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# 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.

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## 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.

**Most experts predict that pandemic influenza is inevitable**

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 al[6] 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.

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

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 complete 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



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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]

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

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



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**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<br>Throat swab<br>Nasal wash<br>Bronchial wash<br>Nasal aspirate<br>Sputum | 5–10 days* | No |
| **Immunofluorescent (direct fluorescent antigen) antibody staining** | A and B | Nasopharyngeal swab<br>Nasal wash<br>Bronchial wash<br>Nasal aspirate<br>Sputum | 2–4 hours | No |
| **Reverse transcriptase polymerase chain reaction** | A and B | Nasopharyngeal swab<br>Throat swab<br>Nasal wash<br>Bronchial wash<br>Nasal aspirate<br>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<br>Throat swab<br>Nasal wash<br>Bronchial wash | 2 hours | No |
| **RAPID DIAGNOSTIC TESTS‡** | | | | |
| **Directigen Flu A**§ (Becton-Dickinson) | A | Nasopharyngeal swab<br>Throat swab<br>Nasal wash<br>Nasal aspirate | < 30 minutes | Yes |
| **Directigen Flu A+B**§ (Becton-Dickinson) | A and B‖ | Nasopharyngeal swab<br>Throat swab<br>Nasal wash<br>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



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

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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



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**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<br>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]

**Oseltamivir would treat avian flu, but high doses are needed**

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 Couch[35]). 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.



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## REFERENCES


1. **Fedson DS.** Pandemic influenza and the global vaccine supply. Clin Infect Dis 2003; 36:1552–1561.
2. **Gordon S.** Avian influenza: a wake-up call from birds to humans. Cleve Clin J Med 2004; 71:273–274.
3. **Gerberding JL, Morgan JG, Shepard JA, Kradin RL.** Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 9-2004. An 18-year-old man with respiratory symptoms and shock. N Engl J Med 2004; 350:1236–1247.
4. **Hien TT, de Jong M, Farrar J.** Avian influenza—a challenge to global health care structures. N Engl J Med 2004; 351:2363–2365.
5. **Ungchusak K, Auewarakul P, Dowell SF, et al.** Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 2005; 352:333–340.
6. **Kobasa D, Takada A, Shinya K, et al.** Enhanced virulence of influenza A viruses with the haemagglutinin of the 1918 pandemic virus. Nature 2004; 431:703–707.
7. **Yen HL, Monto AS, Webster RG, Govorkova EA.** Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis 2005;192:665–672.
8. **Quirk M.** Avian influenza vaccine clinical trial begins in USA. Lancet Infect Dis 2005; 5:266.
9. **Musher DM.** How contagious are common respiratory tract infections? N Engl J Med 2003; 348:1256–1266.
10. **Neuzil KM, Maynard C, Griffin MR, Heagerty P.** Winter respiratory viruses and health care use: a population-based study in the northwest United States. Clin Infect Dis 2003; 37:201–207.
11. **Podewils LJ, Liedtke LA, McDonald LC, et al; Infectious Diseases Society of America Emerging Infections Network.** A national survey of severe influenza-associated complications among children and adults, 2003–2004. Clin Infect Dis 2005; 40:1693–1696.
12. **Fendrick AM, Monto AS, Nightengale B, Sarnes M.** The economic burden of non-influenza-related viral respiratory tract infection in the United States. Arch Intern Med 2003; 163:487–494.
13. **Mutsch M, Tavernini M, Marx A, et al.** Influenza virus infection in travelers to tropical and subtropical countries. Clin Infect Dis 2005; 40:1282–1287.
14. **Louie JK, Hacker JK, Gonzales R, et al.** Characterization of viral agents causing acute respiratory infection in a San Francisco University Medical Center Clinic during the influenza season. Clin Infect Dis 2005; 41:822–828.
15. **Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP.** Does this patient have influenza? JAMA 2005; 293:987–997.
16. **Centers for Disease Control and Prevention.** Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2005; 54:1–40.
17. **Ali T, Scott N, Kallas W, et al.** Detection of influenza antigen with rapid antibody-based tests after intranasal influenza vaccination (FluMist). Clin Infect Dis 2004; 38:760–762.
18. **Centers for Disease Control and Prevention.** Influenza vaccination coverage among persons aged 50–64 years enrolled in commercial managed health-care plans—United States, 2003–04 and 2004–05 influenza seasons. MMWR Morb Mortal Wkly Rep 2005; 54:921–923.
19. **Centers for Disease Control and Prevention.** Interventions to increase influenza vaccination of health-care workers—California and Minnesota. MMWR Morb Mortal Wkly Rep 2005; 54:196–199.
20. **Thompson WW, Shay DK, Weintraub E, et al.** Influenza-associated hospitalizations in the United States. JAMA 2004; 292:1333–1340.
21. **Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA.** Impact of influenza vaccination on seasonal mortality in the US elderly population. Arch Intern Med 2005; 165:265–272.
22. **Voordouw AC, Sturkenboom MC, Dieleman JP, et al.** Annual revaccination against influenza and mortality risk in community-dwelling elderly persons. JAMA 2004; 292:2089–2095.
23. **Lambkin R, Novelli P, Oxford J, Gelder C.** Human genetics and responses to influenza vaccination: clinical implications. Am J Pharmacogenomics 2004; 4:293–298.
24. **Gelder CM, Lambkin R, Hart KW, et al.** Associations between human leukocyte antigens and nonresponsiveness to influenza vaccine. J Infect Dis 2002; 185:114–117.
25. **Centers for Disease Control and Prevention (CDC).** Influenza vaccination and self-reported reasons for not receiving influenza vaccination among Medicare beneficiaries aged > or =65 years—United States, 1991–2002. MMWR Morb Mortal Wkly Rep 2004; 53:1012–1015.
26. **Jones TF, Ingram LA, Craig AS, Schaffner W.** Determinants of influenza vaccination, 2003-2004: shortages, fallacies and disparities. Clin Infect Dis 2004; 39:1824–1828.
27. **Haber P, DeStefano F, Angulo FJ, et al.** Guillain-Barré syndrome following influenza vaccination. JAMA 2004; 292:2478–2481.
28. **Belshe RB, Newman FK, Cannon J, et al.** Serum antibody responses after intradermal vaccination against influenza. N Engl J Med 2004; 351:2286–2294.
29. **Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM.** Dose sparing with intradermal injection of influenza vaccine. N Engl J Med 2004; 351:2295–2301.
30. **Rothberg M.** Prioritizing influenza vaccination. JAMA 2004; 292:2582–2583.
31. **Centers for Disease Control and Prevention (CDC).** Tiered use of inactivated influenza vaccine in the event of a vaccine shortage. MMWR Morb Mortal Wkly Rep 2005; 54:749–750.
32. **Salerno SM, Jackson JL, Berbano EP.** Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. Arch Intern Med 2005; 165:1686–1694.
33. **Little P, Rumsby K, Kelly J, et al.** Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. JAMA 2005; 293:3029–3035.
34. **Mossad SB.** Coping with the influenza vaccine shortage. Cleve Clin J Med 2004; 71:918–927.
35. **Couch RB.** Influenza: prospects for control. Ann Intern Med 2000; 133:992–998.
36. **Kawai N, Ikematsu H, Iwaki N, et al.** Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002–2003 influenza season. Clin Infect Dis 2005; 40:1309–1316.



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