Journal of Global Antimicrobial Resistance 46 (2026) 288–296

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Review

Intervention studies and antimicrobial resistance in Italy: An overview of the latest evidence

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ARTICLE INFO

Article history:
Received 1 September 2025
Revised 17 December 2025
Accepted 30 December 2025
Available online 8 January 2026

Editor: Dr Eric Dannaoui

Keywords:
Antimicrobial resistance
Infectious disease
Pathogens
Italy
Interventions

ABSTRACT

Objective: Antimicrobial resistance (AMR) poses a significant and growing threat to public health globally, with Italy facing some of the highest resistance rates in Europe. This manuscript reviewed recent Italian intervention studies aimed at mitigating AMR across bacterial, fungal, and viral domains.
Methods: Strategies including antimicrobial stewardship (AMS), infection prevention and control (IPC), antifungal stewardship (AFS), and diagnostic advancements were evaluated. The evidence highlighted both the promise and limitations of Italy's current approach.
Results: While AMS and IPC programs have reduced antibiotic use, healthcare-associated infections, and costs, regional disparities, inconsistent implementation, and limited longitudinal surveillance remain critical challenges. The fungal resistance landscape is marked by rising threats like Candida auris, requiring urgent expansion of AFS programs. Italy's AMR strategy would benefit from improved IPC infrastructure, realtime data integration, and alignment with One Health principles.
Conclusions: Strengthening national coordination, supporting innovation, and translating surveillance into action at the local level are crucial for turning policy into measurable progress. This review provides actionable insights to guide a more unified and responsive national AMR framework.

1. Introduction

1.1. Antimicrobial resistance

Antimicrobial resistance (AMR) is a phenomenon that occurs when infectious pathogens are no longer sensitive to the action of antimicrobial drugs and manifest resistance, potentially becoming capable of causing severe disease. To date, the phenomenon of

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https://doi.org/10.1016/j.jgar.2025.12.017

AMR represents one of the major health problems worldwide [1]. Several causes have led to the problem of AMR in recent years, the main ones being the inappropriate use of antimicrobials, combined with limited development of new antimicrobial molecules, the lack of application of appropriate counter strategies and appropriate infection control, inadequate vaccination policies, and increased international travel [2]. The World Health Organization (WHO) listed AMR as one of the top 10 threats to human health in 2019 [3]. It is clear, therefore, that the phenomenon of AMR must be urgently and adequately contrasted by all health systems, in a synergetic manner and in a holistic One Health view, which considers the context of human health interconnected with that of the environment and the animal world [4].

1.2. Objective

Given that Italy is one of the Western countries with the highest prevalence of microbiological resistance and the significant implications for healthcare, due to the need to highlight new evidence in the field, this manuscript analysed the burden of AMR, with sections dedicated to bacterial, fungal, and viral resistance, focusing on interventions adopted in Italy over the last decade. It highlighted innovative Italian strategies for mitigating AMR, such as intervention studies and innovative strategies introduced in Italy, not only from a clinical perspective but also from that of policies and funding applied by public decision-makers. Finally, a focus was made on the main categories of patients who are at risk of resistance due to the conditions they suffer from: patients affected by cystic fibrosis (CF) and those by cardiovascular diseases (CVD).

1.3. Epidemiology

The growing challenge of AMR is now recognised as a global public health emergency that requires concerted efforts by all stakeholders. The recent WHO document reported that country participation in the WHO's Global System for Surveillance of Antimicrobial Resistance and Use has quadrupled since 2016, although regional gaps remain. The rise of antibiotic resistance in Gram-negative bacterial pathogens poses a growing threat. Countries with limited surveillance often report higher levels of antibiotic resistance [5]. Epidemiological data irrefutably demonstrate that AMR is associated with increased mortality among individuals and prolonged hospitalisation times, with major repercussions on the health economies of countries, especially in low-income countries where the burden of infectious diseases is much higher. In fact, recent studies have highlighted the growing impact of AMR even in low- and middle-income countries, where health infrastructures are often unprepared to address this health emergency [5,6]. An important study emphasizes the significant healthcare-associated burden of infections caused by multiresistant organisms across Europe [7]. The burden for the EU and EEA was highest in infants (aged <1 y) and people aged 65 y or older. It had increased since 2007 and was highest in Italy and Greece. EARS-Net data indicate that, as in previous years, AMR levels remained high in the EU/EEA in 2023. Increases were observed in the estimated incidence of bloodstream infections caused by resistant bacteria in the EU for many antimicrobial groups under surveillance. These include antimicrobial-resistant *Klebsiella pneumoniae* (excluding carbapenem-resistant strains), vancomycin-resistant *Enterococcus faecium*, and *Pseudomonas aeruginosa* resistant to piperacillin-tazobactam, ceftazidime, and carbapenems. The highest estimated incidences of antimicrobial-resistant bloodstream infections were generally reported by countries in Southern or Southeastern Europe [8]. In 2023 in Italy, according to the Italian Medicines Agency report, the total consumption of antibiotics for systemic use was 22.4 average daily doses per thousand inhabitants, an increase of 5.4% compared to 2022 [9]. The consumption of antibiotics for nonsystemic, i.e. local, use, which amounted to 28 average daily doses per 1000 inhabitants, showed an increase of 4.3% compared to 2022. The report also indicates that 54.4% of prescriptions concerned antibiotics belonging to the 'Access' group, i.e. those that should be used as first or second choice treatment for the most frequent infections due to a lower risk of generating resistance [10].

2. Italian intervention studies and AMR

2.1. Antibacterial resistance

AMR represents a growing threat to public health, and bacterial resistance accounts for a substantial share of morbidity, mortality, and economic burden. In the last decade, Italy has implemented several targeted strategies, including antimicrobial stewardship (AMS), infection prevention and control (IPC), and diagnostic stewardship interventions, particularly over the past decade.

2.2. Antimicrobial and diagnostic stewardship

A pilot AMS program carried out between 2013 and 2015 in two community hospitals demonstrated notable improvements: appropriate antibiotic prescriptions increased by 6.4%, with fluoroquinolone and glycopeptide appropriateness rising by 16.2% and 17.4%, respectively. Methicillin-resistant *Staphylococcus aureus* (MRSA) incidence declined significantly ($P < 0.0037$) [11]. In another initiative, a network-based, multifaceted AMS program in seven Italian intensive care units (ICUs) reduced total antibiotic consumption and multidrug resistance rates without compromising patient safety [12]. In addition, a study carried out in a community hospital in southern Italy reported a 4.8% reduction in antibiotic consumption, a 23% cost reduction per discharged patient, shorter length of stay, fewer ICU admissions, and reduced infection-related mortality [13]. Diagnostic stewardship, especially the deployment of rapid molecular methods and multiplex PCR for bloodstream infections, has streamlined antimicrobial use. Though no specific Italian RCT has yet been published on this, emerging evidence supports its inclusion as core AMS component [14].

2.3. Infection prevention control

IPC strategies targeting MDROs have also yielded significant results. In a teaching hospital in Southern Italy, outbreak control measures, including cohorting, dedicated staff, contact precautions, environmental cleaning, and active surveillance, curbed a carbapenem-resistant *Acinetobacter baumannii* outbreak in the ICU [15]. In Modena, a five-component infection-control bundle permanently eliminated transmission of carbapenem-resistant *A. baumannii*, demonstrating sustainability of aggressive IPC [16]. A persuasive educational AMS intervention in a Southern Italian university hospital showed that interruption of the program was followed by increased fluoroquinolone and piperacillin/tazobactam prescription. The wards where stewardship lasted less than 30 months saw significant upticks in overall antibiotic consumption (CT 12.9, $P = 0.022$), whereas longer-running programs maintained stable usage [17]. Variability in AMS and IPC models across Italian regions persists, with not always a consistent integration into national frameworks.

2.4. Italian strategies to mitigate ABR

Surveillance data gathering and utilisation remain uneven despite periodic national reporting. Longitudinal impact assessments

of AMR reduction due to stewardship remain sparse [18]. The COVID-19 pandemic significantly disrupted stewardship programs. With the aim to overcome these gaps, the Italian National Plan to Combat Antibiotic Resistance has gathered experts to structure an ABS document to be implemented in all Italian regions in a homogeneous and harmonized way [19]. Overall, Italian intervention studies over the past decade illustrate that AMS and IPC initiatives can effectively reduce broad-spectrum antibiotic use, optimize prescribing practices, control MDRO outbreaks, and cut healthcare costs. However, a lack of standardized national integration, incomplete surveillance linkage, and limited longitudinal resistance trend studies highlight crucial gaps. Leveraging the Italian experience – particularly in One Health frameworks and under the WHO/UN Quadripartite joint action on AMR via the TrACSS platform – can inform stronger, more coordinated intervention strategies both domestically and internationally.

2.5. Antifungal resistance

In recent years, invasive fungal infections (IFI) have become a growing global health concern [20,21], with a marked increase in resistance, including the rapid spread of *Candida auris* and the emergence of resistant strains like fluconazole-resistant *Candida parapsilosis* and azole-resistant *Aspergillus fumigatus* [22]. Despite this clear threat, there are still significant gaps in the knowledge of IFI management among physicians [23], highlighting the urgent need for increased awareness and antifungal stewardship (AFS) programs [24], consisting in multidisciplinary interventions to optimise antifungal therapies, evaluating the indication, dose, streamlining, and duration [25,26].

2.6. AFS and interventions

In Italy, there has been progress in addressing these issues, but efforts are still fragmented. A review of Italian literature over the past decade reveals that AFS programs, in contrast to more established AMS initiatives, are less widespread and mainly integrated within broader antimicrobial strategies [27], often without a specific focus on fungal resistance. This gap in research needs to be addressed, particularly given the growing concern over *C. auris*, a multidrug-resistant pathogen that has surged in Italy during the COVID-19 pandemic, causing multiple outbreaks [28], resulting in national efforts to contain its spread, and underscoring the importance of AFS programs, especially during pandemic periods [29]. Yet, outbreak management in Italy has shown significant central variability in infection prevention strategies, underscoring the urgent need for greater standardization at national and international levels [19]. Notable examples of AFS intervention studies in Italy have demonstrated their potential: for instance, in a solid organ transplant centre, AFS programs led to significant improvements in antifungal selection (from 40.5% to 78.6%), correct dosing (from 51.2% to 79.8%), and appropriate treatment duration (from 55.9% to 75%), along with a 36.7% reduction in antifungal consumption and substantial cost savings [30]. Additionally, in ICU settings, a prospective interventional study has assessed the utility of a post-prescription audit combined with early beta-D-glucan testing, showing a significant reduction in echinocandin therapy duration in patients with suspected invasive candidiasis (7.4 d pre-AFS vs. 4.1 d post-AFS), without any impact in patients' outcome [31]. Moreover, the use of a beta-D-glucan-guided strategy to stop empirical antifungal treatment in critically ill patients has been evaluated in a single-centre, randomized, open-label trial in Italy. The intervention significantly reduced antifungal therapy duration (2 vs. 10 d) and increased stopping rates, without affecting mortality, supporting beta-D-glucan as a useful AFS tool to guide antifungal therapy discontinuation [32]. However, while AFS diagnostic tools, including beta-D-glucan and molecular tests, are integrated into clinical practice in most Italian centres [33], studies formally evaluating their impact on antifungal resistance trends remain scarce. Incorporating AFS into both national and international AMR strategies is essential to tackle this escalating public health concern [34].

2.7. Antiviral resistance

Resistance to antiviral drugs is a growing and important problem, especially in immunocompromised patients, where the possible eradication of the virus imposes greater risks to the patient's health, and prolonged exposure to antiviral drugs induces the selection of resistant strains. Antivirals represent a drug category of great importance in human medicine, as there are limited treatment options for specific viral diseases. Viral evolution always involves new mutations, and those that confer drug resistance are of particular interest for public health: in cases where treatment is not sufficiently effective, or some genomes continue to replicate, selective pressure may lead to rapid adaptation towards resistance.

2.8. Antiviral treatments

Antiviral drugs that inhibit viral DNA replication are commonly used for HSV infections and for preventive treatment [35,36]. The clinical implications of antiviral-resistant HSV infections are linked to a higher risk of the direct effects of the viral infection. In fact, uncontrolled viral replication that is resistant to the antiviral agents used can lead to progressive and sometimes fatal invasive HSV disease [37]. Some strategies are important for treating certain resistant HSV strains, such as the use of topical imiquimod, an immunomodulating agent, or topical cidofovir, which have been successfully used to treat certain cases of drug-resistant mucocutaneous HSV infections [38]. Topical treatments avoid the potential nephrotoxicity of systemically administered agents. In addition, the management of drug-resistant HSV in immunocompromised patients should include efforts to improve the patient's immune status.

2.9. Effectiveness of treatments in reducing viral load

However, the most powerful weapon available to counter resistant HSV forms is vaccination [39]. In recent years, Italy has implemented strong vaccination policies in this direction. Over the past decades, treatments for HIV have become increasingly effective in slowing the development of drug resistance to the point that some patients can be treated for many years without resistance issues. However, mutations in one of the two main classes of anti-HIV drugs – the nucleoside reverse transcriptase inhibitors (NRTIs) and the non-nucleoside reverse transcriptase inhibitors – are not uncommon in infected patients. Resistance to protease inhibitors is rarer [40]. If viral genotyping is performed and a fully effective combination of drugs is chosen, treatment success rates are extremely high. Epidemiological studies show that selecting an active and effective drug combination against HIV infection is essential for viral load suppression [41]. In low-income countries, patients with transmitted drug resistance may start ART regimens that are not sufficiently strong, since viral genotyping is usually unavailable and transmitted resistance goes undetected. Inadequate treatment regimens will be less effective at reducing viral load, which in turn can lead to the development of multiclass drug resistance [42,43]. HIV drug resistance testing should be performed at the time of HIV diagnosis or, if that is not possible, before starting antiretroviral drug treatment, in order to select the best available drug regimen, ideally tailored to each individual patient [44].

2.10. Italian strategies to mitigate AVR

In Italy, a robust public health surveillance system has been monitoring HIV infections and the development of drug-resistant strains for years [45]. In recent years, antiviral therapy against HCV has undergone a therapeutic revolution with the introduction of direct-acting antivirals (DAAs). Although a very high percentage of patients treated with these drugs achieve complete viral eradication, DAA resistance remains a significant issue. Most data on HCV drug resistance primarily concern genotypes 1 and 3. The emergence of resistance-associated substitutions (RASs) impacts antiviral response rates. Several RASs in NS3, NS5A, and NS5B have been linked to reduced susceptibility to DAAs. The main factors associated with DAA failure include treatment adequacy, genotypes 1 and 3, comorbidities, NS5A RASs, and disease severity (e.g. cirrhosis) [46]. Combining new broad-spectrum drugs with high genetic barriers to resistance and strong antiviral potency may overcome the resistance problem. Furthermore, genotypic analysis using next-generation sequencing can rapidly identify individual-specific substitutions within the viral species of interest. Drug-specific RASs detected through next-generation sequencing could help reduce significant resistance with existing DAA regimens. In the scenarios described above, RAS testing can help guide treatment choices [47–49]. In Italy, following the WHO's goal of eliminating HCV infection by 2030, major investments have been made in recent years in innovative antivirals and diagnostic tests to fight HCV infections. Since 2017, universal access to antiviral drugs, as part of the national HCV Elimination Plan, has made it possible to identify and effectively treat over 200 000 patients with chronic hepatitis C infection, the highest number of treated patients in Europe [50–52].

3. European and Italian policies introduced to tackle AMR

3.1. Focus on new antimicrobial agents

Antibiotic resistance is a major global public health challenge, compromising the effectiveness of available therapies and increasing infection-related mortality [53,54]. As illustrated in Fig. 1, to address this crisis, research focuses on both the development of new antibiotics and alternative strategies for infection control and AMR reduction. During the 'golden era of antibiotics' (1940–1960), most of the antibiotic classes used today were discovered. However, in the 50 y following their introduction, only few new molecules have been introduced to the market [55]. In fact, over time, it has been recorded a steady decline in new antibiotic approvals, with only 13 new drugs and new nontraditional antibacterial agents approved between 2017 and 2023. The WHO has established four critical innovation criteria for the development of new antibiotics: novelty in chemical class, molecular target, mode of action, and the absence of cross-resistance with current antibiotics. So far, only 2 of the 13 recently approved antibiotics have met at least one of the WHO's innovation standards: the combination of vaborbactam-meropenem and lefamulin [56]. These two antibiotics were also approved by the Italian Medicines Agency (AIFA) in 2018 and 2020, respectively [57,58]. Vaborbactam-meropenem is a combination of 2 molecules: an old carbapenem and a novel cyclic boronic acid-based β-lactamase inhibitor. This antibiotic is indicated for the treatment of adult patients with complicated urinary tract infections (UTI), complicated intra-abdominal infection, and hospital-acquired pneumonia, including ventilator-associated pneumonia. Lefamulin belongs to a group of medicines called pleuromutilins and is used to treat community-acquired pneumonia in adults. It interferes with bacterial RNA, blocking the production of bacterial proteins and preventing the bacteria from multiplying. Alongside the development of new antibiotics, potential antimicrobial strategies such as antimicrobial peptides (AMPs) and probiotics are gaining attention. AMPs show a broad spectrum of action and a lower propensity to generate resistance, making them potential candidates for infections sustained by multiresistant microorganisms [59]. The combined use of probiotics and antibiotics has also shown promise in preventing antibiotic-associated infections and reducing the risk of *Clostridium difficile* infection, particularly among patients taking 2 or more antibiotics and in hospital settings where the risk of *C. difficile* infection is $\geq$5% [60]. In addition, probiotics such as *Lactobacillus rhamnosus* GG could be used with micronutrients (vitamins B and C and zinc) in the prevention of nosocomial gastrointestinal and respiratory infections, reducing its incidence and the length of hospitalization [61]. At the European level, there are programmes such as Horizon Europe 2021–2027, the funding framework programme for research and innovation, which also allocates resources to conduct studies in the area of AMR, and EU4Health, which also provides for investments in this field. In Italy, after an initial allocation of 40 million euro, the government has decided to invest further in research with a comprehensive plan that provides both incentives for research ('push' phase) and measures to ensure the economic sustainability of new antibiotics ('pull' phase). Moreover, the 2025 Italian budget law provides that new and recently approved antimicrobial agents listed as Reserve under the AWaRe classification of the WHO or active against at least one pathogen considered a priority from the list will gain direct access to the national Fund for Innovative Non-Oncological Medicines. Within the Fund, up to EUR 100 million a year is available to cover the reimbursement of these antibiotics.

3.2. Italian policy and incentives

To ensure effective action against AMR, it is necessary to define and approve policies and strategies, foster their implementation, monitor their progress, and promote investment and research activities [62]. In Italy, the first National Action Plan (NAP) to counter AMR was approved in 2017 and updated in 2022. The latest NAP adopts a multisectoral One Health approach and identifies four key cross-cutting actions: (1) training; (2) information, communication, and transparency; (3) research, innovation, and bioethics; and (4) national and international cooperation [63]. These actions underpin the pillars of the NAP, which include integrated surveillance and monitoring of antibiotic consumption and healthcare-associated infections, infection prevention in both hospital and community settings, and the appropriate use of antibiotics in human and veterinary medicine. The pillars and cross-cutting actions together support the six overarching goals of the NAP, which reflect the One Health approach and address various aspects such as surveillance, promotion of good practices, professional training, public awareness, and international collaboration. Effective implementation of the plan requires strong coordination and collaboration between central institutions and local authorities. Given the structure of the Italian National Health Service, regional governments play a crucial role in translating and implementing national plans at the local level [64]. While this decentralization allows for greater autonomy, it also increases complexity and fragmentation, making it challenging to ensure comprehensive governance of actions and strategies at regional and hospital levels. Transparency, harmonization, accountability, and leadership should guide efforts to combat AMR, enabling the identification of shortcomings and the implementation of corrective actions through close cooperation among central government, hospitals, and local health agencies to ensure consistent governance across the system [65]. In addition to policy implementation focused on strengthening epidemiological surveillance and raising awareness of appropriate antibiotic use, incentive mechanisms, both 'pull' and 'push', play a key role. Italy

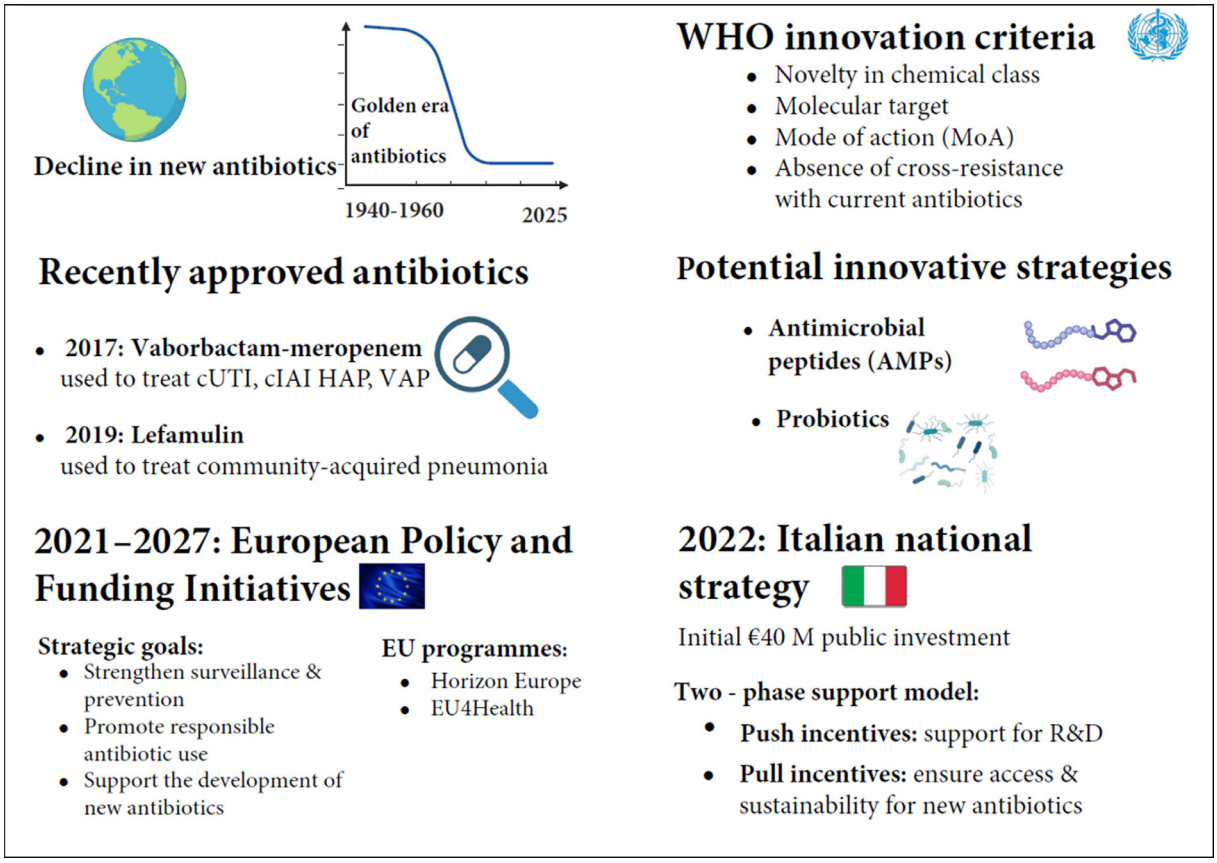

Fig. 1. Main strategies and therapeutic innovations introduced to the Italian market to combat AMR.

serves as a positive example in this regard, having funded in 2025 the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) partnership and included reserve antibiotics, as well as those effective against at least one WHO-priority pathogen, in the Innovative Medicines Fund [66,67].

3.3. Tracking progress on AMR and TrACSS database

TrACSS, which stands for Tracking Progress on Antimicrobial Resistance, is an annual reporting tool administered by the WHO on behalf of the Quadripartite collaboration – comprising the Food and Agriculture Organization (FAO), the United Nations Environment Programme (UNEP), the World Organisation for Animal Health (WOAH), and WHO itself [68]. Countries use the tool to reflect on their progress in areas such as national planning, surveillance, infection control, and responsible antimicrobial use, with a focus on the One Health approach [69]. As useful as TrACSS can be, it has its limits. It relies on countries assessing their own performance, which can lead to over- or underestimations. The descriptions used are broad, making it hard to pinpoint how much actual progress has been made year to year. And since the survey is only done annually, it misses developments that happen more quickly. Finally, it tends to give a national picture, without showing regional differences that can be very important [69]. Italy moved from basic coordination to a more integrated approach by 2023. This shift is encouraging, but a small dip in 2024 suggests that keeping different sectors engaged over time is still a challenge. The process needs long-term commitment, not just short-term momentum. One contextual advantage Italy holds in this area is that both human and animal health fall under the responsibility of the same ministry – the Ministry of Health [70,71]. This institutional arrangement naturally supports a more streamlined and coordinated One Health approach, compared to countries where responsibilities are split across multiple agencies. Italy has moved in the right direction. The action plan was not only approved but backed with funding by 2023. AMR must be a part of how the country prepares for future health emergencies [72]. Focusing on AMR surveillance, Italy has kept a steady hand here. The surveillance system is well-established but hasn't evolved much. The next step could be expanding the scope of what is tracked and improving how data feeds into real-time decision-making. Italy's response is more hesitant on the issue of IPCs. After starting with an operational IPC framework, the country slipped back. By 2022, there was no functioning program in place. Given how central IPC is to stop the spread of resistant infections, this is a serious risk. In the field of AMS, Italy has wavered between issuing guidelines and adopting full policies. The most urgent task is to rebuild and invest in IPC. Without it, even the best surveillance or plans won't stop resistance from spreading. Italy also needs to lock AMR into its broader public health strategy – including preparedness for future outbreaks. And while national policies matter, they should be matched by specific action in hospitals, clinics, and communities [73].

4. Focus on diseases

4.1. Multidrug-resistant bacterial infection in older CVD patients

CVDs are the leading cause of mortality in Europe and Italy, accounting for 45% of total deaths [74]. They represent a significant healthcare burden, particularly in older patients who experience a higher incidence of CVD [75–77]. Older CVD patients are highly susceptible to MDR infections due to prolonged hospitalizations, ICU admissions, invasive procedures (such as cardiac im-

Table 1
Main intervention studies to combat AMR in Italy over the last decade.

Study	Focus on intervention	Main results
Bianco et al. [15]	IPC strategies targeting MDROs	A patient presented an XDRAB ventilator-associated pneumonia at admission. Five patients had a ventilator-associated pneumonia, and two had a central line-associated bloodstream infection
Bolla et al. [11]	Antimicrobial stewardship	Appropriate antibiotic prescriptions increased by 6.4%
De Pascale et al. [32]	Duration of treatment	The intervention significantly reduced antifungal therapy duration and increased stopping rates, without affecting mortality, supporting AFS with beta-D-glucan
Mularoni et al. [30]	Antifungal stewardship	AFS programs led to significant improvements in antifungal selection, correct dosing, and appropriate treatment duration
Macera et al. [17]	Antimicrobial stewardship	The wards saw significant upticks in overall antibiotic consumption (CT 12.9, P = 0.022); longer-running programs maintained stable usage
Meschiari et al. [16]	Infection prevention control	Acinetobacter baumannii transmission was eliminated
Murri et al. [31]	Duration of treatment	Early beta-D-glucan testing showed a significant reduction in echinocandin therapy duration in patients with suspected invasive candidiasis, without any impact in patients' outcome
Mandelli et al. [12]	Antimicrobial stewardship	The median duration of empirical therapy decreased from 5.6 to 4.6 d and the use of quinolones dropped from 15.3% to 6%. The proportion of MDR in ICU-acquired infections fell from 57.7% to 48.8%
Albano et al. [13]	Antimicrobial stewardship	4.8% reduction in antibiotic consumption, a 23% cost reduction per discharged patient, reduced infection-related mortality

plantable electronic devices and mechanical ventilation), colonization with resistant pathogens, and broad-spectrum antibiotic use [78–80]. Both stroke and acute coronary syndrome trigger systemic inflammatory responses, leading to immune dysregulation [81,82]. Notably, stroke-induced immunodepression syndrome predisposes individuals to secondary infections such as pneumonia, UTIs, and bloodstream infections [82]. Additional risk factors – including diabetes, chronic kidney disease, and malnutrition – further impair immune responses, exacerbating the risk of MDR infections [83]. Infections in these patients are often caused by highly resistant bacterial strains, including *K. pneumoniae, P. aeruginosa, A. baumannii*, MRSA, and *Enterobacter cloacae* [84,85]. Stroke patients with dysphagia are particularly vulnerable to aspiration pneumonia, frequently caused by MDR *K. pneumoniae* and *P. aeruginosa* [84]. Recent ECDC data indicate that among ICU patients staying for more than 2 d, 4% develop ventilator-associated pneumonia, 3% bloodstream infections, and 2% UTIs [85]. A multicentre Italian study reported that higher AMR in severe acquired brain injury patients is associated with poor prognosis and poor functional outcomes [86]. Among patients undergoing cardiac surgery, the incidence of MDR infections ranges from 0.6% to 10%, with MDR infections linked to higher mortality rates and more severe illnesses compared to non-MDR infections [87]. Moreover, infections involving pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices are particularly challenging to manage. These infections occur in 1% to 4% of recipients but are associated with a threefold increase in mortality within 12 months [88]. Given the significant impact of MDR infections on mortality and rehabilitation, a multifaceted prevention strategy is essential. This includes early detection, microbial surveillance, and strict infection control measures. In particular, routine screening for MDR pathogens, including rectal *K. pneumoniae* carbapenemase colonization, should be performed upon admission and biweekly thereafter [89]. Healthcare staff education and strict adherence to hand hygiene protocols, as well as contact isolation and geographical segregation of MDR-infected patients in hospitals, can minimize pathogen transmission [89]. For implantable devices, major cardiac implantable electronic device infections can be reduced by 40% using innovative preventive interventions such as absorbable antibacterial envelopes, which contain rifampicin and minocycline [90]. Cost-effectiveness analyses suggest their use aligns with European healthcare benchmarks, making them a valuable strategy for reducing infections and associated healthcare costs [91,92].

4.2. AMR and CF

CF is a chronic genetic disorder that primarily affects the lungs and digestive system, leading to thick, sticky mucus buildup in the airways. This creates an environment conducive to persistent bacterial infections. Over time, individuals with CF experience recurrent respiratory infections, often caused by opportunistic pathogens such as *P. aeruginosa, S. aureus*, and *Burkholderia cepacia*. The frequent and prolonged use of antibiotics to manage these infections has contributed to the emergence of AMR. One of the most concerning drug-resistant pathogens in CF is *P. aeruginosa*, which can form biofilms. Biofilms shield bacteria from antibiotics and immune responses. Over time, *P. aeruginosa* can develop MDR through several mechanisms, including efflux pumps, enzymatic degradation of drugs, and genetic mutations that alter drug targets. Early intervention with inhaled antibiotics, such as tobramycin or colistin, is the first-line approach. Oral fluoroquinolones, like ciprofloxacin, have shown a *P. aeruginosa* eradication rate comparable to that of intravenous antibiotic treatment [93–95]. *S. aureus*, particularly MRSA, has become a prevalent concern in CF care. *B. cepacia* complex is another group of bacteria that pose significant risks. The emergence of AMR in CF patients limits available treatment options. Some resistant bacteria can only be treated with last-resort antibiotics, such as colistin, which may have toxic side effects. Another challenge is that standard antibiotic susceptibility tests may not accurately predict treatment outcomes in CF. To address AMR in CF, researchers and clinicians are exploring alternative therapies and strategies, including personalized antibiotic therapy. Phage therapy, involving bacteriophages that specifically target bacteria, presents a promising alternative to traditional antibiotics [96–97]. Antibiofilm agents help disrupt biofilms, improving antibiotic penetration and effectiveness [98]. Additionally, the development of new antibiotics remains crucial to counteract resistant infections.

5. Discussion

This review confirms that AMR in Italy mirrors the global emergency, but also shows that well-designed interventions can produce measurable benefits when embedded in coherent national strategies. AMS and IPC programmes have reduced inappropriate use of broad-spectrum antibiotics, healthcare-associated infections, and related costs in multiple Italian settings, including ICUs and community hospitals. However, impact remains uneven because AMS and IPC models are variably implemented across regions, surveillance is not fully integrated with routine decision-making, and longitudinal evaluations of resistance trends are still limited.
Fungal and viral resistance represent critical, and partly underrecognised, components of the AMR burden in Italy. Emerging AFS programmes have improved appropriateness of prescriptions and reduced antifungal consumption and costs, but remain fragmented and insufficiently standardised, despite the growing threat of *C. au-*

ris and azole-resistant *A. fumigatus*. In the viral field, Italy's experience with HIV and HCV shows that strong surveillance, access to innovative antivirals, and genotypic testing can achieve high treatment coverage, limit resistance emergence, and inform more equitable policies. From a One Health perspective, Italy has adopted a multisectoral NAP and participates in international initiatives such as TrACSS, moving from basic coordination towards more integrated governance of AMR across human, animal, and environmental health. Yet the lack of a fully functional national IPC programme in recent years, together with persistent regional fragmentation, weakens the capacity to translate surveillance and plans into homogeneous implementation on the ground. The Italian policy framework and incentive mechanisms for new antimicrobials illustrate how regulatory and financial tools can support innovation and access. Recent measures to include reserve antibiotics and agents targeting WHO-priority pathogens in dedicated national funds, alongside investments in research and partnerships such as CARB-X, reduce economic barriers and can make the antimicrobial market more attractive while ensuring availability of critical drugs. At the same time, alternative approaches, including AMPs, probiotics, and AI-supported diagnostics and drug discovery, are promising but require robust evaluation, clear regulatory pathways, and careful integration into stewardship strategies to avoid unintended consequences. Finally, some high-risk patient groups exemplify the clinical consequences of AMR and the need for tailored interventions. Older patients with CVD and people with CF experience high rates of multidrug-resistant infections, which compromise outcomes, prolong rehabilitation, and increase costs, underscoring the importance of early detection, targeted prevention, and innovative technologies such as antibacterial envelopes and phage or antibiofilm therapies.

6. Conclusions

Italy has generated solid evidence that AMS, IPC, AFS, and expanded access to innovative antivirals can curb the impact of AMR when consistently implemented. Future efforts should prioritise harmonised AMS and AFS standards, restoration and reinforcement of a robust IPC framework, and real-time use of surveillance data to guide local action across regions and care settings. Policy levers and dedicated funds must continue to support both truly innovative antimicrobials and alternative strategies, while ensuring their responsible use. Embedding these interventions within a strengthened One Health approach and focusing on high-risk groups such as older cardiovascular patients and individuals with CF will be crucial to achieve durable reductions in AMR and to inform international best practice (Table 1).

Ethical approval: Not applicable. This study is not a clinical trial.

Consent to publish: The authors consent to the publication of the manuscript.

Author contributions: A.V.: Conceptualization, writing – original draft, methodology, supervision, validation. A.Z.: Conceptualization, writing – review and editing, supervision. M.S.: Conceptualization, methodology, writing – review and editing, supervision. E.F., L.V., M.B., A.C., M.G., D.L., F.B., C.B., M.A., M.B.: Writing – original draft, validation. G.R., W.R., F.R.: Writing – review and editing, supervision, validation.

Funding: No funding was received to conduct this study.

Data availability: Full availability of data and materials. All stated data can be provided on request to the reader.

Disclosure: A.Z. and A.V. declare that the opinions expressed are of a personal nature and do not in any way commit the responsibility of the Administrations to which they belong.

Declaration of competing interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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