

FOREWORD

The year 2025 will mark ten years since the adoption of the WHO Global Action Plan (1) on antimicrobial resistance (AMR) and, despite the progress made so far, a solid and effective action is still required to eradicate this phenomenon.

Farmindustria has decided to promote the establishment of a multidisciplinary Task Force to pool the know-how and experience of experts on the subject, with a view to providing recommendations on critical aspects in the fight against AMR.

Task Force members include representatives from the medical and scientific community, the academic world, citizens and patients' associations, pharmacists organizations and the pharmaceutical industry.

The discussions between these experts resulted in this document consisting of three chapters regarding, respectively:

- **The role of vaccination as a prevention tool against antimicrobial resistance**
- **Value, access, and innovation of novel antibiotics against bacterial resistance**
- **Appropriate use of antibiotics**

These three topics were discussed during three parallel work sessions involving the various experts and further feedback and information were obtained through a survey sent to all participants. The document was shared with the whole Task Force panel of experts each step of the way. In drafting the document, attempts were made to focus attention on the specific issues requiring solutions that are sustainable in the long term and effective planning, and for which a direct and solid recommendation can be made.

The recommendations proposed are intended as a complementary tool to those provided by existing technical and institutional panels.

THE ROLE OF VACCINATION AS A PREVENTION TOOL AGAINST ANTIMICROBIAL RESISTANCE

The number of scientific publications that support the positive role of vaccination in the prevention of antimicrobial resistance phenomenon grows from one year to the next. This fundamental role has been recognized by the European Commission, European Parliament, and European Council and the WHO has recently adopted a more decisive stance on this issue (2). Vaccines are able to reduce antimicrobial resistance through various mechanisms by:

- a. directly protecting vaccinated individuals, who will not become infected and will therefore not have to use antibiotics;
- b. reducing viral infections, consequently lowering any associated secondary bacterial infections, and also inappropriate use of antibiotics (3, 4);
- c. reducing the possibility of the illness being transmitted to the unvaccinated population, and therefore reducing the likelihood of the pathogen being transmitted. And since in pediatric and/or geriatric patients in particular, infection often leads to hospitalization, controlling infection (both viral and bacterial) reduces bacterial circulation in hospital settings, therefore preventing the diffusion of resistant bacteria;
- d. also protecting the microbiome from the changes induced by wide-spectrum antibiotics and therefore the development of resistant bacterial species resulting from the acquisition of resistance genes from other organisms present in the microbiome.

RECOMMENDATIONS

1. National Immunization Information System

Complete the National Immunization Information System as soon as possible and make it available nationwide. This is a fundamental tool for planning vaccination campaigns for all preventable diseases, for managing vaccine administration and for the prompt sourcing of enough vaccines to satisfy the population's health demand. It will also contribute to the acquisition of data and evidence on the positive role vaccinations play in preventing AMR and aid the Regional Authorities in implementing Electronic Health Records, with the entry of the vaccinations administered.

2. Vaccinations and diagnostic and therapeutic pathways

Incorporate all vaccinations, including those in the NIP calendar, into diagnostic and therapeutic pathways in a standard manner nationwide to protect individuals with one or more health conditions from the risk of contracting infectious diseases that can be prevented by vaccination.

3. Vaccination culture

Favor healthcare professional training on the issue, particularly the mechanisms by which vaccines are able to prevent the spread of antibiotic resistance and promote awareness initiatives in order to generate a vaccination culture, also with a view to countering antimicrobial resistance, in order to meet the vaccination coverage targets, set in the NIP.

4. National Action Plan on Antimicrobial Resistance and National Immunization Program

Raise awareness of the fundamental role of vaccination in preventing AMR both in the new National Action Plan on Antimicrobial Resistance (NAP-AMR) and in the new National Immunization Program, which are both currently being prepared by the Italian Ministry of Health.

5. Scientific society consensus

Draft an official Scientific Society consensus statement on the role in preventing antibiotic resistance played by the vaccinations included in the NIP calendar, in order to promote the value of vaccination through a multidisciplinary approach.

All vaccinations, including those contemplated in the Italian National Immunization Program (NIP) can potentially play an important direct or indirect role in the prevention of antimicrobial resistance and its consequences, not least the economic and social ones.

However, it is also important to promote research into new specific vaccines for multiresistant micro-organisms, particularly nosocomial ones that can play a significant clinical role in terms of frequency, severity and therapeutic difficulties.

In order to maximize the impact of vaccinations, it is fundamental, on the one hand, to achieve the coverage targets established in the NIP and, on the other, that the Ministry of Health and Scientific Societies raise awareness on the role of these vaccinations.

VALUE, ACCESS, AND INNOVATION OF NOVEL ANTIBIOTICS AGAINST BACTERIAL RESISTANCE (5)

Research on and identification of innovative antibiotics able to get around the current mechanisms of bacterial resistance are an unmet clinical need of great importance for being able to effectively reduce the morbidity and mortality of nosocomial infections from multidrug-resistant (MDR) Gram-negative bacteria.

The pharmaceutical industry has played a fundamental role in the development of antimicrobials, and although research has recently picked up again, there are still several barriers to investments in this therapeutic area.

Despite the significant attention this issue has received over the past decade from important international organizations, such as the World Health Organization and the World Bank, national governments have made little progress in promoting the development of new antimicrobials and particularly new antibiotics, leading to a few pilot projects that have been launched in some countries in recent years. The European Commission has also emphasized the lack of measures able to attract significant investments in this area, by highlighting this issue in its Pharmaceutical Strategy for Europe (6).

In this context, while maintaining actions to support exploratory research thanks to public investments, and hopefully implementing them through the opportunities included in the Italian National Recovery and Resilience Plan (NRRP), it is necessary to create a favorable environment that can attract investments by the pharmaceutical industry and other investors, especially to provide economic support for the more advanced phases of clinical development.

In order to achieve this objective, some countries have started testing new measures, known as Pull incentives (7, 8), both separately and in combination with one another, such as new assessment methods that also analyze aspects other than the therapeutic benefit for treated patients or ad hoc reimbursement schemes (e.g., the subscription model tested in the United Kingdom). As a matter of fact, most Health

RECOMMENDATIONS

1. Methodology for evaluating new antibiotics against resistant bacterial strains

Adapt current methodologies for establishing the value of antibiotics to the characteristics of these medicinal products, considering their life-saving role, taking into account that this will require a wider perspective and the analysis of scenarios and evidence beyond those needed for current marketing authorization applications.

2. Criteria for granting 'innovative' status to new antibiotics against resistant bacterial strains

Use specific indicators able to effectively measure the degree of innovation of new antibiotics, adapting, if necessary, the current elements of assessment supporting applications for innovative status (therapeutic need based on the indicators published each year by the ECDC on antibiotic-resistant pathogens, added therapeutic value on pathogens resistant to available antibiotics and robustness of scientific evidence by adapting the GRADE method to suit the specific characteristics of the new antibiotics, also taking into account their capacity to effectively counter the main mechanisms of bacterial resistance with innovative mechanisms).

3. Ad-hoc reimbursement models for new antibiotics effective against bacterial resistance

As antimicrobial stewardship imposes restrictions on the use of new antibiotics in the treatment of infections caused by resistant strains in order to reduce the likelihood of new forms of resistance developing, it is necessary to identify new methods of reimbursement that guarantee developers economic returns such as to increase and maintain investments in R&D in this area.

Technology Assessment (HTA) systems now primarily focus on assessing the therapeutic and economic benefits solely from an NHS perspective (improvement in patient health and impact in terms of direct health costs).

However, even at international level, several organizations have stressed the need to define a specific value framework for new antimicrobials against resistant strains that takes into consideration also the social and ecological costs (impact in terms of indirect and social security costs).

APPROPRIATE USE OF ANTIBIOTICS

Appropriate use is considered one of the main tools for preventing the selection and spread of resistant microorganisms in the community and in healthcare facilities and, consequently, the transmission of infection by resistant bacteria.

In establishing the short-term rules regarding appropriate use of new antibiotics and training, the National Action Plan on Antimicrobial Resistance (NAP-AMR) stresses the importance of promoting healthcare professional training initiatives on the appropriate use of all antibiotics, and on the prevention and control of infections, including healthcare-associated infections (HAIs), involving all stakeholders, as part of a holistic approach.

The NAP-AMR also aims to assure mechanisms for the governance of these medicinal products when they are placed on the market. So far, these objectives have been only partially achieved and it is there-

fore necessary to increase investments in antimicrobial stewardship programs to overcome the remaining deficits.

In particular, in emergency/urgency settings (e.g., sepsis in the ICU, severe infections in onco-hematology) for which it is essential to have timely access to antibiotic therapy, it is not always possible to obtain an infectious disease consultation, which at present can only be provided by an infectious diseases specialist or other specialist, with specific expertise, identified by the Hospital Infection Control Committee.

In addition, the AIFA product information sheets on new antibiotics are an objective impediment to the use in emergency situations of these potentially life-saving medicinal products. As a matter of fact, these information sheets are in accordance with the authorization indications that define the settings for use and posology and that predominantly refer to syndromic situations (pneumonia, urinary tract infections, abdominal infections), rather than etiological ones, therefore forcing infectious diseases specialists to use them off-label when prescribing them empirically or on the basis of a confirmed or suspected aetiology.

Lastly, empirical use by other specialists in critical patients, with risk factors, epidemiological setting, colonization, is not currently considered or permitted.

RECOMMENDATIONS

1. Healthcare facilities

Use the resources allocated to the “Health” mission of the Italian National Recovery and Resilience Plan (NRRP) to overcome the structural, technological and organizational deficiencies that have so far constituted hindrances to the full implementation of the actions set forth in the PNCAR.

2. Healthcare professional training

Guarantee that the funds allocated by the NRRP to organize extraordinary training initiatives on healthcare-associated infections to all healthcare professionals and non-medical hospital staff, as well as primary-care staff, are directed towards specific programs on antimicrobial stewardship and infection control.

3. Multidisciplinary teams

Guarantee the presence of a multidisciplinary team (specialists, microbiologists, hospital pharmacists, etc.) within healthcare facilities charged with the responsibility of defining and applying stewardship programs.

4. Governance of new antibiotics

Guarantee timely access to new antibiotics in urgent and emergency conditions, extending the possibility of prescribing these new “lifesaving” drugs to other specialists with specific expertise on the use of antibiotics (intensive care specialists, hematologists, etc.), by making provision for it in antimicrobial stewardship programs. In addition, in the context of precise therapeutic recommendations it may be useful to consider a “free and regulated access window” to allow patients to receive the necessary treatment promptly in the decisive earliest few hours.

5. Integration between antibiotic stewardship and diagnostic stewardship

Develop antibiotic stewardship programs closely integrated with diagnostic stewardship in the definition of diagnostic, therapeutic and care pathways in a standard manner across the country, involving all healthcare professionals, especially those working in the community medicine setting. Promote the use of first-level diagnostic devices (e.g., pharyngeal swab for GABHS, PCR testing, urine dipsticks, pneumatic otoscopy, etc.) that, in primary care settings, allow greater diagnostic precision and consequent greater prescriptive appropriateness.

6. Information for citizens

Promote communication campaigns addressing the general public on appropriate and well-informed use of antibiotics, aimed at improving awareness among the citizens.

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Although rapid molecular diagnosis is considered fundamental for reducing the inappropriate use of antibiotics and therefore in the control of resistant infections, to date, antimicrobial stewardship programs have not been fully integrated with diagnostic stewardship programs.

PANEL OF EXPERTS WHO TOOK PART IN AMR TASK FORCE PROJECT

The role of vaccination as a prevention tool against antimicrobial resistance

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Value, access, and innovation of novel antibiotics against bacterial resistance

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One Task Force meeting on "Value, access and innovation of novel antibiotics against bacterial resistance" was also attended by a representative of the AIFA (Dr. **Maria Paola Trotta**).

The Farmindustria Working Group on antimicrobial resistance, composed of **Andrea Pitrelli** (Group leader), **Loredana Bergamini**, **Marzena Bochenska**, **Giovanni Checcucci Lisi**, **Tiziana Di Paolantonio**, **Monica Gori**, **Federico Marchetti**, **Marina Panfilo**, **Maria Adelaide Bottaro** and **Mauro Racaniello**, also contributed to the Task Force project and the drafting of this document.

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