



Influenza 2005–2006: Vaccine supplies adequate, but bird flu looms

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■ ABSTRACT

Influenza vaccine supplies appear to be adequate for the 2005–2006 season, though delivery has been somewhat delayed. However, in the event of a pandemic of avian flu—considered inevitable by most experts, although no one knows when it will happen—the United States would be woefully unprepared.

THE MAJOR ISSUE surrounding influenza over the last 5 years has often not been the virus, but problems with the US vaccine supply. Supplies of influenza vaccine have fallen short in three of the last five influenza seasons in the United States.¹

So far, a shortage is not expected for the 2005–2006 season, but there have still been bumps in the road, with a delay in vaccine production leading the US Centers for Disease Control and Prevention (CDC) to ask physicians to only vaccinate people in the highest priority group until October 24, 2005.

But behind all the preparation for the current influenza season are fears that the simmering outbreak of avian influenza in animals could lead to a pandemic.

This article will provide a brief update of the issues in the current influenza season, the monitoring of avian influenza in animals and humans, and a refresher on the diagnosis and treatment of influenza.

■ THE CURRENT INFLUENZA SEASON

The vaccine for this season is designed to protect people from the A/New Caledonia/20/99-like (H1N1), A/California/7/2004-like (H3N2), and B/Shanghai/361/2002-like viruses.

It is impossible to predict whether this year's epidemic will be severe; however, it appears that vaccine will be available in sufficient quantities. Sanofi-Pasteur will produce 60 million doses, and GlaxoSmithKline has entered the US market with plans to produce 8 million doses.

Chiron was unable to distribute vaccine last influenza season due to problems with its manufacturing process, leading to a major disruption of the US vaccine supply. The manufacturing problems have been resolved, and Chiron is expected to distribute between 18 to 26 million doses this season.

MedImmune Vaccine will produce 3 million doses of FluMist, the live-attenuated flu vaccine that is delivered by intranasal spray.

Because of delays in shipping vaccine, the CDC has asked physicians to limit vaccination to those at high risk until October 24 of this year. But by the time this journal reaches you, the vaccine should be available for all patients. Still, physicians should be especially aggressive in ensuring vaccination of the following high-risk patients:

- People age 65 years and older
- Residents of long-term care facilities
- People age 2 to 64 years with comorbid conditions
- Children age 6 to 23 months
- Pregnant women
- Health-care personnel who provide direct patient care

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- Household contacts and out-of-home caregivers of children younger than 6 months.

■ THE LOOMING THREAT OF AVIAN FLU

Most experts predict that pandemic influenza is inevitable.² If an avian influenza virus and a human influenza virus exchange genetic information in another host, usually swine, this newly assorted virus could cause disease in humans.³

During 2004, a highly pathogenic avian influenza A (H5N1) virus killed millions of ducks and chickens in eight Asian countries. As of August 5, 2005, 112 cases of H5N1 influenza have been reported in humans, of whom 57 died.⁴ Probable person-to-person transmission was found in at least one case in Thailand.⁵

Why are some strains of flu more virulent? Kobasa et al⁶ performed “genetic archeology” of the strain from the 1918–1919 Spanish influenza pandemic, using tissue samples from corpses buried in cemeteries in Alaska (where the ground remains frozen year-round). They determined that the hemagglutinin of that strain was a key determinant of virulence.

The mortality rate of the 1918–1919 pandemic was 2.5%, resulting in 0.5 million deaths in United States alone, many due to hemorrhagic pneumonia. If a similar pandemic were to occur today, many more would die. The numbers would be staggering if the mortality rate were 50%, as in the recent H5N1 outbreak.

■ ARE WE PREPARED FOR A PANDEMIC?

In 2005, the World Health Organization revised its global influenza preparedness plan (www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf). The United States, however, remains unprepared, according to a statement by Andrew Pavia, MD, of the Infectious Disease Society of America to the US House of Representatives on May 26, 2005.

In the event of a pandemic, about 600 million doses of vaccine would be needed, as well as enough antiviral medication to com-

plete 84 million courses of therapy. The current stockpile of oseltamivir, which is active against H5N1, would cover only 2.3 million courses of therapy. (A mouse model has shown that larger doses of oseltamivir and longer duration of a therapy are needed for treatment of highly pathogenic avian influenza.⁷) The estimated cost of vaccine and antiviral drugs needed is \$1 billion.

Several solutions have been proposed, one of which has been to require health care providers to be vaccinated as a patient safety initiative. In 2005, an avian influenza vaccine clinical trial began in the United States, with promising preliminary results.⁸ However, according to Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, “The critical issue now is, can we make enough vaccine, given the well-known inability of the vaccine industry to make enough vaccine?”

■ A REFRESHER ON INFLUENZA

Contagious, potentially serious

Influenza and other viruses causing acute upper respiratory tract infections are very contagious.⁹ Most cases are transmitted by direct contact, large droplet aerosols, and droplet nuclei. Of these viruses, the influenza virus is probably the most contagious, appearing in casual social settings, at school and places of work, and most importantly, at home. Let us not forget simple measures such as covering our cough and washing our hands in preventing the transmission of such common infections.

In people older than 65 years with high-risk conditions, the hospitalization rate due to cardiopulmonary conditions attributable to winter viruses is 10.6 per 1,000 people per year.¹⁰ During the 2003–2004 influenza season, 16% of patients diagnosed with influenza were hospitalized and 0.5% died.¹¹

Complications of influenza include pulmonary complications such as pneumonia and exacerbations of chronic obstructive pulmonary disease as well as nonpulmonary complications such as myositis.

Viral upper respiratory infections not related to influenza also impose a burden—\$39.5 billion annually, of which \$17 billion is

Flu mortality:

- **Most years**
0.5%
- **1918 – 1919**
2.5%
- **Avian flu**
50% ?

in direct costs and \$22.5 billion is in indirect costs. This exceeds the costs attributable to congestive heart failure or chronic obstructive lung disease.¹²

Of note, influenza can be acquired in periods other than the expected annual geographic epidemics in people traveling to tropical and subtropical countries. In fact, a recent survey in Switzerland showed that influenza was the most frequent vaccine-preventable infection in such travelers.¹³

Diagnosis: Symptoms alone do not confirm influenza

The sudden onset of fever, headache, and cough during influenza epidemics is highly suggestive of influenza. However, several other viruses, particularly respiratory syncytial virus and rhinovirus, cause acute respiratory illness during the influenza season.¹⁴ Call et al,¹⁵ in a recent review, concluded that clinical findings are not useful for confirming or excluding influenza. In people older than 60 years, the presence of sneezing reduces the likelihood that the patient has influenza.

During an epidemic, clinicians are advised to either treat patients who have an influenza-like illness empirically or obtain rapid diagnostic tests (which require nasopharyngeal swabs). Molecular diagnostic tests are clearly more sensitive than viral culture in identifying influenza and other respiratory viruses.¹⁴

Diagnostic tests are indicated for all individuals hospitalized during the epidemic period with an influenza-like illness. Such tests can also help in decision-making for patients in whom a bacterial respiratory illness is not highly suspected.

Rapid influenza testing can be done at the point of care and can provide a result in less than 30 minutes. A number of these tests are available; some are approved for use in the office, and others must be performed in the laboratory.

These tests vary—some can detect only influenza A, others can detect both A and B viruses but not distinguish between them, and yet others can distinguish between A and B (TABLE 1).¹⁶ These tests cannot identify viral subtypes.

Because rapid tests are not very sensitive,

the CDC recommends confirming negative tests during a community outbreak, in order to detect false-negatives.

Direct fluorescent antigen detection can be used to identify influenza A and B, respiratory syncytial virus, adenovirus, and parainfluenza virus 1, 2, and 3. Of note, 50% of those receiving the intranasal influenza vaccine FluMist may have detectable influenza antigen for up to 1 week after vaccination.¹⁷

PCR. A combined test for influenza and respiratory syncytial virus by reverse-transcriptase polymerase chain reaction is now available. It provides accurate and timely diagnosis for these viruses. It is more sensitive than the rapid diagnostic tests, but is more expensive and more complex to perform.

Culture and influenza A and B antibody testing are available but are not helpful in acute management. They should be used mainly for epidemiologic purposes.

Vaccination rates have hit a plateau

In the early 1970s, the rate of influenza vaccination was in the range of 20% to 30%; by the late 1990s it had increased to 60% to 70%. This rate has somewhat leveled over the last 5 years, however. Rates are highest in people 65 years and older, and much lower in those 18 to 49 years old (www.cdc.gov/nchs/data/nhis/earlyrelease/200409_04.pdf). In fact, the influenza vaccination rate has decreased by 50% from 2003–2004 to 2004–2005 among persons aged 50–64 years enrolled in commercial managed healthcare plans.¹⁸

Although health care workers should be vaccinated, their rates are low: the US national average is just 40%.¹⁹ Vaccination protects the health care worker as well as patients from nosocomial spread of influenza.

In spite of vaccination, hospitalizations for influenza and pneumonia have actually slightly increased over the last 2 decades.²⁰ Simonsen et al,²¹ in a widely publicized recent paper, suggested that observational studies might have overestimated the benefit of vaccination. However, one explanation for the findings of this study was that very elderly people with fragile health that makes them more likely to die are actually less likely to be vaccinated. Hundreds of other studies have demonstrated the cost-saving benefit in all

**Only 40%
of US health
care workers
get flu shots**

TABLE 1

Diagnostic tests for influenza

TEST	INFLUENZA TYPES DETECTED	TYPE OF SPECIMEN	TIME FOR RESULTS	RAPID RESULT
Viral culture	A and B	Nasopharyngeal swab Throat swab Nasal wash Bronchial wash Nasal aspirate Sputum	5–10 days*	No
Immunofluorescent (direct fluorescent antigen) antibody staining	A and B	Nasopharyngeal swab Nasal wash Bronchial wash Nasal aspirate Sputum	2–4 hours	No
Reverse transcriptase polymerase chain reaction	A and B	Nasopharyngeal swab Throat swab Nasal wash Bronchial wash Nasal aspirate Sputum	1–2 days	No
Serologic testing	A and B	Paired acute and convalescent serum samples†	> 2 weeks	No
Enzyme immunoassay (EIA)	A and B	Nasopharyngeal swab Throat swab Nasal wash Bronchial wash	2 hours	No
RAPID DIAGNOSTIC TESTS‡				
Directigen Flu A§ (Becton-Dickinson)	A	Nasopharyngeal swab Throat swab Nasal wash Nasal aspirate	< 30 minutes	Yes
Directigen Flu A+B§ (Becton-Dickinson)	A and B	Nasopharyngeal swab Throat swab Nasal wash Nasal aspirate	< 30 minutes	Yes

populations assessed. A recent study conducted in the Netherlands showed that annual vaccination prevents 1 death per 302 vaccinations, and 1 death per 195 revaccinations.²²

Several vaccine-related and host-related factors determine vaccine responsiveness. A

recent study found that people with HLA-DRB1*0701 are less likely to mount a neutralizing antibody response.^{23,24}

Some people choose not to be vaccinated. One third of people who do not agree to receive the influenza vaccine say that they did



TEST	INFLUENZA TYPES DETECTED	TYPE OF SPECIMEN	TIME FOR RESULTS	RAPID RESULT
FLU OIA[§] (Thermo Electron)	A and B [¶]	Nasopharyngeal swab Throat swab Nasal aspirate Sputum	< 30 minutes	Yes
FLU OIA A/B[§] (Thermo Electron)	A and B [¶]	Nasopharyngeal swab Throat swab Nasal aspirate Sputum	< 30 minutes	Yes
XPECT Flu A&B[§] (Remel)	A and B [¶]	Nasal wash Nasopharyngeal swab Throat swab	< 30 minutes	Yes
NOW Influenza A&B[§] (Binax)	A and B [¶]	Nasal wash Nasopharyngeal swab	< 30 minutes	Yes
QuickVue Influenza Test[†] (Quidel)	A and B [¶]	Nasopharyngeal swab Nasal wash Nasal aspirate	< 30 minutes	Yes
QuickVue Influenza A+B Test[†] (Quidel)	A and B [¶]	Nasopharyngeal swab Nasal wash Nasal aspirate	< 30 minutes	Yes
SAS Influenza A Test[§]	A [¶]	Nasopharyngeal wash Nasopharyngeal aspirate	< 30 minutes	Yes
SAS Influenza B Test[§]	B [¶]	Nasopharyngeal wash Nasopharyngeal aspirate	< 30 minutes	Yes
ZstaFlu[#]	A and B [¶]	Throat swab	< 30 minutes	Yes

*Shell viral culture, if available, may reduce time for results to 2 days

[†]A fourfold or greater rise in antibody titer from the acute phase (collected within the first week of illness) to the convalescent phase (collected 2–4 weeks after the acute sample) is indicative of recent infection

[‡]List may not include all test kits approved by the US Food and Drug Administration

[§]Moderately complex test—requires specific laboratory certification

[¶]Distinguishes between influenza A and B virus infections

[¶]Does not distinguish between influenza A and B virus infections

[#]Categorized as a waived test, according to the Clinical Laboratory Improvement Amendments; can be used in any office setting; requires a certificate of waiver or higher laboratory certification

CENTERS FOR DISEASE CONTROL AND PREVENTION. [HTTP://WWW.CDC.GOV/FLU/PROFESSIONALS/LABDIAGNOSTICS.HTM#TABLE](http://www.cdc.gov/flu/professionals/labdiagnostics.htm#table)

not know it was indicated, and another third say that they are afraid of its side effects.^{25,26} It is troubling that even a small proportion of those people cite their doctor's recommendation against vaccination as their reason for not getting vaccinated. In fact, numerous

studies have shown the safety of this vaccine.

In the 1976–1977 season, concern about developing Guillain-Barré syndrome following influenza vaccination was raised. However, a recent analysis showed a fourfold reduction in the incidence of

TABLE 2

Antiviral influenza medications

MEDICATION	INFLUENZA TYPES	ROUTE	PREVENTIVE DOSE (ADULTS)	THERAPEUTIC DOSE (ADULTS)	SIDE EFFECTS
Amantadine (Symmetrel)	A	Oral	100 mg twice a day	100 mg twice a day	Gastrointestinal upset Central nervous system symptoms
Rimantadine (Flumadine)	A	Oral	100 mg twice a day	100 mg twice a day	Gastrointestinal upset
Oseltamivir (Tamiflu)	A and B	Oral	75 mg daily	75 mg twice daily	Gastrointestinal upset
Zanamivir (Relenza)	A and B	Oral Inhalation	Pending	10 mg twice a day	Bronchospasm

MOSSAD SB. COPING WITH THE INFLUENZA VACCINE SHORTAGE. CLEVE CLIN J MED 2004; 71:918-927.

Guillain-Barré syndrome since 1990, despite a stable or rising rate of influenza vaccination.²⁷

Coping with shortages

Supplies of influenza vaccine have, unfortunately, fallen short in three of the last five influenza seasons in the United States. It is perplexing that the United States is the only industrialized country in which the distribution of influenza vaccine has actually decreased.¹

Several measures have been considered as solutions for vaccine shortages:

Intradermal injection of one fifth the regular dose has been found to be immunogenic in healthy people 18 to 60 years old, but not in those older than 60 years. However, local side effects are much more common after intradermal injection than intramuscular injection.^{28,29} More importantly, it is not currently known whether intradermal administration is as effective in preventing clinical influenza.

'Wiser' allocation of the flu shot. Of the 98 million Americans for whom the vaccine is currently recommended, the groups at highest risk include people previously hospitalized for pneumonia or influenza, people older than 80 years, and those 65 to 80 years old with dementia, cancer, pulmonary, or cardiac disease, on dialysis, or with a history of stroke. Rothberg has calculated that targeted vaccination of these 2.7 million people would prevent 47% of predicted hospitalizations and deaths without vaccination, and if

targeted vaccination would be chosen over random allocation for all people older than 65 years, 115,100 more hospitalizations or deaths would be prevented.³⁰ The CDC has thus recommended tiered vaccination in the event of shortage.³¹

TREATMENT: SYMPTOMATIC AND ANTIVIRAL

Cases of mild influenza and all other causes of viral upper respiratory infection are treated symptomatically. Patients with controlled hypertension who take oral pseudoephedrine to treat rhinorrhea do not seem to be at greater risk for blood pressure elevation.³² Antimicrobial agents other than anti-influenza drugs have no role in the treatment of viral upper respiratory infection.³³

The M2 blockers amantadine and rimantadine are active only against influenza A (TABLE 2).³⁴ The neuraminidase inhibitors zanamivir and oseltamivir are active against both influenza A and B (reviewed by Couch³⁵). These two groups of agents have never been compared in a randomized study. A recent survey in Japan showed that they are equally effective for influenza A, and that oseltamivir is less beneficial for influenza B than A.³⁶

Antiviral drugs are recommended for treatment of all high-risk persons with influenza, as well as all persons with severe influenza. Treatment should usually be limited to 5 days to avoid the emergence of drug-resistant viruses.



Oseltamivir would treat avian flu, but high doses are needed

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