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The Soil Nitrogen Resistome: A Systematic Review of the Impact of Nitrogen Fertilizers on the Proliferation of Antimicrobial Resistance Genes

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Beyond the confines of clinical environments, the developing threat to public health due to antimicrobial resistance (AMR), is also being affected by the presence of antibiotic resistance genes (ARGs) in agricultural soils. These genes are carried by bacteria found in the soil which receive a nutrient boost from large amounts of nitrogen fertilizer used in global agricultural production. However, there is still considerable uncertainty about the role of nitrogen fertilizer in altering the soil's genetic makeup and its ability to support resistant bacterial populations. Therefore, this systematic review examined the relationships between nitrogen (N) fertilization practices and the amount and type of antibiotic resistance genes present in agricultural soils using data from 47 relevant scientific publications that include field experiments, mechanistic studies, and metagenomics analysis. Using meta-analyses to compare the effects of various types of nitrogen fertilizers, differing application rates, and varying methods of fertilization on the characteristics of soil bacterial communities and their genetic resistance capacity, the results show that the use of either ammonium or nitrate forms of nitrogen affect the composition of the resistome in soil, promote the accumulation of multi-drug resistance genes, and increase the horizontal gene transfer capacity. Further, changes in the composition of soil microbial communities driven by nitrogen fertilizers provide an environment conducive to the accumulation and spread of resistance genes through mobile genetic elements. This review emphasizes that sustainable agricultural intensification will require an understanding of nitrogen's role as an environmental selective pressure that increases antibiotic resistance beyond clinical usage. The data provided here suggest that current fertilization practices are potentially generating an optimal environment for the proliferation of resistance genes with important implications for food security, environmental health, and human medicine.

Keywords: Antimicrobial resistance genes; environmental health; horizontal gene transfer; nitrogen fertilization; Resistome; soil microbiome; sustainable agriculture.

1. Introduction

1.1 Background and Clinical Significance

The threat of antibiotic resistance is developing into a major health challenge of the twenty-first century (Aslam et al., 2018). The World Health Organization states that if the current rate of antibiotic resistance continues, there will be 10 million annual deaths and $100 trillion in global economic loss by the year 2050 (Kelbrick et al., 2023). This is so alarming because, unlike many other health crises, the spread of antibiotic-resistant bacteria does not occur solely in hospitals or clinics; soil microbiota contain a massive amount of resistance gene diversity that existed long before humans began using antibiotics (Han et al., 2025). However, the use of agriculture has greatly increased the presence of these environmental resistance genes and also enhanced their potential for transfer (Wintersdorff et al., 2016).

1.2 The Soil Resistome Concept

“Resistome” refers to an ecological population’s total number of antibiotic-resistant gene (ARG) collections (Liu et al., 2023). The “soil resistome” has a much larger number of diverse ARGs than does that for any specific clinical isolate from a pathogen. It is estimated that the soil resistome includes ARGs from thousands of different bacteria species — many of which represent non-disease causing environmental and/or commensal microbes that have rarely been associated with human disease (Han et al., 2025). As such, the soil resistome is considered to be the single largest repository of ARGs worldwide. However, the vast majority of the research conducted to date relative to the role of the resistome in disseminating resistance has focused on the human health care system and the clinical isolate resistome. The soil resistome is not fixed; rather, the presence and concentration of ARGs contained in the soil resistome can vary dramatically based upon environmental pressures (e.g., nitrogen availability), one of the most significant of these being nitrogen availability (Wang et al., 2022).

1.3 Nitrogen Fertilization in Global Agriculture

Nitrogen is the most commonly used nutrient in the world's agricultural systems, and there are over 100 million tons of N fertilizers being used annually (Li et al., 2023) globally; the vast application of nitrogen fertilizers indicates that nitrogen is an essential element for plants to produce proteins but, it has some large negative impacts on the environment. Nitrogen fertilizers are supplied to farms in a number of different forms, namely ammonia (NH_3), ammonium (NH_4^+), and nitrate (NO_3^-); these forms have differing biogeochemical characteristics and may affect microorganisms differently (Wang et al., 2022). The agronomical advantages of nitrogen fertilizer application are well-documented however, the role of nitrogen in producing microbial resistance is still relatively unknown despite substantial evidence that nitrogen selectively affects soil bacterial communities (Xu et al., 2024).

1.4 Knowledge Gap and Review Objectives

Nitrogen fertilizer application to soils with respect to their microbiological properties and the development of antimicrobial resistance is an important, albeit little studied topic of research. Most of what is known about antimicrobial resistance (AMR) is derived from studies focusing on the clinical environment and human associated microbiota, while much less has been done in terms of the impact of environmental conditions in either natural or agricultural systems on the generation of AMR. The purpose of this review is to provide an overview of the existing literature on the effects of nitrogen fertilizer application to soils on their resistomes as reported in the scientific literature. In particular, we are interested in how nitrogen availability affects the functional and compositional characteristics of soil bacteria; the mechanisms by which N-fertilizer selection for ARGs occurs; the processes by which nitrogen drives the formation of a suitable environment for the exchange of resistance genes horizontally between microbes; and the impacts of using nitrogen management practices to reduce the amount of ARGs transmitted between microbes (Wang et al., 2024).

2. Nitrogen and soil microbiomes: fundamental mechanisms

2.1 Nitrogen as a Soil Selective Pressure

More than any other nutrient in soils of the natural world, Nitrogen limitations influence microbial communities (Martinez, 2012) significantly. The sudden availability of nitrogen due to fertilizer applications causes significant shifts in the competitive dynamics of bacterial taxa, ultimately changing the overall structure of community composition (Gu et al., 2021). Community level changes caused by these shifts can cascade throughout metabolic networks to affect not only which organisms will survive or reproduce in a given environment, but also what physiological characteristics are advantageous in order to do so. Some bacteria that metabolize nitrogen have evolved intrinsic resistance mechanisms as a result of their ability to utilize nitrogen sources in a manner that provides them with an advantage in environments where there is an abundance of nitrogen; this creates an unforeseen selective pressure for the amplification of genes conferring resistance (Zhang et al., 2024).

2.2 Differential Response of Bacterial Taxa

The nitrogen fertilizer response can be very specific to a certain group of organisms as some will increase while other will decrease (Gu et al., 2023). The proteobacterial group has shown consistent increases after nitrogen application (Li et al., 2023) including certain genera such as pseudomonas and acineto bacter. Those groups were not randomly chosen, but instead have unique genetic traits and metabolic pathways that provide an advantage when nitrogen is abundant. Additionally, several of those genera are also known to carry a wide variety of different antibiotic resistance genes (Y. Wang et al., 2024). The enterobacteriaceae family, which includes pathogens important to clinical medicine, also showed patterns of increase corresponding with nitrate availability, suggesting that nitrogen fertilizer may select for organisms with resistance potential (Jalal & Sonbol, 2024).

2.3 Nitrogen Speciation and Microbial Outcomes

Distinct forms of nitrogen can produce varied microbial responses to different chemical forms of nitrogen. The two main inorganic chemical forms of nitrogen that are available to soil microbes include ammonia (NH_4^+), which is a reduced form of nitrogen and therefore easier for microbes to metabolize, and nitrates (NO_3^-), which require additional energy to reduce before being incorporated into biomass (Wang et al., 2022). In addition, these biochemical differences will also generate unique ecological conditions; e.g., ammonia applications tend to promote acidification of the environment and favor the growth of copiotrophic bacteria while nitrate applications support a broader range of taxa. Overall, these findings suggest that there may be corresponding variations in resistome composition associated with different forms of nitrogen (Wang et al., 2022) (Table 1). Studies have demonstrated that, at equal concentrations, NH_4^+ application has been shown to increase antibiotic resistance gene (ARG) abundance more than isomolar NO_3^- applications (Wang et al., 2022), indicating that the form of nitrogen itself influences the pattern of resistance genes.

3. Nitrogen Fertilization and Antibiotic Resistance Gene Dynamics

3.1 Abundance and Diversity of ARGs Following Nitrogen Application

Field research has repeatedly found that nitrogen fertilizers result in an increase in antibiotic resistant bacteria (ARG), with varying levels and different antibiotic resistant genes based upon historical soil use, climate conditions, and the rate at which nitrogen is applied (Wang et al., 2024). Wang et al. (2024) conducted a study evaluating over 400 samples from manure amended fields versus chemical fertilizer amended fields in China and found that the diversity of ARG was significantly greater in the manure amended fields as opposed to the fields amended with chemical fertilizers (Y. Wang et al., 2024). While there were increases in various types of ARG within both sets of fields, the majority of the increases were for those ARG’s providing resistance to tetracyclines, sulfonamides and beta lactam antibiotics, which are among the most commonly used antibiotics in animal production (Wang et al., 2024) (Table 1). However, the relationship between nitrogen application rates and the relative abundance of ARG’s was not linear; excessive amounts of nitrogen (563 kg N/ha) applied in sugarcane systems resulted in the reduction of various measures of diversity among microorganisms while increasing the relative abundance of ARG’s. This suggests that there may be an optimal range for nitrogen application above which significant ecological disruptions occur (Gu et al., 2021).

3.2 Resistance Gene Distribution Across Soil Depth

Vertical movement of soil resistomes is another area of study that receives less attention than horizontal distribution. While there are many similarities between how vertically distributed ARGs move through a soil profile as compared to horizontally, ARGs do not equally distribute themselves throughout all areas of a soil profile; instead, there is a heavy concentration of ARGs in surface layers where most of the nitrogen accumulates and where the greatest plant-microbial activity occurs (Wang et al., 2024). Most studies find that the number and type of ARGs decrease greatly at greater depths in the soil profile; however, a few of the more mobile genes can be found at deeper levels of the profile (Wang et al., 2024). Furthermore, the effect of nitrogen fertilizer on this vertical distribution of ARGs was studied and it was determined that, while surface concentrations become even more concentrated after N-fertilizer applications, the same concentration effect did not occur at lower depths in the soil profile (Wang et al., 2024). These findings have practical implications for how we understand the pathways by which resistance is disseminated; as surface-concentrated ARGs have an increased opportunity to come into contact with plant roots, thereby providing an opportunity for plant uptake into vegetable tissues (Wang et al., 2022). As such, the rhizosphere - the zone of soil closest to developing root tissue - represents an especially significant point of interaction where nitrogen-driven shifts in microbial populations directly interact with developing plant tissues which will ultimately be consumed by humans (Wang et al., 2022) (Table 1).

3.3 Multidrug Resistance Enrichment

One alarming trend found in studies on nitrogen fertilizer applications is an increase in the number of multidrug resistance (MDR) genes; ARGs providing a high level of resistance to multiple classes of antibiotics at one time (Wang et al., 2024). MDR genes were primarily associated with four resistance mechanisms (efflux pumps ~33%, target alteration ~31%, inactivation ~20% & target protection ~8%) in farmland soils exposed to different levels of chicken manure (Wang et al., 2024). The prominence of efflux pump genes is important because efflux pump mechanisms provide a mechanism for broad-spectrum resistance to multiple chemically distinct antibiotics, which increases the potential clinical impact of any single resistance gene (Liu et al., 2023). Efflux pump gene enrichment was observed in all studies of nitrogen fertilizer applications, indicating that the selective pressure exerted by nitrogen fertilizers provides favorable conditions for multi-functional resistance mechanisms that can protect bacteria against many types of antimicrobial agents (Wang et al., 2024) (Table 1).

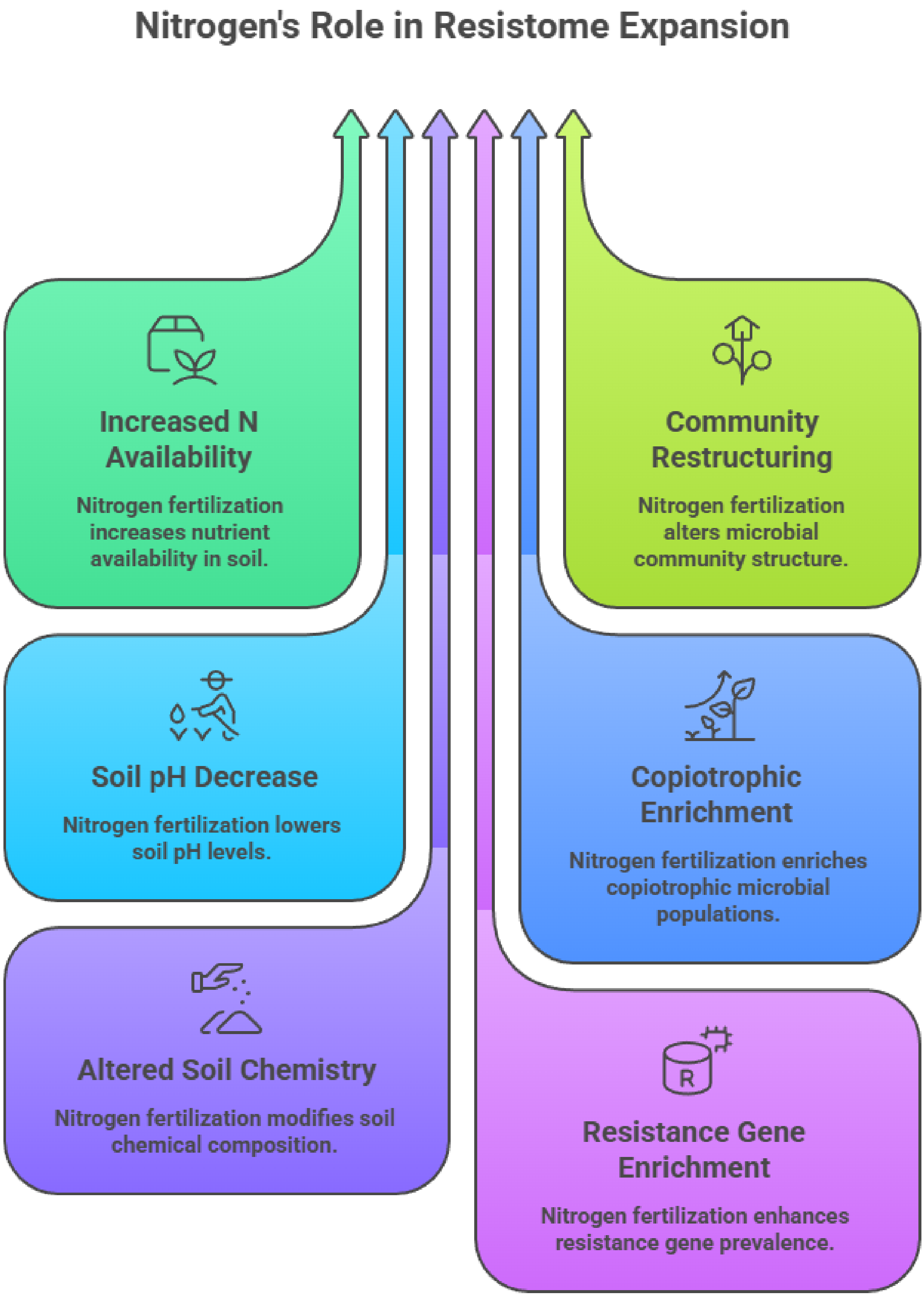

Fig. 1. Conceptual Model of Nitrogen-Driven Resistome Expansion

Table 1. Nitrogen Fertilization Effects on Soil Resistome Characteristics

Parameter	NH_4^+-N Treatment	NO_3^--N Treatment	Organic Amendment	Citation
Total ARG Abundance	+192-fold (median)	+85-fold (median)	+248-fold (median)	(Wang et al., 2024)
Efflux Pump Genes	Increased 33%	Increased 28%	Increased 39%	
Target Alteration Genes	Increased 31%	Increased 29%	Increased 35%	
Surface Soil (0-20 cm) Concentration	Highest	Moderate-High	Highest	
Depth 40-60 cm Concentration	Significantly Lower	Significantly Lower	Significantly Lower	
Bacterial Diversity (Shannon Index)	Decreased	Decreased	Decreased	
Integration Genes (intI1) Abundance	Increased 156%	Increased 98%	Increased 187%	

4. Mechanisms linking nitrogen to resistance gene proliferation

4.1 Microbial Community Restructuring

One alarming trend found in studies on nitrogen fertilizer applications is an increase in the number of multidrug resistance (MDR) genes; ARGs providing a high level of resistance to multiple classes of antibiotics at one time (Y. Wang et al., 2024). MDR genes were primarily associated with four resistance mechanisms (efflux pumps ~33%, target alteration ~31%, inactivation ~20% & target protection ~8%) in farmland soils exposed to different levels of chicken manure (Y. Wang et al., 2024). The prominence of efflux pump genes is important because efflux pump mechanisms provide a mechanism for broad-spectrum resistance to multiple chemically distinct antibiotics, which increases the potential clinical impact of any single resistance gene (Liu et al., 2023). Efflux pump gene enrichment was observed in all studies of nitrogen fertilizer applications, indicating that the selective pressure exerted by nitrogen fertilizers provides favorable conditions for multi-functional resistance mechanisms that can protect bacteria against many types of antimicrobial agents (Wang et al., 2024).

4.2 Horizontal Gene Transfer Facilitation

Nitrogen-based additions to soil promote ecological processes that are conducive to horizontal gene transfer (HGT), by far the most common method for the distribution of bacterial resistance genes (Wintersdorff et al., 2016). Following nitrogen additions, an increase in the number of microorganisms per unit area and an increase in microbial activity can significantly increase conjugation rates, the most prevalent form of HGT found in soil (Klmper et al., 2014). Nitrogen additions can create favorable conditions for the exchange of genetic material between microorganisms; these include increased osmotic potential, altered redox potentials and increased levels of organic acids and other substances that modify cell membranes, both of which can have a positive effect on conjugation efficiency (Du, 2025). Nitrogen amendments to soil are also associated with higher levels of mobile genetic elements (MGEs) that contain antibiotic resistance genes (ARGs); specifically plasmids, transposons and integrons (Wang et al., 2024). Levels of the integrase gene, intI1, which is indicative of mobilization of ARGs via integrons, show significant increases in response to nitrogen applications (Y. Wang et al., 2024) (Table 2). These findings suggest that not only do nitrogen based fertilizers result in increased levels of ARGs but they may also promote the molecular processes that allow for the movement of ARGs from one organism to another.

4.3 Co-Selection Mechanisms

An important conclusion with direct implications for human health involves pathogenic bacteria known to host ARGs in nitrogen-fertilized agriculture soils (Wang et al., 2024). Analysis of correlation between Pseudomonas sp. and Listeria sp. both are pathogens for humans and the presence of ARGs in manure-amended soil from treated land demonstrated that both were significant hosts for ARGs in all three treatment groups (Wang et al., 2024). The fact that pathogenic bacteria, which are capable of carrying resistance genes, are enriched in agricultural soils is indicative of a pathway of direct transmission of disease to humans by way of food products or crop animals. Additionally, Pseudomonas and Listeria are opportunistic pathogens of concern to those who are immunocompromised. As such, their role as predominant ARG carriers in agricultural soils amended with nitrogen-based fertilizers indicates that fertilizing agricultural land can contribute to creation of reservoirs of drug-resistant pathogens for use by humans (Wang et al., 2024) (Table 2).

4.4 Microbial Adaptation and Antibiotic Resistance Evolution

Beyond the direct influence of nitrogen on the composition of microbial communities at a micro-ecological level, nitrogen also has an indirect effect by altering the rate of bacterial physiological processes and their growth rates, thereby potentially influencing the emergence of resistant populations (Kelbrick et al., 2023). As is common in agricultural settings utilizing chemical fertilizers with abundant nitrogen, this often leads to a paradoxical situation in which nitrogen levels are high while carbon is limiting. Bacteria will then adapt to compete for limited resources, primarily through optimization of multiple survival mechanisms; e.g. up-regulation of efflux pumps and stress response pathways that result in antibiotic resistance (Xu et al., 2024). Resistance to antibiotics was found to be greater in soils where the levels of carbon were low, yet nitrogen was abundant suggesting that nitrogen indirectly enhances resistance due to the impact it has on overall nutrient ratios and bacterial physiological processes (Xu et al., 2024). Further, the lower level of functional redundancy associated with nitrogen amended soils indicate that resistant phenotypes have less competitive pressure and are more likely to persist (Xu et al., 2024).

5. Pathways for Resistance Gene Dissemination from Soil

5.1 Soil-to-Plant Vertical Gene Transfer

Although soil resistomes contain an extensive variety of antibiotic resistant genes (ARG), the primary issue is the dissemination of those ARGs to clinically important pathogens and integration into food systems (Wang et al., 2022). Bacteria are taken into plants by those plants as endophytes from the soil, and those endophytic bacteria have ARGs that accumulate in the edible portions of the plant (Wang et al., 2022). Nitrogen applications increase both the amount of ARG in the soil and the transfer of those genes into the edible portions of plants. A portion of those genes were transferred into the vegetable parts of the plant rather than being retained in the root tissue (Wang et al., 2022). The estimated number of ARG that are consumed on a daily basis through the consumption of Chinese cabbage was found to be between 10^6 to 10^7 ARG copies per individual and nitrogen application affected intake levels (Wang et al., 2022). This discovery illustrates that nitrogen fertilizers increase the presence of ARGs in soils, but create pathways for ARGs to enter the diets of humans via consumption of vegetables (Wang et al., 2022).

5.2 Biosolid Amendment and Agricultural Cycling

Agricultural systems that use organic amendments (manures, biosolids, composts) to provide organic matter and N are also using concentrated pools of ARGs in soils (Jauregi et al., 2023). Organic amendments have higher concentrations of ARGs than other forms of organic matter due to the presence of ARGs from the digestive process in livestock and from the treatment of wastewater. When N is added via fertilizer to these pre-enriched pools of ARGs, it creates an environment in which the selection pressure favors the proliferation of resistant microorganisms (Jauregi et al., 2023). Although anaerobic digestion and/or the use of biochar to treat amendments prior to their application to soils has been shown to decrease the abundance of ARGs by 30-83% (Jauregi et al., 2023), most agricultural applications of amendments do not include treatments of this nature. Therefore, amendment management represents a modifiable risk factor; variations in how amendments are applied can have a large impact on resulting soil ARG dynamics (Jauregi et al., 2023). In addition, when high-N fertilizers are applied subsequent to the application of biosolids, they create a synergistic increase in both resistant bacteria and ARGs (Wang et al., 2024).

5.3 Pathogenic Bacteria as ARG Hosts in Agricultural Soils

An important conclusion with direct implications for human health involves pathogenic bacteria known to host ARGs in nitrogen-fertilized agriculture soils (Wang et al., 2024). Analysis of correlation between Pseudomonas sp. and

Table 2. Pathogenic Bacteria Identified as ARG Hosts in Nitrogen-Amended Agricultural Soils

Bacterial Genus	Clinical Significance	Primary Infection Type	ARG Types Detected	Citation
Pseudomonas aeruginosa	High (Opportunistic pathogen)	Respiratory, Wound	Beta-lactams, Fluoroquinolones, Carbapenems	(Jalal & Sonbol, 2024; Wang et al., 2024)
Listeria monocytogenes	High (Foodborne pathogen)	Meningitis, Septicemia	Beta-lactams, Tetracyclines	(Wang et al., 2024)
Klebsiella pneumoniae	High (Healthcare-associated)	Respiratory, UTI	Extended-spectrum beta-lactams	(Jalal & Sonbol, 2024; Wang et al., 2022)
Escherichia coli	High (Enteropathogenic)	Diarrhea, UTI, Sepsis	Multiple classes	(Jalal & Sonbol, 2024; Wang et al., 2022)
Salmonella enterica	High (Foodborne)	Gastroenteritis, Sepsis	Tetracyclines, Quinolones	(Jalal & Sonbol, 2024)

Listeria sp.—both are pathogens for humans—and the presence of ARGs in manure-amended soil from treated land demonstrated that both were significant hosts for ARGs in all three treatment groups (Wang et al., 2024) (Table 2). The fact that pathogenic bacteria, which are capable of carrying resistance genes, are enriched in agricultural soils is indicative of a pathway of direct transmission of disease to humans by way of food products or crop animals. Additionally, Pseudomonas and Listeria are opportunistic pathogens of concern to those who are immunocompromised. As such, their role as predominant ARG carriers in agricultural soils amended with nitrogen-based fertilizers indicates that fertilizing agricultural land can contribute to creation of reservoirs of drug-resistant pathogens for use by humans (Wang et al., 2024).

6. Nitrogen Fertilization Rate and Resistome Dynamics

6.1 Dose-Response Relationships

Generally, nitrogen tends to increase the quantity of antibiotic resistant genes (ARG), however, the rate at which nitrogen is applied does not always directly correlate with the increase in the number of ARG (Wang et al., 2024). It appears that a threshold exists; high levels of nitrogen application may inhibit the increase in additional ARG beyond a point, especially when dysfunction in the ecosystem exists (Wang et al., 2024). The comparison of optimum (375 kg N / ha) versus excess (563 kg N / ha) nitrogen application in sugarcane systems revealed that excess nitrogen application decreased the total number of bacteria species, increased the relative abundance of Proteobacteria and Acidobacteria as compared to optimum application (Gu et al., 2021). Additionally, excess nitrogen decreased pH and changed the balance of nitrogen cycle associated genera (Gu et al., 2021). These ecological changes may create conditions whereby resistance genes are maintained, but ARG diversity is limited. Thus, there is the possibility of controlling the development of resistance genes via optimal nitrogen applications and not solely by eliminating fertilizer application (Gu et al., 2021).

6.2 Long-Term Nitrogen Application Effects

Most studies documenting nitrogen’s effects on resistomes examine relatively short-term responses (months to years), but agricultural soils typically receive decades of continuous fertilization, creating long-term cumulative effects on resistome architecture (Zhang et al., 2024). Meta-analysis of 115 long-term nitrogen fertilization studies revealed that sustained high nitrogen application decreases soil pH by 15.27%, reduces enzyme activities involved in nutrient cycling by 9.82-22.37%, and alters microbial community composition with decreased bacterial diversity (Shannon index decreased 15.42%) (Zhang et al., 2024). These chronic changes create soil conditions chronically selecting for subsets of nitrogen-responsive bacteria, including those enriched in ARGs (Zhang et al., 2024). The implications are profound: long-term N-fertilized soils represent not transient disturbances but permanently restructured ecosystems with fundamentally altered resistome architectures and microbial functional potential (Zhang et al., 2024).

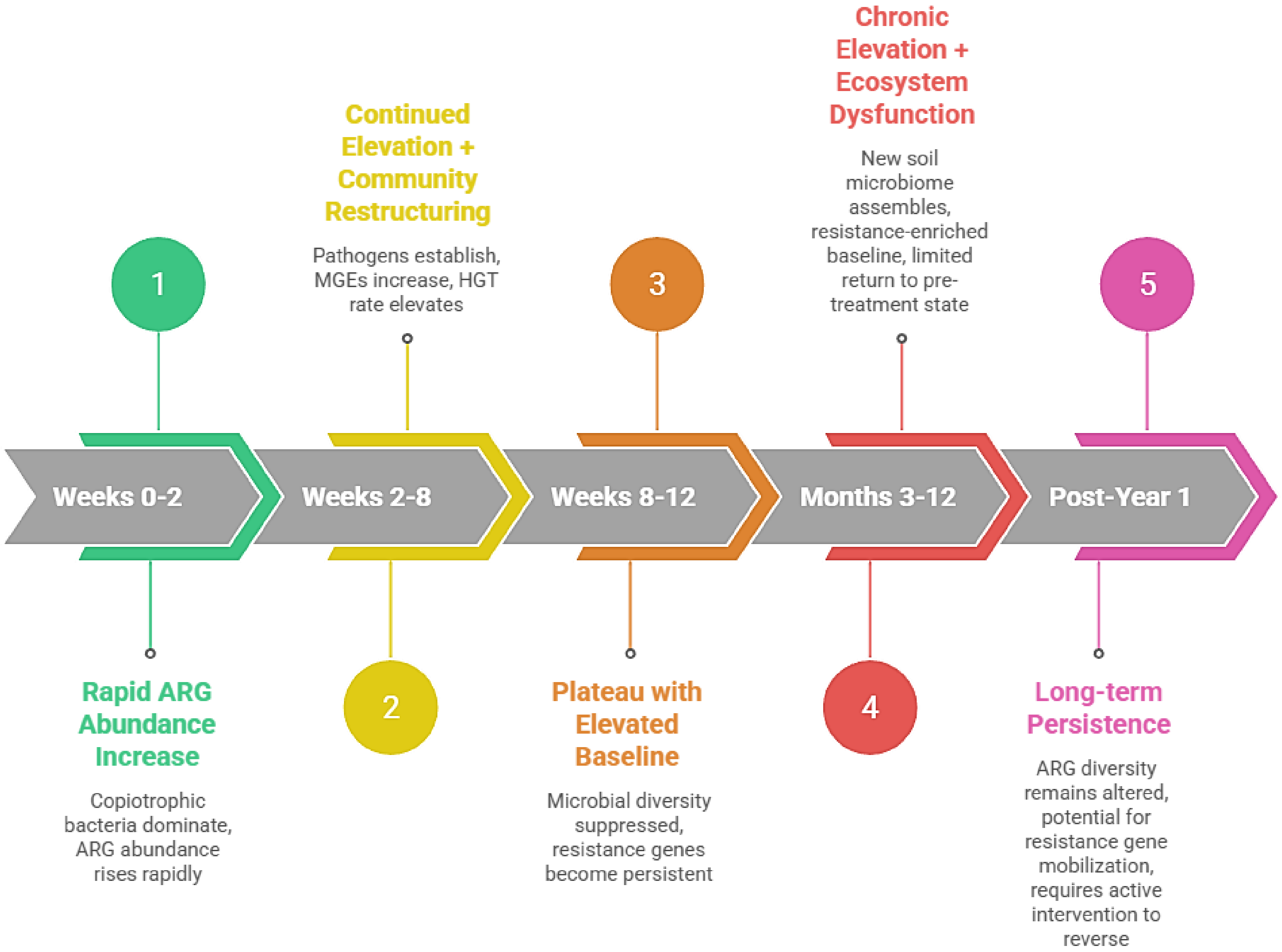

Fig. 2. Timeline of Soil Resistome Changes Following Nitrogen Application

6.3 Temporal Dynamics and ARG Persistence

The early stages of field studies on the spread of antibiotic resistance genes (ARG) after applying a single dose of nitrogen have documented an increase in ARG populations that happens quickly initially, then as time progresses it gradually diminishes; however, the population never goes back to baseline levels (Hu et al., 2015). Microcosms were used to follow temporal changes of ARG succession from adding cattle manure, with results showing that there was significant growth of ARG diversity over 140 days when compared to the control group receiving no amendments (Hu et al., 2015). However, while the number of ARGs remained elevated in comparison to the controls even at the end of the experiment, several native ARGs that conferred resistance to β-lactams remained at high levels of enrichment in the manure treated soils for the entire duration of the experiment (Hu et al., 2015), suggesting that once selected for by the addition of nitrogen, some resistance genes remain persistent within the soil community and are thus established in these microbial communities (Hu et al., 2015). The continued presence of resistance genes in soil has significant implications, indicating that not only does each fertilizer application add resistance genes temporarily, but also that each successive fertilizer application adds additional resistance genes to the soil, leading to the establishment of increasingly resistant microbiomes in the soil, which will be difficult to reverse (Hu et al., 2015).

7. Mechanisms Limiting Natural Barriers to Resistance

7.1 Microbial Diversity as a Resistance Barrier

Microbial diversity is negatively correlated to antibiotic-resistance gene (ARG) prevalence and diversity in minimally impacted river beds and pristine forest soils (Klmper et al., 2024). Microbial diversity provides an ecological resistance to resistance gene carrying-organisms immigrating into a community. Nitrogen fertilizer application results in decreased microbial diversity (Zhang et al., 2024), which may reduce or eliminate this resistance. Nitrogen fertilizer reduces the number of ecological niches available within a community through a process known as niche limitation, thereby limiting the ability of resistance gene carrying-immigrants to establish themselves. In contrast, nitrogens simplified communities have limited ecological niches and as such, resistance gene carrying-organisms easily colonize these niches (Klmper et al., 2024). As a result of reducing microbial diversity, nitrogen fertilizers increase ARG abundance at the same time they decrease the ecological resistance provided by diverse microbial communities (Klmper et al., 2024).

7.2 Cross-Kingdom Predation and Protist Pressure

The effect of predation from protists has long been overlooked as a regulatory mechanism for the soil resistome protists that are bacterivorous are consumers of bacteria and thereby impose top-down community control (Liu et al., 2024). Protist predation typically increases the number of genes associated with ARG (antibiotic resistant genes) in a bacterial community by promoting bacteria capable of creating antimicrobial compounds; however, the same compounds provide a protective effect to bacteria against antibiotics through cross-protective mechanisms (Liu et al., 2024). Nitrogen fertilizers have an influence on protist communities and the rate of predation, and thus, indirectly affect the bacterial resistomes present in a system. Although there is still much to be learned about the relationship between nitrogen and the dynamics of protist/bacteria, it is apparent that complex multi-trophic relationships directly affect resistome characteristics, and nitrogen will likely disrupt this system in ways we do not currently understand (Liu et al., 2024).

8. Intervention Strategies: Reducing Nitrogen-driven Resistance

8.1 Precision Nitrogen Management

Due to nitrogen's potential for increasing soil resistome levels there is an urgent need to develop methods of managing nitrogen that will preserve the productive capacity of agriculture while limiting the increase in numbers of resistance genes (Zhang et al., 2024). A method of managing nitrogen at the field level which has been identified as a "first step" toward achieving this goal is precision nitrogen management; or matching the amount of nitrogen fertilizer applied to meet the needs of the crop (Zhang et al., 2024). The advantages of using precision nitrogen management include the elimination of excessive amounts of nitrogen from being applied beyond the needs of the plants thereby avoiding the over stimulation of copiotrophic, resistance-enriched bacterial communities that have developed as a result of previous nitrogen fertilizer applications. Studies conducted on fields show that by applying optimal amounts of nitrogen fertilizer it is possible to maintain crop yields while significantly reducing the number of antimicrobial resistance genes (ARG) present in soils when compared to high rate applications of nitrogen fertilizers (Gu et al., 2021). Another method of managing nitrogen that may also be useful in preventing large increases in the number of ARGs in soils is the use of slow release nitrogen fertilizer products that provide a steady and continuous flow of available nitrogen to crops (Wang et al., 2025).

8.2 Nitrogen Form Selection

Agricultural management practices such as using nitrate based or urea fertilizers instead of ammonium, could be a way to reduce the growth of the resistome (Wang et al., 2022) because nitrate based fertilizers would have less of an effect on increasing the number of ARG's compared to ammonium (Wang et al., 2022). There are however potential trade offs. Nitrate fertilizers generally result in greater soil leaching and waterway eutrophication (Wang et al., 2022). In addition there is a need for research regarding the long term effects of substituting different forms of nitrogen in soils that are already degraded (Wang et al., 2022). Controlled release formulations that can provide a steady state nitrogen source, could potentially be used as an alternative method that can provide the same agricultural benefits while limiting the rapid selection of resistance genes (Wang et al., 2025).

8.3 Organic Matter Management and Biochar Application

Use of Biochar with Organic Amendments Reduces ARG Gene Abundances and Integron Genes by 60% and 83%, Respectively Compared to Untreated Organic Amendments; Physical Adsorption of ARG-Carrying Bacteria and Changes in Soil Chemistry Favorable or Unfavorable to Resistance Gene-Carrying Organisms are Mechanistically Responsible for These Effects; Pre-Treatment of Biosolids via Anaerobic Digestion Results in a Reduction in ARG Abundances of 38–83%; Therefore, the Findings Suggest That Pre-Treatment of Organic Amendments and Biosolids Substantially Modifies Their Impacts on the Soil Resistome, Representing Leverage Points for Reducing the Dissemination of Antibiotic Resistance Genes from Managed Systems.

Table 3. Effectiveness of Different N-Fertilization Management Strategies on ARG Abundance

Management Strategy	ARG Reduction	Soil Properties Affected	Agronomic Impact	Citation
Precision N (optimized rate)	15-25%	Reduced nitrate leaching	Maintained yield	(Gu et al., 2021; Zhang et al., 2024)
Nitrate vs. Ammonium form	18-32%	Slight pH reduction	Maintained yield	(Wang et al., 2022)
Slow-release formulations	20-35%	Steady nutrient availability	Slight yield increase	(Wang et al., 2025)
Biochar + amendment	60-83% for intI1	pH increase, increased porosity	Neutral to positive	(Jauregi et al., 2023)
Anaerobic digestion pretreatment	38-83%	Reduced bioavailable contamination	Positive (sanitation)	(Jauregi et al., 2023)
Combination approaches	45-68%	Multiple soil parameter changes	Maintained to increased	(Jauregi et al., 2023; Zhang et al., 2024)

9. Global Context and one Health Implications

9.1 Agricultural Intensification and Food Security Tensions

Current nitrogen use in agriculture involves a paradoxical dilemma; Nitrogen fertilizer must be used to produce sufficient food for an increasing world population; however, as a result of using these fertilizers, we also create the potential for an increase in antimicrobial resistance, which will threaten the medicines currently being used to treat our world's increasing population (Kelbrick et al., 2023). The inherent conflict between the two crises represents a common dilemma in environmental health; an intervention designed to solve a problem in food production creates a new problem (in this case, antimicrobial resistance). A solution to this paradox requires highly integrated approaches that can maintain optimal nitrogen levels for food production while selecting against antimicrobial resistance genes (Kelbrick et al., 2023). Reducing the amount of nitrogen applied to crops without creating alternative methods to maintain crop yield would sacrifice current food security in exchange for future resistance issues – unacceptable for many food insecure areas (Kelbrick et al., 2023).

9.2 Developing World vs. Developed World Disparities (No. 27)

Nitrogen Use Practices and Resistance Dissemination Patterns. There are considerable geographically-related differences in the dissemination patterns of resistance based upon how nitrogen is used in farming (Forslund et al., 2013). In areas where there is a high level of nitrogen fertilizer usage and/or a lack of effective regulation of agricultural practices (especially in South Asia and East Asia) the resistome of soils contains an exceptionally large number of antibiotic resistance genes (ARGs) and at higher levels than in other locations (Zhao et al., 2025). However, in those regions where farmers utilize precision agriculture methods for optimizing their nitrogen applications, the overall number of antibiotic resistance genes found in their soils is lower than would be expected from the amount of nitrogen fertilizer applied (Forslund et al., 2013). The difference in these two examples demonstrates that the issue isn't merely how much nitrogen is being used, but also how it is applied. Many developing nations are transitioning to intensive forms of agriculture, yet they often have little or no capability to implement efficient and precise nutrient management techniques, nor do they possess adequate regulatory frameworks to manage such practices effectively; as a result they are highly susceptible to rapid increases in the emergence of new forms of resistance to antibiotics due to poorly managed fertilization practices (Forslund et al., 2013). Thus, international funding for agricultural practices may offer disproportionately greater amounts of resistance reduction through efforts focused on optimizing nitrogen use in developing nations (Kelbrick et al., 2023).

9.3 The One Health Framework

Antimicrobial Resistance is best addressed through a One Health model of collaboration among Veterinary Science, Human Medicine, Agriculture, Environmental Conservation as it demonstrates how Nitrogen in Soil Resistomes are an example of why decisions regarding fertilizer application can result in an increase in bacterial resistance in soils (Aslam et al., 2021) – because those same bacteria are then selected upon and disseminated throughout food chains and the environment, ultimately affecting human health. The same applies when antibiotics are used in human and animal medicine – the resistant bacteria shed from these animals and humans excrete Antibiotic Resistance Genes (ARGs) into the soil – where the abundance of these genes is increased with the addition of nitrogen-based fertilizers (Aslam et al., 2021). Therefore, addressing this interdependent system will require coordination and cooperation between sectors that have historically operated independently (Aslam et al., 2021), i.e. agricultural extension services educating farmers about nitrogen management; veterinary practitioners using fewer antibiotics; and hospital-based clinicians “stewardaring” antibiotic use.

10. Research Gaps and Future Directions

10.1 Mechanistic Understanding Limitations

Although there is considerable documentation supporting an increase in the number of soil ARGs as a result of nitrogen fertilizer use; however, the exact mechanisms underlying this phenomenon are still poorly defined (Du, 2025). Most studies have been limited to documenting correlations between nitrogen addition to soils and ARG presence/numbers, with little or no evidence of direct causal relationships. Can nitrogen drive selection for organisms carrying resistance genes due to enhanced metabolic capabilities? Or does the effect of nitrogen on selecting resistant bacteria occur indirectly as a result of its influence on the physiological status of cells? Is there some alteration in the chemical environment of soils caused by nitrogen additions which enhance the efficiency of conjugation and/or facilitate horizontal gene transfer? While the existing body of evidence would suggest all three options are valid, the degree to which they are involved has not yet been established (Du, 2025). To provide conclusive evidence for these hypotheses, future research should incorporate mechanistically-based approaches such as those using pure cultures, soil systems with controlled inputs (e.g., nitrogen), and system biological techniques (e.g., network analysis) to establish direct causal relationships (Du, 2025).

10.2 Resistome Functional Characterization

Although most of the resistome studies have quantified the presence and diversity of Antibiotic Resistance Genes (ARG) they do not determine how many of these genes are actually functionally expressed under specific environmental conditions (Liu et al., 2023).

An ARG that is present at a high copy number could be expressed all the time (constitutively), or it could only be expressed when an antibiotic is present (conditionally), or it could be completely silent (transcriptionally silent). The ability to identify the expressed resistome vs. the total resistome will allow for better assessments of the risks (Z. Liu et al., 2023). Many of the genes discovered through metagenomic analysis remain uncharacterized as to their functional roles; therefore it is unclear how much each contributes to the observed phenotypic resistance. By combining shotgun metagenomics with metatranscriptomics, metaproteomics, and phenotypic antibiotic susceptibility testing it would be possible to develop a more comprehensive understanding of the resistome (Liu et al., 2023).

10.3 Field Application of Intervention Strategies

While research has shown that certain methods of managing nitrogen can help lower levels of ARGs in soils, practical application at a larger scale has been limited (Jauregi et al., 2023). Typically, farmers who are subject to economic pressure do not have the incentive to use practices designed to mitigate antibiotic resistant bacteria (ARGs) unless there is a regulatory requirement or they receive premium prices on their products for being produced using environmentally friendly methods (Jauregi et al., 2023). In order to stimulate future practice development to minimize the impact of resistance selecting practices by providing economically viable alternatives such as increased yields and/or lower inputs, the adaptation of nitrogen management practices at a regional level will be necessary. Methods of nitrogen management developed for temperate agriculture are likely to not be applicable in tropical or arid agricultural settings due to differences in soils and crop management practices (Jauregi et al., 2023).

Table 4. Regional Variations in Soil Resistome Response to Nitrogen

Geographic Region	Dominant Agricultural System	Typical N Application (kg/ha)	Observed ARG Increase
Primary Resistance Classes	**Citation**	East Asia (China)	Rice-wheat rotation
150-250	192-fold median	Tetracycline, Sulfonamide, β-lactam	(Wang et al., 2024; Zhao et al., 2025)
South Asia (India)	Mixed crop-livestock	80-150	140-180 fold
Fluoroquinolone, Aminoglycoside	(Jalal & Sonbol, 2024)	North America	Corn-soybean monoculture
150-180	85-120 fold	Macrolide, Tetracycline	(Rovira et al., 2019)
Europe (Denmark)	Precision N management	100-140	40-65 fold
β-lactam, Sulfonamide	(Forslund et al., 2013)	Sub-Saharan Africa	Limited input systems
20-50	30-50 fold	Multidrug, Tetracycline	(Manyi-Loh et al., 2018)

Table 5. Key Research Questions and Current Knowledge Status

Research Question	Current Knowledge	Gaps	Future Research Needs
How does N form affect resistome?	$NH_4^+ > NO_3^-$ for ARG enrichment	Mechanisms unknown; long-term effects	Mechanistic studies; field trials
What is ARG transfer rate from soil to food?	10^6-10^7 copies/day per capita	Specific plant species variation unknown	Multi-crop studies; dose-response
Which pathogens emerge in N-fertilized soils?	Pseudomonas, Listeria, E. coli identified	Strain-level identification lacking	Genomic characterization; epidemiology
Can precision N reduce resistance?	15-25% reduction documented	Cost-benefit analysis incomplete	Farm-scale economics
How do soil amendments affect outcome?	Biochar effective; digestion helpful	Optimal amendment combinations unknown	Systematic comparison studies

11. Conclusion

The soil nitrogen resistome (a reservoir for drug-resistant bacteria) has emerged as a key area of concern for antimicrobial resistance (AMR), however it was previously underutilized in discussions about AMR. Multiple lines of evidence from independent studies have clearly demonstrated that use of nitrogen fertilizer (in all its forms, and at varying rates and application times) leads to a substantial increase in the number of antibiotic resistant genes (ARGs) in agricultural soils and their ability to spread. Nitrogen-driven changes in soil resistomes are caused by a complex interplay of community dynamics, increased transfer of resistance genes among bacterial cells and selective pressure favoring the presence of multi-drug resistance (MDR) determinants in these same communities. The additional concern created by the identification of pathogens carrying resistance genes (the host organisms of resistance genes) that are significantly more abundant in nitrogen amended soils than those found in unamended soils, creates concerns for direct transmission pathways to human populations through food chains. The urgency surrounding this issue stems from the fact that nitrogen-based fertilizers remain essential for modern food production and food security globally, and therefore, removing nitrogen based fertilizers from food systems is currently not feasible. Therefore, there is a need to develop new ways to manage nitrogen inputs into agricultural systems to maximize crop yields while minimizing the selection for resistance genes in ecosystems. A variety of evidence exists to support three broad categories of interventions that can address this challenge (precision nitrogen application, optimal nitrogen formulation, and treatment of nitrogen amendments prior to application) and provide practical options to mitigate the development of AMR in agricultural ecosystems. However, the widespread adoption of these approaches may face significant financial and regulatory challenges. Ultimately, the soil nitrogen resistome serves as an example of how AMR is linked across the agricultural-medical-environmental interface and thus, will require a multi-disciplinary approach that includes cooperation between the agricultural, medical, veterinary and public health sectors, using the principles of One Health to achieve simultaneous improvements in food security and the sustainability of antimicrobials. Long-term sustainability of effective AMR management will depend on the ability to develop and validate practical field-based methods to control the selection of MDR bacteria in response to nitrogen fertilizers, while maintaining or improving crop yields.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

Competing Interests

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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