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(REVIEW ARTICLE)

MOLECULAR DETERMINANTS OF ANTIMICROBIAL RESISTANCE AND VIRULENCE IN CLINICAL PSEUDOMONAS AERUGINOSA ISOLATES IN NIGERIA

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ABSTRACT

Pseudomonas aeruginosa remains one of the leading causes of healthcare-associated infections and is recognized for its remarkable ability to acquire antimicrobial resistance while maintaining multiple virulence traits that contribute to persistent and difficult-to-treat infections. In Nigeria, increasing reports of multidrug-resistant (MDR) and carbapenem-resistant *P. aeruginosa* from tertiary healthcare facilities have raised significant concerns regarding treatment outcomes and infection control. This review synthesizes current evidence on the molecular determinants of antimicrobial resistance and virulence among clinical *P. aeruginosa* isolates in Nigeria, with emphasis on epidemiology, resistance patterns, resistance genes, virulence determinants, and existing knowledge gaps. Relevant literature published between 2021 and 2025 was retrieved from PubMed, Scopus, Web of Science, Google Scholar, and African Journals Online (AJOL). Available evidence indicates increasing resistance to β-lactams, fluoroquinolones, aminoglycosides, and carbapenems, driven by intrinsic, acquired, and adaptive resistance mechanisms, including carbapenemase genes, efflux pump overexpression, AmpC hyperproduction, and OprD porin alterations. Virulence determinants, particularly biofilm formation, quorum-sensing systems, and genes such as **lasB**, **toxA**, **exoS**, and **exoU**, remain widely distributed and frequently coexist with antimicrobial resistance determinants, enhancing bacterial persistence and pathogenic potential. However, molecular epidemiological data remain fragmented, with most studies originating from a limited number of tertiary hospitals and few incorporating whole-genome sequencing or comprehensive genomic surveillance. Strengthening nationwide molecular surveillance, integrating genomic epidemiology into antimicrobial resistance monitoring, standardizing laboratory methodologies, and reinforcing antimicrobial stewardship programmes are essential for improving patient management, guiding empirical therapy, and limiting the dissemination of high-risk *P. aeruginosa* clones in Nigeria.

Keywords: *Pseudomonas aeruginosa*, Antimicrobial resistance, Virulence factors, Molecular epidemiology, Clinical isolates, Healthcare-associated infections, Nigeria.

1 INTRODUCTION

Pseudomonas aeruginosa is a common aerobic, non-fermenting, Gram-negative bacillus and one of the most important opportunistic pathogens in hospital settings globally. Its extraordinary metabolic adaptability allows it to flourish in soil, water, medical equipment, disinfectants, and hospital surfaces, and its ability to colonize damp environments and endure nutrient-limited conditions facilitates transmission within healthcare institutions, especially among critically ill and immunocompromised patients (Qin *et al*., 2022). *P. aeruginosa* is one of the ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*), a group of Gram-negative pathogens accounting for a significant proportion of multidrug-resistant hospital infections worldwide, reflecting its capacity to evade antimicrobial therapy through inherent resistance, adaptive responses, and acquisition of mobile resistance determinants. Consequently, *P. aeruginosa* infections are linked to longer hospital stays, higher costs, treatment failure, and higher morbidity and mortality (Nabeshima *et al*., 2026).

The organism's pathogenic success stems from a wide range of virulence factors that facilitate colonization, tissue invasion, immune evasion, and persistence within the host. Flagella, type IV pili, and non-pilus adhesins promote initial attachment, motility, and biofilm development, while extracellular factors such as exotoxin A, elastase (LasB), alkaline protease, phospholipases, pyocyanin, rhamnolipids, and hydrogen cyanide contribute to tissue damage, immune dysregulation, and bacterial dissemination. Production of many of these factors is coordinated by sophisticated quorum-sensing networks that synchronize virulence gene expression according to cell density (Liao *et al*., 2022).

Biofilm formation structured microbial communities embedded in a self-produced extracellular polymeric matrix is another defining trait of *P. aeruginosa*. Biofilms protect bacterial cells from host immune responses, desiccation, disinfectants, and antimicrobials, making biofilm-associated infections notoriously difficult to eradicate. Clinically, biofilms commonly develop on medical devices, chronic wounds, respiratory epithelium, and urinary catheters, contributing significantly to chronic healthcare-associated infections and therapeutic failure (Tuon *et al*., 2022). Highly sophisticated regulatory networks, including numerous transcriptional regulators and two-component systems, further allow *P. aeruginosa* to rapidly sense and adapt to host environments, antimicrobial exposure, oxidative stress, and nutrient limitation, contributing to both survival and the evolution of resistance and persistence during chronic infection.

In response to this growing clinical burden, research has progressively shifted from conventional susceptibility testing toward molecular characterization of resistance determinants, virulence genes, and genomic epidemiology. Understanding the molecular basis of pathogenicity and resistance is essential for improving diagnostics, guiding antimicrobial stewardship, strengthening infection prevention and control, and informing novel therapeutic strategies. In Nigeria, where molecular surveillance remains limited and published data are geographically fragmented, synthesizing current evidence is particularly important for informing national AMR surveillance and evidence-based clinical practice (Qin *et al*., 2022). Accordingly, this review aims to critically synthesize current evidence on the molecular determinants of antimicrobial resistance and virulence among clinical *P. aeruginosa* isolates in Nigeria.

1.1 Burden of Healthcare-Associated Infections in Nigeria

Healthcare-associated infections (HAIs), or nosocomial infections, are infections acquired during healthcare that were neither present nor incubating at admission, and remain a leading cause of preventable morbidity, mortality, prolonged hospitalization, and increased healthcare expenditure worldwide (Abban *et al*., 2023). Nigeria bears a substantial HAI burden owing to its large, expanding population, increasing demand for tertiary care, limited healthcare resources, and variable implementation of infection prevention measures. National estimates were historically scarce because most studies were single-centre investigations using different diagnostic criteria, leaving the true national burden unclear. However, a recent systematic review and meta-analysis of 16 Nigerian studies involving more than 86,000 hospitalized patients estimated a pooled HAI prevalence of approximately 15.8%, confirming HAIs as a significant public health challenge, with urinary tract infections the most common, followed by surgical site infections and skin and soft tissue infections (Onwuliri *et al*., 2025).

The clinical significance of *P. aeruginosa* within Nigerian healthcare facilities extends beyond its frequency of isolation. Its intrinsic resistance to multiple antimicrobials, efficient biofilm formation, metabolic adaptability, and capacity to acquire further resistance determinants through horizontal gene transfer and chromosomal mutation favour successful colonization and persistence in hospital environments. Consequently, *P. aeruginosa* infections are frequently associated with prolonged hospitalization, delayed recovery, increased costs, and higher mortality, particularly among critically ill patients characteristics that have positioned it among the WHO priority pathogens requiring urgent surveillance and new therapeutics (Abban *et al*., 2023).

Recent Nigerian molecular investigations indicate an evolving epidemiology alongside the emergence of multidrug-resistant and highly virulent strains. Studies from Lagos have identified isolates carrying multiple virulence genes alongside multidrug-resistant phenotypes, suggesting resistance and pathogenicity increasingly coexist within circulating strains, while genomic surveillance has reported a high incidence of carbapenemase-producing isolates in tertiary institutions, underscoring the growing threat of carbapenem-resistant infections, for which therapeutic options remain limited and often necessitate last-line agents such as polymyxins (Adenipekun *et al*., 2023).

Despite growing recognition of HAIs as a major public health problem, significant knowledge gaps remain. Most published studies originate from tertiary hospitals in a limited number of states, while secondary and primary facilities are underrepresented, and differences in diagnostic methods, case definitions, susceptibility testing protocols, and molecular techniques complicate cross-study comparison. Relatively few investigations incorporate molecular analyses of resistance genes, virulence determinants, or genomic epidemiology, limiting understanding of the mechanisms driving pathogen dissemination within Nigerian hospitals. The recent national systematic review likewise highlighted the scarcity of data on multidrug-resistant HAIs and called for more robust, integrated surveillance systems (Onwuliri *et al*., 2025).

1.2 Emergence of Antimicrobial Resistance and Virulence

The rapid emergence of antimicrobial resistance (AMR) in *P. aeruginosa* is one of the greatest challenges confronting clinical microbiology and infectious disease management today. The organism survives antimicrobial pressure through a combination of intrinsic, acquired, and adaptive mechanisms, making it one of the most difficult Gram-negative pathogens to treat. Unlike many bacteria that depend primarily on acquired resistance genes, *P. aeruginosa* possesses innate characteristics low outer membrane permeability, inducible chromosomal AmpC β-lactamase production, multidrug efflux pumps, and biofilm formation that collectively reduce susceptibility to numerous agents and provide a foundation on which additional acquired determinants accumulate, leading to multidrug-resistant (MDR), extensively drug-resistant (XDR), and carbapenem-resistant (CRPA) strains (Qin *et al*., 2022; Langendonk *et al*., 2021).

Widespread antibiotic use and misuse in hospital and community settings has accelerated the evolution of resistant *P. aeruginosa* populations, as prolonged or inappropriate therapy exerts selective pressure favoring resistant clones. In Nigeria, unrestricted antibiotic access, empirical treatment without microbiological confirmation, inadequate antimicrobial stewardship, and limited routine susceptibility testing compounded by overcrowded hospitals and inconsistent infection prevention practices have further driven the increasing prevalence of resistant *P. aeruginosa* (Akinduti *et al*., 2023). Molecular characterization of multidrug-resistant isolates from southeastern Nigeria revealed high-frequency resistance to multiple antibiotic classes and confirmed clinically important resistance determinants among isolates from wound, urine, sputum, ear, and high vaginal swab specimens, leading the authors to emphasize the need for continuous molecular surveillance (Agbo *et al*., 2023).

Similarly, Lagos-based studies have demonstrated alarming multidrug resistance, with Adenipekun and colleagues reporting resistance in more than four-fifths of isolates and extensive resistance to several β-lactams, including cephalosporins and meropenem. Molecular analysis confirmed multiple virulence genes among these multidrug-resistant isolates, highlighting the coexistence of resistance and pathogenicity and prompting calls for simultaneous surveillance of resistance and virulence markers within infection prevention and stewardship programmes (Adenipekun *et al*., 2023).

Despite this growing molecular evidence, important gaps remain. Most Nigerian studies are limited to single institutions, small sample sizes, and selected regions, making nationwide comparison difficult, while whole-genome sequencing, multilocus sequence typing, and comprehensive genomic surveillance remain uncommon owing to financial and technical constraints. Consequently, little is known about the national distribution of high-risk clones, the evolution of resistance genes, and the relationship between genomic diversity and clinical outcomes. Addressing these gaps will require coordinated national surveillance integrating phenotypic testing with advanced molecular epidemiology to strengthen stewardship, improve infection control, and support evidence-based management of MDR *P. aeruginosa* in Nigeria (Agbo *et al*., 2023).

1.3 Rationale and Objectives of the Review

The increasing prevalence of antimicrobial-resistant *P. aeruginosa* is a major concern for clinicians, microbiologists, and public health authorities worldwide because of its association with severe healthcare-associated infections, limited therapeutic options, and poor outcomes. In Nigeria, *P. aeruginosa* remains among the most frequently isolated Gram-negative pathogens from clinical specimens, including wound swabs, urine, blood, respiratory secretions, and burn wounds. Over the past decade, numerous studies have documented increasing resistance to commonly used agents alongside the emergence of MDR and carbapenem-resistant isolates, and more recent molecular investigations have demonstrated carbapenemase genes, extended-spectrum β-lactamases, efflux-mediated resistance, and virulence-

associated genes, indicating that resistant isolates often possess enhanced pathogenic potential (Qin *et al*., 2022; Agbo *et al*., 2023; Akinduti *et al*., 2023).

Despite these advances, evidence in Nigeria remains fragmented and geographically uneven. Most published studies are institution-based and originate from a limited number of tertiary facilities, while several regions remain underrepresented, and considerable heterogeneity in study design, sample size, specimen types, and testing methods complicates direct comparison and limits a comprehensive national understanding. Relatively few investigations have explored the relationship between resistance mechanisms and virulence determinants or their implications for clinical outcomes and infection prevention (Agbo *et al*., 2023; Onwuliri *et al*., 2025).

Accordingly, this review aims to critically synthesize current evidence on the molecular determinants of antimicrobial resistance and virulence among clinical *P. aeruginosa* isolates in Nigeria. Specifically, it reviews the epidemiology of clinical isolates, summarizes the major molecular mechanisms of resistance and virulence, examines the distribution of resistance and virulence genes reported across Nigerian healthcare facilities, discusses clinical and public health implications, identifies existing research gaps, and proposes future directions for molecular surveillance, antimicrobial stewardship, and infection prevention and control.

1.4 Review Methodology

This review adopted a narrative synthesis approach to summarise the molecular determinants of antimicrobial resistance and virulence among clinical *P. aeruginosa* isolates in Nigeria. A structured literature search was conducted across PubMed, Scopus, Web of Science, Google Scholar, and African Journals Online (AJOL) for studies published between 2021 and 2025. Search terms combined "*Pseudomonas aeruginosa*" with "antimicrobial resistance," "virulence," "molecular epidemiology," "resistance genes," "biofilm," and "Nigeria," using Boolean operators to broaden or narrow retrieval as appropriate.

Studies were eligible if they reported phenotypic or molecular data on antimicrobial resistance and virulence determinants among clinical *P. aeruginosa* isolates from Nigerian healthcare facilities. Review articles, conference abstracts without accompanying full data, and studies conducted outside Nigeria were excluded unless cited for global or mechanistic context. Titles and abstracts were screened for relevance, followed by full-text assessment of eligible articles. Given the narrative rather than systematic design, no formal risk-of-bias or quality appraisal tool was applied; priority was nonetheless given to peer-reviewed, molecularly characterised studies to ensure reliability.

2 EPIDEMIOLOGY OF CLINICAL *PSEUDOMONAS AERUGINOSA* IN NIGERIA

P. aeruginosa remains one of the most important opportunistic bacterial pathogens responsible for HAIs in Nigeria. Over the past decade it has been consistently isolated from patients in tertiary healthcare facilities nationwide, contributing significantly to wound infections, urinary tract infections, bloodstream infections, lower respiratory tract infections, burn wound infections, and other nosocomial infections. Its increasing recovery from diverse clinical specimens, coupled with the emergence of MDR and carbapenem-resistant strains, underscores its growing clinical and public health significance in Nigeria (Qin *et al*., 2022; Olalekan *et al*., 2023).

2.1 Distribution of Clinical *Pseudomonas aeruginosa* Across Nigeria

P. aeruginosa is widely recognized as one of the leading opportunistic Gram-negative pathogens implicated in HAIs in Nigeria. Although the true national burden remains uncertain owing to the absence of coordinated nationwide surveillance, published evidence indicates the organism is widely distributed across tertiary institutions in all major geopolitical regions where microbiological investigations have been undertaken. Most available data originate from tertiary hospitals in Lagos, Ogun, Oyo, Enugu, Ebonyi, Rivers, Kano, and the Federal Capital Territory, reflecting the concentration of diagnostic and molecular microbiology facilities rather than the pathogen's actual geographical distribution; the epidemiology is therefore likely underestimated, particularly in secondary facilities and rural settings with limited laboratory capacity (Olalekan *et al*., 2023).

Studies from south-western Nigeria consistently report *P. aeruginosa* among the predominant Gram-negative pathogens recovered from hospitalized patients. Molecular investigations from Lagos have identified a high prevalence of MDR and carbapenem-resistant isolates carrying resistance genes including blaVIM, blaNDM, and blaGES, together with virulence determinants such as lasB, toxA, and exoS. Whole-genome sequencing has further demonstrated circulation of internationally recognized high-risk clones and dissemination of carbapenem resistance through both clonal expansion and horizontal gene transfer, emphasizing the pathogen's growing public health significance (Olalekan *et al*., 2023).

Similarly, studies from south-eastern Nigeria have documented widespread recovery of MDR isolates from diverse specimens, including wound swabs, urine, sputum, ear swabs, and catheter-associated samples, with molecular characterization confirming resistance determinants associated with β-lactam resistance, carbapenem resistance, and multidrug efflux, indicating resistant clones are no longer confined to a single region. Comparable reports from Ogun State have demonstrated integrons, metallo-β-lactamase genes, and plasmid-mediated resistance, suggesting ongoing dissemination of mobile genetic elements (Adeyelu *et al*., 2024).

Despite increasing reports from southern Nigeria, molecular epidemiological data from northern Nigeria remain comparatively scarce, with most northern studies focused on phenotypic susceptibility testing and relatively few incorporating PCR, multilocus sequence typing (MLST), or whole-genome sequencing (WGS). This geographical disparity highlights an important knowledge gap and underscores the need for coordinated national surveillance generating representative data across all six geopolitical zones.

2.2 Distribution among Clinical Specimens

The epidemiology of *P. aeruginosa* in Nigeria varies by specimen type and clinical condition. Wound specimens consistently represent the predominant source across most Nigerian studies, accounting for the largest proportion of recoveries from surgical wounds, traumatic injuries, diabetic foot ulcers, pressure ulcers, and burn wounds. In a multicentre genomic investigation across three tertiary hospitals in Lagos, more than 70% of isolates originated from wound specimens, similarly reflected in findings from Enugu and other centres (Olalekan *et al*., 2023).

The predominance of wound isolates largely reflects the organism's ability to colonize damaged tissue, survive under nutrient-limited conditions, and produce robust biofilms that protect bacterial communities from host immune responses and antimicrobials. Secretion of extracellular factors including elastase, exotoxin A, phospholipases, pyocyanin, and proteases further facilitates tissue destruction and persistence, explaining the organism's frequent involvement in chronic wound infections and delayed healing (Adenipekun *et al*., 2023).

Additional specimens yielding *P. aeruginosa* include ear swabs, eye swabs, catheter tips, cerebrospinal fluid, abscess aspirates, pleural fluid, and other sterile body fluids. Although contributing fewer isolates, these specimen types demonstrate the organism's remarkable ecological adaptability and its capacity to exploit both localized tissue damage and systemic host immune dysfunction.

2.3 Healthcare Settings and Patient Populations

The epidemiology of *P. aeruginosa* is closely linked to healthcare delivery, with most infections occurring in tertiary hospitals where critically ill patients undergo invasive procedures. Intensive care units, surgical wards, burn centers, neonatal intensive care units, oncology units, renal dialysis centers, and transplant units consistently report higher infection frequencies because these environments combine prolonged hospitalization, extensive antimicrobial exposure, invasive devices, and immunocompromised patients. Environmental reservoirs, including sinks, humidifiers, ventilator circuits, endoscopes, disinfectant containers, and hospital water systems, also contribute to nosocomial transmission when infection prevention and control practices are inadequate (Olalekan *et al*., 2023).

Several patient populations are particularly vulnerable. Burn patients are at exceptionally high risk because thermal injury compromises the skin barrier, suppresses innate immune defenses, and creates a nutrient-rich environment for colonization. Patients with diabetes, malignancies, chronic kidney disease, HIV infection, cystic fibrosis, chronic obstructive pulmonary disease, and those on immunosuppressive therapy show increased susceptibility owing to impaired immune responses, while mechanical ventilation, urinary and central venous catheterization, haemodialysis, and prolonged broad-spectrum antibiotic therapy further increase colonization by multidrug-resistant strains and promote their persistence and dissemination.

Collectively, available evidence indicates that the epidemiology of clinical *P. aeruginosa* in Nigeria is characterized by widespread geographical distribution, predominance in wound and catheter-associated infections, and increasing recovery from critically ill patients. Important gaps remain, however, in national surveillance, particularly molecular typing, genomic epidemiology, and longitudinal monitoring of high-risk clones. Expanding molecular surveillance through multicentre studies and integrating genomic data into AMR surveillance programmes will be essential for understanding transmission dynamics and strengthening stewardship and infection control (Osei-Kuffour *et al*., 2026).

3 ANTIMICROBIAL RESISTANCE PATTERNS OF CLINICAL *PSEUDOMONAS AERUGINOSA* IN NIGERIA

Antimicrobial resistance (AMR) in *P. aeruginosa* is among the most pressing challenges confronting clinical management of HAIs globally. The organism withstands antimicrobial therapy through the interplay of intrinsic mechanisms, acquired resistance genes, adaptive responses, and biofilm-mediated persistence, and resistant infections are

associated with prolonged hospitalization, increased costs, limited therapeutic options, and poor outcomes. In Nigeria, increasing reports of MDR, XDR, and carbapenem-resistant *P. aeruginosa* (CRPA) from tertiary institutions indicate that AMR is becoming an important public health concern requiring continuous surveillance and effective stewardship (Qin *et al*., 2022; WHO, 2024).

3.1 Resistance to Major Antibiotic Classes

Published studies consistently demonstrate that Nigerian clinical isolates exhibit resistance to multiple antimicrobial classes. Resistance is most frequently reported against β-lactams, particularly third-generation cephalosporins such as ceftazidime and ceftriaxone, and broad-spectrum penicillins including ampicillin and amoxicillin-clavulanate, largely attributed to constitutive chromosomal AmpC β-lactamase expression, extended-spectrum β-lactamase (ESBL) production, carbapenemase acquisition, and reduced outer membrane permeability via OprD porin alterations (Qin *et al*., 2022).

Fluoroquinolone resistance has increased considerably, with ciprofloxacin and levofloxacin—once reliable options for pseudomonal infections showing declining activity across several tertiary institutions, particularly among isolates from wound and other healthcare-associated infections (Adenipekun *et al*., 2023). Molecular evidence indicates this resistance is primarily mediated by mutations within the quinolone resistance-determining regions (QRDRs) of gyrA and parC, frequently accompanied by overexpression of multidrug efflux pumps such as MexAB-OprM and, less commonly, plasmid-mediated determinants, which reduce intracellular drug accumulation and DNA gyrase/topoisomerase IV binding affinity, contributing to treatment failure (Qin *et al*., 2022; Jordana-Lluch *et al*., 2023).

Aminoglycosides, including gentamicin and amikacin, remain important for severe infections, particularly combined with β-lactams, though susceptibility varies across institutions; amikacin generally retains greater activity than gentamicin, but resistance to both is increasing (Maduakor *et al*., 2024; Tula *et al*., 2023). Resistance is mediated through aminoglycoside-modifying enzymes, 16S rRNA methylation, reduced outer membrane permeability, and efflux pump overexpression, reducing intracellular concentrations and underscoring the importance of routine susceptibility testing over empirical treatment alone (Qin *et al*., 2022; Yang *et al*., 2024).

Carbapenems, particularly imipenem and meropenem, have historically been reliable for severe multidrug-resistant Gram-negative infections; however, recent molecular studies report an increasing prevalence of CRPA in Nigerian tertiary facilities (Olalekan *et al*., 2023; Maduakor *et al*., 2024). Carbapenem resistance is mediated through metallo-β-lactamases (MBLs) such as bla-VIM, bla-NDM, and bla-IMP, together with OprD loss or alteration, AmpC overexpression, and efflux pump activation (Qin *et al*., 2022; Yang *et al*., 2024), substantially limiting therapeutic options and increasing reliance on last-line agents.

Conversely, colistin remains among the most active agents against MDR *P. aeruginosa* worldwide and has generally retained activity against most Nigerian isolates tested (Olalekan *et al*., 2023; WHO, 2024). Newer β-lactam/β-lactamase inhibitor combinations, including piperacillin–tazobactam and ceftolozane–tazobactam, have shown favourable *in vitro* activity internationally, though Nigerian data remain limited (Qin *et al*., 2022; Yang *et al*., 2024). Sporadic reports of reduced colistin susceptibility nonetheless underscore the importance of stewardship, routine testing, and continuous surveillance to preserve these last-line agents (WHO, 2024).

3.2 Temporal and Geographical Trends in Nigeria

Evidence accumulated over the past decade indicates a progressive increase in AMR among clinical *P. aeruginosa* isolates in Nigeria. Earlier studies generally reported relatively high susceptibility to carbapenems, aminoglycosides, and fluoroquinolones, whereas more recent investigations show declining susceptibility alongside increasing reports of MDR and CRPA, consistent with global observations and largely attributable to inappropriate prescribing, widespread empirical therapy, unrestricted antimicrobial access, inadequate stewardship, and persistence of resistant healthcare-associated clones (Qin *et al*., 2022; WHO, 2024).

Recent Nigerian studies have demonstrated increasing resistance to β-lactams, fluoroquinolones, aminoglycosides, and carbapenems among isolates from wound, bloodstream, respiratory, urinary, and other HAIs, with molecular investigations documenting emerging carbapenemase- producing isolates harbouring bla-VIM, bla-NDM, and bla-GES, indicating an evolving molecular epidemiology within Nigerian tertiary institutions (Olalekan *et al*., 2023; Maduakor *et al*., 2024).

Geographically, published studies are unevenly distributed, with most molecular epidemiological investigations conducted in South-West and South-East tertiary institutions—particularly Lagos, Ogun, Oyo, and Enugu—where greater diagnostic capacity and research infrastructure exist (Olalekan *et al*., 2023; Akinduti *et al*., 2023). These studies consistently report relatively high frequencies of MDR and carbapenem- resistant isolates, reflecting both improved

detection and substantial antimicrobial selection pressure within large referral hospitals; studies from Ibadan have similarly reported increasing resistance across diverse specimens (Olalekan *et al*., 2023).

Interpretation of geographical variation should be undertaken cautiously, as reported resistance rates are influenced by differences in sample size, specimen type, patient population, healthcare setting, susceptibility testing methodology, interpretive criteria (CLSI versus EUCAST), and molecular diagnostic approaches, and most Nigerian investigations remain single-centre cross-sectional studies limiting generalizability (CLSI, 2025).

Despite these limitations, available evidence consistently indicates increasing AMR among clinical *P. aeruginosa* isolates within Nigerian tertiary institutions. The emergence of MDR, carbapenem-resistant, and carbapenemase-producing isolates represents a significant threat to effective therapy, infection prevention, and patient outcomes, requiring coordinated national surveillance integrating standardized phenotypic testing with molecular characterization and genomic epidemiology to enable early detection of emerging mechanisms, monitor high-risk clone dissemination, and strengthen stewardship and infection control across Nigeria (WHO, 2024; Federal Ministry of Health Nigeria, 2023).

4 MOLECULAR DETERMINANTS OF ANTIMICROBIAL RESISTANCE

The success of *P. aeruginosa* as a nosocomial pathogen largely reflects its ability to integrate multiple resistance mechanisms into a coordinated adaptive network. Unlike pathogens that rely predominantly on acquired resistance genes, *P. aeruginosa* combines intrinsic resistance, mutational adaptation, horizontal gene transfer, and biofilm-associated tolerance to produce highly resilient phenotypes. Resistance is therefore often multifactorial, with individual isolates harbouring several complementary mechanisms partly explaining why phenotypically similar isolates may possess distinct genetic architectures and why susceptibility profiles differ between institutions despite comparable prescribing practices (Langendonk *et al*., 2021).

Recent Nigerian molecular investigations demonstrate a gradual transition from conventional phenotypic testing toward molecular characterization. PCR, sequencing, and, more recently, whole-genome sequencing have enabled identification of carbapenemase genes, ESBLs, integrons, plasmid-associated determinants, and multidrug efflux systems among clinical isolates. Although molecular surveillance remains geographically limited, available evidence indicates resistance in Nigerian isolates is increasingly driven by both chromosomal mutations and horizontally acquired genetic elements, reflecting global evolutionary trends (Adeyelu *et al*., 2024).

Intrinsic resistance constitutes the first line of defence and distinguishes *P. aeruginosa* from many other Gram-negative pathogens. Encoded within the chromosome independently of prior antimicrobial exposure, it includes a naturally impermeable outer membrane, constitutively expressed multidrug efflux pumps, inducible chromosomal β-lactamases, and stress-responsive regulatory systems, which collectively reduce intracellular antibiotic concentrations and allow survival under conditions that inhibit many other species (Langendonk *et al*., 2021).

Although intrinsic resistance provides an important survival advantage, the rapid global expansion of MDR *P. aeruginosa* is largely driven by acquired mechanisms arising through horizontal gene transfer mediated by plasmids, transposons, bacteriophages, and integrons, or through spontaneous chromosomal mutations selected under antimicrobial pressure. Acquisition of additional determinants substantially broadens the antimicrobial spectrum affected and accelerates dissemination of resistant clones within healthcare environments (Letizia *et al*., 2025).

Among acquired mechanisms, carbapenemase production is the most clinically significant. Nigerian molecular studies have identified metallo-β-lactamase genes including blaVIM, blaNDM, and blaIMP, together with blaGES, among isolates from tertiary hospitals. These enzymes hydrolyse carbapenems and numerous other β-lactams, severely restricting therapeutic options, and their location on mobile genetic elements facilitates rapid dissemination within and between institutions, making carbapenemase-producing *P. aeruginosa* a priority surveillance target (Adeyelu *et al*., 2024).

Extended-spectrum β-lactamases (ESBLs), particularly the TEM, SHV, and CTX-M families, have also been reported in selected Nigerian isolates. Although more commonly associated with Enterobacterales, their occurrence in *P. aeruginosa* further complicates β-lactam therapy, particularly when combined with AmpC hyperproduction and porin deficiency, illustrating the cumulative rather than singular nature of resistance evolution in this pathogen (Adeyelu *et al*., 2024).

5 VIRULENCE DETERMINANTS OF CLINICAL *PSEUDOMONAS AERUGINOSA* ISOLATES IN NIGERIA

Virulence and antimicrobial resistance are traditionally regarded as distinct bacterial attributes; however, increasing evidence indicates these characteristics are interconnected through regulatory networks that enhance bacterial survival within both host and hospital environments. In *P. aeruginosa*, pathogenicity is mediated by a broad repertoire of adhesins, extracellular enzymes, toxins, secretion systems, siderophores, quorum-sensing circuits, and biofilm-

associated factors that enable colonization, immune evasion, nutrient acquisition, and persistence despite antimicrobial exposure—meaning clinical outcomes are influenced not only by susceptibility profiles but also by the virulence potential of infecting strains (Qin *et al*., 2022; Liao *et al*., 2022).

Recent molecular studies suggest highly resistant isolates frequently retain, and sometimes overexpress, major virulence determinants, challenging the assumption that acquiring resistance necessarily incurs a fitness cost. Nigerian investigations have detected virulence- associated genes, including lasB, toxA, exoS, oprL, and nan1, among multidrug-resistant clinical isolates, suggesting resistant strains circulating in Nigerian hospitals possess both enhanced pathogenic potential and reduced susceptibility, increasing the risk of persistent HAIs and therapeutic failure (Akinduti *et al*., 2023).

The type III secretion system (T3SS) is another clinically important virulence mechanism, forming a syringe-like apparatus that injects effector proteins into host cells, causing cytotoxicity, cytoskeletal disruption, and impaired phagocytic clearance. Its principal effectors ExoS, ExoT, ExoU, and ExoY are largely mutually exclusive among clinical strains and associated with distinct pathogenic profiles: ExoS-positive strains are typically linked to chronic, invasive infection, whereas ExoU-positive strains exhibit potent phospholipase activity linked to acute cytotoxicity, rapid tissue destruction, and poorer outcomes, particularly in ventilator-associated pneumonia and bloodstream infection (Qin *et al*., 2022; Liao *et al*., 2022). Although Nigerian studies have more frequently reported exoS than exoU, comprehensive T3SS genotyping remains uncommon, representing an important gap given exoU's prognostic significance.

Iron acquisition through siderophore production is a further relevant virulence mechanism in the iron-limited host environment. The organism produces two principal siderophores, pyoverdine and pyochelin, which scavenge iron from host iron-binding proteins to support growth, biofilm development, and expression of additional virulence factors, and have been proposed as targets for anti-virulence and iron-restriction strategies; data on siderophore expression among Nigerian isolates remain scarce, warranting future investigation (Qin *et al*., 2022; Liao *et al*., 2022).

Biofilm formation is widely regarded as one of the most important virulence traits and a major contributor to chronic infection and antimicrobial tolerance. A biofilm is a structured microbial community embedded within a self-produced extracellular polymeric substance composed primarily of polysaccharides, extracellular DNA, proteins, and lipids, providing both structural integrity and protection from host immune responses and antimicrobials.

Evidence from Nigerian studies indicates biofilm-producing isolates frequently exhibit multidrug-resistant phenotypes. Akinduti *et al*. (2023) demonstrated that isolates with enhanced biofilm-forming capacity also exhibited increased efflux-mediated resistance, suggesting functional interaction between biofilm development and resistance mechanisms, while molecular studies from Lagos have reported high frequencies of virulence genes among MDR isolates, reinforcing the hypothesis that persistence and resistance coexist within successful hospital-adapted clones. Comprehensive nationwide studies evaluating quantitative biofilm production and its relationship with resistance phenotypes nonetheless remain scarce.

Quorum sensing (QS) is a density-dependent cell-to-cell communication system that enables *P. aeruginosa* to coordinate collective behaviours according to population density. Through production and detection of diffusible autoinducers, bacterial populations synchronize expression of virulence genes involved in biofilm formation, motility, toxin production, extracellular enzyme secretion, and antimicrobial tolerance, optimizing energy expenditure while maximizing pathogenic potential during infection (Qin *et al*., 2022).

The QS network consists primarily of three interconnected circuits: the Las, Rhl, and Pqs systems. The LasI/LasR system occupies the apex of the regulatory hierarchy and controls transcription of downstream virulence genes including lasB, toxA, and genes involved in biofilm maturation; the RhlI/RhlR circuit regulates rhamnolipid, pyocyanin, elastase, and other extracellular enzyme production; and the Pseudomonas quinolone signal (PQS) system integrates environmental stress responses with biofilm development and secondary metabolite production. Extensive cross-talk among these systems enables dynamic adaptation to changing host environments and contributes to the pathogen's remarkable persistence during chronic infection (Akinduti *et al*., 2023).

6 CLINICAL AND PUBLIC HEALTH IMPLICATIONS, KNOWLEDGE GAPS, AND FUTURE DIRECTIONS

Table 1 summarises representative resistance and virulence genes reported among clinical *P. aeruginosa* isolates across the Nigerian studies discussed in this review, illustrating the geographical concentration of molecular data and the frequent coexistence of resistance and virulence determinants within the same isolates.

Table 1: Resistance and Virulence genes reported among clinical *P. aeruginosa* isolates across the study.

Region/State	Specimen type(s)	Resistance determinants	Virulence genes/traits	Reference
Lagos (South-West)	Clinical isolates (tertiary hospitals)	*bla*VIM, *bla*NDM, *bla*GES (carbapenemases)	*lasB*, *toxA*, *exoS*	Olalekan *et al*., 2023
Lagos (South-West)	Clinical specimens (public hospital)	Multidrug resistance (>80% of isolates)	Multiple virulence genes detected	Adenipekun *et al*., 2023
Lagos (South-West)	Clinical isolates (healthcare-associated infections)	Efflux-mediated resistance	Biofilm formation; *lasB*, *toxA*, *exoS*, *oprL*, *nan1*	Akinduti *et al*., 2023
Nsukka, Enugu (South-East)	Wound, urine, sputum, ear, high vaginal swab	Multidrug resistance (multiple antibiotic classes)	Not reported	Agbo *et al*., 2023
Enugu (South-East)	Clinical isolates	Metallo-β-lactamase (MBL) production	Not reported	Maduakor *et al*., 2024
Ogun State (South-West)	Clinical samples (tertiary hospital)	Integrons; MBL genes; plasmid-mediated resistance	Not reported	Adeyelu *et al*., 2024

6.1 Clinical and Public Health Implications

The molecular findings summarised in this review carry direct implications for clinical management and public health policy in Nigeria. The coexistence of carbapenem resistance with virulence determinants such as lasB, toxA, and exoS in circulating isolates suggests empirical antipseudomonal therapy based on general susceptibility assumptions is increasingly unreliable, particularly in critically ill patients where treatment delay is associated with poor outcomes, underscoring the need for rapid, molecularly informed diagnostics capable of detecting carbapenemase genes and guiding timely selection of active agents, including colistin-based regimens where indicated (Qin *et al*., 2022; WHO, 2024).

At the health-system level, the concentration of high-risk clones within tertiary referral hospitals highlights the importance of strict infection prevention and control practices, including environmental surveillance of wards, medical devices, and water systems, to limit nosocomial transmission (Langendonk *et al*., 2021). These findings also reinforce the objectives of Nigeria's National Action Plan on Antimicrobial Resistance, which identifies strengthened laboratory capacity and antimicrobial stewardship as national priorities (Federal Ministry of Health Nigeria, 2023).

6.2 Knowledge Gaps

Despite growing molecular evidence, several gaps constrain a comprehensive understanding of *P. aeruginosa* epidemiology in Nigeria. First, molecular surveillance remains geographically concentrated in a small number of South-West and South-East tertiary hospitals, leaving northern Nigeria and secondary or primary facilities substantially underrepresented (Onwuliri *et al*., 2025). Second, whole-genome sequencing and MLST remain uncommon owing to cost and infrastructure constraints, limiting insight into the national distribution of high-risk clones and the relative contribution of clonal expansion versus horizontal gene transfer (Agbo *et al*., 2023; Adeyelu *et al*., 2024).

Third, comprehensive genotyping of the T3SS, particularly *exoU*, and of siderophore-associated genes is rarely performed despite their prognostic relevance. Fourth, few studies have quantitatively linked resistance and virulence phenotypes to outcomes such as length of stay, treatment failure, or mortality, limiting translation of molecular findings into prognostic or therapeutic guidance (Olalekan *et al*., 2023). Finally, methodological heterogeneity—including differences in susceptibility testing standards (CLSI versus EUCAST), specimen types, and molecular targets—complicates direct comparison across studies and constrains pooled national estimates.

6.3 Future Directions

Addressing these gaps will require a coordinated, multi-pronged approach. Establishing a national molecular surveillance network linking tertiary, secondary, and, where feasible, primary healthcare facilities across all six geopolitical zones would substantially improve the representativeness of Nigerian AMR data, while expanding access

to whole-genome sequencing, including through regional reference laboratories or shared sequencing hubs, would allow systematic tracking of high-risk clones and mobile resistance elements over time (Letizia *et al*., 2025).

Incorporating standardised molecular panels covering carbapenemase genes, efflux and porin markers, and a broader virulence gene set including *exoU*, siderophore genes, and quorum-sensing regulators would enable more complete characterisation of circulating strains. Prospective studies linking genomic and phenotypic data to clinical outcomes are needed to clarify the real-world impact of resistance-virulence coexistence. Finally, sustained investment in antimicrobial stewardship, clinical microbiology capacity, and infection prevention and control, aligned with Nigeria's National Action Plan on Antimicrobial Resistance, will be essential to translate molecular surveillance into improved patient outcomes (Federal Ministry of Health Nigeria, 2023; WHO, 2024).

7 CONCLUSION

P. aeruginosa remains one of the most clinically significant opportunistic pathogens responsible for HAIs worldwide, particularly among critically ill and immunocompromised patients. Its ability to survive in diverse hospital environments, acquire multiple resistance mechanisms, and express a wide range of virulence determinants has made it a persistent threat to patient care. This review demonstrates that clinical *P. aeruginosa* isolates in Nigeria exhibit increasing resistance to several commonly used antipseudomonal antibiotics, with MDR and carbapenem-resistant strains reported with increasing frequency across tertiary healthcare facilities reflecting the growing burden of AMR in the country and the need for continuous surveillance and evidence-based stewardship (Olalekan *et al*., 2023; WHO, 2024).

The review further highlights that AMR in Nigerian *P. aeruginosa* isolates is driven by a combination of intrinsic, acquired, and adaptive mechanisms. Molecular studies have identified important resistance determinants, including carbapenemase genes such as bla-VIM, bla-NDM, and bla-GES, together with chromosomal mechanisms involving efflux pump overexpression and reduced outer membrane permeability, while clinically important virulence genes such as lasB, toxA, and exoS have been detected among MDR isolates, suggesting resistance and virulence frequently coexist within the same bacterial populations. This coexistence increases bacterial persistence, complicates treatment, and contributes to poorer clinical outcomes, particularly among patients with prolonged hospitalization or invasive medical devices (Qin *et al*., 2022; Akinduti *et al*., 2023).

In conclusion, integrating molecular epidemiology into routine antimicrobial resistance surveillance will significantly enhance understanding of *P. aeruginosa* epidemiology in Nigeria. A coordinated approach involving clinicians, microbiologists, researchers, infection prevention specialists, and public health authorities is essential for limiting the spread of multidrug-resistant and highly virulent strains. Such collaborative efforts will not only strengthen Nigeria's response to antimicrobial resistance but also contribute to regional and global initiatives aimed at preserving the effectiveness of existing antimicrobial agents and improving patient outcomes.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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