

Emerging Non-albicans Candida Species: Insights into Pathogenesis, Virulence and Antifungal Resistance

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ABSTRACT

Over the past three decades, the epidemiology of invasive candidiasis has changed considerably, and non-albicans *Candida* (NAC) species now account for a growing share of candidemia and invasive fungal disease. This review looks at the major NAC pathogens driving that change *Candida glabrata* (*Nakaseomyces glabratus*), *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei* (*Pichia kudriavzevii*), and the multidrug-resistant *Candida auris* focusing on how they cause disease, the virulence traits they rely on, and the molecular basis of their resistance to antifungal drugs. These species matter most in patients who are critically ill, immunocompromised, very young, post-transplant, or dependent on indwelling devices, where invasive procedures, broad-spectrum antibiotics, and prior antifungal exposure all open the door to infection. Notably, most NAC species cause severe disease without the yeast-to-hyphae transition that defines *C. albicans* pathogenesis. Instead, they lean on a different toolkit: strong biofilm formation, adhesion, tolerance of host-induced stress, survival inside immune cells, evasion of host defences, and the secretion of tissue-degrading enzymes such as proteases, phospholipases, and haemolysins.

Drug resistance remains the central clinical problem. Azole resistance typically arises from ERG11 mutation or overexpression, upregulation of efflux pumps such as CDR1, CDR2, and MDR1, or changes to ergosterol biosynthesis. Echinocandin resistance is driven largely by mutations in FKS1 and FKS2, while amphotericin B resistance is linked to reduced ergosterol content and adaptations in oxidative-stress handling. Other, less common routes include defects in 5-flucytosine activation, MSH2-related mismatch-repair defects, aneuploidy, and regulatory crosstalk such as the UPC2A-PDR1-CDR1 axis mechanisms that, together with biofilm-associated drug tolerance, make treatment considerably harder by limiting drug penetration and allowing infections to persist. Taken together, these findings point to a clear need for species-level identification, routine susceptibility testing, molecular surveillance, standardized genomic benchmarks, stronger infection control, and new antifungal and anti-biofilm therapies. Understanding how resistance evolves and how virulence differs across species will be central to managing this expanding threat.

Keywords: *Candida*; non-albicans *Candida*; antifungal resistance; fluconazole; MDR1; ERG11; biofilm; azole resistance

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INTRODUCTION

Invasive candidiasis remains one of the most common healthcare-associated fungal infections, with substantial morbidity and mortality, particularly in immunocompromised, critically ill, and device-bearing patients [1]. For decades, *C. albicans* dominated as the principal causative species. However, a global trend toward declining proportions of *C. albicans* candidemia, accompanied by a corresponding rise in non-albicans *Candida* (NAC) species, has been

consistently documented and this shift has been paralleled by increasing rates of antifungal drug resistance that complicate treatment decisions [1,2]. The last three decades have seen an expanding pool of high-risk patients including those in intensive care units, transplant recipients, neonates and patients on broad-spectrum antibacterials or prior azole exposure susceptible to opportunistic *Candida* infection and this expansion has been accompanied by both an absolute and proportional increase in infections caused by

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reduced-fluconazole-susceptibility NAC species [3]. A retrospective single-centre analysis of 657 candidemia episodes between 2020 and 2024 illustrates this dynamic well: incidence rose sharply during the COVID-19 pandemic and has only partially declined since, with ward-specific distribution patterns and changing susceptibility profiles tracked year on year [4]. Against this backdrop, the emergence of *Candida auris* a globally disseminated, often multidrug-resistant species first identified in the last two decades has amplified international calls for vigilance in surveillance, diagnosis and treatment [2,5]. This review addresses three interlinked questions that dominate the current literature: (i) How has the species distribution of candidiasis changed and which NAC species are driving this change; (ii) What virulence and pathogenic mechanisms allow NAC species, many of which lack the classical hyphal virulence apparatus of *C. albicans*, to cause severe disease; and (iii) What molecular mechanisms underlie the resistance profiles that make NAC infections therapeutically challenging.

Epidemiological emergence of non-albicans candida

Multiple surveillance studies converge on the same conclusion: *C. albicans* remains common but its relative share of candidemia is falling, while NAC species collectively now often exceed 50% of isolates in tertiary care settings [6–8]. A cross-sectional study from a tertiary hospital in South India screening 97 clinical specimens found emerging non-albicans species with markedly varying virulence and antifungal susceptibility profiles, reinforcing that this shift is not confined to high-income health systems but is a global phenomenon [9]. Similarly, an older but frequently cited analysis of more than 500 *Candida* isolates found that NAC species were the predominant pathogens recovered, that they expressed virulence factors once thought characteristic of *C. albicans* alone, and that they showed disproportionately high resistance to azole antifungals prompting the authors to argue that NAC isolates can no longer be dismissed as low-virulence contaminants [6].

Species-level trends differ by geography and patient population. *C. glabrata* has become particularly prominent in North American and European cohorts, often associated with prior azole exposure and older age; a comprehensive review of *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* biology attributes their increasing recognition partly to improved identification methodology (e.g., MALDI-TOF and molecular diagnostics) and partly to genuine shifts driven by patient comorbidities, invasive interventions, and antifungal drug pressure [8]. *C. parapsilosis* is disproportionately associated with catheter-related infections and neonatal candidemia owing to its propensity for biofilm formation on indwelling devices and exogenous transmission via healthcare workers' hands [9]. *C. tropicalis* is especially prevalent in South and Southeast Asia and in patients with hematological malignancy [8,10]. *C. auris*, first reported in the early

2010s, has since caused hospital outbreaks on every inhabited continent; a systematic review focused on neonatal intensive care units found that despite growing global concern, understanding of the clinical course and transmission dynamics of neonatal systemic *C. auris* infection remains limited, underscoring persistent surveillance gaps even for this intensively studied organism [5].

Importantly, several authors caution against an oversimplified "rise of NAC" narrative: some multicentre surveillance networks report that the overall incidence trend has stabilized in recent years and that *C. albicans* still remains the single most frequently isolated species causing fungal bloodstream infection in aggregate, even as the proportional and absolute burden of reduced-susceptibility NAC species has grown [8]. This nuance stabilizing overall incidence alongside a genuine compositional and resistance shift is an active point of discussion in the epidemiological literature and reflects differences in patient case-mix, regional antifungal stewardship practices, and diagnostic capacity between studies [3,4].

Pathogenesis and virulence mechanisms

A central biological puzzle addressed in recent literature is how NAC species cause severe, sometimes fulminant, disease despite lacking several virulence attributes considered essential in *C. albicans*, most notably the yeast-to-hyphae morphological transition. *C. glabrata*, for example, grows almost exclusively in yeast form and does not depend on morphogenesis to establish infection, yet it remains a high-priority pathogen with substantial invasive disease burden [11]. This has driven interest in alternative virulence strategies among NAC species, including rapid intracellular replication and survival within phagocytes, stress tolerance, and robust biofilm formation.

Biofilm formation is now recognized as one of the most clinically consequential virulence traits shared across *Candida* species. Biofilms are structurally organized microbial communities encased in a self-produced extracellular matrix that impedes antifungal drug penetration, shields cells from host immune effectors, and provides a reservoir for persistent and recurrent infection, particularly on catheters, prosthetic devices, and other abiotic surfaces [12,13]. While *C. albicans* biofilm adhesion is mediated substantially by the Als family of glycoproteins and hyphal-associated proteins such as Hwp1, *C. glabrata* instead relies on Epa (epithelial adhesin) family proteins to achieve comparable adhesive and biofilm-forming capacity despite its yeast-only morphology [11]. A recent proteomic and computational analysis of biofilms across WHO critical-priority fungal pathogens, including *C. albicans* and *C. auris*, emphasizes that biofilm research in *Candida* is considerably more advanced than in other priority fungi and is now being

used as a template to identify novel anti-biofilm drug targets across the fungal kingdom [13].

Secreted hydrolytic enzymes constitute a second major virulence axis. *C. tropicalis*, for instance, has been shown in clinical isolate studies to produce phospholipase as its predominant virulence enzyme, alongside coagulase activity and biofilm production in a substantial proportion of isolates, all of which facilitate tissue invasion and immune evasion [14]. Secreted aspartic proteases (Sap), phospholipases, and haemolysins more broadly degrade host tissue barriers and modulate local immune responses, and their expression patterns differ meaningfully between *C. albicans* and NAC species, contributing to species-specific virulence profiles [8,15]. Cell-surface adhesins, including both canonical adhesion proteins and "moonlighting" cytosolic proteins repurposed to the cell surface, further mediate host-cell attachment and contribute to mixed-species biofilm formation with bacterial pathogens, a phenomenon documented in polymicrobial infections such as periodontal disease [15].

C. auris poses a distinctive pathogenesis profile: it exhibits exceptional thermotolerance and salinity

tolerance, persists for extended periods on hospital surfaces and skin, and demonstrates an unusual capacity for both nosocomial transmission and environmental persistence, which together with its resistance profile explain its designation as a critical WHO priority pathogen alongside *C. albicans* [16,17]. Virulence factor comparisons across WHO critical-priority fungi highlight that thermotolerance, biofilm formation, immune-evasion strategies, and enzymatic degradation of host tissue are recurring themes, though the relative contribution of each factor varies considerably by species and by anatomical niche of infection [17].

Antifungal resistance profile of non-albicans *Candida*

The clinical significance of the NAC shift lies substantially in its resistance implications. Three major antifungal classes are used against invasive candidiasis: azoles (fluconazole, voriconazole, itraconazole, isavuconazole), echinocandins (casprofungin, micafungin, anidulafungin), and polyenes (amphotericin B) (Table 1).

Table 1. Mechanisms & Gene Responsible for Antifungal Resistance in Non-Albicans *Candida* Species

Resistance Against	Mechanism	Gene(s) Involved	Notes	Ref.
Azole Resistance	Target enzyme alteration	<i>ERG11</i> (encodes lanosterol 14- α -demethylase)	Point mutations reduce drug-binding affinity; hotspot mutations reported in <i>C. auris</i> (Y132F, K143R, F126L) and <i>C. tropicalis</i>	[18]
	Target overexpression	<i>ERG11</i> upregulation	Increases enzyme quantity, diluting drug effect	[19]
	Efflux pump upregulation (ABC transporters)	<i>CDR1</i> , <i>CDR2</i>	Regulated by transcription factor <i>PDR1</i> ; gain-of-function <i>PDR1</i> mutations are a major driver in <i>C. glabrata</i>	[20]
	Efflux pump upregulation (MFS transporters)	<i>MDR1</i>	Regulated by <i>MRR1</i> ; contributes in <i>C. parapsilosis</i> and <i>C. tropicalis</i>	[21]
	Ergosterol pathway bypass	<i>ERG3</i>	Loss-of-function mutations divert sterol synthesis, reducing toxic sterol accumulation	[22]
	Intrinsic reduced susceptibility	<i>ERG11</i> (low-affinity variant) + constitutive efflux	Characteristic of <i>C. krusei</i> , which is intrinsically fluconazole-resistant	[23]

Echinocandin Resistance	Target enzyme alteration	<i>FKS1</i> (and <i>FKS2</i> in <i>C. glabrata</i>)	Encodes catalytic subunit of 1,3- β -D-glucan synthase; hotspot regions HS1/HS2 are mutation-prone	[24]
	Species-specific dual target	<i>FKS1</i> + <i>FKS2</i>	Unique to <i>C. glabrata</i> ; <i>FKS2</i> mutations are clinically more frequent than <i>FKS1</i>	[24]
	Natural reduced susceptibility	<i>FKS1</i> polymorphism	<i>C. parapsilosis</i> carries a naturally occurring substitution conferring elevated (but not clinically resistant) MICs	[25]
	Compensatory stress response	PKC pathway, calcineurin pathway	Not primary resistance but supports survival/tolerance under echinocandin stress; associated with chitin synthase upregulation	[26]
Polyene (Amphotericin B) Resistance	Reduced/altered ergosterol content	<i>ERG2</i> , <i>ERG3</i> , <i>ERG6</i> , <i>ERG11</i>	Fewer ergosterol-binding sites available for the drug	[27]
	Oxidative stress mitigation	Catalase and related antioxidant genes	Reduces AmB-induced oxidative membrane damage	[28]
5-Flucytosine (5-FC) Resistance	Impaired prodrug conversion	<i>FCY2</i> (permease), <i>FCY1</i> (cytosine deaminase), <i>FUR1</i> (uracil phosphoribosyltransferase)	Mutations block the pyrimidine salvage pathway needed to activate 5-FC intracellularly	[29]
Additional Modifiers of Resistance Evolution	Mismatch repair defects	<i>MSH2</i>	Mutations in <i>C. glabrata</i> produce hypermutator phenotypes, accelerating stepwise, multidrug resistance acquisition across azoles and echinocandins	[30]
	Aneuploidy/chromosomal alterations	<i>ERG11</i> , efflux-pump loci (copy-number changes)	Contributes to resistance, particularly in <i>C. glabrata</i>	[31]
	Cross-pathway regulatory integration	<i>UPC2A</i> $\rightarrow$ <i>PDR1</i> $\rightarrow$ <i>CDR1</i>	Upc2A-mediated activation of the Pdr1–Cdr1 axis links ergosterol biosynthesis regulation to efflux pump expression in	[32]

			<i>C. glabrata</i> , suggesting these pathways are not fully independent	
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Azole resistance is intrinsically more common among NAC species than *C. albicans*. *C. krusei* is intrinsically resistant to fluconazole, and *C. glabrata* frequently exhibits reduced susceptibility or resistance following azole exposure, whereas fluconazole resistance rates in *C. albicans* typically remain below 1% in most surveillance cohorts compared with 6–12% in *Nakaseomyces glabratus* in several regional studies [33]. Global antifungal surveillance data further show that a specific *Erg11* alteration, Y132F, predominates among azole-resistant *C. parapsilosis* and *C. tropicalis* isolates, with country-specific patterns of dissemination suggestive of local clonal spread rather than purely independent emergence [33]. **Echinocandin resistance**, while still comparatively uncommon across most NAC species, is rising in importance, especially in *C. auris* and *C. glabrata*. Global estimates indicate that more than 90% of *C. auris* clinical isolates are resistant to fluconazole, 30–35% to amphotericin B, and 5–7% to echinocandins, with multidrug resistance observed in roughly 41% of isolates and pan-resistance to three antifungal classes in 3–4% [34]. Regional heterogeneity is striking: caspofungin resistance rates as high as 23.6% have been reported among Indian *C. auris* isolates compared with 0.2% in non-Indian isolates in the same multicentre analysis, indicating that local antifungal use patterns and clonal lineage strongly shape resistance phenotypes [34]. **Amphotericin B resistance** remains less common but is clinically consequential when present, particularly in *C. auris*, and is associated with alterations in membrane sterol composition, though molecular characterization of polyene resistance in NAC species remains comparatively underdeveloped relative to azole and echinocandin resistance mechanisms [33,34].

Molecular mechanisms of antifungal resistance

Azole Resistance Mechanisms

The principal molecular routes to azole resistance converge on either modification of the drug target or its reduced intracellular accumulation. The target enzyme, lanosterol 14 α -demethylase, is encoded by *ERG11*; missense mutations in *ERG11* alter drug-binding affinity while preserving enzymatic function, and are among the most frequently reported resistance mechanisms across *Candida* species [10,35]. In *C. tropicalis*, molecular characterization of clinical bloodstream and urinary isolates has demonstrated that *ERG11* mutations, together with upregulation of *ERG11* itself (often secondary to mutations in the regulatory transcription factor *UPC2*) and overexpression of the efflux pump genes *CDR1* and *MDR1*, jointly underlie azole resistance, with all resistant isolates in one recent Brazilian cohort also found to be biofilm producers [10].

Efflux-mediated resistance operates through two structurally distinct transporter families: ATP-binding cassette (ABC) transporters, encoded by genes such as *CDR1* and *CDR2*, and major facilitator superfamily (MFS) transporters, encoded by *MDR1*; overexpression of either class reduces intracellular azole concentration below therapeutic thresholds [10,35]. In *C. glabrata*, this mechanism has been particularly well characterized: gain-of-function mutations in the zinc-cluster transcription factor *PDR1* are the most common resistance determinant, driving constitutive overexpression of *CDR1* and, to a lesser extent, *CDR2* and *SNQ2* [36–38]. Notably, unlike in *C. albicans*, *ERG11* coding mutations are comparatively rare among clinical *C. glabrata* azole-resistant isolates, though experimentally introduced *ERG11* mutations analogous to well-characterized *C. albicans* alleles (Y141H, S410F, and the corresponding double mutant) do confer azole resistance in engineered *C. glabrata* strains and, intriguingly, appear to cross-activate the Pdr1–Cdr1 efflux axis via the transcription factor Upc2A, revealing biological crosstalk between ergosterol biosynthesis and efflux pump regulation that had not previously been appreciated [38,39]. A recent Indian clinical study extended this picture by identifying novel *PDR1* mutations and implicating mismatch repair pathway alterations, specifically in *MSH2*, as a genotypic marker associated with resistance emergence, alongside more conventional *CDR1* overexpression [40]. This raises the possibility that hypermutator phenotypes, driven by defective DNA mismatch repair, may accelerate the stepwise acquisition of resistance-conferring mutations in *C. glabrata*, a mechanism with parallels to bacterial hypermutator resistance evolution.

Echinocandin Resistance Mechanisms

Echinocandins inhibit β -1,3-D-glucan synthase, a multi-subunit enzyme complex essential for fungal cell wall integrity, whose catalytic subunit is encoded by *FKS1* (and *FKS2* in some species). Resistance arises almost exclusively through non-synonymous mutations clustered in two "hot-spot" regions of *FKS1*, which reduce the drug-target binding affinity of glucan synthase[41–43]. In *C. auris*, specific substitutions including S639F, S639Y, D642Y, R1354H and R1354Y have been repeatedly identified in echinocandin-resistant clinical and experimentally selected isolates, with S639F shown to increase cell-wall β -glucan and chitin content, plausibly compensating structurally for reduced glucan synthase drug sensitivity [42,44]. CRISPR-Cas9-based reverse genetic confirmation of a novel R1354H substitution has directly established its causal role in caspofungin resistance, illustrating how gene-editing approaches are now being used to move beyond correlative sequencing data toward mechanistic proof [34].

A particularly important development in this literature is the demonstration that echinocandin resistance in *C. auris* can emerge in vivo during the course of antifungal treatment. A single-patient case series following a lung transplant recipient over one year showed sequential *C. auris* isolates evolving from fluconazole-only resistance to full multidrug resistance encompassing caspofungin and amphotericin B, with a significant rise in micafungin MIC, and *ERG11/FKS1* sequencing confirmed that resistance-associated mutations accrued during therapy itself [39]. Complementing this, whole-genome sequencing of serially collected clinical isolates has shown that mutations in genes other than *FKS1* accumulate incrementally before the eventual acquisition of hot-spot *FKS1* mutations, suggesting a multi-step evolutionary trajectory toward resistance rather than a single-step event [41]. Animal models reinforce that this evolution is not limited to human hosts under overt clinical treatment: enteric colonization studies in mice have shown that echinocandin exposure alone, in the gastrointestinal tract, is sufficient to select for *FKS1* hot-spot mutants and drive in vivo emergence of resistant *C. auris*, with resistance rates of 10% in micafungin-treated and 20% in caspofungin-treated animals [42,43]. This finding has direct implications for understanding intestinal *C. auris* colonization as a reservoir for resistance evolution and subsequent nosocomial transmission. The development of curated benchmark datasets of whole-genome sequenced *C. auris* isolates with validated *FKS1* mutations is now enabling more systematic, genomics-based surveillance for echinocandin resistance in public health laboratories, addressing a previously identified gap in standardized validation resources [42].

Biofilm-Associated and Multifactorial Resistance

Beyond target-site and efflux-mediated mechanisms, biofilm formation itself constitutes an independent, multifactorial resistance mechanism. The extracellular matrix physically restricts antifungal drug penetration, sequesters drug molecules, and creates metabolically dormant persister-cell subpopulations that survive drug exposure independent of classical resistance mutations; biofilm cells characteristically display resistance levels many-fold higher than their planktonic counterparts across nearly all antifungal classes [11–13]. Recent work using proteomic and computational approaches across WHO critical-priority fungal pathogens is beginning to map the shared and species-specific regulatory pathways governing biofilm-associated drug tolerance, with the goal of identifying anti-biofilm adjunctive therapeutic targets that could restore antifungal efficacy without requiring new antifungal drug classes [13].

Clinical and public health implications

The convergence of epidemiological shift and molecular resistance diversification has direct clinical consequences. Species identification alone is now insufficient to guide therapy; genotypic or phenotypic

resistance characterization is increasingly necessary given the substantial heterogeneity in resistance mechanisms even within a single species and geographic region [40,42]. The WHO's 2022 Fungal Priority Pathogens List formally recognized this reality, classifying *C. albicans* and *C. auris* as critical priority pathogens and *Nakaseomyces glabratus* (*C. glabrata*), *C. tropicalis*, and *C. parapsilosis* as high-priority pathogens, a classification explicitly intended to catalyse research investment, surveillance infrastructure, and new antifungal drug development [16,33]. A recent reappraisal of this list notes that the declining proportion of *C. albicans* relative to *N. glabratus* and *C. parapsilosis* globally complicates simple prioritization schemes, since these two NAC species are nonetheless placed in a lower priority tier despite their rising clinical relevance in specific patient populations [33].

Literature gaps and future research directions

Several gaps recur across the recent literature reviewed here:

Despite considerable progress in understanding antifungal resistance in non-albicans Candida (NAC) species, several important gaps persist. Much of the existing epidemiological and molecular resistance data comes from well-resourced tertiary centres in North America, Europe, and parts of Asia, while smaller cross-sectional studies from South Asian and African settings point to a substantial but poorly documented burden, underscoring the need for standardized, longitudinal, multicentre surveillance in low-resource regions [9,10]. Similarly, although amphotericin B continues to serve as a critical salvage agent, particularly against multidrug-resistant *C. auris*, the mechanisms underlying resistance to it remain far less studied than those associated with azoles and echinocandins [34]. At the molecular level, the recent implication of MSH2-associated hypermutator phenotypes and DNA mismatch repair defects in accelerating stepwise resistance acquisition in *C. glabrata* raises the question of whether this represents a broader, generalizable pathway of resistance evolution across other NAC species one that has yet to be systematically explored [40]. Complementing this, emerging murine models of intestinal colonization showing de novo *FKS1* mutation selection under echinocandin pressure suggest that asymptomatic gastrointestinal reservoirs, rather than active infection alone, may play an underappreciated role in driving and transmitting resistance, though in vivo dynamics in this context remain only partially characterized [42,43]. Building reproducible surveillance infrastructure will also require extending standardized genomic benchmarking resources so far exemplified mainly by *C. auris* *FKS1* datasets to additional NAC species and resistance genes, enabling more consistent sequencing-based comparisons across laboratories [42]. On the therapeutic front, biofilm-targeted adjunctive strategies remain largely confined to preclinical stages, with the

translation of proteomic and computational target discovery into validated anti-biofilm agents still an open challenge [13]. Finally, mechanistic work demonstrating Upc2A-mediated activation of the Pdr1-Cdr1 axis in *C. glabrata* has revealed unexpected cross-talk between ergosterol biosynthesis and efflux pump regulation, challenging the assumption that these resistance pathways operate independently; whether similar regulatory interconnections exist in *C. tropicalis*, *C. parapsilosis*, and *C. auris* remains an open question that has not yet been empirically tested [38,39].

CONCLUSION

The epidemiology of candidiasis has undergone a durable shift toward non-albicans *Candida* species, driven by an expanding population of susceptible hosts, diagnostic advances, and selective pressure from widespread antifungal use. NAC species achieve pathogenicity through virulence strategies that diverge meaningfully from the hyphal paradigm of *C. albicans*, relying instead on biofilm formation, hydrolytic enzyme secretion, stress tolerance, and, in the case of *C. auris*, exceptional environmental persistence. Their resistance profiles are similarly heterogeneous, governed by overlapping but species-specific combinations of *ERG11* alteration, efflux pump overexpression via transcription factors such as Pdr1 and Upc2A, and *FKS1* hot-spot mutations conferring echinocandin resistance mechanisms increasingly shown to evolve dynamically within individual patients during treatment. Continued molecular surveillance, expanded genomic benchmarking, and mechanistic research into biofilm biology and in vivo resistance evolution will be essential to keep pace with this evolving threat.

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