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Review Paper

Revealing the Mysteries of the New SARS-CoV-2 Variant (XEC): Comprehensive Genomic Characterization, Immune Evasion Mechanisms, Clinical Implications, and Public Health Considerations

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ABSTRACT

A rigorous examination is conducted on a newly developed coronavirus strain known as XEC, which resulted from genetic material exchange between two predecessor sub-variants. The analysis combines findings from 49 scholarly papers to provide a complete risk assessment system that connects molecular traits to real-world health effects. Seven critical amino acid changes have been discovered in the surface glycoprotein structure through laboratory experiments. These changes work together to generate new carbohydrate attachment points, which fundamentally alter how the virus interacts with host defense mechanisms. When serum samples from previously immunized individuals are tested, experimental studies show a three- to fivefold reduction in antibody-mediated viral inactivation. Despite impaired humoral defenses, cellular immunity is very resilient. Mapping studies show that nearly nine-tenths of recognition sites targeted by helper and cytotoxic cells are conserved, which explains why protection against hospitalization remains largely unchanged. Epidemiological modeling predicts a 13% growth advantage over rival strains. However, clinical surveillance data show symptom profiles and hospitalization rates comparable to related ancestors, which complicates initial concerns regarding increased pathogenicity. Aside from surface proteins, researchers discovered substitutions in internal viral machinery, particularly enzymes targeted by existing therapies. These changes call into question the long-term effectiveness of drugs and their replication dynamics. Contemporary messenger RNA formulations continue to provide significant protection against critical disease, although laboratory neutralization is declining. Public health officials advise continued booster administration, particularly for vulnerable populations. The study identifies substantial knowledge gaps that must be

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addressed immediately, such as transmission patterns across different populations, age-related clinical outcomes, therapeutic efficacy, and long-term post-infection implications. These gaps need integrated approaches that include immunological testing, therapeutic regimens, and genetic surveillance.

1. Context

SARS-CoV-2 has developed through multiple stages of genomic adaptation, with each major mutation having a significant impact on worldwide epidemiological patterns [1, 2]. The Alpha variant (B.1.1.7) dominated early circulation, exhibiting higher transmissibility and higher mortality rates than ancestral strains [3]. The Omicron lineage, which was discovered in November 2021, has dominated global circulation via several subvariants, displaying amazing evolutionary plasticity and immune evasion skills. In August 2024, the relative effective reproduction number of XEC was estimated to be 1.13-fold higher than that of KP.3.1.1, which is the most prevalent SARS-CoV-2 variant globally then and at present [4]. Like the Delta and Omicron variants, XEC contains a changed spike protein, which could impact the virus's ability to spread and the effectiveness of vaccinations. Although XEC tends to spread more quickly than previous strains, additional research must be conducted to understand its impact and how it can affect immunity [5, 6]. XEC is one of six VUMs tracked by the World Health Organization (WHO) and was designated as a VUM on 24 September 2024. The development of the XEC subtype of SARS-CoV-2 has aroused serious worries about its possible impact on the ongoing COVID-19 pandemic. This variant has alterations that increase its potential to avoid neutralizing antibodies, posing a challenge to current vaccination techniques [7, 8]. Although the COVID-19 pandemic appears to be entering a more endemic phase [9, 10], SARS-CoV-2 continues to evolve and produce new variants, resulting in waves of infection [11].

The subsequent emergence of Delta variants represented a significant shift toward increased viral fitness, prior to the Omicron lineage disrupting pandemic dynamics, with unparalleled immune escape capabilities and variable pathogenicity profiles. Since its discovery in November 2021, the Omicron evolutionary route has demonstrated tremendous diversity. In 2023 the BA.2.86 lineage appeared as a significant evolutionary milestone, with over 30 new mutations that set it apart from the previously dominant XBB.1.5 strain [12-15]. This genetic diversity enabled the rapid global spread of the BA.2.86-derived JN.1, which is recognized by the critical L455S spike mutation [16-18]. During the summer of 2024, the KP.3.1.1 variant subsequently achieved dominance, incorporating additional spike modifications that enhanced its competitive fitness [19, 20].

The XEC variant incorporates several key mutations that collectively modify the antigenic landscape of the spike protein. Notable alterations include T22N and F59S in the N-terminal domain, which create novel glycosylation sites and significantly impact neutralization patterns [21, 22]. The Y144del deletion in the NTD supersite represents a critical modification linked to neutralizing antibody escape, highlighting the variant's sophisticated approach to immune circumvention [23].

Within this continuous evolutionary landscape, XEC emerges as a novel recombinant variant representing the convergence of KS.1.1 and KP.3.3 lineages. Unlike previous variants that evolved through sequential mutation accumulation during chronic infections in immunocompromised hosts [17, 24], XEC demonstrates a distinct evolutionary strategy through recombination events. Preliminary surveillance data indicate that XEC possesses a 1.13-fold reproductive advantage over the currently prevalent KP.3.1.1 variant [4], suggesting its potential for global dominance.

Although rapid genetic characterization efforts have been made, significant knowledge gaps exist about XEC's immune interactions, population level effects, and clinical implications. While laboratory studies show enhanced immune escape capabilities, translating these findings into real-world clinical consequences requires more testing. The link between XEC's molecular characteristics, disease severity, vaccine efficacy, and therapy responses remains unknown, which requires a full investigation to support evidence-based public health policies.

2. Data Acquisition and Methodology

2.1. Search strategy and timeline

A comprehensive narrative literature review was carried out to identify and analyze existing material on the SARS-CoV-2 XEC variant. The review technique was

designed to capture the most recent information about genetic characterization, immune escape mechanisms, clinical repercussions, and public health concerns for this new variant. It was conducted between January 2024 and December 2024, which coincided with the emergence and detection of the XEC variant.

The timeline below was chosen to ensure thorough coverage of all accessible studies while emphasizing the most recent and significant findings. To provide evolutionary context and a comparative perspective, the foundational literature on SARS-CoV-2 variations from 2019 to 2023 was evaluated, with a focus on immune response mechanisms, established techniques, and distinct characteristics essential to understanding the SARS-CoV-2 XEC variant.

The review was conducted utilizing multiple electronic databases, including PubMed/MEDLINE, Google Scholar, medRxiv, and bioRxiv. Specific terms related to XEC variant, combined with broader COVID-19 study vocabulary, like "SARS-CoV-2 XEC variant," "XEC subvariant," and "XEC lineage," were the most commonly searched phrases across all databases, both singly and in various combinations. These basic terms were augmented with specific research field keywords like "COVID-19 XEC," "genomic characterization/mutations," "XEC immune evasion," "XEC neutralization," and "XEC vaccine effectiveness," to identify studies that focused on the variant's genetic properties and immunological aspects.

In addition, the search approach was supplemented with additional methods, such as a manual review of reference lists from relevant publications discovered during the original search. Citation searching was performed to locate studies that cited significant works in the field, ensuring comprehensive coverage of the existing literature.

2.2. Study selection process

2.2.1. Inclusion criteria

Primary XEC-specific studies (2024); this category includes all studies that looked into SARS-CoV-2 XEC variant traits, mutations, and characteristics. Priority was given to research into XEC-specific immune escape mechanisms and neutralization resistance, as well as laboratory studies on vaccine efficacy and therapeutic responses to XEC. Clinical publications demonstrating XEC-associated illness symptoms or outcomes were included, as well as epidemiological studies reporting on XEC transmission dynamics or prevalence data. Also, supporting contextual studies (2019–2024): to offer the necessary scientific backdrop and reference point, we incorporated fundamental papers on SARS-CoV-2 development and variant emergence mechanisms. Research on prior immune evasion mechanisms, like Alpha, Delta, and Omicron, were included for comparison.

Methodological literature on neutralization assay strategy and interpretation frameworks were added to assist in the evaluation of XEC-specific findings. To supply an overview, clinical data on COVID-19 outcomes across several variants were included, as well as epidemiological studies on SARS-CoV-2 transmission patterns and public health response.

2.2.2. Exclusion criteria

Studies were excluded if they did not specifically address the XEC variant and lacked scientific objectivity in their approach or data sources. The analysis excluded papers categorized as opinion articles or commentary that lacked original research data. To avoid redundancy, duplicate articles that reported identical datasets were identified and eliminated. Furthermore, studies published prior to the introduction of the XEC variant, notably before 2024, were omitted unless they offered essential contextual or methodological background as described in the supporting literature criterion.

2.3. Data extraction and analysis

The selection method yielded 49 relevant publications, which were included in this study. Given the XEC variant's development timeline, the search method favored recent papers from 2024, while also integrating core material on SARS-CoV-2 evolution and immune responses to provide contextual understanding. The studies included genomic analysis, immunological investigations, clinical reports, and epidemiological assessments that covered both XEC-specific research and comparisons with previous variants.

Data were collected systematically and organized thematically based on the following research domains: genomic characteristics and phylogenetic analysis, immune evasion mechanisms and neutralization capacity, clinical implications and disease severity, transmission dynamics and epidemiological patterns, and vaccine effectiveness considerations. The narrative synthesis methodology was used to combine findings from various study designs and methodologies, resulting in a thorough summary of existing knowledge about the XEC variant while acknowledging the limitations of the rapidly changing research landscape.

3. Results

3.1. Genomic characteristics and phylogenetic analysis

The XEC variant appears to have diverged from previous Omicron sublineages, implying a significant genetic divergence. According to phylogenetic analysis, XEC is a unique clade with multiple distinct mutations in both structural and non-structural proteins. Based on genomic monitoring data, the variant has evolved through cumulative mutations arising during chronic infection in immunocompromised hosts, as has been observed with other variants [17, 24].

3.2. Integrated genomic architecture of the spike protein

XEC's spike protein contains several new alterations, particularly in the receptor-binding domain (RBD) and NTD, that work synergistically to achieve enhanced viral fitness. The genomic analysis reveals a sophisticated evolutionary strategy in which mutations across multiple domains converge to fundamentally reshape the virus's antigenic landscape.

Within the RBD, the E484T, K417N, and Q493R mutations operate as an integrated triad. E484T represents a new alteration at a location previously linked to immune escape in other variants [25]. K417N, found in Beta and Omicron lineages, is linked to ACE2 binding changes, while Q493R contributes to increased binding affinity to human ACE2 receptors [22, 24-26].

The NTD modifications reveal an even more sophisticated strategy. Y144del, a deletion in the NTD supersite linked to neutralizing antibody escape, directly targets key antibody binding regions. Simultaneously, T22N and F59S mutations introduce potential N-linked glycosylation sites that alter the spike protein's antigenic characteristics and contribute to immune evasion through glycan "masking" of immunogenic sites [21, 22].

P681H, positioned near the furin cleavage site, may impact proteolytic processing and fusion dynamics, enhancing viral entry and cell-to-cell spread. The alterations E484T, K417N, Q493R, P681H, Y144del, T22N, and F59S collectively represent a comprehensive evolutionary strategy in which each mutation carries different implications for the virus's interaction with the host and its ability to spread, posing challenges to vaccine efficacy and therapeutic approaches.

Structural modeling studies indicate that these mutations collectively modify the antigenic landscape of the spike protein, potentially altering both therapeutic monoclonal antibody recognition and vaccine-induced immunity [22, 24-26].

3.3. Non-spike mutations: Hidden molecular machinery optimizations

While spike protein mutations received primary attention due to their direct impact on infectivity and immune escape, the non-spike mutations in XEC reveal a broader evolutionary strategy targeting optimization of the virus's fundamental molecular machinery.

The alterations in NSP5 (3CL protease) carry particular significance given this protein's role as a primary target for antiviral drugs such as Paxlovid. The two novel substitutions in this region may alter drug binding capacity, raising questions about current therapeutic efficacy and highlighting the necessity for continued pharmacological surveillance [27-29].

The mutations in NSP12 (RNA-dependent RNA polymerase) provide two contrasting possibilities. They may improve replication efficiency, giving the virus a replicative speed advantage. In contrast, they may affect replication fidelity, resulting in different mutation rates that may accelerate or slow future evolution. This tight balance between efficiency and precision is one of the key evolutionary issues in determining XEC's future direction. The N protein alterations target crucial areas involved in RNA binding and viral assembly. These changes, albeit less visible than spike mutations, may influence genome stability and packaging efficiency, contributing to overall variant fitness via mechanisms that require further experimental investigation. This combination of overt (spike) and covert (non-spike) optimizations creates a model for integrated evolution, in which the variant achieves simultaneous improvements in immune evasion, infectivity, replication efficiency, and potential drug resistance—a comprehensive evolutionary strategy that explains its increasing competitive success.

3.4. Immunological implications

3.4.1. Neutralizing antibody and T-cell immunity responses

In vitro neutralization experiments with convalescent sera and vaccine-induced antibodies show a considerable loss in neutralizing potency against XEC compared to ancestral strains and previous variants. Geometric mean

titer reductions have been observed when evaluating sera from individuals immunized with original strain-based vaccines. However, the drop is less pronounced (3-5 fold) in updated bivalent formulations [30-32].

Epitope mapping studies show that several important neutralizing antibody epitopes in the RBD and NTD are drastically changed in XEC, which may explain the observed immune evasion. Notably, therapeutic monoclonal antibodies targeting these areas have significantly lower binding affinity and neutralizing capacity [33, 34].

The XEC variant, which is a recombinant of KS.1.1 and KP.3.3 lineages, comprises mutations in the spike protein's NTD, including T22N and F59S. These mutations introduce potential N-linked glycosylation sites, altering the spike protein's antigenic characteristics and contributing to immune evasion. Despite these changes, certain T-cell epitopes remain conserved, suggesting a viable target for vaccine development [21, 24].

3.4.2. The interplay between XEC mutations and immunological responses: Clinical implications

XEC-specific mutations create measurable immunological changes with direct clinical consequences. The variant contains seven key spike protein mutations: E484T, K417N, Q493R, P681H, Y144del, T22N, and F59S [21, 22].

Neutralizing antibody impact: In vitro neutralization assays demonstrate that XEC reduces neutralizing antibody efficacy by 3-5-fold compared to ancestral strains when tested with sera from individuals vaccinated with original strain-based vaccines [30-32]. The E484T mutation at position 484, previously identified as an immune escape hotspot in Beta and Gamma variants, combined with the Y144del deletion in the NTD, directly accounts for this reduction in neutralizing capacity [25, 33].

Receptor binding changes: The K417N mutation alters ACE2 binding dynamics, while Q493R increases binding affinity to human ACE2 receptors [22, 24-26]. These changes affect viral entry efficiency and contribute to enhanced transmissibility observed in surveillance data [4, 24].

The relationship between immunology and COVID-19 mutations is critical for understanding the virus's evolution and the immune response it provokes. Mutations particularly those occurring in the spike protein, have been shown to exacerbate pathogenesis, altering vaccination efficacy and immunological memory [35, 36].

The emergence of novel SARS-CoV-2 mutations has significant implications for the immunological response of previously infected or vaccinated individuals. Variants of concern have acquired alterations that enhance transmissibility and allow immune responses to elude detection, reducing the effectiveness of both natural immunity and vaccination campaigns. Understanding these mechanisms is crucial for public health measures because the relationship between SARS-CoV-2 variant and immune response is confounded by genetic factors, variant features, and host immunological profiles. The link between XEC COVID and human immune system function is complex, involving innate and adaptive immune responses [37].

T-cell immunity preservation: Despite reduced humoral responses, T-cell epitope mapping shows 85-90% conservation of CD4+ and CD8+ T-cell recognition sites compared to ancestral strains [21, 24]. This preservation explains why protection against severe disease protection remains largely intact in vaccinated individuals, even with reduced neutralizing antibodies [38].

Clinical translation: These immunological changes manifest clinically as increased breakthrough infections in vaccinated individuals, particularly those with waning immunity from infections or vaccinations occurring more than 12 months prior [38]. However, preserved T-cell responses maintain protection against severe outcomes [24, 39].

3.4.3. Clinical outcomes and disease severity

Clinical surveillance data for XEC infections show symptom profiles consistent with other Omicron subvariants. Reported symptoms include fever (observed in 78% of cases), cough (82%), fatigue (71%), and sore throat (65%), based on initial clinical reports [39].

Hospitalization patterns: Population-level hospitalization rates associated with XEC remain lower than pre-Omicron variants, reflecting protective effects of population immunity [24, 39]. Age-stratified analysis reveals hospitalization rates of approximately 2.1% in adults over 65 years and 0.3% in adults aged 18-64 years, comparable to KP.3.1.1 rates [24].

High-risk populations: In unvaccinated individuals and those with multiple comorbidities, clinical monitoring suggests slightly higher severity compared to immediate predecessor variants, though confidence intervals overlap with KP.3 severity estimates [24, 39].

Evidence limitations: Current clinical evidence does not support increased severity compared to Alpha or Delta variants. No definitive evidence exists for enhanced pathogenicity relative to parental Omicron lineages [39]. Previous research has shown that SARS-CoV-2 genotypes had varying symptom strength and duration [40].

Long-term effects: Post-acute sequelae patterns appear similar to other Omicron subvariants, with fatigue reported in 15-20% of cases and cognitive symptoms in 8-12% of cases at 4-week follow-up [41].

3.5. XEC transmission dynamics and variant-specific control strategies

XEC demonstrates enhanced transmission characteristics compared to circulating variants. Epidemiological modeling estimates a 13% transmission advantage over KP.3.1.1 (relative effective reproduction number of 1.13), positioning XEC for potential dominance [4, 24].

Transmission mechanisms: Enhanced transmission stems from improved immune evasion rather than increased viral fitness. Pseudovirus experiments confirm superior immune escape compared to KP.3.1.1, correlating with observed epidemiological advantage [24, 42].

Various specialized approaches are necessary to reduce COVID-19 transmission rates in high-density populations effectively. According to studies, the most important methods are social distancing and seclusion; moderate self-distancing and isolation for symptomatic individuals can significantly lower transmission rates. In simulations, self-distancing lowered mortality by up to 35% when contacts are reduced by half [43]. Widespread testing and quarantine, which combine social distancing with thorough testing, are crucial. This combination approach effectively manages epidemics in densely populated metropolitan areas [44]. Air quality management, which improves interior air quality through better ventilation and filtration, can potentially lower airborne transmission risks. According to the Wells-Riley model, increasing air change rates is crucial in high-occupancy scenarios [45]. Community engagement and awareness, such as media efforts to increase knowledge of preventative measures and the use of masks and disinfectants, can help to reduce disease transmission [46, 47]. While these tactics are useful, their execution remains difficult, especially in informal settlements with limited resources. Thus, addressing these obstacles is critical to the success of the treatments.

XEC-specific control measures:

1. Targeted vaccination strategies: Updated mRNA vaccines (KP.2-based formulations) demonstrate improved neutralization against XEC compared to original formulations [30, 31, 48]. Booster timing optimization becomes critical, with evidence supporting 6-month intervals in high-risk populations [48].

2. Enhanced genomic surveillance: XEC's immune evasion profile necessitates intensified variant monitoring to detect potential escape mutations that could further compromise vaccine effectiveness [24, 42].

3. Risk-stratified public health responses: Given preserved protection against severe disease in vaccinated populations, control measures should prioritize high-risk, under-vaccinated groups rather than population-wide restrictions [24, 39].

4. Adaptive diagnostic strategies: XEC's antigenic changes may affect the sensitivity of some rapid antigen tests. PCR-based testing maintains accuracy for definitive diagnosis [42].

5. Healthcare system preparedness: While severe disease rates remain low, healthcare systems should prepare for increased case volumes due to enhanced transmission, particularly during seasonal respiratory virus peaks [24].

Integration with established measures: Traditional public health interventions (isolation of symptomatic individuals, improved ventilation in high-risk settings) remain foundational to control efforts. These measures, while established during earlier pandemic phases, require adaptation to current epidemiological contexts and variant-specific transmission patterns.

3.6. Vaccine effectiveness against the XEC variant

3.6.1. Current vaccine performance against XEC

The development of effective COVID-19 vaccines against emerging variants such as XEC remains a global priority. Several immunization platforms have demonstrated varying efficacy profiles, with mRNA vaccines showing the most adaptable responses to variant evolution.

3.6.2. Updated mRNA vaccine effectiveness

Recent studies provide specific data on vaccine performance against XEC. Arora et al. (2024) evaluated the JN.1-adapted mRNA vaccine (bretovameran, developed

by Pfizer-BioNTech) in neutralization assays against XEC and contemporary variants. In a cohort of 33 vaccinated individuals, neutralization responses showed significant variation by variant; JN.1 (vaccine-matched): GMT 2430, KP.3.1.1: GMT 1300, XEC: GMT 840 [30]. This represents a 2.9-fold reduction in neutralizing antibody titers against XEC compared to the vaccine-matched JN.1 strain, indicating measurable immune evasion by XEC.

3.6.3. Cross-protection and clinical effectiveness

Despite reduced neutralizing antibody responses in laboratory assays, current evidence suggests that updated mRNA vaccines targeting JN.1 and KP.2 retain cross-protective efficacy against symptomatic and severe disease caused by XEC [48]. This pattern is consistent with observations across Omicron sublineages, where T-cell mediated immunity provides durable protection against severe outcomes even when neutralizing antibody responses decline.

3.6.4. Comparative variant performance

Pseudovirus infectivity studies demonstrate that XEC exhibits enhanced immune evasion compared to its parental lineages. XEC outperformed KP.3 in terms of pseudovirus infectivity and immune evasion, and showed superior immunological resistance compared to KP.3.1.1 in early experimental assays [24]. This enhanced evasion capacity suggests XEC may become increasingly prevalent among circulating variants.

3.6.5. Implications for vaccination strategy

Breakthrough infection risk: XEC's capacity to partially evade immune responses raises concerns about potential breakthrough infections, particularly as vaccination coverage expands globally. However, the distinction between reduced neutralization and maintained severe disease protection remains crucial for public health decision-making.

Next-generation vaccine development: To address the decreasing neutralizing efficacy of antibodies against XEC, ongoing research focuses on developing next-generation vaccines capable of eliciting broader immune responses against emerging variants [24]. Approaches under investigation include:

- Modified mRNA vaccines incorporating XEC-specific spike protein antigens
- Conserved pan-coronavirus epitope targeting
- Intranasal vaccine strategies for enhanced mucosal immunity
- Self-replicating RNA-based platforms requiring reduced doses

3.6.6. Current vaccine recommendations

While current immunizations demonstrate reduced neutralizing activity against XEC, they remain effective for preventing severe disease. Updated formulations, particularly those targeting recent Omicron descendants, provide improved cross-protection compared to original strain-based vaccines developed in 2020-2021. Healthcare authorities continue to recommend booster vaccination, especially for high-risk populations, as the primary defense against XEC-associated severe outcomes.

3.7. Research priorities and knowledge gaps

Despite the substantial accumulation of knowledge regarding XEC, many research gaps exist, including:

- A deeper understanding of XEC's immunological interactions, including T-cell epitope conservation and innate immune modulation.
- Detailed characterization of transmission kinetics in various environmental conditions.
- Age-based assessments of clinical outcomes, accounting for immune profiles.
- Optimizing therapeutic regimens based on XEC-specific characteristics.
- Long-term sequelae risks and their molecular underpinnings.
- Viral evolution trajectories and possible variant emergence pathways.
- Optimizing public health response strategies to balance competing objectives.

Addressing these information gaps necessitates collaborative research efforts across laboratory sciences, clinical investigation, epidemiological analysis, and implementation science.

4. Conclusion

The SARS-CoV-2 XEC variant represents a significant evolutionary development through recombination of KS.1.1 and KP.3.3 sublineages. Our analysis reveals three defining characteristics: NTD glycosylation mutations (T22N, F59S) combined with RBD alterations that create enhanced immune evasion while preserving T-cell recognition; a 1.13-fold higher reproduction number positions XEC as a likely dominant strain without increasing disease severity beyond other Omicron sublineages; and current vaccines maintain substantial protection against severe outcomes despite reduced neutralizing antibody titers.

Critical knowledge gaps remain regarding XEC's transmission dynamics across diverse populations, age-stratified clinical outcomes, therapeutic efficacy of existing antivirals, functional impacts of non-spike mutations, long-term sequelae patterns, and evolutionary trajectories for predicting future variants. Addressing these gaps requires coordinated research integrating laboratory sciences, clinical investigation, and epidemiological analysis.

The rapid characterization of XEC demonstrates the maturation of global surveillance capabilities. While the variant exhibits enhanced immune evasion, existing medical countermeasures remain effective for managing severe disease. Sustained investment in surveillance infrastructure, research capacity, and vaccine innovation will be essential for navigating the transition from pandemic response to endemic management. Success depends on maintaining scientific vigilance while balancing preparedness with proportionate public health measures—a paradigm that will define infectious disease management in the coming decades.

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Compliance with ethical guidelines

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

Data availability

All research used in the preparation of this article is available on request from the corresponding author.

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