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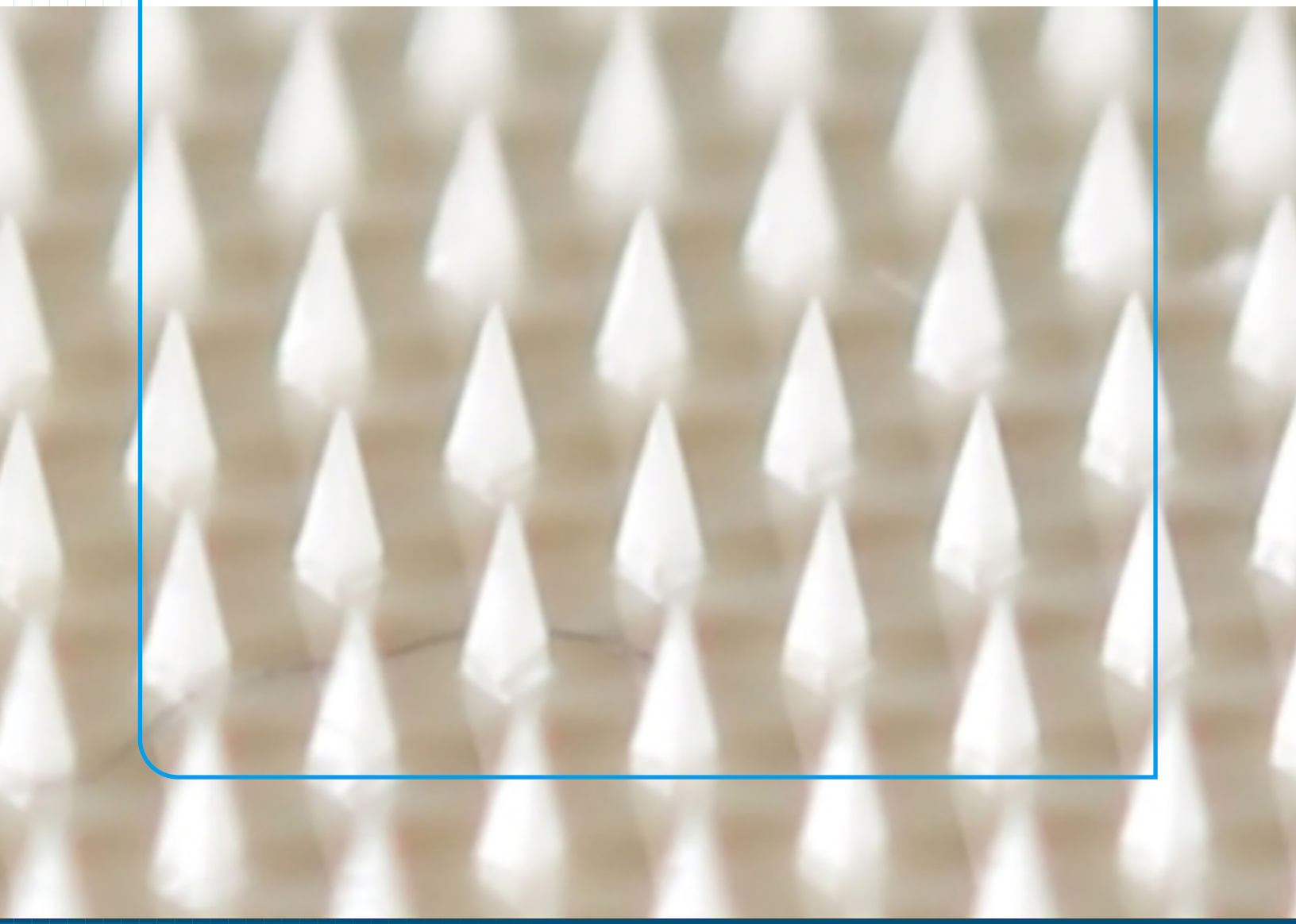
Article

Addressing the Challenges of Vaccines and Intradermal Delivery

BY JOHN P. VASILAKOS, PH.D., KINDEVA DRUG DELIVERY



This article considers six shortcomings in the way vaccines are developed and delivered. Addressing these deficiencies could improve both the efficacy and accessibility of vaccines.

Well before the outbreak of COVID-19, vaccines were a vital tool in promoting public health. The importance of vaccines has become even more apparent as we collectively observe the race to develop a vaccine and wait for good news. The absence of a COVID-19 vaccine predictably resulted in prolonged, deleterious global health, economic, and social outcomes. The pandemic has exposed industry limitations in the development of vaccines, such as the ability to scale-up vaccine supplies quickly. In response to this crisis, the pharmaceutical and healthcare industries should react by both reaffirming the importance of vaccines and by exploring ways to improve vaccine development and delivery.

To make effective vaccines, multiple challenges must be overcome. A vaccine can be suboptimal because of the vaccine itself. The vaccine can also be suboptimal if there are flaws in the selection, compatibility, or manufacture in any of its three major components: the antigen, the adjuvant, and the formulation. The antigen provides a template for the immune system, hence teaching the immune system what specific pathogen it needs to respond to when it encounters the pathogen. The adjuvant enhances or helps the immune system respond to the antigen. The formulation holds the antigen and adjuvant together and gives the vaccine stability. In recent years, there has been a tremendous focus on the physical and chemical properties of vaccines. This includes important advances in the understanding of complex adjuvants along with a resurgent interest in vaccine formulations. There is still progress to be made, but the amount of discovery in this field over the past few decades is encouraging.

In addition to the considerations taken to optimize the three key vaccine components, the vaccine delivery method must also be taken into consideration if optimal vaccine performance is to be achieved. The efficacy of a vaccine can be limited by the manner in which it is delivered to the body. Therefore, the delivery system or device may play an important role in improving the efficacy of the vaccine.

This article considers six shortcomings in the way vaccines are developed and delivered. Addressing these deficiencies could improve both the efficacy and accessibility of vaccines around the world.

Where Vaccines Are Delivered in the Body?

For effective vaccination, the vaccine must have access to the immune system. Ideally, vaccines would be delivered directly to immune cells, such as into an immune organ. These immune organs include the lymph nodes, the spleen, or the skin itself. Immune cells do not normally reside in the muscle tissue. Even though the muscle is not the ideal location to elicit an immune response, the common practice is to administer vaccines intramuscularly. This convention is dominant in part because it is simply more practical to administer a vaccine precisely and accurately into the muscle. However, there is evidence that supports the comparative advantage of intradermal delivery over intramuscular delivery.[1] Intradermal vaccinations have demonstrated enhanced immune responses in some cases.[2]

Practical Difficulties With Intradermal Delivery

Even though evidence supports the benefit of intradermal delivery of vaccines, it is inherently difficult to achieve a precise and reproducible delivery to the intradermal layer using traditional methods. The dermis, the thickest part of the skin, is thin — approximately 1800 micrometers in depth depending on body site, skin type, age, and sun exposure. A device that can deliver to a depth of between 500-1500 microns reliably is key. However, the use of intradermal vaccination in medicine has been limited by the lack of a simple and reliable method of delivery.[3] The practical constraints of delivering a drug intradermally can potentially be overcome with a thoughtfully designed device that enables consistent, reproducible intradermal delivery.

Precise and accurate delivery is especially important in developing countries where there is often only one chance for successful vaccination. Patients in these countries can travel significant distances to receive a vaccine. There needs to be a high one-time success rate so these patients can develop a response to the vaccine and improve their chance of being protected from the pathogen.

Volume of Delivery

Standard bolus intradermal injections are also limited by volume. The standard volume for intradermal injections is less than 0.1 mL, while standard intramuscular injections can have a volume of up to 1 mL. DNA vaccines, for example, typically aren't injected into the skin because of the necessity to administer larger volumes. In addition, DNA vaccinations administered to the skin by some electroporation devices may be less tolerable than DNA vaccination to muscle tissue, because higher electrical field strength is required.[4]

One way around the volume challenge is the device design. A microneedle array of several microstructures offers a good solution for the problem because the needles are spread out over a greater surface area, which enables delivery of a larger volume. The volume of vaccine delivered by some microneedle devices can reach 2 mL. Moreover, vaccine delivery devices that can regulate the delivery rate over a precise period of time can allow for greater control of the vaccine administration process. With an appropriate and scalable design, microneedles can offer an effective solution for delivering drugs to the intradermal layer.

Ability to Scale-Up Manufacturing

Manufacturing a vaccine at scale is a nontrivial challenge. In general, scale-up constraints are caused by the formulation and the vaccine itself, not by the device. To make typical protein-based vaccines, the antigen needs to be produced either in vitro or in a bioreactor (produced by a living organism, e. bacteria, yeast). These methods inherently require significant time and care. For example, maintenance of the bioreactor environment involves careful control of the temperature, CO_2 concentration, pH, salinity, nutrient levels, and O_2 concentrations. Within the bioreactor, there is a risk of poor yield, contamination, and mutations in the antigens. Careful and time-consuming monitoring is needed to mitigate these risks. Scale-up challenges make it very difficult to respond rapidly in emergency or pandemic situations.

Cold Chain Requirements

The cold chain can present a huge problem in developing nations. Many vaccines do not remain stable at room temperature and require refrigerated storage and transportation. This is not feasible in many parts of the world. If vaccines cannot be stored or transported, they are effectively inaccessible to people who need them the most. One way to circumvent this challenge is by modifying the formulation to enhance vaccine stability. Another method is to coat a dry formulation onto microneedles, which would yield the potential to keep the vaccine components stable at room temperature due to the removal of water.

Non-Representative Clinical Trials

Proper patient populations are not always represented in clinical trials. Thus, vaccines often underperform in the developing world. The reasons for suboptimal results are due in part to immune suppression caused by chronic infections, inadequate nutrition, and poor sanitation. Most clinical trials for vaccines destined for the developing world are conducted in industrialized countries, such as the United States.

Similarly, numerous cancer vaccine trials have been conducted in healthy volunteers, which exhibited responses that were not seen in cancer patients, who have a certain level of immune suppression or immune dysregulation. The same can be said about advanced age individuals who often respond less effectively to vaccines than young or middle-aged individuals. Hence, real-world outcomes may differ due to nonrepresentative sampling during clinical evaluation and subject (patient) selection. Therefore, clinical trials that more closely represent the target population need to be given higher priority. A better understanding of the immune response, specifically to vaccines, in the target population should be a crucial aspect of vaccine development.

Conclusion

While there has been significant innovation in vaccine development relating to antigen discovery, adjuvant discovery, and formulation development, there has also been significant development in delivery devices. Specifically, there has been development in devices that deliver drugs to the skin precisely and accurately and do not require significant training to use.

Ideally, vaccine administration to the skin may provide individuals the best chance of eliciting an effective immune response. Drug delivery devices that facilitate precise and accurate intradermal delivery of the vaccines should be taken into consideration for vaccine development.

Vaccines have the greatest potential for impact in developing countries, but they are often not designed with these countries in mind. Addressing this gap could mean developing products that overcome the need for cold chain. It could also mean ensuring devices are designed to be used by relatively unskilled or untrained professionals. Global accessibility should be a priority in order for vaccines to live up to their full potential.

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About the Author

John Vasilakos is a Business Director and Senior Research Immunologist at Kindeva Drug Delivery. Previous industry roles include Senior Research Immunologist and Business Development of TLR Ligands at 3M Drug Delivery Solutions Division and Vice President of Immunology at Biothera. He has spent over 25 years in the biopharmaceutical industry focusing on vaccines and immunotherapy for cancer and chronic viral diseases. He holds a Ph.D. from the University of Cincinnati School of Medicine.