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Influenza and Influenza Vaccination 2004-2005

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Epidemics of influenza—a highly infectious, acute viral illness—were reported in detail as early as 1510, but even earlier accounts of epidemic respiratory illness from the 10th and 11th centuries probably also were a reflection of influenza's influence on early societies. One hypothesis holds that the circa 430 BC plague of Athens was caused by a co-infection of influenza and the toxic shock producing phage of Staphylococcus aureus.[1] *The epidemiologic concept of "excess mortality" initially was developed to describe the effect of an 1847 influenza epidemic in London.[2] Later, the systematic evaluation of excess mortality became an index for recognizing the course of an influenza epidemic.[3]*

There are several types of influenza and many subtypes. For some types, humans are not the only host. Influenza virus first was isolated from chickens suffering from "fowl plague" in 1901—a subtype we now call H7N7.[4] In 1931, an influenza virus closely related to the virus that caused the Great Pandemic of 1918 was identified in swine.[5] The first influenza B virus was isolated in 1940, and the first influenza C virus in 1947. The ability to isolate these viruses and grow them in embryonated eggs eventually led to the ability to develop and test influenza vaccines and antiviral medications, as well as to perform careful seasonal surveillance.

—The Editor

Influenza Disease

Epidemiology. *Incidence and Prevalence.* Influenza can lead to death from pneumonia as well as exacerbations of underlying diseases of the heart, lungs, or other organ systems. More than 90% of deaths attributed to influenza and pneumonia occur in the elderly. In the United States, the mortality rate has been rising. According to a recent study, the average number of influenza-associated deaths was approximately 19,000 per year from 1976 to 1990, but 36,000 per year from 1990 to 1999.[6] It is considered probable that this increase was due in part to the increasing number of seniors and because the relatively

virulent H3N2 subtype predominated in 90% of the more recent influenza seasons. Death from influenza is uncommon among children, even those with high-risk medical conditions. Overall, an estimated average of 92 deaths occur annually from influenza among children younger than 5 years of age,[6] a number that is dwarfed by the incidence of influenza death later in life. However, as demonstrated during the 2003-2004 influenza season (143 pediatric deaths reported as of April 2004), illness resulting in childhood mortality can draw enormous national media attention and lead to parental panic.[7]

Rates of hospitalization depend upon the predominant influenza virus subtype, as well as host factors such as age, underlying medical conditions, and socioeconomic status. Infants and seniors both have been shown to have high rates of influenza-associated hospitalization. In a study of healthy infants and young children with Medicaid insurance from 1973-1993, the influenza-associated hospitalization rate per 100,000 varied: 1,038 (birth to 5 months of age), 496 (6-11 months of age), and 186 (12-23 months of age). In the same study, children with high-risk conditions had higher hospitalization rates than healthy children: 1900 (birth to 11 months) and 800 (12-23 months of age).[8] In a more recent study (1992-1997) of healthy infants and young children enrolled in a health maintenance organization, the influenza-associated hospitalization rate per 100,000 was 144 to 187 in those from birth to 23 months of age.[9] Based on National Hospital Discharge Data, the hospitalization rate for persons 65 or older was 228 per 100,000 from 1969 to 1995 when H3N2 predominated.[10]

Less severe morbidity may be experienced by both children and adults. For children, influenza is a major cause of fevers, ear infections, and other upper respiratory infections that lead to medical visits. These visits, in turn, lead to antibiotic prescriptions and, it can be speculated, a rising incidence of antibiotic resistance. Both the visits and the prescriptions contribute to health care costs.

Epidemic Behavior. Influenza epidemics are an annual event, and usually one or two influenza viruses predominate. It previously was believed that only one influenza A subtype could circulate at a time, but since 1978 both H1N1 and H3N2 viruses have circulated concurrently. It appears that influenza viruses do not continue to spread within a population between epidemics,[11] but must be reintroduced each season.

Geographic Distribution. Influenza has worldwide distribution including tropical regions. Airplane travel makes circulation of the infectious agent rapid.

Temporal Distribution. In temperate climates, influenza is a cold weather disease. In the United States between 1976 and 2004, peak influenza activity was documented from November through April, with the most frequent peaks occurring in January (21%) and February (43%). Because 14% of the peaks were noted in March and April, the Advisory Committee on Immunization Practices reminds readers that influenza vaccine can continue to be offered in December and throughout the influenza season while supplies last.[7]

Host Factors. Rates of serious morbidity and mortality from influenza are highest in persons aged 65 years and older, but school-age children (age 5-14 years) are the age group most often infected. These young people may be the major source of infection for older people. Settings in which there is daily mixing of large numbers of susceptible people—such as day care, schools and colleges, military barracks, and nursing homes—create a fertile setting for the spread of influenza infection. There is no special susceptibility for any racial group or sex. The children of low income families are at greater risk for influenza infection than are those of middle income families[12,13] presumably because of greater crowding. However, this intense exposure in childhood may lead to protection that persists into adulthood as suggested

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by lesser risk for influenza infection among low income as compared to middle income adults.[14]

Nosocomial Infections. Because large numbers of community members are infected during influenza season (including health care workers, hospital staff, patients, and patient visitors) and because influenza easily is transmitted from person to person, the potential for spread of influenza within a hospital is considerable. The occurrence and serious consequences of nosocomial influenza outbreaks are well documented.

Influenza Viruses. Influenza virus was the first human virus to be isolated and characterized. Influenza viruses are single-stranded RNA viruses, categorized as orthomyxoviruses. There are three types of influenza viruses: A, B, and C. Influenza A and B are the two types that cause epidemics in humans; influenza C tends not to cause significant disease. Both influenza A and B have two surface glycoproteins that are important both for immune recognition and categorization: hemagglutinin and neuraminidase. For example, A/Hong Kong/1/68 (H3N2) represents an influenza A virus first isolated in a laboratory in Hong Kong (strain number 1) in 1968 and determined to have a specific combination of hemagglutinin and neuraminidase antigens.[15]

The nucleus of influenza A contains eight gene segments that code for 10 proteins. The segmented nature of the genome allows for the frequent genetic reassortment that is considered the basis for the emergence of new subtypes of type A viruses (antigenic shift). When cells are simultaneously infected with two influenza A viruses with different genetic properties (e.g., a human and an avian virus), RNA assembly may incorporate gene segments from either parent virus. Minor antigenic changes (antigenic drift) occur when there are progressive alterations in antigenic sites for reactivity with human antibodies. The constant antigenic flux of influenza viruses make them particularly difficult to control. An antigenic shift would be the basis for a pandemic.

Mechanism and Route of Transmission. The virus is shed in respiratory secretions of an infected person for 5-10 days.[16] The virus is highly contagious and generally spread from person to person via inhalation of airborne droplets elaborated during coughing or sneezing. Less commonly it is spread by contact with an infected person's secretions, for example from hand to mouth via a doorknob or other inanimate object that has been recently handled by an influenza-infected person. Because influenza passes from person to person, it spreads easily during seasons when people stay indoors, such as winter in northern climates and the rainy season in the tropics.

Pathophysiology

Mechanism of Disease Process.[14] Influenza is an acute infection of the respiratory tract. Influenza virus inhalation can lead to viral deposition in the upper or lower respiratory tract, the latter probably being more susceptible. The influenza hemagglutinin attaches to influenza-specific receptors on mucoproteins in the airway's mucous coating. The influenza neuraminadase probably liquefies mucosal secretions and promotes influenza's access to the epithelial cells of the mucosa.

The incubation phase from exposure to shedding is 1-5 days. Shedding may precede symptoms by a day. Viral concentrations increase over the next 1-2 days and peak during the symptomatic peak of illness. Viral concentrations and disease severity correlate directly.

Disease Course. A simple case of influenza starts suddenly, causing fever, headache, muscle aches, and exhaustion, as well as respiratory tract symptoms such as sore throat, runny or stuffy nose, and dry cough. Very young children also may experience nausea and vomiting,[17] but these symptoms are uncommon in adults with true influenza. (The term "stomach flu" is a misnomer; other viruses and bacteria cause nausea and diarrhea in adults.) Influenza infection usually is short-lived, averaging two to three days, but in some cases it can persist for weeks, especially among the elderly.

It should be noted that influenza B, which primarily affects children, generally causes milder disease than influenza A. This is, in large part, because the Type B virus shows more immunologic stability than Type A.

Potential Complications. Pneumonia is the chief complication of influenza. Pneumonia may be either related primarily to influenza or to a bacterial complication from *S. pneumoniae*, *S. aureus*, or *H. influenza*. Infection of cells by influenza A requires cleavage of the virus hemagglutinin by proteases. Some strains of *S. aureus* produce such proteases, possibly accounting for the frequency with which *S. aureus* pneumonia complicates influenza infections.[18] Influenza may induce an exacerbation of chronic obstructive pulmonary disease or chronic bronchitis. In young infants, influenza infection may lead to croup or bronchiolitis. Upper respiratory infections such as sinusitis and otitis media may complicate the course.

Influenza has been implicated in cardiac disease such as myositis and myocarditis. Though the mechanism is not understood, the virus may induce neurologic symptoms including acute viral encephalitis, Reye's syndrome, and Guillain-Barré syndrome. Miscellaneous other complications attributed to influenza infection include a sepsis picture in infants, toxic shock syndrome, and myoglobinuria.

Immunity. Immunity to influenza depends upon immunity to its surface antigens, including hemagglutinin. Immunity reduces both the likelihood of being infected and, if infected, the severity of clinical symptoms.[19] Immunity to one antigenic variant does not guarantee protection against others, and immunity to one influenza virus type confers limited or no protection against other types.

Clinical Features

Patients may present with high fever, chills, malaise, myalgia, and headache. The chief complaint is typically respiratory, for example nasal congestion, rhinitis, sore throat, conjunctivitis, and nonproductive cough. Photophobia and shivering may be present. Gastrointestinal symptoms are not common in adults, but are reported more frequently in children. Cervical and general adenopathy may be present.

Diagnostic Studies[20]

The purpose of making an early diagnosis of influenza is to

prevent unnecessary use of bacterial antibiotics and maintain the opportunity for more directed antiviral therapy. From a public health perspective, laboratory diagnosis makes surveillance feasible, announcing the presence of influenza viruses in the community and identifying the predominant circulating types, subtypes, and strains.

Tests for influenza include viral culture, rapid antigen testing, serology, polymerase chain reaction (PCR), and immunofluorescence (IF).[21-23] There is a wide range of eligible specimens for viral isolation, including nasopharyngeal swab, throat swab, nasal wash, nasal aspirate, bronchial wash, and sputum. It should be kept in mind that bronchial wash and sputum should not be used for rapid diagnostic testing, and that the nasopharyngeal specimens are more effective than throat swab specimens. Samples should be collected within the first four days of illness.

• Viral cultures remain the gold standard. They are important adjuncts to rapid tests because they provide information on subtypes and strains and help monitor the emergence of antiviral resistance and novel influenza A subtypes that may become pandemic threats. Results typically take 5-10 days and are not useful in the acute situation.

• Rapid antigen tests can detect the virus within 30 minutes to 1 hour, but have a lower sensitivity than culture. Some brands of rapid tests only detect influenza A. If confirmation is necessary, a viral culture should be sent.

• Serology requires two samples per person—one obtained during the first week of illness and another 2-4 weeks later. The length of time necessary to note an antibody level rise excludes this test from helping in the decision to start antiviral treatment.

• PCR may be used to detect viral RNA in respiratory secretions. The full range of specimens used for culture may be used for PCR. Results usually are available in 1-2 days.

• Immunofluorescence DFA antibody staining and enzyme immuno assays (EIA) both can detect influenza A and B and take about two hours.

Differential Diagnosis

Influenza often is difficult to distinguish based solely on clinical symptoms because the early influenza symptoms are similar to those of other infectious agents such as *Mycoplasma pneumoniae*, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, and Legionella.

Prevention

The most efficacious means to combat influenza is via prevention. As often is stated, good hand washing is one of the cornerstones of prevention. The influenza virus is heavier than tuberculosis and it does not stay airborne for prolonged periods; airborne/TB precautions are not necessary in hospitals if influenza is the infecting agent. However, health care workers are advised not to touch their eyes or nose after contact with an infected patient. Vaccination (detailed below) also is an important and cost effective preventive tool. Avoidance of ill persons and crowds seems prudent as a means for the general public to prevent influenza, but such methods have not been shown to be effective[14] and may not be practical in modern society. It has been shown, however, that epidemics do not spread extensively unless schools are in session,[14] so school closings may be in order for severe outbreaks.

Management

Symptomatic. As with all illness, the mantra "airway, breathing, circulation" is of key importance for patients with influenza. Supplemental oxygen and other supportive measures should be used as needed. Antipyretic therapy may include acetaminophen or ibuprofen. Aspirin should be withheld from patients younger than 16 years of age due to the risk of Reye's syndrome.

Antiviral Medications[24] (*See Tables 1 and 2*). In the United States, four prescription medicines are licensed for preventing or treating influenza. Although they may prevent symptoms and shorten the course of the illness by a day or two, they do not interfere with the development of immunity to the infecting influenza strain. It must be kept in mind that these are not panaceas. Their use may cause side effects, and none of them are licensed for use in children younger than 1 year. Some strains of influenza virus already have mutated enough to be resistant to one of these antiviral drugs. More resistant strains may develop.

Two of the antiviral medications, amantadine (Symmetrel) and rimantadine (Flumadine), are related to the adamantanes. They are only effective against influenza A. Both are approved for prophylaxis in children and adults. Both also are approved for treatment, but rimantadine is not approved for treatment of pediatric patients. The two other antiviral medications, zanamivir (Relenza) and oseltamivir (Tamiflu), are neuraminadase inhibitors. They are effective against both influenza A and B. Both are approved for treatment, but zanamivir is only approved for persons 7 years or older. Additionally, oseltamivir is approved for prophylaxis of adults. Table 2 shows the recommended daily dosage of influenza antiviral medications for treatment and prophylaxis by age.

Interim chemoprophylaxis and treatment guidelines have been prepared by the CDC and can be accessed at the CDC influenza website.[25]

Influenza Vaccine

Two Types of Vaccines. There are two main types of influenza vaccine: the injectable inactivated and live intranasal spray vaccines. They are alike in that the viruses for both are grown in eggs, so anaphylactic type allergic reaction to chicken eggs is a true contraindication to all influenza vaccines produced currently. Also, both types of vaccines must be given annually to achieve optimal protection.

Inactivated Influenza Vaccine. Description. The trivalent inactivated vaccine (TIV) is an injectable vaccine made from inactivated or killed influenza viruses. Different manufacturers use different compounds to inactivate the virus, but all manufacturers add antibiotics to prevent bacterial contamination. Because of heated controversy around the use of thimerosal (a mercury-based preservative) in vaccines, a new pediatric formulation that does not contain thimerosal as a preservative has been licensed.[26]

Table 1. Antiviral Medications: Trade Names, Routes of Administration, Precautions, and Toxicities

DRUG ROUTE	PRECAUTIONS*	TOXICITY
Chemically related to adamantanes, these therapies prevent penetration of virus into the host by inhibiting uncoating of influenza A. They are effective only against influenza type A (prophylaxis and treatment within 24-48 hours of symptom onset).		
Amantadine (Symmetrel) Oral	Elderly, seizure disorders, psychiatric illness, anticholinergic drugs Eczematoid dermatitis CNS stimulants Reduce dose in renal disease, liver disease. Effective only against type A	Among some healthy adults and children, side effects can include: CNS effects (nervousness, anxiety, difficulty concentrating, and lightheadedness) GI effects (nausea and loss of appetite) Among some other persons with long-term illnesses, more serious side effects, such as delirium, hallucinations, agitation, and seizures, can occur. Side effects usually diminish or disappear after 1 week.
Rimantadine (Flumadine) Oral	Reduce dose to 100 mg QD if severe renal or hepatic disease Cimetidine increases plasma levels Effective only against type A	CNS side effects happen more often among persons taking amantadine than among persons taking rimantadine.
Chemically related to neuraminidase inhibitors: Release of viruses from infected cells is decreased. They are effective against influenza A and B.		
Oseltamavir (Tamiflu) Oral	Decrease dose for CrCl < 30 mL/min Chronic cardiac or respiratory disease	Nausea, vomiting (may be less severe if taken with food)
Zanamivir (Relenza) Oral inhalation	Children older than 7 yrs Contraindication: COPD, asthma Not approved for influenza prophylaxis	This drug is inhaled; more side effects in those with asthma or other chronic lung disease (e.g., decreased respiratory function and bronchospasm). Other side effects reported by < 5% of those who used this drug are diarrhea, nausea, sinusitis, nasal infections, bronchitis, cough, headache, and dizziness.

* All four of these drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturer's package inserts).

Dose. An intramuscular dose of 0.5 mL of inactivated vaccine is recommended for children 3 years of age or older and for adults (irrespective of body weight). Children 6-35 months of age should receive only 0.25 mL. Children younger than 9 years who have never been immunized should receive two doses at least four weeks apart, optimally timed so that the second dose is administered before December.

Vaccine Efficacy. The effectiveness of TIV depends on two main factors: host characteristics and the degree of similarity between circulating influenza virus and the vaccine virus. If there is a good match, the vaccine prevents influenza in 70-90% of healthy adults younger than 65.[27,28] Among children younger than 16 years, a five-year study found TIV to be 77-91% efficacious in preventing influenza symptomatic illness culture positive for H1N1 and H3N2, respectively, but considerably less efficacious against influenza seroconversion (44% and 49% for children 1-5 years of age; 74% and 76% for those 6-10; and 70% and 81% for adolescents 11-15).[29] Conflicting results regarding the reduction of otitis media have been reported.[30,31]

Among non-institutionalized persons age 60 years or older, influenza vaccine efficacy may be as low as 58% against influenza respiratory illness and even lower among that portion of the population more than 70 years of age.[32] Among HMO patients age 65 years or older, inactivated influenza vaccine was 30-50% effective in preventing hospitalization for influenza and pneumonia[33] and as much as 80% effective in preventing influenza-related death.

Adverse Reactions. Allergic reactions could occur after any vaccine or medicine. These are the other risks and side effects that have been known to occur after influenza vaccines:

• Minor pain or tenderness, swelling, or warmth at the injection site may begin soon after the shot and usually resolve within

Table 2. Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis (from www.cdc.gov/flu/professionals/antiviralback.htm)

ANTIVIRAL AGENT	AGE GROUPS (YRS)				
	1-6	**7-9**	**10-12**	**13-64**	**≥ 65**
Amantadine*					
Treatment, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤ 100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤ 100 mg/day
Rimantadine¶					
Treatment, ** influenza A	NA††	NA	NA	100 mg twice daily§§§	100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	100 mg/day¶¶
Zanamivir*†††**					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,§§§ influenza A and B	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel–tablet and syrup) and Geneva Pharms Tech (Amantadine HCL–capsule); USL Pharma (Amantadine HCL–capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL–syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine–tablet and syrup); Corepharma, Impax Labs (Rimantadine HCL–tablet), and Amide Pharmaceuticals (Rimantadine HCL–tablet). Zanamivir is manufactured by Glaxo SmithKline (Relenza–inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu–tablet). Information based on data published by the U.S. Food and Drug Administration at www.fda.gov.

* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤ 50 mL/min/1.73 m^2.

† 5 mg/kg of amantadine or rimantadine syrup = 1 tsp/22 lbs.

§ Children ≥ 10 years who weigh < 40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg/day.

¶ A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤ 10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

** Only approved by FDA for treatment among adults.

†† Not applicable.

§§ Rimantadine is approved by FDA for treatment among adults. However, certain experts in the management of influenza consider it appropriate also for treatment among children. (See American Academy of Pediatrics, 2000 Red Book.)

¶¶ Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥ 65 years if they experience possible side effects when taking 200 mg/day.

***Zanamivir is administered via inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.

†††Zanamivir is not approved for prophylaxis.

§§§A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance < 30 mL/min.

¶¶¶The dose recommendation for children who weigh ≤ 15 kg is 30 mg twice a day; for >15 to 23 kg children, the dose is 45 mg twice a day; for > 23 to 40 kg children, the dose is 60 mg twice a day; and for children > 40 kg, the dose is 75 mg twice a day.

two days. Between 10% and 64% of people will experience these mild reactions.

• General side effects, including fever, muscle aches, or malaise may begin 6-12 hours after the shot and can persist for a day or two. More children than adults experience these symptoms. Overall, fewer than 1% of vaccine recipients report these side effects.

• Guillain-Barré syndrome, or GBS, causes potentially severe motor peripheral neuropathy. Unrelated to influenza vaccination, GBS affects 10-20 adults out of 1 million. In 1976, the swine influenza vaccine was associated with an increase in the basal incidence of GBS. Since then, influenza vaccines have not been clearly linked to GBS. According to the CDC, "…if there is a risk of GBS from current influenza vaccines, it is estimated at 1 or 2 cases per million persons vaccinated."[34] However, if a patient has a history of GBS and is at high risk of influenza complications, CDC does not consider use of the inactivated vaccine as contraindicated.

• A recent study showed a possible association between inactivated influenza vaccines and an increased risk of Bell's palsy. The authors concluded that a population-based controlled study is needed to determine whether this association could be causal and to quantify the risk.[35]

There has been some publicity about fear of the use of influenza vaccine during pregnancy because of the presence of thimerosal, a mercury-containing preservative, used in minute amounts in the influenza vaccine. Experts believe that related mercury compounds should be avoided in pregnancy, but no clear-cut data are available on the use of thimerosal-containing vaccines during pregnancy. It is very likely that the small amounts and rapid excretion[36] make influenza vaccine safe for pregnant women. The Advisory Committee on Immunization Practices, which advises the CDC, has recommended that women who will be pregnant during influenza season receive the injectable vaccine because of their risk of serious complications from influenza.[7] In previous years, only a minority of pregnant women have been vaccinated.[37]

Live Attenuated Influenza Vaccine. An influenza vaccine in the form of a nasal spray—used for years in Russia—was licensed in the United States in 2003 for use by people between 5 and 49 years of age who are free of chronic illness. The potential advantages of such a vaccine are great. No needle is used, so there is no risk of sharps injury, there is no pain at the injection site, and immunity develops in the lining of the nose as well as systemically. The disadvantages also have been notable—onerous storage and handling requirements as well as greater cost.

Description. The live attenuated influenza vaccine (LAIV) is an intranasal spray comprised of live influenza virus that is attenuated or weakened because it is, through serial culturing, cold-adapted. That is, it replicates in the cooler temperatures of the upper respiratory tract, but not in the warmer lower airways.[15] The fact that this vaccine does contain a living organism makes it quite different than the injectable vaccine. There is only one intranasal influenza vaccine currently licensed for use in the United States influenza virus vaccine (nasal), trade name FluMist.[38]

Dose. Each syringe-like sprayer contains a 0.5 mL dose; 0.25 mL to be sprayed into each nostril. Previously un-immunized children 5-8 years old should receive two doses at least six weeks apart.

Vaccine Efficacy. In one pre-licensure study of the intranasal influenza vaccine during a season in which the circulating virus strains were well matched with those in the vaccine, efficacy was 93% among children receiving two doses.[39] Among adults 18-49 years of age, when compared to placebo recipients, LAIV recipients had fewer upper respiratory infection episodes (26%) and consequently fewer lost days of work (27%), as well as fewer days of health care visits for febrile illness and antibiotic use.[40]

Adverse Reactions. Clinical signs and symptoms that occurred more frequently among children receiving LAIV than among those receiving placebo included nasal congestion or runny nose, headache, fever, vomiting, abdominal pain, and myalgias.[41-43] In contrast, signs and symptoms that occurred more frequently among adults receiving LAIV than among those receiving placebo included nasal congestion or runny nose, headache, and sore throat. The incidence of serious adverse events that would be expected to complicate influenza (e.g., pulmonary or central nervous system events) were not statistically different between LAIV and placebo recipients in the many pre-licensure trials. A study of an inactivated intranasal influenza vaccine used in Switzerland (fundamentally different than the live intranasal influenza vaccine used in the United States) showed a strong association with Bell's palsy.[44] This vaccine is no longer in clinical use in Switzerland and was never licensed in the United States, but this association has prompted concern about intranasal vaccines, and both live and inactivated influenza vaccines.

Composition. The influenza vaccine actually is a combination vaccine that protects against three viruses: two influenza A and one influenza B subtypes. The exact strains used in the United States' vaccine vary from year to year, depending on a scientific prediction of which influenza viruses will circulate here in the following winter. This prediction is based on careful monitoring of circulating strains in Asia. Asia is an important site for influenza surveillance because historically it is in this region that new strains of influenza virus have originated in fowl and pigs, and passed to humans living in close contact with these animals. After the new strain passes from animal to human, it then spreads around the globe from person to person.

The effectiveness of influenza vaccine depends both on how accurately scientists predict which influenza virus strain will circulate in the United States and on host factors such as the age of the recipient. If there is a poor match between the influenza viruses chosen for the vaccine and those that actually make their way to America, the vaccine may not be very effective. Fortunately, the influenza experts from WHO and CDC usually have been successful in predicting which strain will come each year.

Each year, antigenically equivalent strains are used in all U.S. influenza vaccine types and brands.[45]

Timing of Vaccination. Antibodies reach protective levels approximately two weeks after vaccination.[46,47] For optimal protection during influenza season, vaccination has been recommended in October or November. For travelers to the southern hemisphere, it may be advisable to protect patients during April

through September. The first year a child younger than age 9 receives influenza vaccine, he or she should receive two doses separated by at least 4 weeks (injectable) or 6 weeks (intranasal spray); the first dose is only a primer. All other eligible people should receive one dose per year.

There are two chief reasons why annual revaccination is necessary for protection. First, immunity from the vaccine wanes after vaccination and may fall below the protective level within a year, or even within a few months in the elderly.[48] Secondly, the predominant virus usually changes from year to year.

Who Should Receive Influenza Vaccine? For the 2004-2005 influenza vaccination season, the United States Public Health service initially recommended influenza vaccine for four chief categories of people:[7] certain age groups (all persons older than 50 years and healthy children ages 6-23 months), all individuals 6 months of age or older with chronic diseases (including residents of nursing homes), women who expected to be pregnant during influenza season, as well as close contacts (e.g., health care workers, household members) of chronically ill patients and contacts of infants and toddlers 0-23 months of age. The vaccine also was recommended for some international travelers. Because of a severe and acute vaccine shortage (See the section "The 2004 influenza vaccine shortage" below), these recommendations were changed slightly. This year, healthy people 50-64 years of age and contacts of healthy children 6-23 months of age were removed from the recommended list.[49]

It is important to note that health care workers with direct patient contact remain on the list of individuals for whom the influenza vaccine is recommended. Of course, most emergency department (ED) personnel fit this description. Influenza vaccination is important for ED personnel, not only because it limits absenteeism during a very busy season in the ED, but also because it blunts the spread of influenza from patient to health care worker and back to patients. Because influenza viruses easily are transmitted, health care workers are urged to receive the influenza vaccine so they will not put patients, themselves, their families, and others at risk.[50]

New Recommendations for Pediatric Vaccination. In light of the potential severity of influenza among otherwise healthy infants and toddlers,[51-53] and the availability of a safe and efficacious vaccine,[29] in 2004 the American Academy of Pediatrics (AAP)[54] and the Advisory Committee on Immunization Practices (ACIP) issued a new recommendation broadening the pool of children who routinely should be vaccinated. Under the new guideline, healthy children ages 6-23 months routinely should be vaccinated (the previous recommendation was merely that these children be vaccinated "when feasible").[55]

Widespread implementation of the expanded recommendation is expected to reduce the number of healthy young children infected and consequently hospitalized with influenza-related illness. The new recommendation, by increasing herd immunity, also would provide greater protection to high-risk individuals such as children and adults with chronic medical conditions and the elderly. General use of the vaccine among children 6-23 months of age probably also would decrease some families' medical bills and lost days of school and work.

However, significant practical obstacles to implementation exist, even in a year when there was no vaccine shortage. A very large number of U.S. children are in the target age group,[56] and the window of opportunity for vaccination is relatively brief. This problem is compounded for the group who are receiving the influenza vaccine for the first time and so must receive a second dose (and so a second visit)[57] at least four weeks after the first to achieve full immunity. For these reasons, successful implementation of the new guidelines will require a carefully planned campaign in primary care offices.[58]

Who Should Not Receive the Influenza Vaccine?[15] Several contraindications and precautions to vaccination are common to both the injectable and the intranasal influenza vaccines. These vaccines should not be given to a person if he or she:

• had a hypersensitivity reaction to a prior dose of influenza vaccine or to any vaccine component including eggs. Appropriate allergy evaluation and desensitization is in order if the person is at risk for influenza complications.

• has a moderate to severe illness. If this is the case, the person may receive the vaccine when feeling better.

• is outside the age range for which the vaccine is licensed for use. The appropriate ages for the two injectable influenza vaccine brands are 6 months of age or older for Fluzone (Aventis Pasteur) and 4 years of age or older for Fluvirin (Chiron, not available for the 2004-2005 season). The intranasal influenza vaccine, FluMist made by MedImmune, is licensed for persons 5-49 years of age.

The live intranasal influenza vaccine has several more contraindications to its use. Additional groups of people who should not be given the spray include:

• All patients with a chronic illness;

• Pediatric patients on chronic aspirin therapy. Since the nasal spray influenza vaccine is an attenuated live virus, children who take aspirin should not receive this vaccine because of the potential for inducing Reye's syndrome;

• Persons with a personal past medical history of GBS;

• Pregnant women; and

• Health care workers and other close contacts of patients who are in a protected environment because of severe immunosuppression (e.g., receiving a bone marrow transplant). This limitation is because of the remote risk for transmission of the vaccine-strain virus.

Can Influenza Vaccine Give You the Flu? Many patients and health care providers alike believe that influenza vaccine causes influenza disease. There are no live viruses in the injectable flu vaccine, so influenza infection resulting from the injectable vaccine is not possible. Recipients may mistake minor side effects such as fever and muscle aches as influenza. Patients also should be aware that, because the vaccine does not work for about two weeks after it is given, vaccinees may get influenza infection if they are infected before being vaccinated. Finally, the vaccine does not protect against many other viruses that prompt influenza-like symptoms (e.g., adenovirus, respiratory syncytial virus, rhinovirus, and parainfluenza viruses).

The 2004 Influenza Vaccine Shortage. In years prior to 2004

there have been shortages of influenza vaccine, but few in the recent past were as severe or as unexpected as the influenza vaccine shortage of fall 2004. After weeks of announcements regarding possible contamination of some lots of influenza vaccine, on Oct. 5, 2004, Chiron, the leading manufacturer of influenza vaccine for use in the United States, notified the CDC that none of its influenza vaccine for the 2004-2005 influenza season would be available for distribution in the United States. Because of the withdrawal of a previous manufacturer from the influenza vaccine market, Chiron's announcement left only one injectable influenza vaccine manufacturer (Aventis Pasteur) in the market for this year. MedImmune, the only company with an intranasal spray vaccine licensed for use here, had planned to produce just over 1 million doses. Because of the long vaccine production cycle for both injectable and intranasal influenza vaccine, a rapid, extensive expansion of production was not possible. Ironically, the season of this tremendous vaccine shortage was also the first season in which there was a full recommendation to expand influenza vaccination to healthy children 6-23 months of age. (Please see the section "New recommendations for pediatric vaccination" above.)

Because of the shortage, state and local health departments have worked in coordination to develop influenza vaccine distribution plans that guarantee vaccination of the most vulnerable populations. Most states, to support physician adherence to the triage system, have announced sanctions against health care professionals who knowingly give influenza vaccine to persons not included in the interim recommendations.[59]

The Role of the Emergency Department in Vaccinating Patients. Although not standard, there have been EDs that have vaccinated patients against influenza since 1992. A sample of ED visits obtained from National Hospital Ambulatory Medical Care Survey data indicated that, during the nine-year period from 1992-2000, approximately 247,000 influenza vaccinations were administered in the ED setting. In 77% of these cases, patients requested vaccination as their chief complaint. Clearly, because of the large number of chronically ill patients who seek care in the emergency setting, there is room for expansion of vaccination programs if resources permit.[60] The new pediatric recommendation raises the possibility of offering influenza vaccine within the context of pediatric emergency medicine settings as well.[61] Interesting, paramedics have implemented influenza immunization programs in a host of settings such as retail stores, community events, EMS stations, churches, and senior citizen complexes.[62]

Pandemic Influenza

There have been influenza pandemics in 1889, 1918-1919, 1957, 1968-1969, and 1977. In the 1918-1919 pandemic, approximately 21 million people died worldwide, with 549,000 deaths in the United States. Unlike the typical recent influenza epidemics, the Spanish Flu mainly killed young adults. This disease singlehandedly decreased life expectancy by 10 years. Pandemics such as those listed above follow antigenic shifts. New antigenic strains appear, against which the population has no immunity. The next pandemic is thought by many experts to be inevitable and overdue.

In August 1997, a young boy in Hong Kong died of a strain of influenza that previously had infected only birds. By December, 18 people in the region were directly infected with an avian influenza virus and, of these, 6 died.[63] The source of the outbreak was infected fowl. Epidemiologists feared that if this new influenza were to spread, not just from bird to human, but from human to human, a massive pandemic could follow. Attempts to produce a vaccine failed; the viruses killed the very cells in which scientists tried to grow them. Finally, not sure if the intervention would work, officials in Hong Kong ordered the slaughter and disposal of 1.5 million chickens. No cases of this strain of influenza have been identified since then, but there are no guarantees that it will not re-emerge.[64]

The WHO Influenza Surveillance Network serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. Since 1952, the WHO has maintained a network of centers worldwide—currently 112 such institutions in 83 countries. These centers submit new influenza isolates to four WHO collaborating centers, located in Australia, Japan, the United Kingdom, and the United States. One goal of the network is to detect new emerging influenza strains rapidly and alert public health officials if there is pandemic potential.[65]

Much attention has gone into the development of a detailed U.S. pandemic influenza plan, which has three main goals: 1) to limit the burden of disease; 2) to minimize social disruption (e.g., sick leave, hospitalization, and death); and 3) to reduce economic losses attributable to the pandemic. All communities would need to be involved in a coordinated response in the event of a pandemic.[66] To achieve these goals, priority areas to be addressed include:

- global and national influenza surveillance;
- vaccine development and production;
- vaccine use and coverage;
- chemoprophylaxis and therapy;
- guidelines for clinical care and health resources management;
- emergency preparedness; and
- research.

Conclusions

Influenza, a highly communicable infectious disease , is caused by influenza viruses. These viruses will never be eradicated because humans become susceptible again each time the viruses undergo an antigenic change. Influenza takes an enormous toll on humanity with respect to mortality, hospitalization, and medically attended illness. Despite the licensure of antiviral medications, immunization is the best control measure of influenza. Because patients eligible for influenza vaccine frequent EDs, health care providers working in this arena should either offer the vaccine or appropriately recommend and refer patients following current guidelines to sites at which the vaccine is obtainable.

Many experts believe another pandemic is quite possible if antigenic shift occurs and entire populations are without immunity to the new strain. A concerted worldwide effort to detect new strains as soon as they arise is in place, but at present there is no mechanism for the rapid mass production of relevant vaccine. Until difficulties in vaccine development and manufacturing can

be solved, pandemics of influenza will be a threat as long as there are humans to serve as virus incubators and launch pads. When such a pandemic does occur, the ED is sure to be a primary interface of the health care system with those infected. Thus, it essential that ED-based health care workers be familiar with influenza illness, modes of transmission, means of prevention, and therapeutic options. Even during typical yearly epidemics, the impact of influenza on the emergency department is not inconsequential. The drama of pandemics should not lead us to underestimate the destructive power influenza exhibits year after year in this country and throughout the world.

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Physician CME Questions

121. Which of the following is true regarding influenza epidemiology?
    A. The vast majority of deaths attributed to influenza and pneumonia occur in infants.
    B. Rates of hospitalization depend upon the predominating influenza virus strain, as well as host factors such as age, the presence of underlying medical conditions, and socioeconomic status.
    C. Seniors (persons 65 years of age or older) are the only age group with markedly elevated rates of influenza-associated hospitalization.
    D. For children, influenza is an uncommon cause of fevers, ear infections, and other upper respiratory infections that lead to medical visits.

122. Which of the following is true regarding influenza geographic and temporal distribution?

A. Influenza epidemics are an annual event and only one influenza virus can predominate each year.
B. Influenza does not circulate in warm tropical regions.
C. In the United States, peak influenza activity is from November through April, with the most frequent peaks occurring in January and February.
D. Because no peaks have been documented in March and April, the Advisory Committee on Immunization Practices recommends discontinuing vaccination efforts in December.

123. Which of the following is true regarding influenza infection host factors?
A. Seniors (persons 65 years of age or older) are the age group most often infected with influenza virus.
B. The children of middle income families are at greater risk for influenza infection than are those of low income families.
C. Middle income adults are at less risk for influenza infection than are low income adults.
D. There is no special susceptibility for any racial group or sex.

124. Which of the following is true regarding influenza viruses and their transmission?
A. There are three types of influenza viruses, A, B, and C, but A and B are the two types that cause epidemics in humans.
B. Influenza A, but not B, is known to have two surface glycoproteins that are important for immune recognition and categorization.
C. The segmented nature of the influenza genome allows for the frequent genetic reassortment that is considered the basis for the emergence of new subtypes, a process called antigenic drift.
D. The virus is shed in the stool and respiratory secretions of an infected person.

125. Which of the following is true regarding influenza disease and its complications?
A. As with hepatitis B, the incubation phase from exposure to shedding is 45 to 60 days.
B. A simple case of influenza has a slow, gradual onset and can include fever, headache, muscle aches, exhaustion, sore throat, runny or stuffy nose, and dry cough.
C. GI upset (nausea and vomiting) leading to dehydration is the chief complication of influenza.
D. Influenza has been implicated in cardiac disease and in neurologic symptoms including acute viral encephalitis, Reye's syndrome, and Guillain-Barré syndrome.

126. Which of the following is true regarding influenza diagnostic tests?
A. The purpose of making an early diagnosis of influenza is to prevent unnecessary use of bacterial antibiotics and maintain the option for use of antiviral therapy.
B. Samples should be collected within the first 14 days of illness.
C. Viral cultures are of very little value because current rapid antigen tests are more sensitive than culture.
D. All rapid antigen tests can detect influenza A and B viruses within 30 minutes to 1 hour.

127. Which of the following is true regarding influenza prevention?
A. The absence of evidence to support the assertion that good hand washing is important to influenza prevention has led some U.S. hospitals to discontinue this practice.
B. There is evidence that epidemics do not spread extensively unless schools are in session.
C. Airborne/TB precautions are important in hospitals if influenza the infecting agent.
D. Four antiviral medications are approved for preventing influenza A and B in children and adults.

128. Which of the following is true regarding influenza antivirals?
A. Two influenza antiviral medications are licensed for use in children younger than 1 year old.
B. To date, no strains of influenza virus have mutated enough to be resistant to any of the antiviral drugs.
C. Two of the antiviral medications, amantadine and rimantadine, are effective against influenza A and B.
D. Zanamivir and oseltamivir are both approved for treatment of influenza, and oseltamivir also is approved for prophylaxis in adults.

129. Which of the following is true regarding influenza vaccination?
A. For both inactivated and live influenza vaccines, anaphylactic-type allergic reaction to chicken eggs is a true contraindication to influenza vaccination.
B. For both inactivated and live influenza vaccines, pregnancy is a true contraindication to influenza vaccination.
C. After influenza vaccination, antibodies reach protective levels in approximately 3-5 days.
D. The most common side effect of influenza vaccination is influenza infection.

130. Which of the following is true regarding pandemic influenza?
A. While there have been influenza pandemics in the past, scientists believe the risk of another influenza pandemic in the modern era is extremely unlikely because of the production of highly effective vaccines.
B. The WHO Influenza Surveillance Network, which started in 2001, includes 112 institutions in 8 countries and four WHO collaborating centers, each located in Europe or the United States.
C. The U.S. pandemic influenza plan has three main goals: to limit the burden of disease, to minimize social disruption, and to limit antigenic shift.
D. Priority areas to be addressed by coordinated pandemic response plans include vaccine development, production, use and coverage, as well as chemoprophylaxis and therapy.

CME Answer Key

121. B; 122. C; 123. D; 124. A; 25. D; 126. A; 127. B; 128. D; 129. A; 130. D

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Influenza

Antiviral Medications: Trade Names, Routes of Administration, Precautions, and Toxicities

DRUG ROUTE	PRECAUTIONS*	TOXICITY
Chemically related to adamantanes, these therapies prevent penetration of virus into the host by inhibiting uncoating of influenza A. They are effective only against influenza type A (prophylaxis and treatment within 24-48 hours of symptom onset).		
Amantadine (Symmetrel) Oral	Elderly, seizure disorders, psychiatric illness, anticholinergic drugs Eczematoid dermatitis CNS stimulants Reduce dose in renal disease, liver disease. Effective only against type A	Among some healthy adults and children, side effects can include: CNS effects (nervousness, anxiety, difficulty concentrating, and lightheadedness) GI effects (nausea and loss of appetite) Among some other persons with long-term illnesses, more serious side effects, such as delirium, hallucinations, agitation, and seizures, can occur. Side effects usually diminish or disappear after 1 week.
Rimantadine (Flumadine) Oral	Reduce dose to 100 mg QD if severe renal or hepatic disease Cimetidine increases plasma levels Effective only against type A	CNS side effects happen more often among persons taking amantadine than among persons taking rimantadine.
Chemically related to neuraminidase inhibitors: Release of viruses from infected cells is decreased. They are effective against influenza A and B.		
Oseltamavir (Tamiflu) Oral	Decrease dose for CrCl < 30 mL/min Chronic cardiac or respiratory disease	Nausea, vomiting (may be less severe if taken with food)
Zanamivir (Relenza) Oral inhalation	Children older than 7 yrs Contraindication: COPD, asthma Not approved for influenza prophylaxis	This drug is inhaled; more side effects in those with asthma or other chronic lung disease (e.g., decreased respiratory function and bronchospasm). Other side effects reported by < 5% of those who used this drug are diarrhea, nausea, sinusitis, nasal infections, bronchitis, cough, headache, and dizziness.

* All four of these drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturer's package inserts).

Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis (from www.cdc.gov/flu/professionals/antiviralback.htm)

ANTIVIRAL AGENT	AGE GROUPS (YRS)				
	1-6	**7-9**	**10-12**	**13-64**	**≥ 65**
Amantadine*					
Treatment, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤ 100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤ 100 mg/day
Rimantadine¶					
Treatment, ** influenza A	NA††	NA	NA	100 mg twice daily§§§	100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in two divided doses†	5 mg/kg/day up to 150 mg in two divided doses†	100 mg twice daily§	100 mg twice daily§	100 mg/day¶¶
Zanamivir*†††**					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,§§§ influenza A and B	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel–tablet and syrup) and Geneva Pharms Tech (Amantadine HCL–capsule); USL Pharma (Amantadine HCL–capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL–syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine–tablet and syrup); Corepharma, Impax Labs (Rimantadine HCL–tablet), and Amide Pharmaceuticals (Rimantadine HCL–tablet). Zanamivir is manufactured by Glaxo SmithKline (Relenza–inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu–tablet). Information based on data published by the U.S. Food and Drug Administration at www.fda.gov.

* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤ 50 mL/min/1.73 m^2.

† 5 mg/kg of amantadine or rimantadine syrup = 1 tsp/22 lbs.

§ Children ≥ 10 years who weigh < 40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg/day.

¶ A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤ 10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

** Only approved by FDA for treatment among adults.

†† Not applicable.

§§ Rimantadine is approved by FDA for treatment among adults. However, certain experts in the management of influenza consider it appropriate also for treatment among children. (See American Academy of Pediatrics, 2000 Red Book.)

¶¶ Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥ 65 years if they experience possible side effects when taking 200 mg/day.

***Zanamivir is administered via inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.

††† Zanamivir is not approved for prophylaxis.

§§§ A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance < 30 mL/min.

¶¶¶ The dose recommendation for children who weigh ≤ 15 kg is 30 mg twice a day; for >15 to 23 kg children, the dose is 45 mg twice a day; for > 23 to 40 kg children, the dose is 60 mg twice a day; and for children > 40 kg, the dose is 75 mg twice a day.

People Who Should Receive Influenza Vaccine: Recommendations Specific to the 2004-2005 Season

AGE CRITERIA

People in these age groups should receive the vaccine even if healthy.

- Persons 65 years of age or older
- Persons 6-23 months of age

CHRONIC ILLNESS

Adults and children (> 5 months of age) with long-term health conditions including:

- Chronic respiratory disease, including asthma
- Chronic cardiac disease
- Metabolic disorders, such as diabetes mellitus
- Hemoglobinopathies, including sickle cell disease
- Immunosuppression due to disease or treatment
- Chronic renal failure

Children 6 months to 18 years of age on long-term aspirin therapy (due to the risk of Reye's syndrome)

Residents of nursing homes and long-term care facilities

PREGNANCY

Women who will be pregnant during influenza season

CONTACTS OF PEOPLE AT HIGH RISK (EXCEPT PREGNANT WOMEN AND HEALTHY CHILDREN 6-23 MONTHS OF AGE)

- Health care workers who have direct patient contact
- Household and out-of-home caregivers

* Close contacts of children birth to 5 months should be vaccinated.

Supplement to *Emergency Medicine Reports*, December 13, 2004: "Influenza and Influenza Vaccination 2004-2005." *Authors:* **Sharon G. Humiston, MD, MPH,** Associate Professor of Emergency Medicine and Pediatrics, Department of Emergency Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY; and **Dante A. Pappano, MD,** Senior Instructor of Emergency Medicine and Pediatrics, Department of Emergency Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY.

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Emergency Medicine Specialty Reports

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The Systems Approach to Error Reduction in the Emergency Department

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Few topics in medicine are as divisive as medical error. Since the publication of the Institute of Medicine's report on medical errors, an enormous public and private response has called for strict emphasis on safety in every aspect of patient care. The emergency department (ED) as an entity is a set-up for medical error. In addition to the acute and often life-threatening conditions that present at any given moment, the modern ED is challenged by overcrowded conditions, a lack of available and accurate medical information, often sparse on-call specialty physicians, and a chaotic environment filled with distractions. Despite the difficult environment in which emergeny physicians practice, patients deserve emergency medical care that is as error-free as possible.

In recent years, the analysis of complex system errors, such as medical errors occurring in the ED, has changed from simply labeling and punishing individuals to understanding the underlying systems that contribute to medical error. In this issue of Emergency Medicine Specialty Reports*, error in the ED and its contributing factors will be discussed, as well as steps to develop a culture of safety.*

—The Editor

Introduction

The Institute of Medicine (IOM) report, *To Err is Human*,[1] was the health care equivalent of the shot heard round the world. The provocative assertion that more than 1 million injuries and nearly 100,000 deaths occur annually in the U.S. health care system due to medical errors has created public outrage, professional debate, and governmental inquiry.[2-4] The ED appears to be at particular risk for the occurrence of medical errors. ED care is episodic and often marked by incomplete or absent past medical records, noisy physical environments, multiple distractions and interruptions,[5] time pressure, crowding, and disrupted staff sleep cycles, all superimposed upon a complex mixture of patient complaints, conditions, and severities.[6,7] Solutions to the problem of medical errors invariably invoke applications from the industrial quality movement and focus on topics such as human factors, cognitive information processing, and systems thinking.[8] This issue of *Emergency Medicine Specialty Reports* will review today's ED as a system under assault; examine data on safety within emergency medicine; provide a systems framework for assessing why errors occur and why well-intentioned efforts to improve error-prone processes too often fail; and suggest how best to intervene in the ED system to improve patient safety and outcome.

ED as a System Under Assault

Today's ED is a unique system in a dramatic state of flux. Between 1997 and 2000, there was a 2% decrease in the number of U.S. EDs, resulting in a 16% increase in the average number of visits in the remaining centers.[9] Increased volumes have exposed capacity problems that translate into longer waiting times for treatment and longer ED stays.[10] Interacting with increased visit volumes are an array of issues that include: expansion in scope of emergency medicine care with pressure for rapid yet definitive final diagnosis; utilization by non-emergency patients for primary care needs; increased survival rates from critical illnesses/injuries due to advances in emergency medical services (EMS); and prolonged ED stays when hospital inpatient units and intensive care unit (ICU) beds are filled.[11-15] ED crowding manifests in four ways that impact safety and quality of service delivery:[16,17] diversion, boarding, leaving before medical eval-

uation, and prolonged patient pain/discomfort/frustration.

Diversion (or bypass) occurs when the hospital lacks staffing or resources to accept additional emergency patients, and redirects the flow of ambulances to other medical facilities. Amazingly, 69% of the nation's EDs were on diversion at least one time during fiscal year (FY) 2001, and 10% were on diversionary status more than 20% of the time.[9] Boarding is defined as retaining a patient in the ED after the decision has been made to admit him or her to the hospital, due to the immediate unavailability of an appropriate inpatient bed. In FY2001, 90% of EDs reported boarding patients two or more hours while waiting for a bed or transfer to another facility; 20% reported they boarded patients on average for at least 8 hours.[9] Leaving before medical evaluation, also known as leaving without treatment (or LWOT), is most common among those persons triaged with apparently less severe conditions who are bumped by more emergent patients. Forty percent of the nation's EDs report that 1-3% of registered patients leave before the medical evaluation. Of concern is research indicating that nearly half of such LWOTs were later judged to have needed immediate medical attention,[9] and that approximately 10% of LWOTs in a large series subsequently were admitted to a hospital within one week of initial ED visit.[15] These findings lead Asplin et al[15] to suggest that LWOT rates may serve as a useful marker of adverse outcomes related to ED crowding.

For those who eventually are treated, extended waits and delays often lead to prolonged pain, discomfort, and frustration. This certainly complicates the eventual physician-patient interaction, and arguably relates to the findings from a national survey that ED patients are among the least satisfied hospital patients, with only 60% indicating they would recommend that ED to their family or friends.[18] While it has been common to dismiss delays in care as an organizational deficiency, recent reports suggest time-to-treatment as an important predictor of clinical outcome in the ED.[19] Notably, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has identified ED overcrowding as a source for more than half the reported sentinel event cases of patient death or permanent disability.[17]

The Scope and Nature of Errors in Emergency Medicine

While the exact magnitude of the problem of error in emergency medicine is unknown,[20] accumulating evidence suggests that the ED has a higher proportion of adverse events than any other hospital department.[21] In a recent study of nearly 2000 ED patient encounters, errors were detected in nearly 20% of the sample.[7] Most errors were minor, with resulting adverse events occurring in only 1 of every 300 patients. The highest proportion of reported errors (22%) related to diagnostic accuracy. Similar results emerged in a series of more than 30,000 patient hospitalizations.[21] While the ED accounted for only 3% of errors, 70% of these were judged to reflect missed diagnoses, making diagnostic errors among the most common mistakes that occur in the ED.[22,23] A recent review[24] demonstrated that ED physician and radiologist interpretation of radiographic images concurred approximately 90% of the time, though of those judged discrepantly, an alteration of treatment was indicated in up to 3% of cases. Failure to diagnose extremity fracture and identification of foreign body in a wound were the two most frequent causes of disagreement and malpractice action. Autopsy studies[25,26] indicate a 4-15% rate of major diagnostic disagreement between ED and post-mortem diagnoses, though not of such degree as to have prolonged or guaranteed survival. Improvements in diagnostic technologies have failed to significantly reduce these error rates.[27] Premature closure of search for alternate differential diagnostic possibilities, perhaps a reflection of perceived time-pressure under conditions of ED crowding, occurred in 91% of cases reviewed.[28]

Other ED activities with high numbers of errors were administrative procedures (such as errors in registration/admit/discharge or lost/mislabeled paperwork), medication delivery, communication, and environmental maintenance (like malfunctioning or misplaced equipment and supplies). No differences were found between categories of staff (i.e., physician, nurse, technician, or clerk), with a mean error-reporting rate of 5.5 errors per 100 hours worked. Based on these findings, the authors extrapolated that nationally more than 18 million errors and 360,000 adverse events occur each year in U.S. EDs.[28]

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Table 1. Summary of Recommended Definitions[30]

Error	Failure of a planned action to be completed as intended (error of execution) or the use of a wrong plan to achieve an aim (error of planning); the accumulation of errors results in accidents.
Patient safety	Freedom from accidental injury
Potential adverse event	Substandard care that could have resulted in injury (a near-miss)
Preventable adverse event	When an injury occurs as a result of substandard medical care
Quality medical care	The degree to which health services increase the likelihood of desired health outcomes and reflect current professional knowledge
System	A set of interdependent elements interacting to achieve a common aim

Lastly, considering the frequency of chest pain as the presenting chief complaint in ED, an interesting risk profile for such patients mistakenly discharged to home has been proposed.[29] Such a patient is likely to be a woman younger than age 55, to be non-white, to have reported shortness of breath as the chief symptom, and to have normal or equivocal electrocardiogram (ECG). Of their sample of 10,000 ED patients incorrectly sent home, 200 actually met criteria for acute myocardial infarction or unstable angina and had a higher risk-adjusted mortality rate than those patients who were admitted to hospital.

Defining Quality and Error

According to the IOM,[1] quality health care depends on three interacting domains: 1) safety, defined as freedom from accidental injury; 2) provision of services based on current medical evidence; and 3) meeting customer expectations. A consensus committee of the Society of Academic Emergency Medicine[30] recommended the adoption of IOM definitions to reach the goal of improving emergency medical care for patients. (*A summary appears in Table 1.*) Error is defined as the failure of a planned action to be completed as intended (error of execution) or the use of a wrong plan to achieve an aim (error of planning); the accumulation of errors results in accidents.[30-32] The committee further recommended that emergency medicine focus on identifying preventable and potential adverse events as the most direct way to improve the quality of emergency medical care.

A preventable adverse event is when an injury occurs as a result of substandard medical care. A potential adverse event involves substandard care that could have resulted in injury (a near-miss). Experience in many high-risk industries indicates that significant numbers of adverse events can be prevented through the analysis of errors and the factors that contribute to and maintain error-prone processes.[33] Leape and colleagues[34] provide a useful categorization of the types of errors encountered in medical care. (*See Table 2.*)

The Systems Approach to Error Reduction

Two general approaches to understanding medical errors are found in the literature.[6,32] The person approach focuses on the so-called sharp end of the intervention probe: the clinical providers on the front line providing patient care. Focus is on the health care worker's mental and physical state at the time that the unsafe act occurred. Berwick[35] argues that too often efforts at quality improvement in health care boil down to punitive attempts to remove the bad apples that produced the error. Such an approach sets a climate of fear, resistance, demoralization, and secrecy that impedes meaningful change.

Rather, most problems are built right into the complex care systems and procedures. Understanding and simplifying complex processes that produce errors from well-meaning, well-trained professionals is the hallmark of the systems approach that typifies the modern quality movement.[36] A system is a set of interdependent elements interacting to achieve a common aim,[30] and the systems approach focuses on the blunt end latent conditions that often pre-date the problematic patient care episode. Facility design, equipment selection (or non-selection), staff hiring, or work shift assignment decisions made in the past can return to importantly shape current outcome. Within the systems approach, Reason[32] suggests that most care systems contain error but this gets distributed and masked by multiple process layers. Only when the holes in the system align does an adverse event manifest. Under this Swiss cheese model, root cause analysis frequently reveals five to 10 factors in interaction. None of these alone is sufficient to produce the poor outcome; all are necessary in combination to produce the adverse event.[32,37] In one review of medical malpractice cases,[38] an average of nine teamwork failures were reported per case. Thus, Leape[2] points out that medical errors rarely are due to a single clinician's personal failings, inadequacies, and/or carelessness. Faulty delivery systems (the blunt end) typically are at play and should be the focus of change. In an organization marked by a true commitment to error reduction and patient safety, there is a non-punitive system for error reporting, cataloguing, and analysis in an ongoing feedback loop.

Why Quality Initiatives in Health Care Fail

While the notion of importing best safety practices from other industries into health care is attractive, it must be acknowledged that the systematic yield over the past three decades has been fairly meager.[39] Leape and Berwick, the leading advocates for such learning exchange, estimate that health care remains at least a decade behind other major industries in reducing process errors and defects. What factors lead to these disappointing conclusions?

First, conducting process change in the ED is like trying to change the fan belt on your car while the engine is still running. Due to the 24/7/365 operating hours, and relative lack of other

Table 2. Types of Medical Errors[34]

DIAGNOSTIC
- Error or delay in diagnosis
- Failure to employ indicated tests
- Use of outmoded tests or therapy
- Failure to act on results of monitoring or testing

TREATMENT
- Error in the performance of an operation, procedure, or test
- Error in administering the treatment
- Error in the dose or method of using a drug
- Avoidable delay in treatment or in responding to an abnormal test
- Inappropriate (non-indicated) care

PREVENTIVE
- Failure to provide prophylactic treatment
- Inadequate monitoring or follow-up of treatment

OTHER
- Failure of communication
- Equipment failure
- Other system failure

redundant venues for care, EDs never really are taken off-line for retooling or repair. This is unique among high-risk industries. Aviation, manufacturing, and military organizations all regularly take operations centers out of service, typically on a pre-scheduled basis, to allow mechanical upgrades and staff education or rest and relaxation. Relatedly, benchmark safety industries have strict schedules for equipment refurbishment or replacement in a proactive approach to avoid system failure. This is not true in health care, where devices and infrastructure often are pushed long past their expected useful lives unless technology creep makes them unacceptable for use. With one-third of U.S. hospitals reporting negative total financial margins (i.e., they are paid less than the cost of delivering care)[40] and six times as many hospitals receiving bond rating downgrades vs. upgrades in 2001,[41] it appears unlikely that these trends will change any time soon. Liability concerns, information technology infrastructure limitations, and payment systems also are suggested to be unique impediments in health care.[42]

It also has been suggested that a relative void in emergency physician involvement in hospital quality initiatives (due to lack of time, interest, risk concerns, or lack of training/knowledge of how to participate) is a crucial barrier to change.[39,42] As Leape[2] has stated, in a culture of safety, errors are excusable but ignoring them is not. Hence, engagement by all ED staff in error reduction and providing them the context and tools for error reduction, are vital.

The Furthering Limitations of Human Cognition

Additional insights into the causes of systemic errors in the ED come from studies of human information processing. Despite the potential of truly incredible intellectual achievements, it must be admitted that the human brain is a system of limited cognitive processing capacity prone to a host of predictable judgment defects.[43] Indeed, a primary conclusion of the extant medical error literature is that human information processing errors contribute to a large proportion of preventable adverse events.[1,22,27,32,33,44-47]

To deal with complex daily lives, the human brain assigns priorities to both incoming information and outgoing behavioral responses, and suppresses (or automatizes) conscious processing of trivial or redundant primary sensory inputs.[48] People rely on intuitive judgment heuristics, or rules of thumb, to deal with the routines of daily life. (*See Table 3.*) Most of the time, these simplified automatic decision templates save time and yield correct results. However, the ED requirement of integrating complex interdisciplinary data at an escalating pace of production can overwhelm these heuristics. As a result, clinicians may overdiagnose impairment (labeling heuristic); attribute excessive significance to trivial predictors (availability heuristic); ignore statistical realities (regression toward the mean) or base rates; be unduly influenced by early features of the interview (anchoring effects); and/or discount or miss disconfirming evidence (representativeness heuristic and confirmatory bias).[44,45,49]

Despite the extensive literature on these pitfalls of human information processing, even highly trained physicians tend to overestimate the accuracy of their clinical predictions while remaining extremely confident about these predictions. Consequently, salient alternative sources of information may be overlooked or downplayed.[50,51]

Another class of influential yet frequently dismissed cognitive factors have been labeled "mechanics of judgment."[52] Such factors as "serial order effects, position effects, contrast effects, and many types of anchoring effects … should seem particularly implausible as reasons for liking or disliking an object." Nonetheless, these mechanics of judgment may operate outside of awareness to importantly shape acceptance or rejection of important parameters like: differential diagnosis alternatives, diagnostic test selection, treatment alternatives, medication dosages, referral to consulting specialist physicians, decision to admit or discharge, use of physical or chemical restraint, incorporation of collateral others as sources of information, and follow-up referral planning. What is the impact of mechanics of judgment on the individualized care plan of the last patient treated within an 8- or 12-hour shift as opposed to the first?

Compounding these normal limitations of human cognition, the ED environment poses additional challenges to error-free performance in the forms of fatigue, workload, cognitive overload, disrupted interpersonal communication, incomplete patient information, and even anxiety about risk of personal harm from exposure to pathogens or violence.[33] Physicians tend to overestimate their ability to perform under such adverse but common pressures.[53] These issues may be even more pronounced in emergency medicine due to work patterns marked by rotating day/night work shifts. It has been shown that such shifts impact sleep-related cognitive recovery due to circadian rhythm disruption, manifesting in reduced information processing performance in ED physicians. This is most pronounced in visual memory, which may have clinical rele-

Table 3. Common Judgment Heuristics and Limitations

HEURISTIC	LIMITATION
Anchoring	Serial order or position effects that alter acceptance or rejection of important treatment parameters
Availability	Attributing excessive significance to trivial, though common and easily identified, predictors
Labeling	Extreme and rapid data reduction leading to over- or mis-diagnosis
Neglect of base rates	Misinterpretation of uniqueness or significance of a clinical finding
Regression toward the mean	Overinterpretation of performance fluctuations as indicative of clinical change
Representativeness	Downplaying or ignoring evidence that disconfirms prevailing diagnosis or classification
Confirmatory bias	Perceiving only those data that confirm prevailing diagnosis or classification

vance for interpretation of ECG and diagnostic imaging studies.[54]

The key insight from the systems approach is that ED care processes must be built to be resilient despite these known limitations of human information processing. Safety and error-checking must be built into all levels of the care process so that the risk of the potential holes in the system lining up are significantly minimized.

Toward a Culture of Safety

Lasting, reliable, and capable patient care processes that are error resistant likely will come only with the development of a culture of safety within the ED.[55] Organizational culture can be defined as a pattern of basic assumptions that is developed by a given group over time as it successfully adapts to internal and external threats, and that is taught to new group members as the correct way to adapt in the future.[56] Cultural beliefs and values manifest through observable actions and artifacts (i.e., insignia, style of dress, etc.). The development of a safety culture requires activities that promote shared values, language, and artifacts that continually assert that safety is the top priority. Frequent communication of safety goals, safety success stories, and honest discussion of safety concerns will help to move individuals and teams toward this endpoint.

A Tool Box of Recommended Actions

Woolf has stated, "nothing is more contrary to the ethos of medicine than harming individuals who search for care and compassion."[57] That many individuals are harmed while seeking help in EDs underscores the need for immediate action that takes a systems view of the care process. Increased understanding of the truly human factors that can facilitate or derail quality improvement initiatives is needed. Emergency physicians must play an active leadership role in driving an accountability-based safety culture in which every error is our error.[19] Blind faith in technology will be faith unrewarded. As has been learned in many industries, technology can accelerate quality and productivity gains, but it cannot create them.[58] Rather technology must stem from and reflect the core mission and vision of the organization, and that mission/vision must be an enlivened focus on safety.

Stemming from this review, the following items constitute a collective tool box for use in this quest to achieve meaningful error reduction in the ED:

• Develop ED physician leaders who personally are committed to making a reality the IOM goal of reducing medical errors by 50% during the next five years; allocate needed time, training, and resources to ensure that they can maintain focus on key safety goals.

• Promote movement to a culture of safety marked by transparency of safety successes and lapses to promote team learning and process improvement. While errors may be excusable, denying or ignoring them is not.

• Identify and address motivational and/or knowledge features within individuals or teams to overcome resistance to change.

• Consider ergonomic factors (i.e., shift schedules, ambient lighting, visibility and proper location of needed equipment, standardization in device designs and manufacturers of ED equipment)[59] and aggressively address any factors plausibly related to safety risk in the department.

• Build in cognitive forcing strategies such as clinical practice guidelines (CPGs),[60] reminders, and checklists for charting and prescriptions[61] to reduce risk of cognitive errors. Such strategies are based on the premise that proper cueing can effectively prompt needed action. Recognition memory is more reliable then free recall memory, thus order sets or documentation templates that push memory triggers at staff reduce the likelihood of errors of omission.

• Invest significantly in staff training and education. More so than almost any other high-risk industry, those in health care assume that staff know how to operate, maintain, and/or troubleshoot essential equipment, or respond to extraordinary events in some unified predictable way. Health care practitioners need to be more stringent about competency check-offs that ensure that personnel have been drilled to perform needed actions by habit, not by luck. Ongoing training must be built into the work schedule, and participation enforced, to achieve meaningful error reduction.

• Seek alliances with other disciplines to provide checks and balances (as with radiologist over-reads of ED diagnostic studies and verbal order read backs to ensure accurate comprehension) and to act as naïve savants when evaluating the most trusted ED processes for potential defects.

• Employ measurement to realistically portray ED perform-

ance. Such measurement continually must be presented to all ED staff, and is a prime component of the Plan-Do-Study-Act (PDSA) rapid-cycle improvement model.[62] Statistical process control (SPC)[63] is a robust yet practical analytical and data presentation technique that is well matched to the ED environment.

• Continually seek to reduce unnecessary ED waits and delays through use of PDSA and SPC techniques, and thereby reduce potential for pain, suffering, frustration, and medical complications in the patients served.

• Seek benchmark information on best practices, and deploy rapid-cycle change methods to aggressively incorporate best ideas into the department. The recent Urgent Matters[64] and JCAHO Core Measures[65] initiatives offer ED-relevant guidance on best practices to improve the efficiency and effectiveness of care.

• Deploy information technology to extend and support, though not create, positive process change.[58] Personal wireless phone devices can increase point-to-point communication within the ED while simultaneously reducing ambient distracting background noise. Current-generation computerized/electronic medical record (EMR) systems can provide vital access to historical and current patient information to facilitate decision-making. Next-generation EMRs will provide safety surveillance capabilities that alert providers to potential adverse drug interactions or other patient-specific safety alarms.

• Conduct analyses of errors without blame or coercion while reinforcing the expectation of accountability by all participants.

• Work to move all stakeholders to the highest level of perceived accountability, where safety is everyone's job and it is a shared responsibility.

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Physician CME Questions

To participate in this CME program, read the article and then answer the questions below. Review any material related to missed questions. ***In order to receive credit for this activity, you must complete the evaluation form enclosed with this issue.*** *When your completed form has been received, a certificate will be mailed to you.*

1. The person approach to error reduction focuses on:
   A. staff hiring or shift assignment decisions.
   B. the clinical providers giving patient care.
   C. latent conditions that pre-date a problematic patient care episode.
   D. facility design.

2. The systems approach to error reduction focuses on:
   A. the blunt end of intervention.
   B. latent conditions that pre-date a problematic patient care

Emergency Medicine Specialty Reports

CME Objectives

Upon completing this program, participants should be able to:

- understand medical error prevention in the emergency department setting;
- identify factors involved in medical errors; and
- identify methods to help reduce medical errors;

episode.

C. factors such as facility design, equipment selection, staff hiring, and shift assignments.

D. All of the above

3. Human information processing errors contribute to a large proportion of preventable adverse events.
   A. True
   B. False

4. The limitation of confirmatory bias is:
   A. extreme and rapid data reduction leading to over- or misdiagnosis.
   B. attributing excessive significance to trivial predictors.
   C. perceiving only those data that confirm prevailing diagnosis or classification.
   D. overinterpretation of performance fluctuations as indicative of clinical change.

5. Which of the following factors contribute to the difficulty of conducting process change in the ED?
   A. Continuous operating hours
   B. Lack of other redundant venues for care
   C. Liability concerns
   D. Information technology infrastructure limitations
   E. All of the above

6. Steps to promote an error free culture in the ED include:
   A. using clinical practice guidelines (CPGs) reminders and check-lists for charting.
   B. investing in staff training and education.
   C. reducing ED waits and delays.
   D. benchmarking best practices.
   E. All of the above

7. The most common source of error in the ED is:
   A. medication delivery.
   B. malfunctioning equipment.
   C. diagnostic errors.
   D. administrative procedures.

In Future Issues:

Delivering Bad News

CME Answer Key

1. B
2. D
3. A
4. C
5. E
6. E
7. C