Influenza: New Insights Into an Old Disease

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In the United States each year, influenza accounts for an estimated 20,000 to 40,000 deaths, nearly 300,000 hospitalizations, and millions of days lost from work. In the past few years, there has been an explosion of information in the medical literature related to influenza. This paper reviews these latest developments that enhance our understanding of influenza epidemiology and virology and expand our prevention and treatment options. Diminishing the impact of influenza in this country will require continued intense surveillance, increased use of influenza vaccine, and the availability of alternative vaccines and antivirals with the potential for broader protection against shift-and-drift strains of influenza.

Introduction

Influenza is a highly contagious disease that has the ability to cause illness in people of all ages. It has been termed "the most underrated pathogen in the developing world" [1]. A recent outbreak of an avian influenza virus that was highly virulent in humans has reminded us that influenza virus remains a formidable human adversary.

Advances in our knowledge of viral structure and function and host interaction have led to new insights into past influenza epidemics and to the development of new antiviral compounds and vaccines. Rigorous population-based studies and randomized controlled trials have delineated the impact of influenza on various populations and the efficacy, effectiveness, and cost effectiveness of preventive and treatment options.

Influenza Virology and Pandemic Influenza

Three major classes of influenza virus are recognized: A, B, and C. Influenza C is a relatively minor cause of respiratory illness, but influenza A and B strains are major causes of morbidity and mortality. Each tends to occur in well-cir-

cumscribed epidemics during the winter. The severity of influenza epidemics is a function of viral characteristics and underlying immunity in a population. Influenza viruses are orthomyxoviruses that possess a segmented RNA genome. This has allowed periodic introduction into the human pool of viral hemagglutinins or neuraminidases from animal, usually avian, sources, leading to a novel surface glycoprotein against which large segments of the human population have no antibody. This antigenic shift in the glycoprotein structure, coupled with the ability of a virus to replicate and spread rapidly in humans, has led to pandemics of influenza, of which the Asian influenza strain of 1957 and the Hong Kong influenza strain of 1968 are the most recent examples. Variability on a yearly or biyearly basis is afforded by point mutations in the hemagglutinin structure that alter antibody recognition sufficiently to allow epidemic spread of so-called drift strains.

The 1918 influenza pandemic

Although epidemics of influenza have been recognized for centuries, the worst pandemic in recorded history occurred in 1918-1919. The 1918 influenza pandemic was remarkable for the total estimated 20 to 40 million deaths it caused, as well as its extremely high mortality rate among young, healthy adults [2]. The devastating impact of this pandemic has always stimulated interest in and speculation about the influenza strain responsible for the outbreak, which occurred more than a decade before influenza virus was isolated. Serologic studies have long suggested that the virus was of the H1N1 type, but the first confirmation of this came from a series of studies conducted at the Armed Forces Institute of Pathology over the past several years [3,4••]. Using preserved autopsy material from two United States servicemen killed in the 1918 pandemic and one frozen sample obtained by in situ biopsy of the lung of a victim buried in permafrost since 1918, these researchers isolated and sequenced influenza virus RNA. The sequences were consistent with a novel H1N1 influenza virus A. Phylogenetic analyses suggest that the 1918 virus hemagglutinin gene is most closely related to the human and swine influenza strains of the 1930s. The authors postulate that the virus did not pass directly from an avian source to its pandemic form but rather spent some unknown amount of time adapting in a mammalian host [3,4••,5]. The alternative hypothesis, that this virus may be more closely related to avian species of that time

period, cannot be tested, because there are no known samples of avian H1 viruses from 1918 [6].

Avian influenza

In general, viruses with more avian characteristics, although more immunogenic in humans, are also thought to be less transmissible to humans owing to the species specificity of the influenza receptor. Thus, it had been generally believed that viruses cross the avian-human species barrier after prior adaptation in another mammalian species, usually swine. This concept was challenged in 1997, when the first documented outbreak of human respiratory disease caused by avian influenza A (H5N1) viruses occurred in Hong Kong [7•,8]. In predominantly young, healthy patients, the avian influenza A H5N1 virus caused a human influenza-like respiratory illness with a high rate of complications. Of a total of 18 human cases, six were fatal [9]. A temporal association between exposure to live poultry and subsequent clinical H5N1 illness, and between the mass slaughter of poultry in Hong Kong and the end of new cases in humans, suggested that transmission occurred directly from birds to humans [10,11]. A subsequent cohort study, however, identified H5-antibody-positive household contacts, suggesting that human-to-human transmission may have occurred [12]. In 1999, human infection with another avian influenza, H9N2, was reported to cause mild illness in two children [13]. With 15 known hemagglutinin subtypes and nine known neuraminidases, avian species provide an extensive reservoir of influenza viruses that are novel to man. The devastation caused by the influenza pandemic of 1918 and the recent experience in Hong Kong are alarming and remind us that the threat of a future pandemic is real. Global influenzavirus surveillance in humans and animals and the development of control strategies are essential components of pandemic preparedness [14].

Interpandemic Influenza

Even in interpandemic years, the impact of influenza on society is substantial [15]. Influenza is spread primarily by respiratory droplet. During epidemics, attack rates may exceed 40% in preschool children and 30% in school-aged children. In adults, attack rates average 10% to 20%. Children play an important role in the spread of influenza, with school-aged children being the main introducers of influenza into households. The arrival of influenza in a community can be appreciated by increased school absenteeism and an influx of people with febrile respiratory illness with a major systemic component into healthcare facilities. Each year in this country, influenza accounts for excess outpatient visits, excess antibiotic prescriptions, and millions of days lost from school and work. Most important, epidemics are reflected by excess morbidity and mortality. During influenza season, there are approximately 300,000 excess hospitalizations and between 20,000 and 40,000 excess deaths, with mortality occurring primarily in the elderly [15–17].

Although mortality statistics are sensitive indicators of the impact of influenza, they underestimate the overall health impact of influenza on other populations [17]. A series of recent articles more accurately define the serious consequences of influenza in several populations, including children and pregnant women [18•,19•,20].

Influenza morbidity in children

Acute respiratory disease is the most common reason for outpatient visits and hospitalizations among children in the United States. Although respiratory syncytial virus is recognized as the most frequent cause of lower respiratory tract disease leading to hospitalization in infants and young children, two recent retrospective cohort studies demonstrate that influenza can also be a serious disease in this age group [18•,19•]. In these two studies of healthy children with differing socioeconomic backgrounds (one group enrolled in either one of two West Coast health maintenance organizations and one group enrolled in Tennessee Medicaid), the authors showed that children aged younger than 2 years had hospitalization rates attributable to influenza that were comparable to rates in high-risk adults [18•,19•]. Furthermore, in the Tennessee Medicaid study, for every 100 children aged younger than 15 years, there was an average of six to 15 outpatient visits and three to nine antibiotic courses attributable to influenza annually. Influenza accounted for 10% to 30% of the winter excess of antibiotic prescriptions in this population. These authors conclude that young children suffer substantial morbidity from influenza, and improved influenza prevention in children is needed.

Influenza morbidity in pregnant women

Although influenza-associated excess mortality among pregnant women was documented during the 1918–1919 and 1957–1958 pandemics, it has not been documented during interpandemic periods. Case reports and papers on small case series published since that time have described women in the third trimester and early puerperium who died from influenza-related complications, possibly related to the physiologic or immunologic changes that accompany pregnancy. A recent large, retrospective cohort study of all women aged 15 to 44 years enrolled in Tennessee Medicaid during 17 interpandemic influenza seasons reported that otherwise low-risk women in the first trimester of pregnancy or first 6 months postpartum had a risk of influenza-related hospitalizations similar to that of nonpregnant women. Otherwise low-risk women in the second or third trimester of pregnancy experienced approximately 14 and 23 excess acute cardiopulmonary hospitalizations, respectively, per 10,000 women in an average influenza season, however—a rate comparable to that seen in other high-risk groups for whom vaccine is recommended [20]. There were no deaths from acute cardiopulmonary causes during influenza season among pregnant women in this study. Using data from this study, the researchers estimated that an average of one to

two hospitalizations could be prevented for every 1000 pregnant women vaccinated, and pregnant women are now among the high-risk groups targeted for influenza immunization (Table 1).

Influenza Vaccine

Inactivated influenza vaccines are prepared that reflect currently circulating strains of influenza A and B. Vaccination in young adults is 70% to 90% efficacious in preventing clinical illness caused by the same or a closely related influenza virus. Although this efficacy is considerably diminished in the elderly, vaccination reduces the number of hospitalizations and mortality in this population and is cost effective [21]. Available vaccines are highly purified, and in multiple randomized, double-blind trials, the only significant side effect associated with vaccination was arm soreness. Egg allergy is the only contraindication to vaccination. Because influenza vaccine contains only noninfectious viruses, it cannot cause influenza. Although the 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome, recent influenza vaccination programs (for the seasons of 1992–1993 and 1993–1994) were associated with only one or two additional cases of the Guillain-Barré syndrome per 1 million vaccinated persons [22,23].

Recommendations for use

The approach to influenza control in this country has been the administration of inactivated influenza vaccines to persons who are at high risk for influenza-related complications, or to those persons who can transmit the disease to persons at high risk [24••] (Table 1). Although almost 70% of people older than the age of 65 years in the United States have received the influenza vaccine in recent years, only an estimated 30% to 40% of younger high-risk persons and healthcare workers receive the vaccine [25••]. Clearly, more effective strategies for insuring better influenza vaccine coverage of these latter groups are needed.

Influenza vaccine and HIV infection

Although limited information exists regarding the incidence of influenza and vaccine efficacy in HIV-infected persons, recent evidence suggests that the benefits of vaccination outweigh the risk. Early reports of detrimental effects of influenza immunization on viral load measurements have not proven to be clinically relevant. Several case reports suggest that influenza symptoms are prolonged and the risk for complications from influenza increased for some HIV-infected persons. A recent retrospective study of young and middle-aged women enrolled in the Tennessee Medicaid program found that women with HIV infection had a higher risk of influenza-attributable hospitalizations than women with chronic heart or lung diseases; the estimates were as high as 30 hospitalizations for every 1000 HIV-infected women [16]. In a recent

Table 1. Target groups for vaccination

Persons at high risk for influenzavirus-related complications
Persons aged 50 years or older
Residents of nursing homes and other chronic-care facilities housing persons of any age with chronic medical conditions
Adults and children with chronic disorders of the pulmonary or cardiovascular systems, including asthma
Adults and children who have required regular medical follow-up or hospitalization during the preceding year owing to chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression
Children and teenagers (aged 6 months to 18 years) who are receiving long-term aspirin therapy and may be at risk for developing Reye's syndrome after influenza
Women who will be in the second or third trimester of pregnancy during the influenza season
Persons able to transmit influenzavirus to those at high risk
Physicians, nurses, and other personnel in both hospital and outpatient-care settings
Employees of nursing homes and chronic-care facilities having contact with patients or residents
Employees of assisted living and other residences for persons in high-risk groups
Persons who provide home care to persons in high-risk groups
Household members (including children) of persons in high-risk groups
Other groups to consider
Persons infected with HIV
Breastfeeding mothers
Travelers
General population

*Recommendations of the Advisory Committee on Immunization Practices for the Use of Influenza Vaccine.

randomized, double-blind, placebo-controlled trial of predominantly young men with HIV infection, those who received influenza vaccine had modest serologic responses. The vaccine was highly clinically effective, however, with 10 placebo recipients and no vaccine recipients having symptomatic laboratory-confirmed influenza A [26].

Limitations

Although achieving control of influenza through vaccination is a laudable goal, it is problematic. As previously discussed, the influenza virus is capable of antigenic change, requiring that a new vaccine be developed yearly that best matches that year's predicted influenza strain. Likewise, it is impossible to predict before any given influenza season whether it will be a "mild" or "severe" year (Fig. 1). For these reasons, comprehensive influenza vaccine campaigns must occur each year. Patients, their physicians, and insurance providers must understand that one must look at the clinical and cost effectiveness of influenza vaccination over a range of years, never over a single year. This variability is one reason for the often-contradictory findings in cost-

Figure 1. Excess acute cardiopulmonary events (hospitalizations and deaths) during influenza season by year in low- (•) and high- (■) risk women aged 15 to 64 years enrolled in the Tennessee Medicaid Program 1974 to 1993. This graph demonstrates the variable impact of influenza in this cohort from year to year. Strain of virus is shown for each season. (Adapted from Neuzil *et al.* [16].)

effectiveness studies of the use of influenza vaccine in healthy adults and healthcare workers [27–29]. Clearly, the benefits of influenza vaccine will be greatest in a season marked by high attack rates and a good vaccine match. Additionally, we must recognize that the vaccination policy in this country is designed to protect individuals from the complications of influenza. If the goal is to interrupt transmission, then vaccination must be directed toward those members of the community, predominantly school-aged children, who are integral to the dissemination of the virus.

Live and attenuated intranasal vaccines

Several ways to overcome the aforementioned limitations of our current method of influenza control include better methods of predicting future circulating influenza strains [30], the use and development of vaccines that will provide broader protection against drift-and-shift strains, and administering vaccine to a larger segment of the population.

Intranasally administered, cold-adapted, live attenuated vaccines have the potential advantage of inducing a broad mucosal and systemic immune response [31]. Their ease of administration and the acceptability of an intranasal route of administration may serve to increase the total number of influenza vaccine recipients. In a recent study of children aged 15 to 71 months, intranasal vaccine was 93% effective in preventing culture-confirmed influenza. The vaccinated children had significantly fewer febrile episodes, including 30% fewer episodes of febrile otitis media [32••]. In a study of healthy adults younger than 65 years of age, Nichol *et al.* [33] showed that intranasally administered live attenuated vaccines significantly reduced the numbers of severe febrile illnesses and febrile upper respiratory tract illnesses, and that recipients of these vaccines missed fewer days of work and had fewer healthcare pro-

vider visits than placebo recipients. These results are no more impressive than those seen with inactivated vaccine in healthy adults. In a 5-year study, it was found that the trivalent inactivated vaccine and bivalent live attenuated vaccine were approximately equivalent in terms of effectiveness [34]. During the period of the Nichol study, however, the circulating virus demonstrated significant drift from the vaccine virus, suggesting the possibility of broader immunity [33]. These vaccines may be licensed by the 2001–2002 winter season.

Antiviral Agents

Perhaps the most publicized of the many advances related to influenza in the past year has been the development and Food and Drug Administration approval of the first new class of antiviral drugs in 30 years, the neuraminidase inhibitors. The neuraminidase inhibitors are the result of computer-assisted drug design based on the crystal structure of the neuraminidase target protein [35]. Inhibition of neuraminidase enzymatic action causes virus particles to aggregate at the cell surface and with each other. The enzyme-active site is highly conserved across influenza A and B viruses.

Before 1999, amantadine and rimantadine, with efficacy against influenza A but not influenza B, were the only drugs available for the prevention and treatment of influenza and were not widely used. These agents are 70% to 90% effective in preventing disease in adults and children when administered prophylactically throughout the influenza season. Treatment with amantadine and rimantadine shortens the duration of clinical influenza illness by approximately 1 day [36]. The disadvantages of these agents include the rapid development of viral resistance, inactivity against influenza B, and neurologic side effects.

Table 2. Antiviral agents for the prevention and treatment of influenza virus in adults

Drug	Mechanism of action	Major side effects	FDA indication	Dose	Dose reductions
Amantadine	Interferes with M2 protein (influenza A only)	>10% CNS-related (nervousness, anxiety, difficulty concentrating)	Prevention and treatment	100 mg twice daily, oral	Elderly persons, those with renal impairment*
Rimantadine	Interferes with M2 protein (influenza A only)	<10% CNS-related (similar to above)	Prevention and treatment	100 mg twice daily, oral	Elderly persons, those with severe renal impairment†
Zanamivir	Inhibits neuraminidase (influenza A and B)	Bronchospasm in patients with asthma (unknown incidence)	Treatment	10 mg twice daily for 5 days, inhaled	
Oseltamivir	Inhibits neuraminidase (influenza A and B)	>10% gastrointestinal (nausea, vomiting)	Treatment	75 mg twice daily for 5 days, inhaled	Those with renal impairment‡

*Creatinine clearance ≤ 50 mL/min/1.73m².
†Creatinine clearance ≤ 10 mL/min/1.73m².
‡Creatinine clearance ≤ 30 mL/min/1.73m².
CNS—central nervous system; FDA—Food and Drug Administration.

Neuraminidase inhibitors

Zanamivir and oseltamivir are the neuraminidase inhibitors recently licensed for the treatment of influenza A and B infection. Although there are no studies comparing the two neuraminidase inhibitors with amantadine or rimantadine, theoretical advantages of neuraminidase inhibitors over the latter agents include efficacy against type B viruses, rare development of resistance, and a different side effect profile.

Three large, randomized, placebo-controlled trials examining the efficacy and safety of zanamivir in the treatment of influenza virus infections have been published to date [37,38,39]. Participants were generally young (mean ages 30 to 38 years) and healthy. Zanamivir reduced the severity and duration of influenza illness by a day or more when given within 48 hours of onset of symptoms. More substantial reductions in clinical illness were seen in those patients who received therapy within 30 hours of onset of symptoms, in those patients who presented with febrile illness, and in the small subset of patients with underlying high-risk conditions, predominantly respiratory disease. In this high-risk subset, zanamivir significantly reduced pulmonary complications from 46% to 14% and associated antibiotic use from 38% to 14% [38]. Viral titers of nasal washings in the groups given inhaled zanamivir were significantly lower than those in the placebo group, suggesting the possibility for reduced virus transmission [37].

In a randomized, placebo-controlled trial of treatment of experimental influenza in young, healthy adults, oral oseltamivir reduced viral shedding and significantly reduced illness burden and biochemical markers of inflammation. As compared with placebo recipients, fewer oseltamivir recipients used acetaminophen [40]. As yet

unpublished studies using oseltamivir for the treatment of naturally acquired influenza corroborate these results.

It is difficult to know how the clinical efficacy of these agents will translate into community effectiveness. Rapid, site-based diagnostic tests are not widely available, and therefore these drugs will need to be given rapidly after symptom onset, based primarily on clinical criteria. In the clinical trials, 60% to 70% of patients had laboratory-confirmed influenza, suggesting that in clinical practice, many people with diseases other than influenza will be exposed to these agents. The cumulative experience with these drugs remains limited; thus, postmarketing surveillance for less common side effects is essential. Finally, no studies are available comparing the two neuraminidase inhibitors with one another or with amantadine and rimantadine. The choice of which drug to use in any given patient will likely be based on side-effect profile, cost, and ease of administration (Table 2).

The most important role for neuraminidase inhibitors may be as an adjunct to immunization in preventing influenza during years when the vaccine strain is a poor match for the circulating influenza strain or during nursing home or institutional outbreaks. Although both agents have shown efficacy in this regard, neither drug has yet been approved by the Food and Drug Administration for this indication [41–43].

Conclusions

Influenza remains a major cause of morbidity and mortality across a broad segment of the population. The mutability and zoonotic reservoir of the virus challenge our ability to eradicate this infection. Although inactivated influenza

vaccine should remain the cornerstone of influenza control programs, new vaccines and antivirals offer alternative methods of prevention with the potential for broader protection against shift-and-drift strains of influenza virus.

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