cephalosporins

**Modifying enzymes**:
Inactivate chloramphenicol, streptomycin, gentamicin

**Active efflux**:
Resistance to the tetracyclines, chloramphenicol and fluoroquinolones

# Four antibiotic-resistant pathogens of global concern:
# Staphylococcus aureus, non-typhoidal Salmonella, Klebsiella pneumoniae, and Mycobacterium tuberculosis

**Table 1 Resistance to key antibiotics of *S. aureus*, *K. pneumoniae* and NTS in the six World Health Organization (WHO) world regions. The data are derived from WHO[3]**

| WHO regions | | *S. aureus* resistance to methicillin (MRSA) | *NTS* resistance to fluoroquinolones | *K. pneumoniae* resistance to third-generation cephalosporins | *K. pneumoniae* resistance to carbapenems |
|---|---|---|---|---|---|
| Africa region (47 countries) | Countries with national data | 9 (19.1%) | 9 (19.1%) | 13 (27.6%) | 4 (8.5%) |
| | Range (%) | 0–100 | 0–35 | 8–77 | 0–4 |
| | Country with lowest/highest proportion | Lesotho/Guinea-Bissau | Central African Republic/Mauritania | Namibia/South Africa | Central African Republic/South Africa |
| Region of the Americas (47 countries) | Countries with national data | 15 (31.9%) | 13 (27.6%) | 17 (36%) | 17 (36.2%) |
| | Range (%) | 21–90 | 0–96 | 4–71 | 0–11 |
| | Country with lowest/highest proportion | Canada/Chile | Several countries[a]/-Peru | Canada/Peru | Canada-Dominican Republic/-United States of America |
| Eastern Mediterranean region (23 countries) | Countries with national data | 4 (17.4%) | 4 (17.4%) | 4 (17.4%) | 4 (17.4%) |
| | Range (%) | 10–53 | 2–49 | 22–50 | 0–54 |
| | Country with lowest/highest proportion | Bahrain/Iran | Oman/Jordan | Oman/Bahrain | Oman/Iran |
| European region (53 countries) | Countries with national data | 36 (67.9%) | 29 (50.9%) | 33 (62.3%) | 31 (58.5%) |
| | Range (%) | 0.3–55 | 0–21 | 2–82 | 0–68 |
| | Country with lowest/highest proportion | Norway/Portugal | Several countries[a]/Finland | Sweden/Georgia | Several countries[a]/Greece |
| South-east Asia region (11 countries) | Countries with national data | 3 (27.3%) | 2 (18.1%) | 4 (36.4%) | 4 (36.4%) |
| | Range (%) | 10–26 | 0.2–4 | 34–81 | 0–8 |
| | Country with lowest/highest proportion | Bhutan/Myanmar | Thailand/Nepal | Bhutan/Sri Lanka | Bhutan/Myanmar |
| Western Pacific region (37 countries) | Countries with national data | 16 (43.2%) | 9 (24.3%) | 12 (32.4%) | 9 (24.3%) |
| | Range (%) | 4–70 | 0–14 | 1–71 | 0–8 |
| | Country with lowest/highest proportion | Micronesia/Republic of Korea | Brunei Darussalam/Philippines | Kiribati/Micronesia | New Zeland/China |

[a] We reported "several countries" when more than two countries have the same rate of resistance.

-MRSA
-Fluoroquinolones
-Cephalosporins
-Carbapenems

Pathogens and Global Health 2015 VOL. 109 NO. 7

# Let`s blame the doctors (and patients)……

**Primary Care / Patients**:

-Excessive prescription

-Absence of appropriate indications

-Diagnostic uncertainty often fosters over-prescription

-Self-medication, easy availability

-Perception that antibiotics are the "wonder drugs" that can rapidly cure any kind of ailments.

**Hospital care**:

-Absence of appropriate indications

-Intensive and prolonged use of antimicrobial drugs

-Failure to control infections spread from patient to patient

-According to several studies, a mean of approx. 55% of all patients received at least one dose of an antimicrobial agent during their hospital stay.

# Food producing animals

USE OF ANTIBIOTICS* FOR GROWTH PROMOTION IN FOOD-PRODUCING ANIMALS SHOULD BE COMPLETELY RESTRICTED TO PRESERVE THEIR EFFECTIVENESS.

* Medically important antimicrobials

HANDLE ANTIBIOTICS WITH CARE

#AntibioticResistance

World Health Organization

# Message


BACTERIA, INCLUDING THOSE RESISTANT TO ANTIBIOTICS, CAN BE TRANSMITTED FROM FOOD-PRODUCING ANIMALS TO HUMANS VIA FOOD.
HANDLE ANTIBIOTICS WITH CARE
#AntibioticResistance
World Health Organization

# Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis

*Karen L Tang, Niamh P Caffrey, Diego B Nóbrega, Susan C Cork, Paul E Ronksley, Herman W Barkema, Alicia J Polachek, Heather Ganshorn, Nishan Sharma, James D Kellner, William A Ghali*

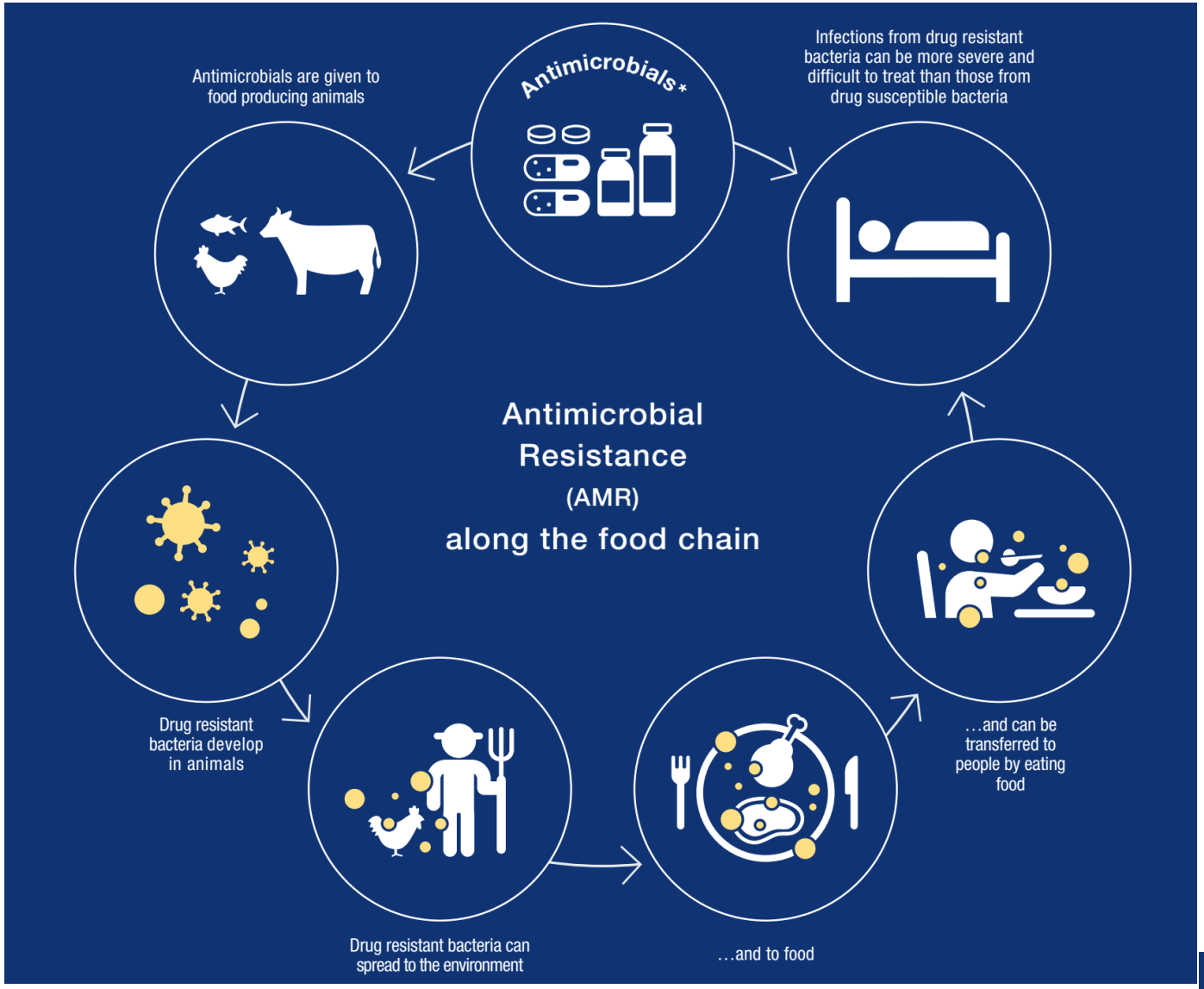
**Message:**

Antibiotics used in food-producing animals **are closely related** to those used in human medicine and can select for resistance in these animals.

Cross-species transmission of resistant bacteria or resistant genetic elements from animals to humans **can and does occur**.

*Lancet Planet Health* 2017;
1: e316–27

# AMR along the food chain

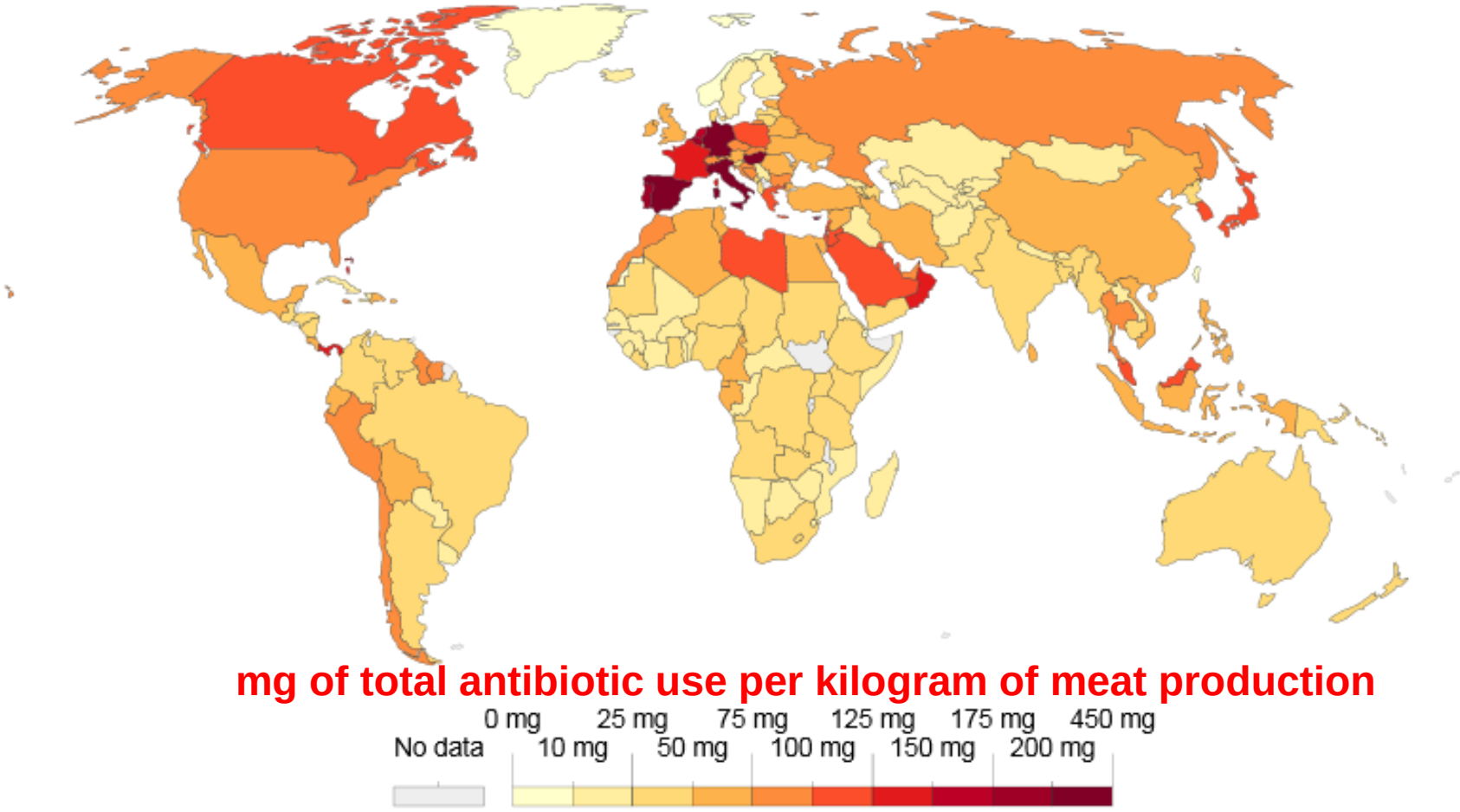



World Health Organization

# Antibiotic use in livestock, 2010

Our World in Data

Antibiotics are used in livestock for animal health and productivity, but also pose a risk for antibiotic resistance in both humans and livestock. Data is measured as the milligrams of total antibiotic use per kilogram of meat production. This is corrected for differences in livestock numbers and types, normalising to a population-corrected unit (PCU).




Source: European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption (2017) & Van Boeckel et al. (2015)
OurWorldInData.org/antibiotic-resistance-from-livestock • CC BY-SA

# Self-medication with antimicrobials

# Self-medication with antimicrobials

Self-medication with antimicrobials almost always involves **unnecessary, inadequate, and ill-timed dosing**, creating an ideal environment for microbes to **adapt rather than be eliminated**.

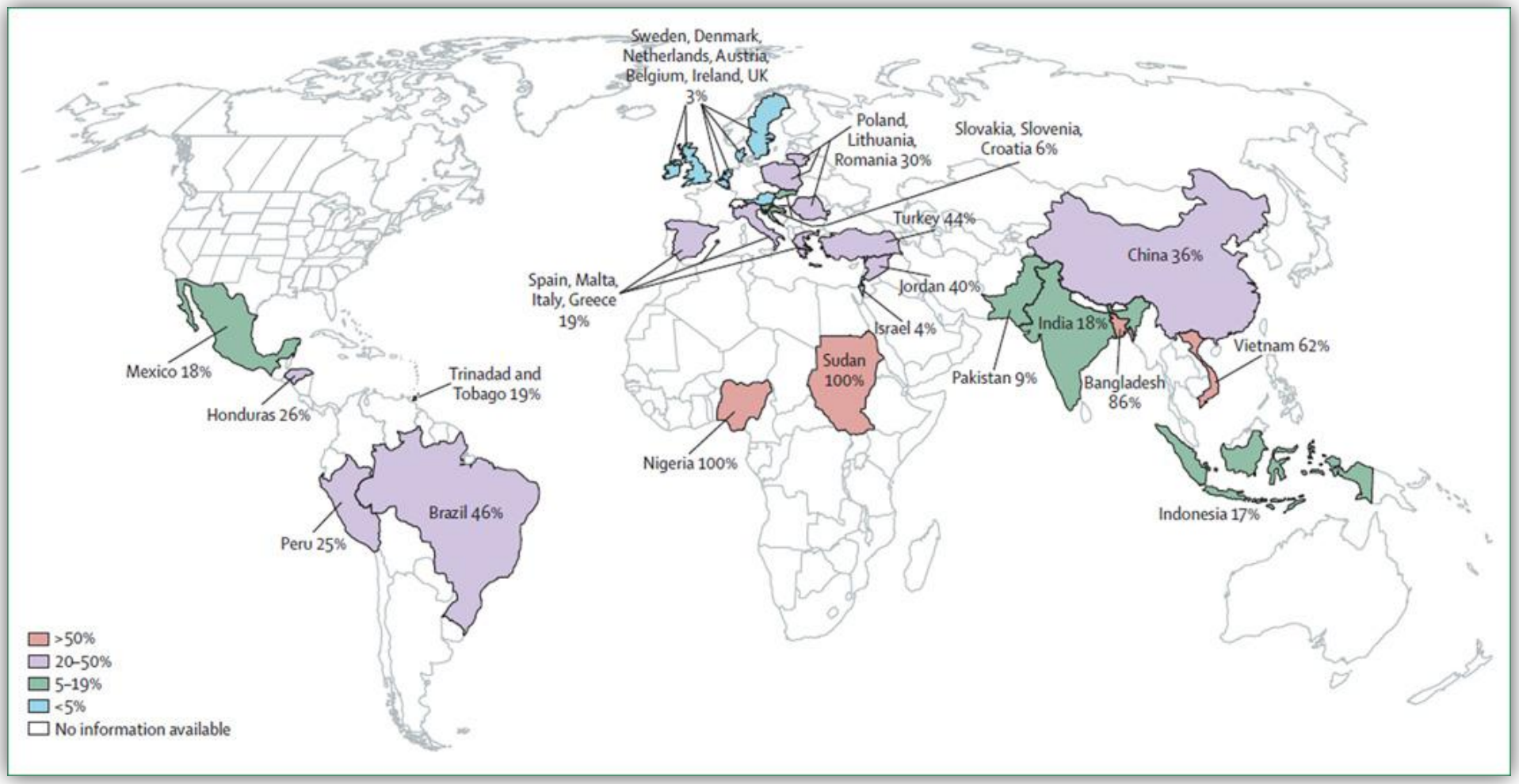
Self-medication with antimicrobials is common in many areas of world, particularly in developing countries with **loose regulatory systems.**

A higher prevalence of self-medication with antibiotics was reported in South Europe (19%) in comparison with northern Europe (3%) and central Europe (6%).

In some countries of Africa, **100%** of antimicrobial use is without prescription and in Asia it reaches **58%.**

*Lancet Infect Dis. 2011;11(9):692–701.*

# Frequency of non-prescription use of antimicrobials in the general population




Lancet Infect Dis. 2011 Sep; 11(9): 692–701.

# Speeding up diagnostics and antimicrobial susceptibility testing (AST)

# THIS WEEK

EDITORIALS





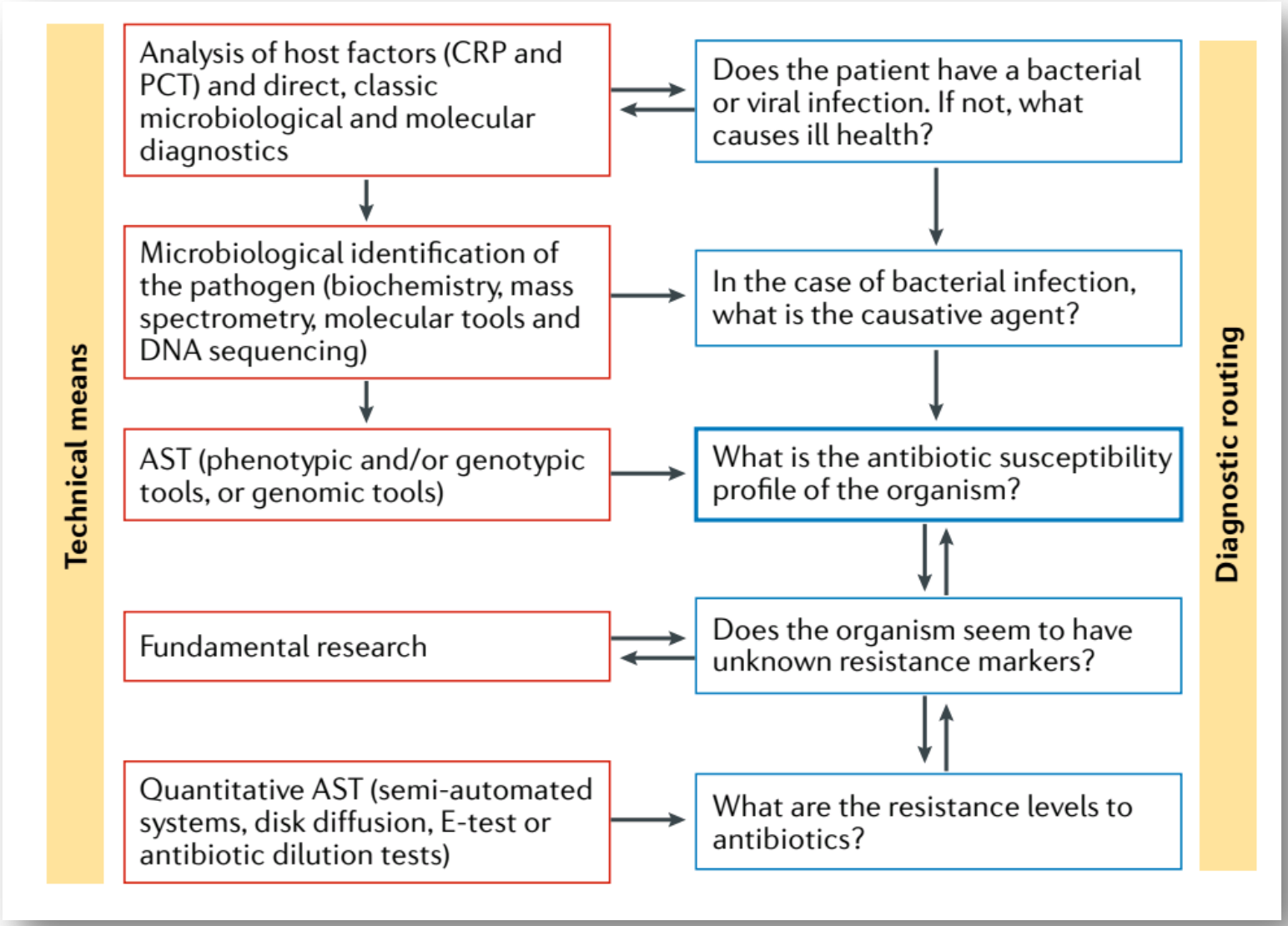
# Progress on antibiotic resistance

*Clinicians, companies and researchers have come together to suggest ways to break the deadlock on finding better ways to prescribe antibiotics.*

A good place to focus urgent action is the delay between a person becoming ill and receiving **effective** treatment.
Shortening that time would reduce unnecessary prescribing, minimize the spread of resistance and, most importantly, give people the best chance of recovering.

**We have to speed up:**
***Bacterial culture*** to identify the infectious agent and ***AB resistance testing***.

# Triaging infections using diagnostic testing



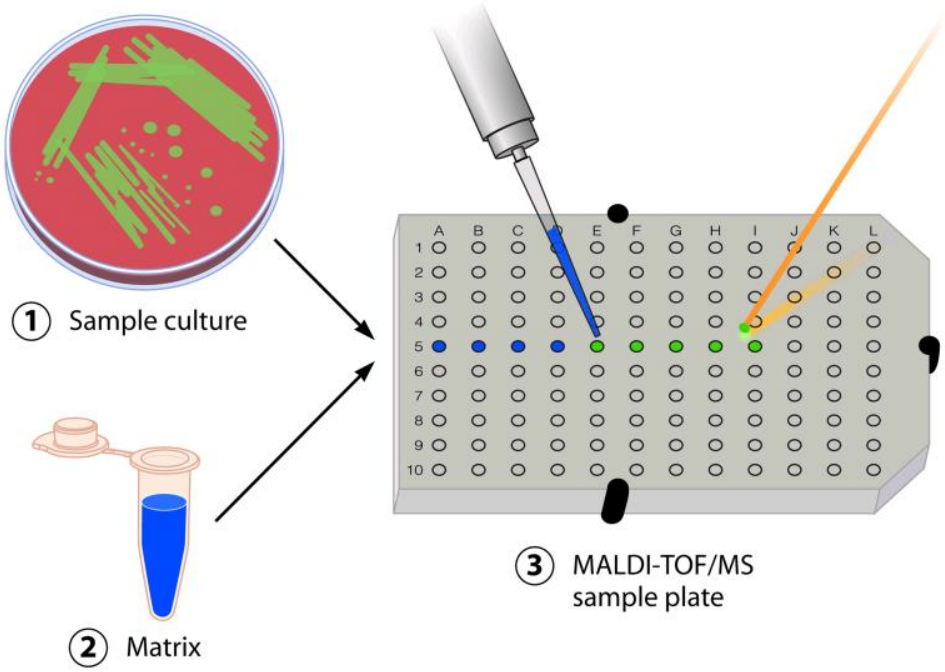

C-reactive protein (CRP), procalcitonin (PCT), antimicrobial susceptibility testing (AST)

*Nature Reviews Microbiology* (2018)

# MALDI-TOF Analysis – An example

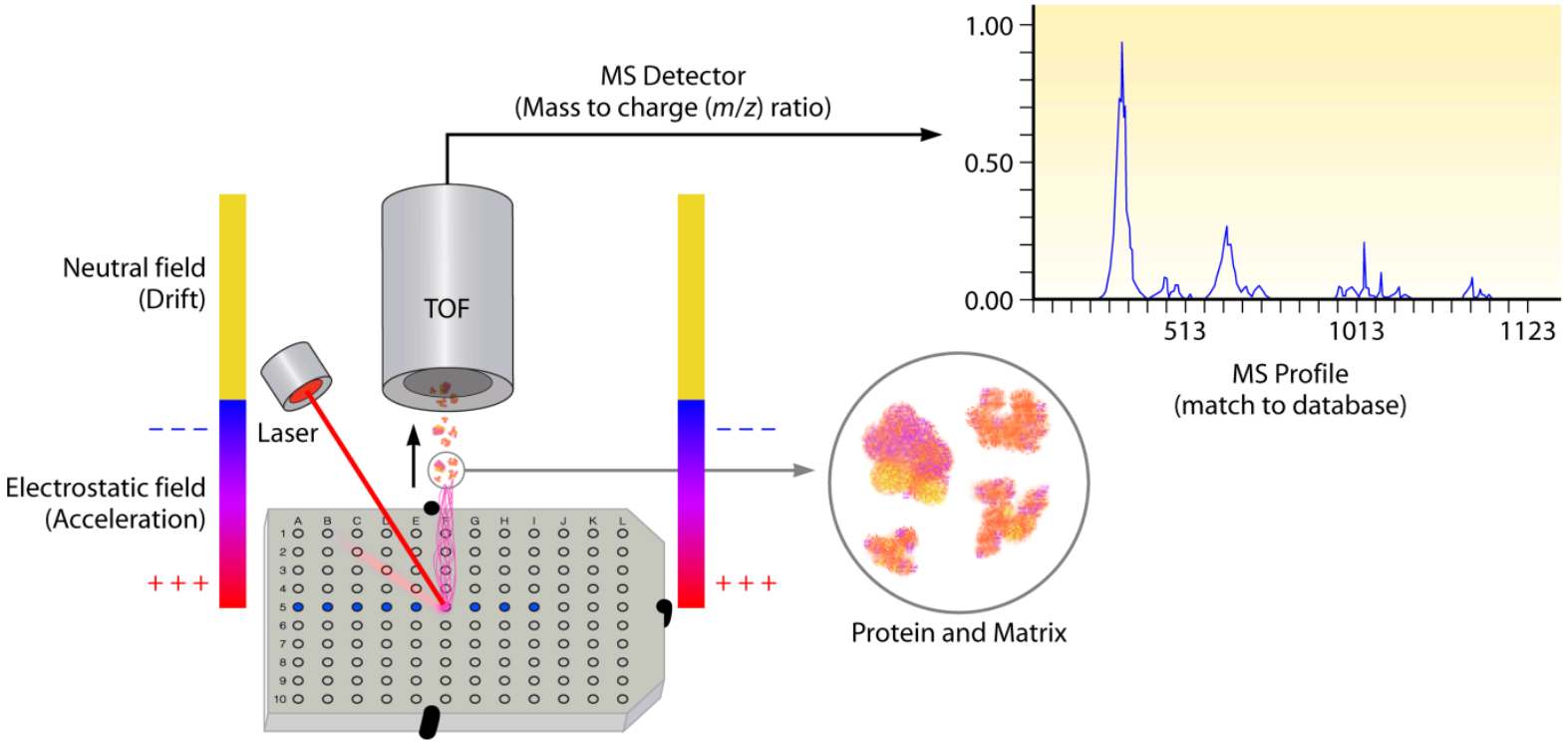
CMR
Journals.ASM.org

## Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry: a Fundamental Shift in the Routine Practice of Clinical Microbiology




Clinical Microbiology Reviews p. 547–603, July 2013 Volume 26 Number 3

# MALDI-TOF Analysis – An example




Clinical Microbiology Reviews p. 547–603, July 2013 Volume 26 Number 3

# Genotype prediction / phenotype susceptibility

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 11, 2018 VOL. 379 NO. 15

## Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

The CRyPTIC Consortium and the 100,000 Genomes Project

The WHO recommends drug-susceptibility testing of *Mycobacterium tuberculosis* complex for all patients with tuberculosis to guide treatment decisions and improve outcomes.

**Whether DNA sequencing can be used to accurately predict profiles of susceptibility to first-line anti-tuberculosis drugs has not been clear.**

**CONCLUSIONS**

Genotypic predictions of the susceptibility of *M. tuberculosis* to first-line drugs were found to be correlated with phenotypic susceptibility to these drugs. (Funded by the Bill and Melinda Gates Foundation and others.)

# What doctors can do against AMR

Avoid excessive prescription !

Check on **appropriate indications** !

No intensive and prolonged use !
*Only as long as necessary*

Help to avoid non-prescription use of antimicrobials
in the general population

# Thank you !