

## CORRESPONDENCE



## An Inactivated Subvirion Influenza A (H5N1) Vaccine

**TO THE EDITOR:** Treanor et al. (March 30 issue)<sup>1</sup> conducted a well-designed study of a poor vaccine produced by methods that are used in the labor-intensive manufacture of conventional inactivated influenza vaccine. This subvirion influenza A (H5N1) vaccine induces a hemagglutinin-dominant immunity that is susceptible to failure resulting from antigenic changes.<sup>2-4</sup> It is not possible to predict how closely related the H5 subtype of hemagglutinin is to influenza A/Vietnam/1203/2004 and how protective the immunity will be against an emerging pandemic strain. Two 90- $\mu$ g doses of the vaccine (which is 12 times as great as the dose used in the conventional influenza vaccine<sup>4</sup>) induced significant immune responses in 54 to 58 percent of subjects. However, the purchase and stockpiling of this vaccine are wasteful of scarce health care dollars. Money would best be directed at research on the use of adjuvants, alternative techniques for producing

recombinant H5 hemagglutinin, and the addition of other influenza proteins (e.g., neuraminidase, eM2, and conserved T-cell epitopes) to broaden the immune response against influenza. Updating production capabilities with a shift in vaccination methods could allow for flexibility in the choice of antigen and decreased production time.

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1. 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;354:1343-51.

2. Johansson BE, Kilbourne ED. Influenza vaccine strain selection: equivalence of two antigenically distinct haemagglutinin variants of 1989 H3N2 influenza A virus in protection of mice. *Vaccine* 1992;10:603-6.

3. Kilbourne ED, Smith C, Brett I, Pokorny BA, Johansson B, Cox N. The total influenza vaccine failure of 1947 revisited: major intrasubtypic antigenic change can explain failure of vaccine in a post-World War II epidemic. *Proc Natl Acad Sci U S A* 2002;99:10748-52.

4. Couch RB, Kasel JA, Gerin JL, Schulman JL, Kilbourne ED. Induction of partial immunity to influenza by a neuraminidase-specific vaccine. *J Infect Dis* 1974;129:411-20.

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**TO THE EDITOR:** Regulatory factors encourage trials that use conventional approaches, such as intramuscular injection of egg-derived hemagglutinin without adjuvants, as reported by Treanor et al., but the threat of an influenza pandemic should expedite the acceptance of new strategies. As of January 24, 2006, 28 vaccines against avian or pandemic influenza were registered at the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), of which 19 vaccines were against the H5N1 subtype.<sup>1</sup> Of those vaccines, none have been investigated with the

use of intradermal delivery, which has already proved to be effective at reducing to just 3  $\mu\text{g}$  per dose the amounts of hemagglutinin required for the induction of theoretically protective antibody titers against the H3N2 and H1N1 subtypes among subjects between the ages of 18 and 60 years.<sup>2,3</sup> Furthermore, none of the vaccine trials listed by the IFPMA use less than 1.7  $\mu\text{g}$  of hemagglutinin.<sup>1</sup> Even if those trials succeed, there will be the scaling-up hurdles pointed out by Poland in his accompanying editorial.<sup>4</sup> If the hemagglutinin dose remains a limiting factor, vaccines that are produced by reverse genetics and culture of mammalian cells should be thoroughly investigated, including those delivered epidurally.<sup>5</sup>

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1. R&D for avian/pandemic influenza vaccines by IFPMA Influenza Vaccine Supply International Task Force (IVS ITF) members (updated 24 January 2006). (Accessed June 1, 2006, at [http://www.ifpma.org/pdf/avian\\_pandemic\\_influenza\\_vaccine\\_24\\_01\\_06.pdf](http://www.ifpma.org/pdf/avian_pandemic_influenza_vaccine_24_01_06.pdf).)
2. Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. *N Engl J Med* 2004;351:2286-94.
3. Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. *N Engl J Med* 2004;351:2295-301.
4. Poland GA. Vaccines against avian influenza — a race against time. *N Engl J Med* 2006;354:1411-3.

5. Drape RJ, Macklin MD, Barr LJ, Jones S, Haynes JR, Dean HJ. Epidermal DNA vaccine for influenza is immunogenic in humans. Vaccine (in press).

**THE EDITORIALIST REPLIES:** I agree with Focosi that in view of a pandemic influenza threat, we must develop new techniques and strategies for the rapid production of new candidates for pandemic vaccines. However, we need to be cautious about the application of results of studies of various delivery methods (such as intradermal injection) and doses of seasonal vaccines to new influenza antigens. This caveat reinforces the need for careful, parallel tracks of ongoing clinical research studies regarding dose, delivery, and concomitant adjuvant agents for new influenza-vaccine candidates. As I pointed out in my editorial, a variety of candidates — including vaccines administered with adjuvant, peptide-based vaccines, and vaccines developed with adenovirus vectors — deserve consideration in order to meet the terrible threat of pandemic influenza. Furthermore, the testing and clinical trials of viable candidates should occur in parallel, rather than in serial studies, in order to expedite the compilation of results.

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## Gatifloxacin and Dysglycemia in Older Adults

**TO THE EDITOR:** Park-Wyllie and colleagues (March 30 issue)<sup>1</sup> advise avoiding the use of gatifloxacin because of the increased risk of dysglycemia, and they suggest using alternative antibiotics, including other fluoroquinolones, that confer little or no increased risk of dysglycemia. This suggestion must be questioned. Although it appears that the administration of moxifloxacin has no clinically relevant effect on blood glucose homeostasis,<sup>2</sup> other fluoroquinolones may trigger dysglycemic events, especially in patients with diabetes who receive sulfonylureas.<sup>3</sup> Clinicians should be aware of the possibility of dysglycemic events in patients receiving fluoroquinolones.

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1. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006;354:1352-61.
2. Gavin JR III, Kubin R, Choudhri S, et al. Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. *Drug Saf* 2004;27:671-86.
3. Mohr JF, McKinnon PS, Peymann PJ, Kenton I, Septimus E, Okhuysen PC. A retrospective, comparative evaluation of dysglycemias in hospitalized patients receiving gatifloxacin, levofloxacin, ciprofloxacin, or ceftriaxone. *Pharmacotherapy* 2005;25:1303-9.

**TO THE EDITOR:** The article by Park-Wyllie et al. has an important implication for countries such as India, where gatifloxacin is widely used for the treatment of multidrug-resistant tuberculosis. Substantial data demonstrate the efficacy of gatifloxacin among patients with tuberculosis.<sup>1-3</sup> In the study by Park-Wyllie et al., 30 of 366 case patients died from dysglycemia. We wonder whether pa-