WebLog Journal of Genetics and Genomic Research

Review Article
Published: 05 Mar, 2026

Pathogenicity, Species, and Resistance: Fixed Categories or Functional Constructs? A Call for Relational Microbiology

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Abstract

Classical microbiology has long relied on discrete categories to define bacterial species, pathogenicity, and antimicrobial resistance. However, comparative genomics of neglected species reveals the limitations of these rigid frameworks. Using *Corynebacterium glucuronolyticum* as a paradigm, we argue that these concepts are better understood as functional constructs that depend on genomic, ecological, and clinical contexts rather than fixed biological entities. This perspective challenges traditional dichotomies and calls for a relational approach to modern microbiology.

Keywords: Bacterial Species Concept; Pathogenicity; Antimicrobial Resistance; Comparative Genomics; *Corynebacterium*

WebLog Open Access Publications
Article ID : wjggr.2026.c0507
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OPEN ACCESS

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Received Date: *07 Feb 2026*
Accepted Date: *03 Mar 2026*
Published Date: *05 Mar 2026*

Citation:
Batista Araújo MR, Azevedo V. Pathogenicity, Species, and Resistance: Fixed Categories or Functional Constructs? A Call for Relational Microbiology. WebLog J Genet Genomic Res. wjggr.2026.c0507. https://doi.org/10.5281/zenodo.19115242

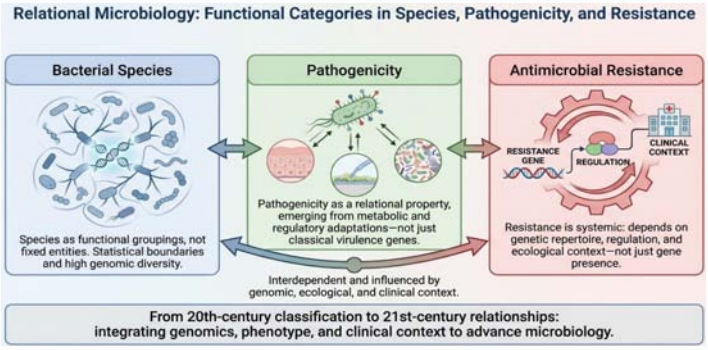

Figure 1: Relational Microbiology.

Introduction

The recent genomic characterization of a multidrug-resistant *Corynebacterium glucuronolyticum* strain isolated from the human genitourinary tract in Latin America[1] raises fundamental questions about three pillars of classical microbiology: **species boundaries**, **pathogenic potential**, and **resistance mechanisms**. Beyond its clinical relevance, this case study serves as a philosophical probe into whether these concepts represent natural categories or functional constructs shaped by context.

The strain IHP2022 exhibited resistance to benzylpenicillin, clindamycin, and tetracycline, harboring putative efflux pump genes (*norB*, *norC*) with low identity that did not confer phenotypic quinolone resistance[1]. Comparative genomics revealed high genetic diversity within the species and positioned this Latin American isolate close to a US strain, suggesting global circulation. More intriguingly, the pathogenic potential appeared to emerge from metabolic and regulatory adaptations rather than classical virulence islands [1].

This case exemplifies a broader challenge: **to what extent are classical concepts like "pathogenicity," "bacterial species," and "antimicrobial resistance" fixed categories versus functional constructions dependent on genomic, ecological, and clinical contexts?**

The Species Concept: Natural Entity or Statistical Boundary?

For decades, bacterial species were conceptualized as discrete, stable units. Genomics provided robust metrics (ANI, dDDH) and reference databases (GTDB [2], TYGS/LPSN [3]), yet simultaneously

revealed the statistical nature of species boundaries. The high genetic diversity observed among *C. glucuronolyticum* genomes and the positioning of IHP2022 within a **taxonomic continuum** challenge essentialist view of species [1].

Pan-genomic analysis reveals species as **families of functional possibilities** rather than closed catalogs. The core/shell/cloud organization demonstrates that "species coherence" may be better understood as **ecological cohesiveness coupled to recombination** [4] rather than genomic uniformity. Recent work suggests that intraspecific units are maintained by environmental processes and gene flow, not by inherent biological essences [4].

For neglected genera like non-diphtheria *Corynebacterium*, this perspective is particularly relevant. Species boundaries remain in flux, and genomic diversity often exceeds expectations based on phenotypic similarity. The species concept remains indispensable, especially for clinical communication and surveillance, but is better treated as an **"informed grouping hypothesis"** requiring constant confrontation with ecological and pan-genomic data.

Pathogenicity: Attribute or Relationship?

The traditional **pathogen-versus-commensal** dichotomy fails to capture the complexity illustrated by *C. glucuronolyticum*. Its presence in the genitourinary tract may represent colonization, dysbiosis, a cofactor in persistent syndromes, or a frank etiologic agent. The answer lies not in taxonomic labels or single "magic genes," but in **emergent pathogenic potential** arising from combinations of adhesion factors, stress control systems, persistence mechanisms, and metabolic reprogramming [1].

This challenges the paradigm of "one classical factor explains everything" (such as *tox* in *C. diphtheriae*). Many contemporary infections result from adaptive pathogenicity organisms that exploit host vulnerabilities, procedural interventions, antibiotic pressure, or immune modulation without resembling classical pathogens [5]. This shift from classical virulence to contextual opportunism reflects the plasticity inherent in pathogen–host interactions under modern clinical conditions [5]. *C. glucuronolyticum* exemplifies this: pathogenic potential appears driven by **metabolic and regulatory gains** rather than acquired virulence islands [1].

Pathogenicity is thus better conceptualized as a **relational property** dependent on temporal dynamics and contextual factors, including host immunity, microbiome status, medical devices, and antimicrobial exposure. The integration of phenotypic and genomic data proposed by Araújo et al. represents the correct approach to transform philosophical speculation into testable inference [1].

Resistance: Beyond Gene Presence

The observation that predicted *norB/norC* genes showed low identity and failed to confer quinolone resistance [1] illustrates the most dangerous assumption of the *in silico* era: **equating homology with function**. This limitation is particularly critical in antimicrobial resistance for several reasons:

Identity and protein architecture matter. Distant homologs may lack substrate specificity or be inefficient, falling below clinical thresholds [6]. **Expression and regulation are crucial.** Silent, repressed, or conditionally expressed genes may not translate to antibiogram resistance [7]. **Genetic background and epistasis influence outcomes.** Resistance often emerges from combinations (target alterations + permeability + efflux + biofilm), with individual components proving insufficient [8]. **Phenotype depends on experimental context.** Media, inoculum, methodology (BrCAST/EUCAST/CLSI), and specific antibiotics modulate results.

Recent literature emphasizes the need to **critically evaluate genotype-to-phenotype predictions** [6, 9], particularly for understudied genera where resistance mechanisms remain poorly characterized. Machine learning approaches show promise in real-world clinical settings but require extensive phenotypic validation to bridge genotype-phenotype gaps [9, 10].

The integration advocated by Araújo et al. is not luxury but necessity: avoiding both **genomic alarmism** ("has gene, therefore resistant") and **phenotypic conservatism** ("sensitive today, genotype irrelevant"). Resistance is better understood as a **systemic property** involving genetic repertoire, regulatory networks, and environmental context rather than mere gene presence.

Three Conceptual Shifts

From Classical Pathogen to Adaptive Pathogen

The hypothesis that host adaptation occurs through metabolic and regulatory gains rather than virulence islands is testable through transcriptomics, proteomics, adhesion/biofilm assays, and microbiome competition studies.

From Stable Species to Pan-genomic Assemblages

Pan-genomes with core/shell/cloud components demonstrate that "species" describes **functional possibility spaces** rather than fixed catalogs, with implications for diagnostics, surveillance, and panel design.

From Gene-Based to Systems-Based Resistance

Resistance emerges from complex interactions involving efflux systems, mobile elements, regulation, and ecological context, making it a **systemic rather than genetic** property.

Conclusion: Functional Categories, Not Arbitrary Constructs

Pathogenicity, species, and resistance are neither fictions nor immutable essences. They are **functional categories** with boundaries that vary according to:

- **Scale** (gene *vs* genome *vs* population).
- **Environment** (microbiome, hospital, community).
- **Clinical context** (immunity, devices, prior antibiotics).
- **Methodology** (cutpoints, techniques, databases, identity thresholds).

The merit of integrating comparative genomics with phenotypic validation and clinical context transforms "philosophy of microbiology" into a concrete research agenda. For neglected genera, this caution is urgent: the cost of error is dual, missed etiologic agents and unfounded resistance attribution.

While 20th-century microbiology sought to **classify**, 21st-century microbiology must **relate**: connecting genotypes to phenotypes, organisms to niches, and laboratory signals to clinical outcomes. The *C. glucuronolyticum* case in Latin America is not merely "the first report"; it exemplifies how our conceptual frameworks, not just the bacteria, must evolve.

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