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Mpox exposes fundamental obstacles for vaccinating children in outbreaks

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The ongoing mpox outbreak has recently passed one year since the WHO declared it a Public Health Emergency of International Concern (PHEIC) on 14 August 2024. It is also over a year since the national mpox outbreak was declared and the new clade Ib was reported in the Democratic Republic of Congo (DRC) and 3 years since the first PHEIC was declared in 2022. Despite international efforts to ensure availability and access to medical countermeasures within the first 100 days of an epidemic or pandemic threat being identified, that moment passed without children—those most at risk of death from this outbreak—being included in the vaccine rollout in the most affected region.

In the current outbreak in the DRC, a large proportion of cases, and the majority of deaths among suspected mpox cases, were known to be in children, especially under 5 years of age, with the highest case-fatality rates seen in infants under 1 year.[1] Despite this, vaccination efforts in the first 100 days in DRC could only include adults. This paradox represented a significant missed opportunity early in the outbreak to reduce the main burden of mortality and attempt to limit transmission—both fundamental objectives of outbreak responses. Mpox has once again highlighted major ongoing structural barriers for inclusion of children in outbreak and pandemic response efforts.

Two vaccines that have WHO recommendations for prevention of mpox in children have been donated for use in the DRC outbreak. The LC-16m8 vaccine, which had a pre-existing licence for children in Japan, received emergency use listing from WHO on day 97 of the PHEIC but was not made available to DRC in the first 100 days. The Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN) vaccine, which lacked a licence in children, is therefore the only vaccine to have been made available for use in DRC in the first 100 days. Two key obstacles appear to have prevented early vaccination of children in this outbreak; through examining these, we aim to highlight lessons for future outbreak and pandemic response.

First, despite longstanding evidence of a large proportion of mpox cases occurring in children in endemic settings, with mortality correlating strongly with younger age,[2] clinical trials of the MVA-BN vaccine including young children had not been completed before the second PHEIC was declared. Studies of the safety and efficacy of MVA-BN were conducted in adults, generating sufficient evidence for it to be licensed by the FDA in those aged 18 years and over in 2019. After a global mpox outbreak began in 2022, the vaccine received WHO prequalification for use in adults in September 2024, with an extension granted to include those aged 12 years and older in October 2024. A study aiming to extend a licence down to 2 years

SUMMARY BOX

⇒ Children could not be included in mpox vaccination roll-out within the first 100 days of the latest Mpox outbreak in the Democratic Republic of Congo and are yet to be rolled out in many countries with rising cases, despite this age group accounting for a large proportion of suspected cases and deaths.
⇒ Mpox has highlighted major ongoing structural barriers for inclusion of children in outbreak and pandemic response efforts.
⇒ These barriers include lack of early inclusion of children and pregnant women in clinical trials, including safety and efficacy studies of vaccines and an underutilisation of emergency regulatory pathways due to legal and financial considerations related to liability and indemnification arising from 'off-label' use of novel medical products.
⇒ WHO-coordinated response mechanisms and international pandemic response coalitions must do more to address these specific obstacles to ensure that children and population groups most at risk are protected during outbreaks.

of age began in October 2024,[3] and studies to demonstrate safety and efficacy for infants and pregnant women were planned for 2025.[4] While efforts to initiate and fund these studies are welcomed, they come far too late for the current outbreak in the DRC.

This delay in conducting clinical trials to understand safety and efficacy and enable licensure in children and pregnant women is familiar in biomedical research and development. Although it has been demonstrated that it is entirely possible to include children and pregnant women in clinical studies of unlicensed vaccines during emerging infectious disease outbreaks, including in the DRC, in multiple disease areas the delay in inclusion of children in clinical trials has led to an average wait of several years after licensure in adults.[5]

Second, although emergency regulatory pathways exist to authorise 'off-label' use of vaccines, their feasibility is inconsistent and inequitable. During the 2022 global mpox clade IIb outbreak, emergency use authorisation of the MVA-BN vaccine allowed vaccination of young children at risk of mpox in high-income countries including the USA from 17 days after declaration of the previous PHEIC.[6] In contrast, for the current outbreak in the DRC, which is caused by clade I—and where a higher mortality among children has been reported, emergency approval for vaccination of young children was not made possible within the first 100 days, despite a recommendation from WHO for 'off-label' use of MVA-BN in infants and children in outbreaks where the benefit is deemed to outweigh the risk.[7]

DRC is subsequently reported to have authorised vaccination above 1 year of age by day 200, while the majority of affected countries are yet to authorise use of the MVA-BN below 12 years of age by day 300, and infants under 1 year at highest risk of death remain uncovered. Of note, despite global increases in vaccine hesitancy, as well as social and logistical barriers, MVA-BN use among children in the DRC was associated with a high acceptance among the population according to the Africa CDC.[8] However, the high price of MVA-BN is posing a significant challenge which risks undermining the sustainable supply and access to this vaccine in affected countries.[9] This is particularly pertinent in the context of the recent unprecedented cuts to international aid funding, including Gavi and UNICEF, which is likely to further impact ability to meet demand.

Among the potential reasons for the delay in utilisation of emergency regulatory pathways in this outbreak are legal and financial considerations related to liability arising from 'off-label' use of novel medical products and the indemnification or compensation of patients having suffered from any adverse events resulting from its administration. In the USA, for example, legal mechanisms are in place to ensure those affected by adverse incidents can access compensation, for example, the US Public Readiness and Emergency Preparedness Act. Countries with fewer resources are less likely to have a dedicated mechanism or liability framework for managing issues related to the off-label use of vaccines, leaving vaccine administrators, such as Ministry of Health or NGO staff, potentially liable for patient compensation. As a result, the countries with the risk of the highest rates of mortality due to emerging infectious disease outbreaks may be the least able to accept the risks of using 'off-label' products.

While regulatory and legal challenges in outbreaks and pandemics are recognised in the recently adopted WHO Pandemic Agreement,[10] urgent solutions have not been forthcoming to address the barriers to mpox vaccine access early enough for young children during this outbreak.

For existing and future emergency approval pathways to be realistic in low-resource settings, strategies and mechanisms for managing unlicensed or off-label use of medical countermeasures, including the issue of liability, must be pre-agreed and then instigated and funded from the beginning of a globally coordinated outbreak response. In addition, beyond recommending emergency use of off-label products where the benefit is deemed to outweigh any theoretical risk, the WHO and regional partners should be supported to do much more to assist states in implementing such strategies and mechanisms, which would still remain exceptional, applied only to the time-limited use of novel vaccines and treatments during public health crises prior to regulatory approval. The WHO should also set and oversee clear parameters and exceptions for use and ensure that information and compensation are accessible to patients. Finally, even if emergency use mechanisms are applied, all efforts should be made to collect the clinical data to support inclusion of children in regulatory approval for the future.

Lessons are already being drawn from the global response to this outbreak, but reflection and learning from the obstacles that prevented vaccination of children in the first 100 days has been limited in the publicly available literature. The slow 'trickle down' process for inclusion of children and pregnant women in clinical trials and licensure of medical products—both in outbreaks and more generally—and the elusiveness of emergency use pathways in the settings where people are most at risk from the consequences of outbreaks has led and will continue to lead to multiplying layers of neglect of children and pregnant women in low-resource settings unless an explicit focus on these groups is strengthened.

WHO-coordinated response mechanisms, international pandemic response coalitions and national and regional public health and regulatory agencies must be supported to do more to address these obstacles to ensure that children and population groups most at risk are protected during outbreaks.

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