disease prevention news

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Treatment and Chemoprophylaxis of Influenza

Influenza viruses circulate every winter and during most winters cause substantial morbidity and mortality. Annual influenza vaccination is recommended for persons at high risk for severe complications following influenza infection and for their caregivers and household contacts.[1] However, vaccinated persons may still become ill in spite of vaccination, and unvaccinated persons, even those who are not at high risk for complications, can still develop serious illness. This article describes the four currently available antiviral agents against influenza.

Elderly persons and those with certain chronic medical conditions are more likely than younger, healthier persons to develop serious complications as a result of influenza infections. However, even those with uncomplicated influenza infection stand to miss work and school days. It has been estimated that the cost of a severe influenza epidemic in the United States may be as high as 12 billion dollars. The greatest cost of influenza is not due to inpatient and outpatient medical care, but to lost productivity.[2]

Uncomplicated influenza can often be managed symptomatically with bed rest, fluids, and simple home remedies or over-the-counter medications such as antipyretics, analgesics, and cough suppressants. The choice of antipyretic and analgesic is important for children and teenagers, who should never be given aspirin when influenza is suspected because of the risk of developing Reye's syndrome.[3]

Antiviral agents offer another option for treating influenza. There are now four different antiviral drugs available with specific activity against influenza. Two of these drugs, amantadine and rimantadine, are effective only against influenza type A. Two very recently approved drugs, zanamivir and oseltamivir, are effective against both influenza types A and B. Amantadine and rimantadine are effective in reducing the severity and duration of influenza A infections when administered within 48 hours of illness onset, but have not been proven to prevent complications.[4,5] Zanamivir and oseltamivir have been shown to reduce the duration of uncomplicated influenza illness when administered within 30 to 36 hours of illness onset. They can also reduce the severity of uncomplicated influenza illness. There is some evidence from clinical studies to suggest that they may also reduce the incidence of influenza-associated complications, and thus the consequent use of antibiotics, but larger studies are needed to confirm these findings and to determine the extent to which they may reduce severe complications.[6-8]

Amantadine and its closely related analogue rimantadine have been studied since the 1960s. Amantadine was approved for treatment and prophylaxis of all type A influenza viruses in 1976, and rimantadine was approved in 1993. These drugs prevent influenza A virus replication primarily by inhibiting virus disassembly after entry into cells by blocking the action of viral M2 matrix protein. Viruses are cross-sensitive and cross-resistant to both drugs. However, the pharmacokinetics of these drugs differ markedly. Both drugs have high oral bioavailability, but amantadine is largely unmetabolized and is associated with a higher incidence of central nervous system and neuropsychiatric side effects, especially among the elderly. Both drugs require dosage adjustments for patients with renal insufficiency, and rimantadine requires adjustment in patients with severe hepatic dysfunction.[4,5]

Zanamivir and oseltamivir interfere with the replication of both influenza type A and type B viruses by inhibiting enzymatic activity of the viral neuraminidase, which plays an

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Also in this issue

important role in the release of virus from infected cells. Zanamivir is administered as a fine powder directly to the respiratory tract by oral inhalation using a specially designed breath-activated plastic device. Only 4% to 17% of the inhaled dose is absorbed systemically and is excreted unchanged in the urine.[9] In clinical trials adverse events have been uncommon; the incidence of adverse events has been similar in treatment and placebo groups. Pharmacokinetic studies have concluded that the potential for drug interactions is very low. [10]

Apparent transmission of resistant virus has been described in nursing homes and within households.

Oseltamivir is well-absorbed after oral administration and is metabolized in the liver to the active compound GS4071. GS4071 is excreted in the urine by glomerular filtration and tubular secretion, and a reduction in dosage is recommended for patients with creatinine clearance <30 mL/min. Because oseltamivir is metabolized by high capacity esterases, no dosage adjustment has been recommended for patients with liver disease. In clinical trials, nausea and vomiting were reported more frequently among subjects receiving oseltamivir than among those receiving placebo. However, there is some evidence that taking the drug with food may reduce the incidence of these side effects.[11]

In addition to their approval for treatment, amantadine and rimantadine are also approved for prevention of influenza type A. Although zanamivir and oseltamivir have been effective in preventing influenza illness and infection in challenge studies using attenuated influenza type A and B strains, there are relatively few published data on their efficacy in preventing naturally occurring influenza. However, larger studies of their prophylactic efficacy have recently been undertaken and further studies are planned. Preliminary findings suggest that these drugs are as effective as amantadine and rimantadine for prophylaxis, and they may be approved for this indication in the future.[12,13]

Many studies have shown amantadine and rimantadine to be approximately 70% to 90% effective in preventing illness caused by naturally occurring strains of type A influenza viruses. Chemoprophylaxis with these drugs has been shown to be effective in stopping outbreaks in long-term-care facilities and boarding schools, and to limit transmission within households.[4,5] However, since persons treated with amantadine or rimantadine may shed resistant virus during the course of therapy, efforts should be made to isolate persons who are being treated from those who are taking prophylactic drugs.[14] Although therapeutic efficacy has not been shown to be reduced in persons who begin to shed resistant viruses during treatment, resistant viruses can be transmitted to contacts, whether or not they are undergoing chemoprophylaxis. Apparent transmission of resistant virus has been described in nursing homes and within households.[15,16]

The extent of transmission of resistant viruses is unknown. Most amantadine- and rimantadine-resistant viruses have been isolated from persons undergoing drug treatment, or less often, from their contacts. In situations when only prophylaxis has been used, isolation of resistant virus has been uncommon. International surveillance for drug-resistant influenza A viruses has shown that few drug-resistant isolates have been obtained from patients with no known history of antiviral treatment.[14-17]

Studies to date suggest that resistant virus does not readily emerge during treatment with zanamivir and oseltamivir, although strains of influenza virus resistant to these compounds have been identified *in vitro* and *in vivo*. However, resistant viruses do not emerge as rapidly during passage in tissue culture in the presence of zanamivir and oseltamivir as they do in the presence of amantadine and rimantadine. In clinical trials, resistant strains have rarely been isolated from subjects taking these drugs for treatment of influenza infection. Furthermore, laboratory studies suggest that many viruses studied to date that have

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developed resistance to zanamivir or oseltamivir may be at a growth disadvantage compared to wild type virus.[18-21] *In vitro* studies have shown that amantadine- and rimantadine- resistant viruses are sensitive to zanamivir and oseltamivir.

Use of rapid diagnostic testing will greatly facilitate early detection and confirmation of influenza in the community and provide guidance in determining options for treatment of patients who present with influenza-like illness.[21] It is not necessary to test every patient once a community outbreak of influenza has been detected and confirmed. There are a number of commercially available assays that can be used to rapidly detect influenza from nasopharyngeal, nasal, or throat swab specimens. One assay detects only influenza type A[22] while the others detect type A or B, but do not distinguish between the two. [23,24] Knowledge of national, state and local influenza surveillance data, which are disseminated by the Centers for Disease Control and Prevention and state and local health departments, can be used to determine which rapid assays are best to use in a given influenza season. During most influenza seasons, only one influenza virus type predominates in any given geographic area at any given time during the season. During the more unusual seasons when influenza types A and B circulate simultaneously, two tests may be needed to determine the etiology of the outbreak. When suspected or confirmed influenza outbreaks occur, specimens should also be sent to state or local health departments for viral culture to characterize the virus and determine how similar it is to the vaccine strains or to test for other agents if influenza is not detected. Submitting specimens is also an important contribution to the accumulation of virologic data needed for annual vaccine strain selection.

References

1. Advisory Committee on Immunization Practices. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(RR-4):1-28.
2. Schoenbaum SC. Economic impact of influenza: the individual's perspective. Am J Med 82(suppl 6A):26-30, 1987.
3. Hurwitz E.S. Reye's syndrome. Epidemiol Rev 1989;11:249-253.
4. Tominack RL, Hayden FG. Rimantadine hydrochloride and amantadine hydrochloride use in influenza A virus infections. Infect Dis Clin North Am 1987;1:459-78.
5. Douglas RG. Drug therapy: prophylaxis and treatment of influenza. N Eng J Med 1990;322:443-450.
6. Hayden FG, Osterhaus ADME, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. N Engl J Med 1997;337:874-880.
7. The Mist Study Group. Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet 1998;352:1877-1881.
8. Aoki F, Osterhaus A, Rimmelzwaan G, Kinnersley N, Ward P. Oral GS4104 successfully reduces duration and severity of naturally acquired influenza [Abstract]. Final Program and Exhibits Addendum of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA. September 24-28, 1998;p. 22 (Abstract #LB-5).
9. Relenza [package insert]. Research Triangle Park, NC: Glaxo Wellcome Inc; 1999.
10. Daniel MJ, Barnett JM, Pearson BA. The low potential for drug interactions with zanamivir. Clin Pharmacokinet 1999;36(Suppl 1):41-50.
11. Tamiflu [package insert]. Nutley, NJ: Roche Lab Inc; 1999.
12. Hayden FG, Atmar R, Schilling M, et al. Safety and efficacy of oral GS4104 in long term prophylaxis of natural influenza [Abstract]. Final Program and Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA. September 24-28, 1998;p.22 (Abstract #LB-6).
13. Monto AS, Robinson DP, Herlocher ML, Hinson JM, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. JAMA 1999;282:31-35.
14. Monto AS, Arden NH. Implications of viral resistance to amantadine in control of influenza A Clin Infect Dis 1992;15:362–367.
15. Mast EE, Harmon MW, Gravenstein S, Wu SP, Arden NH, Circo R, Tyszka G, Kendal AP, Davis JP. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of influenza A(H3N2). Am J epidemiol 1991;13:988-997.
16. Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. N Engl J Med 1989; 321: 1696-1702.
17. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. Curr Top in Microbiol and Immunol 1992;176:120–130.

Use of rapid diagnostic testing will greatly facilitate early detection and confirmation of influenza in the community

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18. Colacino JM, Laver WG, Air GM. Selection of influenza A and B viruses for resistance to 4-guanidino-Neu5Ac2en in cell culture. J Infect Dis 1997;176:S66-S68.
19. Gubareva LV, Bethell R, Hart GJ, Murti KG, Penn CR, Webster RG.. Characterization of mutants of influenza A virus selected with the neuraminidase inhibitor 4-guanidino-Neu5Ac2en. J Virol 1996;70:1818-1827.
20. Blick TJ, Tiong T, Sahasrabudhe A, et al. Generation and characterization of an influenza virus neuraminidase variant with decreased sensitivity to the neuraminidase-specific inhibitor 4-guanidino-Neu5Ac2en. Virology 1995;214:475-484.
21. Tai CY, Escarpe PA, Sidwell RW, et al. Characterization of human influenza virus variants selected *in vitro* in the presence of the neuaminidase inhibitor GS 4071. Antimicrob Agents Chemother 1998;42:3234-3241.
22. Leonardi GP, Leib H, Birkhead GS, Smith C, Costello P, Conron W. Comparison of rapid detection methods for influenza A virus and their value in health-care management of institutionalized geriatric patients. J Clin Microbiol 1994;32(1):70-74.
23. Zstat flu [product package insert]. Oklahoma City, Oklahoma: ZymeTx Inc, 1998.
24. Flu OIA [product package insert]. Boulder, Colorado: BioStar, Inc, 1999.

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Vaccine-Preventable Disease Update
Reported Cases with Onset From 09/01/99 - 10/31/99

Condition	County	Number of Cases	Date of Onset	Condition	County	Number of Cases	Date of Onset
Hep B	Bexar	1	9/3	Hep B	Lamar	1	9/9
		1	9/6		Mclennan	1	9/9
		1	9/7			1	10/13
		1	9/8		Nacogdoches	1	9/3
		1	9/9		Pecos	1	10/13
		1	9/11		Potter	1	10/14
		1	9/21		Smith	1	9/9
		1	10/5		Tarrant	1	9/1
	Brazoria	1	10/19			1	9/3
	Brazos	1	9/30			1	9/4
	Cameron	1	10/14			1	9/6
	Dallas	2	9/9			1	9/8
		1	9/14			1	9/18
		1	10/6			1	10/4
		1	10/12			1	10/7
		2	10/13		Tarrant	2	10/11
	El Paso	1	9/23		Taylor	1	9/9
		1	9/25			1	9/30
	Fannin	1	9/9		TDCJ	1	10/20
	Garza	1	10/05		Tom Green	1	10/23
	Gregg	1	10/6		Travis	1	10/1
	Harris	1	9/1			1	10/18
		1	9/9			1	10/20
	Harris	2	9/23		Wichita	1	9/7
		1	10/21	Mumps	Dallas	1	9/14
	Hidalgo	1	9/9			1	10/1
		1	9/20			1	10/18
		1	9/22	Pertussis	Nueces	1	10/20
		1	9/28		Tarrant	1	9/9
	Hill	1	9/17		Wichita	1	9/22
	Jefferson	1	9/11	Rubella	Dallas	1	10/5
	Johnson	1	10/1		TDCJ	1	9/9

YTD	H Flu Infec	Hep B	Measles	Mumps	Pertussis	Rubella	Tetanus
	4	663	7	29	124	8	4

November is National Diabetes Awareness Month

Influenza and Pneumonia Vaccinations Decrease Relative Morbidity Risk for People with Diabetes

Annually, 10,000 to 30,000 people with diabetes die of influenza and pneumonia complications. Compared with other people who contract influenza or pneumonia, people with diabetes who become ill with influenza and pneumonia

- are about 3 times more likely to die
- are 6 times more likely to be hospitalized
- have death rates 5%-15% higher during influenza epidemics

Their risk is particularly high when additional risk factors such as cardiovascular disease and kidney disease are present.

Annual vaccination against influenza can prevent complications and death associated with influenza; for most people, one vaccination against pneumococcal disease provides lifelong protection. However, among adults with diabetes, about half receive the simple, safe influenza vaccination and only one third are immunized against pneumococcal pneumonia. Worse yet, pneumococcal disease has become more resistant to penicillin and other drugs, making treatment more difficult. Aggressive efforts need to be taken to increase influenza and pneumococcal immunization levels among people with diabetes to decrease the number of preventable influenza- and pneumonia-related deaths.

The Centers for Disease Control and Prevention (CDC) is conducting a national awareness campaign to encourage people with diabetes to get immunized against both influenza and pneumococcal disease. Influenza season is generally November through March, and the pneumococcal vaccine can be give to people with diabetes at the same time as they receive their influenza immunization.

Physicians and other health care providers can help by including influenza and pneumonia vaccinations as part of a regular diabetes management program that includes the following:

- Recommending influenza and pneumonia immunization to patients with diabetes when they come for routine care, especially during the influenza season
- Considering instituting standing orders to make the immunizations a routine part of the health care regimen for patients with diabetes
- Educating patients about how to obtain reimbursement for vaccination
- Educating patients about how dangerous influenza and pneumonia are for people with diabetes and how simple, safe, and effective the immunizations are

Health care providers should encourage their patients to be vaccinated to protect themselves from these preventable risks and take control of their diabetes.

More on diabetes ☞

To help health care providers encourage patients with diabetes to get immunized against influenza and pneumococcal disease, the Texas Diabetes Program/Council, in cooperation with CDC, provides informative posters and brochures in English and Spanish.

These materials are available free of charge while supplies last. Call (512) 458-7490 or FAX (512) 458-7408.

Border Diabetes Prevention and Control Project

Diabetes is an important public health concern for the United States-Mexico border states. The incidence of Type 2 diabetes, the most common kind, is 2 to 3 times greater among Hispanics than among non-Hispanics in the United States. Type 2 diabetes is associated with a host of other risk factors including hypertension, obesity, unhealthy diet, and physical inactivity, most of which are also more prevalent among Mexican Americans. A 1999 Pan American Health Organization report revealed that diabetes mortality rates on the border were higher than national rates.

To address chronic diseases such as diabetes with culturally appropriate and effective programs, it is imperative to obtain accurate data. The United States-Mexico Border Diabetes Prevention and Control Project is planning the first diabetes study conducted in the border region to include a sample representing the entire border population. This project is a binational, multistate, collaborative effort whose participants include representatives from the Centers for Disease Control and Prevention (CDC), the Mexican Sectretariat of Health, the health departments of the four US border states and their counterparts in the six Mexican border states, the Pan American Health Organization, the US-Mexico Border Health Association, and the El Paso Diabetes Association. This project is funded by CDC and the Paso del Norte Health Foundation.

The primary goal of the project, which will be implemented in two phases over a five-year period, is to diminish the impact of diabetes on the US-Mexico border population. The first phase is a door-to-door survey of adults aged 18 years and older. The survey example will include approximately 1,500 respondents from Mexico and 1,700 from the United States. Survey objectives are as follows:

- Determine the prevalence of diabetes and related behavioral risk factors
- Characterize patterns of health care access for the border population

The survey has three parts:

- A 65-item questionnaire to assess diabetes knowledge, health status, health care access, and behavioral risk factors such as diet, physical activity, drinking, and smoking
- Measures of height, weight, waist and hip circumference, and blood pressure
- A laboratory blood draw to determine fasting plasma glucose and hemoglobin A1C (both of which are diagnostic for diabetes)

Survey results will guide the project's second phase: the design and implementation of a multifaceted intervention program. Community health workers, or promotores, will be involved in planning culturally appropriate diabetes education and training programs in this phase.

Bimonthly Statistitical Report Changes

Starting with the Bimonthly Statistical Summary of Reportable Diseases in this issue of *Disease Prevention News* (DPN), a new reporting protocol is in place. Previously, there were six statistical summaries published in DPN annually, and each report covered a two-month period. These reports will still come out every two months, but the data for each report will be cumulative from January 1.

Bimonthly Statistical Summary of Selected Reportable Diseases: Provisional Cumulative Data

Jan-Oct 1999

Selected Diseases/Conditions	HHSC Region											Selected Texas Counties								Cumulative[1]	
	1	2	3	4	5	6	7	8	9	10	11	Bexar	Dallas	El Paso	Harris	Hidalgo	Nueces	Tarrant	Travis	1998	1999
Sexually Transmitted Diseases[2]																					
Syphilis, primary and secondary	2	7	142	39	28	95	24	31	1	8	2	23	123	8	66	0	1	17	11	355	319
Congenital Syphilis	0	1	6	2	1	43	1	5	1	1	9	4	3	1	41	7	0	3	0	81	70
Resistant Neisseria gonorrhoeae	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	8	2
Enteric Diseases																					
Salmonellosis	175	62	283	98	57	193	213	217	64	73	260	104	124	72	113	79	38	47	93	2942	1741
Shigellosis	217	81	244	24	26	104	159	264	45	23	273	192	139	23	93	83	92	37	57	3219	1491
Hepatitis A	102	184	720	30	64	167	313	300	49	19	457	204	471	16	89	170	17	39	228	3111	2416
Campylobacteriosis	83	7	120	23	23	71	159	200	16	18	127	128	85	17	35	39	37	5	84	692	856
Bacterial Infections																					
H. influenzae type b, invasive	1	0	2	0	0	0	0	1	0	0	0	1	0	0	0	0	0	1	0	3	4
Meningococcal, invasive	3	7	18	3	4	18	9	6	0	0	4	3	6	0	14	0	2	9	5	157	72
Lyme disease	0	2	9	7	1	1	8	3	0	0	1	1	4	0	1	0	0	3	2	26	32
Vibrio species	1	1	4	0	2	15	1	5	1	0	2	2	3	0	9	0	0	0	1	15	32
Other Conditions																					
AIDS[4]	68	28	646	86	66	555	309	194	29	73	104	170	460	72	494	28	24	112	217	3572	2369
Hepatitis B	0	0	0	0	0	0	0	0	0	0	0	47	202	12	30	23	15	62	17	1708	663
Adult elevated blood lead levels	0	0	93	0	1	6	1	8	0	1	3	0	3	0	0	0	0	0	0	1165	767
Animal rabies - total	2	6	11	2	0	3	32	7	1	1	7	1	1	1	2	1	0	5	4	276	314
Animal rabies - dogs and cats	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16	30
Tuberculosis Disease[2]																					
Children (0-14 years)	3	0	4	1	0	4	2	1	0	1	1	0	3	1	4	1	0	1	2	119	67
Adults (>14 years)	0	3	51	4	2	60	8	17	1	3	38	13	30	3	50	20	1	15	3	1312	969
Injuries[2]																					
Spinal Cord Injuries (5)	5	3	14	4	11	27	51	5	4	5	11	1	5	5	16	1	6	4	17	60	418

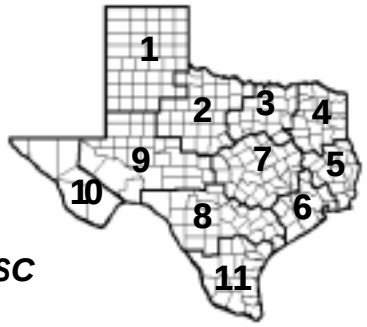
1. Cumulative to this month. 2. Data for the STD's, Tuberculosis, and spinal cord injuries are provided by date of report, rather than date of onset. 3. Voluntary reporting. 4. AIDS totals include reported cases from Texas Department of Corrections, which are not included in the regional and county totals. 5. 6 reports were missing PHR identification *Data incomplete.

Call 1-800-705-8868 to report

1999 POPULATION ESTIMATES

HHSC REGIONS							
1	770,440	**4**	971,877	**7**	1,989,767	**10**	784,287
2	533,633	**5**	690,501	**8**	2,076,931	**11**	1,687,473
3	5,366,008	**6**	4,557,450	**9**	567,058		
STATEWIDE TOTAL			19,995,428				

SELECTED COUNTIES			
Bexar	1,360,411	**Hidalgo**	528,300
Dallas	2,172,486	**Nueces**	315,965
El Paso	755,339	**Tarrant**	1,506,790
Harris	3,268,099	**Travis**	647,366



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