The Spread of Antibiotic Resistance in Iran: A Review of Multidrug-Resistant Pathogens, Resistance Mechanisms, and National Challenges

Running title: Antibiotic Resistance in Iran: A National Review

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Abstract

Background: Antimicrobial resistance (AMR) represents one of the most significant global health threats of the 21st century, undermining advances in modern medicine. Iran, as a geographically and demographically strategic nation, faces a severe and escalating AMR crisis. This review synthesizes current evidence on the epidemiology, molecular mechanisms, and systemic drivers of AMR in Iran, while outlining priorities for effective national response.

Methods: A structured review was conducted of studies published between January 2015 and November 2024 in PubMed, Scopus, and Web of Science, supplemented by national and Persian-language databases. Eligible studies investigated the prevalence, molecular characteristics, and clinical outcomes of antibiotic-resistant bacteria in Iran. Data were extracted and narratively synthesized.

Results: Iran faces an alarming burden of Multi-Drug Resistant and extensively Drug-Resistant Gram-negative pathogens, notably *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and carbapenem resistant Enterobacteriaceae, with carbapenem resistance rates exceeding 80-90%. Widespread dissemination of key carbapenemase genes (*blaNDM*, *blaOXA-48*, *blaVIM*) has been documented. Gram positive pathogens, including methicillin resistant *Staphylococcus aureus* and vancomycin resistant Enterococci, also remain highly prevalent. The crisis is driven by unregulated over the antibiotic use, weak infection prevention and control measures, fragmented surveillance, and limited diagnostic capacity.

Conclusion: AMR in Iran has reached critical levels, constituting a national public health emergency. Urgent, coordinated reforms across integrated surveillance, mandatory antimicrobial stewardship, strengthened infection prevention and control, One Health integration, expanded research, and public engagement are required. Without decisive national action, Iran risks a post antibiotic era in which routine infections and medical procedures become life threatening.

Keywords: Antimicrobial Resistance, Iran, Multidrug Resistance, Carbapenemase, One Health

Introduction

The discovery of antibiotics transformed medicine, dramatically reducing infectious mortality worldwide. Yet this achievement is now being reversed by the relentless spread of antimicrobial resistance (AMR), a phenomenon that endangers all aspects of modern health care (1). By 2050, it is estimated that AMR could cause up to 10 million deaths annually and impose economic losses exceeding USD 100 trillion if unchecked (2). In 2019 alone, AMR was directly responsible for an estimated 1.27 million global deaths and associated with nearly 5 million more, exceeding many major diseases (3). The crisis affects low- and middle-income countries (LMICs) disproportionately due to weak regulatory systems, limited diagnostic capacity, and infrastructural constraints (4). Iran occupies a pivotal position in this global context. It is the second most populous nation in the Middle East, sharing borders with seven countries and serving as a regional hub for medical tourism and labor migration. Its complex healthcare network, varying from tertiary medical centers to rural clinics, faces challenges in drug regulation, hospital infection control, and antibiotic governance (5). The unregulated sale and use of antibiotics, combined with systemic deficiencies in national surveillance and public awareness, has accelerated the rise and dissemination of resistant pathogens. Iran's AMR burden is exacerbated by its location in the Middle East, a region with some of the highest reported rates of multidrug-resistant pathogens globally, influenced by ongoing conflicts, population displacement, cross-border movement, and inconsistent AMR control measures in neighboring countries (6). Although Iran adopted a National Action Plan on Antimicrobial Resistance in 2016–2017, aligned with the WHO Global Action Plan on AMR, implementation has been limited by challenges in inter-ministerial coordination, resource allocation, and enforcement of regulations on antibiotic sales and agricultural use. This review synthesizes the available evidence on AMR in Iran by systematically addressing four core dimensions: the epidemiological trends of key resistant pathogens, the molecular and genetic mechanisms that drive resistance acquisition and dissemination, the systemic and behavioral determinants-including prescribing practices, healthcare infrastructure, and public awareness-that shape the AMR burden, and the strategic imperatives for implementing effective control measures. By integrating these interrelated components within a "One Health" framework that recognizes the interconnectedness of human, animal, and environmental health, this review aims to provide a comprehensive picture of the current AMR landscape in Iran and to identify priority areas for policy development, surveillance strengthening, and targeted interventions to mitigate the growing threat of resistance in the country.

Methods

A structured narrative review was conducted. Literature published from January 2015 to November 2024 was searched in international databases (PubMed, Scopus, Web of Science) and national Persian language databases (Scientific Information Database (SID), MagIran). Search terms combined keywords related to antimicrobial resistance (e.g., antimicrobial resistance, antibiotic resistance, multidrug-resistant, MDR, extensively drug resistant, XDR, carbapenem resistant, ESBL, carbapenemase, MRSA, VRE) and Iran specific terms (Iran, Iranian). No language restrictions were applied. Reference lists of included studies were hand searched for additional relevant articles.

Inclusion and Exclusion Criteria: Studies were included if they focused on bacterial pathogens in Iran with defined resistance profiles, provided laboratory confirmed molecular data (e.g., gene identification, typing), or were surveillance/outbreak reports. Reviews without primary data,

studies on fungal or viral resistance only, and those lacking clear microbiological confirmation were excluded.

Data extraction and quality assessment: Data were extracted thematically and synthesized narratively, with findings categorized into epidemiological trends, molecular mechanisms, and systemic determinants of resistance.

The methodological quality of included studies (Primarily cross-sectional prevalence studies) was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. Studies were classified as high, moderate, or low quality; no studies were excluded based on quality alone.

Results

The epidemiological landscape of AMR in Iran

Gram-negative pathogens

- ***Acinetobacter baumannii*:** *Acinetobacter baumannii* remains the leading cause of hospital-acquired infections in Iranian intensive care units (ICUs), notably ventilator associated pneumonia, bloodstream infections, and sepsis (7). Carbapenem resistance frequently exceeds 90% nationally, with most isolates classified as extensively drug-resistant (XDR) or pan drug resistant (PDR) (8). The dominant resistance mechanisms include OXA-type carbapenemases (blaOXA-23, blaOXA-24, blaOXA-58) and, increasingly, metallo β-lactamases such as blaNDM (9). Clonal complex 92 (international clone II) predominates, indicating both local expansion and importation of high-risk global lineages. Alarmingly, colistin resistance mediated by the plasmid borne mcr1 gene has recently been reported in Tehran and Isfahan, threatening the efficacy of last resort therapy (10). Recent *in vitro* studies have explored the potential of novel 1,3,4-oxadiazole derivatives as alternative therapeutic agents against *A. baumannii*, demonstrating promising antimicrobial properties and highlighting the ongoing need for new drug discovery (11). Furthermore, these compounds have been evaluated for their ability to inhibit biofilm formation, a key virulence factor, by targeting the bap gene expression in *A. baumannii*, showcasing a potential strategy to combat persistent infections (12).
- ***Pseudomonas aeruginosa*:** *P. aeruginosa* demonstrates broad-spectrum resistance through multiple coordinated mechanisms: efflux pumps (MexAB-OprM), porin mutations (OprD loss), β-lactamases (PER, VEB, GES), and biofilm-associated tolerance (13). Carbapenem resistance rates typically range between 60-80% nationally, with ST235, ST111, and ST357 identified as dominant clones (14). Reduced susceptibility to colistin and aminoglycosides has also emerged, challenging combination therapy strategies.
- ***Carbapenem-Resistant Enterobacteriaceae* (*CRE*):** The expansion of carbapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* presents a growing health emergency. Between 2018 and 2024, CRE prevalence increased more than twofold in tertiary hospitals (15). The main carbapenemase genes, blaNDM-1, blaOXA-48, and occasionally blaKPC, have been confirmed through molecular typing (16). Many strains concurrently carry extended-spectrum β-lactamase (ESBL) genes such as blaCTX-M-15, conferring near pan-resistance. Clinical outcomes are poor, with mortality rates exceeding 40% in ICU outbreaks (17).
- **National Trends from Meta-Analyses:** Combined estimates suggest >85% MDR prevalence among ICU Gram-negative isolates. Resistance to ciprofloxacin (≈50%), co-trimoxazole (≈60%), and third-generation cephalosporins (≈70%) remains high across provinces including Tehran, Isfahan, Shiraz, and Mashhad (18).

Gram-positive pathogens

- **Methicillin-resistant *Staphylococcus aureus* (*MRSA*):** *MRSA* remains endemic in both hospital-associated (HA-MRSA) and community-associated (CA-MRSA) contexts. Hospital prevalence averages 35-45% of *Staphylococcus aureus* (*S. aureus*) isolates, though regional variation remains wide (19). Nasal carriage among healthcare workers reaches 25-30%, facilitating nosocomial transmission. Molecular studies identify the ST239 and ST22 (EMRSA-15) clones as dominant, with occasional detection of PVL-positive strains. Reduced susceptibility and intermediate resistance to vancomycin (VISA, hVISA) have also been reported (20).
- **Vancomycin-Resistant Enterococci (*VRE*):** *VRE*, predominantly *E. faecium*, causes bloodstream and urinary tract infections in immunocompromised patients and transplant recipients. Both vanA and vanB genotypes circulate in Iranian hospitals, with resistance rates up to 35% among bloodstream isolates (21). The capacity for horizontal transfer of van genes escalates the regional threat for gene exchange with *S. aureus*.
- **Other Relevant Pathogens:** Increasing reports of non-susceptible *Streptococcus pneumoniae* (20-25% penicillin resistance) and *Enterococcus faecalis* with multidrug resistance highlight community-level implications of antibiotic misuse (22). The challenge of treating *E. faecalis* infections is compounded by its robust biofilm-forming capability, which contributes to antibiotic tolerance. Novel therapeutic approaches are being investigated, such as the evaluation of new oxadiazole compounds that have shown efficacy in inhibiting *esp* gene expression, a critical factor for biofilm formation and virulence in *E. faecalis* (23). Such research is vital for developing targeted strategies against biofilm-associated infections that are often refractory to conventional antibiotics.

The key epidemiological features, resistance rates, and dominant molecular mechanisms for the major Gram-negative and Gram-positive pathogens described in Sections 3.1.1 and 3.1.2 are systematically summarized in the upper sections of Table 1.

Molecular and systemic drivers of resistance

Genetic architecture of resistance

The AMR crisis in Iran is underpinned by efficient horizontal gene transfer (HGT) via mobile genetic elements (MGEs), plasmids, transposons, and integrons (24). Class 1 integrons carrying gene cassettes for aminoglycoside modifying enzymes and ESBLs are prevalent in hospital isolates. The CTX-M lineage, especially blaCTX-M-15, dominates β-lactam resistance across *E. coli* and *K. pneumoniae* community strains (25). The co-occurrence of qnr (Quinolone resistance), mphA (Macrolide resistance), and armA (Aminoglycoside methyltransferase) genes on the same plasmids reflects multidrug linkage selection (26). Whole genome sequencing (WGS) studies from Tehran and Shiraz between 2021 and 2024 confirm plasmid convergence between clinical and environmental reservoirs, supporting a broader resistome across ecosystems (27).

Systemic and behavioral catalysts

- **Inappropriate antimicrobial use:** Non-prescription access to antibiotics continues despite regulations. Surveys indicate that 40-60% of Iranian adults have practiced self-medication with antibiotics in the preceding year, often for viral infections (28). Pharmacists frequently dispense antimicrobials without a prescription under economic or social pressure. In hospitals, empirical therapy is often guided by limited diagnostic data, promoting selection pressure (29).
- **Weak Infection Prevention and Control (IPC):** Hospital overcrowding, insufficient staff-to-patient ratios, poor adherence to hand hygiene, and inadequate environmental

decontamination are widespread issues (30). Surveillance of healthcare-associated infections (HAIs) remains fragmented, often limited to major university hospitals.

- **Agricultural and Environmental Contributions:** Antibiotics are used extensively in the livestock industry for prophylaxis and growth promotion. Studies report significant levels of antibiotic residues and resistance genes in poultry and cattle farms (31). Untreated hospital effluents in urban wastewater contribute to environmental contamination with ESBL and carbapenemase-producing bacteria (32).
- **Deficient National Surveillance:** Iran's participation in the WHO Global Antimicrobial Resistance Surveillance System (GLASS) remains incomplete. Data collection is sporadic and regionally fragmented. Currently, there is no centralized genomic or phenotypic AMR database, impeding national and international comparability (33).

Economic and social impact

The economic toll of AMR in Iran is substantial, although underquantified. Hospital AMR increases the average length of stay by 7-10 days and treatment costs by an estimated 15-25% (34). Indirect costs, lost productivity, and resource diversion exceed USD 400 million annually by some projections. Social determinants, including socioeconomic disparities, healthcare access inequities, and limited public risk perception, further exacerbate the issue (35). Collectively, the molecular genetic architecture, systemic and behavioral catalysts, environmental contributions, and the socioeconomic impacts detailed in Section 3.2 are holistically integrated with the pathogen data in the lower sections of Table 1, providing a comprehensive, at-a-glance summary of the epidemiology, mechanisms, and drivers of AMR in Iran from 2015 to 2024.

Table 1. A Comprehensive Summary of the Epidemiology, Mechanisms, and Drivers of Antimicrobial Resistance in Iran (2015-2024)

Dimension	Pathogen / Key aspect	Epidemiological features and resistance rates	Dominant molecular mechanisms	Clinical Impact / Threat
Critical Gram-Negative Pathogens	*Acinetobacter baumannii*	Leading cause of HAIs in ICUs (VAP, BSI, sepsis). Carbapenem resistance: >90%. High prevalence of XDR/PDR isolates.	OXA-type carbapenemases (e.g., *bla*OXA-23, -24, -58). Emerging metallo-β-lactamases (e.g., *bla*NDM).	Emergence of plasmid-borne *mcr-1*-mediated colistin resistance, threatening last-resort therapy.
	Pseudomonas aeruginosa	Carbapenem resistance rates: 60-80% nationally.	Coordinated mechanisms: efflux pumps (MexAB-OprM), porin loss (OprD), ESBLs (PER, VEB, GES).	Reduced susceptibility to colistin and aminoglycosides, complicating combination therapy.
	Carbapenem-Resistant Enterobacteriaceae (CRE)	Prevalence increased more than twofold in tertiary hospitals (2018-2024).	Carbapenemases: *bla*NDM-1, *bla*OXA-48 (occasionally *bla*KPC). Frequent co-carriage of ESBLs (e.g., *bla*CTX-M-15).	High mortality rates (>40%) in ICU outbreaks. A growing public health emergency.
Critical Gram-Positive Pathogens	Methicillin-Resistant *Staphylococcus aureus* (MRSA)	Hospital prevalence: 35-45%. Nasal carriage in HCWs: 25-30%. Endemic in HA and CA settings.	Presence of *mecA* gene. Reduced susceptibility to vancomycin (VISA/hVISA) reported.	Sustained endemicity with reservoir in HCWs. Threat of vancomycin susceptibility loss.

	Vancomycin-Resistant Enterococci (VRE)	Resistance in *E. faecium* BSI isolates up to 35%. Causes infections in immunocompromised hosts.	Presence of *vanA* and *vanB* gene clusters.	Risk of horizontal transfer of *van* genes to other Gram-positives like *S. aureus*.
Key drivers of resistance	Genetic Architecture	Widespread, facilitated by mobile genetic elements (Plasmids, transposons, integrons).	High prevalence of Class 1 integrons and CTX-M-15. Co-localization of resistance genes (*qnr*, *mphA*, *armA*) on same plasmids.	Fuels rapid dissemination of multi-drug resistance and creates a broad environmental "resistome."
	Inappropriate Antimicrobial Use	40-60% of adults report self-medication with antibiotics (often for viral URIs). Non-prescription dispensing is common. Empirical therapy often lacks microbiological guidance.	Creates direct selection pressure, favoring the survival and spread of resistant clones.	A primary driver of resistance selection in both community and hospital settings.
	Weak Infection Prevention a**nd** Control (IPC)	Hospital overcrowding, low staff-to-patient ratios, and suboptimal hand hygiene compliance. HAI surveillance is fragmented.	Facilitates cross-transmission of resistant organisms within healthcare facilities.	Turns hospitals into epicenters for amplifying and disseminating resistant infections.
	Environmental a**nd** Agricultural Pressure	Extensive use of antibiotics in livestock. Significant levels of antibiotic residues and resistance genes in farm environments.	Direct contamination of ecosystems with resistant bacteria and genes (e.g., from untreated hospital effluents).	Creates external reservoirs that re-seed healthcare and community settings, enabling a One Health crisis.
Impact	Economic a**nd** Social	Increases hospital LOS by 7-10 days and direct treatment costs by 15-25%. Projected annual indirect costs > USD 400 million.	Linked to socioeconomic disparities, inequitable healthcare access, and low public risk perception.	Imposes a substantial, under-quantified burden on the health system and economy, exacerbating health inequities.

Discussion

The evidence paints a picture of a systemic and entrenched AMR crisis in Iran. MDR and XDR pathogens have become endemic across tertiary care centers, leaving clinicians with few therapeutic options. Dependence on legacy drugs such as colistin poses toxicity and resistance risks. Empirical prescription practices persist in the absence of robust diagnostic infrastructure and stewardship oversight. While substantial data describe prevalence, most studies remain cross-sectional and descriptive; few investigate transmission dynamics through genomic analysis or longitudinal surveillance (36). Implementation of whole-genome sequencing and molecular typing across sentinel hospitals would facilitate detection of high-risk clones, plasmid migration, and

outbreak control. From a One Health perspective, AMR epidemiology in Iran cannot be confined to hospitals. There is substantial environmental overlap between clinical, agricultural, and waterborne resistance determinants. National policies have insufficiently integrated human, veterinary, and environmental health sectors, although momentum is growing following Iran's 2019 National Action Plan for AMR (37). Coordination with food safety authorities and environmental ministries is essential for effective monitoring. Public education and behavioral interventions are equally critical. Studies demonstrate that improved awareness and stewardship training among clinicians, coupled with public campaigns discouraging self-medication, can substantially reduce inappropriate antibiotic consumption (38). Economic analyses underscore that investment in surveillance and stewardship is not only medically essential but cost saving in the long term (39). Strengthened IPC infrastructure, hand hygiene enforcement, screening of high-risk patients, and routine resistance audits, must be institutionalized across all hospitals.

Conclusion

AMR in Iran is accelerating despite localized interventions. The nation stands at a pivotal juncture: either implement coordinated national countermeasures or witness a return to a pre-antibiotic era. The following action pillars are recommended:

- **Integrated national surveillance system:** Establish a centralized digital platform for real-time AMR data reporting, connecting clinical, veterinary, and environmental laboratories. Integration with GLASS should be prioritized.
- **Mandatory Antimicrobial Stewardship Programs (ASPs):** Implement standardized ASPs across all healthcare facilities with defined accountability, prescription auditing, and diagnostic stewardship components.
- **Reinforced Infection Prevention and Control (IPC):** Develop enforceable national IPC standards and ensure compliance through regular audits, transparent reporting, and investment in infrastructure.
- **Operationalization of the one health framework:** Coordinate policies across ministries of health, agriculture, and environment to regulate antibiotic use in animals, monitor environmental reservoirs, and align efforts with WHO and FAO frameworks.
- **Research and capacity building:** Expand genomic surveillance capacity through national reference laboratories. Encourage funding for AMR-related economic and social sciences to contextualize interventions.
- **Public engagement and education:** Launch national campaigns to raise awareness of AMR risks, focusing on the dangers of self-medication and the importance of completing prescribed courses.

The AMR crisis in Iran reflects broader global patterns but is intensified by regional and systemic vulnerabilities. Addressing it requires sustained political commitment, cross-sectoral coordination, and scientific innovation. With strategic reforms grounded in surveillance, stewardship, and prevention, Iran can reposition itself as a regional leader in AMR containment. The time for decisive and coordinated national action is now.

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Ethics Statement

This article is a narrative review based on previously published literature and does not involve human participants, human data, or animal experiments.

Conflict of Interest

The authors declare that they have no competing interests.

Consent for Publication

This article does not contain any individual person's data in any form (Text, images, or videos).

Author Contributions

Y.S. conceived the manuscript and revised it; Y.s., B.O., S.Z., and Y.G. wrote the manuscript; Y.S. and B.O. edited and reviewed the manuscript; Y.S. analyzed data and performed statistical analysis; S.Z. and Y.G. conducted data acquisition; and Y.S. prepared the tables.

Data Availability Statement

All data generated or analyzed during this review are derived from publicly available published sources. Data supporting the conclusions of this manuscript are included within the article. Further inquiries can be directed to the corresponding author.

AI Statement

The authors confirm that this manuscript is their original work and has not been generated, written, or substantially assisted by artificial intelligence tools, including large language models or AI-based image generators.

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