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Review Article **Open Access**

A mini-review of the global implications of the emerging SARS-CoV-2 XEC variant: Epidemiology, mutations, and mitigation strategies

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Abstract:

The newly emerged SARS- CoV-2 XEC subvariant (XEC) is a global public health concern. Since its first detection in May 2024, it has spread rapidly to involve more than 45 countries globally. The World Health Organization and the Africa Centers for Disease Control and Prevention designated XEC a variant under monitoring (VUM), highlighting its global concern. XEC sub-variant is a descendant of the omicron lineage and a recombinant product of K.S.1.1 and KP3.3. Increased infectivity, enhanced immune evasion, and immune resistance, have been linked to specific spike protein mutations, S: F59S and S: T22N, alongside Apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 (APOBEC3)-driven mutations that facilitate immune escape and viral survival. Like its predecessor, the novel SARS-CoV-2 XEC variant exhibits flu-like symptoms. However, there is no evidence that it causes more severe illness than previously circulating Omicron variants. Nevertheless, the high reproduction number (Re) of the XEC variant suggests a higher chance of out competing the other major lineages. Wastewater surveillance has shown that XEC variant circulation is approximately 2 to 19 times higher than the number of cases that have been identified. This suggests that underreporting, decreased testing and declining genomic surveillance in many countries may be masking the true epidemiological burden of XEC. Mitigation strategies must prioritize mass vaccination campaigns, incorporating updated 2024-2025 vaccines and infection prevention and control measures. Sadly, vaccine hesitancy poses a significant challenge to the achievement of herd immunity. To address this, targeted public enlightenment campaigns are essential. Additionally, proactive and collaborative global efforts are necessary to curb the spread of emerging variants like XEC. Strengthened IPC practices, and sustained genomic surveillance will be critical in averting future waves and mitigating public health impacts. This review serves to provide insight into the XEC variant and call for action to prevent another looming pandemic.

Keywords: SARS-CoV-2; XEC; subvariant; mitigation; variant of concern

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Mini-analyse des implications mondiales du variant émergent XEC du SARS-CoV-2: Epidémiologie, mutations et stratégies d'atténuation

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Résumé :

Le nouveau sous-variant XEC du SARS-CoV-2 (XEC) constitue un problème de santé publique mondial. Depuis sa première détection en mai 2024, il s'est rapidement propagé, touchant plus de 45 pays. L'Organisation mondiale de la Santé et le Centre africain pour le contrôle et la prévention des maladies (CDC) ont désigné le XEC comme variant sous surveillance (VUM), soulignant ainsi son importance mondiale. Le sous-variant XEC est un descendant de la lignée omicron et un produit recombinant de K.S.1.1 et KP3.3. Une infectiosité accrue, une évasion immunitaire accrue et une résistance immunitaire accrue ont été associées à des mutations spécifiques

de la protéine Spike, S : F59S et S : T22N, ainsi qu'à des mutations induites par l'enzyme d'édition de l'ARNm de l'apolipoprotéine B, le polypeptide catalytique 3 (APOBEC3), qui facilitent l'évasion immunitaire et la survie virale. Comme son prédécesseur, le nouveau variant XEC du SARS-CoV-2 présente des symptômes pseudo-grippaux. Cependant, rien ne prouve qu'il provoque une forme plus grave que les variants Omicron précédemment en circulation. Néanmoins, le taux de reproduction élevé (Re) du variant XEC suggère une probabilité plus élevée de supplanter les autres lignées principales. La surveillance des eaux usées a montré que la circulation du variant XEC est environ 2 à 19 fois supérieure au nombre de cas identifiés. Cela suggère que la sous-déclaration, la diminution des tests et la baisse de la surveillance génomique dans de nombreux pays pourraient masquer le véritable fardeau épidémiologique du XEC. Les stratégies d'atténuation doivent privilégier les campagnes de vaccination de masse, intégrant les vaccins 2024-2025 mis à jour et les mesures de prévention et de contrôle des infections. Malheureusement, l'hésitation vaccinale constitue un obstacle majeur à l'obtention de l'immunité collective. Pour y remédier, des campagnes ciblées de sensibilisation du public sont essentielles. De plus, des efforts proactifs et collaboratifs à l'échelle mondiale sont nécessaires pour freiner la propagation des variants émergents comme le XEC. Le renforcement des pratiques de prévention et de contrôle des infections et une surveillance génomique soutenue seront essentiels pour éviter de futures vagues et atténuer les impacts sur la santé publique. Cette analyse vise à mieux comprendre le variant XEC et à appeler à l'action pour prévenir une nouvelle pandémie imminente.

Mots-clés: SARS-CoV-2; XEC; sous-variant; atténuation; variant préoccupant

Introduction:

Severe acute respiratory syndrome coronavirus-2 (SARS- CoV-2) XEC sub variant (XEC) is a global public health concern and currently the only SARS-COV-2 variant under monitoring (VUM) exhibiting increasing prevalence worldwide. The recent upsurge in COVID-19 cases linked to the newly emerged SARS-CoV-2 XEC variant has caused a global stir. XEC has spread to all three World Health Organization (WHO) regions and has been confirmed in 45 countries across different continents including Europe, Asia, North America and Botswana in Africa (1,2). No cases have been recorded in Nigeria, the most populous country in sub-Saharan Africa.

The WHO and the Africa Center for Disease Control and Prevention designated XEC a variant under monitoring (VUM) highlighting it as a global issue (2). XEC is a recombinant mutant of SARS CoV-2, the cause of the pandemic coronavirus disease 2019 (COVID-19) that shut down the world. SARS CoV-2 is an enveloped, positive-sense, single stranded ribonucleic acid (RNA) virus that belongs to the Coronaviridae family. The genome of SARSCoV-2 is approximately 30kb in length (3).

Immunological adaptations and epidemiological outcomes:

The major variants of SARS-CoV-2 include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) (4). Among these, the Omicron variant is the predominant variant of concern in circulation and was named variant of concern (VOC) by the WHO based on the detrimental change it caused in COVID-19 epidemiology. The Omicron variant was first identified in South Africa and reported to the WHO by the Genomics Surveillance on November 14, 2021. This newly discovered variant which contained a constellation of mutations quickly spread to other parts of the world. Omicron gradually and continuously undergoes antigenic shifts and recombinant mutations resulting in circulating sub-variants (5). The main sub-variants of omicron currently circulating around the world include BA.2.86, JN.1, KP.2, KP.3 and XEC (2).

The XEC sub-variant, first detected in Italy in May 2024 (2) is a descendant of the Omicron lineage and a recombinant product of JN.1 lineage of KS.1.1 (JN.13.1.1.1) and KP. 3.3 (JN.1.11.1.3.3). XEC acquired two spike (S) protein substitutions, S: T22N and S: F59S through recombination when compared with the parent KP.3 lineage (6). In addition, the relative effective reproduction number (Re) of the XEC sub-variant is 1.13-fold higher than that of KP.3.1.1. This implies that it has a higher chance of out competing the other major lineage including KP.3.1.1. The resulting epidemiological outcome of these mutations include increased host viral infectivity attributed to the S: F59S and enhanced immune resistance and evasion attributed to the presence of S: T22N and S: F59S (1.5-fold and 1.6-fold) when compared with the previously circulating variants. The S: T22N mutation does not affect viral infectivity. Moreover, XEC and KP.3.1.1 have been found to have significantly higher infectivity than KP.3 (7).

Additionally, the accumulation of Apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 (APOBEC3)-type mutations confer an epidemiological advantage to the emergent XEC subvariant (8,9). These mutations represent a host defense mechanism, targeting the viral genome during replication when single strands are exposed. This process leads to nucleotide substitutions and changes that enhance viral survival and immune evasion. The APOBEC3A (A3A) cytidine deaminase plays a critical role in the induction of cytosine to uracil substitution in the SARS-CoV-2 genome (8).

The SARS-CoV-2 infected cells exogenously express A3A without the expression of other APOBEC proteins-induced uracil-uracil to uracil-cytosine mutations in the viral RNA (v

RNA). The A3A mRNA expression is drastically increased by increased release of interferons and tumor necrosis factor-α (TNF-α) by the virally infected epithelial cells of the respiratory system, a site for efficient replication of the SAR-CoV-2. This represents a primary host derived mutation involved in editing the viral RNA genome (8,9).

The XEC variant like its predecessor exhibits a wide range of flu-like symptoms ranging from mild to severe illness including but not limited to fever (38^0C or higher), chills, cough, shortness of breath, sore throat, headache, congestion, loss of taste such as high body temperature, body aches, and tiredness (2,10). However, experimental data from researchers across the globe have shown that there is no evidence that it causes more severe illness than previously circulating Omicron variants (2). Notwithstanding, the WHO has highlighted the worrying finding that XEC and KP.3.1.1 (both VUMs) show increasing prevalence globally, despite declining levels of other VUMs (2).

From 16 September to 13 October 2024 (during the 4 weeks period), 90 countries reported COVID-19 cases, and 30 countries reported COVID-19 related-deaths attributed to XEC. Within this period, available data showed 24,000 new cases and 830 new ICU admissions. The quoted figures may just be the tip of the iceberg, and not reflective of the actual number of cases or deaths. This underestimation may be attributable to under reportage, missed diagnosis, decreased testing and sequencing as well as the fact that many countries are no longer reporting or have changed the frequency of reporting of COVID-19 (11).

Furthermore, estimates from wastewater surveillance on the circulation of SARS-CoV-2 revealed that XEC variant circulation is approximately 2 to 19 times higher than the number of cases identified and reported in 30 countries across the WHO five regions as featured on the WHO COVID-19 dashboard (11). Hence, if effective mitigation measures are not put in place, another COVID-19 pandemic may be inevitable.

Mitigation strategies:

Vaccines have demonstrated enormous protective effects in human and animal health (12,13). Hence, effective mass vaccination incorporating all the circulating SAR-CoV-2 sub variants including the newly emergent XEC will ensure the development of herd immunity. The updated 2024-2025 COVID-19 vaccines incorporate the currently circulating strains, and it is highly recommended for persons aged 65 years and above, are at high risk for severe COVID-19, or have never received a COVID-19 vaccine.

The 2024-2025 vaccine protects humans from severe illness, hospitalization, and death. However, as vaccine immunity wanes over time, it is important to ensure compliance with the 2024–2025 COVID-19 vaccine schedule. Sadly, vaccine hesitancy remains a problem which has persisted since the era of the COVID-19 pandemic. Vaccine acceptance rates have ranged from 14-68% (14-17) and researchers have attributed this to bias, propaganda, ignorance, myths, fear of adverse effects and conspiracy theories (15). This development undermines the achievement of the objectives and expectations towards vaccine protection against the circulating sub variants.

It is important that vaccination programs be implemented in conjunction with an effective infection prevention and control (IPC) measures (18) as outlined by the apex health governing stake holders during the COVID-19 pandemic which is now lax in many communities and countries across the globe. These IPC measures include but not limited to physical distancing at 1 meter between person, avoidance of the 3Cs (crowds, close contact and closed spaces), regular wearing of properly fitted face mask preferably covering the nose, mouth and chin when physical distancing is unavoidable and in poorly ventilated settings, adequate hand hygiene with alcohol-based hand rub or soap and water on a regular basis, proper cough etiquette into a bent elbow or use of tissue when coughing and/or sneezing (18).

Other measures include self-isolation following suggestive symptoms or following positive test for COVID-19 until recovery, regular cleaning and disinfection of surfaces including frequently touched sur- faces, such as phones, door handles, faucets and office tabletops (18). Regular public health education and health information dissemination in local languages (12). Reliable sources such as the WHO, local and national health authorities, should provide regular updates on emerging trends on the new variants under monitoring.

Conclusion:

The newly emerged mutant SARS CoV 2-XEC subvariant currently circulating across the globe has resulted in an increased number of cases of COVID-19 with large scale illnesses and fatalities. The resulting rise in viral infectivity and immune evasion have been attributed to the S: F59S and S: T22N substitutions at the spike protein rendering the previous vaccine less effective.

The updated 2024-2025 COVID-19 vaccines confer some protection, although vaccine effectiveness against variants has decreased due to immune escape mutations. Booster and seasonal COVID-19 vaccines are reco-

mmended as strategies for mitigation. Furthermore, public health education should be prioritized to enhance vaccine acceptance and updates should be provides on the newly emergent circulating XEC. These measures should be combined with the institution of effective IPC strategies to further mitigate these ongoing challenges and prevent another looming pandemic.

Contributions of authors:

SOE conceptualized the review. SCE, INN, UCO, INO and SOE wrote the original draft of the manuscript. All authors reviewed, read and approved the final version of the manuscript submitted for publication.

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