IN-VITRO DIAGNOSTICS, VACCINES AND NEW ANTIMICROBIALS: AN INTEGRATED STRATEGY TO CHALLENGE ANTIMICROBIAL RESISTANCE

Index

INTRODUCTION

Antimicrobial resistance (AMR), also described as the "silent pandemic" by the WHO, poses a significant worldwide risk to effective infection prevention and treatment, as well as to advanced medical procedures such as surgeries, chemotherapies, and transplants.

AMR is occurring worldwide and affects all areas of health, with severe consequences for individuals and society (1). The indirect impact of antimicrobial resistance extends beyond health risks and has wide implications for development and the global economy. The World Economic Forum has identified antibiotic resistance as a global risk beyond the capacity of any organization or nation to manage or mitigate alone. Urgent and coordinated efforts are needed to prevent a post-antibiotic era where common infections become deadly once again.

Recognizing the correlation between the misuse of antibiotics, Healthcare-Associated Infections (HAIs) from resistant bacteria, and the emergence of resistance is crucial.

Antimicrobial resistance (AMR) is currently a top priority in the political realm, unprecedented in its level of attention. While this is a positive development, there are still numerous unresolved issues.
To address these, the World Health Organization developed a Global action plan on antimicrobial resistance, with the goal of ensuring the continued effectiveness of treatment and prevention of infectious diseases. The plan outlines five strategic objectives, including improving awareness and understanding, strengthening knowledge through surveillance and research, reducing the incidence of infection, optimizing the use of antimicrobial agents, ensuring sustainable investment in countering antimicrobial resistance and increase investment in new medicines, including vaccines.
Preventing infections through vaccinations is one of the most important intervention strategies for the challenge of AMR. Maintaining investment in the development pipeline for new antibiotics is essential likewise, despite, in the past few decades,

investments have been small compared with those in other public health issues with similar or less impact.

While the discussion focuses largely on the development of vaccines and new antibiotics, it is crucial to recognize the importance of medical diagnostic technologies in addressing AMR. Medical diagnostic technologies are very relevant in all aspects of the AMR pathway, from prevention, diagnosis to control, and this should be acknowledged and supported accordingly. In particular, there should be a stronger focus on prevention and on activities concerning training and information that, starting with pharmacists, general practitioners and finally specialists, can adequately reach citizens and patients for increasingly accurate diagnoses. Early detection and prevention of infections in primary care (Doctors' Hoffice) and healthcare settings is key to limit the overuse and misuse of antibiotics hence reducing the prevalence of infections overall.

IN-VITRO DIAGNOSTICS

Content:

- Diagnostic Stewardship and areas where in vitro diagnostics can support AMR/HAI prevention and management measures
- Examples of enabling technology
- What can be achieved by in vitro diagnostics in the fight against AMR
- Recommendations to make the best use of in vitro diagnostic technologies

DIAGNOSTIC STEWARDSHIP AND AREAS WHERE IN VITRO DIAGNOSTICS CAN SUPPORT AMR/HAI PREVENTION AND MANAGEMENT MEASURES

Diagnostic stewardship can be described as the set of interventions prioritizing the right test, for the right patient, to prompt the right action. By doing so, diagnostic stewardship seeks to improve antimicrobial use, to reduce antimicrobial resistance, and to better use healthcare resources to improve patient outcomes. Traditionally, diagnostic stewardship was primarily a laboratory-based activity aimed at refining specimen collection, processing, and reporting to guarantee accurate test outcomes and interpretations. Recently, awareness has grown regarding the significant impact that test results can have on antimicrobial usage. Consequently, the concept of diagnostic stewardship for microbiologic tests has transformed into a quality improvement initiative that employs multidisciplinary teams, typically led by professionals in clinical and medical microbiology, healthcare epidemiology, and/or antibiotic stewardship.
Identification, prevention, control and tracking are fundamental enablers for effective diagnostic stewardship.

1. **Identification of bacteria and resistant strains**

- **Microbiology Diagnostic tests** can play a key role controlling antibiotics' over-prescription. Diagnostics can allow **identification of the microorganisms involved** (Etiology) and can provide an **early differentiation between bacterial and viral infections.** Identification and differentiation are crucial for guiding optimal care pathways. Prescribing decisions should be based on diagnostic information. In hospital settings, it is essential to identify resistance that can harm patient safety. It is also important to remember that prescribing decisions are made in various health settings, such as primary care, paediatric, and dental offices. Access to and use of diagnostics in all prescribing environments are necessary for proper patient management and the correct use of antibiotics.

- **Molecular diagnostic testing can also indicate whether bacteria are drug resistant**, thus supporting clinicians in selecting the right treatment (targeted therapy).
- Diagnostics can provide **a fast and accurate diagnosis** ensuring a timely and appropriate therapy for better patient outcomes. It has been reported that up to 30% of patients with sepsis receive inadequate empirical antibiotic treatment and that every hour of delay in the administration of an effective antibiotic is associated with an 8% reduction in survival. Therefore, it becomes key in critically ill patients to have rapid diagnostic tests that allow for the initiation of the appropriate antibiotic therapy or its modification as quickly as possible.
- **Patients can be stratified by categories** using biomarkers that can distinguishing bacterial from non-bacterial infection, diagnostics can monitor the response to the prescribed therapy, and can also predict outcomes (prognostication).
- Patients' stratification can improve selection for **patients' participation in the clinical trials** of new antibiotic molecules, thus optimising the development of new antibiotics.

2. Prevention and Control of resistance from developing and spreading

- Diagnostic tests for the detection of pathogens responsible of infectious diseases are crucial for the **success of infection prevention and control programs (IPC).**
- **Rapid screening technologies** can help mitigate the exposure limit the spread of infections in both community and healthcare settings by detecting multidrug-resistant organisms before and during hospitalization.
- A **comprehensive approach** combining detection, monitoring, and prevention can effectively reduce healthcare acquired infections, leading to lower morbidity rates and decreasing reliance on antibiotics to combat resistance.

Detection, control, and prevention are essential for protecting patients, communities, and health systems from bacterial resistance. Prevention efforts in out-of-hospital settings, such as primary care, paediatric care and dental practices, are crucial as they are where most antibiotics are prescribed. Incentivizing and prioritizing prevention in all healthcare settings can help limit the transmission of multidrug resistant organisms and reduce the need for antibiotic therapy, ultimately decreasing the development of antibiotic resistance. Healthcare-associated infections must also be managed effectively to prevent the spread of resistant bacteria.

3. Monitoring and Tracking resistance

- Diagnostic technologies can assist in the **surveillance of antimicrobial resistance patterns**.
- Implementing surveillance efforts ensures **prompt identification of outbreaks** and implementation of containment measures. This can be achieved by incorporating additional human pathogens (such as carbapenemase-producing enterobacteriaceae) and care facilities (like community care centers, non-hospital clinics, etc.) into local, regional/sub-national, and national surveillance initiatives.
- Shared solutions to the AMR challenge will require wide international, collaboration. This will mean greater harmonisation between national plans on

AMR to ensure a common approach on what to measure and how to determine success.
- Diagnostic technologies can inform regarding the **proper duration of antimicrobial treatment**, ensuring prudent and appropriate use by healthcare providers.
- The use of diagnostic tests and clinical surveillance at **single point of care** should be stressed and adequately funded. In this respect connectivity and software can bring together data from various hospital systems, helping clinicians to monitor infection, detect pathogens, comply with reporting protocol, and prescribing practices. To be noted that a clear governance should be discussed including a fundamental set of responsibilities that should be held by the microbiology laboratories.
- **Screening** for resistant microbes can help monitor development and spread of AMR and should be part of a comprehensive surveillance plan within healthcare Institution.

EXAMPLES OF ENABLING TECHNOLOGY

- Syndromic Panels & plexing solutions
- Real-Time PCR, integrating panels for resistance genes
- Host signatures (Virus and Bacterial biomarkers)
- Point of Care (PoC) solutions
- Multiplexed next-generation sequencing (NGS)
- Automated Antibiotic Susceptibility Testing
- MALDI-TOF MS mass fingerprinting technology
- Rapid immunochromatography assay panels for detection of resistance genes
- Fluorescence & Hybridization-based
- Spectroscopy-Based Approaches

WHAT CAN BE ACHIEVED BY IN VITRO DIAGNOSTICS IN THE FIGHT AGAINST AMR

Diagnostics are key resources in the fight against resistant bacteria, they can:
- **Discriminate between bacterial and viral infections** providing early information to the doctor whether an antibiotic should be prescribed.
- **Rapidly identify most pathogens** including multidrug resistant organisms like Methicillin-Resistant Staphylococcus Aureus (MRSA) or Carbapenems Resistant Enterobacteriaceae (CRE). This helps to assign correct treatment and decide isolation if necessary/appropriate.
- **Characterise antibiotic susceptibility**. Specific tests can provide information on the susceptibility of a certain bacteria to a given antibiotic. This helps to guide antibiotic prescription and avoids the use of broad-spectrum antibiotics in favour of a targeted treatment.
- **Classify severity of infection and anticipate outcomes**. Several biomarkers can aid in the clinical assessment of the severity of infections. This can support critical decisions over intensity of care. Similarly, biomarkers can predict outcomes supporting triage decisions and referral to critical care settings, that including decisions over most appropriate antibiotic treatment and resource allocation.
- **Ensure adequate duration of treatment**. Specific biomarkers can be used to guide antibiotic therapy (escalation and de-escalation) and this approach has been shown to be cost effective. Outcome of this may include shorter

hospital length of stay and/ or reduction in duration of treatment limiting the risk of antibiotic side effects or adverse events.

- **Monitor resistance patterns**. Hospital and healthcare facilities can collect data from diagnostic tests to track antimicrobial resistance trends/patterns (e.g. peak events, specific outbreaks etc.). This information can be useful especially in early outbreak detection (sentinel event) and surveillance as well as outbreak management, and it is also vital for the effective implementation of antibiotic stewardship programmes.
- **Sustain research and development of new antimicrobics** by supporting the recruitment of appropriate patients for clinical trials.

BEST USE OF IN VITRO DIAGNOSTIC TECHNOLOGIES (CURRENT AND FUTURE)

- **Multidisciplinary Coordination of efforts** are crucial in the fight against AMR. We are fully committed to continue working with stakeholders from both the public and private sector, scientific societies, manufacturers, and civil society to tackle this health challenge.
- **Recognize the economic value of diagnostic technologies.** The medical and economic value of innovative diagnostics that prevent and control AMR and HAIs must be more clearly recognized. Studies and business models favouring the adoption of such tools should be adequately funded at local, regional/Sub-national and national level.
- **Provide incentives and appropriate reimbursement.** Acknowledging the medical and economic value that diagnostic technologies do offer and considering adequate funding for their deployment in the Laboratory, will help to make them both more accessible and sustainable to healthcare professionals, patients and citizens.
- **Conduct a joint, multistakeholder gap analysis on unmet needs and areas of improvement.** A clear analysis of unmet medical needs can be helpful to direct R&D programs towards effective solutions supporting optimization of new diagnostic and care pathways.
- **Enable the use of rapid diagnostics and PoC in the community setting**. By being able to quickly identify pathogens and differentiate between bacterial and viral infections through rapid test solutions, community settings (e.g. Nursing Homes, Residential Care) would be able to support appropriate antibiotic prescription.
- **Recognize the fundamental need for a clear Governance while enabling community settings**. It is of paramount importance to ensure that operating procedures, quality standards, and results' interpretation are defined alongside with scientific societies, laboratory, and clinical experts.
- **Actively Support "Antimicrobial Stewardship"** contributing to good antimicrobial practices, supporting targeted and timely interventions to improve outcomes.

VACCINES

Content:

- The pivotal role of vaccine prevention to counter AMR
- What can be achieved by vaccination in the fight against AMR
- Recommendations to enhance vaccines' implementation against AMR

THE PIVOTAL ROLE OF VACCINE PREVENTION TO COUNTER AMR

Vaccines fall within 2 of the 5 strategic objectives outlined in the Global Action Plan (GAP) to combat antimicrobial resistance adopted by the World Health Assembly in 2015: on one hand, reducing the incidence of infections through infection prevention measures, and on the other hand, increasing investments in new drugs, diagnostic tools, vaccines, and other interventions1.

There are indeed several mechanisms through which vaccines can reduce antimicrobial resistance, including:

- **Direct protection of the vaccinated individual**, who will not contract the bacterial infection and therefore will not need antibiotics. One of the most relevant examples in this regard is the pneumococcal vaccination, but it also applies to other vaccinations such as meningococcal, Haemophilus influenzae type b, and typhoid vaccines. Furthermore, some promising vaccines targeting pathogens that are particularly critical for antibiotic resistance, such as Clostridium difficile, Shigella spp., S. Aureus, K. Pneumoniae, Enterobacteriaceae, E. faecium, etc., are currently under study.
- **Reduction of viral infections**, which helps limit potential secondary bacterial infections and inappropriate use of antimicrobials. For example, in the case of influenza, the influenza vaccine, as part of an extended vaccination campaign, can reduce hospital overcrowding during seasonal epidemics, limiting viral circulation in the healthcare settings where elderly and fragile individuals are often cared.
- **Decreased likelihood of disease transmission** in the unvaccinated population, thus reducing the probability of pathogen transmission (including within healthcare facilities).
- **Protection of the microbiome from alteration** induced by broad-spectrum antibiotics and the possible development of resistant bacterial species resulting from the acquisition of resistance genes from other organisms present in the microbiome itself.

In this sense, all vaccinations included in National Vaccination Prevention Plans play a direct or indirect role in combating AMR and its health and socio-economic impacts. It is of great importance to immunize healthcare workers against vaccine-preventable diseases, which, in addition to being a tool for worker protection, represents an important measure for preventing and controlling the spread of infections in healthcare settings.

WHAT CAN BE ACHIEVED THROUGH VACCINATION IN THE FIGHT AGAINST AMR

Vaccines can effectively prevent severe cases of infectious diseases, reducing the need for hospitalization. By preventing infections or reducing their severity, vaccination helps to **alleviate the strain on hospital resources** and to **decrease healthcare associated infections** (HAI).

Some infectious diseases, such as influenza or pneumonia, can lead to severe complications requiring intensive care. Vaccination can help prevent these complications and **reduce the demand for intensive care unit (ICU)**.
Vaccination can help individuals recover more quickly from infectious diseases, leading to **shorter hospital stays**. By reducing the duration of hospitalization, vaccination helps hospitals accommodate more patients and improve access to care for those in need.

The economic benefits of vaccination in combating antimicrobial resistance (AMR) are significant. Studies have shown that for every euro invested in vaccination, healthcare systems can **save several euros in healthcare costs**. The exact savings vary depending on the specific disease and vaccine, but the cost-effectiveness of vaccination is generally high.

RECOMMENDATIONS TO ENHANCE VACCINES' IMPLEMENTATION AGAINST AMR

- **Improve awareness and understanding of AMR through effective communication, education and training.** In order to increase awareness of the link between vaccines and AMR towards the general population, public communication programmes and adequate training on this issue are necessary. Furthermore, making antimicrobial resistance a core component of professional education training and development in the health and veterinary sectors and agricultural practice will help to ensure proper understanding and awareness among professionals.
- **Implement vaccination campaigns especially in adults**, **promoting organizational pathways and spreading the culture of vaccination to achieve the vaccination coverage goals set out in the National Vaccination Prevention Plans.** Protecting frail with vaccines prevents the onset of bacterial infections and therefore the indiscriminate use of antibiotics in both the adult population and in pediatrics;
- **Take action to address vaccine hesitancy and fatigue**. Vaccine hesitancy has become a significant issue in many countries, leading to lower vaccination rates and outbreaks of vaccine-preventable diseases. Addressing vaccine hesitancy requires a multi-faceted approach, including improved communication, public education, and efforts to counter misinformation.
- Quickly **complete National Vaccination Registry** where needed and make these accessible throughout the whole national territory, as a support tool in collecting data and evidence on the positive role of vaccinations in countering AMR.

ANTIBIOTICS

Content:

- The pivotal role of antibiotics qualified as Reserve to counter AMR
- Incentives models are needed to stimulate R&D, access and ensure availability of new antibiotics
- Recommendations to enhance the value and sustainability of antibiotics

THE PIVOLTAL ROLE OF ANTIBIOTICS QUALIFIED AS RESERVE

The Reserve group of antibiotics includes antibiotics that still have relevant levels of activity against some of the multidrug-resistant bacteria listed in the WHO priority pathogen list, including bacteria which are resistant to most or all of the WHO Model List of Essential Medicines (EML) antibiotics in the Access and Watch groups. **All Reserve antibiotics are categorized as either high priority or highest priority in the WHO list of critically important antimicrobials for human medicine**.

Between 2017 and 2021, the list of Reserve antibiotics was updated, and some antibiotics were removed, and others added to this group. Only antibiotics listed on the EML and WHO Model List of Essential Medicines for Children (EMLc) are considered essential for all health systems.

The overarching principle for listing an antibiotic as a Reserve antibiotic in the EML is evidence of **its usefulness to effectively treat a severe clinical infection for which the currently available treatment options are very limited, indicating a clear unmet global public health need**. Furthermore, there are strong evidence of their: **better efficacy, safety, and durability** (low likelihood of selection of resistance on treatment) than comparable medicines; **low impact on the microbiome; and simplicity of administration.** There is therefore likely to be a range of Reserve antibiotics that cover different serious clinical infections[i].
These antibiotics should be available for clinical care when needed but used only in certain situations where their use is likely to have clear clinical benefits. Reserve antibiotics are ideally used for targeted treatment once multidrug-resistant bacteria are confirmed[ii].
Ensuring the optimal use of Reserve antibiotics is complex and difficult at both a patient and country level, but control of the use of Reserve antibiotics is critical to maintaining their future effectiveness. In this context, the **stewardship of Reserve antibiotics** plays a pivotal role as preserving the effectiveness of these antibiotics is key to maintaining their longevity in clinical use.
Today, almost every antibiotic in use is based on a discovery made **over 37 years ago**.
Since 2017, only 12 new antibiotics have been approved, 10 of which belong to existing classes that already have mechanisms of antimicrobial resistance[iii]. Furthermore, these show a **limited degree of innovation**. Only two of the approved agents are considered innovative, representing a new chemical class, while more than 80% of recently approved agents are derivatives of known classes to which multiple resistance mechanisms already exist. In the field of antibacterial R&D, effectively combatting the emergence of drug resistance stands as a primary challenge. However, **this critical issue remains inadequately addressed** by newly authorized agents[iv].

The annual analysis by the WHO show that in 2021 there were 77 antibiotics in clinical development, of which 45 were traditional direct-acting molecules and 32 were non-traditional agents. In addition, out of the 45 traditional molecules, only 27 were found to be effective against pathogens identified as priority by the WHO.
In this context, the number of major **pharmaceutical companies active in this sector** has decreased **from 18 in 1990 to 8 in 2021** due to:

- high uncertainty about return on investment.
- insufficient economic incentives.
- technical challenges that can arise throughout the entire drug development process.
- lengthy and complex regulatory processes.

The antibiotic market is therefore very **risky** and **unattractive**.

INCENTIVES MODELS ARE NEEDED TO STIMULATE R&D, ACCESS AND ENSURE AVAILABILITY OF NEW ANTIBIOTICS

- **Push incentives** – Directly support the research and development of antibiotics through public and/or private resources (e.g., public-private partnerships, financing, tax breaks, innovation awards, etc.) In recent decades, policymakers, the industry and the philanthropic community in the United States and the European Union, among others, have activated several programs of national and international importance to finance the research and development of new antibiotic.

- **Pull incentives** – Ensure a fair return on investments for the most innovative antibiotics and promote access and stewardship efforts (e.g., market exclusivity, early purchase contracts, exemption from clawback mechanism, etc.). Some European countries and the UK have introduced

pull mechanisms, which are characterized by their potential to "decouple" R&D investments from sales volumes and prices, thus achieving a dual objective:

- **ensuring a fair return on investment** for the most innovative antibiotics
- **encouraging accessibility and stewardship efforts**

Among these Country:

- In **Germany**, Reserve antibiotics are not subject to price negotiations, allowing companies to maintain the price without future renegotiations, thus incentivizing market entry.
- In **Sweden**, a minimum annual revenue is guaranteed for a predetermined quantity of antibiotics: the difference between the antibiotics not purchased by the regions and the total antibiotics is covered by the state.
- In **France**, various measures have been introduced, including some exemptions to current Health Technology Assessment (HTA) criteria for new antibiotics and exclusions from the clawback mechanism for existing ones.
- In the **United Kingdom**, a pilot program has been initiated where a Reserve antibiotic (appropriately evaluated) is assured an annual revenue, regardless of actual usage (subscription model), thus ensuring economic return for Reserve antibiotics.
- As part of the review of the European pharmaceutical strategy, the **European Commission** has proposed the experimental granting of an additional 1-year patent protection for those developing a new antibiotic, in the form of a voucher.

There is general consensus that no single incentive is sufficient to foster the development of antibiotics: a combination of Push and Pull incentives is needed along the entire R&D path.

RECOMMENDATIONS TO ENHANCE THE VALUE AND SUSTAINABILITY OF ANTIBIOTICS

Promote and implement a new model of pull incentives, complementary and not an alternative to existing Push incentives.
New regulatory framework and processes are needed both **to facilitate renewed investment in research and development of new antibiotics**, and to ensure that use of new products is governed by a public health framework of stewardship that conserves the effectiveness and longevity of such products[v].
Improving rapid and accurate identification of infectious agents can enhance healthcare professionals' ability to effectively treat infections. Advanced infection control methods can also play a crucial role in managing infections that are resistant to multiple drugs.
Control antibiotic overuse together with the availability of new antibiotics to fight multidrug resistant strains can fundamentally contrast the growth of the "silent pandemic".
Create a new, ad hoc pathway for Reserve antibiotics by identifying, experimenting with, and introducing pricing and reimbursement models based on those adopted in other European and G7 countries. This recognition acknowledges the status of priority and innovation granted by the WHO definition
Governments should take the lead educating public, but also **support the health care industry, prioritizing diagnostics, vaccines and new antibiotics' development**.
It is furthermore paramount for all countries to closely monitor antibiotic usage and to launch public awareness campaigns educating the population on the risks of antibiotic overuse.

CONCLUSIONS

Addressing antibiotic resistance, requires the implementation of **integrated strategies that include the key role of vaccines, new antimicrobials, and diagnostic tools**.
By increasing vaccination rates, antibiotic use can be reduced, and the emergence of new resistance mechanisms can be halted.
Improving rapid and accurate identification of infectious agents can enhance healthcare professionals' ability to effectively treat infections. Advanced infection control methods can also play a crucial role in managing infections that are resistant to multiple drugs.
A strict control over antibiotic overuse together with the availability of new antibiotics to fight multidrug resistant strains can fundamentally contrast the growth of the "silent pandemic".
However, despite significant progresses, the effort of academics, diagnostics, and pharmaceutical companies alone are insufficient to modify the current trajectory of things.
Government interventions are necessary to educate the public but also to sustain the health care industry, prioritizing diagnostics, vaccines and new antibiotics' development. Major pharmaceutical companies in fact have stopped research in infectious diseases and antimicrobials due to both strong market access limitations and poor return on investment. As it already happened in other G7 countries (e.g. Germany, UK, Sweden and France), new incentives or innovation reward mechanism should be rapidly identified to accelerate investment in research and development

for new antimicrobials. On the same line, new vaccines' development should be encouraged as vaccines are typically long-term, sustainable solutions that help preventing and restraining AMR. To this end, the WHO emphasized the need to increase funding for R&D and to develop a regulatory framework that accelerates approvals for new vaccines directed against key pathogens with complex resistance profiles and high incidence rates of related severe infection.
It is furthermore paramount for all countries to closely monitor antibiotic usage and to launch public awareness campaigns educating the population on the risks of antibiotic overuse.
Collaboration, efficient resource utilization and will be crucial in the fight against multidrug-resistant pathogens in healthcare settings.

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