Effectiveness of Oseltamivir in Preventing Influenza in Household Contacts

A Randomized Controlled Trial

Robert Welliver, MD
Arnold S. Monto, MD
Otmar Carewicz, MD
Edwig Schatteman, MD
Michael Hassman, DO
James Hedrick, MD
Helen C. Jackson, PhD
Les Huson, PhD
Penelope Ward, MD
John S. Oxford, PhD
for the Oseltamivir Post Exposure Prophylaxis Investigator Group

Context Influenza virus is easily spread among the household contacts of an infected person, and prevention of influenza in household contacts can control spread of influenza in the community.

Objective To investigate the efficacy of oseltamivir in preventing spread of influenza to household contacts of influenza-infected index cases (ICs).

Design and Setting Randomized, double-blind, placebo-controlled study conducted at 76 centers in North America and Europe during the winter of 1998-1999.

Participants Three hundred seventy-seven ICs, 163 (43%) of whom had laboratory-confirmed influenza infection, and 955 household contacts (aged ≥12 years) of all ICs (415 contacts of influenza-positive ICs).

Interventions Household contacts were randomly assigned by household cluster to take 75 mg of oseltamivir (n=493) or placebo (n=462) once daily for 7 days within 48 hours of symptom onset in the IC. The ICs did not receive antiviral treatment.

Main Outcome Measure Clinical influenza in contacts of influenza-positive ICs, confirmed in a laboratory by detection of virus shedding in nose and throat swabs or a 4-fold or greater increase in influenza-specific serum antibody titer between baseline and convalescent serum samples.

Results In contacts of an influenza-positive IC, the overall protective efficacy of oseltamivir against clinical influenza was 89% for individuals (95% confidence interval [CI], 67%-97%; $P<.001$) and 84% for households (95% CI, 49%-95%; $P<.001$). In contacts of all ICs, oseltamivir also significantly reduced incidence of clinical influenza, with 89% protective efficacy (95% CI, 71%-96%; $P<.001$). Viral shedding was inhibited in contacts taking oseltamivir, with 84% protective efficacy (95% CI, 57%-95%; $P<.001$). All virus isolates from oseltamivir recipients retained sensitivity to the active metabolite. Oseltamivir was well tolerated; gastrointestinal tract effects were reported with similar frequency in oseltamivir (9.3%) and placebo (7.2%) recipients.

Conclusion In our sample, postexposure prophylaxis with oseltamivir, 75 mg once daily for 7 days, protected close contacts of influenza-infected persons against influenza illness, prevented outbreaks within households, and was well tolerated.

JAMA. 2001;285:748-754 www.jama.com

INFLUENZA IS SPREAD WITHIN THE community by aerosol infection.[1,2] Its incidence is increased in family contacts of a primary case compared with sources of infection outside the immediate household.[3-5] Prevention of influenza in family contacts is recognized as a means of controlling the spread of influenza within communities.[6]

The M2 inhibitors amantadine and rimantadine have been used with variable success in postcontact prophylaxis in families and nursing homes,[7-9] but their use is limited by the rapid development of resistance and, for amantadine, poor tolerance.[10-13] In addition, these agents have no activity against influenza B. Neuraminidase inhibitors are a new class of anti-influenza agents that overcome these limitations.[14]

Oseltamivir (Ro 64-0796) is the orally bioavailable ethyl ester prodrug

Author Affiliations: Children's Hospital, Buffalo, NY (Dr Welliver); University of Michigan School of Public Health, Ann Arbor (Dr Monto); Comprehensive Clinical Research, Berlin, NJ (Dr Hassman); Kentucky Pediatric and Adult Research, Bardstown, Ky (Dr Hedrick); Roche Global Development, Welwyn, England (Drs Jackson, Huson, and Ward); and St Bartholomew's and Royal London Hospital School of Medicine and Dentistry, and Retroscreen Virology Ltd, London, England (Dr Oxford). Dr Carewicz is in private practice in Heidelberg, Germany, and Dr Schatteman is in private practice in Drogen, Ghent, Belgium. A list of the members of the Oseltamivir Post Exposure Prophylaxis Investigator Group and Financial Disclosures appear at the end of this article.
Corresponding Author and Reprints: John S. Oxford, PhD, The Medical Building, 327 Mile End Rd, London, England E1 4NS (e-mail: j.s.oxford@retroscreen.com).

of Ro 64-0802, a potent and selective inhibitor of influenza neuraminidase in vitro.[15] Oseltamivir is the first orally administered neuraminidase inhibitor with demonstrated efficacy in the treatment of naturally acquired influenza in humans.[16] Orally administered oseltamivir protects against experimental influenza in animals and humans.[17-19] Daily administration of one 75 mg capsule for 6 weeks was effective and well tolerated in preventing influenza during a seasonal outbreak.[20]

In this study, we investigated the efficacy of oseltamivir in prevention of the secondary spread of disease to household contacts of influenza-infected cases.

METHODS

This cluster-randomized, double-blind, placebo-controlled study was performed in 76 centers in North America and Europe during community outbreaks of influenza in the winter of 1998-1999. The study was approved by local institutional review boards or ethics committees at each center and was conducted in full compliance with the amended Declaration of Helsinki.[21] Each participant provided written informed consent.

Study Population

Families were informed about this study by means of posters and leaflets in the participating clinics and from local press advertisements both prior to and during the influenza season. During the influenza outbreak, family practitioners recruited eligible households with a minimum of 2 and a maximum of 8 contacts within 48 hours of symptom onset (minimum cough and coryza) in a primary (index) case (IC). Children (<12 years) were excluded from participation as contacts, but households in which other members met the conditions for eligibility and in which the child was the IC were permitted entry. Households that contained women who were pregnant or breastfeeding, and any individual with cancer, immunosuppression, human immunodeficiency virus infection, or chronic liver or renal disease were also excluded from the study. Household members with other well-controlled comorbidities and those who were vaccinated were eligible. Elderly subjects (≥65 years) were required to achieve a Mental Status Questionnaire score of 7 or higher.[22]

Study Procedures

Index Cases. Nose and throat swabs and a serum sample were collected from all ICs within 48 hours of symptom onset. The IC did not receive any antiviral therapy. All ICs were followed up at a clinic visit and serum samples were drawn between study days 17 and 25.

Contacts. Before the first dose of study medication, all contacts underwent a physical examination including vital signs and oral temperature measurement. Nose and throat swabs for influenza virus culture and a serum sample for influenza-specific antibodies were taken from all contacts at baseline. Baseline (predose) samples of blood and urine were collected for routine laboratory tests. All contacts returned for a physical examination on day 8, and a serum sample and clinic visit between study days 17 and 25.

Study Drug

Randomization to 75 mg of oseltamivir or matching placebo once daily for 7 days was by household cluster such that all members of the same family received the same therapy. The first dose was taken within 48 hours of first reported symptoms in the IC. Contacts were instructed to take 1 capsule with water and a light snack at approximately 24-hour intervals, and were provided with symptom-relief medication (500 mg of acetaminophen) if needed.

Identification of Clinical Influenza

Clinical influenza was defined as an oral temperature of 37.2°C or higher and at least 1 respiratory symptom (cough, nasal congestion, or sore throat) and at least 1 constitutional symptom (headache, aches/pains, chills/sweats, or fatigue) occurring in a single 24-hour period. Household contacts recorded their oral temperatures and completed a checklist to record the presence of influenza symptoms daily. Nose and throat swabs were collected from contacts who developed any of the checklist symptoms on days 2 through 8. All ICs had clinical influenza but a subset had laboratory-confirmed infection. All contacts had to have clinical symptoms and laboratory confirmation to be classified as having influenza.

Laboratory Confirmation of Influenza Infection

The diagnosis of influenza infection in both ICs and contacts was made either by isolation of influenza virus from nose and throat swabs or detection of 4-fold or higher increase in influenza-specific hemagglutinin inhibition assay (HAI) titer between baseline and convalescent serum samples.

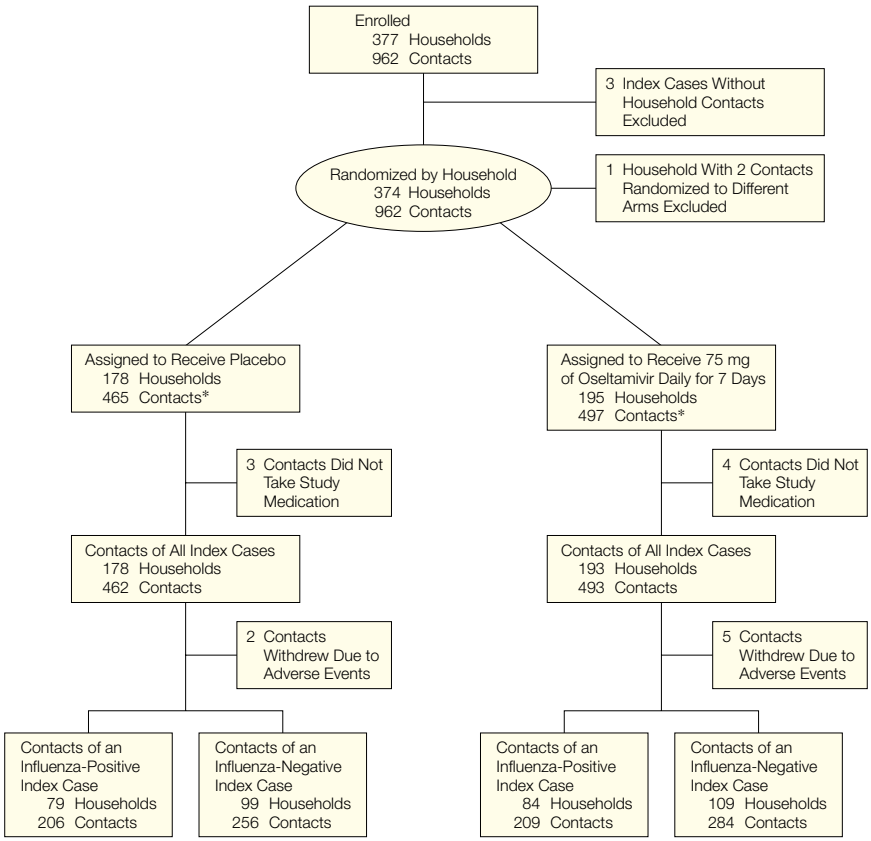
Nose and throat swabs in a chilled viral transport medium were eluted and cryopreserved at a central laboratory within 36 hours of collection from the subject (Covance, Princeton, NJ). The presence of influenza virus was confirmed by indirect fluorescent antibody immunofluorescent assay staining (using monoclonal antibodies [Chemicon International, Temecula, Calif] raised to influenza A and B nucleoproteins) following incubation of swab eluates for up to 7 days in rhesus monkey kidney cell cultures (Bio Whittaker, Walkersville, Md).

Convalescent serum samples were taken from all index and contact cases at study follow-up visits (study days 17-25). Influenza-specific antibody titers were measured by HAI assay. The method used turkey erythrocytes; the antigens tested were the virus strains influenza A/Sydney/5/97(H3N2), A/Beijing/262/95(H1N1), and B/Beijing/184/93 (ViroMed Laboratories, Minneapolis, Minn).

Influenza Neuraminidase Sensitivity

Secreted neuraminidase enzyme in all influenza virus–positive culture supernatants was examined for sensitivity to inhibition by the active metabolite, Ro64-0802 (GS4071) (Hoffmann-La Roche, Basel, Switzerland, data on file).

Figure. Flow Diagram of Enrolled Household Contacts



Asterisk indicates all randomized contacts regardless of whether they took any medication.

Statistical Analyses

The population for safety analysis included all randomized contacts who received at least 1 dose of study drug and at least 1 safety follow-up even if he/she was withdrawn prematurely. Efficacy analyses were performed on 2 populations: contacts of all ICs and contacts of influenza-positive ICs. Contacts of all ICs were defined as those who were randomized, received at least 1 dose of study medication, and reported efficacy data with or without a confirmed influenza-positive IC. Contacts of an influenza-positive IC were defined as those who were randomized, had efficacy data, received at least 1 dose of study medication, and with a confirmed influenza-positive IC.

Primary End Point. The primary efficacy end point was the proportion of contacts of an influenza-positive IC with laboratory-confirmed clinical influenza during the dosing period (study days 1-7 inclusive). The active and the placebo groups were compared using χ^2 tests and test-based confidence intervals (CIs) adjusted to take into account the probable intracluster correlation in end point incidence.[23]

Other Analyses. Other analyses comparing numbers of contacts meeting a given end point used χ^2 tests and CIs adjusted to take into account the probable intracluster correlation in endpoint incidence. Analyses comparing numbers of infected households/families used Fisher exact test. The level of significance was $P<.05$.

RESULTS

A total of 377 households (comprising 962 potential contacts) were enrolled. The majority (>90%) of households consisted of family groups; the remainder were groups of students or young adults. There were 955 eligible contacts of all ICs (99%) in 371 households (FIGURE). The 7 excluded persons did not take any trial medication. One percent of these contacts (12/955) were shedding influenza virus at baseline.

Of the 377 ICs, 163 (43%) had laboratory-confirmed influenza. This is a lower frequency of infection than observed during oseltamivir treatment studies (60%); however, in those studies the case definition also included body temperature of 38°C or higher.[16] The mean age of influenza-infected ICs was 27 years (range, 1-76 years). Ten percent (16/163) were children younger than 11 years (2.5% [4/163] were <5 years), 33% (54/163) were adolescents (12-17 years), and the remainder were older than 18 years, reflecting the recruitment focus on families with teenage siblings (≥12 years). There were 415 contacts in the 163 households in which the IC had laboratory-confirmed influenza infection (Figure, TABLE 1). This subset of contacts included 10 subjects (6 received placebo and 4 oseltamivir) who were already shedding influenza virus at baseline. Five of these were asymptomatic (4 placebo and 1 oseltamivir) and remained asymptomatic throughout the study. Three (2 placebo and 1 oseltamivir) had low-grade symptoms that did not meet the case definition at entry; none developed an illness meeting the case definition during the study. One (who received oseltamivir) met the case definition at study entry and was admitted in violation of the protocol. One other subject had fever at entry and developed an illness meeting the case definition on day 2 of oseltamivir prophylaxis.

The difference between the 2 populations (955 minus 415) identifies the 540 subjects who were household contacts of ICs who were not subsequently confirmed to have influenza infection (contacts of an influenza-negative IC; Figure). These individuals were, nevertheless, likely to have been exposed to influenza virus outside the household in the wider community.

Assignment of household contacts to placebo or active drug is shown in the Figure. In both analysis populations (contacts of all ICs and contacts of an influenza-positive IC), the comparator groups were well-matched, both demographically and in immune status (TABLE 2).

Both influenza types A and B were circulating during the study; 86 (53%) of 163 infected ICs had laboratory evidence of infection with influenza A. Laboratory evidence of infection with both type A and B viruses in the same household was infrequent (3% of households).

Table 1. Contacts Receiving Oseltamivir or Placebo With Laboratory-Confirmed Clinical Influenza During the Treatment Period*

	No./Total (%)		Percentage With Protective Efficacy (95% Confidence Interval)	*P* Value
	Placebo	Oseltamivir		
Contacts of all index cases				
Individuals	34/462 (7.4)	4/493 (0.8)	89 (71-96)	<.001
Affected households	26/178 (14.6)	4/193 (2.1)	86 (60-95)	<.001
Contacts of an influenza-positive index case				
Individuals	26/206 (12.6)	3/209 (1.4)	89 (67-97)	<.001
Affected households	18/79 (22.8)	3/84 (3.6)	84 (49-95)	<.001
Contacts of an influenza-negative index case				
Individuals	8/256 (3.1)	1/284 (0.4)	89 (10-99)	.009
Affected households	8/99 (8.1)	1/109 (0.9)	89 (10-99)	.01

*All randomized contacts with any efficacy data who received 1 or more doses of study medication.

Table 2. Demographic Data for Contacts of All Index Cases and Contacts of an Influenza-Positive Index Case*

	Placebo	Oseltamivir
Contacts of All Index Cases		
	(n = 462)	(n = 493)
Women, %	51	51
Age, mean (range), y	33.7 (12-85)	33.2 (13-82)
>48-hour delay to first dose		
Infected index case	5 (2.4)	0
Noninfected index case	11 (4.2)	9 (3.2)
Vaccinated	64 (13.9)	56 (11.4)
Baseline serum HAI titers ≥1:40		
Influenza A H3N2	362 (78.4)	390 (79.1)
Influenza B	301 (65.2)	335 (68.0)
Contacts of an Influenza-Positive Index Case		
	(n = 206)	(n = 209)
Women, %	52	52
Age, mean (range), y	36.1 (13-83)	34.3 (13-78)
Infected index cases with >48-hour delay to first dose	5 (2.4)	0
Vaccinated	28 (14)	33 (16)
Baseline serum HAI titers ≥1:40		
Influenza A H3N2	155 (75)	160 (77)
Influenza B	133 (65)	141 (67)

*Values are expressed as number (percentage) unless otherwise indicated. HAI indicates hemagglutinin inhibition assay.

Efficacy

Protective efficacy of oseltamivir was determined on the basis of the number of individuals and households exposed to all ICs (Table 1). Protective efficacy in this situation was very high, 89% for individuals (95% CI, 71%-96%; $P<.001$) and 86% for households (95% CI, 60%-95%; $P<.001$) (Table 1). The minor difference between the 2 estimates reflects the effect of multiple clinical cases in single households. In the contacts of all ICs who received oseltamivir, all cases of laboratory-confirmed clinical influenza occurred in separate households, whereas for those taking placebo multiple cases occurred in 7 of the 26 affected households (Table 1), possibly as a result of the prolonged exposure afforded by the second household case.

Oseltamivir demonstrated the same high-protective efficacy in contacts of infected ICs. In this population, the incidence of laboratory-confirmed clinical influenza in individuals and households receiving oseltamivir during the 7-day prophylaxis period was reduced by 89% (95% CI, 67%-97%; $P<.001$) and 84% (95% CI, 49%-95%; $P<.001$), respectively (Table 1). Five contacts in the 163 households developed influenza due to a virus type that was different from that detected in the IC. These individuals probably acquired influenza infection from contact with a case outside the home environment.

There was a larger number of influenza cases reported in the contacts of all ICs compared with contacts of an influenza-positive IC (Table 1). Of 540 contacts of an influenza-negative IC, 3.1% (8/256) of placebo recipients developed laboratory-confirmed clinical influenza compared with only 0.4% (1/284) of oseltamivir recipients. Protective efficacy for individuals exposed to influenza outside the household was therefore also 89% (95% CI, 10%-99%; $P=.009$) (Table 1).

Twenty-one of the clinical cases among the placebo recipients were infected with influenza A and 13 with influenza B virus. None of the clinical cases in the group of oseltamivir-treated contacts was infected with influenza A virus. The protective efficacy against influenza B illness in contacts of all ICs was 78.5% ($P=.02$).

Households were followed up between study days 10 and 18 after the last day of study medication. Only 2 new cases of laboratory-confirmed clinical influenza (1 placebo and 1 oselta-

Table 3. Contacts Receiving Oseltamivir or Placebo With Symptomatic or Asymptomatic Laboratory-Confirmed Influenza Infection*

	No./Total (%)		
	Placebo	Oseltamivir	*P* Value
Contacts of all index cases			
Individuals	60/462 (13)	33/493 (6.7)	.007
Affected households	45/178 (25.3)	29/193 (15)	.02
Contacts of an influenza-positive index case			
Individuals	43/206 (20.9)	16/209 (7.7)	.003
Affected households	28/79 (35.4)	13/84 (15.5)	.004
Contacts of an influenza-negative index case			
Individuals	17/256 (6.6)	17/284 (5.9)	.76
Affected households	17/99 (17)	16/109 (14.7)	.71

*All randomized contacts with efficacy data who received 1 or more doses of study medication.

mivir) occurred during follow-up; these were likely due to exposure during the off-prophylaxis period.

Since 10 subjects among the contacts of an influenza-positive IC were confirmed to be shedding virus prior to the first dose of study medication, an additional analysis of the primary end point was made excluding these individuals. In this analysis, 24 (12%) of 200 contacts in the placebo group developed clinical influenza compared with 2 (1%) of 205 oseltamivir recipients. The protective efficacy of oseltamivir in this population was 92% (95% CI, 71%-98%; $P<.001$) for prevention of clinical influenza.

An additional analysis examined only those individuals who were shedding virus and therefore more likely to transmit influenza to others. The frequency of viral shedding during the study period was significantly reduced in oseltamivir recipients (4/209 contacts of an influenza-positive IC and 5/493 contacts of all ICs) compared with placebo (24/206 contacts of an influenza-positive IC and 30/462 contacts of all ICs). The protective efficacy in contacts of an influenza-positive IC was 84% (95% CI, 57%-95%; $P<.001$). No isolates from patients who shed virus demonstrated reduced sensitivity to the active metabolite of oseltamivir.

Laboratory evidence of influenza infection (whether confirmed by viral shedding or seroconversion) in both symptomatic and asymptomatic contacts was reduced with oseltamivir (16/209 contacts of an influenza-positive IC with 8 [50%] who were asymptomatic; 33/493 contacts of all ICs with 18 [55%] who were asymptomatic) compared with placebo (43/206 contacts of an influenza-positive IC with 7 [16%] who were asymptomatic; 60/462 contacts of all ICs with 14 [23%] who were asymptomatic). A protective efficacy of 63% (95% CI, 40%-80%; $P=.003$) was found for contacts of an influenza-positive IC and 49% (95% CI, 25%-67%; $P=.007$) for contacts of all ICs (TABLE 3).

Tolerability

The dosage of 75 mg of oseltamivir once daily for 7 days was well tolerated. Gastrointestinal tract effects were reported with similar frequency in recipients of oseltamivir (9.3% [46/494]) and placebo (7.2% [33/461]). Nausea, which was reported by 5.5% (27/494) of oseltamivir and 2.6% (12/461) of placebo recipients, was predominantly mild and transient. There were no abnormal shifts in laboratory measures of safety or vital signs and no serious adverse events in those receiving treatment. Withdrawal rates due to adverse events were low in both groups: 5 (1%) of 494 receiving oseltamivir and 2 (0.4%) of 461 receiving placebo. The 2 placebo subjects (who withdrew on developing an influenzalike illness) had influenza virus identified from nose and throat swabs collected on the day of withdrawal. In the oseltamivir-treated group, 2 subjects withdrew after developing bronchitis on day 6 (neither had influenza infection), 1 for headache, 1 for vomiting, and 1 for dyspepsia.

COMMENT

When one family member develops influenza, others in the family are known to be at heightened risk of being infected. In this study, the risk of infection within the household was 20%. Also, the period at risk is generally at a time when the outbreaks are continuing in the community, so new introductions of infection into families are also possible. Whatever the source of infection, this study shows that oseltamivir prophylaxis resulted in significant reductions in influenza illness in contacts. This was the case whether the end point was based on numbers of individuals or numbers of households with additional influenza-related illnesses.

As in previous studies with antiviral agents (and in line with the mode of action of neuraminidase inhibitors), efficacy in preventing clinical influenza (89%) was greater than preventing initial viral infection (63%). Fifty percent of the subjects in the oseltamivir group who became infected with influenza remained asymptomatic compared with 16% of those taking placebo. These data again demonstrate that curtailing viral replication early following infection effectively prevents the development of clinical disease.[20,24] Virus shedding was also significantly reduced, thus reducing the potential for further spread of influenza within the household.

The reduction in the incidence of clinical influenza by oseltamivir occurred whether the source of infection was identified within the household or not (89% protective efficacy in both cases). This suggests that oseltamivir is equally effective at preventing clinical influenza whether primary exposure occurs within the family or outside the household in the wider community. Furthermore, this substantial level of protection was achieved without treating the IC, thereby maximiz-

ing exposure of contacts to influenza. These data corroborate the 92% protective efficacy of oseltamivir demonstrated in elderly persons (64-96 years) in skilled nursing homes[24] and a 6-week seasonal prophylaxis study carried out in healthy adults (aged 18-65 years).[20]

The virus isolation rate in the oseltamivir-treated group was low and none of the isolates were resistant to the carboxylate. As the IC was not treated in this study, the possibility of transmission of resistant virus, as described in a similar study with rimantadine,[12] could not be studied. The incidence of emergence of virus resistance to neuraminidase inhibitors is low[16,25] and, in contrast to rimantadine-resistant viruses that retain full infectivity,[26] resultant viral mutants are 100- to 1000-fold less infectious than wild-type virus in animal studies.[27] Given the low frequency of resistance to neuraminidase inhibitors and the reduced infectivity of the viruses detected to date, transmission seems unlikely to occur in practice, although this needs to be confirmed by further study.

The 84% level of protection afforded by oseltamivir to families in our study compares with the 72% protection achieved using the inhaled neuraminidase inhibitor zanamivir in a similar household study.[28] In the zanamivir study, prophylaxis was initiated within a narrower window (36 hours) of symptom onset in the IC. In addition, that study gave drug or placebo to the IC for 5 days and gave contacts drug or placebo for 10 days compared with a 7-day treatment course in our study. Furthermore, since in the zanamivir study all household members, whether ICs or contacts, were placed together with drug or placebo, it is impossible to say how much of the preventive effect seen in the contacts was due to actual prophylaxis by the drug or how much was related to reduction in viral shedding in the IC. Since oseltamivir is now approved for prophylaxis as well as treatment, a physician can elect to treat or not treat the IC with oseltamivir, but still prescribe oseltamivir for household contacts.

A limitation of this study was the inability to include children younger than 13 years at the time it was conducted. Reduction of virus transmission in children should be an aim of family prophylaxis, and its importance was most recently emphasized by the study by Hurwitz et al[29] involving the influenza vaccine. The recent demonstration of efficacy[30] of oseltamivir in the treatment of influenza in children aged 1 to 12 years suggests that the protective efficacy in children can be anticipated to be similar to that demonstrated in adolescents and adults. Children are important both in the introduction and spread of influenza in families, and inclusion of such families in a postexposure prophylaxis strategy will further extend the value of this approach. Only 2.5% of the ICs were preschool-aged children. Very young children with influenza shed virus for up to 10 days compared with between 3 and 5 days reported in adults and adolescents. For this reason, a longer period of prophylaxis may be required in contacts of infected preschool-aged children to cover the period of risk.

This study demonstrates that 75 mg of oral oseltamivir taken once daily for 7 days was highly effective in protecting close contacts against influenza illness when initiated within 48 hours of exposure to a symptomatic case of influenza and was well tolerated. Oseltamivir effectively prevented further transmission of influenza within households following prompt initiation of short-term prophylaxis in families. This occurred even when the IC was not treated, as would probably occur in many circumstances in clinical practice. Treating the IC would further reduce the risk of transmission. Use of oseltamivir short-term will selectively reduce the burden of influenza in those likely to have been exposed to an IC in their household, a group at particularly high risk of developing influenza.

Author Contributions: Dr Welliver participated in acquisition of data, critical revision of the manuscript for important intellectual content, and provided administrative, technical, or material support.
Dr Monto participated in study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and provided statistical expertise.
Dr Carewicz participated in acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, provided statistical expertise, and supervised conduct of the study.
Dr Schatteman participated in acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and provided administrative, technical, or material support.
Dr Hassman participated in acquisition of data, critical revision of the manuscript for important intellectual content, and provided administrative, technical, or material support.
Dr Hedrick participated in analysis and interpretation of data, drafting of the manuscript, and provided administrative, technical, or material support.
Dr Jackson participated in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, provided administrative, technical, or material support, and supervised conduct of the study.
Dr Huson participated in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and provided statistical expertise.
Dr Ward participated in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervised conduct of the study.
Dr Oxford participated in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervised conduct of the study.
Full Access to Data: Dr Oxford had full access to all data in this study and has taken responsibility for the integrity of data collection and accuracy of data analysis.
Funding/Support: This study was funded by Hoffmann-La Roche.
Financial Disclosure: Dr Hassmann has done clinical research with Roche Pharmaceuticals and has given several lectures and presentations on influenza and treatment with oseltamivir. Dr Oxford has received honoraria, traveling expenses to scientific meetings, and research funding support from Hoffmann-La Roche.

Oseltamivir Post Exposure Prophylaxis Investigator Group: *Belgium:* Moorsel: N. Van Mulders; Tessenderlo: A. Ceulemans. *Canada:* British Columbia: Coquitlam: D. Shu; Vancouver: P. Vohora; Winnipeg, Manitoba: F. Y. Aoki, G. W. Hammond, P. H. Orr, and J. N. Simonsen; Ontario: Mississauga: P. Patel; Oshawa: P. Whitsitt; Ottawa: F. Diaz-Mitoma; Toronto: E. Wang; Quebec: Montreal: B. Pynn; St Jerome: G. Tellier; Ste-Foy: S. Trottier; Regina, Saskatchewan: G. Achyuthan. *Denmark:* Lyngby: L. Hergel. *Finland:* Espoo: O. Amzil and T. Aronkytö; Pori: E. Karra; Salo: S. Junnila; Vantaa: J. Anttila and K. Piispanen. *Germany:* Bechhofen: R. Lebmeier; Deggingen: T. Jung; Gau-Algesheim: C. Raddatz; Goch: T. Menke; Hermaringen: R. Fuchs. *the Netherlands: Castricum: P. Buitenhuis; Losser: A. J. M. Boermans; Nijverdal: J. Veerman.* Norway: *Oslo: H. Gjessing; Sorum: R. Hellebo.* Switzerland: *Genève: D. Lew, J. Garbino, and S. Huget.* United Kingdom: Buckinghamshire: W. I. C. Clark; Cornwall: R. C. Cook; Hants: M. MacLeod; Perth: F. Currie; Plymouth: C. P. Fletcher and K. Gillespie; Plympton: A. Golding-Cook; Sheffield: M. Davidson; *United States:* Birmingham, Ala: S. Touger; Tempe, Ariz: T. Fiel; California: Buena Park: W. Jannetti and D. J. Sunga; Carmichael: J. Champlin; Chico: M. Vichare; Fresno: J. McCarty; La Mesa: M. Nosan; Orange: S. Galant; San Diego: D. Brandon and H. Hassman; Miami, Fla: H. Schwartz; Augusta, Ga: A. Carr;

New Orleans, La: W. Smith; Duluth, Minn: I. Abolnik; St Louis, Mo: R. Barbarash; Missoula, Mon: C. Cone; Papillon, Neb: T. Casale; Winston Salem, NC: T. Littlejohn; Cincinnati, Ohio: M. Noss; Pennsylvania: Downingtown: L. Alwine; Philadelphia: V. Bralow; Pittsburgh: K. Reisinger; Memphis, Tenn: D. Peterson; Houston, Tex: C. McKeever; Vienna, Va: R. Schwartz; and Washington: Edmonds: R. Bettis; Spokane: M. Wukelic.

REFERENCES

1. Human influenza. In: Nicholson KG, Webster RG, Hay AJ, eds. *Textbook of Influenza.* Oxford, England: Blackwell Science; 1998:219-264.
2. Stuart-Harris CH, Schild GC, Oxford JS. *Influenza: The Viruses and the Disease.* 2nd ed. London, England: Edward Arnold; 1985:264.
3. Foy HM, Cooney MK, Allen I. Longitudinal studies of types A and B influenza among Seattle school children and families, 1968-1974. *J Infect Dis.* 1976; 134:362-369.
4. Fox JP, Hall CE, Cooney MK, Foy HM. Influenza virus infections in Seattle families, 1975-1979. *Am J Epidemiol.* 1982;116:212-242.
5. Taber LH, Paredes A, Glezen WP, Couch RB. Infection with influenza A/Victoria virus in Houston families, 1976. *J Hyg.* 1981;86:303-313.
6. Longini IM, Koopman JS, Monto AS, Fox JP. Estimating household and community transmission parameters for influenza. *Am J Epidemiol.* 1982;115: 736-751.
7. Clover RD, Crawford SA, Abell TD, Ramsey CN Jr, Glezen WP, Couch RB. Effectiveness of rimantadine prophylaxis of children within families. *Am J Dis Child.* 1986;140:706-709.
8. Galbraith AW, Oxford JS, Schild GC, Watson GI. Study of 1-adamantanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family. *Environ Bull WHO.* 1969;41: 677-682.
9. 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; 2:1026-1028.
10. Degelau J, Somani SK, Cooper SL, Guay DR, Crossley KB. Amantadine-resistant influenza A in a nursing facility. *Arch Intern Med.* 1992;152:390-392.
11. Hayden FG, Gwaltney JM Jr, van de Castle RL, Adams KF, Giordani B. Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adults. *Antimicrob Agents Chemother.* 1981; 19:226-233.
12. 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.
13. 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;35:1741-1747.
14. Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet.* 2000;355:827-835.
15. Kim CU, Lew W, Williams MA, et al. Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. *J Am Chem Soc.* 1997;119:681-690.
16. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA.* 2000;283:1016-1024.
17. Mendel DB, Tai CY, Escarpe PA, et al. Oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS4071 protects mice and ferrets against influenza infection. *Antimicrob Agents Chemother.* 1998;42:640-646.
18. Sidwell RW, Huffman JH, Barnard DL, et al. Inhibition of influenza virus infections in mice by GS4104, an orally effective influenza virus neuraminidase inhibitor. *Antiviral Res.* 1998;37:107-120.
19. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA.* 1999;282:1240-1246.
20. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med.* 1999;341:1336-1343.
21. World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *JAMA.* 1997;227:925-926.
22. Wilson LA, Brass W. Brief assessment of the mental state in geriatric domiciliary practice: the usefulness of the Mental Status Questionnaire. *Age Ageing.* 1973;2:92-101.
23. Donner A. Some aspects of the design and analysis of cluster randomization trials. *Appl Stat.* 1998;47: 95-113.
24. De Bock V, Peters P, von Planta T-A, et al. Oral oseltamivir for prevention of influenza in the frail elderly. *Clin Microbiol Infect.* 2000;6(suppl 1):140.
25. Gubareva LV, Matrosovich MN, Brenner MK, et al. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis.* 1998;178:1257-1262.
26. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. *Curr Top Microbiol Immunol.* 1992;176: 120-130.
27. Covington E, Mendel DB, Escarpe P, et al. Phenotypic and genotypic assay of influenza virus neuraminidase indicates a low incidence of viral drug resistance during treatment with oseltamivir [abstract P-326]. *J Clin Virol.* 2000;18:253.
28. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med.* 2000;343:1282-1289.
29. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA.* 2000;284:1677-1682.
30. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J.* In press.