

Review Article

Italy's Opportunity to Stop Superbugs, from the National Action Plan on Antimicrobial Resistance to the Italian G7 Presidency

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Received: April 09, 2024; **Accepted:** May 02, 2024; **Published:** May 10, 2024

Citation: Votta M. Italy's Opportunity to Stop Superbugs, from the National Action Plan on Antimicrobial Resistance to the Italian G7 Presidency. Arch Virol Infect Dis. 2024;2(1):1-6.

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ABSTRACT

The World Health Organization has recognized antimicrobial resistance (AMR) as one of the top ten threats to humanity, which needs to be addressed with the utmost urgency and multi-sectoral interventions. If no effective action is taken, by 2050 the economic impact of AMR could be more severe than the 2008-2009 financial crisis. A recent OECD assessment estimated that, to date, AMR costs about EUR 1.1 billion per year in European countries and will cost EUR 11 billion in Italy by 2050.

Recently, a multi-stakeholder policy initiative has been launched in Italy to include AMR on the agenda of the G7, which the Italian government will lead in 2024. The call to action called "Keeping AMR as a priority for the Italian G7 presidency. Antimicrobial resistance: An urgent problem, a challenge to be launched thanks to Italy" has been endorsed by the scientific society, civic organizations, PAGs, the private sector, etc. to bring the issue of AMR to the forefront of the political agenda. Recommendations include increasing investments in the push and pull incentives to accelerate AMR innovation, implementing stewardship while expanding access to treatments, leading target-setting and monitoring mechanisms, and prioritizing professional training and public health literacy programs.

World leaders have begun to recognize the urgency of taking concrete action to limit the progression of AMR. In September 2024, world leaders will meet at the United Nations General Assembly for a high-level AMR meeting. This exceptional event will take place in conjunction with the Italian G7 Presidency. No other opportunity seems to us better than this to make significant progress in the fight against AMR. This is why we believe the Italian government must make AMR an independent and priority issue at this year's Health and Finance Ministerial meetings, demanding and promulgating concrete actions and adequate funding.

Keywords: National Health Service; Antimicrobial Resistance (AMR); G7; United Nations; Italy; bacterial infections; civic society; Patients' Advocacy Groups (PAGs).

INTRODUCTION

Antimicrobial resistance (AMR) - the ability of microbes (particularly bacteria) to modify and mutate their behavior,

making drugs normally used against them ineffective - is a global public health crisis with a significant economic impact. Drug-resistant bacterial infections already kill 1.27

million people globally each year (more than HIV/AIDS and malaria). Low- and middle-income countries (LMICs) are responsible for almost 90% of direct deaths and more than 99.5% of AMR-related deaths among children under five. However, even wealthier countries face frightening statistics: 11,000 Italians are estimated to die each year from AMR (the highest number among all European countries) [1].

The availability of effective antibiotics not only saves lives but also makes fundamental practices possible for our societies and economies, from basic medical procedures to workers' productivity and the stability of food chains. For this reason, numerous reports have highlighted the significant public returns on potential public investments to stop superbugs. The Center for Global Development estimated that a new EU-wide incentive program paying EUR 150 million per year for an innovative antibiotic for ten years would save 385,000 lives and generate USD 541 billion in total benefits for the EU over 30 years, with an ROI of 11:1. The OECD has found that every euro invested in a mixed policy package of actions

against AMR in the health and food sectors generates returns equivalent to EUR 5 in economic benefits from reduced healthcare expenditure and increased productivity at work.

Against this background, policy actions do not match the urgency of the situation. Past policy commitments to address AMR, including the 2016 Political Declaration of the High-Level Meeting on AMR at the UN General Assembly and the 2023 EU Council Recommendation on scaling up EU actions to combat AMR according to a single health approach, have been important milestones in global efforts to prioritize policy actions against AMR. In addition, recent G7 and G20 declarations demonstrated a broad consensus on the importance of supporting R&D, promoting prudent use, encouraging surveillance initiatives, and building capacity in low- and middle-income countries. However, there remains an urgent need for more effective and sustained action by governments and other stakeholders. Remarkably, Italy can play a key role in this in 2024.

Paesi UE/SEE	Totale (J01)	Δ% 21-20
Austria	7,21	1,3
Belgio	16,02	5,1
Bulgaria	22,34	7,7
Croazia	16,22	15,5
Danimarca	12,59	0,6
Estonia	8,66	-1,6
Finlandia	9,45	-5,1
Francia	19,86	6,2
Germania	8,13	-9,1
Grecia	21,77	-17,4
Irlanda	16,32	-4,5
Islanda	15,75	2,4
Italia	15,99*	-3,1
Lettonia	10,15	1,8
Lituania	11,70	-1,8
Lussemburgo	14,61	-1,6
Malta	14,11	-1,9
Norvegia	12,84	0,7
Olanda	7,63	-1,8
Polonia	18,82	9,8
Portogallo	13,74	0,2
Rep. Ceca*	11,49	-
Romania	24,28	2,2
Slovacchia	14,53	10,5
Slovenia	8,75	-1,1
Spagna	18,52	1,7
Svezia	8,90	-0,2
Ungheria	10,82	7,8
UE/SEE**	15,01	0,4

^ dati generati dal Sistema di Sorveglianza Europeo (ESAC-Net) e disponibili in TESSy alla data del 1 dicembre 2022

* dato del 2020 non presente

** UE/SEE: media pesata sulla popolazione dei Paesi che hanno fornito i dati per l'anno 2021

* il valore non corrisponde esattamente alla somma dei valori riportati nelle Tabelle 2.1 (convenzionata: 11,5 DDD/1000 abitanti die) e 3.1 (acquisto privato: 4,1 DDD/1000 abitanti die) per approssimazioni decimali nel calcolo

Source: The use of antibiotics in Italy - 2021, AIFA April 2023

Table 1 - Territorial consumption of systemic antibiotics (DDD/1000 ab die) by country: comparison

ANTIBIOTIC USE IN ITALY: EUROPEAN COMPARISON

Before the COVID-19 pandemic, the phenomenon caused around 33.000 deaths every year in Europe from infections caused by antibiotic-resistant bacteria [2]: of these, more than 10.000, a third of the total, occur in Italy. This is the sad record held by Italy, which tops the continental ranking for the number of deaths linked to antimicrobial resistance, according to a report published by the Italian National Health Institute (Istituto Superiore di Sanità) on the annual World Antimicrobial Awareness Week 2019 [3]. According to the European Centre for Disease Prevention and Control (ECDC), in 2019 the risk - in Italy - of contracting infections during a hospitalization was about 6%. On an absolute level we are talking about 530.000 cases each year, data that puts Italy in last place among all countries in Europe [4].

To all this should be added that antibiotic consumption in Italy is higher than the European average (both at the territorial and hospital level, especially in the age groups between 2 and 5, and over 85 age groups) and that, above all, in my country antibiotics are inappropriately prescribed in a quarter of cases, according to the 2020 National Report on the Use of Antibiotics in Italy, edited by the Italian Medicines Agency (AIFA) [5]. In 2021, overall consumption in Italy remains higher than in many European countries. Italy is above the EU/EEA average (15.01 DDD/1000 inhabitants per day), in tenth place, with a consumption of 15.99 DDD/1000 inhabitants per day, slightly decreasing (-3.1%) compared to 2020. The countries that recorded the largest decreases in consumption compared to 2020 were Greece (-17.4%) and Germany (-9.1%), while Croatia and Slovakia recorded the largest increases (+15.5% and +10.5% respectively).

New expectations arise in Italy from the implementation of the new National Action Plan on Antimicrobial Resistance (PNCAR) 2022-2025. The first one in Italy was adopted in November 2017 [6], expired in 2020 in the middle of the COVID-19 pandemic, and extended to December 2021.

The National Action Plan on Antimicrobial Resistance 2022-2025 (PNCAR), approved in November 2022, was created to provide the country with strategic guidelines and operational indications to address the AMR emergency in the coming years, according to a multidisciplinary approach and a One Health vision.

The Plan was drafted by a Working Group of experts, set up in 2015 at the DG of Health Prevention, in collaboration with the relevant DGs of the Ministry of Health and other interested Italian institutes and ministries, integrated by the observations

The National Strategy for combating AMR also defines six general objectives to reduce the incidence and impact of antibiotic-resistant infections:

1. Strengthen prevention and surveillance of HAI in hospital and community settings.
2. Strengthen the “One Health” approach, including through the development of coordinated national surveillance of AMR and antibiotic use, and prevent the spread of AMR in the environment.
3. Promote the appropriate use of antibiotics and reduce the frequency of infections caused by resistant microorganisms in humans and animals.
4. Promote innovation and research in the prevention, diagnosis, and treatment of antibiotic-resistant infections.
5. Strengthen national cooperation and Italy’s participation in international initiatives in the fight against AMR.
6. Improve public awareness and promote training of health and environmental professionals in the fight against AMR.

To implement the measures and interventions foreseen by the PNCAR in Italy, it is encouraging that the last multi-annual state budget authorized an expenditure of EUR 40 million for each of the years 2023- 2024-2025, already distributed among the regions.

AMR in the International Political Agenda

Given the urgency and complexity of the problem, however, more can and must certainly be done, both locally and internationally. In this regard, a multi-stakeholder policy initiative was recently launched in Italy to include AMR on the agenda of the G7, which will be led by the Italian government in 2024. The call to action called “Keeping AMR as a priority for the Italian G7 presidency. Antimicrobial resistance: An urgent problem, a challenge to be launched thanks to Italy” was drafted in August 2023 by Cittadinanzattiva [10], Menarini [11] and Società Italiana di Microbiologia [12], with international contributions from the AMR Action Fund [13], BEAM Alliance [14] and CARB-X [15], and endorsed by scientific society, civic organizations, PAGs, private sector, etc. with the common objective of bringing the issue of antimicrobial resistance to the top of the political agenda.

World leaders have begun to recognize the urgency of taking concrete action to limit the progression of AMR. The last three G7 summits (UK 2021 [16], Germany 2022 [17], and Japan 2023 [18]) have all prioritized a discussion on the main measures to be taken. Research and innovation for new drugs,

vaccines, and diagnostics, access to existing products and the preservation of their efficacy, microbiological surveillance, primary prevention with a focus on care-associated infections, promotion of the correct use of antimicrobials (stewardship) [19] were highlighted as essential elements for the implementation of an effective countermeasures plan.

In September 2024, world leaders will gather for a high-level meeting on AMR [20] at the United Nations General Assembly. This exceptional event will take place in conjunction with the Italian Presidency of the G7. We believe there is no better opportunity than this to make significant progress in the fight against AMR. This is why we consider it essential that the Italian government makes antimicrobial resistance an independent and priority issue at next year's Health and Finance ministerial meetings, demanding and promulgating concrete actions and adequate funding.

This year, 2024, is a special year for renewing and accelerating progress against AMR. Five key meetings will take place in 12 months:

- Evidence for Action Dialogue on AMR in February in Malta,
- G7 Summit in June at Borgo Egnazia,
- UN High-Level Meeting (UN HLM) on AMR in New York in September,
- G7 Health Ministers' Meeting in October in Ancona, and
- 4th Ministerial Conference on AMR in November in Saudi Arabia.

Italy has a crucial role as G7 Presidency in directing partners to implement impactful actions that accelerate, sustain, and track progress on AMR, in close collaboration with partners in the UN process leading to the HLM, the G20, and low- and middle-income countries.

Key Areas for Action Include:

- Increase investments in push and pull incentives to accelerate AMR innovation: There is still a significant gap in public and private investment to develop better products that could prevent, diagnose, and treat bacterial infections. Some G7 governments have done much to accelerate early-stage antibiotic R&D through new 'push' mechanisms such as CARB-X. All G7 governments should now support "push" mechanisms through direct funding but also attract private investments through the implementation of national or regional 'pull' incentives (i.e., sufficient financial rewards to incentivize R&D and market access). Investment in research capacity will also be crucial, as the AMR innovation ecosystem

faces a shortage of experienced researchers with skills and knowledge in the field of infectious diseases.

- Implement stewardship while expanding access to treatments: Antimicrobial treatments are frequently misused, mainly due to a lack of awareness and the difficulty of implementing comprehensive stewardship. The Italian G7 Presidency could initiate concrete initiatives to safeguard international antibiotic stewardship, in addition to the WHO AWaRe antibiotic stewardship book for hospitals. On the other hand, many countries, and especially the Low- and Middle- Low-income countries (LMICs) have populations that do not have access to basic and necessary antibiotics. Policy action is needed to improve access in an evidence-based way, focusing on critical antibiotics in the most medically relevant situations.

- Lead target-setting and monitoring mechanisms: Progress in the fight against AMR has been too slow in recent years. Clear targets for national governments and the international community could raise ambition and drive sustained action. During its G7 Presidency, Italy could support a union of countries to institutionalize stronger accountability and target-setting mechanisms, allowing for more transparent monitoring of progress in the fight against AMR. G7 leadership on this issue in 2024 would be of great benefit to the discussions at the UN General Assembly in September, where the issue is likely to feature prominently.

- Harmonize vaccination policy in the fight against AMR: Vaccines help to combat antibiotic resistance, as they prevent bacterial infections and help to limit the use of antibiotics, for example in the case of pneumococcus. Through vaccines, such as the flu vaccine, we can also reduce inappropriate prescriptions and bacterial infections, which often overlap with viral infections and require antibiotic treatment. There is also a further indirect effect because through vaccines we can reduce the number of hospital admissions of vulnerable people, reducing overcrowding and the possibility of complications or HAI. Within this framework, which also sees vaccines as a tool to combat HAIs and antibiotic resistance, it will be useful to make recommendations on their use based on all these considerations when they are placed on the market.

- Prioritize professional training and public health literacy programs: The AMR knowledge of healthcare professionals must be always up to date. From a "One Health" perspective, this concerns the competencies of doctors, veterinarians and pharmacists. In the context of the "European Year of Skills", institutions are called upon to help people get the right skills for quality jobs and to support companies in addressing the

skill shortage in Europe. Moreover, civil society and PAGs play a crucial role in ensuring that everyone, including normal citizens and animal owners, each with their sense of responsibility to use antibiotics consciously and always as prescribed by a doctor, contributes to the fight against antibiotic resistance. Investing in public health literacy programs and supporting existing initiatives in this field [21] is crucial to move in this direction correctly.

The Cost of Inaction

The costs of AMR are immense, both in public health and economic terms. At least 1.27 million people die each year worldwide [22] from antibiotic-resistant bacterial infection, a third more than HIV/AIDS and twice as many as malaria. Even high-income countries are increasingly affected by AMR: in the European Union alone, almost 100 people die every day [23] from these infections. In Italy, AMR causes 10,000 deaths a year. Even the most ordinary hospitalization or surgery can lead to dramatic consequences.

Without effective interventions, by 2050 the economic impact of AMR could be more severe than the financial crisis of 2008-2009. A recent OECD assessment [24] estimated that, to date, AMR costs about EUR 1.1 billion per year in European countries and will cost EUR 11 billion in Italy by 2050. Fighting AMR would save EUR 445 million per year.

Since their discovery almost 100 years ago, antibiotics have not only saved millions of lives but have made possible medical practices that we now consider routine such as cesarean sections, chemotherapy, and transplants. Yet, about one-third of *Staphylococcus aureus* infections are already resistant to methicillin and multi-resistant to common antibiotics. Also of great concern is the increase in carbapenem resistance [25] in *Klebsiella pneumoniae* and other Enterobacteria. The most vulnerable and fragile individuals, such as newborns, the elderly, and the immunocompromised, constantly rely on the efficacy of antibiotics, but, as an example, bacterial infections are the second leading cause of mortality [26] in cancer patients.

Data, recommendations and messages that were addressed to the Italian Ministry of Health on 10 January 2024 in Rome by a delegation of the promoters of the “call to action” – including Cittadinanzattiva – and independent experts on the “Dialogue on AMR and Italy’s G7 Presidency”, organized by CARB-X and Wellcome Trust, received encouraging support to make AMR one of the central themes of the Italian G7 Presidency.

DECLARATIONS

This manuscript has not been previously published by

another international peer-reviewed journal and is not under consideration by any other journal. Additionally, all the authors have approved the contents of this paper and have agreed to the submission policies of the journal.

AUTHOR CONTRIBUTION AND CONFLICT OF INTEREST

The author has substantially contributed to conducting the underlying research and drafting this manuscript. Additionally, to the best of our knowledge, the author listed on the first page declares that they do not have any conflict of interest, financial or otherwise.

ACKNOWLEDGMENTS

For the valuable contribution to the advocacy activities with the Italian Minister of Health about AMR and G7 Italy, the authors thank in particular: Damiano de Felice, Director of Development and External Engagement at CARB-X; Deepali Patel, Director of International Policy at AMR Action Fund; Dr. Najy Alsayed MD; M.Sc. Global Therapeutic Area Head - Infectious Diseases at Menarini LLC; Stefania Stefani, Full Professor of Microbiology and Clinical Microbiology. Dept of Biomedical and Biotechnological Sciences and Policlinico Hospital - University of Catania; Valeria Fava Head of Health Policy Coordination of Cittadinanzattiva; Daniela Zinzi, VP, Clinical R&D at F2G; Andrea Pitrelli, Market Access & Government Affairs Lead at Shionogi srl Italy.

The author would also thank all the entities (scientific societies, civic organizations, PAGs, private sector) that endorsed the call to action “Keeping AMR as a priority for the Italian G7 presidency. Antimicrobial resistance: An urgent problem, a challenge to be launched thanks to Italy” in the second half of 2023.

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