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Emerging Subvariants of Covid-19 Subvariant Cicada Variant, a Systemic Overview: Diagnostic and Therapeutic Challenges Navigating the High Antigenic Shift of The Covid-19 Cicada Variant

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Abstract:

The ongoing evolution of SARS-CoV-2 has resulted in the emergence of several subvariants that are more transmissible, immune-evasive, and exhibit varying pathogenicity. Among them, the newly discovered Cicada variant is of interest to scientists because of its enormous antigenic drift and explosive dissemination worldwide. This review presents an in-depth discussion of the etiology, mutation pattern, transmission, diagnostic issues, and treatment considerations of the Cicada variant. The variant has wide mutations in the spike protein, especially in receptor-binding regions, that aid immune evasion and reduce vaccine efficacy. The available methods of diagnosis, such as RT-PCR and antigen-based methods are limited by mutation-related target failure. Monoclonal antibodies and antiviral drugs are therapeutically questionable because their efficacy is not always the same, which poses a concern regarding treatment. Implications for public health, surveillance plans, and future research directions are also discussed in this review. The dynamic character of the Cicada variant is critical to comprehending diagnostic preparedness and maximizing therapeutic interventions to support the current COVID-19 pandemic.

Keywords: COVID-19, SARS-Cov-2, Cicada Variant, Antigenic Shift, Immune Escape, Diagnostics, Therapeutics, Viral Mutations, Pandemic, Variants of Concern.

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1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), which is caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to unprecedented public health crisis, with severe effects on healthcare systems, economies, and societies around the globe. After its first discovery at the end of 2019, the virus has already shown an impressive ability to undergo genetic evolution, giving rise to new variants and subvariants with varying biological and epidemiological properties[1]. This evolutionary flexibility is mainly facilitated by viral genome mutations, especially in the spike (S) glycoprotein, which facilitates viral entry into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor and is the main target in neutralizing antibodies[2].

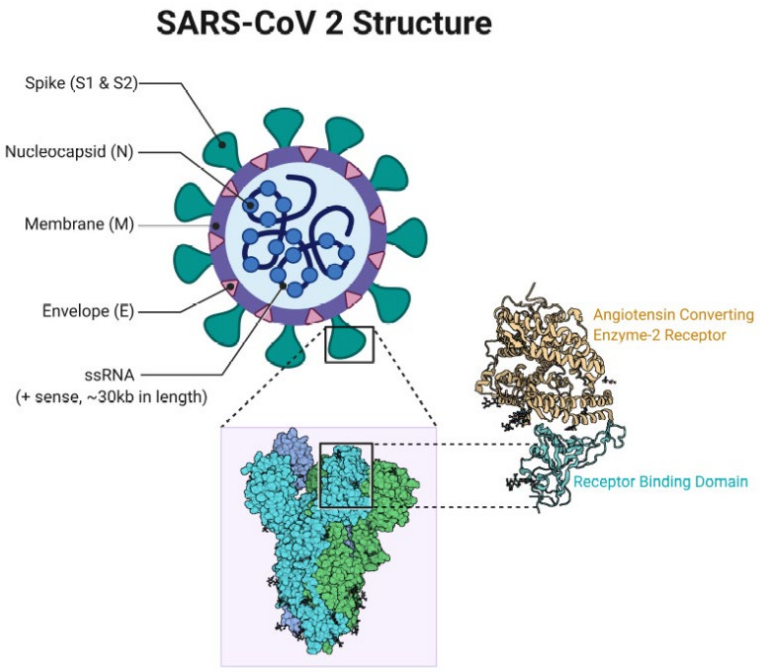

Figure 1: SARS-CoV-2 structure

Mutation of the virus, particularly in functionally important region, receptor-binding domain (RBD), and N-terminal domain (NTD) has led to variants with increased transmissibility, altered pathogenicity, and high immune escape potential. These alterations have presented significant challenges to healthcare systems around the world, affecting the dynamics of infections, exposing the reinfection risk, and decreasing the efficacy of vaccines and treatment measures. Strains of concern have shown that they can outcompete earlier strains many times, with new waves of infection and the need to keep adjusting the approaches of the public health system[3].

The appearance of the Cicada variant, in this case, can be a crucial stage in the evolutionary process of SARS-CoV-2. This type is marked by a strong antigenic shift, which is a phenomenon of significant genetic changes that considerably changes the antigenic characteristics of viruses. In contrast to antigenic drift, which is a slow and gradual process with accrued point mutations over a prolonged period, antigenic shift may confer sudden and

significant alterations to viral structure, thus enabling the virus to avoid the previous immunity that was developed through previous vaccination or infection. The Cicada variant has a high mutation rate, especially in the spike protein, which makes it more transmissible, more strongly bound to host receptors and less vulnerable to neutralizing antibodies.

Additionally, in preliminary findings, the Cicada version could have a higher immune evasion ability and possible resistance to some antiviral treatments and monoclonal antibody treatment. All of these aspects raise serious questions about how it affects the existing diagnostic accuracy, vaccine efficacy, and therapeutic effectiveness. This variant is spreading at an alarming rate and is genetically complicated, which is why it is important to investigate it thoroughly and monitor genomic surveillance[4].

The purpose of the review is to offer a systematic and detailed discussion of the Cicada variant in terms of its genetic and structural features, antigenic shift mechanisms, diagnostic issues, and therapeutic opportunities. The review also discusses the wider implications of public health in relation to this new subvariant and the significance of changeable measures in the context of adapting to changing viral hazards. These aspects should be well understood to enhance the global preparedness, direct the evidence-based policymaking, and provide the effective responses to the present and future stages of the COVID-19 pandemic.

1.1. Background and Context

Since it first appeared in 2019, SARS-CoV-2 has been actively genetically diversified to give rise to a number of significant variants, such as Alpha, Delta, and Omicron. All these variants have portrayed some different traits; in terms of transmissibility, virulence, and immune escape. An example is that the Alpha variant was found to be more transmissible, the Delta variant was also found to be more severe and the Omicron variant was demonstrated to be highly immune evasive with a significant number of spike protein mutations[5].

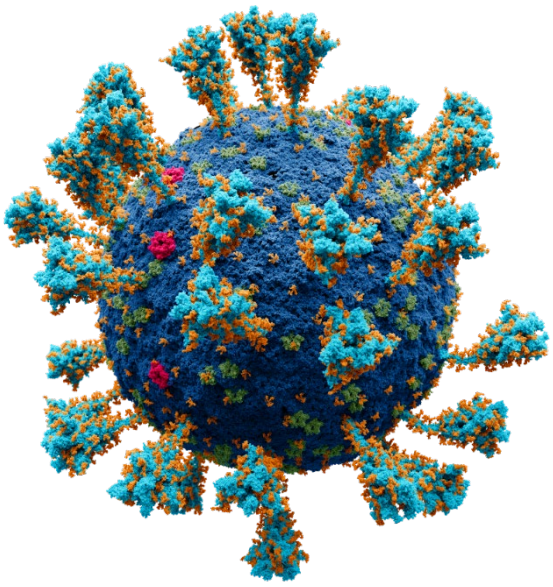

Figure 2: Omicron subvariants

Host immune response, mass vaccination, and antiviral therapy are major forces of evolution of SARS-CoV-2. Such pressures prefer mutations that make the virus more fit to survive and propagate among people[6]. The Cicada variant stands out as a mutated subvariant in this evolutionary scenario characterized by accelerated mutation accumulation and massive antigenic remodelling.

The ability to overcome immunity caused by other infections or vaccination is one of the characteristic features of the Cicada variant. This is mainly due to mutations on important antigenic sites of the spike protein that change the structural conformation of epitopes that neutralizing antibodies recognize. Consequently, the formerly effective immune response can be less effective, and it can result in higher reinfection and breakthrough infections.

Also, recombination events, in which genetic material is shared by the different viral lineages, are thought to contribute heavily to the development of the Cicada variant. These events may increase the rate of virus evolution, which may integrate beneficial mutations of other strains, increasing transmissibility and immune resistance[7].

1.2. Objectives of the Study

This review aims to:

- Examine the emergence and genetic characteristics of the Cicada variant.
- Analyze diagnostic challenges associated with mutation-driven test limitations.
- Evaluate therapeutic strategies and their effectiveness against the variant.
- Identify research gaps and future directions for managing emerging subvariants.

1.3. Importance of the Study

The research will boost the preparedness of the population to health since it will be more informed about the variants that arise and the response measures[8]. It points out the drawbacks of the existing diagnostic techniques, contributes to the optimization of treatment options, and gives information on the development of the vaccine strategy, especially in relation to immune escape.

Also, it highlights the importance of global genomic surveillance in surveillance and control of the transmission of emerging SARS-CoV-2 variants.

2. CLASSIFICATION AND MUTATIONAL PROFILE OF THE CICADA VARIANT

The Cicada variant falls under the continuous range of sublineages of SARS-CoV-2 that has undergone vast genomic diversification due to the accumulation of mutations, recombinations, as well as the pressure of adaptation[9]. The Cicada variant, unlike previous variants that showed gradual changes, is a highly mutated lineage with a high concentration of mutations in key genomic regions, especially in the spike (S) glycoprotein. It is a central protein in the viral infectivity because the protein is the one that mediates entry into host cells through interaction with the angiotensin-converting enzyme 2 (ACE2) receptor and is the main target of host immune responses.

The characteristic of the Cicada variant is that mutations are clustered in the receptor-binding domain (RBD) and at the N-terminal domain (NTD) of the spike protein. These areas play a vital role during viral binding and antibody identification. The changes in the structure of these regions can profoundly affect the viral fitness increasing the receptor affinity and, at the same time, decreasing the neutralizing antibody binding capacity. Besides mutations in spike proteins, there is also the emerging evidence that non-spike proteins such as ORF1ab and nucleocapsid proteins also contain mutations, which impact the viral replication efficiency and immune modulation[10].

This categorization of the Cicada variant as a subvariants of SARS-CoV-2 underscores its evolutionary importance as a possible immune escape lineage characterized by heightened transmissibility and a change in pathogenic behavior.

2.1. Genetic Characteristics and Mutation Patterns

The Cicada variant has a complicated mutational landscape, which demonstrates adaptation evolution and genetic restructuring through recombination. It has genetic peculiarities, in particular, it is characterized by a high concentration of mutations, especially in functionally important regions of the viral genome.

Key features include:

- **High number of spike protein mutations:** The Cicada variant carries an unusually large number of amino acid substitutions, deletions, and insertions within the spike protein. Many of these mutations are located in antigenic “hotspots,” which are known to influence antibody binding and immune recognition.

- **Enhanced receptor binding affinity:** Mutations within the RBD increase the binding strength between the viral spike protein and the ACE2 receptor. This enhanced affinity facilitates more efficient viral entry into host cells, thereby increasing infectivity and transmission potential.

- **Altered antigenic properties:** Structural modifications in antigenic epitopes lead to conformational changes that reduce the effectiveness of neutralizing antibodies. These antigenic alterations allow the virus to evade both naturally acquired and vaccine-induced immunity.

- **Increased recombination events:** The Cicada variant is hypothesized to arise partly from recombination between different SARS-CoV-2 lineages. Recombination enables the virus to combine advantageous mutations from multiple variants, accelerating its evolutionary fitness and adaptability.

These mutations, in combination, at the molecular level lead to immune escape through interference with antibody-antigen interactions[11]. To illustrate, mutations in essential residues of the RBD can substantially reduce neutralizing antibody binding without affecting or even

increasing receptor binding. There are also possibilities of mutation of the NTD that can influence antibody recognition sites, further complicating immune evasion.

These genetic changes in addition to immune escape affect viral replication kinetics, tissue tropism and pathogenicity. The selection pressure is a variant with a higher survival benefit in the context of selective pressures like host immunity and antiviral interventions[12].

2.2. Antigenic Shift and Immune Evasion

Among the most serious aspects of Cicada variant is its pronounced antigenic shift, that sets it apart in comparison to previous SARS-CoV-2 variants. Antigenic shift is a drastic and significant alteration of antigenicity of viruses leading to a markedly different immunophenotype.

The consequences of antigenic shift in the Cicada variant include:

- **Reduced neutralization by existing antibodies:** The extensive mutation profile alters the structure of key epitopes targeted by neutralizing antibodies. As a result, antibodies generated from prior infection or vaccination show diminished binding efficiency, leading to reduced neutralization capacity.

- **Increased reinfection rates:** Due to immune escape, individuals previously infected with other variants may remain susceptible to reinfection by the Cicada variant. This undermines herd immunity and contributes to sustained viral circulation.

- **Decreased vaccine-induced immunity:** Current vaccines, primarily designed against earlier viral strains, may exhibit reduced effectiveness against the Cicada variant. Breakthrough infections are therefore more likely, even among fully vaccinated individuals.

In contrast to antigenic drift and gradual accumulation of mutations, the antigenic shift as observed in the Cicada variant is a more dramatic and widespread rearrangement of viral antigenic structures[13]. This transition may be eased by the recombination process and convergent evolution whereby similar mutations occur independently to provide a selective benefit.

Immunologically, this implies that the memory response by the immune system is not effective in identifying the modified viral antigens. As a result, humoral (antibody-mediated) and to a certain degree cellular immunity can be impaired, creating a challenge to long-term immunity and immunizations[14].

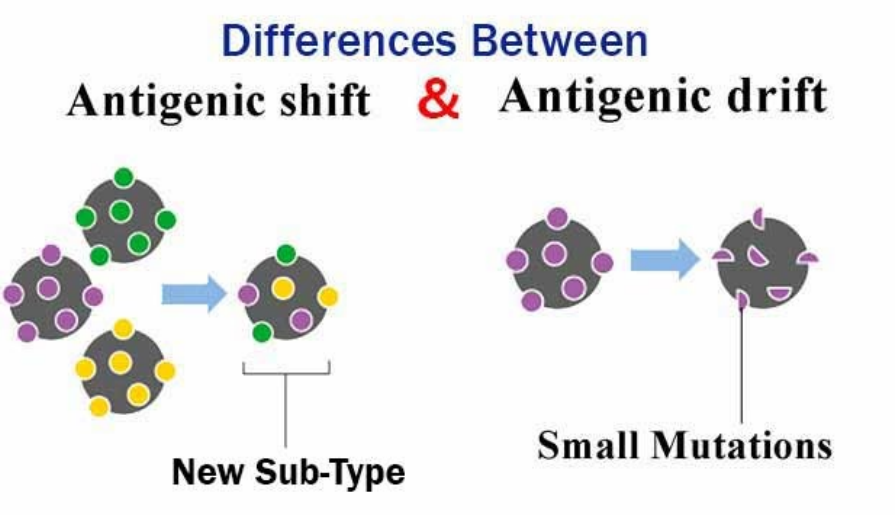

Figure 3: Schematic Representation of Antigenic Shift and Antigenic Drift in Viral Evolution

2.3. Comparison with Previous Variants

The Cicada variant demonstrates distinct differences when compared to earlier variants such as Delta and Omicron, particularly in terms of mutation burden, immune escape capacity, and transmissibility[15].

Table 1: Differential Characteristics of Delta/Omicron Variants versus the Cicada Variant

Feature	Earlier Variants (Delta/Omicron)	Cicada Variant
Mutation Rate	Moderate to high, with gradual accumulation	Extremely high with dense mutation clustering
Immune Escape	Partial escape; vaccines retain moderate protection	Extensive escape; significant reduction in antibody neutralization
Vaccine Effectiveness	Reduced but still protective against severe disease	Markedly reduced; higher breakthrough infection rates
Transmission	High transmission efficiency	Very high transmission with enhanced infectivity

Previously dominant variants like Delta were mainly linked to the severity of the disease whereas Omicron has exhibited greater transmissibility along with immune evasion. Nevertheless, the Cicada version seems to synthesize and enhance these features, displaying high transmissibility and a wide range of immune avoidance[16].

In addition to that, the structural and functional consequences of mutations in the Cicada variant are even deeper, which may indicate the transition to more adaptive and resilient viral phenotype. It is especially difficult to manage by means of the current public health measures, diagnostic tools, and therapeutic interventions.

3. METHODOLOGIES AND FINDINGS

New studies of the Cicada variant have utilized a multidisciplinary strategy of using high-level genomic sequencing, computational modeling, structural biology, and epidemiological tests on a large scale, to serve in explaining its virological and clinical pathology. Next-generation sequencing (NGS) has played a key role in determining mutation patterns and evolution of the lineage as well as bioinformatics tools and molecular dynamics simulations have contributed to understanding structural changes in the spike protein and their consequences with regard to receptor binding and immune escape[17]. More contributions to the understanding of the spread and public health impact of the variant have been due to epidemiological modeling, such as phylogenetic analysis and studies of transmission dynamics.

The overall results of these methodologies suggest that the Cicada variant is more transmissible, has pronounced immune-evasion properties, and has a mutation pattern that makes it difficult to detect it diagnostically and treat it therapeutically. All these features underscore the potential of the variant to perpetuate its spread even among previously immunized populations and pose a challenge to current health care strategies.

3.1. Diagnostic Challenges

The timely and accurate diagnosis is one of the pillars of successful pandemic management. Nonetheless, its wide scale mutational alterations in Cicada type have posed significant constraints to the current diagnostic methods, especially methods that aim at a particular viral gene or protein[18].

3.1.1. RT-PCR Limitations

The most popular method of COVID-19 detection is reverse transcription polymerase chain reaction (RT-PCR). Its usefulness, however, depends on the stability of the target genomic regions. Mutations in the regularly targeted genes, such as the spike (S) gene, nucleocapsid (N) gene, and ORF1ab region are observed in the Cicada variant[19].

A major problem is the so-called S-gene target failure (SGTF), when mutations or deletions in the spike gene do not allow its amplification in RT-PCR tests. Although SGTF has been previously utilized as a proxy marker of some variants, in the case of the Cicada variant, widespread mutations can be the result of it:

- False-negative results
- Reduced assay sensitivity
- Misclassification of variant types

Also, the mismatches between primers and probes may occur due to the substitution of the nucleotide that may affect the efficiency of the amplification process, especially when the assay

is based on the detection of a single target[20]. This highlights the importance of multiplex RT-PCR tests of various conserved areas of the viral genome to guarantee accuracy in diagnosis.

3.1.2. Rapid Antigen Tests

Rapid antigen detection tests (RADTs) offer advantages such as speed, cost-effectiveness, and ease of use, making them valuable for large-scale screening. However, these tests detect viral proteins—primarily the nucleocapsid protein—and are therefore sensitive to structural changes resulting from mutations.

In the Cicada variant, alterations in viral protein conformation may reduce antigen–antibody binding efficiency, leading to:

- Lower sensitivity, particularly in early or asymptomatic infections
- Increased false-negative rates
- Reduced reliability in community screening programs

These limitations are especially concerning in high-transmission settings, where undetected cases can contribute to silent spread. Consequently, reliance solely on antigen testing may be insufficient, and confirmatory molecular testing is often required[21].

3.1.3. Genomic Surveillance

Whole-genome sequencing (WGS) remains the most definitive method for identifying and characterizing SARS-CoV-2 variants, including the Cicada variant. It enables:

- Precise identification of mutation profiles
- Detection of recombination events
- Tracking of viral evolution and transmission pathways

Despite its accuracy, genomic surveillance faces several practical challenges:

- High cost and technical complexity
- Limited availability in resource-constrained settings
- Delayed turnaround times compared to routine diagnostics

To address these limitations, many public health systems are adopting targeted sequencing and real-time genomic surveillance networks. Integration of sequencing data with epidemiological information is critical for early detection of emerging variants and timely implementation of control measures[22].

3.2. Therapeutic Challenges

The evolving genetic landscape of the Cicada variant presents significant challenges for existing therapeutic strategies, including antiviral drugs, monoclonal antibodies, and vaccines.

3.2.1. Antiviral Drugs

Nucleoside analogs and protease inhibitors are antiviral agents that have been the main focus in the COVID-19 treatment. These medications attack preserved viral elements of replication and protein processing. Although certain antivirals still show activity against the Cicada variant, new mutations in viral enzymes, including RNA-dependent RNA polymerase (RdRp) and main protease (Mpro), have been noted, leading to concern over possible drug resistance.

Key challenges include:

- Reduced drug-binding affinity due to structural changes
- Emergence of resistant viral strains under selective pressure
- Variability in treatment outcomes across different populations

These factors necessitate continuous monitoring of antiviral effectiveness and the development of next-generation drugs targeting conserved viral regions.

3.2.2. Monoclonal Antibodies

The monoclonal antibody therapy is aimed at neutralizing the virus by binding to special epitopes on the spike protein, especially the receptor-binding domain. The vast mutations in the Cicada variant however, greatly change these epitopes leading to a decrease in binding affinity and neutralization ability[23].

Consequences include:

- Loss of efficacy of previously authorized monoclonal antibody treatments
- Need for combination antibody therapies targeting multiple epitopes
- Requirement for rapid redesign of therapeutic antibodies

This highlights the vulnerability of targeted therapies to antigenic variation and underscores the importance of developing broadly neutralizing antibodies that can withstand viral evolution.

3.2.3. Vaccine Effectiveness

Vaccination remains the most effective strategy for preventing severe COVID-19 outcomes. However, the antigenic shift observed in the Cicada variant has led to reduced neutralization by vaccine-induced antibodies.

Key observations include:

- Increased incidence of breakthrough infections
- Reduced effectiveness against infection and mild disease
- Retention of partial protection against severe disease and hospitalization

The reduced vaccine effectiveness is primarily due to mutations in spike protein epitopes targeted by vaccine-induced antibodies. This necessitates:

- Development of updated or variant-specific vaccines
- Implementation of booster dose strategies
- Exploration of universal or pan-coronavirus vaccine approaches

Additionally, T-cell-mediated immunity may still provide protection against severe disease, emphasizing the importance of multi-layered immune responses.

3.3. Epidemiological Impact

The Cicada variant has demonstrated a significant impact on global epidemiological trends, reflecting its enhanced transmissibility and immune escape capabilities.

Key epidemiological features include:

- **Rapid global spread:** The variant shows accelerated transmission across regions, driven by increased viral fitness and reduced immune protection in populations.
- **Increased breakthrough infections:** A higher proportion of infections is observed among vaccinated or previously infected individuals, indicating compromised immunity.
- **Potential for new infection waves:** The combination of immune evasion and high transmissibility increases the likelihood of recurrent waves of infection, even in highly immunized populations.

Furthermore, epidemiological modeling suggests that the Cicada variant may alter traditional transmission patterns, with shorter incubation periods and higher secondary attack rates[24]. These changes complicate containment strategies and necessitate adaptive public health responses, including enhanced surveillance, updated vaccination programs, and continued non-pharmaceutical interventions where necessary.

Table 2: Summary of Literature on Emerging COVID-19 Variants, Diagnostics, and Therapeutics

Author Name	Topic Covered	Research Study Title
Jacobs, J. L. et al. (2023)[25]	Challenges posed by SARS-CoV-2 variants including immune escape, transmission dynamics, and impact on vaccines and therapeutics.	COVID-19: Challenges of Viral Variants
Iacopetta, D. et al. (2022)[26]	Overview of COVID-19 variants, drug design strategies, and therapeutic approaches with emphasis on antiviral resistance and treatment optimization.	COVID-19 at a Glance: An Up-to-Date Overview on Variants, Drug Design and Therapies
Tholary, R. M. (2025)[27]	Analysis of emerging variants focusing on symptoms, diagnostic challenges, and evolving treatment strategies.	The Evolving Landscape of SARS-CoV-2: A Comprehensive Review of Signs, Symptoms, Diagnosis, and Treatment of New Variants
Wimalawansa, S. J. (2024)[28]	Role of natural immunity and strategies for pandemic resilience, highlighting host immune response against evolving variants.	Unlocking Insights: Navigating COVID-19 Challenges and Emulating Future Pandemic Resilience Strategies with Strengthening Natural Immunity
Biancolella, M. et al. (2023)[29]	Genomic evolution of SARS-CoV-2, mutation patterns, and implications for transmission, diagnostics, and immune escape.	COVID-19 Annual Update: A Narrative Review

4. DISCUSSION

The appearance of the Cicada variant highlights the extremely dynamic and adaptive character of the SARS-CoV-2 evolution in response to the continuous selective pressures like host immunity, vaccination efforts, and antiviral treatment[30]. The Cicada variant, in contrast to older variants, which had either a higher transmissibility factor or a more moderate immune escape, seems to combine various evolutionary benefits, such as the large-scale antigenic shift, higher binding affinity of the receptor, and a large amount of immunity.

The combination of features has complex challenges in the diagnostics, therapeutics, and vaccination approaches. This large mutation load, especially in antigenically important sites of the spike protein, undermines the effectiveness of current countermeasures and requires the ongoing evolution of clinical and public health responses. Furthermore, the variant highlights the limitations of reactive approaches and emphasizes the need for proactive, scalable, and evolution-resilient strategies in pandemic management[31].

4.1. Interpretation and Analysis

Critical examination of the mutational profile of the Cicada variant shows a good evidence of adaptive evolution of immune selection pressure. The mutations in the critical functional regions, particularly in the receptor-binding domain (RBD), are indicative of the virus maximizing its capacity to avoid neutralizing antibodies without sacrificing or diminishing infectivity. This evolutionary trend indicates a transition to immune escape as one of the most prevalent survival mechanisms.

Diagnostically, the RT-PCR assays have been found to be less sensitive and sometimes fail to work due to mutations in the primer- and probe-binding regions. Such results point to a basic drawback of single-target diagnostic systems as they are susceptible to genetic variation. This has caused an ever-growing necessity to develop multi-target and multiplex diagnostic methods that concentrate on conserved genomic area to guarantee dependability across emerging variants.

In therapy, the decreased potency of monoclonal antibodies and the possibility of antiviral resistance suggest that the single-modality treatment approach can no longer be relied upon. Multi-mechanism combination therapies, which aim to inhibit a variety of viral functions at the same time, can be a more effective method of resistance overcoming and better clinical outcomes. Also, the fact that treatment response differs in diverse patient groups indicates the need to consider individualized and dynamic treatment methods.

In general, the Cicada variant is a vivid example of the complicated interactions between the evolution of viruses and human intervention and the need to employ more flexible and prospective healthcare policies[32].

4.2. Implications and Significance

The widespread emergence and transmission of the Cicada variant carry significant implications across multiple domains:

- **Healthcare Systems:** The rising cases of reinfections and breakthrough further burden the healthcare systems. Hospitals are at risk of new surges of inpatient admissions, and healthcare workers are at risk of greater exposure. This may result in the depletion of resources such as hospital bed shortage, shortage of medical supplies, and shortage of trained personnel.

- **Vaccine Development:** The diminished neutralization ability of current vaccines against the Cicada variant underscores the urgency of new vaccine preparations. The future vaccine directions might require to be in variant-adapted boosters, multivalent vaccines or universal (pan-coronavirus) vaccines against conserved viral epitopes to long-term immunity.

- **Diagnostics:** Due to the genome-wide occurrence of mutation-induced diagnostic failures, it is essential to establish assays to address genetically stable and conserved

areas of the viral genome. Moreover, molecular diagnostics in conjunction with genomic surveillance can enhance early diagnosis and identification of variants.

- **Policy Making and Public Health Response:** The Cicada variant has the ability to spread rapidly and avoid immunity, which requires evidenced-based policymaking. The governments and health authorities should adopt the real-time surveillance, rapid response strategies, and adaptive containment measures such as targeted testing, vaccination campaigns and risk communication[33].

- **Global Health Equity:** Inequality in access to vaccines, diagnostics, and sequencing technologies may worsen the transmission of such variants. The need to engage in international cooperation and evenly share resources is the key to successful pandemic control.

4.3 Gaps and Future Research Directions

Despite significant advancements in understanding SARS-CoV-2 evolution, several critical gaps remain in addressing the challenges posed by the Cicada variant:

- **Development of Mutation-Resilient Diagnostic Tools:** There is a need for next-generation diagnostic platforms capable of maintaining accuracy despite ongoing viral mutations. Techniques such as CRISPR-based diagnostics and AI-assisted assay design may offer promising solutions.

- **Broad-Spectrum Antiviral Therapies:** Future therapeutic development should focus on antivirals targeting conserved viral components to minimize the risk of resistance. Host-targeted therapies may also provide alternative strategies less affected by viral mutations.

- **Universal or Pan-Coronavirus Vaccines:** Research should prioritize vaccines that provide cross-protection against multiple coronavirus strains by targeting conserved antigenic regions, thereby reducing the impact of antigenic shift.

- **Long-Term Evolutionary Studies:** Continuous monitoring of viral evolution through longitudinal studies is essential to understand mutation trends, recombination events, and their implications for transmissibility and virulence.

- **Integration of Artificial Intelligence in Genomic Surveillance:** AI and machine learning can enhance early detection of emerging variants by predicting mutation patterns, assessing transmission risks, and optimizing public health responses.

- **Immunological Correlates of Protection:** Further research is needed to define robust correlates of immunity, including the role of T-cell responses, to guide vaccine design and evaluation.

- **Real-World Effectiveness Studies:** Large-scale clinical and epidemiological studies are required to assess the real-world performance of diagnostics, vaccines, and therapeutics against emerging variants like Cicada.

5. CONCLUSION

The development of the Cicada variant is a turning point in the evolutionary history of SARS-CoV-2, as the virus is more and more capable of adapting to enduring immunological and therapeutic pressures[34]. This variant is described as highly antigenic, with a large mutational burden, and with more immune evasion mechanisms, which makes the variant a major challenge to the current diagnostic models, treatment regimens, and vaccination efforts[35]. Contrary to the previous versions which showed more gradual progression of evolutionary changes, the Cicada variant shows a more elaborate and faster genetic diversification process, allowing it to partially overcome the well-established immune responses and continue transmission even in highly immunized populations.

This review has critically analysed the genetic make up, diagnostic restriction, therapeutic restriction and epidemiological implication of the Cicada variant[36]. The results emphasize the fragility of existing healthcare systems to the swiftly changing viral threats and point to the shortcomings of the static or single-target strategies in dealing with dynamic pathogens. The causes of diagnostic errors, such as mutation-associated assays failure, low efficacy of monoclonal antibodies, and loss of neutralization caused by vaccination, all highlight the importance of adaptive and resolute healthcare practices[37].

Also, the Cicada variant demonstrates why genomic surveillance needs to be integrated with clinical and epidemiological data to facilitate early detection and quick response[38]. The ongoing surveillance of the viral evolution, combined with ongoing progress in molecular diagnostics and immunology, will be crucial in the reduction of the effects of the present and coming variants. International cooperation, fair distribution of healthcare resources, and long-term investment in research and innovation are also key in enhancing the preparedness to pandemics.

Finally, a set of multidisciplinary efforts comprising scientific innovation, preparedness to face the challenge of the Cicada variant, and international collaboration must be applied to tackle the issue[39]. This will be a proactive approach toward the spread of emerging subvariants rather than reactive measures to control it, which will reduce their impact on the healthcare systems of countries in the long term[40].

5.1. Summary of Main Insights

- The Cicada variant has a high mutation burden, and a strong antigenic shift, which adds to its high immune evasion.
- There have been limitations on the sensitivity and specificity of existing diagnostic tools associated with mutations in the target regions.
- Adaptation in therapeutic strategies is necessary especially with declining efficacy of monoclonal antibodies and new orthaviral resistance.

- Efficacy of vaccines is reduced particularly against infection, but some partial activity against severe disease may remain.
- The variant is more transmissible and can cause repeat waves of infection, even in already immunized populations.

5.2. Reiteration of Importance

- Addresses an emerging global health threat: The Cicada variant represents a new phase in viral evolution with significant implications for pandemic control.
- Supports evidence-based policy decisions: Insights from this review can guide policymakers in implementing adaptive and timely public health interventions.
- Enhances preparedness for future variants: Understanding mutation patterns and immune escape mechanisms is essential for anticipating and mitigating future outbreaks.
- Strengthens scientific and clinical response frameworks: The findings contribute to improving diagnostic, therapeutic, and vaccination strategies in a rapidly evolving scenario.

5.3. Recommendations

- Strengthen genomic surveillance systems: Expand global sequencing capacity and integrate real-time data sharing to detect and monitor emerging variants promptly.
- Develop next-generation vaccines: Focus on variant-adapted, multivalent, or universal (pan-coronavirus) vaccines targeting conserved viral regions.
- Improve diagnostic accuracy: Design multi-target and mutation-resilient diagnostic assays capable of maintaining performance despite viral evolution.
- Promote global data sharing and collaboration: Encourage transparent and rapid exchange of genomic, clinical, and epidemiological data across countries and institutions.
- Invest in antiviral research and combination therapies: Develop broad-spectrum antivirals and explore combination treatment strategies to minimize resistance and enhance efficacy.
- Adopt integrated public health strategies: Combine vaccination, diagnostics, therapeutics, and non-pharmaceutical interventions for a comprehensive response.

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