Evolving Technology in Vaccine Administration

Some promising new methods for how vaccines are administered may soon eliminate many of the problems encountered by the healthcare industry.

BY DIANE L.M. COOK

FOR MORE THAN two decades, significant research and development progress has been made into evolving technologies in vaccine administration. The safety of hypodermic needle administration is evolving to help reduce injury and protect against virus contamination. And, it’s feasible that in a few short years, the use of hypodermic needles to administer vaccines could be a thing of the past — replaced instead by new devices such as needle-free injectors, patches and nasal mists. The benefits of these devices in comparison with hypodermic needles include lower production costs, increased manufacturing in a shorter period of time, increased vaccination rates among people with needle phobia, elimination of costs associated with sharps disposal, elimination of cold chain storage, improved management of pandemics through mass-
quantity shipping, and self-administration by nonhealthcare workers and even patients themselves.

While many devices are still in clinical trial stages, some of the world’s biggest vaccine and device manufacturers are already offering new technologies in vaccine administration to the global market. Following is a small sample of what’s now available and what’s to come.

**Needle-Free Injection**

Pharmajet has developed two needle-free injectors for delivering vaccines. The Stratis Needle-Free Injector for intramuscular or subcutaneous injection received an indication for influenza delivery from the U.S. Food and Drug Administration (FDA) in August 2014 and was introduced to the marketplace during the 2014-2015 flu season. The spring-powered injector delivers vaccines through a narrow stream of fluid that penetrates the skin in about one-tenth of a second. It includes the injector, a 0.5 mL needle-free syringe, a 13 mm/20 mm vial-filling adapter and a reset station. It has a CE Mark and is PQS (performance, quality and safety)-certified by the World Health Organization (WHO).

“The Pharmajet injection technology is an especially important innovation for the millions of individuals who suffer from the fear of needles (20 percent of the population) and the many millions more who are needle-adverse, who consequently forgo their annual flu vaccination,” says Ron Lowy, CEO of Pharmajet. “We believe this is a significant step forward in the effort to improve public health through broader immunization coverage, as well as improved safety of providers.”

Because the device does not use needles, it eliminates the possibility of needlestick injuries and reuse, and reduces sharps management costs. “The injector addresses both provider safety concerns and patient issues with needles,” says Lowy. “It has also been well-received by patients and healthcare providers alike. In post-market surveys, 93 percent of patients and 87 percent of providers reported that they would choose the Pharmajet needle-free option again.”

The Stratis is currently available in 33 states and in approximately a dozen countries outside of the U.S. “The Stratis is available in India, and we are currently conducting several studies in that country, which will make the injector more widely available soon,” adds Lowy. “The injector is also available in the larger countries in the Middle East. Additionally, in Europe, we are working on a prefilled format to administer vaccines.”

And, the learning curve is relatively simple. “Educational materials are provided on the Pharmajet website,” says Lowy. In addition, use of the Stratis “is part of the American Pharmacists Association training module used for new and current pharmacists. The average person can be trained in about 20 minutes and become proficient with the device after 10 to 15 injections.”

Pharmajet is also producing another needle-free injector that has similar technology to the Stratis and is optimized for intradermal delivery. The Tropis is being used with nucleic acid vaccines in development, as well as others such as polio, and is expected to receive FDA approval in 2016.

**Microneedle Patches**

The benefits of microneedle patches are similar to needle-free injectors. However, Yasmine Gomaa, a research scientist at the School of Chemical and Biomolecular Engineering at the Georgia Institute of Technology, says the biggest benefit compared to hypodermic needles is that researchers “found immunization using dissolvable microneedle patches to increase vaccine immunogenicity and to allow dose sparing.”

There are four types of microneedles that deliver vaccines through the skin. “Solid microneedles utilize the ‘poke and patch’ and the ‘coat and poke’ approaches,” explains Gomaa. “The ‘poke and patch’ approach involves the application of a solid microneedle array to create micropores that is followed by removal of the array and application of the drug formulation in the form of a transdermal patch, gel or solution. The ‘coat and
poke’ approach relies on coating the vaccine formulation onto the solid microprojections and insertion of the microneedle patch into the skin. This coating can dissolve within a few minutes after insertion into the skin, after which the microneedles can be withdrawn and discarded, and the dissolved vaccine diffuses through the skin into the blood capillaries.”

The third type, dissolvable microneedles, delivers vaccines through the “poke and release” approach. They release their encapsulated payload when inserted into the skin for bolus or sustained delivery. The fourth type, which uses mediated transdermal delivery, is through the “poke and flow” method. This consists of hollow microneedles that puncture the skin followed by infusion of liquid formulation through the needle lumens in a manner similar to hypodermic injections.

“With the rapid progress of this technology, microneedle patches should be readily available in pharmacies for patients to buy and self-administer within three to five years,” says Gomaa.

Mark Prausnitz, PhD, a professor of biomolecular engineering at the Georgia Institute of Technology, has for the past decade been researching a number of vaccines that use microneedle patches to administer vaccines against influenza, poliomyelitis, hepatitis B, rubella, measles, tetanus and others. Currently, a Phase I clinical trial, sponsored by the National Institute of Biomedical Imaging and Bioengineering, is ongoing for inactivated influenza vaccine microneedle patches to assess safety, reactogenicity, acceptability and immunogenicity compared with hypodermic needles. The trial started in June 2015, and the last patient visit was in March. It has not yet been determined when Phase II of the trial will begin.

The microneedle patches used in the clinical trial are about a centimeter square and consist of arrays of 50 to 100 microscopic needles about as tall as the thickness of a few hairs that can be absorbed into the skin within minutes. When used to administer a vaccination, the patch is pressed onto a person’s forearm to carry the vaccine into the outer layers of the skin, where they prompt an immune reaction from the body.

Another microneedle patch is under development by Vaxxas. Professor Mark Kendall, PhD, group leader, delivery of drugs and genes group with the Australian Institute for Bioengineering and Nanotechnology at the University of Queensland, invented the Nanopatch in 2004. Since then, he has been working on advancing the Nanopatch toward the first human applications, first at the University of Queensland and then through Vaxxas, a company he founded in 2011 in Cambridge, Mass. This has required scaling the technology from use in small animals to larger models, prototyping the human implementation of the device, and ensuring the manufactured product is economically compelling and industrially scalable. The company recently established the cGMP aseptic manufacturing infrastructure and operations that are required for clinical work in support of commercializing the technology. “Based on successful clinical demonstrations, the Nanopatch will be a game changer in the vaccine industry,” said David Hoey, CEO of Vaxxas.

In 2012, Merck & Co., one of the world’s largest vaccine manufacturers, entered into an agreement with Vaxxas to help fund research that will evaluate the Nanopatch technology. According to Kendall, the technology is based on the theory that vaccines can be more effective if they are delivered into the narrow layer just beneath the skin surface that contains a high density of antigen-presenting cells (APCs) required to generate an immune response, rather than into the muscle where such cells present at a much lower density.

The Nanopatch is a new method of controlled and targeted delivery of vaccine. The device is composed of an array of densely packed gold-coated silicon projections coated with vaccine antigen in dry form. Since the vaccine is dry, it offers thermostability and improved immune responses because it is targeted to a rich population of immune cells in the skin, which a needle misses when it delivers vaccines to muscles. When applied to the skin, the Nanopatch projections will penetrate the epidermis and upper dermis, depositing antigen directly to high populations of APCs residing within these skin layers. “The Nanopatch is distinct from existing microneedle devices by having very high packing density of projections tailored by a probability analysis to deposit antigen directly to thousands of epidermal and dermal APCs mapped within the skin, with the smaller diameter far less likely to damage cells near the projections,” says Kendall.

During preclinical testing, the Nanopatch was applied to many different vaccines, including influenza (monovalent and trivalent), HPV, chikungunya, malaria, West Nile virus, HSV 2, pneumococcal, dengue and monovalent type 2 inactivated poliovirus vaccine. It is scheduled for vaccine clinical trials in 2016. “If the benefits seen in the animal model are translated to people, then the Nanopatch opens up more effective, cheaper vaccination to more people,” says Kendall. “This can mean making existing vaccines work better by reducing the cost profiles (through lower doses), addresses needle phobia and eliminates the cold chain management process.”

The benefits of the Nanopatch during a pandemic are three-fold, he adds: “Due to dose sparing, the need for a lower dose means that the vaccine could be rolled out more quickly to more people. As it relates to thermostability, the resource infrastructure for vaccine storage and transportation could be less. And, there is potential for self-administration. Taken together, these three benefits could potentially mean that the Nanopatch could be mailed out to people in a pandemic or even air-dropped into remote areas or a crisis zone.”
**Nasal Mists**

FluMist Quadrivalent, a registered trademark of MedImmune, is licensed to AstraZeneca, a global biopharmaceutical company. AstraZeneca received approval for its FluMist Quadrivalent from FDA in February 2012 and approval from Health Canada in October 2015. The live attenuated influenza vaccine (LAIV) is administered through the nose, where the flu virus typically enters the body. Carlo Mastrangelo, director of corporate communications, says “this method closely mimics natural infection, which contributes to its superior efficacy when compared to the conventional flu vaccine.” The vaccine does not contain any preservatives such as thimerosal (a mercury-based preservative). However, because it contains no preservatives of any kind, it needs to be refrigerated.

In the U.S., FluMist Quadrivalent is used to prevent the flu in people between 2 years and 49 years of age, and in Canada, in people between 2 years and 59 years of age. Compared to a conventional flu vaccine, the National Advisory Committee on Immunization recommends an LAIV vaccine like FluMist for children aged 2 years to 17 years because it has been shown to be 48 percent more effective across all strains. And, when compared with a placebo, the efficacy of two doses of an LAIV administered to children who have never been vaccinated was 83 percent against similar strains.

**Increasing Safety and Reach**

PATH, an international nonprofit health organization whose work in vaccine administration technologies, advanced in collaboration with numerous public and private sector partners, focuses on the development of devices, tools and methods that improve the safety, acceptability and effectiveness of vaccine delivery in developing countries. Darin Zehrung, program advisor for vaccine and pharmaceutical delivery technologies at PATH, says the organization has developed several evolving technologies and is currently working on other evolving technologies for administering vaccinations in low- to middle-income countries (LMICs) on a global scale.

For instance, PATH developed the SoloShot syringe, the first commercialized autodisable syringe. The syringe has a fixed needle that automatically disables after a single injection. After the vaccine has been administered, a barbed metal clip around the neck of the plunger locks into place prohibiting its reuse. SoloShot is used for the delivery of basic childhood vaccines and the introduction of new parenteral vaccines like MenAfriVac.

“PATH also developed the Uniject, the world’s only compact, easy-to-use, prefilled, single-dose syringe with autodisable features,” says Zehrung. The Uniject injection system contains a small plastic reservoir (bubble) prefilled with a single dose of vaccine. The bubble is attached to an injection-ready needle. Healthcare workers only need to depress the plastic reservoir to administer the vaccine, and the autodisable feature prevents its reuse. Uniject is currently used for the routine birth dose delivery of hepatitis B vaccine in Indonesia, and has helped to immunize millions of neonates since its introduction into the country’s immunization program.

In addition, “PATH helped develop the West Intradermal Adapter that fits over needles like a sleeve, standardizing the injection depth and angle so healthcare workers can more easily and precisely administer vaccines intradermally using the Mantoux technique with a hypodermic needle and syringe,” says Zehrung. PATH has also evaluated an autodisable version of the adapter to improve injection safety by preventing reuse.

“There are other evolving technologies, too, such as microarray patches (MAPs) that are placed over hypodermic needles. Although MAPs are still in development, “the technology platform has demonstrated the potential for greater thermostability, which could reduce cold storage and transportation burdens for immunization supply chains in LMICs,” says Zehrung. “Research additionally shows less training may be required for their safe and effective administration, possibly allowing for self-administration. With these attributes, MAPs hold promise for increasing the number of people vaccinated in remote clinics or campaign settings that are common in LMICs, which could help public health programs to address coverage gaps.”

**Solutions Continue to Improve Vaccination Rates**

Vaccine and device manufacturers, as well as academic and research institutions, are continuing their research and development of new and evolving technologies in vaccine administration to address the healthcare industry’s concerns with hypodermic needles and to provide more people globally with vaccinations when and where they are needed. Clearly, the industry is just on the cusp of what promises to be revolutionary developments in the very near future.

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