

CLINICAL PRACTICE

Prevention and Treatment
of Seasonal Influenza

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

In February 2007, fever developed in a previously healthy 15-year-old girl, with a peak temperature of 102°F (38.9°C) and mild upper respiratory congestion. The next day she was seen by her primary care physician. A rapid screening test for group A streptococcus was negative, and oseltamivir was prescribed. After two doses, she continued to have fever and also had nausea and emesis, malaise, and restlessness but could not get out of bed. Two days later, she was taken to the local emergency room, where she was found to be hypotensive. Despite intensive resuscitative efforts, she died 12 hours later; the postmortem examination showed necrotizing pneumonia and extensive alveolar hemorrhage. A viral culture confirmed an influenza A (H1N1) infection, and methicillin-resistant *Staphylococcus aureus* was isolated from a tracheal aspirate. Could this death have been prevented?

THE CLINICAL PROBLEM

This girl was one of 12 children who were reported to have died in Texas during the 2006–2007 influenza season. Most were healthy school-age children who were unvaccinated. The major influenza virus that was prevalent during that season was influenza A/New Caledonia (H1N1), a strain that was included in the available vaccine.¹ The total number of deaths of children and adolescents reported to the Centers for Disease Control and Prevention (CDC) for the 2006–2007 influenza season was 76. This number is likely to be a substantial underestimate. The passive reporting system used for reporting cases of influenza to the CDC requires confirmation by laboratory tests; however, viral testing may not be performed in some cases or the virus may no longer be detectable in persons in whom death results from secondary bacterial infection. Furthermore, studies have shown that there is substantial underrecognition of the diagnosis of influenza even in laboratory-confirmed cases.²

During the 2006–2007 season, the number of deaths from pneumonia or influenza reported weekly by 122 U.S. cities did not exceed the epidemic threshold. However, even in relatively mild epidemic years, influenza is — for all age groups — the most important cause of acute respiratory illness that results in medical consultation.³ Each year, children have high attack rates of acute respiratory illness that requires medical attention, regardless of the type (or types) of influenza virus circulating. During the influenza epidemics between 1997 and 2001, the rates of illness among unvaccinated children ranged from 58 to 90 cases per 100 children for those younger than 5 years of age, 23 to 52 per 100 for those 5 to 11 years of age, and 13 to 27 per 100 for those 12 to 17 years of age.^{4,5}

Between 1990 and 1999, the average annual number of deaths from any cause

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that were attributable to influenza was 51,000,⁶ and the number of hospitalizations for respiratory and circulatory diagnoses attributable to influenza was 365,000.⁷ From 1996 to 2000, the average annual number of hospitalizations rose to 517,319 for four consecutive severe epidemics caused by the influenza A (H3N2) virus. It is estimated that the average annual cost of direct medical care associated with influenza A is \$10 billion, and the total annual economic burden is \$87 billion.⁸

Rates of hospitalization due to influenza increased steadily in the United States from 1979 to 2001⁷; almost two thirds of these hospitalizations were among persons 65 years of age or older. This increase, as well as an increase over time in deaths from any cause attributed to influenza,⁶ occurred despite the fact that the percentage of persons in this age group who received the influenza vaccine increased from 32% to 67% between 1989 and 1997.⁹

STRATEGIES AND EVIDENCE

PRIORITIES FOR VACCINATION

As is evident from the information presented above, the standard risk-based strategy, according to which the priority for influenza vaccination is given to persons who are at the highest risk for death (e.g., elderly persons and those with chronic heart or lung conditions), does not control influenza epidemics and does not effectively prevent serious illness and death.^{6,7} One reason is that many older persons and persons with debilitating chronic conditions have a reduced ability to respond immunologically to the currently available influenza vaccines.¹⁰⁻¹² To counter the suboptimal immune responsiveness of vulnerable patients, annual influenza vaccination has been recommended since 1985 for caretakers and household contacts of high-risk persons. However, compliance with this recommendation has been low, even among health care workers.⁹ During the 2003–2004 season, only 43% of health care workers and 21% of healthy adult household contacts of high-risk persons were vaccinated against influenza.

According to the Advisory Committee on Immunization Practices (ACIP),¹³ influenza vaccination is currently recommended for all persons 50 years of age or older, all children between 6 months and 18 years of age, and persons 19 to 49 years of age who have underlying medical conditions, are pregnant, are employed as health care workers, or are household contacts of high-

risk persons (a group that includes all children in the household who are younger than 5 years of age). Infants younger than 6 months of age, who have the highest hospitalization rates, although ineligible for vaccination, can be protected by immunization of their mothers during pregnancy.¹⁴ These categories encompass at least 85% of the total U.S. population, or about 250 million persons. Persons at increased risk for complications from influenza virus infection may benefit most by having the healthy persons around them vaccinated. The province of Ontario, Canada, has provided influenza vaccination for all eligible citizens for the past 7 years and has attained higher coverage rates for all high-risk groups, as well as for healthy persons, than those achieved in the United States.¹⁵ Recently, it was reported that Ontario has lower rates of death, hospitalizations, emergency room visits, and visits to doctors' offices than those in other Canadian provinces, a finding that may be attributable to universal influenza vaccination.¹⁶

COMPOSITION AND DISTRIBUTION OF INFLUENZA VACCINE

The formula for the influenza vaccine is updated every year on the basis of worldwide surveillance by the collaborating centers of the World Health Organization (WHO).¹³ Advisory committees of the CDC and of the Food and Drug Administration review the information and select for inclusion those variants of the three prevalent viruses in the human population that are most likely to cause outbreaks in the upcoming season. The strains included in the vaccine for the 2008–2009 season are listed in Table 1.¹³

The current production system requires that the viruses used for vaccine production be selected in February and March of each year,¹⁷ and it is not unusual for new variants to appear in the southern hemisphere after the vaccine formula for the northern hemisphere has been set and production has begun. In the past 5 years, a new variant that was not contained in the vaccine has been the major virus involved in 80% of the epidemics.¹⁸ Cross-protection by the unmatched vaccine strain varies, but in the 2003–2004 and 2007–2008 seasons, the influenza A (H3N2) component of the vaccine provided suboptimal protection.¹⁹⁻²¹ Since 2002, influenza B has been represented in the United States by two lineages.²¹ These lineages are antigenically distinct, but only one is included in the annual vaccine, and on

Table 1. Influenza Vaccines Available in the United States, 2008–2009.*

Vaccine	Trade Name	Manufacturer	Approved Age	Mercury Content <i>µg per 0.5 ml</i>	Route
LAIV	FluMist	MedImmune	2–49 yr (healthy persons)	0	Intranasal
TIV	Fluzone	Sanofi Pasteur	≥6 mo	25 (multidose vial); 0 (single-dose prefilled syringe)	Intramuscular
TIV	Fluvirin	Novartis Vaccines	≥4 yr	25.4 (multidose vial); 0 (single-dose prefilled syringe)	Intramuscular
TIV	Fluarix	GlaxoSmithKline	≥18 yr	<1.0 (single-dose prefilled syringe)	Intramuscular
TIV	FluLaval	GlaxoSmithKline	≥18 yr	25 (multidose vial)	Intramuscular
TIV	Afluria	CSL Biotherapies	≥18 yr	25 (multidose vial); 0 (single-dose prefilled syringe)	Intramuscular

* All of these vaccines contain A/Brisbane/59/2007(H1N1), A/Brisbane/10/2007(H3N2), and B/Florida/4/2006. LAIV denotes live attenuated influenza vaccine, and TIV trivalent inactivated vaccine.

several occasions, the influenza B epidemic has been due to the lineage that was not included.

Although the vaccine supply was limited in some past seasons, the quantity of vaccine currently available is more than adequate to meet demand and will expand if the demand increases in the future. Table 1 lists the six influenza vaccines that are licensed to be distributed in the United States for the 2008–2009 season.¹³ Delivery of the vaccines to clinics began in August 2008, to allow time for planning and distribution. For maximum effectiveness, the vaccine should be administered before influenza viruses begin to spread; structured programs for the delivery of the vaccine are needed.²² The 2008–2009 ACIP recommendations for extending universal coverage to schoolchildren are a challenge for primary care providers. Walk-in vaccination clinics should be open at times that are convenient for families and that will not conflict with attendance at work and school. To increase the numbers of people who receive vaccinations, clinicians can work cooperatively with community organizations to promote delivery of the vaccine in non-traditional settings. A sustainable solution may be the establishment of clinics based in schools and workplaces for the rapid distribution of the vaccine to large numbers of healthy, susceptible persons who would otherwise have high rates of infection and might be responsible for the dissemination of influenza in the community.²² Immunizing schoolchildren has been reported to confer herd protection against influenza in several settings, and these reports provide models for the development of sustainable programs.²²

EFFICACY OF THE VACCINE

The efficacy of influenza vaccines in healthy schoolchildren and adults in the workforce ranges from 70 to 90% in years in which a good match is attained between the vaccine antigen and the epidemic virus.¹³ (In a year in which there is a bad match between the vaccine antigen and the epidemic virus, the efficacy of the vaccine can range from 0 to 50%.) Both the trivalent inactivated vaccine and the live attenuated influenza vaccine are well tolerated; the most common side effects are tenderness at the site of injection in the case of the trivalent inactivated vaccine and transient sore throat or nasal stuffiness in the case of the live attenuated influenza vaccine. Both vaccines are contraindicated for persons who are allergic to eggs. The efficacy of the live attenuated influenza vaccine is superior to that of the trivalent inactivated vaccine for preschool and elementary-school children.^{3,4,20,23,24} In randomized trials directly comparing the two vaccines, the live attenuated influenza vaccine has been shown to provide 30 to 50% better protection than the trivalent inactivated vaccine. Live attenuated influenza vaccine has the advantage of administration by nasal spray, initiating a limited infection that stimulates mucosal as well as humoral immunity, and often results in better cross-protection against new variant viruses than does the trivalent inactivated vaccine,^{20,25,26} although this is not always the case.²⁷

CASE MANAGEMENT

An essential component of good case management is real-time regional or community surveil-

lance of influenza virus activity. Surveillance is best accomplished by prospective investigation, with the use of rapid-detection methods and viral culture, of cases of febrile acute respiratory illness in sentinel clinics that serve patients who are representative of the community population.⁵ Obtaining cultures is important in order to provide a sample of viruses that can be characterized for both antigenic properties and sensitivity to antiviral drugs.¹³ All clinicians should receive frequent reports from a sentinel laboratory (at a public health agency or a hospital) that note the type and subtype of viruses circulating in the community and their sensitivity to antiviral treatments and that include information from the CDC and WHO about the expected antigenic match between the available vaccine and the epidemic strains.

Rapid point-of-service tests are useful tools that help clinicians make decisions regarding the use of antiviral therapy. Several rapid tests are available. The sensitivity of these tests varies according to the type of test and the properties of the circulating viruses, and typically ranges from 60 to 80%; the specificity of these tests is about 90%.¹³ However, confirmation of the diagnosis of influenza by means of a rapid test is not an essential prerequisite for antiviral treatment if it is known that influenza viruses are prevalent in the community. Under those circumstances, the clinical diagnosis that is based on symptoms of fever and cough at presentation is as accurate as most point-of-care rapid detection tests for persons older than 5 years of age.^{28,29}

WHO SHOULD BE TREATED?

Antiviral treatment is most effective when it is initiated within 48 hours after the onset of illness. Recommendations state that anyone who may have a serious outcome should be treated^{13,30}; applying this recommendation is complicated by the difficulty of predicting the outcome early in the course of the disease. Data from randomized trials involving healthy, young volunteers who are expected to have a self-limited illness show that antiviral therapies reduce the duration of illness by 1 day, on average, and also significantly reduce nasal shedding of the virus; newer data suggest that reductions in the rates of serious illness and death are possible with prompt treatment.³¹ Because viral neuraminidase may have a role in promoting bacterial superinfection, treat-

ment with neuraminidase inhibitors may also reduce the risk of secondary bacterial infections.³² Equally important is the opportunity to reduce the risk of viral spread to contacts.^{33,34} Although the effectiveness of treatment is greater the earlier the treatment is initiated, treatment is indicated for patients who are hospitalized with influenza virus even if the duration of illness is more than 48 hours,¹³ since treatment may not only benefit the patients but may also reduce the risk of nosocomial spread of infection.

Short-term prophylaxis is indicated for household contacts of infected persons, especially if they are at high risk for complications. As recommended in the ACIP guidelines, persons who are vaccinated with the trivalent inactivated vaccine after influenza viruses have started circulating in the community should receive antiviral prophylaxis for 14 days, the time necessary for a serum antibody response to develop.¹³ Prophylaxis is not necessary for those who receive live attenuated influenza vaccine,¹⁹ since experimental studies^{35,36} and clinical experience^{19,37,38} show that this vaccine confers almost immediate protection. Health care workers who have been exposed to the virus should receive prophylaxis if they have not been immunized.

ANTIVIRAL TREATMENTS

The mutability of influenza viruses complicates the recommendations for treatment. Table 2 lists the available antiviral drugs. The older adamantanes, amantadine and rimantadine, are currently not recommended for use in the United States because almost all influenza A (H3N2) viruses are resistant to them,¹³ and they are not effective against influenza B viruses. When influenza A (H1N1) viruses predominate, however, these drugs may still be useful if they are used in combination with a neuraminidase inhibitor. An increasing proportion of influenza A (H1N1) viruses are resistant to oseltamivir, the oral neuraminidase inhibitor, but not to zanamivir.¹³ Zanamivir is a neuraminidase inhibitor that is administered by active inhalation, a method that may not be practical for debilitated patients or for children younger than 7 years of age, and is contraindicated for those with reactive airway disease. Influenza B viruses have decreasing sensitivity to both of these neuraminidase inhibitors in Japan, where oseltamivir is used extensively.³⁹ The use of combination therapy may be considered.⁴⁰ Ribavirin, a

broad-spectrum antiviral drug delivered in aerosol form, which is licensed for use against respiratory syncytial virus infection, has been effective in clinical trials involving young adults with influenza A or B infection,⁴¹⁻⁴³ although it is not currently approved for this indication. The use of ribavirin in combination with appropriate adamantanes or neuraminidase inhibitors has been proposed in immunocompromised patients with influenza,^{13,30,44} although this therapy has not been tested in controlled clinical trials.⁴⁵

AREAS OF UNCERTAINTY

Orthomyxoviruses are mutable by nature, and changes involving these viruses occur often, including changes in the timing and severity of epidemics (related to increasing population density and more rapid spread of new viral variants due to increasing air travel), changes in antigenic properties that may nullify the effectiveness of a vaccine, and rapid development of resistance to antiviral treatments. Constant worldwide surveillance is necessary to update vaccines and monitor antiviral resistance. Better vaccines and antiviral drugs are being developed, but the process should be expedited. The emergence of a new pandemic strain is the greatest threat; the development of the necessary infrastructure to control seasonal influenza is the best preparation for the next pandemic.⁴⁶

GUIDELINES

Guidelines are available from the ACIP,¹³ the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Obstetricians and Gynecologists. These organizations specify priorities for vaccine administration that currently encompass about 85% of the total population. The recommendations I provide differ in that they support universal vaccination on the basis of the recognized community benefits from routine vaccination of healthy persons and the fact that there is currently an adequate vaccine supply to support this approach.

CONCLUSIONS AND RECOMMENDATIONS

Influenza vaccination is currently recommended not only for high-risk persons (including children

Table 2. Antiviral Agents for Treatment of and Prophylaxis against Influenza.

Drug	Formulation	Adult Dose	Common Side Effects
Oseltamivir (Tamiflu, Roche)	75-mg capsule	Treatment 1 capsule twice a day for 5 days	Prophylaxis 1 capsule/day
Zanamivir (Relenza, GlaxoSmithKline)*	5 mg per inhalation (Diskhaler)	2 inhalations twice a day for 5 days	2 inhalations/day
Amantadine (Symmetrel, Endo Pharmaceuticals) †‡	100-mg tablet	1 tablet twice a day for 3–5 days§	1 tablet/day§
Rimantadine (Flumadine, Forest Laboratories) †	100-mg tablet	1 tablet twice a day for 5 days	1 tablet/day
Ribavirin (Virazole, Valeant Pharmaceuticals) ¶	60 mg/ml in reservoir	Aerosol for 2 hr every 8 hr for 5 days or as indicated	Not applicable

* Zanamivir is contraindicated for persons with reactive airway disease and for children younger than 7 years of age.

† This drug is not currently recommended for use in United States, because most influenza A (H3N2) viruses are resistant to them.

‡ Amantadine is contraindicated for persons with a seizure disorder.

§ The dose may be adjusted in the case of renal insufficiency.

¶ Ribavirin aerosol is licensed for treatment of respiratory syncytial virus; it is not currently approved by the Food and Drug Administration for influenza virus but has been used in hospitalized immunocompromised patients with influenza virus infections.

and pregnant women) but also for healthy adults who are likely to come into contact with those at risk. Given strong evidence that immunization of healthy persons benefits the community,²² I would extend this recommendation to include universal vaccination, although I recognize the need for an improved infrastructure in order to achieve this goal. The vaccine supply for this influenza season is the largest ever, and the vaccine contains three new antigens for the prevalent influenza viruses.⁴⁷ In the case of persons in whom influenza nonetheless develops, antiviral treatment is routinely recommended for all those who are hospitalized and for those presenting to ambulatory facilities

in the early phase of illness who are considered to be at high risk for serious consequences. Cases like the one in the vignette may be prevented by effective vaccination strategies; the use of antiviral therapy early in the course of the disease may also reduce the risk of complications or death from influenza, although it remains difficult to predict the eventual outcomes in the early stages of the disease.

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An audio version of this article is available at www.nejm.org.

REFERENCES

- Update: influenza activity — United States, October 1, 2006–February 3, 2007. *MMWR Morb Mortal Wkly Rep* 2007;56:118-21.
- Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. *N Engl J Med* 2006;355:31-40.
- Glezen WP. Universal influenza vaccination and live attenuated influenza vaccination of children. *Pediatr Infect Dis J* 2008;27:Suppl:S104-S109.
- Halloran ME, Longini IM Jr, Gaglani MJ, et al. Estimating efficacy of trivalent, cold-adapted, influenza virus vaccine (CAIV-T) against influenza A(H1N1) and B using surveillance cultures. *Am J Epidemiol* 2003;158:305-11.
- Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine* 2005;23:1540-8.
- Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179-86.
- Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333-40.
- Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;25:5086-96.
- Lu P, Bridges CB, Euler GL, Singleton JA. Influenza vaccination of recommended adult populations, U.S., 1989-2005. *Vaccine* 2008;26:1786-93.
- Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med* 2006;166:1121-7.
- Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine* 2006;24:1159-69.
- McElhaney JE, Dutz JP. Better influenza vaccines for older people: what will it take? *J Infect Dis* 2008;198:632-4.
- Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep* 2008;57(RR-7):1-60.
- Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* 2008;359:1555-64.
- Kwong JC, Rosella LC, Johansen H. Trends in influenza vaccination in Canada, 1996/1997 to 2005. *Health Rep* 2007;18:9-19.
- Kwong JC, Stukel TA, Lim J, et al. The effect of universal influenza immunization on mortality and health care use. *PLoS Med* 2008;5(10):e211.
- Wright PF. Vaccine preparedness — are we ready for the next influenza pandemic? *N Engl J Med* 2008;358:2540-3.
- Nyquist A-C. Influenza virus mutation and transmission. *Manag Care* 2007;16:Suppl 8:6-10.
- Piedra PA, Gaglani MJ, Kozinetz CA, et al. Trivalent live attenuated intranasal influenza vaccine administered during the 2003-2004 influenza type A (H3N2) outbreak provided immediate, direct, and indirect protection in children. *Pediatrics* 2007;120(3):e553-e564.
- Halloran ME, Piedra PA, Longini IM Jr, et al. Efficacy of trivalent, cold-adapted, influenza virus vaccine against influenza A (Fujian), a drift variant, during 2003-2004. *Vaccine* 2007;25:4038-45.
- Influenza activity — United States and worldwide, 2007–08 season. *MMWR Morb Mortal Wkly Rep* 2008;57:692-7.
- Glezen WP. Herd protection against influenza. *J Clin Virol* 2006;37:237-43.
- Ashkenazi S, Vertruyen A, Aristegui J, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infection. *Pediatr Infect Dis J* 2006;25:870-9.
- Ambrose CS, Yi T, Walker RE, Conner EM. Duration of protection provided by live attenuated influenza vaccine in children. *Pediatr Infect Dis J* 2008;27:744-8.
- Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults. *JAMA* 1999;282:137-44.
- Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults. *JAMA* 2000;284:1655-63.
- Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med* 2006;355:2513-22.
- Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000;160:3243-7.
- Ohmit SE, Monto AS. Symptomatic predictors of influenza virus positivity in children during the influenza season. *Clin Infect Dis* 2006;43:564-8.
- American Academy of Pediatrics Committee on Infectious Diseases. Antiviral therapy and prophylaxis for influenza in children. *Pediatrics* 2007;119:852-60.
- McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.
- McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev* 2006;19:571-82.
- Whitley RJ, Monto AS. Prevention and treatment of influenza in high-risk groups: children, pregnant women, immunocom-

- promised hosts, and nursing home residents. *J Infect Dis* 2006;194:Suppl 2:S133-S138.
34. Halloran ME, Hayden FG, Yang Y, Longini IM Jr, Monto AS. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. *Am J Epidemiol* 2007;165:212-21.
35. Whitaker-Dowling P, Maassab HF, Youngner JS. Dominant-negative mutants as antiviral agents: simultaneous infection with the cold-adapted live virus vaccine for influenza A protects ferrets from disease produced by wild-type influenza. *J Infect Dis* 1991;164:1200-2.
36. Youngner JS, Treanor JJ, Betts RF, Whitaker-Dowling P. Effect of simultaneous administration of cold-adapted and wild-type influenza A viruses on experimental wild type influenza in humans. *J Clin Microbiol* 1994;32:750-4.
37. Gaglani MJ, Piedra PA, Herschler GB, et al. Direct and total effectiveness of the intranasal, live attenuated, trivalent cold-adapted influenza virus vaccine against the 2000-2001 influenza A(H1N1) and B epidemics in healthy children. *Arch Pediatr Adolesc Med* 2004;158:65-73.
38. Piedra PA, Gaglani MJ, Riggs M, et al. Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial. *Pediatrics* 2005;116(3):e397-e407.
39. Hatakeyama S, Sugaya N, Ito M, et al. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. *JAMA* 2007;297:1435-42.
40. Ilyushina NA, Bovin NV, Webster RG, Govorkova EA. Combination chemotherapy, a potential strategy for reducing the emergence of drug-resistant influenza variants. *Antiviral Res* 2006;70:121-31.
41. Knight V, McClung HW, Wilson SZ, et al. Ribavirin small-particle aerosol treatment of influenza. *Lancet* 1981;2:945-9.
42. McClung HW, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of influenza B virus infection. *JAMA* 1983;249:2671-4.
43. Gilbert BE, Wilson SZ, Knight V, et al. Ribavirin small-particle aerosol treatment of infections caused by influenza virus strains A/Victoria/7/83 (H1N1) and B/Texas/1/84. *Antimicrob Agents Chemother* 1985;27:309-13.
44. Kirshon B, Faro S, Zurawin RK, Samo TC, Carpenter RJ. Favorable outcome after treatment with amantadine and ribavirin in a pregnancy complicated by influenza pneumonia: a case report. *J Reprod Med* 1988;33:399-401.
45. Ilyushina NA, Hoffman E, Salomon R, Webster RG, Govorkova EA. Amantadine-oseltamivir combination therapy for H5 N1 influenza virus infection in mice. *Antiviral Ther* 2007;12:363-70.
46. Strikas RA, Wallace GS, Myers MG. Influenza pandemic: preparedness action plan for the United States: 2002 update. *Clin Infect Dis* 2002;35:590-6.
47. Influenza activity — United States and worldwide, May 18–September 19, 2008. *MMWR Morb Mortal Wkly Rep* 2008;57:1046-9.

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