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Concomitant administration of seasonal trivalent and pandemic monovalent H1N1 live attenuated influenza vaccines

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To the editor:
In the United States, live attenuated influenza vaccine (LAIV) will play a prominent role in the novel A(H1N1) pandemic vaccination campaign; more than 40 million doses have been purchased by the US Government. Additionally, approximately 10 million doses of seasonal trivalent LAIV will be available for use during the 2009–2010 influenza season. Seasonal trivalent LAIV is currently approved for use in eligible individuals aged 2–49 years in the United States, South Korea and Hong Kong.

Because some US populations have been recommended to receive both seasonal trivalent and pandemic monovalent vaccine during the 2009–2010 influenza season, questions have arisen regarding concomitant vaccination with seasonal trivalent and pandemic monovalent LAIV. Historically, recommendations of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) have stated, 'In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent. Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Inactivated or live vaccines can be administered simultaneously with LAIV. However, after administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered'.[1] Specific guidance was published in 2009 related to vaccination with pandemic monovalent vaccines, which stated, 'Simultaneous administration of inactivated vaccines against seasonal and novel influenza A (H1N1) viruses is permissible if different anatomic sites are used. However, simultaneous administration of LAIV against seasonal and novel influenza A (H1N1) virus is not recommended'.[2] It was subsequently noted that the recommendation against simultaneous intranasal administration of seasonal and pandemic LAIV was because of theoretical concerns for potential interference between the vaccines.[3] Here, we report the results of a study designed to examine the potential for interference following concomitant administration of seasonal and pandemic LAIV in ferrets, a widely accepted and relevant animal model often used to examine influenza virus and influenza vaccine immunogenicity, including annual World Health Organization and US Food and Drug Administration evaluation of candidate vaccine strains.[4–8]

Twenty 8-week-old male ferrets (Triple F Farms, Sayre, PA, USA) seronegative for all four influenza strains were used in the study. One cohort ($n = 4$) was inoculated intranasally with a 0·2-ml dose (0·1 ml per nostril) of seasonal trivalent LAIV containing $10^{6·5–7·5}$ fluorescent focus units (FFU) of each of the three cold-adapted, temperature-sensitive vaccine strains recommended for inclusion in the 2009–2010 vaccine: A/South Dakota/6/2007 (H1N1) (A/Brisbane/59/2007-like), A/Uruguay/716/2007 (H3N2) (A/Brisbane/10/2007-like) and B/Brisbane/60/2008. A second cohort ($n = 4$) was inoculated intranasally with $10^{6·5–7·5}$ FFU per dose of the cold-adapted, temperature-sensitive 2009 H1N1 monovalent vaccine, A/California/07/2009 (H1N1). A third group ($n = 12$) was inoculated intranasally with pandemic monovalent LAIV followed by seasonal trivalent LAIV approximately 15 seconds later. This third cohort included more animals to allow for further division into three subgroups to investigate second-dose responses if interference was observed. Sera were collected weekly, and the immunogenicity and kinetics of the immune response were determined by strain-specific serum hemagglutination inhibition (HAI) on days 0 (pre-dose), 14 and 28 post-inoculation using standard methods with 0·5% chicken erythrocytes. Cold-adapted virus antigen was used for A/California/07/2009; wild-type antigen was used for seasonal strains.

Serum antibody responses to the four vaccine strains are depicted in Figure 1. All strains were immunogenic and strain-specific responses were statistically similar in the cohorts receiving seasonal vaccine, pandemic vaccine and both vaccines concomitantly. No interference with concomitant vaccination was observed at either 14 or 28 days post-vaccination. LAIV viruses replicate primarily in the ciliated epithelial cells of the nasopharyngeal mucosa to induce immune responses via mucosal immunoglobulin A (IgA), serum IgG and cellular immunity. Serum antibody responses are not a correlate of protection; in fact, some studies have shown protection in the absence of significant antibody responses.[9–11] However, consistent with their use in the present study, HAI responses have been used to establish comparability of different LAIV formulations and evaluate concomitant vaccination regimens.[12–14]

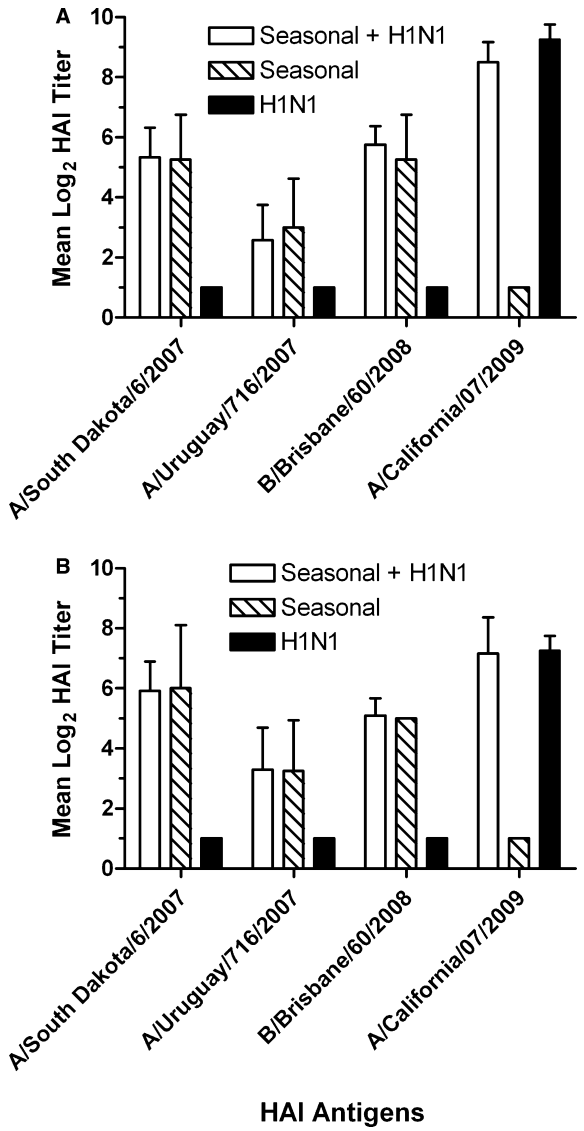

Figure 1. Mean (log_2) hemagglutination inhibition (HAI) titer for each vaccine strain 14 (A) and 28 days (B) after one dose of seasonal trivalent or pandemic monovalent H1N1 influenza vaccine or one dose of each vaccine administered concurrently. The limit of detection was 1·0 HAI unit.

These data in ferrets indicate the development of a robust and consistent immune response at 14 and 28 days post-inoculation with seasonal trivalent and pandemic monovalent H1N1 vaccines. There was no evidence of interference in the cohort receiving concomitant seasonal and pandemic vaccination. These data may help inform vaccination recommendations for the 2009–2010 influenza season in the United States. It should be noted that no data regarding concomitant vaccination exist for humans at this time.

Author's contributions

All authors contributed to the experimental design of the study described here and the writing and revising of the text.

Conflict of interest statement

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References

1 Fiore AE, Shay DK, Broder K *et al.* Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009; 58(RR-8):1–52.
2 National Center for Immunization and Respiratory Diseases. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009; 58(RR-10):1–8.
3 Atkinson WL, Kroger AT. Ask the experts: general vaccine questions. Needle Tips 2009; 19:1, 19–22.
4 Barber WH, Small PA Jr. Local and systemic immunity to influenza infections in ferrets. Infect Immun 1978; 21:221–228.
5 Fenton RJ, Clark A, Potter CW. Immunity to influenza in ferrets. XIV: comparative immunity following infection or immunization with live or inactivated vaccine. Br J Exp Pathol 1981; 62:297–307.
6 Potter CW, Oxford JS, Shore SL, McLaren C, Stuart-Harris C. Immunity to influenza in ferrets. I. Response to live and killed virus. Br J Exp Pathol 1972; 53:153–167.
7 Smith H, Sweet C. Lessons for human influenza from pathogenicity studies with ferrets. Rev Infect Dis 1988; 10:56–75.
8 van der Laan JW, Herberts C, Lambkin-Williams R, Boyers A, Mann AJ, Oxford J. Animal models in influenza vaccine testing. Expert Rev Vaccines 2008; 7:783–793.

9 Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis 1994; 169:68–76.

10 Treanor JJ, Kotloff K, Betts RF *et al.* Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. Vaccine 1999; 18:899–906.

11 Tam JS, Capeding MR, Lum LC *et al.* Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr Infect Dis J 2007; 26:619–628.

12 Block SL, Reisinger KS, Hultquist M, Walker RE. Comparative immunogenicities of frozen and refrigerated formulations of live attenuated influenza vaccine in healthy subjects. Antimicrob Agents Chemother 2007; 51:4001–4008.

13 Breiman RF, Brooks WA, Goswami D *et al.* A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. Vaccine 2009; 27:5472–5479.

14 Nolan T, Bernstein DI, Block S *et al.* Safety and immunogenicity of concurrent live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines in infants 12 to 15 months of age. Pediatrics 2008; 121:508–516.