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Haste makes waste: an old vaccine works for Mpox saving the children at risk in 100 days

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Abstract

The resurgence of monkeypox virus (MPXV) has reinvigorated global concern for zoonotic diseases and the critical need for effective vaccines. This resurgence emphasized the urgent need for vaccination in vulnerable paediatric populations. Vaccines like LC16m8 are being prioritized for children in the DRC, and the WHO has supported emergency deployment, in part due to these alarming paediatric outcomes. Recent evidence in various animal models offers detailed immunological analysis of LC16m8, supporting its efficacy against diverse MPXV clades. This manuscript highlights these findings in the context of Sustainable Development Goal (SDG) 3 and the global 100 Days Mission, emphasizing LC16m8's potential in outbreak response and public health resilience for the vulnerable populations.

2nd PHEIC; MPOX is back

Emerging infectious diseases continue to pose a major global health threat, as demonstrated by outbreaks of H1N1 influenza virus (swine flu), severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola, Zika, SARS-CoV-2, and monkeypox virus (MXPV). Mpox (monkeypox) is a re-emerging zoonotic disease caused by MPXV, a double-stranded DNA virus belonging to the Orthopoxvirus genus. While historically confined to Central and West Africa, MPXV outbreaks have expanded globally since 2022, prompting the World Health Organization (WHO) to declare two Public Health Emergencies of International Concern (PHEIC). The second PHEIC, declared in 2024, was fuelled by the emergence of the clade Ib lineage in the Democratic Republic of the Congo (DRC), which displayed higher transmissibility and significant paediatric mortality (Vakaniaki EH et al 2024). According to the World Health Organization (WHO) African Region Weekly Regional Situation Report #18, published in December 2024, children under 5 years accounted for 22.5% of confirmed mpox cases, and those aged 5 to 9 years accounted for 13.0%, totaling 35.5% for children under 10. Additionally, the NICD reported that children under the age of 15 years accounted for 68% of total cases and 85% of total deaths in the DRC.

Vaccination is crucial for controlling poxvirus outbreaks, particularly smallpox. Vaccinia virus (VACV) serves as the vaccine strain against poxviruses. First-generation smallpox vaccines, such as the Dryvax and Lister, were derived from calf lymph and played a key role in smallpox eradication. The second-generation ACAM2000 vaccine, developed using cell culture technology, is stockpiled for bioterrorism preparedness. Third generation live-attenuated smallpox vaccines, including the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) and LC16m8, have demonstrated immunogenicity with tolerable safety in clinical trials. However, they were approved after smallpox eradication. The discontinuation of routine smallpox vaccination has left younger generations susceptible to orthopoxvirus infections. The rapid spread of clade Ib highlights the urgent need for updated vaccines to prevent future outbreaks.

Old vaccine made in Japan

LC16m8, an attenuated vaccine developed from the Lister strain of vaccinia virus, offers a viable solution for Mpox prevention. The recent study by Kobiyama et al. offers critical insights into its immunogenic and protective characteristics. LC16m8 was developed through serial passaging of the Lister strain in primary rabbit kidney (PRK) cells under low temperature conditions, leading to attenuation by the 36th passage. Subsequent selection processes yielded a clone with low replication potential and a single nucleotide deletion in the B5R gene, eliminating expression of the virulence-associated B5 protein. This molecular modification underpins the vaccine's safety profile while preserving its immunogenic potential.

Approved in Japan for smallpox in 1975 and for Mpox in 2022, LC16m8 is one of the few available countermeasures during Mpox outbreaks. Following the second PHEIC declaration, WHO granted Emergency Use Listing (EUL) to LC16m8 in November 2024. Japan subsequently pledged 3.05 million doses for deployment in the DRC, where children under five accounted for over 44% of confirmed cases.

Immunogenicity in Preclinical Models

Recent evidence published by Kobiyama et al. evaluated LC16m8 in BALB/c, C57BL/6J, and CAST/EiJ mice, as well as non-human primates. The vaccine induced strong

antibody responses against multiple MPXV and vaccinia antigens, including A35, H3, and M1. Notably, responses against B5 were absent, consistent with the genetic deletion in LC16m8. CAST/EiJ mice, which are highly susceptible to MPXV, exhibited reduced lung viral loads and tissue inflammation post-vaccination, indicating protective efficacy.

The vaccine also induced robust germinal center B (GC B) cell and T follicular helper (TFH) cell responses in inguinal lymph nodes, essential for long-term immunity. BALB/c mice demonstrated superior immunogenic responses compared to C57BL/6J, suggesting genetic background influences vaccine efficacy.

Human Immunogenicity and T-Cell Responses

In vaccinated human cohorts, LC16m8 elicited strong antibody responses against MPXV A35 and M1 proteins. These responses extended across MPXV clades Ia, IIa, and IIb, signifying broad neutralization potential. Additionally, A35 synthesized from clade Ib elicited comparable antibody titers, supporting LC16m8's cross-clade effectiveness.

In addition to humoral immunity, the T-cell mediated cellular immunity, acritical arm of the adaptive immune system that can overcome the mutational variants of the viruses. In the same cohort study by Kobiyama K et al, although the size of the samples are small, T-cell profiling showed activation of both CD4+ and CD8+ populations, with specific cytotoxic and helper functions. These results align with murine findings and underscore LC16m8's capability to stimulate both arms of adaptive immunity.

Safety Assessment in Non-Human Primates

Cynomolgus monkeys intravenously administered LC16m8 developed transient skin lesions and mild systemic inflammation, as evidenced by temporary increases in C-reactive protein (CRP), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). No significant changes in body weight, temperature, or hematological parameters were observed. These findings confirm the vaccine's safety in higher mammals.

Relevance to the 100 Days Mission

The 100 Days Mission seeks to accelerate vaccine deployment within 100 days of identifying a pandemic threat. LC16m8's prior development for smallpox positioned it for rapid deployment during the 2024 Mpox resurgence. Its WHO EUL approval within this timeframe represents a practical realization of the mission's objectives. Africa CDC's Kinshasa campaign, which vaccinated 24,000 individuals in four days, exemplifies the operational feasibility of LC16m8. However, scaling these efforts requires sustained supply, further efficacy data in vulnerable populations, and streamlined logistics, especially for the children.

Alignment with SDG 3 and Broader SDGs

SDG 3 (Good Health and Well-being) directly relates to Mpox control. Target 3.3 aims to end epidemics of communicable diseases. LC16m8 supports this goal by providing an effective, accessible vaccine for outbreak containment and epidemic preparedness.

SDG 1 (No Poverty) and SDG 10 (Reduced Inequalities) are addressed through LC16m8 distribution to underserved regions, mitigating healthcare burdens and ensuring equitable vaccine access.

SDG 9 (Industry, Innovation, and Infrastructure) is reflected in Japan's sustained investment in vaccine R&D, while SDG 17 (Partnerships for the Goals) is embodied in collaborative efforts between Japan, WHO, and the DRC.

Research Gaps and Future Directions

Despite promising results, further studies in the deployed countries for the Mpox vaccines are warranted:

Safety in Special Populations: Ongoing trials (e.g., PregInPoxVac) aim to evaluate LC16m8 in pregnant women and children under two.

Antigen Profiling: Mapping immunodominant epitopes among the 180 MPXV-encoded proteins will refine future vaccine designs.

Comparative Studies: Direct comparisons between LC16m8 and mRNA vaccines are needed to optimize outbreak-specific immunization strategies.

Funding and Infrastructure: Political instability and decreased overseas development assistance (ODA) threaten vaccine rollout, necessitating resilient funding mechanisms.

Conclusion

LC16m8 represents a scientifically validated, operationally feasible, and ethically aligned vaccine for Mpox control including the volunerable populations such as children and immune deficient patients. Recent evidence substantiates its broad immunogenicity, cross-clade efficacy, and favourable safety profile. Its role in the 100 Days Mission and alignment with SDGs exemplify the power of preparedness, innovation, and global cooperation in addressing public health crises. Future investments in research, production, and equitable distribution will ensure that LC16m8 and similar platforms fulfil their potential in safeguarding global health.

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