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The Johns Hopkins University  
School of Medicine, The Institute  
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## eInfluenza Review



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**July 2007: VOLUME 1, NUMBER 9**

### *Influenza Vaccines*



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### **In this issue...**

Annual influenza vaccination of healthcare personnel, children, and populations at high risk for influenza complications is one of the most effective means of limiting the transmission, morbidity, and mortality of influenza. Compliance with recommended influenza vaccination is limited — among other factors — by dislike of injections, fear of adverse effects, and periodic vaccine shortages. While intranasal administration of live attenuated influenza vaccine avoids the need for an injection, it raises concerns about potential secondary transmission of live vaccine virus from vaccine recipients to immunocompromised individuals. In addition, influenza vaccine shortages and the threat of pandemic influenza necessitate the development of more efficient and reliable vaccine production methods, as well as vaccines that are effective against avian influenza viruses such as H5N1.

In this issue, we examine a study of the duration of viral shedding after live attenuated influenza vaccination in adults; review current evidence regarding the safety and transmissibility of live attenuated influenza vaccine; report on strategies for distribution of a limited vaccine supply; review recent data on an influenza vaccine production technique that does not rely on the use of embryonated eggs; and discuss the safety and immunogenicity of a new vaccine against avian influenza H5N1.

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**At the conclusion of this activity, participants should be able to:**

- Describe recent evidence on the safety, efficacy, and transmissibility of live attenuated influenza vaccine
- Detail the proposed strategies of influenza vaccine allocation to be used during a vaccine shortage in an annual epidemic or pandemic setting
- Discuss the challenges inherent in the development of new production techniques for vaccines against avian influenza viruses

## COMMENTARY

Influenza vaccination is the primary tool to prevent transmission, morbidity, and mortality from the influenza virus. Despite this, vaccination rates among healthcare personnel and high-risk populations remain low due to a variety of factors, including dislike of injections and concern about vaccine side effects.<sup>1</sup> Live attenuated influenza vaccine (LAIV) administered intranasally alleviates the need for injection and may be more easily accepted for that reason; however, concern about secondary transmission of the live attenuated vaccine virus from vaccine recipients to other individuals has limited acceptance of LAIV, especially by healthcare personnel. The article by Talbot and colleagues addresses this concern by measuring the amount and duration of vaccine virus shedding in adults following LAIV administration. Before this (and other) evidence-based data about the duration of viral shedding were available, LAIV was rarely used for vaccination of healthcare personnel; when it was, prolonged furloughs for as long as a month were used to prevent transmission of live vaccine virus to patients. From Talbot et al, we now know that the duration of viral shedding is less than a week, and the amount of virus shed is well below the amount required to infect another individual. Similarly, in their randomized, controlled trial study of LAIV in young children, Vesikari and colleagues demonstrated that transmissibility of the vaccine strain is extremely low even in the daycare setting. These investigators also found that viral shedding after vaccine administration showed stable attenuation and temperature sensitivity that limited the LAIV vaccine strain's ability to cause clinical disease. These data should reassure practitioners that LAIV is a safe alternative to inactivated influenza vaccine, even in the healthcare setting, and that secondary transmission of LAIV strains should not be a concern except in the most severely immunocompromised individuals. However, more data are needed to assess the risk of secondary transmission for this vulnerable population.

The threat of pandemic influenza has been highlighted by direct transmission of highly pathogenic avian influenza viruses such as H5N1 to humans, and influenza vaccine production, distribution, and allocation are critical to effective preparedness planning. The influenza vaccine shortage of 2004-2005 taught us an important lesson about how quickly the cumbersome process of influenza vaccine production can be brought to a halt. Both the article by Cosgrove et al and the position paper from the Society of Healthcare Epidemiology of America were written in response to this vaccine shortage: these documents provide important guidance about how to best deal with the allocation of influenza vaccine in the event of a shortage, and reinforce the importance of influenza vaccination of healthcare workers.

The two articles by Treanor and colleagues address other important topics relevant to preparedness planning for pandemic influenza. The first describes a new influenza vaccine production technique that is more efficient and much less cumbersome than the egg-based method currently employed. New and more efficient vaccine production methods are critical to ensuring that our health care system can respond to an identified influenza strain in a timely manner and avoid vaccine shortages. The second article describes a study of the newly developed and recently licensed human vaccine against avian influenza H5N1.

Taken together, the articles in this review inform us about new options for using, allocating, producing, and developing new vaccines to optimize protection from — and preparedness for — epidemic and pandemic influenza.

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## DURATION OF VIRAL SHEDDING AFTER LIVE ATTENUATED INFLUENZA VACCINATION

Talbot TR, Crocker DD, Peters J, et al. **Duration of virus shedding after trivalent intranasal live attenuated influenza vaccination in adults.** *Infect Control Hosp Epidemiol.* 2005;26:494-500.

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In this study of healthy adults, Talbot and colleagues prospectively examined the duration of viral shedding from the nasal mucosa following intranasal administration of live attenuated influenza vaccine (LAIV). Investigators recruited 20 healthy adult volunteers between the ages of 18 and 49 years and administered trivalent LAIV (FluMist™) intranasally with 0.25 mL in each nostril. The vaccine contained the A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Hong Kong/330/2001 influenza strains. After LAIV vaccination, study participants returned for scheduled clinic visits on days 3, 7, 10, and between days 17-21. Investigators collected nasal wash samples using 15 mL of lactated Ringer's solution prior to vaccination and at each clinic visit. The nasal wash specimens were inoculated into tissue culture and cytopathic effect was used to detect influenza viruses, with indirect immunofluorescent and specific monoclonal antibody assays used to identify the influenza strains recovered. Each subject's immunity was assessed at baseline and between 17 through 21 days after vaccination by performing hemagglutination inhibition antibody titers to each of the 3 vaccine strains, as well as mucosal and serum IgA antibody detection.

All 20 subjects completed the study, although 3 study subjects missed one of the follow-up clinic visits. Prior to vaccination none of nasal washes contained influenza virus. On day 3 after LAIV administration, 10 of 20 (50%) of subjects' nasal washes contained vaccine strain influenza. By day 7 following LAIV, there was a significant decline in viral shedding, with influenza virus detected in only 1 of 18 (5.5%) nasal wash specimens. No influenza virus (0%) was recovered from nasal washes on days 10 or 17 to 21. Quantitative titrations were used to determine the amount of virus shed, with only 1 of the 11 samples found to contain enough virus to register at the lowest level of detection (5 plaque-forming units [PFU]/mL). All 3 vaccine strains were recovered from various study subjects. While the investigators found that subjects with evidence of influenza B-specific mucosal IgA antibody at baseline were significantly less likely to shed the vaccine influenza B strain, no such association was found regarding baseline influenza A immunity.

This study – demonstrating that mucosal shedding of influenza virus following intranasal administration of LAIV occurs at low levels for several days and significantly declines by 7 days – should help to allay concerns about the potential inadvertent transmission of vaccine virus strains from adult LAIV vaccine recipients to unvaccinated individuals. Quantities of viral shedding were well below estimates of the dose required to infect another person, and the investigators did not recover any mucosally shed influenza viruses beyond 7 days. Other studies of viral shedding after LAIV, including the one by Vesikari and colleagues discussed herein, have found similar results; however, somewhat longer periods of viral shedding were observed in children as compared with adults.<sup>1</sup> It should be noted that even though some vaccine strains of influenza are shed at low levels, these strains are attenuated and modified to restrict the virus' ability to replicate above 37°C.<sup>2</sup> Therefore, even if transmission of vaccine strains does occur, the cold-adapted virus is not suited to cause disease because it cannot replicate efficiently in the warm temperatures of the lower airways.<sup>3</sup> The Vaccine Adverse Event Reporting System (VAERS) reported 22 cases of possible secondary transmission among 2,500,000 vaccinees.<sup>4</sup> The majority of possible transmissions occurred in healthcare personnel who administered the vaccines, and there was no documented transmission to immunocompromised individuals. Nonetheless, due to a lack of clinical data and concern about potential transmission, LAIV is not recommended for close contacts or healthcare personnel caring for severely immunocompromised individuals.<sup>3,5</sup> Talbot and colleagues provide data, however, that indicate that 7 days after LAIV administration is sufficient time for avoiding contact even with severely immunocompromised patients, and their study is reassuring for other uses of LAIV without concern of secondary transmission.

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Ref Type: Generic
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## SAFETY AND TRANSMISSIBILITY OF LIVE ATTENUATED INFLUENZA VACCINE

Vesikari T, Karvonen A, Korhonen T, et al. **A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine.** *Pediatr Infect Dis J.* 2006;25:590-595.

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Vesikari and colleagues conducted this prospective, randomized, double-blind, placebo-controlled trial to assess the safety, transmissibility, and stability of live attenuated influenza vaccine (LAIV) in children. The main objective of the study was to estimate the probability of transmission of LAIV vaccine strains from vaccine recipients to unvaccinated individuals (placebo recipients) in a daycare setting. Investigators randomized 197 healthy children between the ages of 9 and 36 months who attended daycare to receive either intranasal placebo or LAIV. They measured viral shedding with nasal swabs for 21 days after vaccination and also assessed the safety and stability of the vaccine strain.

Ninety-eight randomly selected healthy children received the LAIV vaccine. Eighty percent of them shed one or more influenza vaccine strains following vaccination, with almost all viral shedding occurring in the 12 days after LAIV administration. Safety and adverse events were similar between LAIV and placebo groups. Phenotypic assessment of shed LAIV vaccine strains showed that the strains maintained the cold-adaptation and temperature sensitivity that limits their ability to replicate in the lower airways. Genotypic analysis also demonstrated stability of the shed viruses, as all retained their attenuated genotype, with no reversion to wild-type virus seen. One episode of LAIV vaccine strain transmission occurred from a LAIV recipient to a placebo recipient. Investigators therefore calculated the probability of vaccine strain transmission to a child after contact with a vaccinated child as 0.58% (95% confidence interval, 0-1.7%). Further, the transmission event did not result in any adverse outcomes or clinical evidence of influenza.

This study demonstrates several important features of LAIV. As discussed above in the report by Talbot et al, the vaccine strains have 3 characteristics that limit their ability to cause clinical disease: they are genetically altered to attenuate their virulence; they are cold-adapted to grow at low temperatures; and they are heat-sensitive to prevent them from efficiently replicating in the lower airways. Vesikari and colleagues have elegantly demonstrated that the vaccine strains remain genotypically and phenotypically stable after LAIV administration, so that the viruses that are shed retain their intended characteristics rather than reverting to a more virulent state. In addition, this study shows that LAIV was well tolerated among young children 9 to 36 months. Although the children showed both high rates and



long duration of vaccine virus strains shedding, and despite the daycare setting being ideal for transmission of organisms, the investigators found an extremely low rate of secondary transmission of the vaccine strains, with only one documented episode. Importantly, the placebo recipient who later acquired the vaccine strain did not have any signs or symptoms of disease from the transmission event. Like Talbot's findings above, these data are reassuring and indicate that LAIV is a well-tolerated alternative to inactivated, injectable influenza vaccine, and should pose little concern about secondary transmission outside of the severely immunocompromised population.

## STRATEGIES FOR USE OF A LIMITED VACCINE SUPPLY

Cosgrove SE, Fishman NO, Talbot TR, et al. **Strategies for use of a limited influenza vaccine supply.** *JAMA*. 2005;293:229-232.

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Talbot TR, Crocker DD, Peters J, et al. **Duration of virus shedding after trivalent intranasal live attenuated influenza vaccination in adults.** *Infect Control Hosp Epidemiol*. 2005;26:494-500.

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The shortage of inactivated influenza vaccine during the 2004-2005 influenza season challenged healthcare institutions to examine vaccine allocation strategies in order to best protect patients and healthcare personnel. These 2 articles — a commentary by Cosgrove and colleagues published during the shortage, and a Position Paper from the Society for Healthcare Epidemiology of America (SHEA) — present guidance for the allocation of influenza vaccine during times of shortage. Given the arduous nature of influenza vaccine production and the probability of an upcoming influenza pandemic, it is likely that the topic of vaccine allocation in the face of insufficient supply will remain an important one to consider.

The commentary by Cosgrove et al, in addition to discussing appropriate allocation of inactivated influenza vaccine, also examined the potential for an expanded role of LAIV for the vaccination of healthcare personnel. The most obvious goal of such vaccination is to protect healthcare workers so that they can remain healthy and at work to provide patient care and keep the healthcare facility functioning. Another less obvious but extremely important reason to vaccinate healthcare workers (which is often overlooked by healthcare workers themselves) is that vaccinating healthcare personnel reduces patient mortality. A study of influenza vaccination in a long-term care facility found that, while vaccination of patients had no effect on mortality, vaccination of healthcare personnel lowered patient mortality from 17% to 10%.<sup>1</sup> Cosgrove and colleagues clearly place vaccination of healthcare personnel as a high priority for these reasons. Talbot et al also outline the rationale for vaccination of healthcare personnel in the SHEA Position Paper, which proposes a comprehensive program to improve compliance with influenza vaccination. The proposed strategy calls for healthcare workers to sign an "active declination" form if they choose not to have the vaccine, and for vaccine uptake to be used as a patient safety measurement.

Patient benefit from vaccination of healthcare personnel makes allocation decisions even more complex in times of vaccine shortage. While the Centers for Disease Control and Prevention provides guidance for defining groups of individuals who are at high risk of complications from influenza and who should therefore be vaccinated, in times of vaccine shortage, it becomes more difficult to reach consensus on what constitutes a "chronic medical condition" that places a patient at higher risk. One vaccine allocation strategy espoused by Cosgrove et al is to avoid influenza vaccination in times of shortage for people who are unlikely to have an adequate immunologic response to the vaccine. These groups



include patients who received a hematopoietic stem cell transplant within less than 6 months, a solid organ transplant within less than 3 months, and patients with HIV and CD4 counts <100/microliter. Cosgrove suggests that other prevention and prophylaxis methods may be more effective for these patients, while simultaneously conserving a scarce vaccine supply. Other strategies involve the use of syringes with minimal dead space to yield up to 2 additional doses per 5 mL vial, and as yet unproven but promising strategies such as administration of partial doses of vaccine to stretch limited supplies.<sup>2,3</sup> In addition, the SHEA document reminds us of the importance of utilizing other infection control and prevention strategies, including proper respiratory etiquette, restriction of febrile healthcare workers from patient care activities, droplet precautions, rapid diagnostic tests, prompt treatment of influenza cases, and the appropriate use of antiviral chemoprophylaxis. This type of comprehensive program, in conjunction with strategies to extend and appropriately allocate vaccine in times of shortage, is likely to remain at the forefront of planning for future shortages and the threat of pandemic influenza.

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## NEW INFLUENZA VACCINE PRODUCTION STRATEGIES

Treanor JJ, Schiff GM, Hayden FG, et al. **Safety and immunogenicity of a baculovirus-expressed hemagglutinin influenza vaccine: a randomized controlled trial.** *JAMA.* 2007;297:1577-1582.

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The production process for traditional inactivated influenza vaccine is cumbersome, lengthy, and relies on massive numbers of embryonated eggs as substrate. Thus, the development of more rapid and efficient methods of vaccine production is a high priority. This article by Treanor and colleagues reports on the results of a randomized controlled trial designed to determine the safety and efficacy of an experimental influenza virus hemagglutinin vaccine (rHA0) produced using recombinant baculoviruses in insect cells. The trial randomized 460 healthy adult patients at 3 medical centers to receive a single injection of saline placebo (n=154), or 75 micrograms (n=153) or 135 micrograms (n=153) of rHA0 vaccine containing influenza A/New Caledonia/20/99 (H1N1), influenza A/Wyoming/3/03 (H3N2), and influenza B/Jiangsu/10/03 virus. Serum samples were examined both prior to and 30 days after immunization to assess immunogenicity. The primary efficacy endpoint was culture-proven influenza illness. Adverse events and safety were also assessed.

The investigators report that no differences were found in safety or adverse outcomes between the 2 vaccine groups and the placebo arm, with low rates overall. Serum studies revealed that hemagglutinin inhibition antibody response to H1 occurred in 3% of the placebo patients, 51% of the low-dose rHA0 vaccine recipients, and 67% of the high-dose rHA0 recipients. Antibody responses to H3 were 77% of high-dose recipients vs 11% of placebo recipients; responses to influenza B were even better, with 92% of high-dose recipients compared to 4% of placebo recipients. Seven cases (4.6%) of culture-confirmed influenza occurred in the placebo arm, as compared to 2 cases (1.3%) in the low-dose arm, and 0 cases in the high-dose arm.

By both immunogenicity and efficacy outcomes, this trial showed the experimental rHA0 vaccine to be safe, immunogenic, and effective in conferring some degree of protection against a drifted H3Ns virus during the 2004-2005 influenza season. These results are encouraging, since the newly developed

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production method avoids many of the pitfalls of the traditional embryonated egg process — particularly the problem of amassing so many eggs, which cannot be accomplished rapidly in response to an emerging threat. The threat of avian influenza further complicates the picture, with the potential prospect of pandemic human disease coupled with avian disease that reduces the supply of hens' eggs needed to produce influenza vaccine. The recombinant DNA techniques utilized in this trial seem well suited to influenza vaccine production — they do not utilize eggs and are already used to produce other vaccines (eg, hepatitis B virus). Although the numbers were too small to conclusively demonstrate efficacy of the vaccine, preliminary results showing protective efficacy in a healthy adult population are very promising.

## HUMAN VACCINE AGAINST THE AVIAN INFLUENZA VIRUS H5N1

Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. **Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine.** *N Engl J Med.* 2006;354:1343-1351.

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In this article, Treanor and colleagues describe a multi-center, double-blind study of the safety and immunogenicity of an inactivated subvirion influenza A H5N1 vaccine. Four hundred fifty-one healthy adults from 18 to 64 years of age were randomly assigned to receive 2 doses of intramuscular injection (28 days apart) of placebo, or 1 of 4 different doses of H5N1 vaccine containing H5 hemagglutinin antigen. Serum samples were obtained prior to vaccination and at 28 days after the second injection, and were tested for the presence of H5 antibody to demonstrate immunogenicity. Study subjects were followed clinically for 56 days to assess safety of the vaccine.

The vaccine was developed from a human isolate of influenza A/Vietnam/1203/2004. Fifty-four percent of study subjects who received 2 doses of 90 micrograms of vaccine, the highest vaccine dose in this trial, achieved H5 neutralization antibody titers of greater than 1:40, the level generally associated with protection against influenza. This level of antibody was seen in 43%, 22%, and 9% of the subjects receiving the lower doses of vaccine. None of the placebo recipients developed H5 antibodies. The most common adverse events were mild pain at the injection site, headache, and muscle pain, and were apparently dose-dependent. There were no differences in systemic complaints between vaccine groups and placebo recipients.

The H5N1 subtype of avian influenza continues to cause widespread infections in domestic and wild birds, particularly in Asia, Africa, and Europe, and has demonstrated the ability to be transmitted directly from birds to humans, with an extremely high (54%) human mortality rate. While human-to-human transmission has apparently been quite rare, the threat of pandemic H5N1 avian influenza in a human population naïve to this viral sub-type urgently necessitates the development of vaccine against this virus. Contrary to the novel influenza vaccine production technique outlined in the article above, in this study Treanor and colleagues elected to use the traditional method employed to produce annual inactivated influenza vaccine in embryonated eggs. The investigators chose this method with the intention of expediting the acceptance and licensure of the vaccine, since this production method would be viewed by regulatory agencies as a change in strain rather than the development of a brand new product. Indeed, the United States Food and Drug Administration (FDA) recently approved this vaccine as the first US vaccine for humans against the avian influenza virus H5N1.<sup>1</sup> The 2-dose administration schedule was chosen because the investigators recognized that higher doses would likely be required to generate immunity to a completely novel strain such as H5. The vaccine has been purchased by the US government for the National Stockpile in order to enhance preparedness for pandemic avian influenza. Further research is now focusing on adjuvants, priming, and other dose-sparing strategies to make vaccination against H5N1 more feasible should pandemic H5N1 influenza occur.

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Available at: [www.fda.gov/bbs/topics/NEWS/2007/NEW01611.html](http://www.fda.gov/bbs/topics/NEWS/2007/NEW01611.html)

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