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Perspective

Intradermal Vaccination for Monkeypox — Benefits for Individual and Public Health

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Intradermal vaccination delivers antigen into the space between the epidermis and the dermis. This space is an anatomically favorable site for immune stimulation, enriched in a heterogenous population of dendritic cells, macrophages, and monocytes that endow this tissue with a potent capacity to detect and respond robustly to immunologic stimuli, including those present in vaccines. For these reasons, the role of the dermis in adaptive immunity has been exploited for allergen testing and tuberculosis skin testing. And smallpox vaccination was developed by Jenner using something similar to intradermal administration: variolation, or the practice of scratching immunizing material into the skin.

Intradermal vaccination has been extensively studied for prevention of a wide range of viral diseases, including influenza (for which there is a licensed intradermal vaccine), Japanese encephalitis, hepatitis A, hepatitis B, human papillomavirus disease, polio, rabies, varicella zoster, and yellow fever. In the 1970s, Germany's smallpox eradication campaign deployed it for vaccinating more than 100,000 persons with modified vaccinia Ankara (MVA), which forms the basis for the JYNNEOS vaccine currently being used to combat monkeypox.

Among the advantages of intradermal vaccination is that it can generate immune responses equivalent to those achieved with subcutaneously or intramuscularly administered vaccine but with as little as one fifth to one tenth the dose, while avoiding the rare risk of nerve, blood-vessel, or joint-space injury. To address the technical challenge of shallow administration with a needle, technologies have been developed to ensure proper vaccine placement in the intradermal space, and some have been approved for use by the Food and Drug Administration (FDA). However, such technologies must be tested with each specific category of vaccine before being deployed, to ensure that the vaccine's potency and safety are maintained. The robust response generated by intradermal vaccination can also sometimes lead to increased and prolonged skin irritation, induration, granuloma formation, and discoloration, but these effects are most often temporary. Also, people who have had keloids should not receive intradermal vaccination.

JYNNEOS (also sold as Imvamune and Imvanex) vaccine contains a live but attenuated nonreplicating MVA strain and is

licensed for prevention of both smallpox and monkeypox. It was developed and added to the Strategic National Stockpile specifically for smallpox vaccination of immunocompromised persons for whom the alternative smallpox vaccine, ACAM2000, may not be appropriate because it contains attenuated but replicating vaccinia. JYNNEOS was thus neither intended nor scaled up for use in a national monkeypox outbreak. But its intradermal administration at one fifth the standard dose is an attractive option that could ameliorate current supply shortages while ensuring similar levels of immunogenicity. In a randomized, controlled trial, a one-fifth dose given intradermally achieved levels of neutralizing antibodies similar to those produced with standard doses given subcutaneously on the same FDA-approved schedule,[1] though by some measures cellular immunity levels were lower.[2] A dose-finding study using a different but closely related MVA vaccine showed that even a one-tenth dose of MVA given intradermally was as immunogenic as the full dose given subcutaneously or intramuscularly.[3]

There are no data from clinical trials specifically evaluating the effectiveness of JYNNEOS against monkeypox using either route of administration, and we don't know what level of immune response in someone given the vaccine as pre- or post-exposure prophylaxis would correlate with functional immunity against monkeypox infection or protection against severe disease. But there are no a priori reasons to doubt that JYNNEOS will be effective by the intradermal route, and we have reasonable evidence that intradermal dosing will be similarly immunizing as compared with subcutaneous dosing, at least in the short term, as a means of outbreak control to break chains of transmission.

The FDA label for JYNNEOS describes its safety when it is given subcutaneously to people with HIV and CD4 cell counts of 200 per cubic millimeter or higher.[3] On the basis of current knowledge, intradermal dosing can reasonably be expected to be similarly safe and immunogenic in this population, which is substantially overrepresented among people who have become infected with monkeypox thus far. Although the intradermal immunogenicity of MVA vaccine in persons with more advanced HIV disease or other serious immunocompromising disorders has not been studied directly, intradermal versus intramuscular administration of influenza vaccines has. In these studies, both routes of administration produced lesser responses in persons with CD4 cell counts below 200 per cubic millimeter than in persons with higher counts. However, even among persons with low CD4 cell counts, the extent of the humoral and cellular immune responses were effectively equivalent, albeit with full or half doses used intradermally.[4,5]

Vaccines work only if they are accessible, trusted, and used. We believe intradermal dosing of JYNNEOS will safely provide the populations that have been disproportionately affected by monkeypox with rapid access to a limited resource without sacrificing the level of immune response achieved (a condition that might not be met by an untested single- or delayed-dose strategy), while increasing our ability to give the vaccine according to the tested and approved dosing schedule. The smaller dose needed for intradermal administration will translate into greater available supply and opportunity for vaccination. Ideally, such availability will avert inequities like those seen when JYNNEOS first became available, when access to the vaccine by all groups, especially marginalized persons, was not equal. Providing more doses also augments prevention efforts by allowing vaccine product to be directed now to clinical providers and large events serving more marginalized communities.

Despite limited clinical evidence, all available data suggest that intradermal administration of JYNNEOS will be as immunogenic as subcutaneous dosing for preventing monkeypox infection and illness, which leads us to favor intradermal use from both the individual and public health perspectives. The Centers for Disease Control and Prevention and the FDA are committed to performing the studies needed to assure that our expectations are borne out. In the meantime, we urge people who are at the highest risk for infection to receive both doses of the two-dose vaccine, and we encourage manufacturers to consider routinely testing intradermal dose administration in future clinical vaccine trials, in order to expand our understanding of this operationally attractive option. The currently available evidence suggests that shifting to intradermal dosing that requires less vaccine is not a lesser option. Rather, it is a rational, evidence-informed means of advancing access, equity, and our chances of controlling the monkeypox outbreak.

Disclosure forms provided by the authors are available at NEJM.org.

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