MAJOR ARTICLE

Management of Influenza in Households: A Prospective, Randomized Comparison of Oseltamivir Treatment With or Without Postexposure Prophylaxis

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We determined the efficacy of postexposure prophylaxis (PEP) and treatment of ill index cases with oseltamivir, in an attempt to prevent influenza transmission in households, in a study conducted in 277 households with 298 index cases (62% with laboratory-confirmed influenza) and 812 contacts aged ⩾1 year. Contacts were randomized by household to receive treatment (5 days; $n = 402$), if illness developed, or PEP for 10 days ($n = 410$), and the number of households with at least 1 contact developing laboratory-confirmed influenza was measured. PEP provided a protective efficacy of 58.5% (95% confidence interval [CI], 15.6%–79.6%; $P = .0114$) for households against proven influenza and 68.0% (95% CI, 34.9%–84.2%; $P = .0017$) for individual contacts, compared with treatment of index cases alone. No oseltamivir-resistant variants were detected in treated index cases or contacts. PEP of household contacts of those with influenza reduces the secondary spread of influenza in families when the initial household case is treated.

Households are an important site of influenza virus transmission during community outbreaks [1–4]. In some epidemics, up to 50% of households have ⩾1 member who become infected. The secondary illness attack rates among family members depend on the circulating strains and range from 10% to nearly 40% in different studies [3–10]. The prevention of influenza transmission in family contacts is therefore a potentially valuable strategy for reducing the effect of this illness. For example, preseason influenza immunization of school-aged children has been shown to reduce the risk of illness in adult and sibling contacts [11] and has been associated with reduced morbidity and mortality in community-dwelling adults [12, 13]. However, the vaccination of otherwise healthy adults and children is not routinely performed in most countries.

Unlike vaccination, antiviral chemoprophylaxis offers the possibility of immediate protection during household introductions of influenza virus. Indeed, antiviral chemoprophylaxis of children with an M2 protein inhibitor appeared to reduce the occurrence of influenza infection in adult household members [14, 15]. However, although these agents appear to be effective against influenza illness when used for postexposure prophylaxis (PEP) alone, they lose effectiveness when combined with the treatment of ill index cases. One possible explanation is the emergence and transmission of drug-resistant variants from treated index patients to other family members [8], an outcome that limits the utility of such agents. The neuraminidase inhibitors oseltamivir and zanamivir are effective for

Received 9 July 2003; accepted 24 October 2003; electronically published 26 January 2004.

Presented in part: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, 16–19 December 2001 (abstract H-663); 42nd ICAAC, San Diego, 27–30 September 2002 (abstract V-244).

F.G.H. has served as a paid consultant to Hoffman–La Roche. Several coauthors are employed by Roche (C.H., I.S., R.D., P.W., and J.C.).

Financial support: Hoffman–La Roche, Inc.

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The Journal of Infectious Diseases 2004;189:440–9

0022-1899/2004/18903-0011$15.00

PEP of both influenza A and B in households [10, 16, 17]. When combined with the treatment of index cases, prophylaxis of family members aged >5 years with once-daily inhaled zanamivir reduced the risk of influenza in contacts. In addition, there was no evidence of the emergence of zanamivir-resistant variants [10]. However, preschool-aged children and elderly persons may not be able to reliably use an inhaler or to produce the inspiratory effort needed to deliver zanamivir reliably to the airways [18, 19]. Unlike zanamivir, oseltamivir is available as an oral formulation that has been shown to be highly effective for PEP in family contacts aged ⩾13 years [16]. However, the latter study did not include younger children or incorporate concurrent treatment of the ill index cases. Therefore, we undertook the present study to compare the efficacy of combining oral oseltamivir treatment of ill index cases with or without PEP of close household contacts (including young children) for the prevention of influenza transmission in households. In addition, we monitored the possibility of oseltamivir resistance emergence and transmission.

SUBJECTS AND METHODS

Study design. The study was a prospective, open-label, parallel-group trial conducted in Europe and North America during the 2000–2001 influenza season. Household contacts of index cases presenting with an influenza-like illness (defined by temperature ⩾37.8°C plus cough and/or coryza) during a documented community influenza outbreak were randomized by household to receive PEP with oseltamivir for 10 days or treatment at the time of developing illness (expectant treatment) during the postexposure period. All index cases received oseltamivir treatment for 5 days. Study approval was obtained from local institutional review boards or ethics committees, and the study was conducted in compliance with the Declaration of Helsinki and subsequent amendments. Written informed consent was obtained from all individuals (or their legal guardian, where appropriate) prior to their participation in the study.

Study population. Eligible households had 3–8 members, including at least 1 index case and at least 2 eligible contacts aged ⩾1 year. Children aged ⩽1 year were excluded from participation. Households that contained women who were pregnant or breast-feeding or any individual with cancer, immunosuppression, HIV infection, chronic liver or renal disease, or significant cardiac failure (New York Heart Association class IV) were also excluded, as were individuals who had received anti-influenza antiviral drugs and those who had experienced a previous episode of acute respiratory tract infection within the preceding 2 weeks. Households containing an individual who was not eligible for the study could participate, provided that no more than 1 contact was ineligible. All contacts were required to present for an evaluation by a study physician, including a nasal or throat swab to test for influenza infection, prior to the receipt of medications.

Drug administration. All index cases received treatment with oseltamivir twice daily for 5 days, beginning within 48 h of the reported onset of symptoms. Contacts randomized to the expectant treatment arm were also given a standard 5-day treatment course if illness developed (adults and adolescents [children aged >12 years] received 75-mg oseltamivir capsules twice daily, whereas children aged 1–2, 3–5, and 6–12 years received 30, 45, and 60 mg oseltamivir suspension, respectively, twice daily). Compliance was high, with >98% of subjects taking medications for the intended periods. At the discretion of the treating physician, a second course of treatment could be provided in the event that the subject developed an influenza-like illness after the completion of the first course of oseltamivir. Household contacts randomized to the PEP group began oseltamivir prophylaxis within 48 h of the first onset of influenza-like symptoms in the index case(s). The age-adjusted dose was the same as that used for treatment but was given once daily for 10 days.

Households were randomized by cluster, so that all contacts in the household received the same treatment. Randomization was stratified by the presence or absence of an infant (age <1 year) in the household and by the presence or absence of a second index case in the household.

Clinical and virological monitoring. Index cases and contacts recorded body temperature and the presence or absence and severity of any influenza-like symptoms at the enrollment visit and twice daily, during a 30-day follow-up period, on diary cards. Individuals who developed an influenza-like illness during the follow-up period reported to the study center for assessment and viral culture. Throat and nose swabs were taken for influenza viral culture from all index cases at the initial visit and at the end of the 5-day treatment period. Swabs were also taken from all contacts at enrollment, at the time of the development of an influenza-like illness, and again on day 10. Swabs were also obtained at the end of any course of oseltamivir treatment received by contacts. Serum samples for determining influenza strain–specific hemagglutination-inhibition (HAI) antibody titers were obtained at baseline and on day 30.

Influenza infection was laboratory confirmed by detection of viral shedding in nose/throat swabs (shell-vial culture [Madin-Darby canine kidney cells]; Covance Laboratories) or by a ⩾4-fold increase in the HAI antibody measurement (MRL Laboratories), as described elsewhere [20, 21]. All virus isolates were tested for phenotypic susceptibility to oseltamivir by a neuraminidase inhibition assay based on that of Potier et al. [22] but using 200 μmol/L 2′-(4-methylumbelliferyl)-α-D-N-acetylneuraminic acid substrate. This higher substrate concentration increased assay sensitivity but disproportionately elevated IC_{50} values for influenza B neuraminidases.

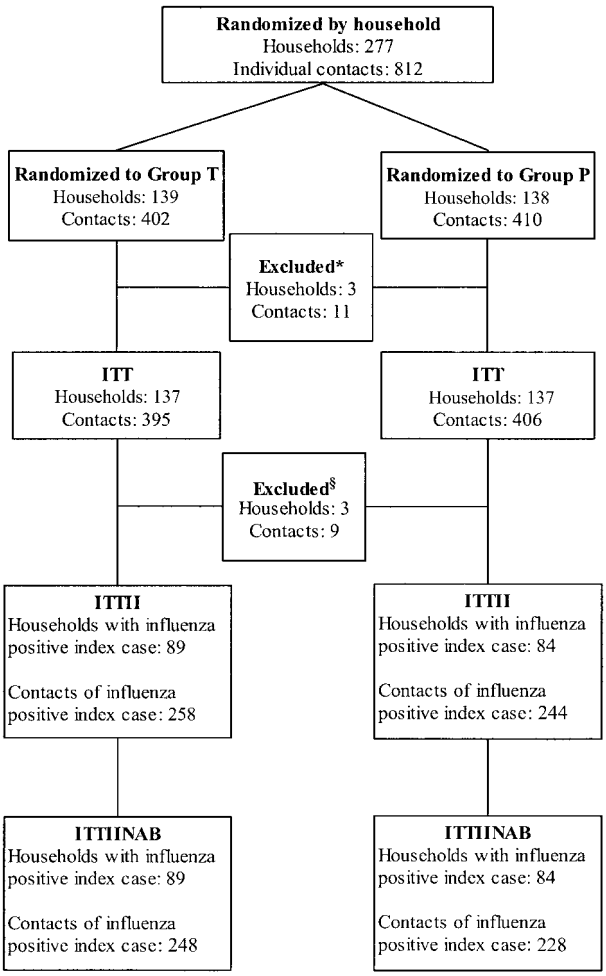

Figure 1. Flow diagram of randomized household contacts. *Exclusions due to missing efficacy data, after baseline; §Exclusions due to missing serology/virology data. ITT, overall intent-to-treat population (all randomized households and contacts, regardless of infection status in the index case); ITTII, intent-to-treat index of the infected population (households and contacts of influenza-infected index cases); ITTIINAB, subpopulation of contacts who were virus-negative at baseline.

Outcomes. The primary efficacy variable in the present study was the percentage of households with at least 1 secondary case of laboratory-confirmed influenza illness during the 10-day period after the start of treatment in the index case(s). This analysis was also performed for households without proven influenza in the index case and for households with introductions of influenza A or B virus. Similar analyses were completed for individual contacts and specifically for children aged 1–12 years.

The duration of illness, defined as the time to alleviation of symptoms [20, 21], was determined for treated index cases and for those who developed illness, to evaluate the burden of illness in the household. Symptom alleviation was considered to occur at the start of the first 24-h period in which the severity of all influenza symptoms were scored as mild or none and remained so for at least 24 h.

Safety and tolerability. All adverse events encountered during the study were recorded, irrespective of whether they were considered to be related to treatment. Symptoms and sequelae of influenza were not considered to be adverse events unless they were considered to be serious and/or they fulfilled predefined criteria for a complication of influenza.

Statistical analysis. The primary population for efficacy analysis was the intent-to-treat index–infected (ITTII) population, defined as those households and contacts of laboratory-confirmed, influenza-infected index cases. Additional analyses were completed for the subpopulation of contacts who were virus-negative at baseline (ITTIINAB) and for the overall intent-to-treat (ITT) population (i.e., all randomized households and contacts, regardless of infection status in the index case). Between-group comparisons were made using Fisher's exact test. The treatment effect was measured by calculating the percentage protective efficacy of oseltamivir together with the corresponding 95% confidence interval (CI). Weighted Mantel-Haenszel tests were performed to compare times to the alleviation of illness, and nonparametric methods were used to compare measures of illness burden.

Sample size calculations for the study were based on assumptions concerning the potential incidence of febrile, laboratory-confirmed influenza in households derived from previous studies. Under the assumption that 50% of the index cases would have confirmed influenza infection, 200 influenza-affected households (100 each in the expectant treatment and PEP arms, respectively) were required to provide >80% power, under the assumption that the incidence of influenza in households was >20% and that oseltamivir would be at least 80% effective in preventing further spread to household contacts.

RESULTS

Characteristics of Households and Index Cases

A total of 298 index cases across 277 households were included in the study, with 139 households being randomized to the expectant treatment arm and the remainder ($n = 138$) to PEP (figure 1). Overall, the 2 groups were comparable in terms of their household characteristics and index cases therein, most of whom were children aged ≤12 years or adolescents aged 13–17 years (table 1). Of those index cases with laboratory-confirmed influenza ($n = 184$), 66% were infected with influenza type A (predominantly influenza A H1N1) and 34% with influenza type B.

Some 812 household contacts were included in the expectant treatment and PEP arms ($n = 402$ and $n = 410$, respectively) (figure 1). In both groups, contacts were randomized within an average of 24 h of the onset of symptoms in the index case. Of the 402 contacts randomized to expectant treatment, 258 (64%) were contacts of influenza-positive index cases, compared with

Table 1. Characteristics of households and index cases, by treatment group.

Characteristic	Expectant treatment	Postexposure prophylaxis
Household		
No.	139	138
Households with laboratory-confirmed infected index case	90[a] (65)	84 (61)
No. of contacts		
1	…	1 (1)
2	41 (46)	34 (40)
3	27 (30)	27 (32)
4	13 (14)	17 (20)
5–7	9 (10)	5 (6)
Children aged <1 year in the household		
None	85 (94)	82 (98)
1	5 (6)	2 (2)
Households with 2 index cases at baseline	6 (7)	9 (11)
Index cases		
No.	148	150
Sex		
Male	76 (51)	58 (39)
Female	72 (49)	92 (61)
Age range, years		
⩽12	65 (44)	69 (46)
13–17	24 (16)	19 (13)
18–64	58 (39)	62 (41)
⩾65	1 (1)	0 (0)
Age, median years (range)	14.0 (2–66)	14.0 (1–60)
Laboratory-confirmed influenza type	94 (64)	90 (60)
A	65 (69)[b]	56 (62)[b]
B	29 (31)[b]	34 (38)[b]
Time to first dose of oseltamivir, median h (range)	23.2 (1.8–47.9)	23.0 (1.4–53.3)

NOTE. Data are no. (%) of households or subjects, except where noted.

[a] One household had no eligible contact cases.

[b] Percentage of those with laboratory-confirmed infection.

244 (60%) of 410 in the PEP group (figure 1). The proportion of current influenza immunizations was low (<10%) among contacts in both groups (table 2). A total of 26 contacts of influenza-infected index cases were shedding influenza virus at baseline (predominantly influenza type A H1N1): 10 in the expectant treatment group and 16 randomized to PEP.

Twenty contacts (10 in each group) were excluded from the primary end-point analysis: 11 (from 3 families) because there was no information permitting assessment of efficacy and 9 (from 3 families) because no serology/culture information was available to assess the influenza infection status. The primary end point included those households in which the index case was confirmed by laboratory evaluation to have true influenza infection. Excluding households where this criterion was not met, a total of 173 households and 476 individual contacts were evaluable and included in the ITTII efficacy analyses (figure 1).

A total of 20 individuals, 74% of whom were age ⩽18 years, received a second oseltamivir course; 4 index cases received a second course of treatment, and 16 contacts either switched to treatment during prophylaxis ($n = 9$) or received a treatment course after completing the 10-day prophylaxis period ($n = 7$). All 20 subjects were tested for influenza illness, and 2 of 4 index cases and 6 of 16 contacts had laboratory-confirmed influenza infection.

Prophylactic Efficacy of Oseltamivir

Households. Postexposure prophylaxis with oseltamivir was effective in preventing the secondary spread of influenza in households (table 3). In the expectant treatment households with an influenza-positive index case (ITTII population), the attack rate for laboratory-proven febrile influenza was 26% of households. The protective efficacy of PEP with oseltamivir was 58.5% (95% CI, 15.6%–79.6%) in such households. This figure increased to 78.8% (95% CI, 40.6%–92.4%) when contacts who tested positive for influenza at baseline were excluded (IT-

Table 2. Summary of contact characteristics at baseline (randomized patient population).

Characteristic	Expectant treatment	PEP
No. of contacts	402	410
Sex		
Male	183 (46)	183 (45)
Female	219 (54)	227 (55)
Age range, years		
⩽12	115 (29)	107 (26)
13–17	54 (13)	64 (16)
18–64	224 (56)	229 (56)
⩾65	9 (2)	10 (2)
Age, median years (range)	25.0 (1–83)	23.5 (1–80)
Previously vaccinated	29 (7)	31 (8)
Smoking status	NA	NA
Concomitant medications		
Nonsteroidal anti-inflammatory drugs	5 (1)	16 (4)
Oral contraceptives	11 (3)	17 (4)
Inhaled corticosteroids	12 (3)	12 (3)
Inhaled short-acting bronchodilators	14 (3)	7 (2)

NOTE. Data are no. (%) of subjects, except where noted. NA, not available; PEP, postexposure prophylaxis.

TIINAB population). In all households (ITT population), the protective efficacy of PEP with oseltamivir was 62.7% (95% CI, 26.0%–81.2%).

Individual contacts. Similar findings were observed when the analysis was performed at the individual contact level (table 3). Thus, the number of contact cases with febrile, laboratory-confirmed influenza was reduced by 68.0%, 84.5%, and 73.1%, respectively, for PEP with oseltamivir in the ITTII, ITTIINAB, and ITT populations. Most of the illnesses occurred early after recognition of the ill index case (figure 2). If illnesses developing on the first or second day were excluded, 17 (6.6%) contacts in the expectant treatment group developed proven illness between days 3 and 10, compared with only 3 (1.2%) subjects in the PEP group (protective efficacy, 81.3%; 95% CI, 35.9–94.6%; $P = .0077$). Only 5 influenza-positive cases (4 in the expectant treatment group and 1 in PEP group) were documented after day 10. Overall, laboratory-confirmed influenza infection, regardless of associated symptoms, was confirmed in 75 (29%) of 258 contacts of influenza-infected index cases in the expectant treatment group, compared with 46 (19%) of 244 in the PEP group (protective efficacy, 35.1%; 95% CI, 8.5–54.0%; $P = .0137$). There were 8 contacts of influenza-negative index cases who had febrile, laboratory-confirmed influenza (7/134 [5.2%] and 1/156 [0.6%] in the expectant therapy and PEP groups, respectively) with onset occurring within the first 10 days (protective efficacy, 87.7%; 95% CI, 14.3–98.2; $P = .0344$).

Pediatric contacts. To our knowledge, this was the first study to investigate the use of oseltamivir prophylaxis in children aged 1–12 years. Among those children who received PEP, the incidence of febrile, laboratory-confirmed influenza was 24% in children residing in households with an influenza-positive index case (ITTII population) and 19% in the ITT population (table 3). The overall frequency of influenza virus infection, regardless of symptoms, was 41% (30/74) among contacts aged 1–12 years in the expectant treatment households. In pediatric contacts, oseltamivir PEP reduced the likelihood of febrile influenza by 55% in households with influenza-positive index cases (ITTII population), by 80% when contacts who were already culture-positive at enrolment were excluded (ITTIINAB population), and by 64% in the ITT population (table 3).

Type-specific protection. The study was not designed to detect a significant difference in efficacy between influenza types. However, the prophylactic efficacy of oseltamivir was similar in households and contacts of both influenza A and B virus–infected index cases (table 3). Concordance of virus serotype between primary and secondary cases was high (76% of contacts of an influenza A [H1N1]–infected index case contracted influenza of the same antigenic strain, whereas 64% of contacts with an influenza B–infected index case became infected with that strain). Such findings are consistent with the conclusion that most transmission was occurring in the household, although approximately one-third of cases appeared to have arisen through new introductions.

Morbidity Measures

Illness severity. The median time from the start of treatment to the alleviation of symptoms among the influenza-infected index cases ($n = 94$) was 56.7 h (range, 0–709 h) in the expectant therapy group and 75.1 h (range, 0–701 h) in the PEP group ($n = 90$; $P = .1520$). In comparison, the median duration of febrile, laboratory-confirmed influenza was generally shorter among contacts, possibly because of the likelihood of earlier intervention on developing illness. Notably, contacts in the PEP group ($n = 10$) tended to have a shorter median duration of illness (5.5 h; range, 0–87 h) if they developed laboratory-confirmed influenza during prophylaxis, compared with those ($n = 33$) in whom treatment began only after the onset of symptoms (39.8 h; range, 0–627 h; $P = .103$).

Burden of illness. During the 10-day period after the start of treatment of the index case, substantially fewer households in the PEP group had contacts with laboratory-confirmed influenza who were sufficiently unwell to necessitate staying in bed for at least 0.5 day (3/37 [8%] households vs. 15/47 [32%] households in the expectant treatment group; $P = .0032$). The number of contacts with laboratory-confirmed influenza who were bed-bound during the same time window was also markedly lower in the PEP group than in the expectant treatment

Table 3. Protective efficacy of oseltamivir against influenza illness.

Analysis, population	No. (%) who received[a]		*P*	% protective efficacy (95% CI)
	Expectant treatment	PEP		
Households				
ITTII	23/89 (26)	9/84 (11)	.0114	58.5 (15.6 to 79.6)
Households whose index case had influenza A	18 (29)	7 (13)	.0446	54.5 (−0.5 to 79.4)
Households whose index case had influenza B	5 (19)	2 (6)	.2332	65.2 (−65.2 to 92.7)
ITTIINAB	20/89 (22)	4/84 (5)	.0008	78.8 (40.6 to 92.4)
ITT	27/136 (20)	10/135 (7)	.0042	62.7 (26.0 to 81.2)
Individual contacts				
ITTII	33/258 (13)	10/244 (4)	.0017	68.0 (34.9 to 84.2)
Contacts whose index case had influenza A	25 (14)	7 (4)	.0067	67.9 (27.1 to 85.9)
Contacts whose index case had influenza B	8 (10)	3 (3)	.1322	66.4 (−39.0 to 91.9)
ITTIINAB	28/248 (12)	4/228 (2)	.0002	84.5 (59.1 to 94.1)
ITT	40/392 (10)	11/400 (3)	.0001	73.1 (47.1 to 86.3)
Children aged 1–12 years				
ITTII	18/74 (24)	6/55 (11)	.0890	55.2 (−13.0 to 82.2)
Contacts whose index case had influenza A	11 (24)	3 (13)	.2776	48.9 (−71.6 to 84.8)
Contacts whose index case had influenza B	7 (24)	3 (10)	.2177	59.9 (−71.5 to 90.6)
ITTIINAB	15/70 (21)	2/47 (4)	.0206	80.1 (22.0 to 94.9)
ITT	21/111 (19)	7/104 (7)	.0188	64.4 (15.8 to 85.0)

NOTE. CI, confidence interval; ITT, intent-to-treat; ITTII, influenza-infected index case; ITTIINAB, baseline influenza-positive contacts; PEP, postexposure prophylaxis.

[a] No. with laboratory-documented influenza illness in a contact/total no.

arm (7% [3/46] and 28% [21/75], respectively). Analysis of the corresponding odds ratios showed that household or individual contacts in the PEP group were 5.9 and 6.3 times more likely, respectively, to have a lower number of days in bed with influenza illness, compared with the expectant treatment group (both $P = .003$).

The proportion of contacts with laboratory-confirmed influenza who experienced at least 1 secondary complication (prospectively defined as bronchitis, pneumonia, lower respiratory tract illness, otitis media, and sinusitis) was low and comparable in the 2 groups (expectant therapy, 5% [4/75]; PEP, 7% [3/46]). However, more severe complications—namely. bronchitis and pneumonia—were only recorded in the treatment arm of the study.

Viral Susceptibility

A total of 177 individuals (132 index cases and 45 contacts) provided samples that were culture-positive and neuraminidase assay–positive; the majority of these were pretreatment samples. A further 91 individuals provided samples that were culture-positive pretreatment but could not be expanded for neuraminidase assay (i.e., they could not be tested properly). Because posttreatment samples from these patients were culture negative, the patients were assumed not to carry drug-resistant virus. IC_{50} values for neuraminidase susceptibility to oseltamivir of both pre- and posttreatment isolates ranged 0.9–10.6 and 23.5–177.5 nmol/L, respectively, for influenza A and B viruses, values that are within the ranges previously obtained for wild-type isolates (data on file). Eleven patients (7 index cases and 4 contacts) shed virus after treatment, with no evidence of the emergence of strains with reduced susceptibility to oseltamivir (table 4).

Safety

Oseltamivir was generally well tolerated when it was administered for both treatment and prophylaxis across all subjects (children, adolescents, and adults), with gastrointestinal, respiratory, and general disorders being the most frequently reported adverse events. The majority of adverse events were of mild or moderate intensity, and few were considered to be drug related. In total, 5 oseltamivir recipients withdrew from the study because of adverse events (1 subject receiving prophylaxis developed a mod-

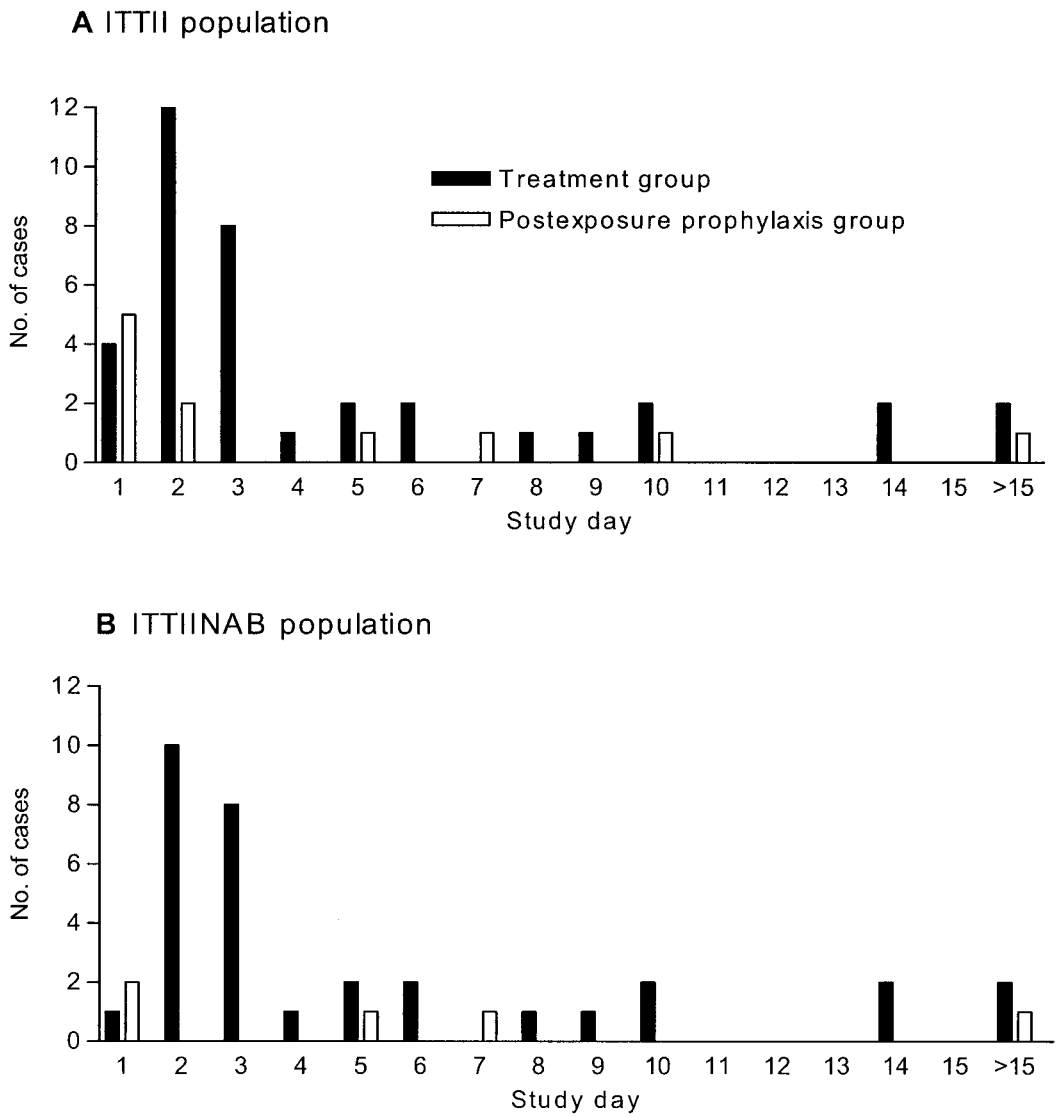

Figure 2. Day of onset of illness in the intent-to-treat index-infected (ITTII) population *(A)* and the ITTII subpopulation of contacts who were virus-negative at baseline (ITTIINAB) during the study *(B)*. Subjects received oseltamivir twice daily for 5 days (treatment group) or once daily for 10 days (postexposure prophylaxis group).

erate allergic reaction that resolved on withdrawal, and 4 subjects prescribed twice-daily treatment withdrew because of epistaxis [$n = 1$], nausea [$n = 1$], and vomiting [$n = 2$]). No children withdrew because of tolerability problems.

Gastrointestinal problems were reported with lower frequency in subjects who received oseltamivir once daily for PEP than in those receiving twice-daily treatment (ill contacts and index cases). Although nausea was reported by 33 (8%) of 399 who received once-daily PEP and by 24 (7%) of 347 of those who received treatment twice daily, the incidence of vomiting was more frequent in the group that received twice-daily administration for treatment (35/347 [10%]) than in those who received once-daily administration for prophylaxis (18/399 [4.5%]). This pattern was also evident in the pediatric subgroup (aged 1–12 years), in that vomiting occurred in 31 (20%) of 158 of those who received twice-daily treatment, compared with 10 (10%) of 99 of those who received oseltamivir once daily for PEP. Analysis of the age category (1–2, 3–5, and 6–12 years) showed a comparable incidence of vomiting across these pediatric age groups. The small number of subjects who received a second course of therapy or switched to a treatment dose during prophylaxis shared a safety profile similar to those of subjects who completed a single course of treatment or PEP.

DISCUSSION

The present study investigated the efficacy of 2 options for the management of influenza in households and found that PEP

Table 4. Oseltamivir susceptibility of pre- and posttreatment (day 6 or 10) isolates, as determined by neuraminidase inhibition assay.

Group, subject no.	Age, years	Influenza type	Treatment group	IC_{50}, nmol/L	
				Pretreatment	Posttreatment
Index cases					
0450	10	B	ET	84.5	Negative
0717	3	B	ET	62.8	53.3
4851	8	B	PEP	49.4	177.5
4853	4	B	PEP	43.2	51.2
5700	7	A	PEP	3.8	1.8
6517	13	A	PEP	9.6	Negative
6256	4	B	PEP	32.3	Negative
Contacts					
4738	4	B	ET	46.8	87.9[a]
6610	9	B	ET	142.2	30.7
6611	6	B	ET	151.8	125.5
6612	2	B	ET	83.4	65.7

NOTE. ET, expectant treatment; PEP, postexposure prophylaxis.

[a] Value obtained on virus sample collected on day 10.

with oral oseltamivir, combined with the treatment of ill index cases, was more effective than treating index cases alone in preventing influenza illness in household contacts. One prior report suggested that the treatment of an ill index case with amantadine or rimantadine might reduce the risk of influenza infection in household contacts to a limited extent (~30%) [23]. In the current trial, we found that PEP with oseltamivir was 58.5% more effective in reducing secondary cases of influenza illness in households (and 68% more effective in individuals), compared with treating index cases alone. Moreover, the administration of oseltamivir PEP was well tolerated and provided protection against illnesses caused by both influenza A and influenza B viruses. Our findings confirm the efficacy of oseltamivir for PEP seen previously in adult and teenage household contacts [16] and are consistent with those of an earlier study that used combined index case treatment and PEP with inhaled zanamivir in households [10]. The early occurrence of illnesses in both groups of household contacts (figure 2) indicates that PEP must be initiated quickly for optimal protection. Indeed, when those already infected with influenza at the time of randomization were excluded from the analysis, the protective efficacy of PEP increased to 79% for households and 84.5% for individuals.

The open-label nature of our trial raises the possibility of bias in outcomes that would have been avoided by a double-blind, placebo-controlled design. However, the use of objective end points with laboratory confirmation of infection in index and contact participants mitigates this problem. There is minimal likelihood that temperature measurements or collection of respiratory samples were affected by the nonblinded design. Furthermore, the additional objective laboratory measure of serological evidence for infection provided further confirmation of prophylactic efficacy.

In contrast to the results of previous studies with M2 protein inhibitors [8], oseltamivir treatment of the index case did not select for drug-resistant virus or reduce the protective efficacy of oseltamivir against influenza illness in close contacts. Viruses that are resistant to amantadine and rimantadine emerge rapidly during treatment, are transmissible to close contacts in households and nursing homes, and remain pathogenic in humans [8]. Drug-resistant virus was recovered by the fifth day of treatment in ~30% of children and adults who received rimantadine. Although the reported overall incidence of emergence of oseltamivir-resistant virus is higher among children (4.5%) than adults (<1%) [24], the associated mutations reduce the biological fitness of the virus, such that transmission appears to be unlikely [25, 26]. In the current trial, there was no evidence for the generation or transmission of oseltamivir-resistant virus. Further studies are clearly warranted to confirm that the risk of transmission of oseltamivir-resistant virus is very low.

To our knowledge, the present study represents the first investigation of the efficacy of oseltamivir prophylaxis in children aged 1–12 years. The overall incidence of influenza illness in pediatric contacts managed expectantly was almost 3-fold higher than among contacts aged >13 years (24% vs. 8%). More than 50% of reported secondary cases were children aged 1–12 years in both groups, a finding that reflects the greater susceptibility of children to influenza infection and illness [4, 5, 27]. PEP reduced the incidence of febrile influenza illness by 55% among pediatric contacts and by 80% among those

who were not already infected with influenza. Of interest, the observed failure rate among contacts who received oseltamivir for PEP (i.e., breakthrough incidence of laboratory-confirmed influenza) was higher in children (11% among contacts of an influenza-infected index case and 4% of those culture-positive individuals at enrollment were excluded) than in adults or adolescents aged ⩾13 years (1%–2%). Whether the earlier initiation of PEP or possibly higher doses might provide greater protection in children remains to be determined. In unimmunized adults, however, once-daily seasonal prophylaxis with oseltamivir was as effective as twice-daily administration [28], which suggests that once-daily treatment would be sufficient to provide adequate protection against influenza in the majority of children.

The present study also provided the opportunity to compare the clinical effectiveness of oseltamivir with its efficacy in preventing laboratory-confirmed influenza among the contact population. Clinical effectiveness was defined as the number of contacts receiving treatment for influenza-like illness or switching from prophylaxis to treatment for an influenza-like illness. Among households, 26% of the expectant treatment group and 10% of the prophylaxis group had at least 1 contact treated, a clinical effectiveness of 61% ($P = .0009$). Therefore, the clinical effectiveness of PEP with oseltamivir was similar to its confirmed clinical efficacy. Additionally, in the group of contacts managed expectantly, more than two-thirds of those developing febrile influenza-like illness had laboratory-confirmed infection, compared with only one-third (3/9) of the subjects who switched to treatment from PEP. Furthermore, comparison of the characteristics of the illness and of the amount of time that subjects stayed in bed suggested that those who developed influenza while receiving PEP were more likely to have a mild illness of short duration than those who started treatment only after the development of first symptoms. These findings further confirm the reduction in household disruption associated with the use of PEP.

Although not a substitute for vaccination, chemoprophylaxis may be clinically valuable because it affords immediate protection for individuals. Chemoprophylactic agents may also be of benefit 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. In the current study, the number of households given prophylaxis (number needed to treat) to prevent one household reporting a secondary case was 6. Among individual contacts, the number needed to treat to prevent one secondary case was 11.

In summary, our findings indicate that prophylaxis with oseltamivir is an effective option for preventing the transmission of influenza within households. Moreover, the treatment and prophylaxis of close contacts with this drug is less likely to result in the transmission of resistant virus than has been described for M2 protein inhibitors. Further studies of PEP in subjects at increased risk of influenza-related morbidity and mortality during influenza outbreaks, such as immunocompromised persons and residents of nursing homes, are clearly warranted.

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