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Correspondence

Monkeypox vaccines and vaccination strategies: Current knowledge and advances. An update – Correspondence

Dear Editor,

Monkeypox (MPX) has now been declared a global public health emergency due to its rising cases and rapid spread in more than 80 countries with over 25,000 cases. Smallpox vaccines cross-protect against MPXV owing to antigenic similarity. However after smallpox eradication, cessation of smallpox vaccination program in 1980 has led to virtual lowering or loosing immunity, thus the risk of human-to-human transmission of monkeypox virus (MPXV) has increased. In this correspondence, we present current status and advances made in developing effective vaccines and vaccination strategies to counteract MPX. Vaccination against smallpox may provide protection against MPXV along with amelioration of clinical disease. At present, there exist three vaccines against smallpox in the Strategic National Stockpile (SNS) of the USA, with licensing of two vaccines: JYNNEOS™ (also known as Imvamune or Imvanex or MVA-BN) and ACAM2000®, and the third one is Aventis Pasteur Smallpox Vaccine (APSV). These vaccines are currently being offered to afflicted people in some countries such as the United Kingdom (UK) and Spain in an effort to curb the MPXV spread [1].

For primary vaccination and booster doses, JYNNEOS and ACAM2000 vaccines are now available for pre-exposure prophylaxis (PrEP) [2]. MVA-BN is a live non-replicating third-generation vaccine [Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) strain, attenuated Vaccinia virus, replication-deficient] and marketed as JYNNEOS™ in the USA, and is approved for vaccination against both smallpox and MPX [3]. In September 2019, The Food and Drug Administration (FDA) licensed this vaccine for use in people of age 18 years and above who are considered to be at increased likelihood of MPXV infection [1,4]. The MVA-BN vaccine is 85% effective in protecting against MPX. However its efficacy and safety against pregnant or breastfeeding women is still debatable [3,5]. The Advisory Committee on Immunization Practices (ACIP) has considered the use of JYNNEOS™ for PrEP purpose as a potential alternative to ACAM2000 during 2020–2021 [6]. The safety, effectiveness, and immunogenicity of IMVAMUNE® have also been evaluated among the Congo healthcare personnels at risk of MPXV infection [7]. The Centers for Disease Control and Prevention (CDC) recommends MPX vaccination within four days of exposure for the best chance of preventing disease onset. If administered between 4 and 14 days of exposure, vaccination may lessen symptoms but will not prevent the disease [8].

IMVAMUNE vaccine does not cause any lesions at the immunization site and no longer poses a danger of autoinoculation, unintentional transmission, or systemic dissemination. It showed a reduced risk of injury than standard smallpox vaccines, and the potential benefits outweigh the dangers. The vaccine is contraindicated in individuals who have a history of life-threatening anaphylactic reaction to a previous IMVANEX dose, or any component of the vaccine viz., benzonase, chicken protein etc, even if present in limited quantity (https://www.nhsinform.scot/healthy-living/immunisation/vaccines/vaccination-to-help-protect-against-monkeypox). Unlike the ACAM2000 and APSV vaccines, this vaccine was found to be safe for use in people having HIV infection, AIDS patients or those with atopic dermatitis [7]. However, it is not yet clear how effective this vaccine is in endemic areas.

The ACIP has recommended the use of Orthopoxvirus vaccine ACAM2000 in 2015, which is a preparation of live vaccinia virus (replication competent), for active immunization against smallpox disease in persons determined to be at high risk [9]. Its inoculation is done by perforating the surface of skin. Upon successful inoculation, there will be development of a lesion at the immunization site, and there may be occurrence of accidental virus transmission. The inoculated virus can show spread to other body parts or even to other individuals. Virus transmission can also occur vertically that may result in fetal vaccinia which can be lethal for fetal life or newborn. Thus, those who receive ACAM2000 vaccine must take precautionary measures for preventing the spread of vaccine virus (https://www.cdc.gov/poxvirus/monkeypox/clinicians/monitoring.html). In some people, there may be occurrence of eczema vaccinatum and progressive vaccinia after immunizing due to virus replication in an uncontrolled manner. Immunocompromised people are more prone to progressive vaccinia whereas those suffering from eczema or atopic dermatitis may develop eczema vaccinatum. ACAM2000 should be avoided in HIV infected persons as it can give rise to complications in those having serious problems of the immune system. Importantly, due to less chances of occurrence of myopericarditis and encephalitis after vaccination with JYNNEOS™, this vaccine is considered to be safer in comparison to ACAM2000 (https://www.fda.gov/media/75792/download) [10]. The protective effect of IMVAMUNE and ACAM2000 after their post exposure administration which was studied in prairie dogs infected intranasally with MPXV revealed protection to a certain degree. IMVAMUNE was found more effective when administered at 1 day rather than 3 days post exposure, but the efficacy of ACAM2000 was similar at both these time-points [11]. The side effects along with untoward effects are potentially more with ACAM2000 in comparison to JYNNEOS vaccine (https://www.cdc.gov/poxvirus/monkeypox/clinicians/monitoring.html) [9]. APSV is another replication-competent vaccinia virus that may be used under Investigational New Drug Application [IND] or Emergency Use Authorization [EUA] in a smallpox emergency.

MVA-BN (IMVAMUNE) vaccine is very important in the currently ongoing MPX outbreak as it is a non-replicating virus vaccine [3,12]. However, data still are needed on what the role the vaccine is playing and whether it is effective among the most affected population (men who have sex with men, MSM). Moreover, ring vaccination among MSM

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is challenging as these individuals do not want to share details. Based on animal studies, MVA has been shown to protect prairie dogs, and macaques, and data also showed a strong antibody response in humans [12]. In a monkey model, antibody binding, neutralizing titres and T-cell responses were found equivalent or higher after two doses of highly attenuated MVA or one dose of MVA followed by the licensed smallpox vaccine Dryvax, when the data was compared with the Dryvax vaccine (used predominantly in the United States) alone [13,14].

Frequent booster doses are also recommended for persons working with more virulent Orthopoxviruses including Variola virus and MPXV [9]. Animal models have shown no evidence of harm to a developing fetus in cases of pregnant women who received JYNNEOS. However, there are limited human data available on its administration to pregnant women or breastfeeding women. It is also not clear whether JYNNEOS is excreted in human milk or not [2]. After 2 weeks of receiving a second dose of JYNNEOS vaccine, the peak antibody response is achieved [15]. Further studies on JYNNEOS vaccine are highly needed to determine the duration of protection after vaccination and booster doses. Moreover, it is also very essential to evaluate the risk of any serious adverse event(s) for co-administration of JYNNEOS with COVID-19 vaccines [2].

The first-generation smallpox vaccines (based on Vaccinia virus) are reactogenic, and hence they are not appropriate for mass vaccination during the current scenario of rising cases of MPX. The second and third generation vaccines which are available against smallpox can be used against MPX as well. The antibody mediated responses elicited are similar to that produced by the first-generation vaccines. Vaccines belonging to the second-generation category cause side effects rarely, but such effects can be serious, whereas the third-generation vaccines which contain a virus that is weakened cause less side effects. Evaluation of a recombinant protein-based subunit vaccine in rhesus macaques revealed its ability to induce protective antibody response. This vaccine has been suggested to be a safer substitute of a live vaccinia virus (VACV) smallpox vaccine (Dryvax) that is contraindicated in immunocompromised individuals, **and could** protect against smallpox and monkeypox [16]. For developing a modern and safer live vaccine, a candidate based on VACV using genetic engineering, which is a recombinant and attenuated VACΔ6 strain, has recently been created from the VAC LIVP clonal variant by using transient dominant selection, five virulence genes deletion, one gene inactivation, and 71 times passaging in CV-1 cells [17].

Pre-exposure prophylaxis (PrEP) of individuals at high risks of exposure is the most effective technique to employ vaccinations to limit a MPX outbreak if contact tracing fails to discover a large percentage of infected contacts. A focus on MSM and front-line health workers at high risks of occupational exposure should be taken into account when devising immunization plans [18]. Personnels in research and clinical laboratories, those who are involved in diagnosis of MPXV, healthcare workers along with members of teams involved in public health response need to be immunized preferably. Post-exposure prophylaxis (PEP) is not warranted for people who follow all the standard precautionary measures and use personal protective equipments (PPE) as they are not at a greater risk of contracting the disease. Vaccination should also be performed for persons who are exposed to MPXV and have not been vaccinated with smallpox vaccine within a period of last 3 years.

Currently, mass immunization against MPX is not warranted as all people are not at heightened risk of MPX. Various nations where MPX outbreaks have occurred have accumulated stocks of second generation vaccines. Due to the side effects of the stockpiled vaccines, they are prohibited from use in pregnant women or children, immunocompromised individuals, or those having conditions of the skin like eczema. Fewer nations have gained access to the third generation vaccines which definitely could have a greater coverage due to their limited side effects. Risk-benefit analysis could be altered if the virus spreads to at-risk groups, such as pregnant women or young children, or if a higher death rate than projected is observed (https://www.nature.com/articles/d41586-022-01587-1).

Ring vaccination is a valuable strategy to counter MPX rather than immunizing the population entirely, wherein a ring of human beings around the MPXV infected people is vaccinated, thus facilitating immunization of people at close contact as well as those in contact with the contacts of the infected people. The application of ring vaccination can have a high value in breaking the MPXV transmission chain, act as post-exposure prophylaxis, and prevent severe disease development, while addressing MPX associated possible challenges [19]. This approach will mainly be successful when there are vigorous testing and contact-tracing facilities, and rapid vaccination of people at higher risks of contact need to be conducted. Identifying the proper target group for available vaccines on the basis of risk and benefit analysis could play a crucial role in MPX vaccination program, such as healthcare workers, high-risk target group, and identifying MPX cases and their sexual partners.

Reaching individuals who are most at risk of MXV infection and ensuring vaccine uptake necessitate global health promotional efforts that focus on specific targeted populations. Moreover, further clinical studies and pharmacovigilance monitoring among vulnerable groups are needed to ensure herd immunity against this viral illness. Better surveillance, diagnostics, enhanced infection prevention and control procedures in hospitals, and social and safety containment countermeasures are current requirements. Besides developing effective and advanced vaccines specifically against MPX, high global efforts must be made to ensure wide access to vaccines, effective contextual risk communication, increasing awareness and public engagement strategies to target MPX vaccination coverage to the most vulnerable, marginalized poor and rich people, and outbreak affected areas. A holistic vaccination strategy is needed to be formulated to counteract the rising cases of MPX before these could further increase exponentially and pose a pandemic threat amid the ongoing COVID-19 pandemic.

Ethical approval

The authors declare no involvement of animal studies or human participants in the study as it is a compiled letter article.

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SC, KD: designed the study. SC: made the first draft. RKM, DC, MA, PSV, MAI, CC: updated the manuscript. KD: reviewed and edited the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Sandip Chakraborty
Department of Veterinary Microbiology, College of Veterinary Sciences and Animal Husbandry, R.K. Nagar, West Tripura, Tripura, Pin-799008, India
E-mail address: chakrabortysandip22@gmail.com.

Ranjan K. Mohapatra**
Department of Chemistry, Government College of Engineering, Keonjhar, 758002, Odisha, India

Deepak Chandran
Department of Veterinary Sciences and Animal Husbandry, Amrita School of Agricultural Sciences, Amrita Vishwa Vidyapeetham University, Coimbatore, 642109, Tamil Nadu, India
E-mail address: c_deepak@cb.amrita.edu.

Mahmoud Alagawany
Poultry Department, Faculty of Agriculture, Zagazig University, Zagazig, 44511, Egypt
E-mail address: dr.mahmoud.alagwany@gmail.com.

Praveen Sv
National Institute of Technology, Tiruchirappalli, 620015, Tamil Nadu, India
E-mail address: praveenscissci@gmail.com.

Md Aminul Islam
COVID-19 Diagnostic Lab, Department of Microbiology, Noakhali Science and Technology University, Noakhali, 3814, Bangladesh
Advanced Molecular Lab, Department of Microbiology, President Abdul Hamid Medical College, Karimganj, Kishoreganj, 834001, Bangladesh
E-mail address: aminulmbg@gmail.com.

Chiranjib Chakraborty
Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, 700126, West Bengal, India
E-mail address: drchiranjib@yahoo.com.

Kuldeep Dhama*
Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Izatnagar, Uttar Pradesh, 243122, India

** Corresponding author. , Department of Chemistry, Government College of Engineering, Keonjhar, 758002, Odisha, India.

* Corresponding author. Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Izatnagar, Uttar Pradesh, 243122, India.
E-mail address: ranjank_mohapatra@yahoo.com (R.K. Mohapatra).
E-mail address: kdhama@rediffmail.com (K. Dhama).