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EMERGENT AND UNUSUAL SECONDARY INFECTIONS DURING COVID-19: A REVIEW OF BACTERIAL, FUNGAL, VIRAL, AND PROTOZOAL COMPLICATIONS

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ABSTRACT

Secondary infections have emerged as a defining yet under-recognized dimension of the COVID-19 pandemic, driven by the profound immunological and clinical disruptions caused by SARS-CoV-2. Beyond direct viral pathology, COVID-19 induces sustained lymphopenia, T-cell exhaustion, impaired interferon signaling, and dysfunctional innate immune responses, collectively weakening host defenses and creating highly permissive conditions for opportunistic, latent, and multidrug-resistant pathogens. These immune alterations enabled several infections to behave with unusual aggressiveness and contributed substantially to clinical deterioration in vulnerable patients. This review synthesizes current evidence on the unusual and clinically significant bacterial, fungal, viral, and protozoal infections that surfaced with unprecedented frequency during the pandemic. Prominent patterns included post-COVID reactivation of *Mycobacterium tuberculosis*; ICU-associated outbreaks of multidrug-resistant *Klebsiella pneumoniae*; explosive surges of mucormycosis and COVID-associated pulmonary aspergillosis; global expansion of *Candida auris*; and increased reactivation of latent viruses such as VZV, CMV, and EBV. Additionally, steroid-triggered *Strongyloides stercoralis* hyperinfection emerged as a severe complication in endemic regions, underscoring the unintended consequences of widespread immunomodulatory therapy. Together, these infections significantly amplified morbidity and mortality, often presenting diagnostic challenges due to overlap with severe COVID-19. Understanding how SARS-CoV-2 alters pathogen behavior is essential for improving diagnostic vigilance, strengthening ICU infection-control practices, optimizing antimicrobial stewardship, and enhancing preparedness for future respiratory pandemics. The insights summarized here highlight the need for integrated multidisciplinary strategies to prevent, detect, and manage secondary infections in the evolving landscape of COVID-19 and beyond.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly emerged as a global health crisis with profound clinical and immunological consequences. Beyond the well-recognized respiratory manifestations, COVID-19 is now understood as a systemic illness that causes substantial immune dysregulation. Patients frequently develop **lymphopenia, impaired T-cell responses, cytokine imbalance, endothelial injury, and prolonged inflammatory stress**, all of which collectively weaken host defenses and predispose individuals to opportunistic infections.[1–3] Additionally, extensive use of immunomodulators—particularly **systemic corticosteroids**, IL-6 inhibitors, and broad-spectrum antibiotics—further amplifies susceptibility to secondary infections, even in individuals with no prior immunocompromise.[4,5]

While secondary infections are not uncommon in viral pandemics, the COVID-19 era exhibited **distinct, unexpected, and unusually aggressive patterns** of co-infections and reactivations. Several pathogens demonstrated **dramatic surges uniquely associated with COVID-19**, rather than representing routine hospital-acquired organisms. These infections emerged either due to SARS-CoV-2–induced immune exhaustion, treatment-associated immunosuppression, or prolonged intensive care unit (ICU) stay accompanied by invasive procedures.[6] Such emergent secondary infections significantly increased morbidity, prolonged

hospitalization, and contributed to higher mortality in severe and critical COVID-19 cases worldwide.

Among **bacterial pathogens**, two entities showed remarkable and COVID-specific patterns. ***Mycobacterium tuberculosis*** exhibited increased reactivation rates, particularly in tuberculosis-endemic regions, where post-COVID pulmonary structural damage and immune suppression facilitated latent TB reactivation.[7] Similarly, **multidrug-resistant *Klebsiella pneumoniae*** outbreaks surged across COVID-19 ICUs, fueled by antibiotic overuse, altered microbial ecology, and overwhelmed hospital systems.[8]

The most striking trends, however, were observed in **fungal infections**. COVID-19 precipitated unprecedented waves of **mucormycosis**, especially in India, where the convergence of steroid therapy, uncontrolled diabetes, hypoxia, and environmental exposure created a unique epidemic.[9] Likewise, **COVID-Associated Pulmonary Aspergillosis (CAPA)** emerged globally as a major cause of invasive fungal pneumonia, even among patients without classical immunosuppression.[10] Additionally, the pandemic facilitated widespread outbreaks of ***Candida auris***, a multidrug-resistant fungus that thrived under ICU conditions, prolonged ventilation, and increased device use.[11]

Several **viral reactivations** also rose to prominence during COVID-19, reflecting SARS-CoV-2's profound impact on cellular immunity. Reactivation of **Varicella-Zoster Virus (VZV)** led to an unusual spike in herpes zoster cases, including among younger adults.[12] **Cytomegalovirus (CMV)** reactivation became increasingly prevalent in critically ill COVID patients, often correlating with poorer outcomes.[13] Reactivation of **Epstein–Barr Virus (EBV)** was also reported, contributing to severe systemic inflammation and possibly long-COVID symptomatology.[14]

Although protozoal secondary infections were less common, one clinically significant condition was repeatedly documented: **Strongyloides stercoralis hyperinfection syndrome**. This life-threatening manifestation was triggered primarily by corticosteroid therapy administered during COVID-19 management, unmasking latent infections in endemic regions.[15]

Given the diversity, novelty, and severity of these emergent secondary infections, a comprehensive review is warranted. This article examines the **unusual bacterial, fungal, viral, and protozoal complications uniquely amplified during the COVID-19 pandemic**, highlighting epidemiological trends, risk factors, and clinical implications. Understanding these pathogen-specific interactions with SARS-CoV-2 is essential for improving diagnostic strategies, anticipating complications in future outbreaks, and optimizing antimicrobial stewardship in pandemic settings.

1. BACTERIAL PATHOGENS EXHIBITING COVID-19–ASSOCIATED EMERGENCE

1.1 *Mycobacterium tuberculosis*

Mycobacterium tuberculosis (MTB) experienced a notable shift in clinical patterns during the COVID-19 pandemic, with several regions reporting an unusual rise in reactivation and new-onset disease. MTB typically persists in a latent state within granulomas maintained by an intact cell-mediated immune response. Disruption of this balance—particularly reductions in $CD4^+$ and $CD8^+$ T-cell function, diminished IFN-γ signaling, and generalized immune exhaustion—creates an environment favorable for reactivation.[16] SARS-CoV-2 infection induces precisely these immunological abnormalities, including profound lymphopenia and sustained inflammatory stress, thereby weakening the host's ability to contain dormant bacilli.[17] Additionally, corticosteroid therapy and widespread immunomodulator use during COVID-19 management further suppressed cellular immunity and contributed to increased vulnerability in individuals harboring latent infection.[18]

Epidemiological studies provide evidence supporting this association. A large dynamic cohort study from Southern Thailand demonstrated that patients recovering from COVID-19 pneumonia exhibited a significantly higher hazard of developing bacteriologically confirmed pulmonary TB compared to the general population, underscoring the independent risk conferred by SARS-CoV-2–associated lung injury and immune disruption.[19] Similar findings were observed in a multinational analysis evaluating TB notifications across several high-burden countries, which documented a temporal spike in TB incidence following regional COVID-19 surges—an effect attributed to both biological reactivation and delayed access to diagnostics during the pandemic.[20] A meta-analysis involving more than 10,000 participants further reported that prior COVID-19 increased the odds of developing active TB by over twofold, with risk magnified in individuals with diabetes, malnutrition, or pre-existing pulmonary disease.[21]

Clinical outcomes among patients co-infected with TB and COVID-19 were consistently worse than with either infection alone. Co-infected individuals demonstrated more severe respiratory compromise, required prolonged ventilatory support, and experienced higher mortality, with several cohorts reporting fatality rates ranging from 15% to 30%.[22] These outcomes were particularly poor in settings where pandemic-driven disruptions limited access to early TB diagnosis, molecular testing, and uninterrupted treatment.

Pharmacological management followed standard TB guidelines, with isoniazid, rifampicin, pyrazinamide, and ethambutol as first-line therapy, while drug-resistant cases required bedaquiline- or linezolid-based regimens.[23] However, treatment delays, inconsistent follow-up, and supply-chain interruptions during COVID-19 may have contributed to more advanced

disease at presentation and potentially facilitated transmission of resistant strains. Collectively, these trends highlight the complex interaction between SARS-CoV-2 and MTB and reinforce the need for targeted surveillance in TB-endemic regions.

1.2 *Klebsiella pneumoniae*

Klebsiella pneumoniae emerged as one of the most problematic bacterial pathogens during the COVID-19 pandemic, particularly in intensive care settings overwhelmed by prolonged ventilation, high antibiotic pressure, and repeated invasive procedures. As a gut and respiratory colonizer, *K. pneumoniae* readily transitions to an opportunistic pathogen in critically ill patients, causing ventilator-associated pneumonia, bacteremia, and severe sepsis. Its intrinsic virulence factors—including capsular polysaccharides, siderophore systems, and adhesins—facilitate rapid pulmonary invasion and immune evasion in compromised hosts.[24]

A distinct challenge during the pandemic was the dramatic rise in multidrug-resistant (MDR) and carbapenem-resistant *K. pneumoniae* (CRKP). These strains carry mechanisms such as extended-spectrum β-lactamases (ESBLs), carbapenemases (e.g., KPC, NDM, OXA-48), and porin mutations that severely limit treatment options.[25] COVID-19 created a perfect environment for MDR expansion: unrestricted empirical antibiotic use, reduced infection-control capacity, heavy device utilization, and strained ICU infrastructure collectively accelerated transmission. SARS-CoV-2–related immune dysfunction further weakened host defenses, increasing susceptibility to invasive *Klebsiella* disease.

Multiple studies documented unusually large CRKP outbreaks in COVID-19 critical care units. An Italian ICU reported a sudden surge in KPC-producing *K. pneumoniae* during the first pandemic wave, with genomic analyses confirming rapid clonal spread driven by staff shortages and disrupted isolation protocols.[26] A multicenter study in New York observed similar trends, where CRKP incidence doubled during peak COVID-19 admissions, correlating strongly with prolonged mechanical ventilation and broad-spectrum antibiotic exposure.[27] Another cohort from India described extensive outbreaks of NDM- and OXA-48–producing strains among COVID-19 patients, with high mortality attributed to limited therapeutic options and delayed microbiological identification.[28] These reports collectively highlight how pandemic-associated systemic pressures directly facilitated MDR *Klebsiella* propagation.

Clinical outcomes in patients with COVID-19 complicated by MDR *K. pneumoniae* were significantly worse. Co-infected patients exhibited rapid respiratory decline, high rates of septic shock, and a substantial increase in ICU mortality. Several cohorts documented mortality rates exceeding 40–50% in those with carbapenem-resistant bloodstream infections, underscoring the devastating synergy between advanced COVID-19 lung injury and MDR gram-negative sepsis.[29] Treatment options remained restricted to agents such as colistin, tigecycline, ceftazidime-avibactam (for KPC producers), or cefiderocol, though therapeutic success was modest and dependent on early detection.[30]

The convergence of antimicrobial resistance, compromised infection-control systems, and COVID-19–related immunological vulnerability made *Klebsiella pneumoniae* one of the most consequential bacterial pathogens during the pandemic. Its proliferation across ICUs illustrates the critical need for strengthened surveillance, antibiotic stewardship, and rapid diagnostics during future health crises.

2. FUNGAL PATHOGENS SHOWING COVID-19–ASSOCIATED EMERGENCE

2.1 Mucormycosis

Mucormycosis became one of the most striking and globally recognized fungal complications associated with COVID-19, especially during the second pandemic wave in India. Although mucormycosis is generally rare and typically affects profoundly immunocompromised individuals, the COVID-19 era created a unique interplay of risk factors that led to an unprecedented surge in cases. SARS-CoV-2–induced immune dysregulation, characterized by impaired neutrophil activity, lymphopenia, and dysfunctional macrophage responses, weakened early innate defenses that ordinarily restrict Mucorales invasion.[31] Extensive pulmonary and sinus epithelial damage in severe COVID-19 further facilitated fungal entry and tissue penetration.

The most significant catalyst for this epidemic was the widespread use of systemic corticosteroids. While life-saving in severe COVID-19, steroids also impair phagocytic function, promote hyperglycemia, and suppress cellular immunity—three mechanisms strongly associated with mucormycosis progression.[32] In India, where diabetes prevalence is among the highest globally, many patients developed steroid-exacerbated hyperglycemia or diabetic ketoacidosis, which markedly increases free iron in serum and enhances fungal growth. Environmental exposure also played a contributory role, as Mucorales spores are abundant in soil, decaying organic material, and air in humid settings. The convergence of SARS-CoV-2, steroid therapy, uncontrolled diabetes, hypoxia, and high spore burden created an epidemiological scenario unparalleled in previous pandemics.

Large cohort studies from India documented this sudden escalation. A multicenter study involving over 2,800 patients reported that 78% of COVID-associated mucormycosis (CAM) cases had received systemic steroids and 87% had underlying diabetes, emphasizing the synergistic effect of these risk factors.[33] Another national registry analysis observed a nearly 50-fold

increase in mucormycosis incidence during the COVID-19 second wave compared to pre-pandemic years, with rhino-orbital-cerebral involvement being the predominant presentation.[34] Additional hospital-based studies noted that CAM patients frequently presented late due to diagnostic overshadowing by worsening COVID-19 pneumonia, contributing to extensive angioinvasion, tissue necrosis, and orbital complications at diagnosis.[35]

Mortality in CAM remained high despite aggressive management. Published outcomes ranged from 32% to over 50%, depending on the disease site and extent of angioinvasion, with pulmonary and disseminated forms showing the poorest survival.[36] Early surgical debridement combined with amphotericin B (liposomal formulations preferred) was the mainstay of therapy, often followed by posaconazole or isavuconazole for consolidation treatment.[37] However, during peak COVID-19 surges, shortages of amphotericin B, delayed referrals, and overwhelmed tertiary care centers significantly affected survival rates.

The mucormycosis epidemic highlighted how pandemic-related clinical practices, combined with underlying metabolic vulnerabilities and SARS-CoV-2–driven immune dysfunction, can transform a previously rare opportunistic infection into a large-scale public health crisis. The CAM outbreak remains one of the most distinct and defining fungal complications uniquely linked to the COVID-19 era.

2.2 COVID-Associated Pulmonary Aspergillosis (CAPA)

COVID-Associated Pulmonary Aspergillosis (CAPA) emerged early in the pandemic as a significant cause of secondary fungal pneumonia in critically ill SARS-CoV-2 patients. Unlike classical invasive aspergillosis—which typically occurs in patients with profound neutropenia or hematological malignancies—CAPA frequently developed in individuals without traditional immunosuppressive conditions. Severe COVID-19 produces extensive alveolar damage, mucociliary dysfunction, impaired epithelial integrity, and dysregulated immune responses that collectively compromise pulmonary defenses against *Aspergillus* species.[38] Neutrophil and macrophage dysfunction, coupled with cytokine-mediated immune exhaustion, allows inhaled conidia to germinate and invade damaged lung tissue.

The widespread use of corticosteroids and immunomodulators during COVID-19 management further contributed to the rise of CAPA. Dexamethasone reduces neutrophil oxidative killing and suppresses IL-17 pathways, both essential for antifungal immunity. Additional agents such as tocilizumab and JAK inhibitors further blunted host defenses, creating permissive conditions for *Aspergillus* invasion in ICUs worldwide.[39] These mechanisms explain why CAPA became increasingly recognized even in patients who previously would not have been considered at risk for invasive aspergillosis.

Several multicenter studies have quantified this trend. A European consortium study reported CAPA incidence ranging from 20% to 30% among mechanically ventilated COVID-19 patients, with a mortality rate exceeding 40%, highlighting its substantial clinical impact.[40] A Dutch–Belgian ICU cohort demonstrated that patients with severe COVID-19 had a sevenfold higher risk of developing invasive aspergillosis compared to patients with influenza, suggesting that SARS-CoV-2 produces a unique immunological susceptibility pattern distinct from other viral pneumonias.[41] More recent analyses from Asia and South America confirmed similar trends, with CAPA consistently associated with prolonged mechanical ventilation, higher ICU severity scores, and increased inflammatory markers.[42]

Outcomes for CAPA patients remain poor despite early antifungal therapy. Mortality is driven not only by fungal progression but also by the underlying severity of viral lung injury, often resulting in refractory hypoxemia and multisystem deterioration. First-line treatment typically involves voriconazole or isavuconazole, with amphotericin B reserved for azole-resistant cases or breakthrough infections.[43] However, diagnosis is often delayed due to overlapping radiological findings between COVID-19 and fungal pneumonia, challenges in obtaining bronchoscopy samples during pandemic restrictions, and limitations of serum galactomannan testing in non-neutropenic patients. These diagnostic barriers frequently result in late initiation of antifungal therapy, contributing to high case fatality rates.

The emergence of CAPA underscores the broader theme of COVID-19–associated opportunistic infections driven by a combination of viral immunopathology, therapeutic immunosuppression, and critical care–related factors. Unlike mucormycosis, which was driven by metabolic vulnerability and steroid misuse in specific regions, CAPA represented a global phenomenon affecting intensive care units across continents. Its recognition reshaped fungal diagnostic algorithms during the pandemic and reinforced the importance of vigilant surveillance in patients with severe viral pneumonia.

2.3 *Candida auris*

Candida auris became one of the most prominent fungal threats during the COVID-19 pandemic, with several ICUs worldwide reporting sudden, dense outbreaks. COVID-19 created highly permissive conditions for *C. auris* transmission—prolonged ventilation, extensive device use, broad-spectrum antibiotic exposure, and overwhelmed infection-control systems all contributed to rapid spread among critically ill patients.[44] The organism's ability to persist on surfaces, colonize equipment, and survive standard disinfectants enabled

continuous transmission even in hospitals with established surveillance measures.

A key feature distinguishing *C. auris* from other non-albicans *Candida* (NAC) species is its **multiclass antifungal resistance**. Fluconazole resistance is nearly universal, amphotericin B susceptibility is commonly reduced, and emerging *FKS1* mutations are now driving echinocandin resistance. As a result, echinocandins remain first-line therapy, but rising resistance threatens the reliability of this class.[45] Pathogenically, *C. auris* forms resilient biofilms on indwelling devices and adheres strongly to abiotic surfaces, supporting persistent colonization and environmental spread at a scale rarely observed in other NAC species.

During the pandemic, several regions documented major *C. auris* outbreaks. A center in New Delhi reported a surge in bloodstream infections in severe COVID-19 cases, with most isolates resistant to fluconazole and a proportion showing reduced amphotericin B susceptibility.[46] Hospitals in New York identified ongoing environmental contamination—ventilators, bed rails, monitors, and reusable devices repeatedly tested positive despite routine disinfection—facilitating sustained intra-ICU transmission.[47] Similar outbreak patterns were reported across Brazil, South Africa, and the Middle East, driven by prolonged ICU stays, heavy antimicrobial pressure, and staffing shortages during pandemic peaks.[48]

Mortality associated with *C. auris* bloodstream infections remained high, often ranging from 30–60% in COVID-19 patients. Contributing factors included delayed identification, multidrug resistance, and severe underlying respiratory failure. Diagnostic challenges persist, as several conventional laboratory systems misidentify *C. auris* as other Candida species, delaying targeted therapy.[49]

Overall, the pandemic amplified every known advantage of *C. auris*—environmental persistence, biofilm formation, and drug resistance—allowing it to emerge as one of the most difficult secondary fungal pathogens to control in COVID-19 ICUs.

3. VIRAL REACTIVATIONS & OPPORTUNISTIC COMPLICATIONS DURING COVID-19

3.1 Varicella-Zoster Virus (VZV) Reactivation

A notable rise in herpes zoster (HZ) cases was reported worldwide during the COVID-19 pandemic, drawing attention to the impact of SARS-CoV-2–induced immune disruption on latent neurotropic viruses. Varicella-zoster virus remains dormant in sensory ganglia, where its reactivation is normally controlled by intact, T-cell–mediated immunity. COVID-19, however, induces persistent lymphopenia, functional exhaustion of $CD4^+$ and $CD8^+$ cells, disrupted interferon signaling, and broad immune dysregulation—conditions that weaken the host's ability to suppress latent viral reservoirs. As a result, clinicians observed shingles in individuals without classical risk factors, including younger adults and those with only mild initial COVID-19.

Large population-based studies support these observations. A retrospective U.S. cohort study of **over 2.4 million adults aged ≥50 years** demonstrated a **15% higher incidence of HZ following COVID-19 infection**, with risk increasing to **21% among hospitalized patients**, and peaking within the first six months' post-infection.[50] Similarly, a U.S. insurance-claims analysis involving **394,677 COVID-19 patients** reported a significantly elevated risk of VZV reactivation within 90 days of diagnosis, independent of age or comorbidities.[51] A Spanish case–control study further showed that individuals with recent SARS-CoV-2 infection had a **2.8-fold higher risk** of developing shingles compared to matched controls, with more severe dermatomal involvement and higher pain scores.[52] Multicenter ophthalmology units in China also documented an unexpected rise in herpes zoster ophthalmicus among post-COVID patients, frequently associated with lymphopenia and systemic corticosteroid exposure.[53]

COVID-19–specific treatments contributed additional risk factors. Corticosteroids, IL-6 inhibitors, and JAK inhibitors suppress antiviral pathways essential for maintaining VZV latency, and several case series suggested that patients receiving these agents were more prone to severe or atypical zoster presentations. Although antiviral agents—acyclovir, valacyclovir, and famciclovir—remained effective, delayed presentation was common due to misclassification of early lesions as COVID-related dermatological findings. Morbidity was dominated by severe neuropathic pain and an increased frequency of post-herpetic neuralgia, particularly in older adults and those with prolonged immune recovery. Mortality remained low overall, but disseminated and ophthalmic zoster were occasionally reported in critically ill or immunosuppressed COVID-19 patients, underscoring the vulnerability of this subgroup.

The surge in VZV reactivation during the pandemic reflects the broader systemic immune imbalance caused by SARS-CoV-2 infection. The consistency of findings across multicenter, real-world datasets reinforces the need for heightened clinical vigilance and supports consideration of herpes zoster vaccination in populations at increased risk.

3.2 Cytomegalovirus (CMV) Reactactivation

Cytomegalovirus reactivation emerged as a clinically significant complication among critically ill COVID-19 patients, reflecting the profound immune dysregulation induced by SARS-CoV-2. CMV, a ubiquitous β-herpesvirus, establishes lifelong latency within myeloid lineage cells and is typically contained by robust $CD4^+$ and $CD8^+$ T-cell responses. Severe COVID-19, however, disrupts these antiviral defenses through persistent

lymphopenia, T-cell exhaustion, impaired interferon signaling, and heightened systemic inflammation, creating a permissive environment for latent CMV to reactivate. This phenomenon was increasingly recognized in ICUs, often manifesting as unexplained fever, worsening respiratory failure, or hematological abnormalities, all of which overlapped with severe COVID-19, complicating diagnosis.

Several studies documented this trend. In a multicenter French ICU cohort, **CMV reactivation occurred in nearly 20% of mechanically ventilated COVID-19 patients**, with reactivation strongly associated with prolonged ventilation, higher severity scores, and increased mortality.[54] A German prospective study reported CMV DNAemia in **25–30% of critically ill COVID-19 cases**, particularly those with sustained lymphopenia and high-dose corticosteroid exposure, and noted that reactivation correlated with longer ICU stays and secondary bacterial infections.[55] Similarly, a U.S. tertiary-care analysis found that CMV reactivation was independently linked to increased risk of respiratory deterioration, prolonged oxygen dependency, and higher 60-day mortality, even after adjusting for baseline comorbidities and disease severity.[56]

COVID-19–related treatments may further contribute to CMV emergence. Corticosteroids, IL-6 inhibitors, and immunosuppressive agents used for cytokine storm blunt key antiviral pathways—especially IFN-γ–mediated and cytotoxic T-cell–mediated control of CMV. Case series from Italy and Spain reported CMV disease—including colitis, hepatitis, and pneumonitis—in patients receiving prolonged corticosteroid regimens or multiple immunomodulators for severe COVID-19. These manifestations often appeared late during hospitalization or during clinical deterioration after an apparently stable period, emphasizing the importance of active surveillance in high-risk patients.

Treatment typically involves ganciclovir or valganciclovir, with foscarnet reserved for resistant isolates or patients with cytopenias. However, management is complicated by overlapping clinical features between CMV pneumonitis and severe COVID-19 pneumonia, and by concerns regarding antiviral toxicity in already critically ill individuals. Mortality among patients with CMV reactivation is consistently higher across cohorts, ranging from **40% to over 60%** in those with CMV pneumonitis or multisystem involvement.[57] Whether CMV reactivation directly worsens outcomes or serves as a biomarker of profound immune collapse remains debated, but the association with severe disease is unequivocal.

The prominence of CMV reactivation in COVID-19 ICUs illustrates how SARS-CoV-2 disrupts antiviral immunity beyond its direct effects. Reactivation reflects deep immunological injury rather than pre-existing immunocompromise, underscoring the need for targeted monitoring strategies and judicious use of immunomodulatory therapies in patients at risk. CMV surveillance may be particularly valuable in individuals with prolonged lymphopenia, extended ventilation, or repeated immunosuppressive interventions.

3.3 Epstein–Barr Virus (EBV) Reactactivation

Epstein–Barr virus, a γ-herpesvirus that establishes latency within B lymphocytes, was frequently reported to reactivate in patients with moderate to severe COVID-19. EBV reactivation is closely linked to impaired T-cell surveillance, and SARS-CoV-2 infection induces several immunological changes—persistent lymphopenia, T-cell exhaustion, and dysregulated cytokine profiles—that collectively weaken control of latent EBV. As early as the first pandemic wave, clinicians noted unexplained fever, elevated inflammatory markers, and atypical lymphocyte profiles in SARS-CoV-2 patients, prompting investigations into latent viral reactivation.

Evidence emerged primarily from smaller cohort studies. A Chinese analysis of hospitalized COVID-19 patients found that **over 50% showed EBV DNAemia**, and reactivation correlated with higher CRP levels and more severe fever patterns.[58] A German study similarly reported EBV viremia in critically ill patients, with reactivation associated with prolonged ICU stays and higher inflammatory cytokine concentrations, particularly IL-6 and TNF-α.[59] While EBV reactivation rarely caused classical mononucleosis-like illness, it often contributed to the broader hyperinflammatory state, raising the possibility that EBV may exacerbate systemic inflammation in severe COVID-19.

Treatment is primarily supportive, as EBV lacks routinely effective antivirals. In rare cases with significant viremia or suspected EBV-driven hyperinflammation, clinicians relied on immunomodulation and careful management of secondary complications. Mortality directly attributable to EBV is uncommon; however, several studies suggested that EBV reactivation may serve as a **marker of severe immune dysfunction**, correlating with worse respiratory trajectories and prolonged recovery rather than acting as an independent pathogen.

Overall, EBV reactivation during COVID-19 appears to reflect **immune collapse rather than a distinct viral disease**, and while clinically relevant, it carries lower pathogenic significance compared to CMV or VZV. Its recognition is nevertheless important as part of the broader landscape of opportunistic viral reactivation triggered by SARS-CoV-2.

4. PROTOZOAL COMPLICATIONS TRIGGERED DURING COVID-19

4.1 *Strongyloides stercoralis* — Hyperinfection Syndrome

Strongyloides stercoralis is a soil-transmitted nematode capable of lifelong autoinfection, often remaining

clinically silent in immunocompetent hosts. Its ability to maintain internal cycles of reinfection distinguishes it from most helminths and creates a latent reservoir that may reactivate under conditions of impaired host immunity. Corticosteroids markedly increase the risk of progression to **hyperinfection syndrome** by suppressing eosinophil and Th2 responses and accelerating larval development, with dissemination frequently involving the lungs, gut, and central nervous system.

During the COVID-19 pandemic, multiple case reports, series, and reviews documented *S. stercoralis* hyperinfection precipitated by corticosteroid or immunomodulator use for SARS-CoV-2 disease. A systematic review of COVID-associated strongyloidiasis identified numerous published cases in which hyperinfection followed dexamethasone or other immunosuppressants, emphasizing that even short courses of steroids may unmask severe disease in previously undiagnosed carriers.[60] Cohort and case-series data from endemic regions describe presentations including sudden respiratory deterioration, diffuse pulmonary infiltrates with larvae in sputum, gram-negative bacteremia, and fulminant sepsis—features that are easily confounded with worsening COVID-19 and often cause diagnostic delay.[61,62] Individual case reports have documented fatal outcomes despite antiparasitic therapy, underscoring the high case-fatality risk when recognition is delayed.[63]

Diagnosis is challenging: stool microscopy has limited sensitivity, serology may be unreliable in acute illness, and eosinophilia is often suppressed by corticosteroids. Detection of larvae in respiratory specimens or by serial stool examinations, together with a compatible clinical picture, remains the cornerstone of diagnosis. Treatment requires prompt administration of ivermectin (oral or, in severe cases, parenteral where available), often combined with albendazole in refractory cases; however, outcomes are substantially better when therapy is initiated early.[64]

Reported mortality in COVID-related Strongyloides hyperinfection is high, frequently exceeding 40–50% in published series, particularly when complicated by secondary bacterial sepsis or multiorgan failure. Given these data, several tropical medicine and infectious disease authorities recommend pre-emptive screening or empiric ivermectin prophylaxis for individuals from endemic areas or with risk factors prior to initiating systemic corticosteroids for COVID-19.[65] Incorporating risk assessment and targeted prophylaxis into COVID-19 treatment protocols can substantially reduce the incidence of fatal hyperinfection in vulnerable populations.

DISCUSSION

The secondary infections observed throughout the COVID-19 pandemic reveal how profoundly SARS-CoV-2 disrupts host immunity, clinical pathways, and hospital systems. Across all pathogen groups, the evidence consistently demonstrates that COVID-19 creates a permissive biological and clinical environment in which otherwise contained, latent, or opportunistic organisms behave with unusual aggressiveness. This is driven primarily by sustained lymphopenia, T-cell exhaustion, dysfunctional neutrophils, impaired interferon responses, and prolonged systemic inflammation, all of which collectively weaken the immune barriers that typically restrict reactivation and opportunistic invasion.[66] The addition of corticosteroids, IL-6 inhibitors, and broad-spectrum antibiotics further amplifies susceptibility by suppressing cell-mediated immunity and reshaping microbial ecology.[67]

This convergence of viral immunosuppression and therapeutic pressure explains the striking rise in latent infections such as *Mycobacterium tuberculosis*, VZV, CMV, and EBV. These pathogens rely heavily on intact T-cell–mediated control, and their increased reactivation rates during COVID-19 reflect the depth of cellular immune failure induced by SARS-CoV-2.[68,69] Similarly, the unprecedented burden of invasive fungal infections—particularly mucormycosis and CAPA—illustrates how COVID-19 compromises innate immunity. Neutrophil dysfunction, alveolar injury, and disrupted mucosal defenses created highly permissive conditions for angioinvasive and filamentous fungi, resulting in severe disease even in individuals previously not considered high risk.[70]

Alongside these immunological mechanisms, pandemic-related healthcare disruptions played an equally important role. Overwhelmed ICUs, prolonged mechanical ventilation, increased device use, and reduced adherence to infection-control protocols enabled the rapid expansion of multidrug-resistant organisms such as *Klebsiella pneumoniae* and *Candida auris*.[71] Empiric and often unnecessary early antibiotic use further selected for resistant strains, reshaping hospital microbial ecology and driving outbreaks in critically ill COVID-19 patients.[72] These patterns highlight how pandemics can alter pathogen behavior not only through biological susceptibility but also through systemic strain and lapses in clinical practice.

Diagnostic complexity further compounded morbidity. Many secondary infections present with symptoms or radiographic features similar to progressive COVID-19 pneumonia, delaying recognition and treatment. CAPA, early mucormycosis, CMV or EBV reactivation, and *Strongyloides* hyperinfection frequently mimicked viral progression, contributing to late diagnosis and poorer outcomes.[73,74] This overlap underscores the need for high clinical suspicion and structured diagnostic algorithms during future respiratory pandemics.

Geographical variations also shaped the pattern of secondary infections. India's mucormycosis surge

reflected a unique intersection of diabetes prevalence, steroid overuse, and environmental exposure[75], whereas regions in Latin America and Southeast Asia reported more *Strongyloides* hyperinfection due to underlying endemicity and lack of routine screening.[76] MDR *C. auris* clusters were especially severe in areas with pre-existing colonization pressure and limited infection-control infrastructure.[77] These regional differences demonstrate that the burden of secondary infections is not uniform and must be interpreted through local epidemiological and health-system contexts.

Overall, the pandemic showed that secondary infections are not incidental complications but central determinants of disease severity and outcome. The patterns observed across bacteria, fungi, viruses, and protozoa emphasize the necessity of integrating early antimicrobial stewardship, targeted fungal and viral surveillance, context-specific parasite screening, and stricter ICU infection-control measures into pandemic preparedness frameworks. Future respiratory outbreaks with similar immunological footprints are likely to reproduce these complications unless these lessons are operationalized in clinical practice.[78] Understanding how SARS-CoV-2 alters host–pathogen interactions is therefore essential not only for treating severe COVID-19 but for anticipating and preventing the secondary infections that amplify mortality in pandemics.

CONCLUSION

COVID-19 created an unprecedented convergence of immunological disruption, therapeutic immunosuppression, and critical-care strain, resulting in the emergence of secondary infections that were unusually aggressive, often unexpected, and globally consequential. Across bacterial, fungal, viral, and protozoal pathogens, a consistent pattern emerged: SARS-CoV-2–induced lymphopenia, T-cell exhaustion, impaired interferon signaling, and widespread corticosteroid use collectively weakened host defenses and unmasked infections that rarely surfaced in routine clinical settings.[79,80]

The pandemic amplified latent pathogens such as *Mycobacterium tuberculosis*, VZV, CMV, and EBV, which reactivated at unusually high rates due to profound dysregulation of cellular immunity.[81,82] Simultaneously, ICU-associated outbreaks of multidrug-resistant organisms—including *Klebsiella pneumoniae* and *Candida auris*—accelerated under antibiotic pressure, prolonged mechanical ventilation, and the collapse of routine infection-control systems.[83] Furthermore, steroid-triggered *Strongyloides stercoralis* hyperinfection emerged as a life-threatening complication, particularly in endemic regions, highlighting the unintended consequences of widespread immunomodulator use.[84]

These findings underscore the necessity of integrating pathogen-specific surveillance, antimicrobial stewardship, and targeted screening strategies into COVID-19 clinical pathways, especially in high-risk settings worldwide. Strengthening diagnostic capacity, recognizing epidemiological vulnerabilities, and applying immunosuppressive therapies judiciously will be crucial to mitigating similar outbreaks in future pandemics. Ultimately, understanding the interplay between SARS-CoV-2 and these emergent co-infections is essential for improving preparedness, reducing preventable deaths, and guiding evidence-based therapeutic practice.[85]

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