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Patches Among New Vaccine Delivery Methods

Innovative vaccines in the pipeline offer needleless alternatives that will help alleviate the human pincushion problem as well as facilitate immunization in the developing world.

Transdermal patches, oral administration via food or drink, and new intranasal vaccines are three exciting technologies that I foresee becoming available within the next 2-5 years.

Such alternative vaccine delivery systems are particularly critical in the developing world, where shortages of needles, contamination problems, and lack of trained personnel often make injections risky or impossible.

And of course, injections are uncomfortable no matter where in the world you happen to be.

It's logical to assume that one would target an infection that enters the body through the respiratory tract by an intranasal vaccine, while gastrointestinal pathogens would be more amenable to vaccines delivered orally.

However, that's not necessarily the case. Intranasal vaccine administration could be used for gastrointestinal pathogens, and oral administration for respiratory ones, because the process proceeds in the same fashion once the antigen gains access to the antigen-presenting cells and is taken to the B cells and T cells in the lymph nodes and spleen. And of course, antigens delivered via patch can go anywhere once they are delivered to the regional lymph nodes draining the skin.

Typically, these new technologies are developed with venture capital by small firms and, if successful, get picked up by the larger vaccine manufacturers.

The latest buzz has come from a recent phase II randomized, double-blind, placebo-controlled field trial of a traveler's diarrhea vaccine skin patch that contains heat-labile enterotoxin (LT) from *Escherichia coli*.

Of 201 healthy adults who were planning trips to either Mexico or Guatemala, 67 were randomized to receive the LT patch and 134 assigned placebo. A total of 59 received a second LT patch and completed in-country surveillance, as did 111 who received a second placebo patch. Patches were worn for about 6 hours and then discarded, at 3 weeks and 1 week prior to travel. The average stay in Mexico or Guatemala was 12.4 days (Lancet 2008;371:2019-25).

The results were promising: The proportion of individuals with diarrhea of any cause—as recorded in diary cards—was 15% with the LT patch, compared with 22% with placebo. Severe diarrhea occurred in 2% vs. 11%. The proportions with diarrhea caused by enterotoxigenic *Escherichia coli* (ETEC) were 5% with the LT vaccine patch vs. 10% with placebo, for a protective efficacy of 49%. For severe diarrhea, those proportions were 5% vs. 2%, translating to 62% protective efficacy.

Moreover, those who did develop diarrhea with the LT patch had a milder course of disease, with a mean stool frequency of 3.7 per episode, compared with 10.5 with placebo. Duration of diarrhea was also much less, 0.5 vs. 2.1 days. For ETEC diarrhea, the frequencies were 4.3 vs. 10.5 per episode, and the duration 0.4 vs. 2.2 days.

As it turns out, patches are very attractive delivery systems for vaccines because they introduce the antigens just below the epidermis. This local epidermal delivery appears to produce a more robust immune response than does an intramuscular injection.

On the downside, patches do involve greater potential for local site irritation. In the ETEC patch trial, application of the patch—which involves scraping the skin with a mild abrasive prior to affixing the patch—caused local pruritus in 67% vs. 4% with placebo, rash in 61% vs. 1%, respectively, and pigmentation changes in 7% vs. 0. However, there were no significant differences in systemic events such as fever, malaise, or headache. In my view, the local irritation is minor, compared with the benefits of needleless technology.

Patch technology also is being studied for the prevention of disease caused by a variety of other pathogens, including tetanus and *Helicobacter pylori*.

I'm also excited about the use of transgenic plants such as potatoes and corn as another alternative vaccine delivery method. Thus far in early human trials of diarrheal diseases, transgenic plant-derived vaccines appear to be safe and immunogenic without the need for a buffer or vehicle other than the plant cell.

Among these are transgenic potatoes and corn that express the B subunit of the ETEC toxin, another transgenic potato that expresses the hepatitis B surface antigen, and a third, the capsid protein of norovirus (NV).

In a study of the last, 24 healthy adult volunteers were randomly assigned to one of three regimens: Three doses of transgenic potato expressing NV capsid protein on days 0, 7, and 21, two doses of the transgenic potato on days 0 and 21 plus a dose of wild-type potato on day 7, or three doses of wild-type potato on days 0, 7, and 21. The potatoes were peeled and diced and ingested raw on the day of vaccination.

The volunteers in all three studies completed a diary each day for 7 days after ingesting each dose to record the occurrence of nausea, vomiting, cramps, diarrhea, or other symptoms. Blood was collected before and at 7, 14, 21, 28, and 60 days after the first dose of transgenic plant for measurement of serum antibodies to LT or NV capsid protein. Whole blood was collected for antibody-secreting cell assays on days 0, 7, 14, 21, and 28 (J. Infect. Dis. 2000;182:302-5).

Nineteen of the 20 subjects who ingested transgenic potatoes developed significant increases in the numbers of specific IgA antibody-secreting cells, 4 developed specific serum IgG, and 6 developed specific stool IgA.

Overall, 19 of 20 subjects developed an immune response of some kind, although the level of serum antibody increases was modest.

As for the intranasal route, my lab under National Institutes of Health–funded grants is working on anthrax, botulism, and tularemia in the bioterrorism arena.

Others are investigating intranasal vaccines against respiratory syncytial virus.

I doubt that companies will attempt to transition already-existing injectable vaccines to other modes of delivery, with a few exceptions like those for tetanus and hepatitis B. Rather, I think that much of this work will apply to the prevention of diseases that we currently are unable to prevent, both here and in the developing world.

I have no financial relationships with any of the companies developing these alternative vaccines. ■

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Third-Trimester Maternal Flu Vaccine Also Protects Infant

BY ROBERT FINN
San Francisco Bureau

Honolulu — When women are given influenza vaccine in their third trimester of pregnancy, their infants receive protection against flu infection, results of a randomized controlled trial of more than 300 pregnant women confirm.

"This is the first randomized controlled trial of maternal immunization with influenza vaccine," Dr. Mark C. Steinhoff reported at the annual meeting of the Pediatric Academic Societies. "Although [maternal immunization] is a U.S. government policy, it's one of the few not based on randomized controlled trials."

The study was part of the Maternal Gift Study, which involved 340 pregnant women and 331 live births in a middle-class urban population in Bangladesh. Women in the study were randomized to receive either influenza vaccine or pneumococcal conjugate vaccine during their third trimester of pregnancy. For the purposes of this analysis, the investigators used the mother-infant pairs receiving pneumococcal vaccine as the control group.

The vaccine's protective effect appeared to last until infants were 5 months old, important because flu shots generally are not given until the age of 6 months.

The mothers were an average 25 years old, and were vaccinated an average 55 days before giving birth. Ninety-two percent gave birth in a hospital or clinic, 46% by cesarean delivery. The infants averaged just above 3 kg at birth and were breast-fed exclusively an average of 14 weeks.

The investigators looked both at proven influenza illness and at all febrile respiratory illnesses as outcome measures. The trivalent influenza vaccine was associated with a 63% reduction in proven influenza in infants 0-6 months of age and a 30% reduction in all febrile respiratory illnesses in infants and their mothers.

The fact that the influenza vaccine was compared with the pneumococcal vaccine and not with placebo probably resulted in an underestimate of the influenza vaccine's effectiveness, said Dr. Steinhoff of Johns Hopkins University, Baltimore. "It's possible that pneumococcal vaccine could reduce some of the viral illnesses."

Furthermore, the vaccine's protective effect appeared to last at least until the infants were 5 months old. This is particularly important because current U.S. guidelines do not recommend influenza vaccine for children younger than 6 months old.

And it's those very children who are responsible for almost half of childhood influenza hospitalizations. According to one study, children 0-6 months old accounted for 48% of all the influenza hospitalizations among children below the age of 5 years (N. Engl. J. Med. 2006;355:31-40).

Dr. Steinhoff disclosed that he has served on Sanofi's speakers' bureau and has received research support from Sanofi-Aventis, Wyeth, and Merck & Co. "None of these interactions had any bearing on this particular study." ■

Catch-Up Immunization Software

The Centers for Disease Control and Prevention is offering an online software tool designed to help health care providers and parents determine how to adjust complex childhood immunization schedules to catch up on missed vaccinations in children aged 6 years and younger. To download the Catch-up Immunization Scheduler tool, visit www.cdc.gov/vaccines/scheduler/catchup.htm. ■