Epidemiology & Health Data Insights
(eISSN 3080-8111)

Review Article

Anti-Virulence Therapy as a Low-Resistance Alternative to Conventional Antibiotics: Mechanistic Insights, Evolutionary Considerations, and Translational Prospects

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Received: Mar 04, 2026
Accepted: Apr 07, 2026

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Citation: Olowookere AK, Uwakwe VI, Peteranaba SF. Anti-Virulence Therapy as a Low-Resistance Alternative to Conventional Antibiotics: Mechanistic Insights, Evolutionary Considerations, and Translational Prospects. Epidemiology and Health Data Insights. 2026;2(3):ehdi036. https://doi.org/10.63946/ehdi/18354

ABSTRACT

The growing pace of antimicrobial resistance (AMR) is a serious threat to modern infectious disease control, as it has significantly undermined the clinical value of traditional antibiotics. Traditional antimicrobial agents, which act by preventing the growth of bacteria or causing cell death, place a lot of selection pressure on the microbial population, therefore, promoting the rapid emergence and spread of resistance determinants. Besides spurring the evolution of resistance, such strategies often destabilize commensal microbiota and help transfer resistance genes between different bacteria of various species. These restrictions have shown that there is an urgent need to establish alternative treatment measures capable of reducing infections and reducing evolutionary pressures that promote resistance. Anti-virulence therapy (AVT) has developed as an exciting paradigm that has sought to lay emphasis on the molecular aspects of bacterial pathogenicity, as opposed to microbial viability. AVTs are designed to disrupt virulence-related processes such as quorum sensing, toxin secretion, host adhesion, immune evasion, and nutrient acquisition by selectively interrupting virulence in endotoxin-producing bacteria with the aim of attenuating virulence and promoting host-mediated clearance without necessarily endangering the survival of bacteria. It is theorized that this mechanistic difference will decrease the selective advantage provided to resistant variants, which may retard the tempo of resistance emergence and dissemination in bacterial populations. In this case, we will analyze the mechanistic foundations of bacterial virulence and will compare the existing anti-virulence therapies used as therapeutic approaches and their application in an evolutionary context. We also evaluate the new preclinical and clinical findings under the effectiveness of AVTs, along with the most important translational obstacles in terms of pharmacological optimization, target specificity, and regulatory validation. Together, these observations provide support to anti-virulence interventions as complementary or alternative therapies to conventional antibiotics in the treatment of multidrug-resistant infections, and highlight the necessity of interdisciplinary collaboration in order to support the adoption of such interventions into new-generation antimicrobial treatment programs.

Keywords: Anti-Virulence Therapy; Antimicrobial Resistance; Quorum Sensing; Multidrug-Resistant Pathogens; Biofilm Disruption

Introduction

The Escalating Threat of Antimicrobial Resistance

Antimicrobial resistance (AMR) has become one of the most urgent global issues of the 21st century that compromises decades of achievements in the management of infectious diseases. The rising rates of resistant bacterial infections have been a major contributor to the morbidity and mortality rates of humans across the globe, with millions of deaths attributed to drug-resistant pathogens according to current estimates. In addition to clinical implications, AMR has a high economic cost to the health systems due to its long hospital stay, higher treatment expenses, loss of productivity, and higher complexity of the therapeutic interventions required [1,2].

Worsening this crisis is a sharp decline in the creation of new antibiotics. The innovation pipeline of antibiotics has consistently decreased during the last few decades because of scientific, regulatory, and economic barriers to discovering antimicrobial drugs. The reduced funding in the research of antibiotics by pharmaceutical companies has also been influenced by the inability of the industry to make much money when compared to the returns that are made on drugs that are used in managing chronic illnesses [3]. As a result, the rate of introduction of new antibiotics in clinical practice has not kept up with the emergence and spread of mechanisms of resistance. At the same time, the spread of multidrug-resistant (MDR) bacterial pathogens around the world, such as those resistant to more than one type of antibiotic, has also limited treatment choices [4].

Examples of pathogens that have shown extraordinary adaptability in terms of resistance determinants acquisition due to mutation and horizontal gene transfer include Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli. This intersection of growing resistance rates and a declining pipeline in antibiotic development underscores the necessity of alternative treatment modalities that can reduce the pathogenicity of bacteria without hastening the development of resistance[5,6].

Limitations of Conventional Antibiotic Strategies

The traditional antibiotics are effective through their therapeutic action on killing the bacterial cells (bactericidal agents) or preventing their growth (bacteriostatic agents). Although they are effective in the treatment of acute infections, these methods exert a heavy selection pressure on the bacterial populations, which stimulates the survival and growth of variants resistant to these methods. This Darwinian selection mechanism increases the rate of selection of resistant strains, especially where the mode of administration is suboptimal or where the exposure period is excessive [7]. Besides increasing resistance, the use of broad-spectrum antibiotics may alter the structure and activity of the host microbiota. This dysbiosis has been attributed to predisposition to opportunistic infections, defective immune response, and chronic metabolic and inflammatory conditions. The adverse effect on the healthful microbial communities highlights a significant drawback of the conventional antimicrobial treatments. Moreover, bacteria have the ability to transmit resistance in a very short period of time, and this occurs via horizontal gene transfer, including transformation, transduction, and conjugation. Mobile genetic elements such as plasmids, integrons, and transposons contribute to the dissemination of resistance determinants among various bacterial species, and as such, exacerbate the AMR burden at both clinical and environmental tiers[8,9]. The other major problem is the capability of most pathogens to organize themselves into biofilms, which are microbial communities enclosed in an extracellular matrix produced by the community of cells themselves. The presence of biofilm-related bacteria raises the level of resistance to antibiotics and host immunity, which leads to chronic and device-associated infections. The acquired resistance to antimicrobial agents and the modified metabolic conditions of biofilms frequently make the traditional antibiotic treatment inadequate to eliminate them fully [10].

Conceptual Shift: From Bacterial Killing to Virulence Disarmament

Due to the shortcomings of traditional antimicrobial methods, in a response to this, there has been increased interest in therapeutic action that is focused on bacterial virulence and not on bacterial viability. Anti-virulence therapy (AVT) is described as a treatment that disrupts the molecular pathways that lead to pathogenic infection, such as toxin production, adhesion, evasion of immune responses, quorum sensing, and nutrient uptake systems. The theoretical basis of AVT may be identified as the initial observation that pathogenicity is often dictated by a set of regulatory networks controlling the expression of virulence factors and not by the presence of bacteria in isolation [7,11]. Contrary to the conventional antibiotics, which are designed to reduce the number of bacteria, anti-virulence agents are designed to reduce the pathogenic activity of bacteria, thus making them less efficient in testing infection or inflicting host damage. AVTs may help host immunity to eliminate infections more efficiently with fewer adverse effects on commensal microbiota by maintaining the viability of

bacteria but reducing the pathogenicity of their functions [11]. Notably, the effectiveness of the application of anti-virulence strategies in treatment will probably be determined by the level of infection at the time of therapy, since virulence factor expression is dynamic and the ability of the host immune system to clear viruses is dynamic (Figure 1).

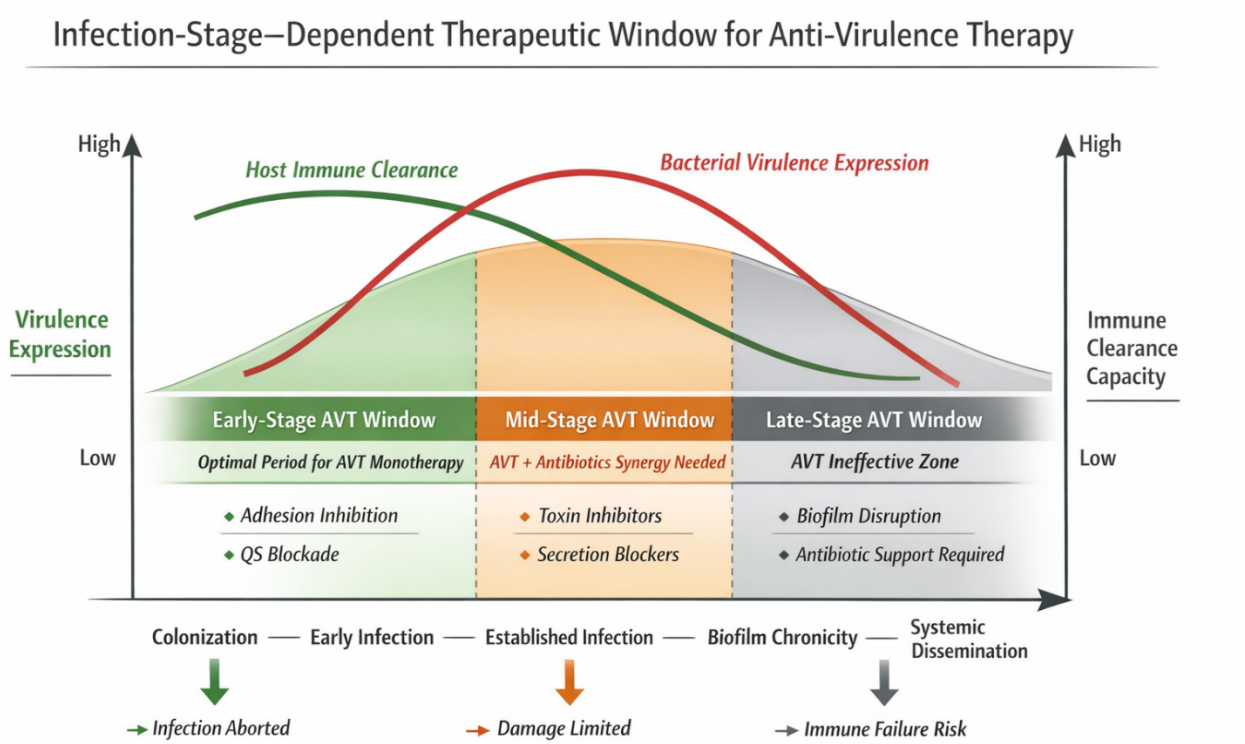

Figure 1. Infection stage–dependent therapeutic window for anti-virulence therapy (AVT).

The effectiveness of anti-virulence therapy depends on the stage of infection and host immune competence. During early infection, when virulence factor expression is low and immune function is robust, AVT may prevent infection establishment. At intermediate stages, targeting toxin activity or secretion systems can reduce host tissue damage, often requiring a combination with antibiotics for optimal efficacy. In advanced infection, characterized by high virulence expression, biofilm formation, or systemic dissemination, reduced immune clearance limits the effectiveness of AVT monotherapy, making combination therapy necessary. This model highlights the importance of treatment timing and host–pathogen dynamics in determining clinical outcomes.

Literature Search and Selection Approach

This review was conducted using a narrative literature approach. Relevant studies were identified through searches of major scientific databases, including PubMed, Scopus, and Web of Science. Keywords such as anti-virulence therapy, antimicrobial resistance, quorum sensing inhibition, biofilm disruption, and bacterial virulence mechanisms were used in various combinations.

Priority was given to recent peer-reviewed articles, including original research studies, systematic reviews, and meta-analyses, particularly those published within the last decade. Seminal earlier studies were also included where necessary to provide foundational context.

Studies were selected based on their relevance to the mechanistic, evolutionary, and translational aspects of anti-virulence strategies. No formal systematic inclusion/exclusion criteria were applied; however, emphasis was placed on studies with clear experimental design, clinical relevance, or significant conceptual contributions to the field.

Mechanistic Basis of Bacterial Virulence

Host–Pathogen Interaction Dynamics

The formation of the bacterial infection is a complex interaction between the host defense mechanisms and the pathogen-derived virulence determinants. To invade host tissues and cause disease, successful pathogens have to cross several barriers to the host immunity, such as physical defense, the innate immune response, and adaptive immune surveillance. It is a series of organized events that usually go through adhesion of microbes to host surfaces, invasion, Immune modulation, and acquisition of necessary nutrients in a hostile host environment [12].

Virulence is not then an intrinsic quality of bacterial presence in itself but is a dynamic result of

host-pathogen interactions, which dictates the degree of tissue destruction and disease progression. Pathogenic bacteria use the highly-regulated genetic programs to detect environmental signals, including host-derived signals, nutrient availability, or population density, and use them to adjust the expression of virulence-associated genes. These adaptive interactions support the survival of organisms in a variety of host niches as well as help pathogens to escape immune clearance and develop chronic infections. Notably, many virulence factors are energetically expensive and are conditionally expressed only in situations of infection, indicating that they are conditional fitness factors but not important determinants of survival. This also offers a mechanistic explanation of why virulence pathways are a good therapeutic target, because disrupting these processes could reduce pathogenicity without causing lethal selection on bacterial populations [13,14].

Major Virulence Determinants

Quorum Sensing Systems

Quorum sensing (QS) is a cell-density-dependent signaling whereby bacterial groups communicate to execute collective actions by synthesizing and sensing diffusible signaling molecules called autoinducers. When the critical concentration level of these signals is attained, QS systems cause transcriptional networks to switch on that involve the regulation of virulence factors such as toxin secretion, motility, and biofilm formation. QS in several clinically significant pathogens is a key factor in coordinating the pathogenic activity, and this results in improved efficiency of infection and resistance against host defenses [15,16].

Toxin Secretion Pathways

Bacterial toxins form one of the biggest groups of virulence factors that damage host cells and modify the immune system. The secretion systems, Type III, Type IV, and Type VI secretion systems, are used by many Gram-negative pathogens to directly transfer effector proteins into the host cells. These effectors may destabilize the cytoskeleton, interfere with intracellular signaling transduction, or trigger apoptosis of host cells, thus providing access to bacterial invasion and evasion of immune response. The toxin secretion systems are usually highly regulated and deployed in response to environmental signals that are encountered during infection [17].

Adhesion Factors

An essential requirement in the colonization and infection is adherence to host tissues. Mechanisms of adhesion in bacteria include surface-associated structures, including pili, fimbriae, and adhesins, that identify and bind to host cell receptors. This adhesiveness makes pathogenic agents resistant to mechanical clearance action, localized site of infection, and a downstream virulence action, such as invasion and biofilm formation. Tissue tropism is often determined by the specificity of adhesion interactions, as well as host range [18].

Immune Evasion Mechanisms

To persist within the host, pathogenic bacteria have evolved diverse strategies to evade or subvert immune responses. These include the production of capsules that inhibit phagocytosis, antigenic variation to avoid immune recognition, and the secretion of factors that neutralize antimicrobial peptides or disrupt complement activation. Some pathogens are also capable of modulating host inflammatory pathways to create a more permissive environment for survival and replication [19].

Nutrient Acquisition Systems

In the host, critical nutrients such as iron are closely contained as a defense mechanism that is referred to as nutritional immunity. In order to avoid this constraint, most bacteria produce iron-chelating molecules with high affinities termed siderophores that steal iron by way of host proteins, including transferrin and lactoferrin. Bacterial metabolism, growth, and virulence in infection, which are often upregulated in response to host-imposed nutrient restriction, all rely on these iron acquisition systems [20].

Biofilm Formation

The ability of bacteria to survive in adverse environments and reduced responsiveness to antimicrobial agents is promoted by biofilm formation, which is a major virulence mechanism. Biofilms are a form of organized microbial community that is entrapped in an extracellular polymeric matrix of polysaccharides, proteins, and nucleic acids. In such structures, bacterial cells are found in distorted metabolic conditions and are less vulnerable to antibiotics and clearance by the immune system [21]. The infections associated with biofilms are usually involved in chronic and device-related infections, which are very difficult to treat.

Anti-Virulence Therapeutic Strategies

Anti-virulence therapeutic measures are aimed at reducing bacterial pathogenicity by directly interfering with infection establishment and progression, specific molecular processes, as opposed to direct impairment of microbial viability. These strategies seek to nullify virulence-associated pathways, augment host-mediated clearance, and mitigate the selective forces that normally mediate

resistance acquisition during conventional antibiotic treatment. Some of the most important virulence targets are good candidates for pharmacological intervention [22].

Quorum-Sensing Inhibitors

Since quorum sensing (QS) is central to the organization of collective pathogenic behaviors, interference with bacterial communication networks has become one of the key anti-virulence strategies. There are several ways through which QS inhibitors can disrupt signal-mediated gene regulation. Signal synthesis inhibitors act on the enzymatic pathways involved in the formation of the autoinducer molecules, thus inhibiting the concentration of the signaling compounds needed to activate virulence in a population. Receptor antagonists, on the contrary, bind to QS receptors competitively to inhibit the recognition of endogenous signalling molecules and effectively silence downstream transcriptional responses even in the presence of autoinducers. Moreover, signal degradation enzymes, including lactonases and acylases, may act on the extracellular environment by enzymatically inactivating QS signaling and preventing intercellular communication and the coordinated expression of virulence factors like toxins and biofilm-forming factors [23].

Toxin Neutralization and Secretion System Inhibition

Most of the pathogenic bacteria use special secretion systems to inject virulence effectors into the host cells. Attacking these systems is one of the potential strategies for attenuating the destruction of the host tissues without influencing the survival of bacteria. Type III and Type IV secretion systems inhibitors can prevent the translocation of the effecter proteins that disrupt the host cell signaling, cytoskeletal stability, and immune responses. The complementary approaches can involve the use of anti-toxin antibodies, or small-molecule inhibitors that have been engineered to be able to neutralize the bacterial toxins or inhibit their binding to host cellular targets [24]. The interventions can limit disease severity by inhibiting host cell injury and inflammatory responses caused by infection by blocking toxin activity at the host/pathogen interface.

Anti-Adhesion Therapies

The initial step in the infection process is the bacterial adhesion to host tissues, enabling colonization and further virulence factor release. Anti-adhesion treatment is associated with inhibiting this mechanism by attacking surface structure features like pili and fimbriae, which confer bacterial attachment. Assemblies or functions of these structures may be inhibited by small molecules or biologics, which in turn decrease adherence in bacteria and decrease colonization efficiency [25].

Another strategy is the application of host receptor analogues that interfere competitively with the adhesins of bacteria, and hence prevent interactions with host cell receptors. These types of decoy molecules may efficiently prevent attachment points as well as induce clearance of pathogens by mechanical or immune-mediated mechanisms [26].

Biofilm Disruption Strategies

Biofilms also provide a great deal of protection against antimicrobial agents and host immune response, which helps in the maintenance of the acute infection. Anti-virulence strategies against biofilm formation are aimed at destabilizing the extracellular polymeric matrix responsible for the structural integrity of these communities. The enzymes and other factors of degrading matrices (DNases, proteases, and other polysaccharide-degrading agents) may interfere with biofilm structure and increase the vulnerability of bacteria to immune clearance or adjunctive antimicrobial therapy. Also, dispersal agents that disrupt biofilm regulatory pathways can cause sessile bacteria to shift into planktonic forms, making them more susceptible to host defenses and traditional therapeutics [27].

Targeting Bacterial Nutritional Virulence

Availability of vital nutrients in the host environment is a decisive factor in the pathogenicity of bacteria. The specific nutritional immunity of iron is the tight sequestration of the element by host proteins. This limitation is circumvented by the production and release of siderophores by many pathogens, which take up the iron supplied by the host. Effective control of bacterial growth and pathogenicity in tissues of the host can be achieved in response to the use of therapeutic methods that involve the inhibition of siderophore biosynthesis or the blockage of iron uptake systems. Anti- virulence agents have the potential to reduce the severity of infection by interfering with the process of nutrient uptake and reducing the selective pressures in bactericidal treatments [28].

Evolutionary Dynamics and Resistance Potential

A central premise of anti-virulence therapy (AVT) is its potential to reduce the emergence of antimicrobial resistance by imposing weaker selective pressure on bacterial populations. Unlike conventional antibiotics, which directly threaten survival or replication, AVTs target conditionally expressed virulence traits. Understanding the evolutionary

consequences of this distinction is essential for assessing their long-term utility [29].

Selective Pressure in Conventional Antibiotic Therapy

Traditional antibiotics impose strong directional selection by targeting essential cellular processes such as cell wall synthesis, protein translation, and nucleic acid replication. Even rare resistant variants gain a significant survival advantage and rapidly expand. This process is further accelerated by suboptimal dosing, prolonged exposure, and widespread use in clinical and agricultural settings [30].

Additionally, bactericidal stress can promote mutagenesis and horizontal gene transfer, facilitating rapid dissemination of resistance across populations and species. As a result, resistance often emerges faster than new antibiotics can be developed [31].

Theoretical Basis for Reduced Resistance in AVTs

The evolutionary rationale for AVTs lies in targeting pathogenic fitness rather than survival.

Survival vs. fitness cost:

Virulence factors are often metabolically costly and expressed only during infection. Inhibiting these traits may impose weaker selection, as resistant mutants do not necessarily gain a survival advantage in the absence of lethal pressure [32].

Public goods theory:

Many virulence factors function as shared resources (e.g., toxins, siderophores). Inhibiting these can create scenarios where resistant individuals incur metabolic costs while still benefiting from susceptible populations, thereby limiting resistance spread [33].

Social evolution of virulence:

Disrupting coordinated behaviors such as quorum sensing can destabilize cooperative dynamics within bacterial populations, potentially constraining resistance emergence [34].

Together, these concepts indicate that resistance evolution under AVTs is governed by the interplay between selective pressure and the fitness costs associated with virulence. Consequently, the likelihood of resistance emergence depends on how treatment-induced selection interacts with the metabolic burden of virulence expression, ultimately shaping the adaptive landscape of bacterial populations (Figure 2).

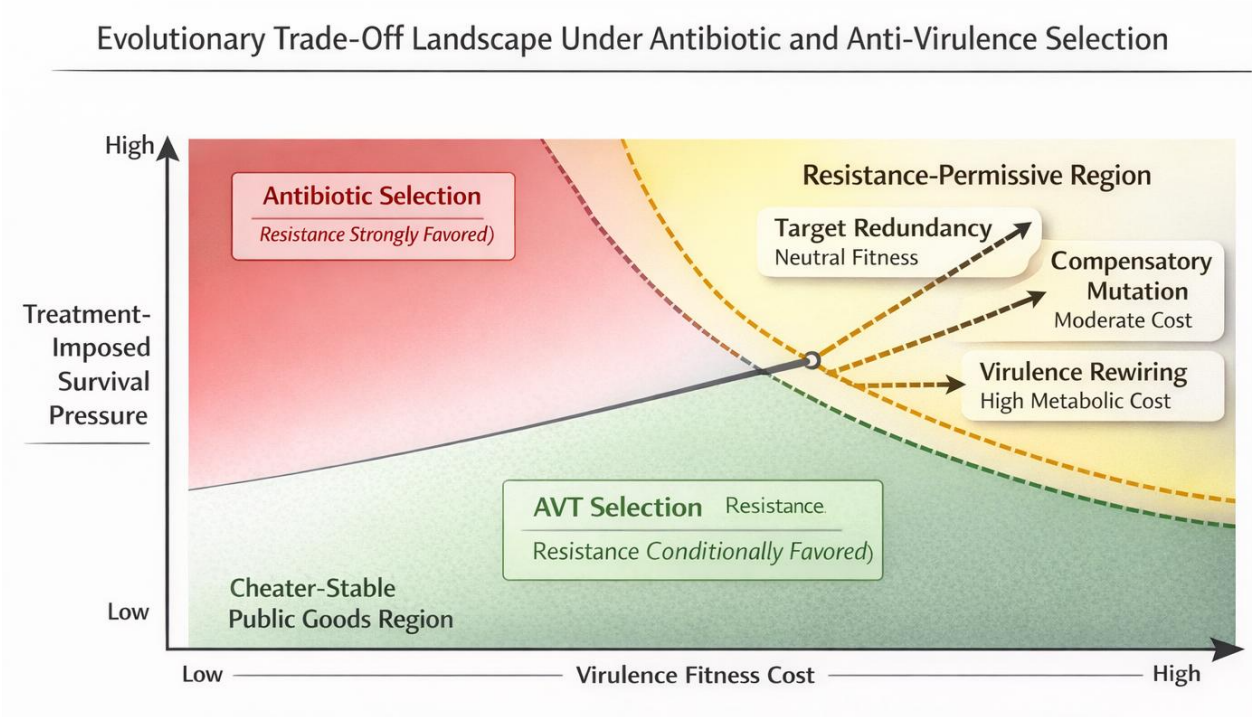

Figure 2. Evolutionary trade-off landscape under antibiotic and anti-virulence selection.

Resistance emergence is governed by the interaction between treatment-imposed selective pressure and the fitness cost of resistance. Conventional antibiotics exert strong directional selection by targeting essential cellular processes, leading to rapid expansion of resistant variants when resistance carries minimal fitness cost. In contrast, anti-virulence therapies (AVTs) impose weaker selection by targeting non-essential pathogenic traits. In this context, resistance may incur higher fitness costs due to compensatory adaptations or pathway rewiring, potentially slowing its spread—particularly in systems where virulence factors function as public goods. However, resistance can still arise when fitness costs are minimized, or alternative pathways restore pathogenicity. This framework illustrates the conditional and context-dependent evolutionary robustness of anti-virulence strategies.

Empirical Evidence

Experimental studies indicate that targeting virulence pathways (e.g., quorum sensing or siderophore production) can reduce pathogenicity without strongly selecting for resistance in the short term[33,35]. Compared to conventional antibiotics, resistance tends to emerge more slowly and often requires more complex adaptations.

However, these outcomes are context-dependent, varying with the specific target and ecological environment. AVTs may delay but not entirely prevent resistance evolution [36].

While theoretical models consistently predict reduced selection for resistance under anti-virulence therapies, empirical findings remain context-dependent. Some studies report delayed resistance emergence in quorum-sensing and siderophore-targeting systems, whereas others demonstrate that resistance can still arise through compensatory mutations or pathway redundancy. These discrepancies suggest that the evolutionary robustness of AVTs is not universal but varies according to the specific virulence target, pathogen ecology, and infection environment. Notably, targets involving public goods appear more resilient to resistance than those linked to private or essential functions, highlighting the importance of target selection in therapeutic design

Potential Resistance Pathways Against AVTs

Despite their advantages, AVTs are not evolutionarily immune to resistance. Potential mechanisms include:

- Target redundancy: Alternative virulence pathways may compensate for inhibited functions.
- Compensatory mutations: Genetic adaptations may restore fitness under therapeutic pressure.
- Pathway rewiring: Regulatory changes may bypass inhibited mechanisms or activate alternative strategies.

These possibilities highlight the importance of combination therapies and continued evolutionary monitoring to sustain AVT effectiveness [37].

Importantly, these resistance mechanisms differ in both likelihood and evolutionary cost compared to classical antibiotic resistance. Whereas antibiotic resistance often arises rapidly through well-characterized genetic pathways, resistance to AVTs may require more complex adaptations involving regulatory or metabolic trade-offs. However, evidence from experimental systems indicates that such adaptations can still occur under sustained selective pressure, underscoring that AVTs are not inherently "evolution-proof" but instead exhibit a context-dependent resistance profile [29].

Host Immune System as a Therapeutic Ally

The main characteristic of anti-virulence therapy (AVT) is that it is based on host immune mechanisms to induce effective pathogen clearance after attenuation of bacterial pathogenicity. AVTs can potentially sensitize bacterial populations more to host defense systems by selective interference with virulence determinants that mediate immune evasion, tissue invasion, or toxin-mediated damage, but do not require direct microbial elimination [27,38]. A major effect of virulence inhibition is the immune sensitization effect of AVT, in which blockage of bacterial defenses, i.e., capsule formation, secretion systems, or quorum-sensing-controlled defenses, can promote immune cell recognition and elimination. In this regard, AVTs can lay bare hitherto latent pathogen-associated molecular patterns (PAMPs) and, as such, promote phagocytosis and subsequently activate the immune response. Moreover, AVTs can be synergistic with the elements of innate immune response, such as neutrophils, macrophages, and antimicrobial peptides [39]. Anti-virulence agents have the ability to enhance the power of innate immune clearance mechanisms by down-regulating the expression of factors that suppress phagocytic uptake or disrupt immune signaling pathways. This collaborative working can be especially useful in infections with biofilm formation or local immunosuppression. Nevertheless, host immune status is likely to determine the efficacy of AVT. Therapeutic response in immunocompromised persons might be inhibited by the weakened immune system's ability to destroy attenuated pathogens, thus decreasing the immune system's power. The given consideration highlights the necessity of patient stratification and indicates that AVTs would be the most effective in use in groups with compromised immunity that could be combined with adjunctive antimicrobial or immunomodulatory therapy [40].

Combination Therapy Approaches

Anti-virulence agents are especially applicable to be used together with the current antimicrobial or immunotherapeutic interventions due to their non-lethal mode of action. The strategies could improve the effectiveness of the treatment and reduce the forces of evolution that promote the development of resistance.

AVT–Antibiotic Synergy

AVTs can be used in combination with traditional antibiotics, whereby the effect on bacterial viability and pathogenicity will have a positive effect on

the therapeutic outcome. Virulence pathways inhibition can make bacteria more susceptible to antibiotics by interfering with protective mechanisms, e.g., biofilm formation or efflux-mediated defense mechanisms. On the other hand, sublethal exposure to antibiotics could increase the effects of AVTs by undermining the bacteria's stress responses, and this will help in immune-mediated clearance. Such synergies can help reduce the dose and reduce the toxicity of antibiotics [41].

AVT with Immunotherapy

The combination of AVTs with immunotherapeutic regimens such as monoclonal antibodies or immune stimulators is another potential therapy that is promising to manage infections. AVTs have the potential to augment the effectiveness of host-directed therapies that target the augmentation of antimicrobial immunity by blocking virulence factors that obstruct immune recognition or inflammatory signaling [42].

Impact on Biofilm-Associated Infections

Infections related to biofilms are also infamously resistant to the effects of antibiotics since there is decreased drug penetration and a change in bacterial physiology. Anti- virulence intervention based on biofilm regulatory pathways or components of the extracellular matrix can destabilize these structures and thus increase the efficacy of adjunctive antibiotics and the immune system. In this regard, combination therapy might help to clear complicated infections with the help of implanted medical devices or chronic wounds [10].

Resistance-Suppressive Treatment Models

Evolutionary, combination regimens involving the use of AVTs might mitigate the risk of the development of resistance because the selective forces are spread on various bacterial targets. The resistance-suppressive models of treatment suggest that co-inhibition of virulence and fundamental cellular capabilities has the potential to restrict the adaptive responses to which the bacterial populations can adapt, and hence, this is likely to extend the therapeutic effect. These strategies imply the prospect of AVT-based combination therapy as one of the integrated antimicrobial stewardship strategies [43,44].

Preclinical and Clinical Progress

Advances in molecular microbiology and drug discovery have accelerated the development of anti-virulence therapies (AVTs) toward clinical application. Although most candidates remain in early stages, growing preclinical and translational evidence supports their therapeutic potential [41].

In Vitro and Animal Model Studies

In vitro studies consistently demonstrate that targeting virulence pathways—such as quorum sensing, toxin secretion, adhesion, and biofilm formation—reduces pathogenicity without significantly affecting bacterial growth.

In animal models of infection, AVT candidates have been shown to:

- reduce bacterial burden
- limit host tissue damage
- improve survival outcomes

These findings suggest that virulence attenuation enhances host immune clearance, even in the absence of bactericidal activity. Some studies also report reduced selection for resistance compared to conventional antibiotics, although long-term effects remain to be fully established [39]

Despite encouraging findings, results across preclinical models are not entirely consistent. While many studies demonstrate reduced virulence and improved host outcomes, the magnitude of these effects varies depending on pathogen species, infection model, and targeted virulence mechanism. In some cases, attenuation of virulence does not translate into significant reductions in bacterial burden, raising questions about the reliability of AVTs as standalone therapies. These inconsistencies highlight the need for standardized models and comparative studies to better evaluate therapeutic efficacy [14,40].

Clinical Trials and Candidate Molecules

Several AVT candidates have entered early-stage clinical evaluation, including:

- quorum-sensing inhibitors
- anti-toxin monoclonal antibodies
- small-molecule inhibitors targeting secretion systems and adhesion factors

Preliminary results indicate acceptable safety and tolerability, with signals of therapeutic benefit in selected patient populations. In many cases, AVTs are being explored as adjuncts to antibiotics to enhance treatment efficacy and reduce complications.

Although definitive clinical validation is still pending, ongoing trials are expected to clarify their role in managing multidrug-resistant infections [45].

Additionally, the clinical evidence base remains limited, and most studies are restricted to early-phase trials with small cohorts. While safety profiles are generally favorable, clear demonstrations of clinical superiority or equivalence to standard therapies are still lacking. This gap underscores the need for larger, well-controlled trials that assess not only safety but also long-term outcomes, resistance dynamics, and effectiveness across diverse patient populations.

Translational Barriers

Despite promising progress, several challenges remain:

- **Pharmacokinetics:** Achieving sufficient tissue concentrations may be difficult due to the non-lethal mechanism of action, which often requires sustained target engagement.
- **Target specificity:** Many virulence determinants are species- or strain-specific, limiting broad applicability and necessitating accurate pathogen identification.
- **Regulatory challenges:** The absence of traditional endpoints (e.g., bacterial killing) complicates clinical trial design, requiring alternative measures such as reduced disease severity or enhanced immune clearance.

Implications for Microbiome Preservation

Taken together, current evidence suggests that the effectiveness of anti-virulence therapies emerges from the interplay between pathogen biology, host immune competence, and evolutionary dynamics. Rather than functioning as direct substitutes for antibiotics, AVTs are better conceptualized as components of integrated therapeutic strategies, where their value lies in modulating pathogenicity, enhancing immune clearance, and reducing selective pressures that drive resistance [5].

Among the benefits of anti-virulence therapy that can be expected is the fact that the integrity of the host microbiome can be preserved. The AVTs are also selective to pathogenic mechanisms, as opposed to broad-spectrum antibiotics that typically disrupt commensal microbial populations, thereby having no effect on bacterial viability in general.

Reduced Dysbiosis

AVTs can prevent opportunistic infections and immune dysregulation, potentially caused by the excessive presence of negative microbiota, by lowering the prevalence of dysbiosis-related complications.

Ecological Advantages

Microbial community structure can be maintained to aid colonization resistance to pathogenic organisms, which can lead to host resilience to repeat infection

Infection Recurrence Risk

Microbiome balance can also help decrease the risk of recurrence of infection by eliminating the ecological niches that frequently emerge after the destruction of microbes due to the use of antibiotics.

Challenges and Limitations

Although anti-virulence therapies (AVTs) have therapeutic potential, numerous conceptual and practical constraints have the potential to impact their clinical feasibility and efficacy in a variety of patient groups and settings of infection

Pathogen Specificity

Numerous virulence determinants are very well preserved by isolated species but differ considerably between bacterial taxa. Consequently, AVTs tend to have a narrow-spectrum activity, which requires accurate diagnosis of the causative pathogen before the establishment of treatment. This narrowness may restrict its use in empirical work in acute clinical environments where the rapidity of intervention is needed.

Therapeutic Timing

The success of AVTs can be dependent on the time of infection when it is conducted. The effect of interventions aiming at inhibiting early stages in colonization or virulence-activating mechanisms could be less effective when the infection has already reached more advanced phases of infection, featuring extensive tissue damage or systemic spread

Immune Dependence

Since pathogenicity is neutralized with AVTs, without the direct elimination of bacteria, the success rate of AVTs depends on the ability of the host immune system to eliminate the infection. In immunocompromised patients, the competence of the immune response is low, and, therefore, virulence-targeting strategies cannot be as effective as monotherapy in these patients. It can be thus expected that the clinical relevance of anti-virulence therapy will be different based on host immune competence as well as based on the ecological circumstances of an infection [46]. Such parameter-based stratification of the therapeutic deployment can enhance the success of the treatment regardless of the risk of resistance development that follows the failure to clear the pathogen (Table 1).

Table 1. Clinical Suitability Matrix for Anti-Virulence Therapy Based on Host Immune Status and Infection Ecology

Infection Context	Host Immune Status	Pathogen Virulence Dependence	AVT Monotherapy Suitability	Combination Therapy Requirement	Predicted Resistance Risk
Acute localized infection	Immunocompetent	High	✓ Recommended	Low	Low
Early-stage colonization	Immunocompetent	Moderate	✓ Recommended	Low	Low
Chronic biofilm infection	Immunocompetent	High	⚠ Adjunct only	Moderate	Moderate
Device-associated infection	Immunocompetent	High	⚠ Adjunct only	High	Moderate
Acute systemic infection (Sepsis)	Immunocompetent	Variable	✗ Not suitable	High	High
Localized infection	Immunocompromised	High	⚠ Adjunct only	High	Moderate
Chronic infection	Immunocompromised	Moderate	✗ Not suitable	High	High
Recurrent MDR infection	Immunocompetent	High	⚠ Adjunct only	Moderate	Low–Moderate

Table Footnote: *AVT: Anti-virulence therapy; MDR: Multidrug-resistant.* ✓ *Recommended = suitable for AVT monotherapy;* ⚠ *Adjunct only = AVT should be used in combination with conventional antibiotic therapy;* ✗ *Not suitable = AVT monotherapy unlikely to achieve adequate pathogen clearance.*

Diagnostic Requirements

Effective deployment of AVTs may require rapid and accurate diagnostic tools capable of identifying both the infecting organism and relevant virulence traits. The integration of such diagnostics into routine clinical practice remains a logistical and economic challenge in many healthcare settings [47].

Future Directions

Several critical knowledge gaps remain in the development of anti-virulence therapies. First, the long-term evolutionary dynamics of resistance under clinical conditions are poorly understood. Second, there is limited insight into how host immune variability influences therapeutic outcomes. Third, the lack of standardized biomarkers for measuring virulence inhibition complicates clinical evaluation. Finally, the extent to which AVTs can be generalized across pathogens versus requiring highly specific targeting remains unresolved. Addressing these gaps will be essential for translating AVTs into reliable clinical interventions [1,29].

It is anticipated that the future of anti-virulence therapeutics will be initiated by further developments in molecular biology, computational modeling, and systems microbiology.

AI-Guided Virulence Target Discovery

Methods that utilize machine learning can be used to enable the identification of new virulence determinants and regulatory networks that can be targeted pharmacologically. By synthesizing the data of genomic, transcriptomic, and proteomic information, predictive analysis of the behavior of pathogens and therapeutic susceptibility may become possible.

Broad-Spectrum AVTs

The use of agents that attack conserved virulence pathways expressed by multiple pathogens could increase the usefulness of AVTs and improve their applicability in empirical treatment approaches.

Personalized Anti-Virulence Therapeutics

Individualized treatment using strategies based on pathogen genotyping and host immune profiling is a form of precision medicine that can be used to maximize the efficacy and minimize adverse effects of treatment.

Integration into Antimicrobial Stewardship Programs

The integration of the use of AVTs into antimicrobial stewardship can decrease the use of traditional antibiotics, thus reducing resistance development and lowering the impact on the effectiveness of the available antimicrobial agents [48].

Conclusion

Anti-virulence therapy can be seen as an alternative new paradigm to the old antimicrobial approaches to bacterial infections, which are based on direct elimination. AVTs can reduce the severity of the disease without reducing the survival of the bacteria, as they can target the molecular pathways that are associated with pathogenicity, diminishing the selection pressures that cause resistance evolution.

Anti-virulence interventions can be used together with the current therapies and augment the outcome of treatment in the case of infections by multidrug-resistant pathogens as a part of the next-generation antimicrobial approaches. Nonetheless, to achieve the optimal clinical role of AVTs, a more interdisciplinary approach, which entails microbiology, immunology, pharmacology, and bioengineering, will be necessary to resolve the problem of translation and provide strong chances of effectiveness in a variety of clinical settings.

Acknowledgements

Acknowledgements: The authors would like to acknowledge the contributions of colleagues and institutions that supported the conceptual development of this review. No external technical assistance was received for manuscript preparation.

Author Contributions: Adepeju Kafayat Olowookere conceptualized the study, supervised the overall structure, and contributed to critical revisions. Victoria Ifeyinwa Uwakwe conducted the literature review and contributed to drafting key sections of the manuscript. Sylviastella Favour Peteranaba contributed to data synthesis, writing, and editing of the manuscript. All authors reviewed and approved the final version of the manuscript.

Disclosures: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Funding: This research received no external funding.

Disclosure of AI Use: The authors used artificial intelligence tools (e.g., language models) to assist with language refinement, organization of content, and editing for clarity. All scientific content, interpretation, and conclusions were independently developed and verified by the authors.

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