new candidate vaccine is based on a similar principle as previously licensed vaccines (so-called biosimilars), use of an immunogenicity endpoint should be sufficient. There were specific quality requirements formulated, in particular that antibody concentrations must be reported in international units and that neutralising antibody assays are preferable.[2]

The paper by Zhu and colleagues is reporting exactly what was anticipated by the consensus workshop: the candidate HPV vaccine Cecolin 9 contains the same HPV types as the original second-generation vaccine Gardasil 9 does. Cecolin 9 is produced in *Escherichia coli* (Gardasil 9 is produced in yeast), but the basic principle (immunogenic L1 capsid proteins) is the same. The antibody concentrations induced by the two vaccines were found to be quite similar,[1] which is also in accordance with previous studies comparing Cecolin 9 to the first-generation vaccine Gardasil.[3] The results are presented in international units for HPV16 and 18, but in in-house units for the other HPV types. As international units for the other 7 vaccine types were only established in October 2022,[4] the authors have probably not yet had time to report the antibody concentrations for the other HPV types in international units. However, it is simple to afterwards calculate the conversion factor between an in-house standard and international units and we expect the authors to in due course report also these antibody concentrations in international units. This subsequent reporting in international units will allow comparison between all studies in the area, as international units are independent of the specific antibody assay used. A minor issue for comparability is that Zhu and colleagues have reported geometric mean international units, whereas we typically report the median international units.[5] Some standardisation of reporting or reporting of both measures seems desirable. Seroconversion rates seem less useful as an outcome of head-to-head immunogenicity studies as different vaccines based on HPV L1 capsid protein typically give close to 100% seroconversion rates.

In summary, the similar neutralising antibody concentrations induced by the biosimilar second-generation HPV vaccine is good news for the global efforts to eliminate HPV and cervical cancer. Increased supply of second-generation vaccines could ameliorate the unsatisfactory situation that many LMICs are still using first-generation HPV vaccines. Furthermore, as we are entering the era of unlimited supply of HPV vaccines, additional strategies to facilitate accelerated elimination of oncogenic HPV infections could become more widely used, such as vaccination of both sexes[6] and concomitant HPV vaccination and HPV screening in the young screening ages.[7] If there is unlimited supply of second-generation HPV vaccines, the question is not so much if there will be global elimination of HPV-related cancer but how long it will take.

We declare no competing interests.

*Laila Sara Arroyo Mühr, *Joakim Dillner*
joakim.dillner@ki.se

Center for Cervical Cancer Elimination, Karolinska Institute and Karolinska University Hospital, Stockholm 14186, Sweden (LSAM, JD)

1 Zhu F-C, Zhong G-H, Huang W-J, et al. Head-to-head immunogenicity comparison of an *Escherichia coli*-produced 9-valent human papillomavirus vaccine and Gardasil 9 in women aged 18–26 years in China: a randomised blinded clinical trial. *Lancet Infect Dis* 2023; published online July 17. https://doi.org/10.1016/S1473-3099(23)00275-X.

2 Lowy DR, Herrero R, Hildesheim A. Primary endpoints for future prophylactic human papillomavirus vaccine trials: towards infection and immunobridging. *Lancet Oncol* 2015; **16:** e226–33.

3 Shu Y, Yu Y, Ji Y, et al. Immunogenicity and safety of two novel human papillomavirus 4- and 9-valent vaccines in Chinese women aged 20-45 years: a randomized, blinded, controlled with Gardasil (type 6/11/16/18), phase III non-inferiority clinical trial. *Vaccine* 2022; **40:** 6947–55.

4 WHO Expert Committee on Biological Standards. Collaborative study to evaluate candidate 1st WHO international standards for antibodies to human papillomavirus types 6, 11, 31, 33, 45, 52 and 58. https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/2022-documents/new-2022-document-susan/bs-2022.2428_wilkinson_d_report-hpv-ab-who-international-standards_final.pdf?sfvrsn=9aba8576_1&download=true (accessed May 3, 2023).

5 Arroyo Mühr LS, Eklund C, Lagheden C, et al. Head-to-head comparison of bi- and nonavalent human papillomavirus vaccine-induced antibody responses. *J Infect Dis* 2022; **226:** 1195–99.

6 Vänskä S, Luostarinen T, Baussano I, et al. Vaccination with moderate coverage eradicates oncogenic human papillomaviruses if a gender-neutral strategy is applied. *J Infect Dis* 2020; **222:** 948–56.

7 Dillner J, Elfström KM, Baussano I. Prospects for accelerated elimination of cervical cancer. *Prev Med* 2021; **153:** 106827.

Mpox breakthrough infections: concerns and actions

Published **Online**
September 6, 2023
https://doi.org/10.1016/S1473-3099(23)00546-7

There have been more than 88 000 cases of mpox (formerly known as monkeypox) disease, caused by monkeypox virus (MPXV), since May, 2022. In 2019, the US Food and Drug Administration (FDA) approved the modified vaccinia Ankara–Bavaria Nordic (MVA–BN) vaccine as a two subcutaneous dose regimen to prevent

smallpox and mpox infection.[1] During the 2022–23 outbreak, the pooled estimated vaccine effectiveness in preventing mpox infection was 89%.[2] Despite that good effectiveness, breakthrough infections can occur, due to various factors, including the host immune response variations or exposure to high viral loads. A recent study in the UK reported that eight of 363 mpox cases assessed were likely to have occurred at least 14 days after receiving a single-dose MVA–BN vaccine.[3] Notably, 32 cases occurred within two weeks of vaccination. In another study,[4] 77% of post-vaccination cases occurred within two weeks.

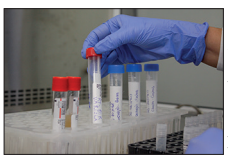
In another study,[5] prodromal symptoms, skin lesions, and the need for symptomatic treatment were similar between cases of mpox diagnosed after vaccination with a single MVA–BN dose and those in individuals who were not vaccinated. It was suggested that these cases were more likely incubating during vaccine administration as there was a short interval (median of 4 days) between vaccination and initial symptoms. Interestingly, three (20%) of 15 diagnosed people were HIV positive. This finding was further supported by studies in the UK[3] and in the USA,[4] which found that 50% and 36% of mpox cases occurring within 2 weeks of vaccination, respectively, were in people who were HIV positive, raising concerns about lower protection among this group.

The fact that people with HIV can be immunocompromised and can have an insufficient immune response, as shown by the US study, in which 96% of cases in people with HIV occurring within 2 weeks and all cases in people with HIV occurring 28 days after vaccination were virologically suppressed, supports this hypothesis.[4] A previous trial[6] comparing the safety of MVA–BN in people with HIV and people without HIV demonstrated significantly higher total antibody titres in people without HIV compared with those living with HIV. Notably, high seropositivity rates were observed in groups after two doses of MVA–BN, supporting the conclusion that immune responses associated with protection were induced in this immunocompromised population.[6] However, no statistically significant association was found in real-world data when analysing the link between immunosuppression and HIV status and the effectiveness of vaccines.[7,8]

A retrospective study[7] assessed the effectiveness of a single dose of MVA–BN vaccine in 108 individuals exposed to mpox within 14 days of receiving the vaccine. Of them, 11 (10%) had breakthrough mpox infection, with mild symptoms around 5 days postvaccination. The authors found that sexual exposure was significantly associated with breakthrough infection, whereas immunosuppression, HIV infection, history of smallpox vaccination, and age did not show a significant association.[7] Another study[8] reported an effectiveness rate of 86% for the MVA–BN vaccine in men at high risk of mpox. However, due to limitations in the study design, such as significant characteristics differences between study groups, this effectiveness rate might have been overestimated. The authors found no significant association between HIV pre-exposure prophylaxis, HIV history, recent sexually transmitted infections, and mpox.[8]

Given these findings, breakthrough infection should be considered. Clinical suspicion still needs to be high, even in people who are vaccinated, and both clinicians and patients need to be informed of this. Unlike most cases in individuals who are vaccinated that tend to be mild or moderate, another report[9] showed five severe breakthrough mpox cases following recent MVA–BN vaccination. All five patients experienced localised anogenital symptoms. Four had proctitis requiring antibiotics and analgesics, including opioids. The two patients who received a second dose had less severe symptoms than the others.[9] The genetic variations found in the MPXV outbreak viruses might impact the effectiveness of vaccinia virus-based vaccines by affecting immune responses. Therefore, four patients' viral DNA was sequenced and analysed, revealing that the genomes belonged to both existing and distinct MPXV clade IIb lineages. However, no common mutation pattern was identified among the four viral genomes, indicating no clear genomic traits associated with potential immune escape.[9] A single-centre study[10] reported two non-severe proctitis cases within 12 PCR-confirmed breakthrough infections among 276 participants who were vaccinated. The lack of a standardised definition of disease severity might hinder the comparability of studies. Additionally, breakthrough cases will need thorough tests to identify the risk factors, ideally, including taking samples for viral sequencing.

It is crucial to emphasise that these isolated breakthrough infections should not be interpreted as undermining the effectiveness of the mpox vaccine in reducing disease burden at a population level;[4,8] rather, these findings highlight the significance of taking viral



Flickr - Tony Oliveira/ Agência Brasília

and individual factors into account when assessing vaccine effectiveness in future studies. When available, it is advised to finish the two-dose vaccination course to boost immune response. Additionally, pairing vaccination with other preventive measures should be encouraged among people with a high risk for mpox, especially in the early weeks following vaccination. Finally, more research is needed to find out how to protect people at the highest risk (eg, those living with HIV) as well as for the development of new vaccines against mpox.

We declare no competing interests.

*Amira Mohamed Taha, Alfonso J Rodriguez-Morales, *Ranjit Sah*
ranjitsahdoc@gmail.com

Faculty of Medicine, Fayoum University, Fayoum, Egypt (AMT); Medical Research Group of Egypt (MRGE), Negida Academy, Arlington, MA, USA (ATM); Clinical Epidemiology and Biostatistics Program, Faculty of Health Sciences, Universidad Científica del Sur, Lima, Peru (AJR-M); Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, Lebanon (AJR-M); Department of Microbiology, Institute of Medicine, Tribhuvan University Teaching Hospital, Kathmandu 44600, Nepal (RS); Department of Microbiology, Dr DY Patil Medical College, Hospital and Research Centre, Dr DY Patil Vidyapeeth, Pune, India (RS); Datta Meghe Institute of Higher Education and Research, Jawaharlal Nehru Medical College, Wardha, India (RS)

1 US FDA. JYNNEOS. Package insert. March, 2023. https://www.fda.gov/media/131078/download (accessed Aug 9, 2023).
2 Xu M, Liu C, Du Z, Bai Y, Wang Z, Gao C. Real-world effectiveness of mpox (monkeypox) vaccines: a systematic review. *J Travel Med* 2023; published online April 11. https://doi.org/10.1093/jtm/taad048.
3 Bertran M, Andrews N, Davison C, et al. Effectiveness of one dose of MVA–BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. *Lancet Infect Dis* 2023; **23:** 828–35.
4 Hazra A, Rusie L, Hedberg T, Schneider JA. Human monkeypox virus infection in the immediate period after receiving modified vaccinia Ankara vaccine. *JAMA* 2022; **328:** 2064–67.
5 Agunbiade S, Burton F, Muirhead J, Whitlock GG, Girometti N. Clinical characteristics of mpox infection in individuals who received a first dose of modified vaccinia Ankara immunisation. *Sex Transm Infect* 2023; **99:** 198–99.
6 Overton ET, Stapleton J, Frank I, et al. Safety and immunogenicity of modified vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced human immunodeficiency virus-infected individuals: an open-label, controlled clinical phase II trial. *Open Forum Infect Dis* 2015; **2:** ofv040.
7 Merad Y, Gaymard A, Cotte L, et al. Outcomes of post-exposure vaccination by modified vaccinia Ankara to prevent mpox (formerly monkeypox): a retrospective observational study in Lyon, France, June to August 2022. *Euro Surveill* 2022; **27:** 2200882.
8 Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. *Nat Med* 2023; **29:** 748–52.
9 Berens-Riha N, De Block T, Rutgers J, et al. Severe mpox (formerly monkeypox) disease in five patients after recent vaccination with MVA–BN vaccine, Belgium, July to October 2022. *Euro Surveill* 2022; **27:** 2200894.
10 Thy M, Peiffer-Smadja N, Mailhe M, et al. Breakthrough infections after postexposure vaccination against mpox. *N Engl J Med* 2022; **387:** 2477–79.

Main autopsy findings of visceral involvement by fatal mpox in patients with AIDS: necrotising nodular pneumonia, nodular ulcerative colitis, and diffuse vasculopathy

Published **Online** October 9, 2023 https://doi.org/10.1016/S1473-3099(23)00574-1

Since 2022, monkeypox virus (MPXV) has been causing a multinational epidemic with Brazil as one of the most affected countries.[1,2] During the current mpox (formally known as monkeypox) epidemic, men with AIDS are at increased risk of severe illness and death, although it remains unclear whether deaths are directly attributed to MPXV.[2] We report clinical and autopsy findings of two men in their early 20s, who had severe mpox associated with AIDS in São Paulo.

Case 1 was a street market worker, declared as bisexual, who presented with fever, myalgia, inguinal lymphadenopathy, and headache in mid-July 2022, then progressing with maculopapular lesions in the perianal region on the 8th day of illness (DOI). He was diagnosed with HIV in 2016, and previously had neurotuberculosis, neurotoxoplasmosis, neurosyphilis, disseminated histoplasmosis, and cytomegalovirus and herpes virus-1 glossitis. He was treated for HIV and tuberculosis irregularly, with right hemiparesis and seizures as sequelae. In early July 2022, his CD4+ T-cell count was 3·0 cells per µl. On the 16th DOI, he sought emergency help for painful perianal vesicles when the mpox diagnosis was made by RT-PCR of vesicular fluid. On the 28th DOI, he was hospitalised at the Instituto de Infectologia Emílio Ribas (IIER) with disseminated mpox lesions and skin and soft tissue sepsis. During hospitalisation, several new lesions appeared, including on the edges of pre-existing lesions in a centrifugal pattern, in places of dressings and venous access, and many with confluence and dermal necrosis that were constantly painful, which required high doses of opioids. Tecovirimat (TPOXX) was started on the 51st DOI; on the following day the patient had two episodes of generalised tonic-clonic seizures that were controlled with benzodiazepines, allowing for TPOXX treatment for 28 days. On the 55th DOI, he had wheezing with