Evolutionary blind spots: how systematic barriers obscure effective antimicrobial options

Antimicrobial resistance is accelerating faster than the global capacity to develop, approve, and distribute new antimicrobial agents. Dennis Nurjadi and colleagues[1] convincingly argue that antimicrobial strategies should incorporate evolutionary dynamics, a position that is both timely and essential. However, another equally important aspect is the systematic underutilisation of compounds that already possess strong pharmacological and evolutionary advantages but remain overlooked because of regulatory and structural constraints. Sitafloxacin is a particularly illustrative example of such an evolutionary blind spot.

Sitafloxacin is a fourth-generation fluoroquinolone with potent activity against Gram-positive and Gram-negative bacteria, atypical pathogens, anaerobes, and intracellular organisms. The unique configuration of sitafloxacin, with a fluorocyclopropyl group at N-1 and chlorine at C-8, confers greater intracellular penetration and reduces susceptibility to established resistance pathways.[2,3] Experimental studies show strong efficacy of sitafloxacin against multidrug-resistant *Mycobacterium tuberculosis*, *Mycobacterium abscessus*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*,[3-5] suggesting a versatility rarely matched in its class. From a clinical perspective, sitafloxacin is approved and used in Japan for respiratory, urinary, and otological infections;[2] however, it remains almost entirely unavailable elsewhere.

This global underuse of sitafloxacin does not reflect a lack of its efficacy. Rather, the underuse stems from regulatory fragmentation, limited commercial incentives, and the absence of US Food and Drug Administration and European Medicines Agency approval, which prevents the inclusion of sitafloxacin use in guidelines and discourages investment in large-scale clinical trials. Concerns about the toxicity of fluoroquinolones further complicate the assessment of sitafloxacin; however, sitafloxacin has not shown significant cytotoxicity in comparative models,[3] indicating that safety assumptions extrapolated from older compounds might be misleading.

Antibiotic stewardship policies, although essential for controlling resistance, often inadvertently reinforce dependence on obsolete fluoroquinolones, whose clinical utility is declining. This conservatism limits the adoption of promising agents such as sitafloxacin, despite growing evidence of synergistic interactions with multiple antimicrobial and non-antimicrobial compounds.[4,5] Such combinations might limit adaptive responses, alter fitness landscapes, and counteract the evolutionary mechanisms highlighted by Nurjadi and colleagues.[1]

In low-income and middle-income settings, including Nepal, where the burden of antimicrobial resistance is high and treatment options are scarce, the potential relevance of sitafloxacin is considerable. The intracellular and broad-spectrum activities of sitafloxacin might offer advantages for persistent, biofilm-associated, or multidrug-resistant infections, for which conventional regimens often fail.

Therefore, reformulating antimicrobial resistance management through an evolutionary lens requires not only the prudent use of existing agents but also a systematic re-evaluation of therapies whose potential remains unrealised because of structural rather than scientific limitations. Sitafloxacin is an example of how a potentially valuable antimicrobial agent can remain marginalised despite its compelling pharmacological and evolutionary characteristics.

We declare no competing interests.

Copyright © 2025 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

*Francesco Branda, Dipti Shrestha, Kalyan Subedi, Krishna Prasad Acharya, Yogendra Shah, Sher Bahadur Pun
f.branda@unicampus.it

Unit of Medical Statistics and Molecular Epidemiology, Università Campus Bio-Medico di Roma, Rome 00128, Italy (FB); Department of Microbiology, KIST College of Management, Kamalpokhari, Kathmandu, Nepal (DS, KS); Animal Disease Investigation and Control Division (ADICD), Department of Livestock Services (DLS), Hariharbhawan, Lalitpur, Nepal (KPA); Planetary Health Research Center, Kathmandu, Nepal (YS); Clinical Research Unit, Sukraraj Tropical & Infectious Disease Hospital, Kathmandu, Nepal (SBP)

1 Nurjadi D, Schulenburg H, Niemann S, Zinkernagel AS, Rupp J. Are we overlooking the obvious? Bacterial evolution is at the heart of antimicrobial resistance. *Lancet Microbe* 2025; **6:** 101069.
2 Kuhn EMA, Sominsky LA, Chittò M, Schwarz EM, Moriarty TF. Antibacterial mechanisms and clinical impact of sitafloxacin. *Pharmaceuticals* 2024; **17:** 1537.
3 Keating GM. Sitafloxacin: in bacterial infections. *Drugs* 2011; **71:** 731–44.
4 Piddock LJV, Johnson MM. Accumulation of 10 fluoroquinolones by wild-type or efflux mutant *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2002; **46:** 813–20.
5 Shi G, Chen X, Wang H, Wang S, Guo X, Zhang X. Activity of sitafloxacin against extracellular and intracellular *Staphylococcus aureus* in vitro and in vivo: comparison with levofloxacin and moxifloxacin. *J Antibiot (Tokyo)* 2012; **65:** 229–36.

Lancet Microbe 2026; 7: 101325
Published Online December 16, 2025
https://doi.org/10.1016/j.lanmic.2025.101325
See Correspondence https://doi.org/10.1016/j.lanmic.2024.101069