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VIRAL INTERFERENCE AND CO-PATHOGENESIS: HOW SARS-COV-2 MODULATES THE INCIDENCE OF SECONDARY VIRAL INFECTIONS

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Abstract

The advent of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has shaken the dynamic nature of the human respiratory virome and caused robust interactions among pathogens either through viral interference or co-pathogenesis. SARS-CoV-2 can suppress host innate immunity in a process known as viral interference, namely, the use of viral proteins to suppress interferons via viral protein NSP1 to establish dominance over the cellular setting. On the other hand, synergistic co-pathogenesis consists of initial infection causing immune exhaustion, hyper inflammation, and necroptosis of respiratory epithelium, which creates a very susceptible microenvironment that allows secondary viral and bacterial invaders to bypass the immune mechanism. Epidemiologically, the de-escalation of COVID-19 non-pharmaceutical interventions (NPIs) has left the population-wide with an immunity debt that has seen, off-season increases with endemic viruses, such as Respiratory Syncytial Virus (RSV) and Influenza, to create a post-pandemic tripledemic. Also, the extreme immune dysregulation and lymphopenia of the severe cases of COVID-19 have been found to stimulate the opportunistic reactivation of latent pathogens, such as the Epstein - Barr virus. To address the issue of these molecular mechanisms and epidemiological changes, this review highlights the urgency of using the holistic approach to molecular surveillance and the development of new dual-target pharmacologic interventions, including probenecid, in the future to cope with the complex pathology.

1. INTRODUCTION

The development of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has changed the clinicists conceptualization of how clinical experts perceive respiratory pathogens, as it no longer represents just another acute infection but should be viewed in the context of a more dynamic human virome. When intruding into the respiratory tract, SARS-CoV-2 determines the immunological background of the host, responding to old and new pathogens in two ways in an interesting clinical paradigm viral interference and co-pathogenesis.

Viral interference is a relationship of antagonism. The phenomenon has been historically seen during the interaction of viruses H1N1 in 2009 and Rhinovirus that the initial virus induces an intense host response with interferon that suppresses secondary viral infection in a competitive manner (Piret & Boivin, 2023). In contrast, co-pathogenesis is synergistic as a port of entry to super infection. Under such conditions, the initial infection of SARS-CoV-2 causes severe immune drain and necroptosis in the respiratory epithelial barrier (Li et al., 2023), which makes the

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human body very susceptible to secondary bacterial and viral invasors (Finsterer, 2024).

With the unprecedented changes in the seasonal viral processes and the apparent clinical threat of concurrently running tripledemic waves, it is essential to synthesize the molecular interactions of these processes. The purpose of this review is to deconstruct the immunological processes that SARS-CoV-2 uses to regulate the occurrence of the secondary viral infections to offer an integrative view of how these changes are likely to predict and control complex co-infection patterns in the future.

2. The Baseline Immunological Landscape of COVID-19

To fully comprehend how SARS-CoV-2 prepares the ground (or welds the window) to other viruses we have to first determine the underlying immune response that the virus provokes in the host.

Rapid, multi-layered innate and adaptive response is an immune reaction of the host that is formed at an early infection (Finsterer, 2024). The pattern recognition receptors enable the innate immune system to detect viral RNA, and this is made in an effort to establish instant antiviral condition. Simultaneously, adaptive immune response is triggered in order to get rid of the virus and the process is based on the selective growth of memory T-cells to the virus and fabrication of neutralizing antibodies by B-cells.

This is the initial acute response which predetermines complicated COVID-19 case, and, in keeping with hyper inflammation to ensuing immune fatigue, the consecutive dysregulation program.

Hyper inflammation becomes uncontrolled, usually evolving into pathological hyper inflammation, which is also known as a cytokine storm, in addition to unchecked overproduction of pro-inflammatory mediators, when they cause gross damage to host tissues.

The immune system produces conditions that are predetermined by the secondary events following active and sustained hyper inflammatory response and then switches to the extreme exhaustion frequently soon (Li et al., 2023). Such depletion and inactivity of the lymphocytes significantly impairs the lymphocytes populations which are later capable of guaranteeing the creation of the biological susceptibility when secondly infected with viruses and bacteria.

A cytokine storm is one of the main drivers of COVID-19-associated severe infections, which can be defined as a systemic inflammatory response characterized by excessive activities of immune cells, as well as uncontrolled secretion of proinflammatory factors IL-1 8 -TNF-a, IL-1 8 -IL-1-F and IL-1 8 -IL-6 (Alhumaid et al., 2022). The cause of such an exaggerated release of cytokines is the subsequent rapid viral invasion followed by cell death, which is a major factor in acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) (Alhumaid et al., 2022). This inflammatory process does not only cause damage to the lungs but also causes extensive tissue damage of the vascular endothelium and cardiac myocytes (Swetha et al., 2023). Of paramount importance is that the systemic anarchy of the cytokine storm substantially impairs host resistance to secondary pathogenic agents, so such patients are much more vulnerable to both secondary microbial co-infections and super infections (Alhumaid et al., 2022).

Infectious disease SARS-CoV-2 infection has been demonstrated to decrease the major immune cells, such as that of natural killer (NK) cells, dendritic cells (DC), and T cells in severe cases, which destabilizes the antiviral immune response (Liao et al., 2020). This intense immunosuppression actively compromises the primary immune obstacles of the host, which creates a very accessible microenvironment towards secondarily invading viruses (Dee et al., 2022).

3. Viral Pathogenesis: Interference vs Co-pathogenesis

Viral interference is a phenomenon in which infection with one virus affects or inhibits infection or replication of another virus in a single host.

SARS-CoV-2 disrupts normal antiviral defense mechanisms by modulating host immune responses and cell signaling (Thirumugam et al., 2023). SARS-CoV-2 has been shown to suppress host immune signaling, and this effect has been

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attributed to various viral proteins, including non-structural protein 1 (NSP1) (Zhu et al., 2022), which inhibits host mRNA translation and antiviral immune responses, including interferons, thereby suppressing host innate immune responses (Zhang, Chen, et al., 2021; Zhang, Garner, et al., 2021). This suppression of host immune responses has been shown to alter the host environment and disrupt antiviral response to other viruses. SARS-CoV-2 infection has been shown to reduce key immune cells, thereby disrupting antiviral defense mechanisms (Liao et al., 2020). The suppression of host immune responses allows SARS-CoV-2 to dominate the host cell environment and disrupt normal antiviral competitions between viruses.

Moreover, the virus has developed mechanisms to promote its entry and replication in host cells, including binding to the host cell's ACE2 receptor (Zipeto et al., 2020), uptake via clathrin-mediated endocytosis (Zhao et al., 2021), and stimulating the host cell's endocytic trafficking regulators (Kliche et al., 2021), including SNX27 (Sorting Nexin 27), to promote efficient uptake of the virus (Zhao et al., 2021). This, in turn, disrupts the host's immune response to other viruses, creating a condition in which the host's response to other viruses will be impaired.

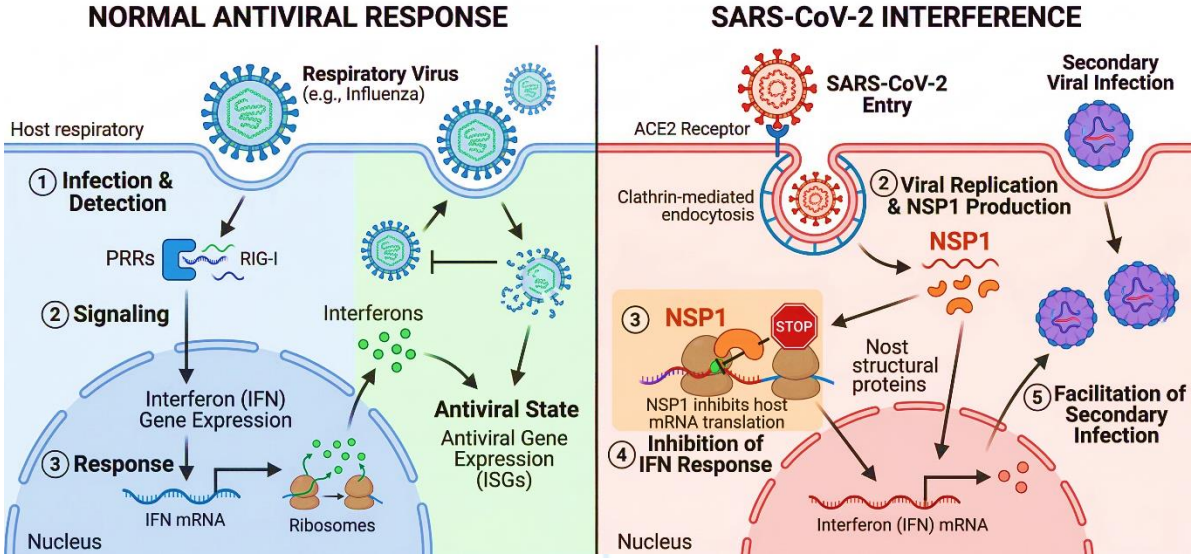

Figure 1: Mechanism of Viral Interference by SARS-CoV-2

The competitive exclusion rule has a strong influence on the relations of SARS-CoV-2 to the rest of respiratory viruses. Through this ecological phenomenon, the competition between two viruses occupying the same niche, such as host respiratory cell, will eventually force one of them to eventually crowd out the other one as far as both of them multiply in a similar manner and how adaptable is the host to it (Yahya et al., 2021). Conducting an example, human rhinoviruses have been found to be able to halt the replication of SARS-CoV-2 in the airways and thus trigger an early and strong interferon response (Fomenko et al., 2021). However, given the large-scale capabilities to reproduce and evade immunity in case it manages to establish an infection, the disease is often accompanied by other variations of viruses with which it provides identical cell conditions (Volpert et al., 2023).

The concept of co-pathogenesis was developed when more than two infectious agents worked together in the host, causing increased anti-immune regulation and further tissue damage. The capabilities to break into the cellular system and avoid innate immune recognition indicate an intensive dependence of the virus on its virulence. ACE2 receptor binding as well as the use of viral proteins to act as interferon antagonists suppresses essential early innate immune responses (Nadraga et al., 2025).

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This significant immunosuppression actively undermines the immune major barriers of the host and it forms a highly conducive microenvironment to secondary invaders, i.e., viruses. Moreover, recuperating patients also experience a long-term immune dysregulation; an instance in point is an observed decrease of the percentage of un-switched memory B cells in post-infection profiles and a cellular response after second pathogen exposure. Once an invasion of a secondary virus arrives into this soiled terrain, it experiences a low antiviral activity, which facilitates a viral burst, hyper-inflammatory cytokine cascades, and a speedy respiratory epithelium destruction (Dee et al., 2022).

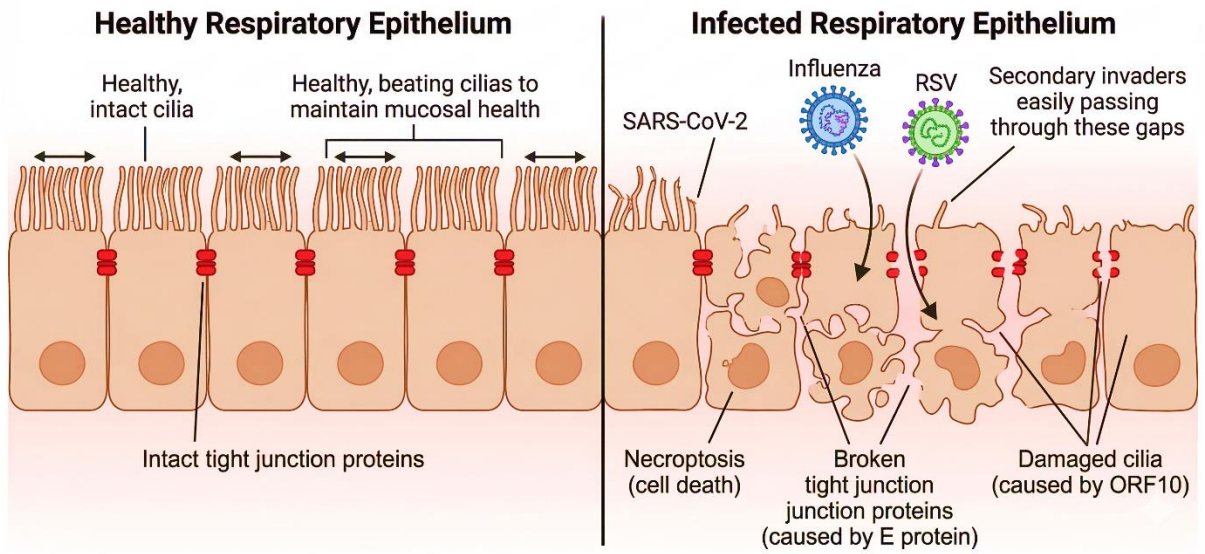

Figure 2: Shattered Barrier Mechanism

Airway epithelial mucosal is the physical and immune defense of respiratory pathogens of a mucosal. The immediate impact of SARS-CoV-2 on this structural integrity is the induction of necroptosis in human airway epithelial cells in polarized cells (Li et al., 2023). More so, one can say that E (envelope) protein of SARS-CoV-2 proactively represses the expression of the tight junction proteins and interrupts transepithelial chloride flow to result in the severe impairment of the barrier function and inflammation at the skin level (Zhang et al., 2023). Stabilizing the mechanical barrier, SARS-CoV-2, de-facto creates an aperture and permits entry to the lower respiratory tract by secondary pathogens without restrictions (Aslam et al., 2023).

One of the primary defense mechanisms is mucociliary clearance (MCC) which entails the mechanical entrapment and elimination of pathogens inhaled. SARS-CoV-2 is extremely capable of avoiding and causing the destruction of this pathway; the virus targets cilia cells directly, and the open reading frame 10 (ORF10) protein facilitates the destruction of key proteins like cilia (Fonseca et al., 2022). This rupture affects mucosal movement causing extremely serious mucus blockage in the deep lung tissues (Garcia et al., 2023). It has been clinically established that COVID-19 causes OCC to be transported much more slowly, forming a stagnant microenvironment that makes patients highly vulnerable to the subsequent infection (Kahraman et al., 2021).

4. Epidemiological Shifts and the Post-NPI Tripledemic

The non-pharmaceutical interventions for COVID-19 have greatly impacted the epidemiology of common respiratory viruses. The detection rate of influenza A virus (IAV), influenza

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B virus (IBV), and adenovirus (ADV) decreased significantly during the non-pharmaceutical intervention period (2020-2022) due to decreased social contact. However, in 2023-2024, which is known as the post-non-pharmaceutical intervention period, there was a dramatic increase in these viruses, with the overall positive detection rate for acute respiratory tract infections (ARTIs) increasing from 15.47% during the pandemic to 32.76% in the non-pharmaceutical intervention period (Zheng et al., 2025). The detection rate of IAV increased from 4.46% to 10.58%, and that of ADV increased from 3.25% to 8.17% in 2023-2024.

The removal of NPIs resulted in a significant disruption in the natural seasonal pattern of respiratory viruses and has resulted in an "immunity debt."

Although the detection rates for RSV were relatively low before the pandemic (3.16%), there was a notable increase in the detection rates post-NPI, peaking at 9.26% (Zheng et al., 2025).

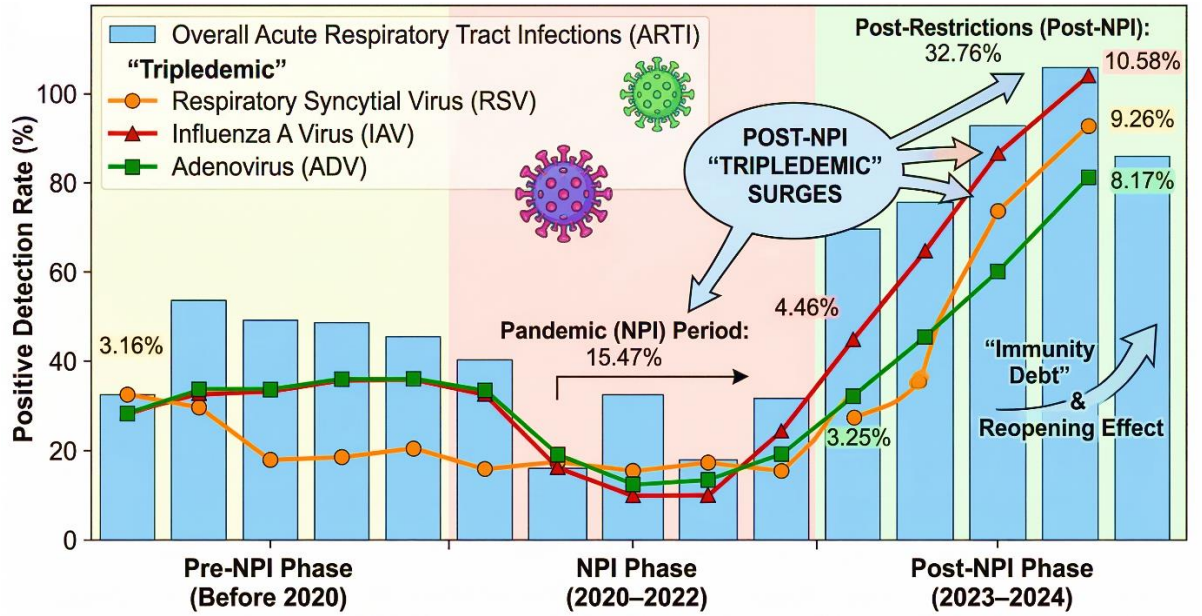

Figure 3: Epidemiological Shifts and the Post-NPI "Tripledemic"

The post-NPI results showed unexpected peaks in the detection rates in the autumn and spring seasons. In the autumn season, the detection rates increased significantly from 13.77% before the implementation of the NPIs to 33.05% post-NPI (Zheng et al., 2025). The detection rates for the RSV virus were atypically high in the spring season at 9.89% post-NPI, as opposed to the typical winter season (Zheng et al., 2025).

Though the peak of viral waves has changed, the burden of illness has been significant, especially when compared to SARS-CoV-2 mono-infections. Infants (0-1 years) were found to be the most affected following the resurgence of RSV, with the highest rate of detection at 18.92% after NPI (Zheng, Zhou et al., 2025). In contrast, IAV and IBV were found to have higher rates of detection in older children (6-14 years) (Zheng et al., 2025).

Hospital data suggests that SARS-CoV-2 has a higher 30-day mortality rate (aHR 4.43) compared to influenza, though the co-circulation of these viruses has complicated the illness (Hedberg et al., 2022). There is a "substantial overlap" in the presence of clinical symptoms such as fever, cough, and dyspnea among SARS-CoV-2, influenza, and RSV, which makes differential diagnosis difficult without molecular diagnosis (Hedberg et al., 2022).

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5. Clinical Profiles of Key Secondary Viral Infections

The change of natural seasonal cycles caused complicated co-circulation of respiratory pathogens as they have been determined through the epidemiological shifts of the post-NPI period. Finding the boundaries between SARS-CoV-2, influenza, and RSV on the basis of clinical manifestation, i.e., fever, cough, and dyspnea is becoming more and more difficult without detailed molecular diagnostics (Hedberg et al., 2022).

Different report studies show evidences of the co-infection of SARS-CoV-2 and influenza (Ozaras et al., 2020; Kondo et al., 2020; Singh et al., 2020) with viral pathogens (Touzard-Romo et al., 2013), and bacterial pathogens (Khaddour et al., 2020; Edrada et al., 2020; Cucchiari et al., 2020; Sohal et al., 2020). Findings from a number of reported case studies also support the evidence of co-infection but later got confused with superinfection (Feldman & Anderson, 2024). In 2023, Wong et al., provide evidences on synergistic effect of co-infection of Influenza and SARS-CoV-2 resulting in severe pathological conditions.

Co-infection between SARS-CoV-2 or Respiratory Syncytial Virus (RSV) is among the problems that have been clinically complicated with severe outcomes, particularly in children. It was the simultaneous presence of the large numbers of infants and young children with both causes of the disease that resulted in the combined exposure of infants to both pathogens simultaneously (Morris et al., 2023). The clinical outcomes of these co-infections are terrible because in most cases these infections lead to the aggravation of respiratory distress and increased hospitalization of children. It is also of note that such severity in the pathogenesis of the co-pathogens highly depends on the chronological order of infection. Despite minor attenuation of SARS-CoV-2 replication by innate response despite a transient response to primary RSV infection, reinfection of SARS-CoV-2 viruses by RSV leads to a huge respiratory pathology. In this respect, current-day pharmacological studies are looking into dual target agents such as probenecid exhibiting possibilities of controlling ACE2 expression besides having the ability to suppress RSV replication (Hong et al., 2025).

Clinical observation of infected patients with COVID-19 has shown that, among all the opportunistic pathogens, the Epstein - Barr virus (EBV) has been consistently detected during the course of the disease (Paolucci et al., 2021). EBV DNA was detected in 95.2% of ICU patients and 83.6% of sub-intensive care units. The median EBV DNA was significantly higher in ICU than in sub-intensive care units, i.e., 4709 IU/mL vs. 1890 IU/mL, showing a clear correlation between the viral load of EBV and the severity of the outcome. While all the infected patients were seropositive for CMV and Parvovirus B19, the reactivation was specific only to EBV.

The reactivation of latent EBV seems to be strongly correlated with the severe immunological dysregulation and immune exhaustion induced by SARS-CoV-2 (Paolucci et al., 2021). Severe cases of COVID-19 are associated with a considerable decrease in the number of $CD8^{+}T$ cells and Natural Killer (NK) cells. In the ICU group, the number of $CD8^{+}T$ cells were found to be as low as 95 cells/µl in comparison to 181 cells/µl in less severe cases (Paolucci et al., 2021).

Unlike T cells, B cells were found in much higher numbers in severe cases (81 cells/µl vs. 69 cells/µl). B cells are the primary site for the latent infection of EBV and hence are likely to contribute to the increase in EBV DNA (Paolucci et al., 2021). There is a strong correlation between the reduced number of $CD8^{+}T$ cells and NK cells and the increase in EBV DNA. It acts as a marker for the severity of COVID-19 (Paolucci et al., 2021).

The presence of detectable EBV DNA implies a status of extreme immune impairment that can be a contributing factor in the overall pathogenesis of the respiratory infection. Although a direct linear correlation between lymphocyte counts and EBV was not consistently demonstrated, the similarity in lymphopenia and reactivation implies a window for opportunistic reactivation by latent viruses when SARS-CoV-2 is present (Paolucci et al., 2021).

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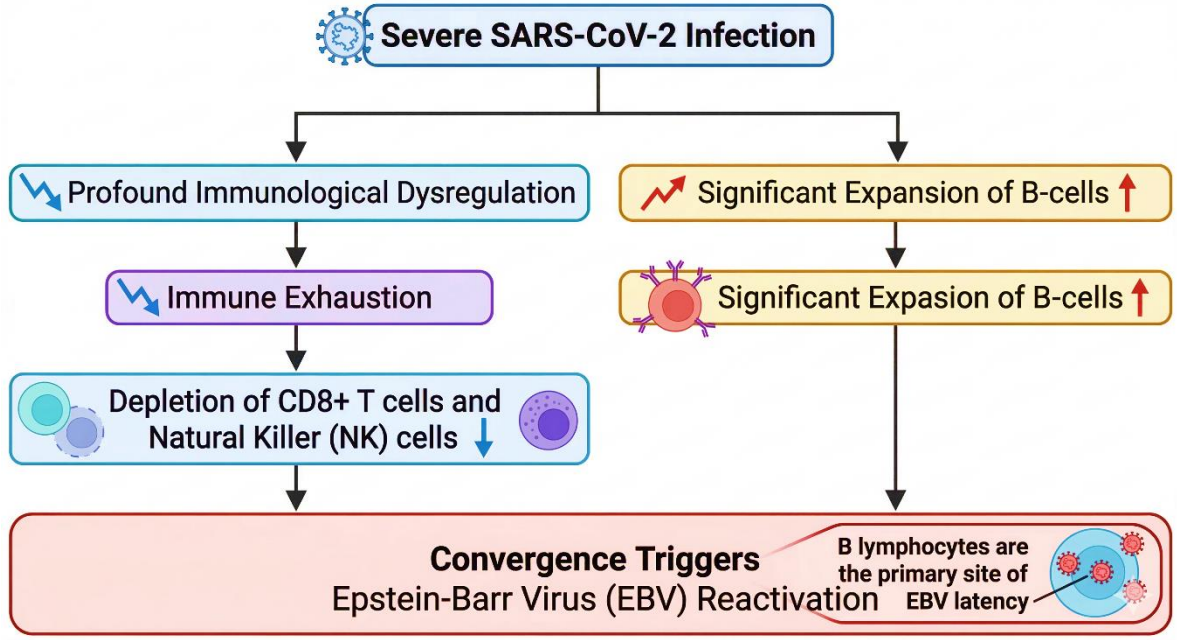

Figure 4: Latent Virus Reactivation

6. Clinical Implications and Changing Treatment Paradigms

The shift to the endemic virome of SARS-CoV-2 has dramatically complicated patient management and diagnostic guidelines and differentiation of clinical manifestations (via clinical symptoms of fever, cough, and dyspnea) among SARS-CoV-2, influenza, and RSV is now not a reliable method of patient management. Knowledge-based comprehensive molecular surveillance is a key to properly detect co-infection and provide the necessary care.

The reduction of nonpharmaceutical interventions (NPIs) has left an immunity debt that has caused unprecedented, off-season RSV and Adenovirus waves. In addition, clinicians are to suspect that, in contrast to severe and critically ill COVID-19 patients, who display overt lymphopenia, children with endemic viral co-infections can have normal immune responses or slight lymphopenia, and, as a result, the release of latent viruses would be an opportunity. Pediatricians should be on the lookout of these unusual upsurges, especially of immunologically naive babies, whose susceptibility to active RSV has continued to be of a critical nature amid the post-NPI environment. EBV test should be suggested to be screened in the intensive care facilities as it has been shown consistently to reactivate in severe cases and is an appropriate biological indicator of immune fatigue and degree of the disease.

The reduced effectiveness of conventional monotherapies against SARS-CoV-2 and RSV co-infections requires the change in the pharmacological approach. The clinical guidelines might eventually require the review and integration of dual-target candidates, including probenecid, with the capability both to inhibit the production of the host receptors, like ACE2 expression, and to block the RSV replication.

7. Future Directions and Conclusion

The changed pattern of seasonal peaks and off-season surges of endemic respiratory viruses following NPI will need continuous monitoring in order to map them. The predominant focus of virological studies should be on the determination of the precise order of co-infection since in vivo experimental models indicate that sequential order of infection reverts clinical disease and pathology radically. Also, there should be faster

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pharmacological studies of dual-target candidates such as probenecid.

The onset of SARS-CoV-2 disrupted the mechanism of transmission and coexistence of conventional respiratory variables in the host population radically. The virus silences key initial innate immune responses by binding viral proteins as interferon antagonists and ACE2 receptors. This great immunosuppression creates a very favorable microenvironment to secondary invaders of viruses. Co-infection and superinfection are dynamic, which is important to control in the transition to endemicity of the pandemic. The molecular aspects of regulation of these interactions will be at the heart of generating effective antiviral action within a post-pandemic virome.

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