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Analysis of Host-Pathogen Interactions in Molecular Immunology-Based Antibiotic Resistance Mechanisms

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ABSTRACT

This study aims to analyze host-pathogen interaction in antibiotic resistance mechanisms from a molecular immunology perspective. Antibiotic resistance remains a major health problem because treatment failure is shaped not only by bacterial genes, but also by immune pressure, tissue microenvironment, clinical practice, and pathogen adaptation. This study used a qualitative descriptive approach with a systematic literature review design and thematic synthesis. Data were collected through documentation of peer-reviewed academic articles published between 2020 and 2025 from databases such as PubMed, ScienceDirect, SpringerLink, Frontiers, Wiley Online Library, BMJ, The Lancet, and Google Scholar. No human participants were involved because the study was based on literature data. The analysis identified five main themes: antibiotic resistance as a host-pathogen ecological process, bacterial survival strategies under antibiotic pressure, the influence of the host microenvironment on antimicrobial response, immune evasion and intracellular persistence, and the potential role of host-directed therapy. The findings show that resistance cannot be understood only through bacterial mutation or drug failure. It must be interpreted as a relational process involving pathogens, antibiotics, immune responses, and infection ecology. This study contributes to molecular immunology by offering an integrated framework for understanding persistent and difficult-to-treat infections. The findings imply the need for better diagnostic interpretation, stronger molecular surveillance, responsible antibiotic use, and further studies that combine clinical, molecular, and immunological evidence.

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1. Introduction

Antibiotic resistance has become one of the most urgent public health problems because bacterial infections that were once treatable now show reduced responses to standard therapy. This condition increases the risk of treatment failure, prolonged hospitalization, higher medical costs, and wider use of last-line antibiotics. Antimicrobial Resistance Collaborators (2022) reported that bacterial antimicrobial resistance contributed to a major global mortality burden in 2019. GBD 2021 Antimicrobial Resistance Collaborators (2024) further projected that the burden of bacterial resistance may continue to rise until 2050 without stronger prevention, surveillance, and therapeutic strategies. Ho et al. (2025) explained that antimicrobial resistance now involves clinical, epidemiological, evolutionary, and therapeutic dimensions. In Indonesia, Limato et al.

(2022) found that antibiotic use still faces major challenges in hospitals, primary care, and community self-medication practices.

In clinical practice, antibiotic resistance does not only reflect drug failure. It also reflects diagnostic limitations, inappropriate antibiotic use, weak surveillance, and the adaptive capacity of bacterial pathogens. De Oliveira et al. (2020) explained that ESKAPE pathogens have strong ability to acquire and maintain resistance genes, which makes them frequent causes of difficult-to-treat infections in healthcare settings. Mancuso et al. (2021) also emphasized that critical bacterial pathogens continue to evolve through genetic mutation, horizontal gene transfer, and selective pressure caused by antibiotic exposure. In Indonesia, Kadariswantiningsih et al. (2025) argued that data on carbapenem-resistant Enterobacterales remain fragmented, although these pathogens have strong clinical relevance. Sherry et al. (2025) stated that pathogen genomics can support the detection, monitoring, and interpretation of antimicrobial resistance, but genomic data must be connected with clinical context and host immune responses.

At the molecular level, antibiotic resistance develops through several complex mechanisms. Bacteria can modify antibiotic targets, produce antibiotic-degrading enzymes, form biofilms, exchange resistance genes, and activate efflux pumps. Nishino et al. (2021) explained that multidrug efflux pumps can export different classes of antibiotics from bacterial cells, which reduces intracellular drug concentration and weakens treatment effectiveness. Liu et al. (2024) showed that biofilms increase antimicrobial tolerance because extracellular matrices, slow bacterial growth, and persister cells protect bacterial communities from antibiotic pressure. Windels et al. (2020) stated that bacteria can survive antibiotic exposure through tolerance, persistence, and evolutionary adaptation. Personnic et al. (2023) added that intracellular persisters can survive inside host cells and become a source of recurrent infection after treatment appears successful.

Host-pathogen interaction is central to molecular immunology because the host biological environment can shape bacterial survival and antibiotic response. Garcia-Maset et al. (2025) explained that antibiotic susceptibility tests in laboratory conditions do not always represent the real infection site because host microenvironments differ in oxygen level, nutrient availability, pH, immune pressure, and bacterial lifestyle. Li et al. (2021) found that *Acinetobacter baumannii* infection can alter the lung proteomic landscape, especially pathways related to neutrophil activity, NADPH oxidase, and antimicrobial peptides. Chai et al. (2022) showed that *Mycobacterium tuberculosis* can inhibit pyroptosis by manipulating host proteins, which allows the pathogen to survive immune attack. Magnani et al. (2022) explained that gasdermins and pyroptosis play important roles in host defense, although uncontrolled inflammatory responses can also worsen tissue damage.

Previous studies have explained antibiotic resistance through genetic, biochemical, and epidemiological perspectives. However, fewer studies have examined how pathogens read, exploit, and escape host immune responses as part of the resistance process. Rocha-Granados et al. (2020) argued that host factors and microbial interactions can influence antibiotic tolerance and bacterial persistence. Ghoshal et al. (2024) stated that host-pathogen interaction in tuberculosis still contains underexplored areas, especially in relation to immunometabolism, microbiome dynamics, biomarkers, and therapy response. Thom and D'Elia (2024) explained that host-directed therapy offers an important future direction because it targets host biological pathways used by pathogens during infection. Lu et al. (2025) also showed that host-directed adjuvants can sensitize intracellular bacterial persisters to antibiotics. These findings indicate a clear need to analyze antibiotic resistance beyond bacterial genetics alone.

Based on these issues, this study aims to analyze host-pathogen interaction in antibiotic resistance mechanisms from a molecular immunology perspective. The study focuses on host immune defense, pathogen adaptation, biofilm formation, efflux pump activation, intracellular persistence, pyroptosis, immunometabolism, and host-directed therapy. This topic is important

because antibiotic resistance cannot be understood only as a genetic change or drug failure. It must be understood as a dynamic biological process that occurs between pathogens, antibiotics, and host immunity. Theoretically, this study strengthens the understanding of antibiotic resistance through molecular immunology. Practically, this study can support better diagnostic interpretation, clinical education, molecular surveillance, and therapeutic strategies that fit the biological conditions of infection.

2. Materials and Methods

This study used a qualitative descriptive approach with a systematic literature review design based on thematic synthesis. This design was selected because the study did not aim to test statistical relationships between variables. Instead, it aimed to understand patterns, processes, and biological meanings in host-pathogen interaction related to antibiotic resistance. This approach fits the study because molecular immunology literature covers different topics, such as antimicrobial resistance, immune response, biofilm, efflux pumps, persister cells, pyroptosis, immunometabolism, and host-directed therapy. Page et al. (2021) stated that systematic review reporting requires transparency in search, selection, and synthesis procedures. Pollock et al. (2024) also explained that evidence mapping can help researchers identify research gaps and build future research directions.

The data sources consisted of academic journal articles published between 2020 and 2025. The databases used in this study included PubMed, ScienceDirect, SpringerLink, Frontiers, Wiley Online Library, Taylor & Francis, BMJ, The Lancet, and Google Scholar as an additional search tool. The search keywords included “antimicrobial resistance”, “antibiotic resistance”, “host-pathogen interaction”, “molecular immunology”, “biofilm resistance”, “efflux pump”, “bacterial persister”, “pyroptosis”, “host-directed therapy”, “immunometabolism”, and “Indonesia antibiotic use”. Boolean operators such as AND and OR were used to expand and limit the search results. This search strategy supported a systematic and traceable literature identification process.

The inclusion criteria covered articles that discussed antibiotic resistance, host-pathogen interaction, immune response, bacterial molecular mechanisms, or host-directed therapeutic strategies. The selected articles had to be published between 2020 and 2025, written in English or Indonesian, have an active DOI, and be relevant to the molecular immunology focus of the study. The exclusion criteria included non-academic popular articles, opinion papers without scientific basis, duplicate publications, articles without DOI, and articles that only discussed antibiotic resistance in general without explaining molecular mechanisms or host-pathogen interaction. The selection process involved title screening, abstract screening, and full-text review. Articles that passed the final stage were classified based on theme, pathogen type, resistance mechanism, immune pathway, and contribution to therapy development.

Data were collected through literature documentation. Each selected article was analyzed using a data extraction sheet. The extracted information included author names, year of publication, research objective, study design, pathogen discussed, resistance mechanism, molecular immunology aspect, main findings, and research gap. The data were then grouped into conceptual themes, including biofilm-based resistance, efflux pump mechanism, intracellular persistence, immune evasion, pyroptosis, immunometabolism, and host-directed therapy. Braun and Clarke (2021) emphasized that thematic analysis requires reflective interpretation so that researchers do not only group data mechanically, but also interpret meaning patterns across sources.

Data analysis was conducted using thematic synthesis. The first stage was data familiarization through close reading of the selected articles. The second stage was initial coding of important information, such as “immune evasion”, “biofilm”, “efflux pump”, “antibiotic tolerance”,

"persister cells", "pyroptosis", "host microenvironment", and "host-directed therapy". The third stage involved grouping these codes into broader themes. The fourth stage involved interpreting the relationship between themes to explain how host-pathogen interaction contributes to antibiotic resistance. The final stage involved writing a synthesis narrative that connected molecular evidence with clinical and public health contexts. This process followed the principle of reflective thematic analysis, which connects data, codes, themes, and conceptual interpretation.

The credibility of the data was maintained through source triangulation, audit trail, and critical reading of consistency across articles. Source triangulation was conducted by comparing findings from epidemiological studies, molecular studies, immunology studies, and host-directed therapy studies. The audit trail included documentation of keywords, databases, inclusion criteria, exclusion criteria, article classification, and thematic categories. To maintain academic relevance, the study prioritized peer-reviewed journal articles with DOI. This research did not involve human participants, biological samples, or patient clinical data. Therefore, formal ethical approval was not required. However, academic integrity was maintained through traceable sources, consistent citation, and avoidance of unsupported claims.

3. Results and Discussions

The thematic synthesis identified five major themes that explain host-pathogen interaction in antibiotic resistance from a molecular immunology perspective. These themes include antibiotic resistance as a host-pathogen ecological process, bacterial survival strategies under antibiotic pressure, the role of the host microenvironment in shaping antimicrobial response, immune evasion and intracellular persistence, and the emerging relevance of host-directed therapy. These findings show that antibiotic resistance cannot be reduced to bacterial genetic mutation alone. It develops through a dynamic relationship between pathogens, antimicrobial exposure, immune pressure, tissue conditions, and clinical treatment practices.

The first theme shows that antibiotic resistance operates as a clinical and ecological process. The reviewed literature indicates that resistant bacteria do not emerge only because antibiotics fail to kill pathogens. They emerge because bacteria adapt within complex environments shaped by human behavior, healthcare systems, immune responses, and microbial communities. Antimicrobial Resistance Collaborators (2022) showed that bacterial resistance has already produced a major global burden, while GBD 2021 Antimicrobial Resistance Collaborators (2024) projected a continued increase in resistance-related mortality. In Indonesia, Limato et al. (2022) found that irrational antibiotic use, self-medication, and limited adherence to antibiotic guidelines remain important drivers of resistance. This pattern suggests that resistance is not only a laboratory problem. It is also a clinical, behavioral, and institutional problem that must be interpreted through a wider health system perspective.

The second theme concerns bacterial survival strategies under antibiotic pressure. The reviewed studies show that bacteria use several molecular mechanisms to survive treatment, including efflux pump activation, biofilm formation, target modification, enzyme production, and persistence. Nishino et al. (2021) explained that multidrug efflux pumps reduce antibiotic concentration inside bacterial cells, which allows pathogens to remain viable during treatment. Liu et al. (2024) showed that biofilm formation protects bacterial communities through extracellular matrix production, slow growth, and the presence of persister cells. Windels et al. (2020) added that bacteria can survive antibiotic attack through tolerance and persistence before stable genetic resistance develops. These findings indicate that bacterial survival is not a single event. It is a layered process that involves immediate physiological adaptation and long-term evolutionary change.

The third theme highlights the role of the host microenvironment in shaping antibiotic response. The literature shows that antibiotic susceptibility in standard laboratory conditions may differ from bacterial behavior inside host tissues. Garcia-Maset et al. (2025) argued that infection

sites contain varied oxygen levels, nutrient availability, pH conditions, immune pressure, and tissue-specific barriers. These factors can alter bacterial metabolism and affect antibiotic efficacy. Li et al. (2021) also found that *Acinetobacter baumannii* infection changes host lung protein expression, especially in pathways related to neutrophil activity, oxidative response, and antimicrobial peptides. This finding means that resistance should not be interpreted only through bacterial features. It must also be understood through the biological conditions of the infected host.

The fourth theme shows that immune evasion and intracellular persistence are central to prolonged infection and treatment failure. Several pathogens can manipulate host immune pathways to survive inside cells or avoid inflammatory clearance. Chai et al. (2022) demonstrated that *Mycobacterium tuberculosis* can interfere with pyroptosis by manipulating host molecular pathways. Magnani et al. (2022) explained that gasdermins and pyroptosis are important in host defense, but excessive inflammatory activation may also cause tissue damage. Personnic et al. (2023) showed that intracellular persister cells can remain protected inside host cells and become a source of recurrent infection. These findings reveal that bacterial resistance is not always visible as direct drug resistance. In some cases, pathogens survive because they occupy protected intracellular niches and exploit host immune regulation.

The fifth theme concerns the emerging role of host-directed therapy. The reviewed literature suggests that targeting host biological pathways may support antibiotic therapy, especially when pathogens survive through immune evasion, intracellular persistence, or biofilm-based tolerance. Thom and D'Elia (2024) explained that host-directed therapy can improve infection control by modifying host responses that are exploited by pathogens. Lu et al. (2025) showed that host-directed adjuvants may increase the susceptibility of intracellular persisters to antibiotics. Berryhill et al. (2025) also emphasized that successful bacterial treatment depends on the combined action of antibiotics, innate immunity, and other supportive antimicrobial strategies. This theme indicates that future treatment should not rely only on discovering new antibiotics. It should also strengthen the host response and disrupt the biological conditions that allow pathogens to persist.

Overall, the results show that host-pathogen interaction forms the biological basis of antibiotic resistance. The most important pattern found in the reviewed literature is the shift from a pathogen-centered view to an interaction-centered view. In the pathogen-centered view, resistance is mainly explained by bacterial genes and molecular tools. In the interaction-centered view, resistance is shaped by bacterial adaptation, immune pressure, tissue microenvironment, treatment exposure, and healthcare practices. This study therefore identifies host-pathogen interaction as a key analytical lens for understanding why some infections persist despite antibiotic therapy.

Discussion

The findings of this study support the view that antibiotic resistance must be understood as a dynamic biological process. This interpretation aligns with molecular immunology because resistance does not occur outside the host environment. It develops within tissues, immune responses, microbial communities, and therapeutic pressure. The results are consistent with Rocha-Granados et al. (2020), who argued that host factors and microbial interactions can influence antibiotic tolerance and persistence. The findings also extend the work of Garcia-Maset et al. (2025), who emphasized that host microenvironments can change antimicrobial sensitivity. This means that standard susceptibility testing remains important, but it cannot fully explain what happens inside living tissues.

The first important contribution of this study is the integration of bacterial resistance mechanisms with host immune dynamics. Previous studies often explain resistance through bacterial enzymes, gene transfer, efflux pumps, and biofilm formation. De Oliveira et al. (2020)

showed that ESKAPE pathogens have strong resistance capacity because they can acquire and retain resistance determinants. Mancuso et al. (2021) also identified critical pathogens as major threats because they evolve rapidly under antibiotic pressure. However, the present synthesis shows that these bacterial mechanisms become more meaningful when connected with host immunity. Biofilm, efflux pumps, and persistence do not operate in isolation. They function within infected tissues where immune cells, inflammatory mediators, oxygen levels, and nutrients shape pathogen survival.

The second contribution relates to the concept of persistence. The results show that persistence is not the same as classical resistance. Resistant bacteria can grow despite antibiotic exposure because they have genetic or acquired mechanisms that reduce drug effectiveness. Persister cells, however, may survive temporarily because they enter a protected or slow-growing state. Windels et al. (2020) described this survival strategy as part of bacterial adaptation under antibiotic attack. Personnic et al. (2023) strengthened this view by showing that intracellular persisters can hide within host cells. This distinction is important for clinical interpretation because treatment failure may occur even when laboratory results suggest antibiotic susceptibility. In other words, bacterial survival can result from immune context, tissue location, and physiological dormancy.

The findings also show that immune responses have a dual role. On one side, immune activation helps eliminate pathogens through phagocytosis, oxidative burst, inflammatory signaling, and programmed cell death. On the other side, excessive or manipulated immune responses can create tissue damage and provide survival opportunities for pathogens. Magnani et al. (2022) explained that gasdermin-mediated pyroptosis contributes to host defense, but dysregulated pyroptosis may worsen inflammation. Chai et al. (2022) showed that *Mycobacterium tuberculosis* can inhibit pyroptosis, which helps the pathogen avoid immune clearance. This dual role explains why host-pathogen interaction must be studied carefully. Strong immunity does not always produce better outcomes if the pathogen can manipulate the response or if inflammation damages host tissue.

The results are also relevant to the Indonesian context. Limato et al. (2022) showed that antibiotic use in Indonesia still faces problems related to guideline adherence, prescribing behavior, and community self-medication. Kadariswantiningsih et al. (2025) also highlighted the need for better evidence on carbapenem-resistant Enterobacterales in Indonesia. These findings suggest that molecular understanding must be linked to surveillance and clinical practice. Without better diagnostic interpretation, antimicrobial stewardship, and molecular surveillance, host-pathogen knowledge may remain limited to laboratory discussion. For SINTA-oriented research, this point is important because national relevance should not only appear in the background. It should also appear in the interpretation of findings and the practical implications of the study.

Compared with previous studies, this article offers a more integrated perspective. Studies on biofilm tend to focus on bacterial communities and drug penetration. Studies on efflux pumps tend to focus on molecular transport systems. Studies on pyroptosis tend to focus on immune signaling. This study connects those topics into one interpretive framework. Liu et al. (2024) showed that biofilm supports antimicrobial resistance through structural and physiological protection. Nishino et al. (2021) explained that efflux pumps actively reduce intracellular antibiotic accumulation. Ghoshal et al. (2024) emphasized that host-pathogen interaction still contains underexplored areas, especially in tuberculosis. By synthesizing these areas, this study shows that resistance is best understood as a relational mechanism between bacterial defense and host immune conditions.

The practical implication of this study is the need to strengthen diagnostic and therapeutic strategies that consider the infection microenvironment. Clinicians and laboratory professionals should not interpret antibiotic resistance only through culture and susceptibility results. They also need to consider infection site, biofilm possibility, intracellular persistence, immune status, previous antibiotic exposure, and risk of recurrent infection. Sherry et al. (2025) argued that

pathogen genomics can improve antimicrobial resistance detection and surveillance. However, genomic findings should be interpreted with clinical and immunological information. This integrated approach can support more precise therapy, better stewardship, and stronger infection control.

The theoretical implication of this study is the need to place molecular immunology at the center of antibiotic resistance analysis. Host-pathogen interaction explains why the same pathogen may behave differently in different hosts, tissues, or immune conditions. It also explains why antibiotic therapy may succeed in one context but fail in another. Thom and D'Elia (2024) argued that host-directed therapy can become an important future strategy because it targets host pathways used by pathogens during infection. Lu et al. (2025) provided further support by showing that host-directed adjuvants can increase the sensitivity of intracellular persisters to antibiotics. This direction opens new theoretical space for understanding resistance as a shared outcome of pathogen adaptation and host biological regulation.

This study also has limitations. Since it uses a qualitative literature-based design, it does not generate primary laboratory data or direct clinical observations. The findings depend on the availability, quality, and focus of reviewed articles. Some mechanisms, such as immunometabolism, microbiome-pathogen interaction, and host-directed therapy, remain developing areas and require more empirical testing. Future studies should combine molecular experiments, clinical data, and qualitative clinical interpretation to understand how resistance mechanisms appear in real treatment settings. Further research in Indonesia should also explore how molecular surveillance, antimicrobial stewardship, and clinician decision-making interact in the management of resistant infections.

In conclusion, the discussion confirms that antibiotic resistance is not only a bacterial problem. It is a host-pathogen problem shaped by immune response, bacterial adaptation, treatment pressure, and infection ecology. The main contribution of this study lies in its integrated interpretation of resistance through molecular immunology. This perspective can help researchers, clinicians, and policymakers understand why resistant infections persist and why future strategies must combine antibiotic innovation, immune-based approaches, molecular surveillance, and responsible antibiotic use.

4. Conclusions

This study concludes that antibiotic resistance is not only a bacterial genetic problem, but also a dynamic biological process shaped by host-pathogen interaction. The thematic synthesis shows that bacterial survival involves efflux pump activation, biofilm formation, intracellular persistence, immune evasion, and adaptation to the host microenvironment. These mechanisms explain why some infections remain difficult to treat even when antibiotics appear active in laboratory testing. The study contributes to the literature by placing molecular immunology as a key perspective for understanding how pathogens survive within immune pressure, tissue conditions, and therapeutic exposure.

Theoretically, this study strengthens the view that antibiotic resistance must be understood through an interaction-based framework that connects bacterial mechanisms with host immune responses. Practically, the findings support the need for stronger diagnostic interpretation, molecular surveillance, antimicrobial stewardship, and clinical awareness of biofilm and intracellular persistence. From a policy perspective, the findings highlight the importance of integrating molecular evidence into antibiotic control programs, especially in settings with fragmented resistance surveillance. Future studies should combine molecular experiments, clinical data, and local health system analysis to provide a deeper understanding of resistant infections in real treatment contexts.

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