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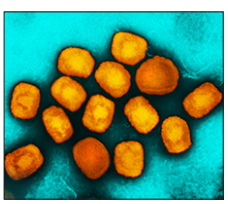
# Modified vaccinia Ankara–Bavarian Nordic vaccine against mpox in children



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Starting in May, 2022, the first large global outbreak of mpox (formerly known as monkeypox) with sustained human to human transmission occurred. The 2022 outbreak was due to clade IIb monkeypox virus, an orthopoxvirus and close relative of smallpox.

The third-generation smallpox vaccine, modified vaccinia Ankara–Bavarian Nordic (MVA-BN), a highly attenuated strain of the poxvirus chorioallantois vaccinia virus Ankara, is licensed for both pre-exposure and post-exposure mpox prophylaxis.[1] MVA-BN has been used extensively as part of the global public health response, and new cases have decreased.

There is little information on the use of MVA-BN in children. Although most cases in this outbreak were adult men,[2] children have been household contacts of patients and are, therefore, potentially at risk. In this issue of *The Lancet Infectious Diseases*, Shamez Ladhani and colleagues endeavour to fill this knowledge gap,[3] in a study of 87 children who received a single dose of MVA-BN for post-exposure prophylaxis during the public health response to mpox in the UK. None of the children developed any serious adverse events or mpox disease after vaccination. 45 of the 87 children completed a follow-up questionnaire, 18 (40%) of whom reported local reactions only and 11 (24%) of whom reported systemic symptoms with or without local reactions.

Seven children provided blood samples for post-vaccination assessment of immunogenicity. The samples showed IgG reactivity to several monkeypox virus antigens, including proteins B2, B6, and C18, some of which are present in the virus particle and probably take part in the process of infection. Similar antibody reactivity was seen in adults after a single dose of MVA-BN and in people who have recovered from mpox.[4]

Measurement of T-cell responses against MVA and a pool of pan-poxviridae peptide antigens showed correlation of these responses. This result indicates that T cells can recognise and cross-react with both MVA-BN and other orthopoxviruses, including monkeypox virus. Phenotypic differences in MVA responses between $CD4^+$ and $CD8^+$ T cells post-vaccination showed that memory responses tended to be $CD4^+$, whereas $CD8^+$ T cells displayed a ready-to-go so-called effector phenotype. Five out of the seven children gave a second blood sample at approximately 15 weeks post-vaccination and antibody and cellular responses were still present in all participants.

Early work from the 1980s in the Democratic Republic of Congo (then Zaire) showed that smallpox vaccination was 85% effective against disease caused by clade I monkeypox virus about 3–5 years after cessation of routine vaccination.[5] However, in an outbreak in 2003 in the USA, people vaccinated at least 31 years earlier (when smallpox vaccination ended in the USA) were not completely protected against mpox.[6] In the current outbreak, MVA-BN vaccine effectiveness in adults within a few months of vaccination is estimated to be 80% using a case coverage approach.[7]

These data provide crucial information about the vaccine. However, more work needs to be done. Given that the research was operational and not a prospectively designed study, the sample size was small, and 42 of 87 subjects did not give follow-up information. The effectiveness of MVA-BN as post-exposure prophylaxis in children remains unknown, despite the fact there were no cases among these children. Although all of the children who gave blood samples had immune responses to MVA-BN, this was only seven children. The T-cell phenotyping experiments only measured responses to MVA, not cross-reactive responses to monkeypox virus. Neutralising antibodies to monkeypox virus were not measured; other investigators have found these to be low in magnitude.[8]

Outstanding questions on the effectiveness of MVA-BN against mpox include how many doses will be required for long-lasting immunity, what the optimum dosing interval is, and whether immune correlates of protection exist. After vaccination with vaccinia, antibodies protect against smallpox, but the T-cell response limits the replication of vaccinia itself.[9] However, the mechanism of protection against mpox is not known. Poxvirus neutralising antibodies seem to persist for longer after MVA vaccination in mpox endemic settings,[10] but it has to be determined whether the durability of responses or vaccine effectiveness will be similar in a non-endemic population.

The contributions of antibodies (whether neutralising or non-neutralising) and T cells to vaccine immunity to mpox have not been determined. Future experiments should compare the longevity of these responses with natural monkeypox virus infection, the similarities between vaccine-induced and natural monkeypox virus responses, and functional differences between virus-specific and cross-reactive T cells. The identification of robust and easy to measure correlates of protection would be clinically beneficial. However, anti-viral immunity has never been straightforward.

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