

## EDITORIAL

# Avian Influenza: Exploring All the Avenues

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As the clock continues to tick, health officials worldwide are scrambling to find viable means to head off the next pandemic. To date (9 August 2006), 236 recognized cases of avian (H5N1) influenza virus infections have occurred in humans, resulting in 138 deaths. New human cases are now being detected in Thailand after initial hope that the disease had been controlled there. The vast majority of these cases have been the result of transmission directly to humans from infected birds, although person-to-person transmission has occurred in a few instances. The potential for these avian viruses to completely bridge the species barrier and acquire the ability to spread between humans is unclear; recent experiments suggest that adaptation to mammals may be complex (1). However, if at some point this virus, or some other influenza virus with a novel hemagglutinin or neuraminidase, does emerge as a human-to-human pathogen, the world will confront an extremely severe public health threat.

Our options for combating an H5N1 pandemic are limited. Vaccines will represent the ultimate method of control but, given the limits of current vaccine production technology, may not be available in time to prevent the first wave of pandemic cases. In addition, for reasons that are not clear, effective immunization using conventional inactivated vaccines will require relatively high doses, which will reduce vaccine availability during a pandemic (2, 3). Antiviral agents have some promise. Most of the attention has focused on the neuraminidase inhibitor oseltamivir, because early isolates of H5N1 viruses were resistant to the adamantanes (4). Effective use of oseltamivir in a pandemic will present significant supply and logistical hurdles, and we do not understand fully the appropriate dose and duration of therapy (5) or the influenza virus's potential to develop resistance. Clearly, we urgently need additional, alternative approaches.

This issue contains news of an alternative approach from an unlikely source: research reports published shortly after the 1918 pandemic. In a thorough review and analysis of the historical literature, Luke and colleagues (6) document the effects of passive immunotherapy. They found 8 studies that evaluated the effects of therapy with serum or plasma from convalescent patients on the course of clinically diagnosed influenza pneumonia during the 1918 Spanish influenza pandemic. Although the quality of these studies was relatively poor by modern standards, they all reached similar conclusions. In 6 of these studies, treatment was compared with a control group that received standard care, and in each of these reports, the mortality rate was lower in treated patients, although the decrease was statistically significant in only 3 reports. Two of the studies also compared the outcomes in those who received early treatment and those who received late treatment. An additional 2 reports compared early and late therapy but did not have an untreated control group. These studies demonstrated that only those who received early intervention experienced a beneficial effect of serum therapy, which is consistent with reports of serotherapy for other human infectious diseases. Luke and colleagues discarded multiple other reports that did not meet the methodologic criteria for inclusion in their meta-analysis. These weaker studies also supported the hypothesis that passive serotherapy was useful in treating Spanish influenza.

Would a similar approach be effective and feasible in the event of a pandemic of H5N1 influenza? Passive immunotherapy to treat infection with influenza viruses, including H5N1, has been effective in a mouse model. Other viral diseases offer ample precedent: Passive antibody prevents many human viral diseases, including varicella, rabies, hepatitis A and B, and respiratory syncytial virus (RSV). However, the distinction between prevention of disease and treatment of active disease is important. Few recent data support the use of passive antibody therapeutically after disease manifestations have already begun. For example, although passive antibody is highly effective at prevention of RSV infection in high-risk infants, systemic administration of antibody with high levels of RSV neutralizing activity is not useful therapeutically in infants with RSV disease (7).

Nevertheless, the concept is important and it should be explored further, especially given our lack of proven interventions to prevent or treat illness due to H5N1 influenza. The use of serum from recovered patients as the source of antibody for passive

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immunotherapy has the advantage of being technically simple, and ample numbers of convalescing patients should be available for plasmapheresis. The resulting antibody would be polyclonal, which would decrease the chance of an escape mutant developing in treated patients. The serum also might have antibody to other bacterial pathogens, which might decrease the severity of coexisting bacterial superinfections (a mechanism that may account for some of the efficacy of serotherapy in 1918). Balanced against these optimistic considerations are several major concerns. Formidable logistical hurdles would complicate the ability to obtain, characterize, and prepare these materials for use in the midst of an outbreak. As yet, we don't know if patients who recover from H5N1 influenza develop particularly high levels of antibody (8). Other types of antibody preparations might be more effective, such as pools of serum with high titers of antibody generated from individuals who had received vaccines. With the recent advances in antibody technology, rapid production of humanized monoclonal antibodies with neutralizing activity is possible (9). We lack sufficient understanding of the immune response to H5N1 infection in humans, as well as the potentially protective humoral and cellular responses associated with recovery from disease. We don't know the level of antibody that needs to be achieved to confer protection or the appropriate dose of serum needed to achieve useful antibody levels in recipients. The evidence supporting serotherapy in humans appears to be limited to the experience in 1918.

We can, should, and must explore these issues about serotherapy now, in advance of the pandemic. We could evaluate the effectiveness of transfusing high-titered plasma for the treatment of immunocompromised patients with severe influenza, a situation in which prolonged shedding of influenza viruses often occurs and development of resistance to antiviral agents is common (10). Ultimately proving the concept of serotherapy for treatment of severe H5N1 in advance of a pandemic would require the development of infrastructure and protocols for controlled trials of therapy in regions of the world where such infections are currently occurring. We urgently need more coordination of clinical research among institutions in countries currently experiencing cases (11). Although many logistical hurdles exist, controlled clinical studies done now will probably pay a considerable dividend when the pandemic begins.

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