TECHNOLOGY
WATCH REPORT

Antimicrobial Resistance

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TECHNOLOGY WATCH REPORT
Antimicrobial Resistance

Autors
Roser Salvat Jofresa, UAB Research Park.
Marta Tort Xirau, UAB Office of Patent Valuation.
With the collaboration of the IRTA Technology Watch Unit,
Hafsa El Briyak Ereddam (UAB PUE - University Business Program) and Jordi Serratosa (PRUAB).

Edition and design
Communication and Promotion Area
UAB Research Park

UAB Research Park
Av. de Can Domènech s/n - Eureka Building - UAB Campus
08193 Bellaterra (Cerdanyola del Vallès) Barcelona · Spain
www.hubb30.cat

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Overview of innovation and tendencies in Antimicrobial Resistance

The phenomenon of **antimicrobial resistance** (AMR) describes the capacity of micro-organisms such as **bacteria, fungi, virus and parasites** react against antimicrobial drugs, often by means of mutation, so that they are not inhibited and therefore can continue multiplying and spreading.

This give rise to **resistant strains** capable of withstanding the therapeutic effects of antibiotic, antiviral, antifungal and anthelmintic drugs, among others. This natural phenomenon has been accelerated by the systematic **abuse of antimicrobial drugs**, especially antibiotics, for the treatment of **humans, animals and vegetables**.

The global movement of people, food products, animals and plants makes it very easy for **pathogens to circulate** along simultaneous routes. The World Health Organisation (WHO) has published a list1 classified in **three categories of priority**:

- Critical: *Acinetobacter baumannii: Pseudomonas aeruginosa; Enterobacterias*
- High: *Enterococcus faecium; Staphylococcus aureus; Helicobacter pylori; Campylobacter; Salmonella spp; Neisseria gonorrhoeae*
- Medium: *Streptococcus pneumoniae; Haemophilus influenzae; Shigella spp*.

The European Commission gives priority to tuberculosis, HIV/AIDS, malaria and rare infectious diseases in addition to this list of pathogens.

“The WHO has declared AMR as a serious health threat”

The propagation of antimicrobial resistance potentially complicates the capacity to treat common infectious diseases and affects higher **morbidity and mortality rates**. But drug-resistance also implies longer duration of infections and this involves medical complications and disabilities such as amputations and vital organ damage. This resistance also affects the frequency of visits to the doctor, the duration of hospital stays and treatments with more expensive drugs. All this leads to increases in the healthcare **costs for treatment and management of the patient** for infections with serious symptoms related to resistant microbes. According to the World Bank (2016) antimicrobial resistance puts public spending sky high, seriously increases **mortality** among the **population** (10 million deaths in 2050 according to the 2014 O’Neill report) and has a negative impact on the **economy**, with a drop in the GDP estimated at close to 2%.

The WHO has declared antimicrobial resistance as a serious threat to global public health and has demanded coordinated **intergovernmental action** for its prevention and management. In response to this situation, plans and measures are being adopted within the framework of various international organisations and national governments. The private sector and some NGOs are also investing efforts to **promote and finance research and development** related to antimicrobial resistance.

Antimicrobial resistance is eroding the capacity to control infections with traditional antibiotics and represents scientific challenges not only related to the need to administer high doses to cover the worst case scenarios, but also the opportunity to apply fast diagnostics to enable old and new treatments, improve healthcare criteria and preventive programmes. This means that activity in research and innovation, in this field, not only considers **antimicrobial** approaches, but also includes **diagnostics**, a central element of the response to aid in selecting the appropriate devices to treat a disease. Furthermore vaccines play an important role in the prevention of diseases and limitation of the need for antimicrobials. Finally, finding an **alternative to antibiotics** is also decisive.

"It is important to achieve advances in various R+D areas"

In order to tackle this situation, the **European Commission**[1] identified various **areas of research and development** where it is essential to achieve advances:

1. **Prevention, detection, control and surveillance of infections**
   - Cleaning methods and actions that limit AMR.
   - AMR Epidemiology; development of surveillance units and predictive indexes.
   - Smart sensors; smart containers.
   - Computerised tools for the early detection of resistant pathogens.
   - Personalised medicine.
   - Digital technologies to support the development of therapeutic processes.
   - E-health solutions: prescription, self-management, assistance and training in AMR.
2. **New, alternative and combined therapies**
   - Management of host factors; host modulation.
   - Blocking bacterial virulence factors.
   - Hijack of active uptake pathways and potentiator approaches.
   - Monoclonal antibodies.
   - Bacteriophage therapies.
   - Microbiome.
   - Genomics.
3. **New preventive vaccines for humans and animals**
   - Reverse vaccinology.
   - New adjuvants and membrane vesicles.
   - Polysaccharide conjugation and antigen design.
4. **New diagnostics**
   - Monitoring of microbial contamination; real time bio-monitoring.
   - New diagnostic tools and, in particular, in situ in tests humans.
   - Use of computer-based solutions for the development of tools for the diagnosis of human infections.
5. **The environment**
   - Release and propagation of environment resistant micro-organisms and antimicrobials and control tools.
   - Waste and resistant components in aquatic ecosystems of agricultural and healthcare environments.

- Evaluation and analysis of the risk for animal and human health.
- New fast and efficient degradation technologies in wastewater and the environment, and reduction of AMR propagation.

The meteoric evolution of **genomics, bioinformatics** and, in general, the transfer and valorisation of knowledge between **research centres, hospitals and industry**, represents an important step towards improving the possibilities of diagnosis and treatment.

The need to prevent epidemic outbreaks and control infections is not only essential in the human and animal healthcare sector, but extends into industry, the challenges facing two sectors are outstanding: **Pharmacy and cosmetics, and Food and beverages**. Identification of possible exposures and disruptive events that can potentially lead of damage and contamination, not only at the production site but also across the supply chain in these industries is related to safety guarantees and product quality.

"Microbial monitoring is essential in some industries"

In this context smart sensors, nanotechnology and the IoT play a key role. Some of the tendencies in this regard are:

- **Selective sampling and monitoring** for different microbial strains (bacteria, bacterial spores, fungal conidia and viruses).
- **Sensors** based on various detection techniques such as surface plasmon resonance (SPR) or electrochemical detection.
- **Smart sensors** throughout the supply chain, and applications for efficient use of all the big data generated.
- **Microbial genomics** for tracking sources of contamination.
- **Nanomaterials** used as microbe detecting materials in detection solutions such as smart kits, smart sensors, which are used during the production process or incorporated into smart packaging
- **Nanoparticles** (magnetic particles, nanotubes, fullerenes, graphene nanosheets, quantum dots, metal nanoparticles, core-shell structures, or hybrid materials) are commonly used in test kits and in pathogen detection applications.
- **Nanoadditives** are another key element and additive manufacture is also a tendency.
- **Smart labels and intelligent packaging solutions** that can inform and warn consumers before they consume or use contaminated products.
- **Robotics** to detect microbial contamination, but also to prevent further spoilage by taking smart decisions in real-time.
- **IoT** to enhance interconnectivity and interoperability between devices and industry platforms.

ESystems for the follow-up of pathogens integrated with product and process monitoring solutions for the prevention of epidemics are inherent to the competitiveness of these industries related to human and animal health, where **applied research** solutions are widely implemented.

But antimicrobial resistance is, especially, an area of **basic research**. AMR has often been described as a rather **unattractive basic field of research**, characterised by high burnout. The preclinical phase of development of antibiotics is in general also driven by small and medium-sized enterprises, which have to assume the combination of high risks and considerable cost.

"The financing of R+D is a key challenge"

Along these lines, the International Agriculture Consulting Group identifies **challenges in R+D+I throughout the value chain** (basic and preclinical research, clinical trials and regulatory approval) **in human, animal and plant health and the environement**[1]:

1. The uncertainty related to the expected return on the investment in basic research into human antibiotics in comparison, for example, to that of drugs used in oncology and the treatment of chronic diseases, generally of greater efficiency in humans as well as animals.

2. The **unclear market potential for diagnostics and vaccines**, related to the often unclear propensity of patients to use these products and that of public healthcare systems to incur higher treatment costs, may even discourage innovation in preclinical and clinical phases. In the field of animal production, these doubts about the potential market of diagnostics and vaccines are related to the lack of inclination of agricultors to pay for diagnostics and treatments without clear evidence of profitability, and even less so if they do not benefit from public subsidies.

3. **Clinical trials** for health technologies against resistant strains are particularly **complex**. Identifying a sufficient number of eligible patients who are infected with resistant strains and are available to participate in clinical trials can be difficult and result in long and/or costly processes. In animals and vegetables, the scientific difficulty of product testing is also significant, as well as expensive.

4. Surveillance and studies of the interaction of transmissions and risks **between the human, animal, vegetable and environmental cycles** also present considerable methodological challenges, nevertheless the impact of research is maximized through joint approaches that avoid unproductive duplication of activities.

5. **Regulatory pathways** to secure registration and ensure commercialization of antimicrobials, diagnostics and vaccines can be complex and burdensome; divergences in approval requirements and processes in many countries pose additional hurdles for manufacturers. Regulatory pathways may also be increasingly complex in the context of rising concern about the effects of plant protection products and chemicals on the environment and their safety to humans, other mammals and organisms.

6. As a result, scientifically complex and costly **basic research** is not usually sufficiently funded by the public or private sector.

In summary, **significant and coordinated investment** is required to extend the application of platforms of innovative vaccines to additional pathogens and widen research to embrace new approaches that improve the success of the traditional and alternative antibacterial discovery.

In this context of little expectation that sales based on price and volume justify **investments in R+D+I** to confront priority pathogens, the United Nations General Assembly and other organisations are studying the design and **application** of monetary and non-monetary

push and pull incentives of type, but experience is still limited in this area. The experts, therefore, unanimously recognise the need for the evolution of **supportive policies and the acceleration of research and innovation** in health technologies related to antimicrobial resistance.

Paradoxically, however, studies4 show that infectious diseases and microbiology are among the specialties less subscribed to in medicine and research, resulting in a **lack of experts** in these areas.

In conclusion, advancing our capacity to control antimicrobial resistance requires a coordinated effort in research and development that takes advantage of the opportunities offered by new technologies, combined with adequate **political measures**. Antimicrobial resistance is a global and multisectorial problem that affects all countries and requires coherent and integral action in the field of human, animal, vegetable and environmental health within the framework of a One Health approach, that is, recognising **people's health is closely related with that of vegetable, animals and the environment.**

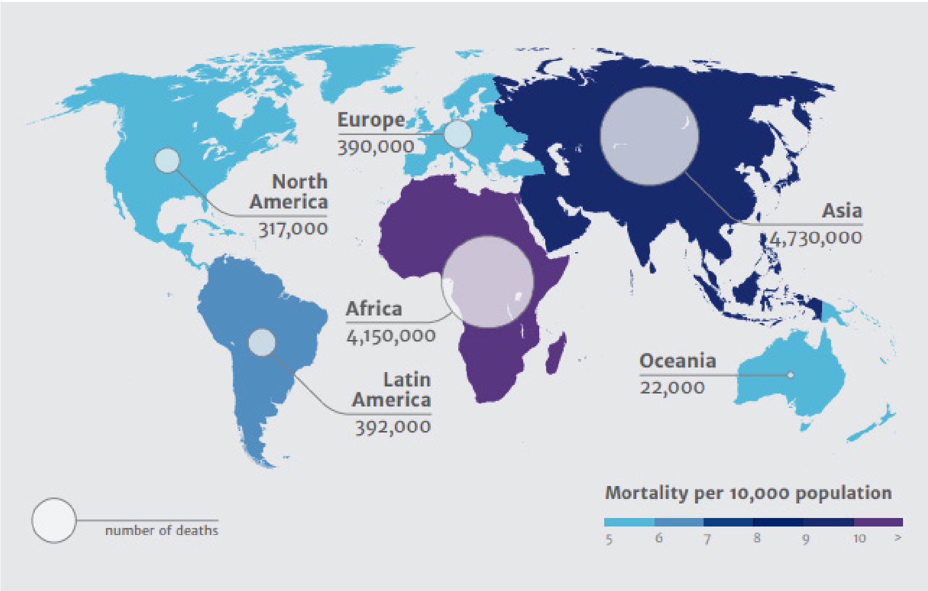
"Integrated action is required with a "One Health" approach

There are circumstances where **antibiotics are required in agriculture** and **aquaculture** provided they are appropriately used to maintain **animal** welfare and food security. However, much of their global use is not for treating sick animals, but rather to prevent infections or simply to promote growth. Experts point out that, just like in humans, the quantity of antibiotics used in cattle is excessive and at times prejudicial for humans, and they encourage taking actions to restrict their use.

On the other hand, there are still complaints that there is **insufficient access to these products**. The threat of antimicrobial resistance would be reduced if everywhere in the world human and animal diseases with a risk of resistance could be correctly diagnosed, and existing treatments were accessible and correctly used, in the sense of being available, high quality, affordable, demanded and supplied to the population of the countries of the world.

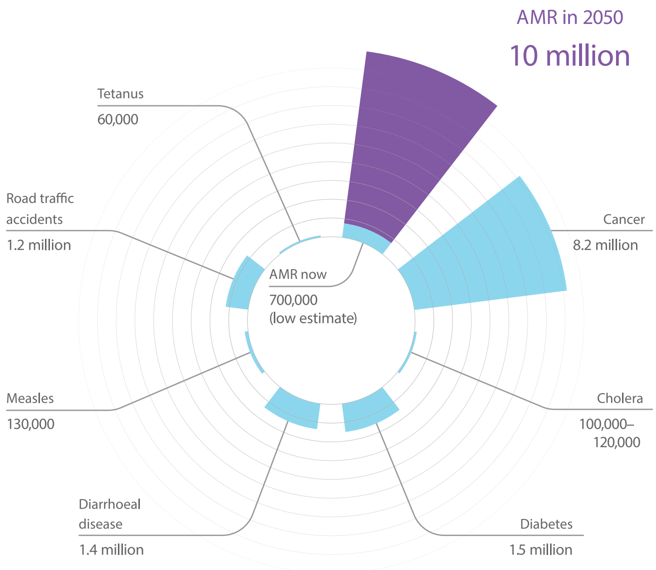
2
Antimicrobial Resistance: Key infographics

2.1. Deaths attributable to AMR every year by 2050



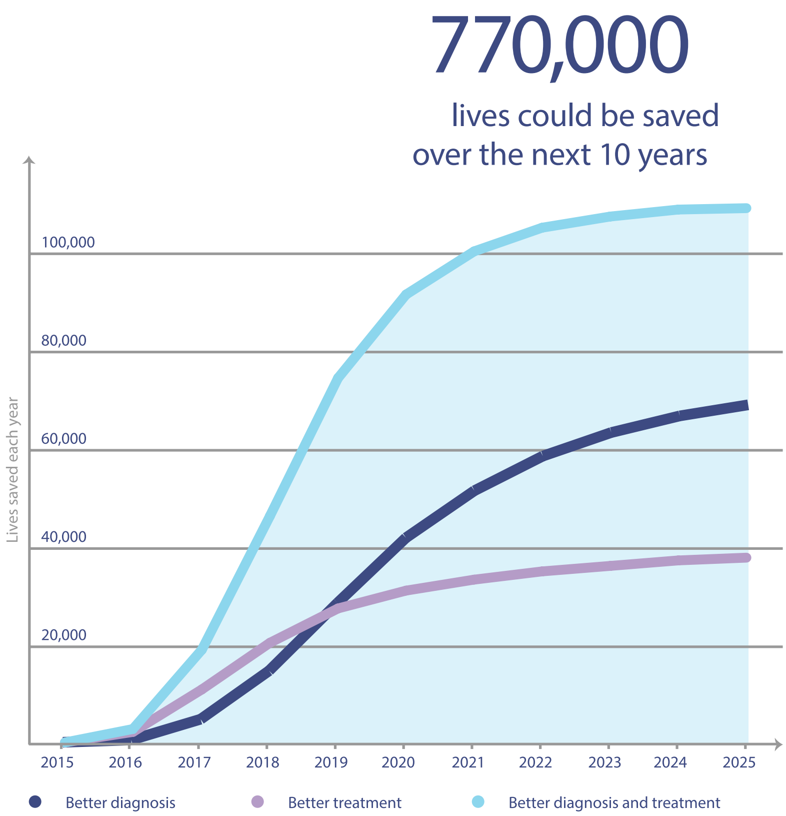
Source: Jim O'Neill (December 2014) - The Review on Antimicrobial Resistance Chaired - Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations

2.2. Deaths attributable to AMR and other diseases every year



Source: Jim O'Neill (May 2016) - The Review on Antimicrobial Resistance Chaired - Tackling drug-resistant infections globally: Final report and recommendations.

2.3. Better diagnostics and treatments for TB could save numerous lives

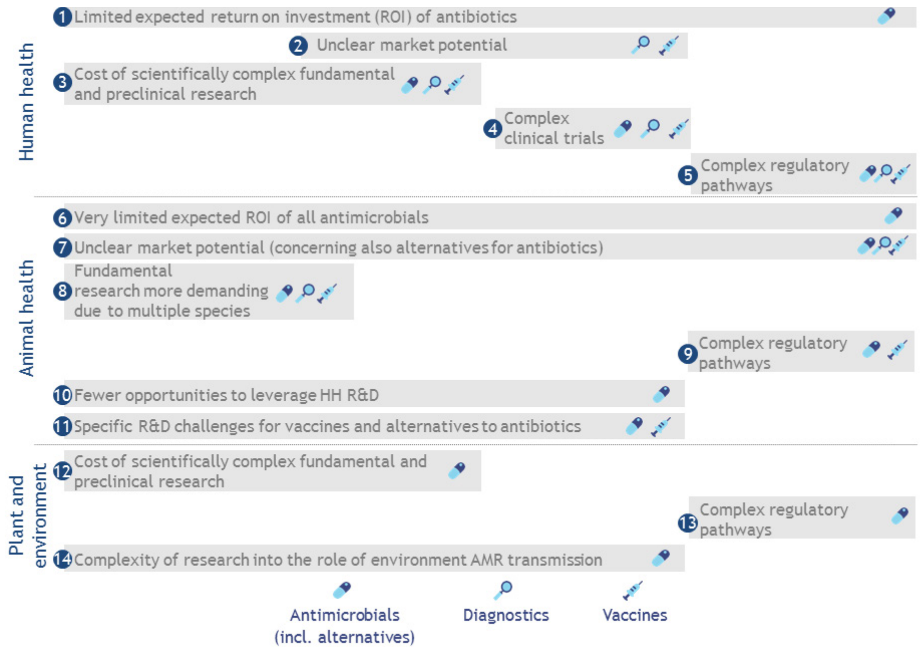


Source: Jim O'Neill (May 2016) - The Review on Antimicrobial Resistance Chaired - Tackling drug-resistant infections globally: Final report and recommendations.

2.4. Global action plan objectives of the FAO on AMR

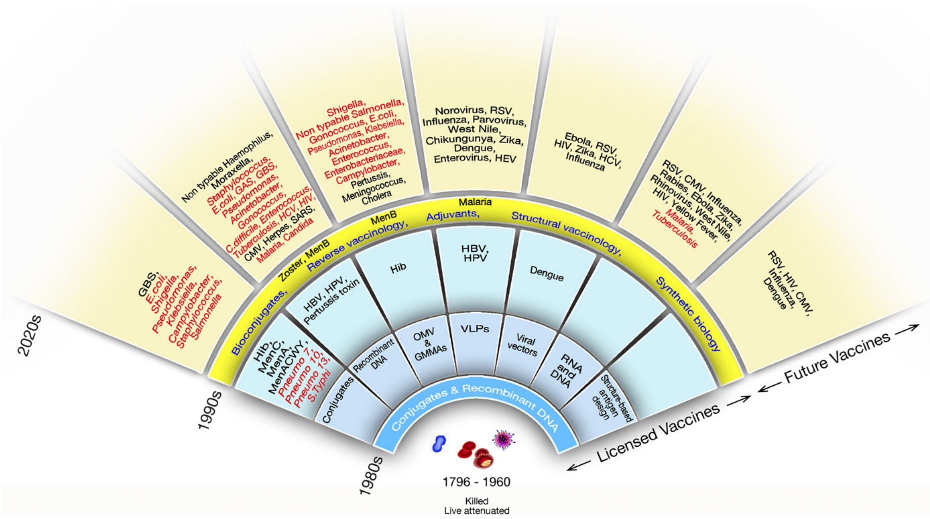
Source: FAO (2018) - Antimicrobial resistance: The role of food and agriculture

2.5. Challenges identified in R&D for AMR by IACG



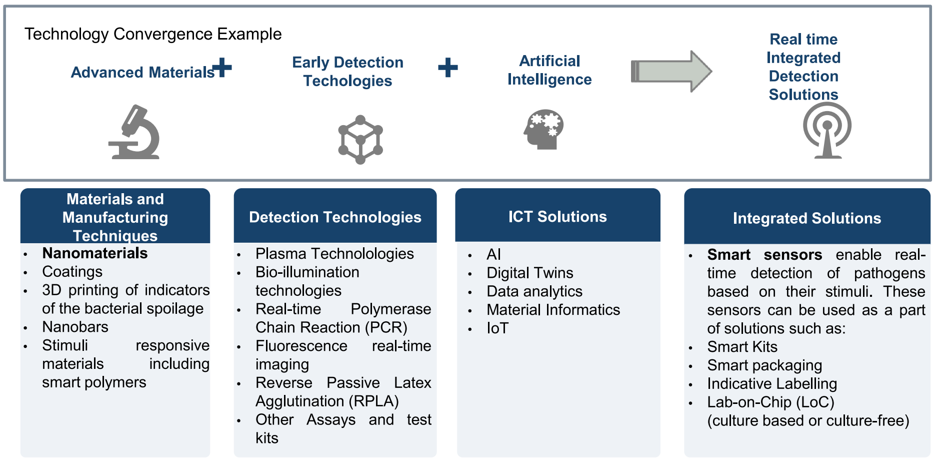
Source: IACG (2018) Antimicrobial resistance: Invest in innovation and research, and boost R+D and access.

2.6. Evolution of vaccine tecnologies and platforms



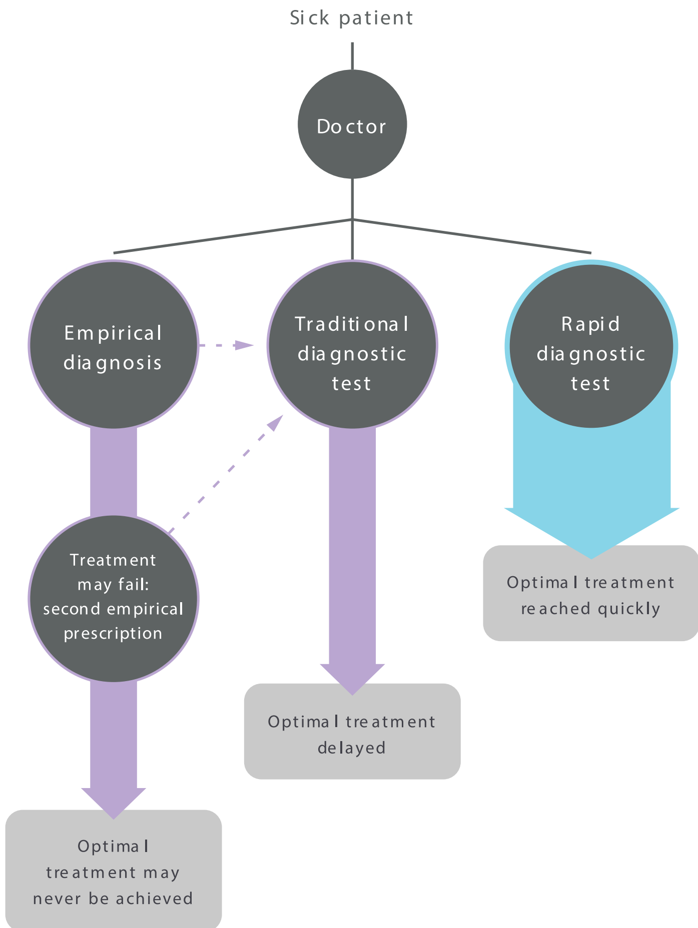
Source: Stephen J. Baker, David J. Payne, Rino Rappuoli, and Ennio De Gregorio (2018) - Technologies to address antimicrobial resistance

2.7. Enabling microbial monotoring with technology convergence



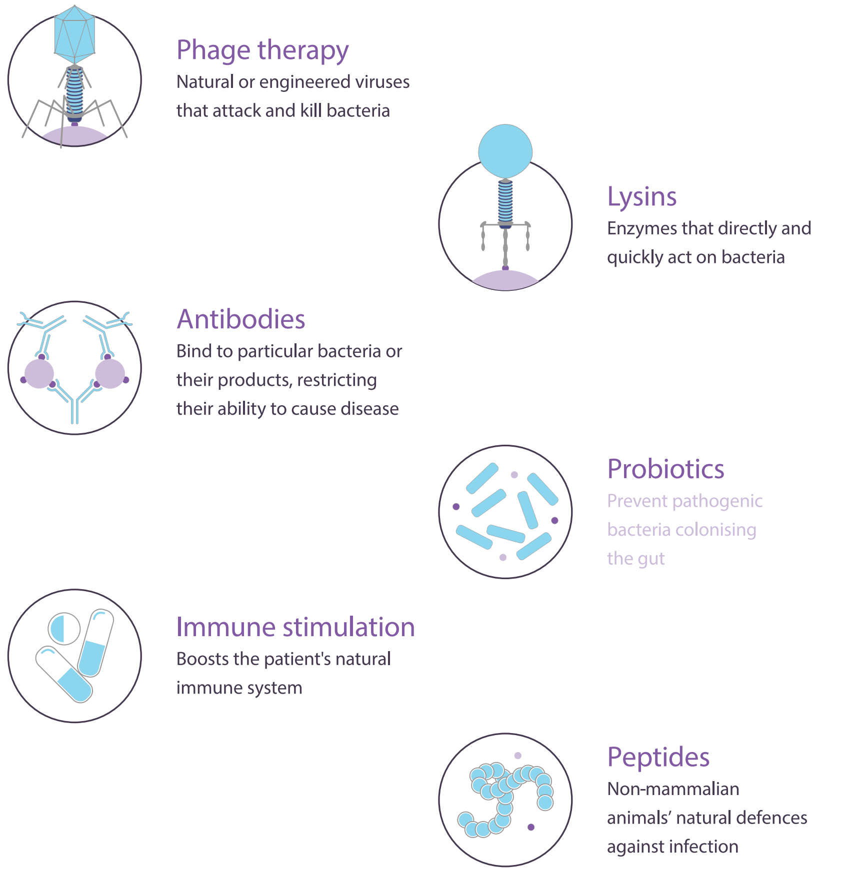
Source: Frost & Sullivan (2018). Technologies Facilitating Microbial Contamination Monitoring – Futuretech TechVision Opportunity Engine

2.8. Empirical, traditional and ràpid diagnòstics for AMR



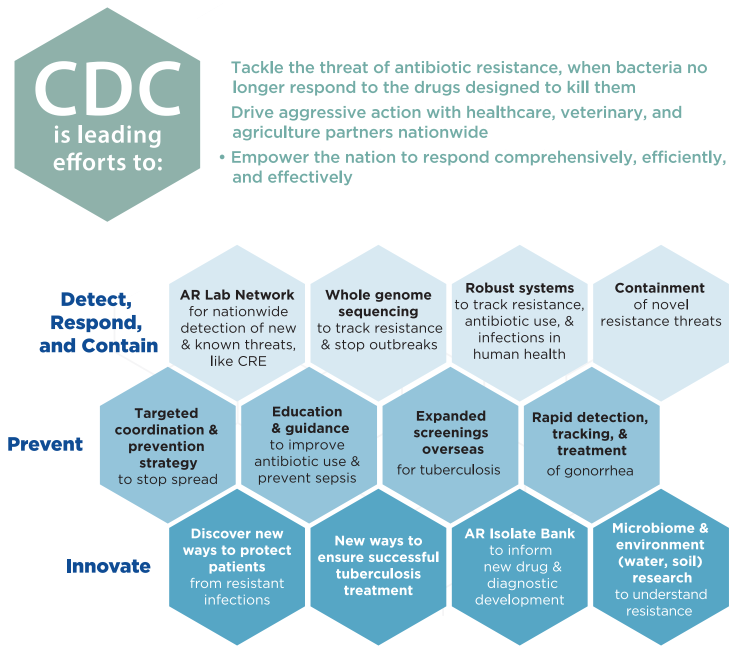
Source: Jim O'Neill (May 2016) - The Review on Antimicrobial Resistance Chaired - Tackling drug-resistant infections globally: Final report and recommendations.

2.9. Alternative products to tackle infections



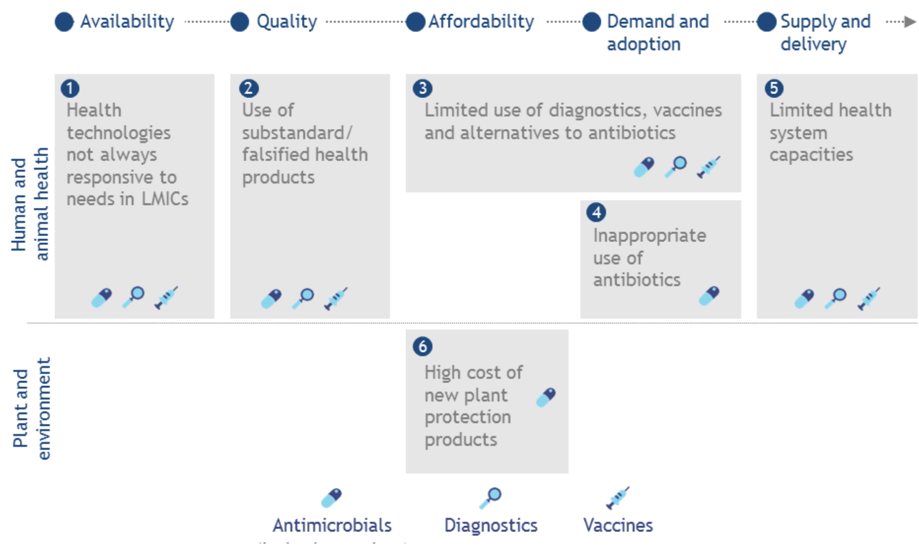
Source: Jim O'Neill (May 2016) - The Review on Antimicrobial Resistance Chaired - Tackling drug-resistant infections globally: Final report and recommendations.

2.10. Antibiotic resistence solutions



Source: Centers for Disease Control and Prevention (2018) What CDC is Doing: Antibiotic Resistance (AR). Solutions Initiative

2.11. Challenges in access to AMR-related technologies in LMICs



Source: IACG (2018) Antimicrobial resistance: Invest in innovation and research, and boost R+D and access.

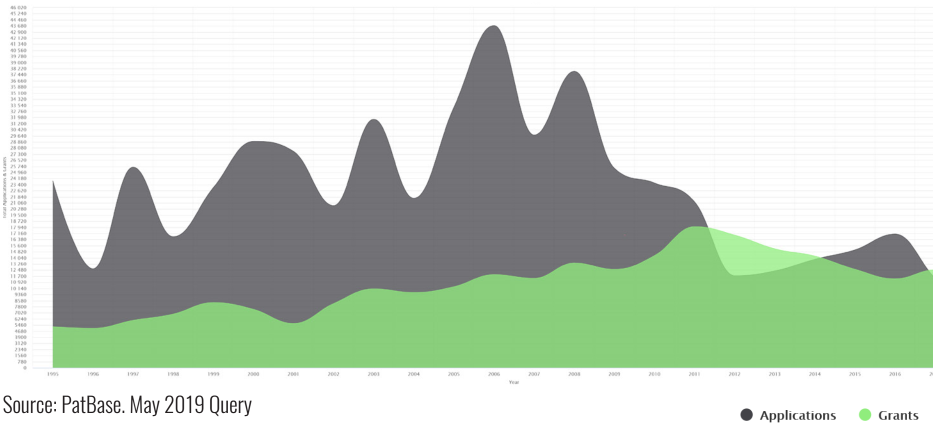
3
Patent analysis

The patent analysis associated with Antimicrobial Resistance was dominated by the inclusion of the following fields:

- New antimicrobial medicinal products (including chemical molecules, biological medicinal products, peptides and vaccines)
- Methods of microbial Diagnosis including bacterial, viral or fungicide
- Coatings and antimicrobial material

3.1. Evolution of patents applied for and granted

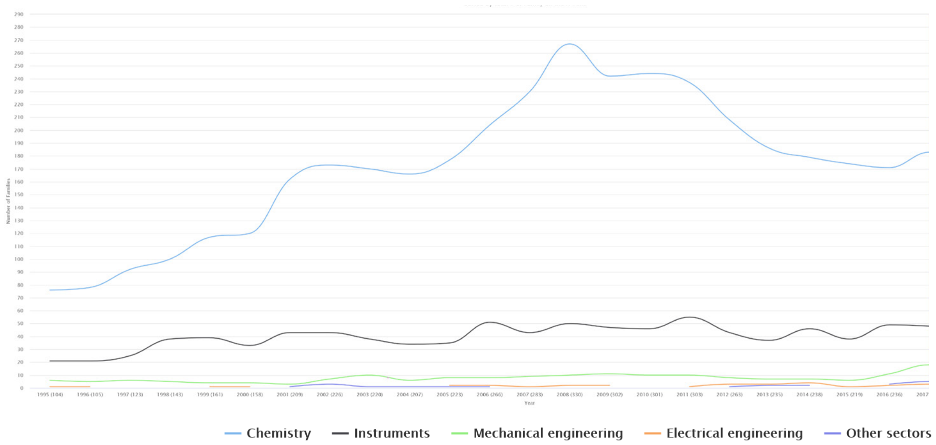
The analysis of both requested and granted patents shows a clear tendency towards the growth in the ambit of AMR in the last 25 years. Furthermore, such analysis illustrates that the magnitude of the granted **requests** reached 47.7%.



Source: PatBase. May 2019 Query

3.2 Technological sector of the patents applied for

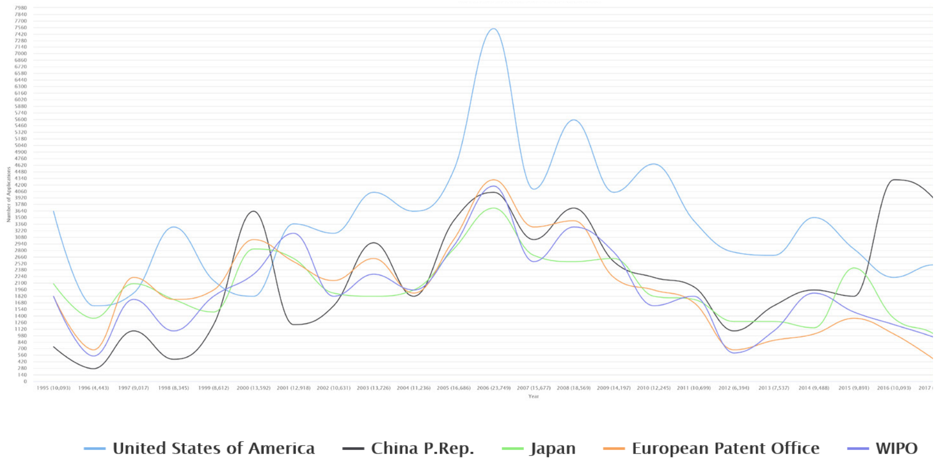
Over the last 20 years, the technologies more involved in the patents applied for in the field of antimicrobial resistance belong to the following fields: chemistry, instruments, mechanical engineering, electrical engineering and, finally, “other fields”.



Source: PatBase. May 2019 Query

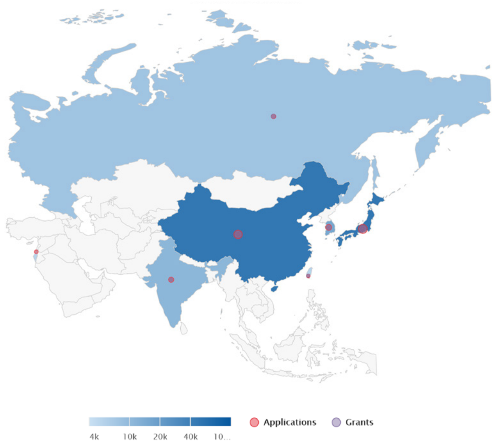
3.3. Location of the application for patents

On a world-wide level, the countries where most patent applications have been filed over the last 25 years are the **United States, Japan, China and the European Union.**



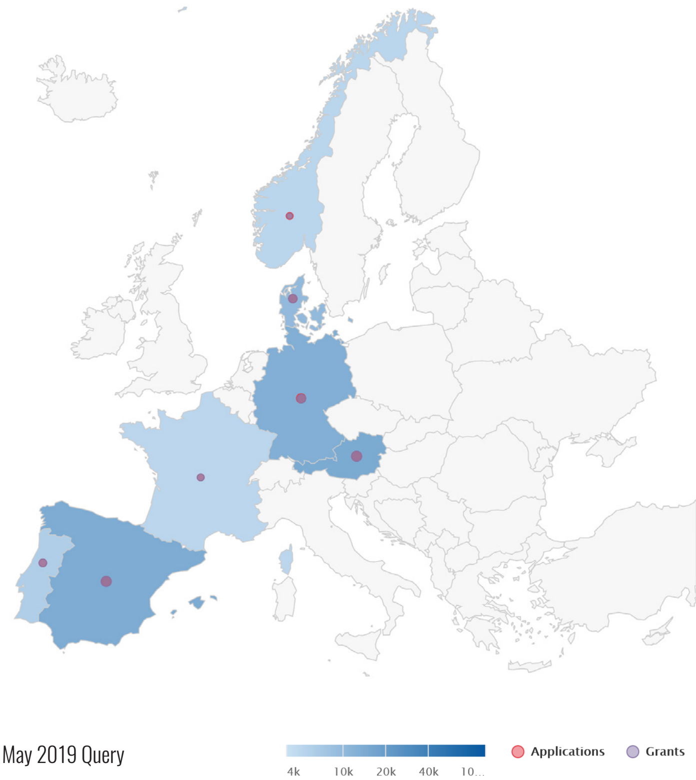
Source: PatBase. May 2019 Query

The United States and Canada are very active in patent applications in the field of AMR. On the **Asian continent**, Japan and China are the most active countries, with a very small difference in applications, even though Japan has more patents granted than China.



Source: PatBase. May 2019 Query

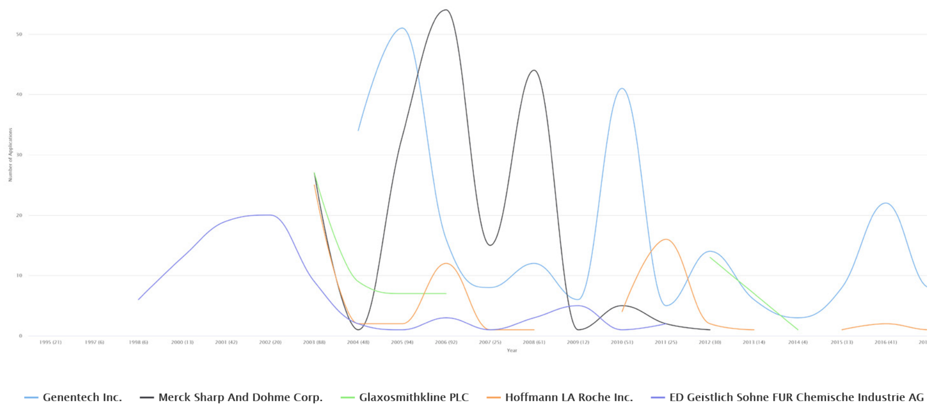
Within the European Union, as shown on the map, the countries with most patent applications are, in descending order, Austria, Spain, Germany, Denmark and Norway.



Source: PatBase. May 2019 Query

3.4. Patent applicants over the last 25 years

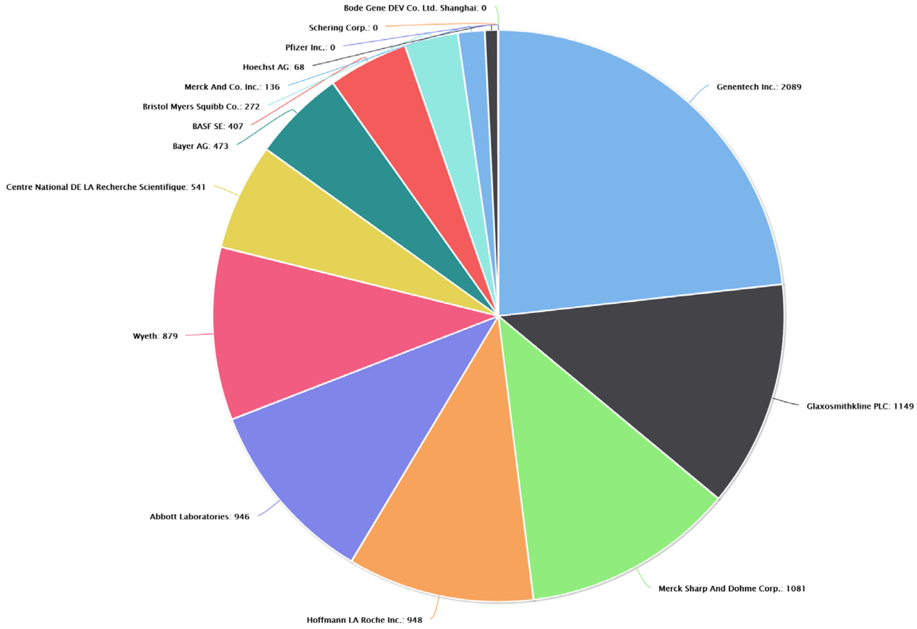
The graph below shows the eight most active organisations in patent applications over the last 25years, as well as which time periods these applications were concentrated in. Outstanding, among others, Genetech, Merck Sharp & Dohme, and Galaxosmithkline.



Source: PatBase. May 2019 Query

3.5. The most active applicants

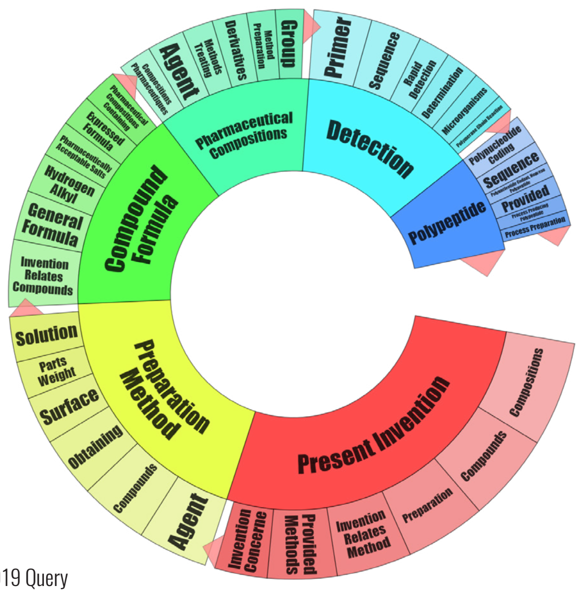
The most active **bodies** (companies, institutions or people) filing patent applications, including the **number of applications** for each one are shown below. Note that multinational pharmaceutical and biotechnology companies, **Genentech, Glaxosmithkline, Merck Sharp & Dohme**, are the most active applicants in this field; among public institutions, the activity of the **CNRS** (Centre National de La Recherche Scientifique) in France is noteworthy.



Source: PatBase. May 2019 Query

3.6. Keywords attributed to patents in this field

The main keywords associated with patent applications in the field of study are: polypeptide, detection, pharmaceutical compositions, method of preparation, and compound formula.



Source: PatBase. May 2019 Query

3.7. METHODOLOGICAL APPENDIX

The information provided in the "Patent analysis" section refers to the study performed on a sample of **664,972 patent applications** in the area of AMR related to **antimicrobials, coatings, and diagnostic methods**.

The study was focused on global patent activity over the last 20 years, with special emphasis on Europe.

101.176	59.670	664.972	876.996
Patent family	Family of patents granted	Applications	Publications
Total number of families in this set of results	Total number of families with publications granted with this set of results	Applications with this result	Publications within this result

Source: PatBase. May 2019 Query

The criterion used for the query referred to in this report has been **maximum concentration** of the field under scrutiny while maintaining the principle of scope, or consideration of various related fields. The **most active** area referring to Antimicrobial Resistance is **new antimicrobial** agents, followed by antimicrobial coatings and, to a lesser extent, methods of diagnosis.

It is well-known that Patent documents are classified under different international classification systems; the most often used being the International Patent Classification (**IPC**) because it is most useful in more specific fields. Pursuant to IPC and CPC nomenclature, obtaining of the sample for this report considered the inclusion of the following indexes:

- A61P31/00: Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics
- C07G11/00: Antibiotics
- A61P 31/00: Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics
- C12Q 1/04: Determining presence or kind of microorganism; Use of selective media for testing antibiotics or bacteriocides; Compositions containing a chemical indicator therefor
- C12N7/00: Viruses; Bacteriophages; Compositions thereof; Preparation or purification thereof
- G01N2333/00: Assays involving biological materials from specific organisms or of a specific nature
- C12Q1/04: Determining presence or kind of microorganism; Use of selective media for testing antibiotics or bacteriocides; Compositions containing a chemical indicator therefor
- A61L2300/00: Biologically active materials used in bandages, wound dressings, absorbent pads or medical devices

- A61L2300/404: Biocides, antimicrobial agents, antiseptic agents
- A61L2300/406: Antibiotics
- A61L2300/408: Virucides, spermicides
- C09D5/14: Paints containing biocides, e.g. fungicides, insecticides or pesticides
- A61L2/00: Methods or apparatus for disinfecting or sterilising materials or objects other than foodstuffs or contact lenses; Accessories therefor (for contact lenses A61L12/00; atomisers for disinfecting agents A61M; sterilisation of packages or package contents in association with packaging B65B55/00; treatment of water, waste water, sewage or sludge C02F; disinfecting paper D21H21/36; disinfecting devices for water closets E03D; articles having provision for disinfection, see the relevant subclasses for these articles, e.g. H04R1/12)
- A61L31/00: Materials for other surgical articles , e.g. stents, stent-grafts, shunts, surgical drapes, guide wires, materials for adhesion prevention, occluding devices, surgical gloves, tissue fixation devices (shape or structure of stent-grafts A61F2/07, of stents A61F2/82, of surgical gloves A61B42/00, of surgical drapes A61B46/00, of occluding devices A61B17/12022)
- G01N2333/00: Assays involving biological materials from specific organisms or of a specific nature
- A61L2420/00: Materials or methods for coatings medical devices.

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