

# The New England Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

VOLUME 343

NOVEMBER 2, 2000

NUMBER 18



## INHALED ZANAMIVIR FOR THE PREVENTION OF INFLUENZA IN FAMILIES

FREDERICK G. HAYDEN, M.D., LARISA V. GUBAREVA, PH.D., ARNOLD S. MONTO, M.D., THOMAS C. KLEIN, M.D.,  
MICHAEL J. ELLIOTT, M.D., JANET M. HAMMOND, M.D., PH.D., STEPHEN J. SHARP, M.A., AND MICHAEL J. OSSI, M.D.,  
FOR THE ZANAMIVIR FAMILY STUDY GROUP\*

### ABSTRACT

**Background** As prophylaxis against influenza in families, amantadine and rimantadine have had inconsistent effectiveness, partly because of the transmission of drug-resistant variants from treated index patients. We performed a double-blind, placebo-controlled study of inhaled zanamivir for the treatment and prevention of influenza in families.

**Methods** We enrolled families (with two to five members and at least one child who was five years of age or older) before the 1998–1999 influenza season. If an influenza-like illness developed in one member, the family was randomly assigned to receive either inhaled zanamivir or placebo. The family member with the index illness was treated with either 10 mg of inhaled zanamivir (163 subjects) or placebo (158) twice a day for 5 days, and the other family members received either 10 mg of zanamivir (414 subjects) or placebo (423) once a day as prophylaxis for 10 days. The primary end point was the proportion of families in which at least one household contact had symptomatic, laboratory-confirmed influenza.

**Results** The proportion of families with at least one initially healthy household contact in whom influenza developed was smaller in the zanamivir group than in the placebo group (4 percent vs. 19 percent,  $P < 0.001$ ); the difference represented a 79 percent reduction in the proportion of families with at least one affected contact. Zanamivir provided protection against both influenza A and influenza B. A neuraminidase-inhibition assay and sequencing of the neuraminidase and hemagglutinin genes revealed no zanamivir-resistant variants. Among the subjects with index cases of laboratory-confirmed influenza, the median duration of symptoms was 2.5 days shorter in the zanamivir group than in the placebo group (5.0 vs. 7.5 days,  $P = 0.01$ ). Zanamivir was well tolerated.

**Conclusions** When combined with the treatment of index cases, prophylactic treatment of family members with once-daily inhaled zanamivir is well tolerated and prevents the development of influenza. In this study there was no evidence of the emergence of resistant influenza variants. (N Engl J Med 2000; 343:1282-9.)

©2000, Massachusetts Medical Society.

**I**NFLUENZAVIRUSES are frequently transmitted within households. In some epidemics, up to 50 percent of households have one or more members who become infected. The average secondary attack rates among family members is 25 percent,<sup>1</sup> although family composition, the circulating viral strain, and the presence or absence of exposure outside the household<sup>2</sup> influence the likelihood of secondary cases.

Amantadine and rimantadine selectively inhibit the ion-channel function of the M2 protein of influenza A viruses.<sup>3</sup> These drugs have been used for post-exposure prophylaxis in households, with reductions in influenza among family members (household contacts) of the index patient ranging from 3 to 100 percent.<sup>4,7</sup> No significant protection was found in two studies that involved concurrent treatment of ill household members who had index cases of influenza,<sup>4,6</sup> in part because of the rapid emergence of a drug-resistant strain of virus in the treated index cases and its apparent spread to household contacts.<sup>4</sup>

Inhaled zanamivir, a potent and selective inhibitor of influenza A and B virus neuraminidases, is effective in treating acute influenza in adults and adolescents.<sup>8-10</sup> In addition, seasonal prophylaxis with once-daily zanamivir is effective in preventing influenza in adults.<sup>11</sup>

We performed a study to assess the efficacy of post-exposure prophylaxis with zanamivir in household contacts and to assess the possible emergence of drug-resistant variants when the drug was used concurrently to treat household members with index cases of influenza.

From the University of Virginia, Charlottesville (E.G.H., L.V.G.); the University of Michigan, Ann Arbor (A.S.M.); Heartland Research, Wichita, Kans. (T.C.K.); Glaxo Wellcome, Research Triangle Park, N.C. (M.J.E., J.M.H., M.J.O.); and Glaxo Wellcome Research and Development, Greenford, United Kingdom (S.J.S.). Address reprint requests to Dr. Hayden at the University of Virginia, Health Sciences Center, Box 800473, Charlottesville, VA 22908.

\*Other members of the Zanamivir Family Study Group are listed in the Appendix.

## METHODS

### Study Design

The study was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 15 centers in the United States, Canada, the United Kingdom, and Finland from October 1998 through April 1999.

### Families

Eligible families (those with two to five members, including at least one adult and at least one child who was 5 to 17 years old) were prospectively recruited during the fall of 1998. Family members who met any of the following criteria were not assigned to a study drug: an age of less than five years, hypersensitivity to zanamivir, an immunocompromised state, use of an anti-influenza agent, pregnancy, or breast-feeding. Female participants of child-bearing potential were required to use an acceptable means of contraception and to have a negative urine test for pregnancy. All subjects or their legal guardians provided written informed consent. The consent form was approved by the ethics committee of each participating center.

### Administration of the Study Drugs

Once laboratory-confirmed influenza activity had been documented in the community, families in which one member contracted an influenza-like illness (the index case) began to take the study drug. Influenza-like illness was defined by the presence of at least two of the following signs or symptoms: fever (temperature,  $\geq 37.8^{\circ}\text{C}$ ), feverishness, cough, headache, sore throat, and myalgia. Families were randomly assigned in a 1:1 ratio to receive zanamivir or placebo administered through an inhaler (Diskhaler, Glaxo Wellcome, Ware, United Kingdom). All eligible family members who were at least five years old started taking the study drug within 36 hours after the onset of symptoms in the member with the index illness. The intervention phase of the study lasted from December 1998 through April 1999. During this period, both influenza A virus, predominantly A/Sydney/5/97(H3N2), and influenza B virus circulated.

The family members with index cases of influenza received inhaled zanamivir (10 mg) or placebo twice a day for five days. The other, healthy family members received the same study drug as the ill member in their household, either zanamivir (10 mg) or placebo once daily for 10 days. Study participants who did not take at least 8 of the 10 doses of the study drug were considered not to have complied with the treatment regimen. Compliance was determined primarily from the diary records of the number of doses taken. Medications for the relief of symptoms (acetaminophen and dextromethorphan or pholcodine) were provided, but participants were asked to use them only if symptoms were disabling.

### Clinical Monitoring

The study participants recorded the absence or presence of seven symptoms of influenza (headache, sore throat, feverishness, myalgia, nasal symptoms, weakness, and loss of appetite) and the severity of cough and overall symptoms on diary cards twice daily for 14 days. The severity of the illness and of specific symptoms was graded on a scale from 0 (absent) to 3 (severe), with higher scores indicating greater severity. Temperature was also recorded twice daily, with the use of a tympanic thermometer. Patients with index cases of influenza were assessed in the home or during a clinic visit on days 1 and 5 and, if symptoms continued, on day 14. Household contacts were screened by telephone on days 5 and 14 and in person on days 11 and 28. Adverse events and concurrent use of other medications were documented, and diary cards were inspected to ensure appropriate use of medication and to monitor for illness.

### Virologic Monitoring

Respiratory secretions (from nasopharyngeal or throat swabs or both, nasal washings, or nasal aspirates) were collected from the sub-

jects with the index cases on days 1 and 5 and from the household contacts within two to three days after the onset of their illness. The most common samples collected were throat swabs (58 percent of all samples), followed by combined throat and nasopharyngeal swabs (15 percent), and nasopharyngeal swabs (13 percent).

Influenza infection was identified by viral isolation (performed by Covance Central Laboratory Services, Indianapolis, for the North American centers and by local laboratories for the European centers), reverse-transcriptase polymerase chain reaction (RT-PCR)<sup>12</sup> (performed by the Public Health Laboratory Service, London), and seroconversion studies. Serum was collected from all household members at the same time that the member with the index case started to take the study drug. Serum samples obtained during the acute phase of the illness (on day 1) and during the convalescent phase (on day 28) were analyzed for the presence of hemagglutination-inhibition antibodies to B/Harbin/7/94, A/Sydney/5/97(H3N2), and A/Beijing/262/95(H1N1) antigens<sup>13</sup> at the National Institute for Biological Standards and Control (Hertfordshire, United Kingdom). Seroconversion was defined as a serum antibody titer on day 28 that was at least four times as high as the titer on day 1. Viral isolates were tested for susceptibility to zanamivir at the University of Virginia by sequence analysis of the neuraminidase and hemagglutinin genes<sup>14</sup> and by a neuraminidase-inhibition assay.

### Neuraminidase-Inhibition Assay

The neuraminidase-inhibition assay was performed according to the method of Potier et al.,<sup>15</sup> with modifications. A/turkey/Minnesota/833/80 (H4N2) and its zanamivir-resistant mutant with an R292K substitution in the neuraminidase were used as susceptible and resistant controls, respectively.<sup>16</sup> The mean value for the concentration of zanamivir that inhibited neuraminidase activity by 50 percent (the  $\text{IC}_{50}$  value) was 40 nM for the zanamivir-resistant mutant.

### Sequence Analysis of the Hemagglutinin and Neuraminidase Genes

Viral RNA was extracted from cell-culture supernatants with a kit (RNeasy, Qiagen, Santa Clarita, Calif.). Amplification of the viral RNA was performed by RT-PCR assay as previously described,<sup>17</sup> and the PCR products were sequenced. (The sequences have been deposited in the GenBank data base under accession nos. AF297094, AF297095, AF297096, and AF297097.) Sequence analysis of the hemagglutinin gene (the region encoding the HA1 subunit) and the neuraminidase gene was performed to detect nucleotide and amino acid substitutions in viruses isolated sequentially from one subject and those isolated from members of the same family. The sequences were compared with those of other viral isolates obtained in the present study and with the sequences of recent strains of influenza virus (1995 to 1998, obtained from the GenBank data base).

### Study End Point

The primary efficacy end point was the proportion of families with at least one initially healthy member in whom symptomatic, laboratory-confirmed influenza A or B developed. Symptomatic influenza was defined by the presence of at least three consecutive diary-card entries listing at least two of the following signs or symptoms: fever (temperature,  $\geq 37.8^{\circ}\text{C}$ ), feverishness, cough, headache, sore throat, and myalgia.

### Statistical Analysis

Between-group comparisons were performed with an exact test<sup>18,19</sup> for stratified two-by-two tables, with the analysis stratified according to the center. Two-sided statistical tests were performed at the 5 percent level of significance, and corresponding estimates of odds ratios and 95 percent confidence intervals were calculated. The relative risks and 95 percent confidence intervals were estimated on the basis of Mantel-Haenszel stratified analyses, and values for protective efficacy were expressed as 1 minus the relative risk. The primary analysis was performed according to the intention-to-treat principle.

Wilcoxon's rank-sum test, stratified according to the center, was used to compare the median time to the alleviation of clinically significant symptoms of influenza, with no use of relief medication, in the zanamivir and placebo groups. The comparison was performed separately for the subjects with index cases of influenza and the household contacts in whom influenza developed.<sup>20</sup> The alleviation of symptoms was defined as the absence of fever (temperature, <37.8°C), with feverishness, cough, headache, myalgia, and sore throat recorded as absent or minimal, for at least 24 hours.

Assuming that prophylactic administration of zanamivir would have at least a 70 percent rate of efficacy, we calculated that a sample comprising 35 families with at least one household contact in whom influenza developed would give the study 90 percent power to detect a difference in efficacy between the study groups that was significant at the 5 percent level.<sup>21</sup> Assuming that 20 percent of the families in the placebo group would have at least one household contact with influenza, the required overall sample size was at least 270 families (135 per group).

All analyses were prespecified in a plan that was written before the treatment assignments were revealed.

## RESULTS

### Families

A total of 799 families underwent prospective surveillance for influenza. The characteristics of the 337 families randomly assigned to receive either placebo or zanamivir were similar at base line (Table 1). A total of 18 participants (2 percent) (8 in the placebo group and 10 in the zanamivir group) discontinued the study medication early, and 11 (7 in the placebo

group and 4 in the zanamivir group) withdrew from the study prematurely (Fig. 1). The numbers of families in which the index case of influenza developed in a child younger than five years, who did not receive treatment, were small (10 in the placebo group and 6 in the zanamivir group).

The rate of compliance with the medication regimen was high in both groups, with at least 98 percent of all participants and 98 percent of all children 5 to 11 years old taking 8 to 10 doses of the study drug.

### Prophylactic Efficacy

Among all randomized families, the proportion of families with one or more household contacts in whom symptomatic, laboratory-confirmed influenza developed was 19 percent in the placebo group and 4 percent in the zanamivir group ( $P<0.001$ ) (Table 2). Among families in which the index illness was laboratory-confirmed influenza, the proportion of families in which influenza developed in contacts was 29 percent in the placebo group and 8 percent in the zanamivir group ( $P<0.001$ ). Among families in which the index illness was not influenza, the proportions were 8 percent and 1 percent, respectively ( $P=0.04$ ). The rate of protection against influenza in healthy household contacts was 79 percent in the overall sample, 72 percent in the group of families with influ-

TABLE 1. CHARACTERISTICS OF THE STUDY PARTICIPANTS.

CHARACTERISTIC	SUBJECTS WITH INDEX ILLNESSES		HOUSEHOLD CONTACTS*	
	PLACEBO (N=158)	ZANAMIVIR (N=163)	PLACEBO (N=423)	ZANAMIVIR (N=414)
Female sex — no. (%)	99 (63)	86 (53)	225 (53)	236 (57)
Age — yr†	18.9±13.1	20.0±14.5	26.5±16.4	25.9±15.6
White race — no. (%)	138 (87)	148 (91)	372 (88)	377 (91)
Vaccinated — no. (%)	13 (8)	20 (12)	78 (18)	57 (14)
Influenza confirmed — no. (%)‡	79 (50)	78 (48)	66 (16)	26 (6)
Influenza A	52 (33)	51 (31)	48 (11)	21 (5)
Influenza B	27 (17)	27 (17)	18 (4)	4 (1)
Influenza not confirmed — no. (%)	79 (50)	85 (52)	357 (84)	388 (94)
Smoker — no. (%)	15 (9)	16 (10)	30 (7)	38 (9)
Underlying respiratory conditions — no. (%)§	11 (7)	10 (6)	25 (6)	26 (6)

\*The mean number of contacts per family was 2.5 in the placebo group and 2.4 in the zanamivir group.

†Values are means ±SD.

‡Infection was documented on the basis of one or more of the following findings: viral isolation, the detection of viral RNA by RT-PCR assay, or an increase in the serum HA1 antibody titers during the convalescent phase. The diagnosis of influenza was based on the combination of culture, serologic, and RT-PCR findings in samples obtained on days 1 and 5 from subjects with index cases and in samples obtained from household contacts within two to three days after the onset of an influenza-like illness (i.e., during prophylaxis). Overall, influenza was diagnosed by RT-PCR assay in 38 household contacts (28 in the placebo group and 10 in the zanamivir group; 42 percent of 91 infected) and in 135 subjects with index illnesses (86 percent of 157 infected). It was not possible to determine the type of influenza virus in one household contact with confirmed infection.

§Chronic respiratory conditions included asthma and obstructive airway disease requiring regular use of medication.

enza-positive index cases, and 87 percent in the group with influenza-negative index cases (Table 2).

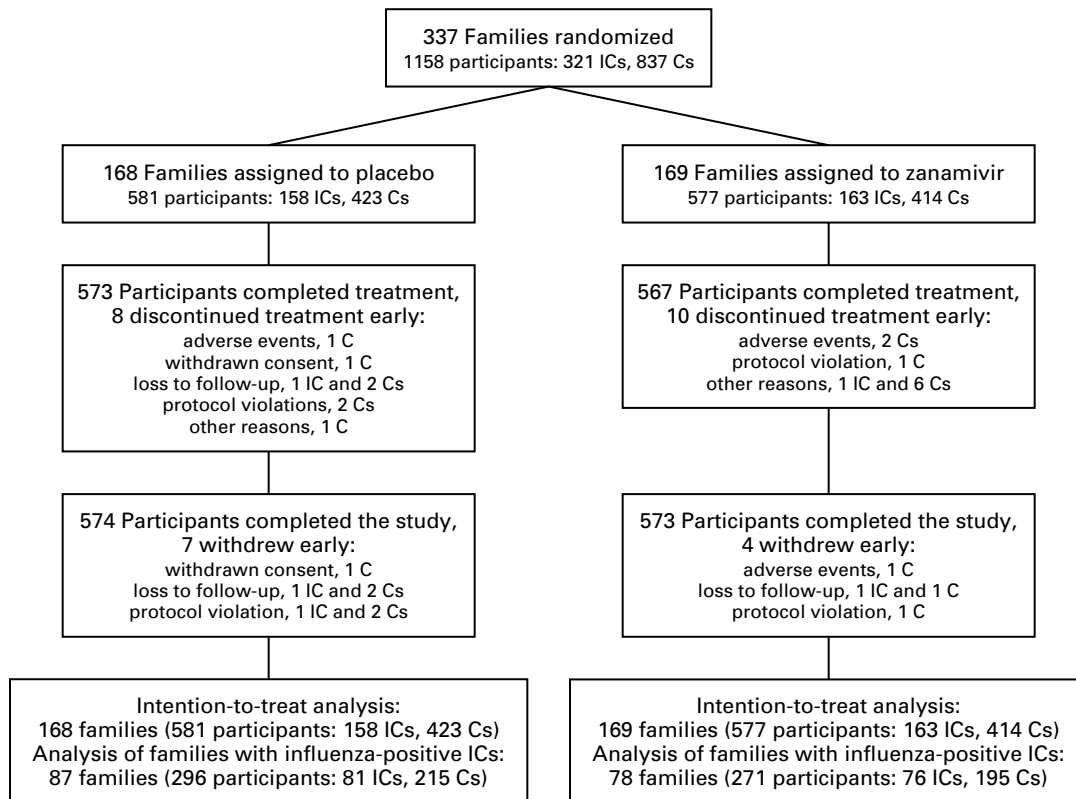
Although the study did not have sufficient statistical power to detect a significant difference in efficacy between influenza types, zanamivir prophylaxis was effective against both influenza A and influenza B (Table 2). Illnesses developed within half a day after the start of prophylaxis in three of the seven ill household contacts (43 percent) in the zanamivir group, suggesting that in these subjects, the infection probably developed before the start of prophylaxis. In the placebo group, 7 of 40 illnesses (18 percent) developed within half a day after the start of the study regimen, and 22 (55 percent) started within 2.5 days; the remainder developed during the first week. With the exclusion of household contacts in whom symptoms developed less than one day after the start of prophylaxis, the proportion of families with at least one contact who had symptomatic, laboratory-confirmed influenza was 15 percent in the placebo group and 2 percent in the zanamivir group ( $P < 0.001$ ), representing an 84 percent rate of protection from influenza with the use of zanamivir (Table 2).

The administration of zanamivir was also associat-

ed with significant reductions in laboratory-confirmed influenza irrespective of the presence or absence of symptoms. Infection with influenzavirus in contacts was reduced by approximately 50 percent in all randomized families and in the families in which the index case of influenza was confirmed (Table 2). In the families in which the member with the index case was not assigned to receive a study drug because of an age of less than five years, influenza did not develop in any of the 21 household contacts. In 13 families, a household contact became ill with a type of influenza that was different from the type in the index case (4 families in the placebo group and 1 in the zanamivir group) or a household contact contracted influenza even though the index case proved not to be influenza (7 families in the placebo group and 1 in the zanamivir group) ( $P = 0.02$ ), indicating probable acquisition of the virus outside the household.

**Efficacy of Treatment**

Among the subjects with index cases of laboratory-confirmed influenza, the median time to the alleviation of symptoms without the use of medications for relief was 2.5 days shorter for the 76 subjects who



**Figure 1.** Treatment Assignments and Numbers of Subjects Who Completed Treatment and Who Completed the Study. Participants in the study were at least five years old. IC denotes index case, and C contact.

**TABLE 2. RELATIVE RISK OF LABORATORY-CONFIRMED INFLUENZA IN HOUSEHOLD CONTACTS.\***

LABORATORY-CONFIRMED INFLUENZA IN CONTACT	PLACEBO	ZANAMIVIR	RELATIVE RISK (95% CI)	P VALUE	PROTECTIVE EFFICACY (95% CI)
	no. of families/total no. (%)				%
All symptomatic cases					
Intention-to-treat analysis††	32/168 (19.0)	7/169 (4.1)§	0.21 (0.11–0.43)	<0.001	79 (57–89)
Influenza-positive index case†¶	25/87 (28.7)	6/78 (7.7)	0.28 (0.13–0.58)	<0.001	72 (42–87)
Influenza A	15/58 (25.9)	3/52 (5.8)	0.23 (0.08–0.64)	0.009	77 (36–92)
Influenza B	10/29 (34.5)	3/26 (11.5)	0.32 (0.10–1.00)	0.099	68 (0–90)
Influenza-negative index case¶	7/83 (8.4)	1/89 (1.1)	0.13 (0.02–0.72)	0.04	87 (28–98)
Onset of symptoms ≥1 day after start of prophylaxis					
Intention-to-treat analysis	25/168 (14.9)	4/169 (2.4)	0.16 (0.06–0.38)	<0.001	84 (62–94)
All cases (symptomatic and asymptomatic)					
Intention-to-treat analysis	47/168 (28.0)	22/169 (13.0)	0.47 (0.30–0.73)	0.001	53 (27–70)
Influenza-positive index case	33/87 (37.9)	15/78 (19.2)	0.52 (0.32–0.85)	0.014	48 (15–68)

\*Analyses were performed separately for all randomized families (intention-to-treat analysis), families with influenza-positive index cases, and families with influenza-negative index cases.

†Symptomatic, laboratory-confirmed influenza developed in a total of 40 of the 423 household contacts (9 percent) in the placebo group and in 7 of the 414 (2 percent) in the zanamivir group. Among household contacts of subjects with influenza-positive index cases, 33 of 215 (15 percent) in the placebo group and 6 of 195 (3 percent) in the zanamivir group had laboratory-confirmed influenza. Asymptomatic or symptomatic influenza developed in 66 household contacts (16 percent) in the placebo group and in 26 (6 percent) in the zanamivir group overall and in 51 (24 percent) and 18 (9 percent) of contacts in families with influenza-positive index cases in the placebo and zanamivir groups, respectively. No families in the intention-to-treat analysis were enrolled twice in the drug-administration phase. In six families in the placebo group, prophylaxis failed in more than one member; there were two failures in five of the families and four in one family. There were no multiple prophylactic failures in the families treated with zanamivir.

‡In the intention-to-treat analysis, the proportion of families in which at least 1 household contact had symptomatic influenza confirmed by culture or serologic tests (but not by RT-PCR assay alone) was 18 percent (30 of 168) in the placebo group and 4 percent (6 of 169) in the zanamivir group (P<0.001). The approximate relative risk of 0.19 represents a protection rate of 81 percent (95 percent confidence interval, 59 to 91 percent) for zanamivir as compared with placebo.

§Two other zanamivir recipients had fever (temperature, ≥37.8°C) and culture-positive influenza that did not meet the case definition.

¶In five families with influenza-positive index cases (four families in the placebo group and one in the zanamivir group), household contacts had influenza of a different type from that of the index case.

||Four families were given the wrong treatment. In the analyses of influenza in household contacts according to whether the index case was positive or negative for influenza, the number of families in each treatment group was the number that actually received the treatment, whereas in the intention-to-treat analysis, the number of families in each group was the number randomly assigned to the group. For this reason, within each treatment group, the number of families with influenza-positive index cases and the number with influenza-negative index cases do not add up to the total number in the intention-to-treat analysis.

received zanamivir than for the 81 who received placebo (5.0 vs. 7.5 days, P=0.01). Among household contacts with laboratory-confirmed influenza, the median time to the alleviation of symptoms without use of medications was 5.5 days for the 7 subjects who received zanamivir and 8.0 days for the 40 who received placebo. The proportion of subjects with complications leading to the use of antibiotics was low in both the placebo group (8 percent) and the zanamivir group (5 percent).

#### Monitoring of Viral Susceptibility

All 64 viral isolates recovered from household contacts and their respective family members with index infections were sensitive to zanamivir in the neuro-

minidase-inhibition assay (IC<sub>50</sub> value, <11 nM) (Table 3). In five subjects with index infections who received zanamivir, the sensitivity of the isolate obtained on day 1 was similar to that of the isolate obtained on day 5 (the IC<sub>50</sub> values differed by a factor of no more than three). Similarly, in five families in the zanamivir group and five representative families in the placebo group, viral isolates from both the family member with the index case and the ill household contact showed no changes in IC<sub>50</sub> values that were indicative of the emergence of resistance.

We also performed sequence analysis of the hemagglutinin gene (the region encoding the HA1 subunit) of viruses recovered from ill household contacts (17 with influenza A and 8 with influenza B) and their re-

**TABLE 3.** INHIBITION OF NEURAMINIDASE ACTIVITY BY ZANAMIVIR IN INFLUENZA A AND B ISOLATES FROM SUBJECTS WITH INDEX CASES AND HOUSEHOLD CONTACTS.\*

INHIBITION OF NEURAMINIDASE ACTIVITY (IC <sub>50</sub> )†	INFLUENZA A				INFLUENZA B			
	PLACEBO		ZANAMIVIR		PLACEBO		ZANAMIVIR	
	Index (n=12)	Contact (n=18)	Index (n=6)	Contact (n=6)	Index (n=8)	Contact (n=8)	Index (n=3)	Contact (n=3)
Mean ±SD (nM)	2.3±0.7	2.5±0.8	2.6±0.6	2.6±0.7	6.0±1.9	7.2±2.2	7.5±2.3	7.7±1.3
Range (nM)	1.3–3.3	1.6–4.3	1.8–3.5	1.6–3.5	3.8–9.0	4.1–10.5	4.9–9.5	6.5–9.0

\*The values are the mean results of one to three replicative assays. Values for index cases are from isolates obtained on day 1.

†IC<sub>50</sub> denotes the concentration of zanamivir that reduced neuraminidase activity by 50 percent.

**TABLE 4.** ADVERSE EVENTS DURING TREATMENT OR PROPHYLAXIS.

ADVERSE EVENTS	SUBJECTS WITH INDEX CASES				HOUSEHOLD CONTACTS	
	PLACEBO (N=160)		ZANAMIVIR (N=161)		PLACEBO (N=430)	ZANAMIVIR (N=407)
	no. (%)					
All events	49 (31)	40 (25)	214 (50)	179 (44)		
Possible drug-related event	7 (4)	4 (2)	20 (5)	26 (6)		
Serious event	0	1 (1)*	0	0		
Event leading to discontinuation of study drug	0	0	1 (<1)†	2 (<1)‡		
Event leading to withdrawal from study	0	0	0	1 (<1)§		

\*Pneumonia developed in this subject four days after the start of treatment with zanamivir and resolved approximately one week later.

†The patient had nausea and vomiting.

‡One patient had gastrointestinal discomfort and pain, and the other had headaches.

§The patient had headaches.

spective family members with index infections (14 with influenza A and 6 with influenza B). In the zanamivir group, sequence analysis showed no differences in amino acid sequences between viral isolates from members of the same family. Similarly, sequence analysis of the neuraminidase gene in viral isolates from patients treated with zanamivir did not reveal any amino acid substitutions within the same family (a total of 5 families and 11 viruses). Sequence analysis of the hemagglutinins of four unmatched isolates (one from a subject with an index infection, obtained on day 5, and three from household contacts) revealed one amino acid substitution in the stalk region of the HA1 subunit (Gly40Asp) in the isolate obtained on day 5 from the index patient and one amino acid substitution in the stalk region of the neuraminidase (Ala67Thr) in an isolate from a household contact. Hence, there was no evidence of the development of resistance due to the use of zanamivir.

**Tolerance**

The frequency of adverse events, most of which were of mild or moderate intensity, was similar in the overall zanamivir and placebo groups, as well as among children who were 5 to 11 years old. Possible drug-related adverse events were reported by 27 subjects in the placebo group and by 30 in the zanamivir group; 11 subjects with index illnesses (3 percent of all such subjects) and 46 household contacts (5 percent of all the contacts) reported possible drug-related events (Table 4). Among subjects with asthma requiring regular use of medication, the proportion with an exacerbation was small (11 percent in the placebo group and 6 percent in the zanamivir group).

**DISCUSSION**

When used for the treatment of index cases of influenza and for postexposure prophylaxis in healthy household contacts, inhaled zanamivir was associat-

ed with a 79 percent rate of protection against influenza in the household contacts, and there was no evidence of the emergence of resistant viral strains. The administration of zanamivir provided protection against both influenza A and influenza B, regardless of whether influenza was confirmed in the subject with the index illness, and it also provided protection against laboratory-documented infection regardless of whether there were symptoms. The reduction in cases of influenza among the household contacts of subjects with influenza-negative index cases in the zanamivir group, as compared with the placebo group, indicates that most of the protection was due primarily to chemoprophylaxis, not to the treatment of subjects with index cases. Data on the limited number of household contacts who received zanamivir prophylaxis and in whom symptomatic influenza developed suggested that the continued administration of zanamivir reduced the duration of the illness.

The early occurrence of illnesses in both groups of household contacts indicates that postcontact prophylaxis needs to be initiated quickly for optimal protection. The rate of protective efficacy in our study compares favorably with the rates of protection against influenza (67 percent), febrile influenza (84 percent), and infection with or without symptoms (31 percent) in a study of inhaled zanamivir administered daily for four weeks in adults.<sup>11</sup> In both trials, the rates of protection against laboratory-documented infection were lower than the rates of protection against illness due to influenza virus. Hence, zanamivir is better at preventing clinical illness than infection. Subclinical infection allows a humoral immune response for protection against subsequent infection.

Viruses that are resistant to amantadine and rimantadine emerge rapidly during treatment with these agents, are transmissible to close contacts in households and nursing homes, and remain pathogenic in humans.<sup>22,23</sup> In a family-based study, treatment with rimantadine in subjects with index illnesses, especially young children, was associated with the rapid emergence and transmission of drug-resistant influenza A virus and with the failure of prophylaxis in household contacts.<sup>4</sup> Drug-resistant virus was recovered by the fifth day of treatment in about 30 percent of children and adults who received rimantadine.<sup>23,24</sup> The development of resistance to zanamivir has been reported in one immunocompromised child.<sup>14</sup> In our studies and in others, however, there was no evidence of drug resistance after five days of treatment with zanamivir.<sup>8-10,25,26</sup> These findings suggest that the risk of drug resistance and transmission in households is low when zanamivir is used, but further studies of resistance, including studies involving high-risk groups such as immunocompromised hosts and young children, are needed.

The benefits of inhaled zanamivir for the treatment of index cases in our study confirm the therapeutic

efficacy observed in previous studies involving adults, adolescents, and children five years of age or older.<sup>8-10,27</sup> In our study, the period during which subjects with index illnesses used medication for the relief of symptoms was significantly shorter in the zanamivir group than in the placebo group, indicating that the use of supplementary medications was not a factor in the clinical benefit observed. Zanamivir was well tolerated by the participants in our study, including the small number of subjects with chronic respiratory conditions requiring regular use of medication.

Although not a substitute for vaccination, chemoprophylaxis may be clinically valuable because it affords immediate protection. Chemoprophylactic agents may be of benefit under certain circumstances: if vaccines are not available, in conjunction with vaccination late in the influenza season, before the vaccine has induced an immune response, or if there is no immune response to vaccination. Zanamivir does not impair the humoral immune response to inactivated influenza vaccine.<sup>28</sup> Our findings indicate that prophylaxis with zanamivir is an effective option for preventing the transmission of influenza within households. Further studies of prophylactic administration of inhaled zanamivir in other high-risk groups, such as severely immunocompromised patients who are unlikely to have a response to vaccine or residents of nursing homes or other institutions in which there are outbreaks of influenza, are warranted.

Supported by Glaxo Wellcome, which also provided the study drug. Drs. Hayden and Monto are paid consultants for Glaxo Wellcome.

## APPENDIX

In addition to the authors, the following investigators participated in the Zanamivir Family Study Group: A.D. Bremner, Glasgow, Scotland; R. Broker, MedQuest Centers for Research, Greer, S.C.; D.M. Fleming, West Midlands, United Kingdom; D. Henry, Salt Lake City; L. Herlocher, University of Michigan, Ann Arbor; R. Keeney, WakeMed Clinical Research Institute, Raleigh, N.C.; J. Perry, Endwell, N.Y.; M. Pichichero, University of Rochester Medical Center, Rochester, N.Y.; O. Ruuskanen, Turku, Finland; R. Stoltz, GFI Pharmaceutical Services, Evansville, Ind.; R. Turner, Medical University of South Carolina, Charleston; C. VanHook, Longmont Medical Research, Longmont, Colo.

## REFERENCES

- Nicholson KG. Managing influenza in primary care. Oxford, England: Blackwell Science, 1999:24.
- Longini MI Jr, Koopman JS, Monto AS, Fox JP. Estimating household and community transmission parameters for influenza. *Am J Epidemiol* 1982;115:736-51.
- Hayden FG, Aoki FY. Amantadine, rimantadine, and related agents. In: Yu VL, Merigan TC Jr, Barriere SL, eds. *Antimicrobial therapy and vaccines*. Baltimore: Williams & Wilkins, 1999:1344-65.
- 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;321:1696-702.
- Galbraith AW, Oxford JS, Schild GC, Watson GI. Protective effect of 1-adamantanamine hydrochloride on influenza A2 infections in the family environment: a controlled double-blind study. *Lancet* 1969;2:1026-8.
- Idem*. Study of 1-adamantanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family environment. *Bull World Health Org* 1969;41:677-82.
- Bricaire F, Hannoun C, Boissel JP. Prévention de la grippe A: efficacité et tolérance du chlorhydrate de rimantadine. *Presse Med* 1990;19:69-72.

8. 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;337:874-80.
9. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet* 1998;352:1877-81. [Errata, *Lancet* 1999;353:504, 1104.]
10. Makela MJ, Pauksens K, Rostila T, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. *J Infect* 2000;40:42-8.
11. Monto AS, Robinson DP, Herlocher ML, Hinson JM Jr, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999;282:31-5.
12. Ellis JS, Fleming DM, Zambon MC. Multiplex reverse transcription-PCR for surveillance of influenza A and B viruses in England and Wales in 1995 and 1996. *J Clin Microbiol* 1997;35:2076-82.
13. Hirst GK. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. *J Exp Med* 1942;75:49-64.
14. Gubareva LV, Mastrovovich MN, Brenner MK, Bethell RC, Webster RG. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998;178:1257-62.
15. Potier M, Mameli L, Belisle M, Dallaire L, Melancon SB. Fluorometric assay of neuraminidase with a sodium (4-methylumbelliferyl- $\alpha$ -D-N-acetylneuraminic) substrate. *Anal Biochem* 1979;94:287-96.
16. Gubareva LV, Robinson MJ, Bethell RC, Webster RG. Catalytic and framework mutations in the neuraminidase active site of influenza viruses that are resistant to 4-guanidino-Neu5Ac2en. *J Virol* 1997;71:3385-90.
17. 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;70:1818-27.
18. Gart JJ. Point and interval estimation of the common odds ratio in the combination of  $2 \times 2$  tables with fixed marginals. *Biometrika* 1970;57:471-5.
19. Cox DR. A simple example of a comparison involving quantal data. *Biometrika* 1966;53:215-20.
20. Koch GG, Edwards S. Clinical efficacy trials with categorical data. In: Peace KE, ed. *Biopharmaceutical statistics for drug development*. New York: Marcel Dekker, 1988:403-57.
21. Shuster JJ. Fixing the number of events in large comparative trials with low event rates: a binomial approach. *Control Clin Trials* 1993;14:198-208.
22. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. *Curr Top Microbiol Immunol* 1992;176:119-30.
23. Hayden FG, Sperber SJ, Belshe RB, Clover RD, Hay AJ, Pyke S. Recovery of drug-resistant influenza A virus during therapeutic use of rimantadine. *Antimicrob Agents Chemother* 1991;35:1741-7.
24. Hall CB, Dolin R, Gala CL, et al. Children with influenza A infection: treatment with rimantadine. *Pediatrics* 1987;80:275-82.
25. Boivin G, Goyette N, Hardy I, Aoki F, Wagner A, Trottier S. Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. *J Infect Dis* 2000;181:1471-4.
26. Barnett JM, Cadman A, Gor D, et al. Zanamivir susceptibility monitoring and characterization of influenza virus clinical isolates obtained during phase II clinical efficacy studies. *Antimicrob Agents Chemother* 2000;44:78-87.
27. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children 5 to 12 years of age: a randomized controlled trial. *Pediatr Infect Dis J* 2000;19:410-7.
28. Webster A, Boyce M, Edmundson S, Miller I. Coadministration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of antihaemagglutinin antibodies in the serum of healthy volunteers. *Clin Pharmacokinet* 1999;36:Suppl 1:51-8.

---

IMAGES IN CLINICAL MEDICINE

---

In January 2001, the *Journal* will resume consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* Web site at [www.nejm.org](http://www.nejm.org). At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.

---