ORIGINAL ARTICLE

Efficacy of Baloxavir Treatment in Preventing Transmission of Influenza

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ABSTRACT

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CME

BACKGROUND
Baloxavir marboxil (baloxavir) rapidly reduces influenza virus shedding, which suggests that it may reduce transmission. Studies of treatment with neuraminidase inhibitors have not shown sufficient evidence that they prevent transmission to contacts.

METHODS
We conducted a multicountry, phase 3b trial to assess the efficacy of single-dose baloxavir treatment to reduce influenza transmission from index patients to household contacts. Influenza-positive index patients 5 to 64 years of age were randomly assigned in a 1:1 ratio to receive baloxavir or placebo within 48 hours after symptom onset. The primary end point was transmission of influenza virus from an index patient to a household contact by day 5. The first secondary end point was transmission of influenza virus by day 5 that resulted in symptoms.

RESULTS
Overall, 1457 index patients and 2681 household contacts were enrolled across the 2019–2024 influenza seasons; 726 index patients were assigned to the baloxavir group, and 731 to the placebo group. By day 5, transmission of laboratory-confirmed influenza was significantly lower with baloxavir than with placebo (adjusted incidence, 9.5% vs. 13.4%; adjusted odds ratio, 0.68; 95.38% confidence interval [CI], 0.50 to 0.93; P=0.01), with an adjusted relative risk reduction of 29% (95.38% CI, 12 to 45). The adjusted incidence of transmission of influenza virus by day 5 that resulted in symptoms was 5.8% with baloxavir and 7.6% with placebo; however, the difference was not significant (adjusted odds ratio, 0.75; 95.38% CI, 0.50 to 1.12; P=0.16). Emergence of drug-resistant viruses during the follow-up period occurred in 7.2% (95% CI, 4.1 to 11.6) of the index patients in the baloxavir group; no resistant viruses were detected in household contacts. No new safety signals were identified.

CONCLUSIONS
Treatment with a single oral dose of baloxavir led to a lower incidence of transmission of influenza virus to close contacts than placebo. (Funded by F. Hoffmann–La Roche and others; CENTERSTONE ClinicalTrials.gov number, NCT03969212.)

SEASONAL INFLUENZA REPRESENTS A MAjor public health threat, leading to up to 650,000 deaths worldwide each year.[1] The influenza vaccine was first developed nearly a century ago to mitigate the effect of seasonal and pandemic influenza.[2] It was recognized that protecting only vaccinated persons would be insufficient for community control unless the spread of influenza to unvaccinated persons could also be reduced. Several studies of the role of vaccines for indirect protection in seasonal outbreaks have been carried out since vaccine development.[3-5]

The use of antiviral drugs for influenza complements vaccination. Although antiviral drugs such as neuraminidase inhibitors are efficacious for postexposure prophylaxis, their greatest use has been in the treatment of existing illness to reduce symptoms and complications.[6-11] There was hope that, in addition to benefiting the infected patient, the antiviral effect of reducing viral loads may reduce transmission to contacts, but the data to date are not definitive.[12]

Baloxavir marboxil (baloxavir), an influenza virus cap-dependent endonuclease inhibitor ("cap" refers to a 7-methyl guanosine that is added to the 5′ end of the host messenger RNA strand), is administered orally as a single dose and has shown efficacy as treatment and postexposure prophylaxis for influenza.[13-16] In phase 3 studies, baloxavir was shown to rapidly reduce influenza virus titers and stop shedding of infectious virus faster than oseltamivir,[13,14] findings that suggest the potential for baloxavir to reduce transmission.[12,17]

Approximately one third of influenza virus transmission occurs within households,[18] and the risk of transmission from infected index patients to their household contacts can be as high as 38%.[19] Therefore, households offer a unique opportunity to evaluate the effect of baloxavir for "treatment to reduce transmission" more efficiently than in other settings. We conducted the CENTERSTONE trial, a phase 3b, double-blind, randomized, placebo-controlled trial, to evaluate the efficacy of baloxavir in the prevention of influenza virus transmission in households.

METHODS

TRIAL DESIGN AND PARTICIPANTS

Patients were enrolled by 142 investigators across 15 countries (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) from October 2019 through April 2024. Eligible index patients were 5 to 64 years of age, had a positive polymerase-chain-reaction (PCR) test or antigen test for influenza, had a negative PCR or antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (requirement implemented on August 10, 2020), underwent screening within 48 hours after symptom onset, and lived in a household with at least one eligible household contact. The required number of eligible, unvaccinated household contacts was changed from at least two to at least one after trial commencement to permit households with only two occupants or those in regions where the number of influenza vaccinations may have increased during the coronavirus disease 2019 (Covid-19) pandemic to participate. Index patients were ineligible for enrollment if they were at high risk for influenza-related complications. Household contacts underwent screening within 24 hours after the index patient had undergone randomization and were eligible for enrollment if all the contacts in the household tested negative for influenza and SARS-CoV-2, at least one contact in the household had not received an influenza vaccine within 6 months, and no contacts in the household were younger than 2 years of age, immunocompromised, or pregnant. For complete inclusion and exclusion criteria, see the Supplementary Appendix and protocol, available at NEJM.org.

This trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. All the participants (or a parent or caregiver of a participant) provided written informed consent. The protocol, informed-consent form, and relevant supporting information were reviewed and approved by the institutional review board or independent ethics committee at each trial site. The sponsor, F. Hoffmann–La Roche, was involved in the design of the trial; the collection, analysis, and interpretation of the data; and the preparation of the manuscript. All the authors signed confidentiality agreements with the sponsor. The first draft of the manuscript was written by the first and last authors with the assistance of a medical writer funded by the sponsor. The authors reviewed the data, confirmed the accuracy of the results, had final responsibility for the decision to submit the manuscript for publication,

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and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

RANDOMIZATION AND TREATMENT

Eligible index patients were randomly assigned in a 1:1 ratio to receive either a single oral dose of baloxavir or matching placebo, within 2 hours after randomization. Randomization was performed with the use of an interactive Web-response system. In patients 12 years of age or older, baloxavir was administered in tablet form at a dose of 40 mg for those weighing less than 80 kg or 80 mg for those weighing 80 kg or greater. In patients younger than 12 years of age, baloxavir was administered in an oral suspension at a dose of 2 mg per kilogram of body weight for those weighing less than 20 kg or 40 mg for those weighing 20 kg or greater.

Randomization was stratified according to age (5 to 11 years, 12 to 30 years, or ≥31 years), household size (≤2 or ≥3 household contacts), region (United States or Europe, Asia, or the rest of the world), and duration of symptoms (≤24 hours or >24 to 48 hours). The patients, investigators, and sponsor were unaware of the trial-group assignments (see the Supplementary Appendix).

END POINTS

The primary efficacy end point was transmission of influenza virus from an index patient to a household contact by day 5 after randomization, as determined by a positive PCR test for influenza and a virus type and subtype consistent with those of the index patient. All household contacts were tested for influenza on or before day 5, regardless of whether they had symptoms. The first secondary efficacy end point was transmission of influenza virus to a household contact by day 5 that resulted in clinical symptoms, as determined by a positive PCR test for influenza, a virus type and subtype consistent with those of the index patient, and influenza symptoms meeting defined clinical criteria (see the Supplementary Appendix); the symptoms used to define whether the criteria had been met could have occurred at any time. Other secondary efficacy end points included transmission of influenza virus by day 5 and transmission by day 5 that resulted in symptoms, as assessed at the household level (i.e., households were counted only once for an end-point event if the event occurred in any contact in the same household); transmission of influenza virus by day 9 and transmission by day 9 that resulted in symptoms, as assessed at the household-contact level (i.e., household contacts were counted for each end-point event); and any virologic infection in a household contact by day 9. Additional efficacy end points included the percentage of index patients and household contacts with influenza viruses bearing amino acid substitutions associated with baloxavir resistance. Safety end points included the frequency, severity, and timing of adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events) in index patients.

CLINICAL AND LABORATORY ANALYSES

Respiratory swab samples were obtained from index patients and household contacts at screening and on days 5 and 9; an additional sample was obtained from index patients at day 3 (with a visit window of ±1 day from the scheduled day). Respiratory swab samples were also obtained at unscheduled visits for any household contacts with influenza symptoms on days other than the scheduled visit days. Samples were tested for influenza with the use of a quantitative reverse-transcriptase–PCR (RT-PCR) assay (see the Supplementary Appendix). The influenza virus titer was determined in the index patient samples by means of RT-PCR assay and a 50% tissue-culture infectious dose ($TCID_{50}$) assay, which were performed at a central laboratory. Sanger sequencing of the viral polymerase acidic gene PA was conducted at baseline and after treatment in index patients in the baloxavir group and in any of their household contacts who tested positive for influenza. Index patients were monitored for adverse events until day 9 (for patients 12 to 64 years of age) or day 21 (for patients <12 years of age).

STATISTICAL ANALYSIS

Assuming that the incidence of influenza transmission would be 20% in the placebo group,[7] we estimated that a sample of 2030 evaluable household contacts would provide the trial with 90% power at a 5% significance level to detect a 30% lower risk of influenza transmission with baloxavir than with placebo by day 5. Assuming that there would be 2.5 household contacts per index patient, that 15% of households would

be excluded from the evaluable population, and that 15% of the household contacts would be excluded from the evaluable population, we estimated that approximately 1130 index patients would need to be enrolled to provide 2030 evaluable household contacts (see the Supplementary Appendix). Secondary efficacy end points were to be tested in a hierarchical, sequential manner if the result for the primary end point was found to be significant (Table S2).

An interim analysis was conducted in July 2023 for an independent data monitoring committee to review the data to determine whether to stop the trial either for sufficient evidence of efficacy (i.e., significant results for the primary and first secondary end points) based on group-sequential boundaries or for futility; the committee recommended to continue the trial as planned. Because of the alpha that was spent at the interim analysis and the final sample size of the primary analysis population, the significance level for the confirmatory tests was 0.0462. Consequently, 95.38% confidence intervals are presented for all end points in the hierarchical chain up to the first nonsignificant end point. All other tests were considered to be exploratory, and the corresponding 95% confidence intervals are presented. The 95% confidence intervals may not be used in place of hypothesis testing.

The primary and secondary efficacy end points at the household-contact level were evaluated in the primary analysis population (or set) of household contacts (PAS-HHC — all unvaccinated, RT-PCR–negative household contacts enrolled in the full trial from households in which the index patient was RT-PCR–positive for influenza A or B and received baloxavir or placebo and in which all other household contacts in the household were RT-PCR–negative for influenza at baseline); the household contacts in the PAS-HHC were grouped according to the trial-group assignment of their associated index patient. To assess the primary end point and the secondary end points at the household-contact level, we used a generalized-estimating-equation approach, accounting for clustering within households and the randomization stratification factors. Secondary efficacy end points at the household level were evaluated in the primary analysis set of households (PAS-HH — all the households of infected index patients that had at least one household contact who was in the PAS-HHC); households in the PAS-HH were

grouped according to the trial-group assignment of their associated index patient. Subgroup analyses of the primary and first secondary efficacy end points were prespecified (see the Supplementary Appendix).

Safety end points were evaluated in the safety population, which included all index patients who received at least one dose of baloxavir or placebo. Full details of the statistical methods are provided in the statistical analysis plan, available with the protocol.
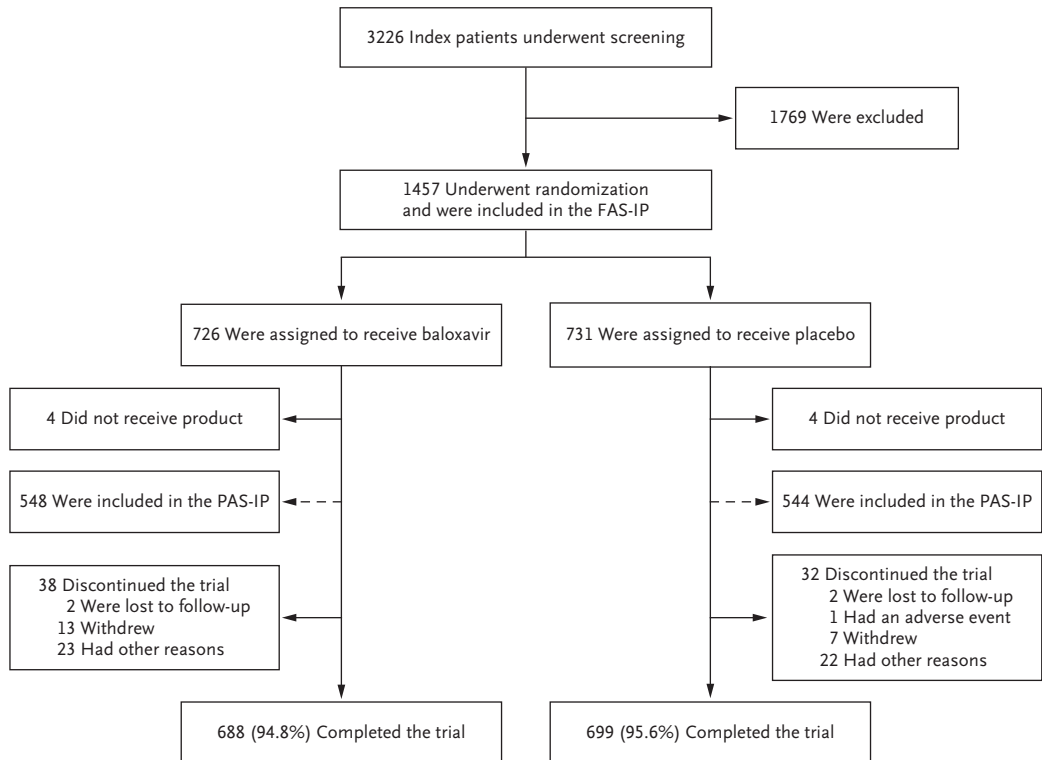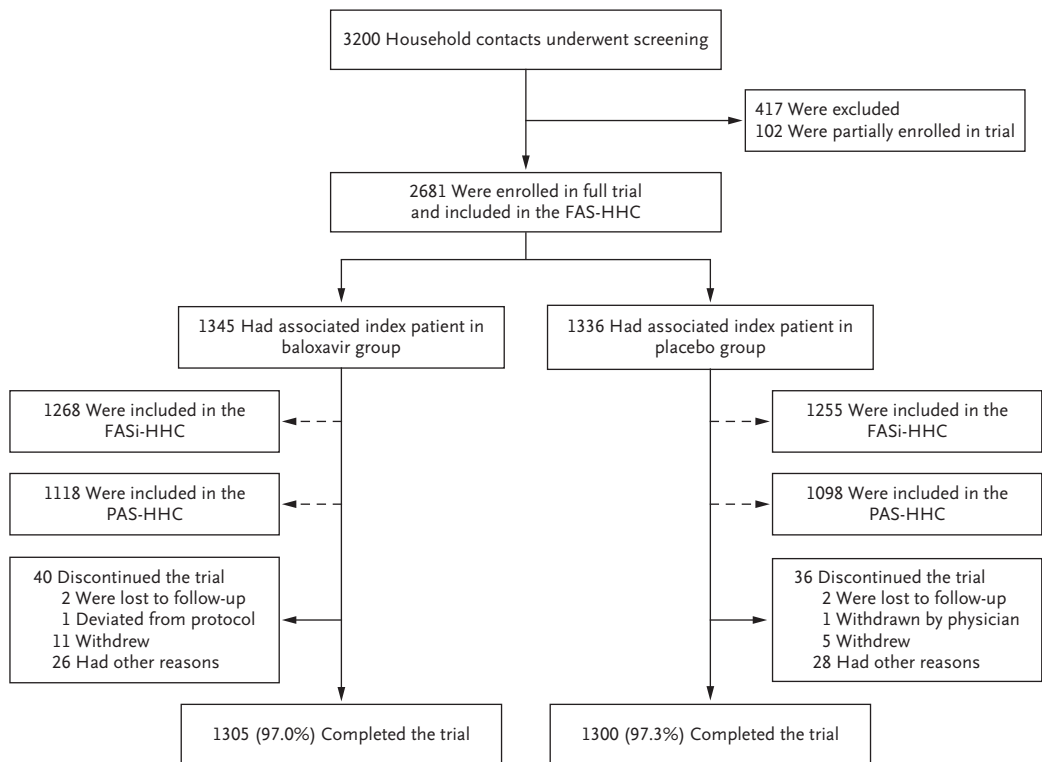
RESULTS

INDEX PATIENTS AND HOUSEHOLD CONTACTS

Overall, 1457 index patients were enrolled and underwent randomization; 726 were assigned to the baloxavir group and 731 to the placebo group (Fig. 1). A total of 2681 household contacts were enrolled; 1345 were associated with an index patient in the baloxavir group and 1336 were associated with an index patient in the placebo group. The primary analysis population of index patients (PAS-IP; all index patients who had undergone randomization and had at least one household contact who was in the PAS-HHC) included 548 patients in the baloxavir group and 544 in the placebo group, and the PAS-HHC included 1118 household contacts with an associated index patient in the baloxavir group and 1098 with an associated index patient in the placebo group (see the Supplementary Appendix). Baseline characteristics of the index patients and household contacts were well balanced between the two trial groups (Table 1). Patients were enrolled across the 2019–2024 influenza seasons. Most index patients had influenza A infection (H1N1pdm09 or H3N2); approximately 20% had influenza B infection. The patient population was reasonably representative of the local populations at the locations where the trial was conducted (Table S3).

PRIMARY AND SECONDARY END POINTS

The adjusted incidence of transmission of influenza virus to household contacts by day 5, as calculated with the use of a generalized-estimating-equation approach to account for clustering within households and the randomization stratification factors, was 9.5% with baloxavir and 13.4% with placebo. The adjusted odds ratio for transmission with baloxavir, as compared with placebo,

A Index Patients

3226 Index patients underwent screening

1769 Were excluded

1457 Underwent randomization
and were included in the FAS-IP

726 Were assigned to receive baloxavir

731 Were assigned to receive placebo

4 Did not receive product

4 Did not receive product

548 Were included in the PAS-IP

544 Were included in the PAS-IP

38 Discontinued the trial
  2 Were lost to follow-up
  13 Withdrew
  23 Had other reasons

32 Discontinued the trial
  2 Were lost to follow-up
  1 Had an adverse event
  7 Withdrew
  22 Had other reasons

688 (94.8%) Completed the trial

699 (95.6%) Completed the trial

B Household Contacts

3200 Household contacts underwent screening

417 Were excluded
102 Were partially enrolled in trial

2681 Were enrolled in full trial
and included in the FAS-HHC

1345 Had associated index patient in
baloxavir group

1336 Had associated index patient in
placebo group

1268 Were included in the
FASi-HHC

1255 Were included in the
FASi-HHC

1118 Were included in the
PAS-HHC

1098 Were included in the
PAS-HHC

40 Discontinued the trial
  2 Were lost to follow-up
  1 Deviated from protocol
  11 Withdrew
  26 Had other reasons

36 Discontinued the trial
  2 Were lost to follow-up
  1 Withdrawn by physician
  5 Withdrew
  28 Had other reasons

1305 (97.0%) Completed the trial

1300 (97.3%) Completed the trial

was 0.68 (95.38% confidence interval [CI], 0.50 to 0.93; P=0.01), which translates to an adjusted relative risk reduction of 29% (95.38% CI, 12 to 45) (Table 2). The direction of the treatment-effect estimates across subgroups, such as those defined according to the age of the index patient, the time to administration of baloxavir or placebo to the index patient, influenza subtype, and season, was consistent with the overall treatment effect in the primary analysis (Fig. S1). The results of a supportive analysis of influenza virus transmission by day 5 in the full analysis population of household contacts who were linked to an influenza-infected index patient (FASi-HHC — all household contacts, including those who were vaccinated and those who were not confirmed to be influenza negative at baseline, whose associated index patient had a positive PCR test for influenza A or B test at baseline) were consistent with the results observed in the PAS-HHC (Table S4).

The adjusted incidence of transmission of influenza virus by day 5 that resulted in symptoms was 5.8% with baloxavir and 7.6% with placebo, with an adjusted odds ratio for transmission with baloxavir, as compared with placebo, of 0.75 (95.38% CI, 0.50 to 1.12; P=0.16), which translates to an adjusted relative risk reduction of 24% (95.38% CI, −2 to 46) (not significantly different) (Table 2). Similarly, the direction of the treatment-effect estimates across subgroups was consistent with the overall treatment effect (Fig. S2).

The adjusted incidence of transmission of influenza virus by day 9 was 10.8% with baloxavir and 15.4% with placebo, and the adjusted incidence of transmission of influenza virus by day 9 that resulted in symptoms was 6.2% and 8.3%, respectively. Because the result for the first secondary end point was not significant, these and further secondary end points could not be tested for confirmatory purposes, and P values are not presented (Table 3).

Baloxavir resulted in a more rapid reduction in virus titer in index patients than placebo; by day 3, the adjusted mean reduction from baseline was 2.22 $\log_{10}$ $TCID_{50}$ per milliliter with baloxavir and 1.85 $\log_{10}$ $TCID_{50}$ per milliliter with placebo (Table S5). Viral loads ($\log_{10}$ virus particles per milliliter) were also more rapidly reduced with baloxavir than with placebo (Table S6). In a subgroup analysis of the effect of baseline virus titer and viral RNA loads in index patients on transmission of influenza virus by day 5, the direction of the treatment-effect estimates across subgroups was generally consistent with the overall treatment effect (Figs. S3 and S4).

SAFETY

Within the safety population, 33 index patients (4.6%) in the baloxavir group and 51 index patients (7.0%) in the placebo group had one or more adverse events (Table S7). Most adverse events were of grade 1 or 2 in severity; 6 patients had a grade 3 or higher adverse event (in 2 patients [0.3%] in the baloxavir group and in 4 patients [0.6%] in the placebo group). In total, 10 patients had adverse events that were considered by the investigator to be related to baloxavir or placebo (in 4 patients in the baloxavir group and in 6 in the placebo group). Four serious adverse events were reported by 3 patients: spontaneous abortion in the baloxavir group and hyponatremia, pneumonia, and bronchitis in the placebo group). No patients in the

Table 1. Demographic and Clinical Characteristics of the Index Patients and Household Contacts (HHCs) at Baseline.*

Characteristic	Index Patients in Baloxavir Group (N = 548)	Index Patients in Placebo Group (N = 544)	HHCs of Index Patient in Baloxavir Group (N = 1118)	HHCs of Index Patient in Placebo Group (N = 1098)
Age — yr				
Mean	30.8±15.2	31.8±15.9	35.4±18.6	35.1±18.3
Median	30.0	30.0	36.0	35.5
Age group — no. (%)				
Index patients				
<12 yr	44 (8.0)	46 (8.5)	—	—
12 to 30 yr	245 (44.7)	235 (43.2)	—	—
>30 yr	259 (47.3)	263 (48.3)	—	—
Household contacts				
2 to <12 yr	—	—	121 (10.8)	118 (10.7)
≥12 yr	—	—	997 (89.2)	980 (89.3)
Sex — no. (%)				
Male	248 (45.3)	266 (48.9)	525 (47.0)	486 (44.3)
Female	300 (54.7)	278 (51.1)	593 (53.0)	612 (55.7)
Geographic region — no. (%)				
Europe	243 (44.3)	250 (46.0)	418 (37.4)	444 (40.4)
Asia	139 (25.4)	139 (25.6)	284 (25.4)	289 (26.3)
United States	141 (25.7)	135 (24.8)	373 (33.4)	334 (30.4)
Rest of the world	25 (4.6)	20 (3.7)	43 (3.8)	31 (2.8)
Maximum duration of influenza symptoms — no. (%)				
≤24 hr	292 (53.3)	288 (52.9)	NA	NA
>24 to 48 hr	256 (46.7)	256 (47.1)	NA	NA
No. of household contacts in the PAS-HHC†				
Mean	2.04±1.09	2.02±1.09	NA	NA
Median	2	2	NA	NA
Influenza season — no. (%)‡				
2019–2020	92 (16.8)	87 (16.0)	257 (23.0)	230 (20.9)
2020–2021	0	0	0	0
2021–2022	41 (7.5)	41 (7.5)	88 (7.9)	98 (8.9)
2022–2023	184 (33.6)	182 (33.5)	346 (30.9)	341 (31.1)
2023–2024	231 (42.2)	234 (43.0)	427 (38.2)	429 (39.1)
Influenza virus type — no. (%)§				
Type A¶	450 (82.1)	451 (82.9)	907 (81.1)	899 (81.9)
Type B‖	93 (17.0)	91 (16.7)	201 (18.0)	193 (17.6)
Type A and B	5 (0.9)	2 (0.4)	10 (0.9)	6 (0.5)

Table 1. (Continued.)

Characteristic	Index Patients in Baloxavir Group (N = 548)	Index Patients in Placebo Group (N = 544)	HHCs of Index Patient in Baloxavir Group (N = 1118)	HHCs of Index Patient in Placebo Group (N = 1098)
Influenza virus A subtype — no./total no. (%)§				
H1N1pdm09	220/455 (48.4)	228/453 (50.3)	451/917 (49.2)	454/905 (50.2)
H3N2	213/455 (46.8)	202/453 (44.6)	420/917 (45.8)	404/905 (44.6)
H1N1pdm09 and H3N2	2/455 (0.4)	2/453 (0.4)	3/917 (0.3)	3/905 (0.3)
Unknown	20/455 (4.4)	19/453 (4.2)	43/917 (4.7)	42/905 (4.6)
Missing	0/455	2/453 (0.4)	0/917	2/905 (0.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NA denotes not applicable.
† The primary analysis population (or set) of HHCs (PAS-HHC) included all unvaccinated, reverse-transcriptase–polymerase-chain-reaction (RT-PCR)–negative HHCs enrolled in the full trial from households in which the index patient was RT-PCR–positive for influenza A or B and received baloxavir or placebo and in which all other HHCs in the household were RT-PCR–negative for influenza at baseline.
‡ Influenza season lasts from October 4 of the former year to October 3 of the latter year.
§ For HHCs, the influenza virus type and influenza A subtype of their associated index patient are shown.
¶ This count included only those with influenza type A who were negative for influenza type B or had missing data on influenza type B status.
‖ This count included only those with influenza type B who were negative for influenza type A or had missing data on influenza type A status.

Table 2. Primary and First Secondary End Points.*

End Point	HHCs of Index Patient in Baloxavir Group (N = 1118)	HHCs of Index Patient in Placebo Group (N = 1098)
Primary end point: transmission of influenza virus by day 5		
HHCs with an end-point event — no. (%)	94 (8.4)	131 (11.9)
Adjusted incidence of transmission (95.38% CI) — %†	9.5 (7.4 to 12.1)	13.4 (10.7 to 16.8)
Adjusted odds ratio (95.38% CI)†‡	0.68 (0.50 to 0.93)	—
P value†	0.01	—
Adjusted relative risk reduction (95.38% CI) — % ‡§	29 (12 to 45)	—
First secondary end point: transmission of influenza virus by day 5 that resulted in symptoms¶		
HHCs with an end-point event — no. (%)	56 (5.0)	72 (6.6)
Adjusted incidence of transmission (95.38% CI) — %†	5.8 (4.1 to 8.2)	7.6 (5.7 to 10.2)
Adjusted odds ratio (95.38% CI)†‡	0.75 (0.50 to 1.12)	—
P value†	0.16	—
Adjusted relative risk reduction (95.38% CI) — %‡§	24 (–2 to 46)	—

* Analyses were conducted in the PAS-HHC. An adjusted significance level of 0.0462 was used to account for the efficacy interim analysis. Confidence intervals were also adjusted.
† The analysis was conducted with the use of a generalized-estimating-equation approach to account for clustering within households and the randomization stratification factors.
‡ Adjusted odds ratios and adjusted relative risk reductions are given for the HHCs with an associated index patient in the baloxavir group as compared with those with an associated index patient in the placebo group.
§ Estimates of the adjusted relative risk reduction, a supportive summary measure, were derived from the adjusted odds ratio and incidence in the placebo group. The confidence interval was derived with the use of the bootstrap method.
¶ To meet the criteria for this end point, HHCs 12 years of age or older must have had either a body temperature of at least 38.0°C plus one respiratory symptom or one respiratory symptom plus one general systemic symptom with or without fever, and HHCs younger than 12 years of age must have had a body temperature of at least 38.0°C plus signs or symptoms of an upper respiratory tract infection. Symptoms could have occurred at any time and must have been new or, among HHCs with symptoms at baseline due to a preexisting medical complication, must have worsened since baseline.

baloxavir group were withdrawn from the trial because of an adverse event, and no fatal adverse events or adverse events of special interest were reported.

During the follow-up period, drug-resistant PA I38X substitutions emerged in 15 of the 208 index patients (7.2%; 95% CI, 4.1 to 11.6) who had received baloxavir and had prebaseline and postbaseline samples for sequencing analysis — 5 patients had influenza A(H1N1pdm09), and 10 had influenza A(H3N2) (Table 4). Of these 15 index patients, 13 had household contacts (27 in total) enrolled in the trial; resistant viruses were not detected in any of these 27 household contacts (of whom 7 were positive for influenza) or in any of the 1268 household contacts of the index patients who received baloxavir.

DISCUSSION

The possibility that an influenza antiviral drug that reduces disease severity in treated index patients might also reduce further transmission of the virus to other persons has been explored, but the results have not been conclusive.[12] This uncertainty may be due to a lack of antiviral potency, trial designs that did not include a reduction in virus transmission as the primary end point, or research that relied on secondary data. A randomized, double-blind trial in Bangladesh showed that administration of oseltamivir to index patients resulted in a lower incidence of secondary illness among household contacts than when the index patients received placebo, but the incidence of PCR-confirmed influenza among the contacts did not differ significantly between trial groups.[20] In a retrospective, observational trial in Japan, administration of zanamivir — but not oseltamivir — to index patients within 24 or 24 to 48 hours after symptom onset resulted in a significantly lower transmission of influenza virus than when the index patients received zanamivir more than 48 hours after symptom onset or no zanamivir treatment.[21]

Table 3. Other Secondary End Points at the Household (HH) or HHC Level.*		
End Point	HHs or HHCs of Index Patient in Baloxavir Group	HH or HHCs of Index Patient in Placebo Group
Transmission of influenza virus by day 5 at the HH level		
HHs with ≥1 HHC with an end-point event — no./total no. (%)	85/548 (15.5)	106/544 (19.5)
Odds ratio (95% CI)	0.76 (0.56 to 1.05)	—
Relative risk reduction (95% CI) — %	20 (–4 to 38)	—
Transmission of influenza virus by day 5 that resulted in symptoms at the HH level†		
HHs with ≥1 HHC with an end-point event — no./total no. (%)	47/548 (8.6)	65/544 (11.9)
Odds ratio (95% CI)	0.69 (0.46 to 1.03)	—
Relative risk reduction (95% CI) — %	28 (–3 to 49)	—
Transmission of influenza virus by day 9 at the HHC level‡		
Evaluable contact cases — no./total no.	1081/1118	1038/1098
HHCs with an end-point event — no./total no. (%)	101/1081 (9.3)	141/1038 (13.6)
Adjusted incidence of transmission (95% CI) — %§	10.8 (8.4 to 13.7)	15.4 (12.2 to 19.2)
Adjusted odds ratio (95% CI)§	0.66 (0.48 to 0.91)	—
Adjusted relative risk reduction (95% CI) — %¶	30 (13 to 44)	—
Transmission of influenza virus by day 9 that resulted in symptoms at the HHC level†‡		
Evaluable contact cases — no./total no.	1079/1118	1037/1098
HCCs with an end-point event — no./total no. (%)	57/1079 (5.3)	73/1037 (7.0)
Adjusted incidence of transmission (95% CI) — % §	6.2 (4.4 to 8.5)	8.3 (6.1 to 11.0)
Adjusted odds ratio (95% CI)§	0.73 (0.49 to 1.09)	—
Adjusted relative risk reduction (95% CI) — %¶	26 (1 to 47)	—

End Point	HHs or HHCs of Index Patient in Baloxavir Group	HH or HHCs of Index Patient in Placebo Group
Table 3. (Continued.)		
Any infection with influenza virus by day 9 at the HHC level‖		
Evaluable contact cases — no./total no.	1071/1118	1040/1098
HHCs with an end-point event — no./total no. (%)	130/1071 (12.1)	173/1040 (16.6)
Adjusted incidence of transmission (95% CI) — %§	14 (11.4 to 17.1)	18.7 (15.4 to 22.5)
Adjusted odds ratio (95% CI)§	0.71 (0.54 to 0.94)	—
Adjusted relative risk reduction (95% CI) — %¶	25 (8 to 37)	—
Any infection with influenza virus by day 9 that resulted in symptoms at the HHC level†**		
Evaluable contact cases — no./total no.	1069/1118	1039/1098
Household contacts with an end-point event — no./total no. (%)	61/1069 (5.7)	80/1039 (7.7)
Adjusted incidence of transmission (95% CI) — %§	6.4 (4.6 to 8.9)	8.7 (6.5 to 11.6)
Adjusted odds ratio (95% CI)§	0.72 (0.49 to 1.06)	—
Adjusted relative risk reduction (95% CI) — %¶	26 (3 to 46)	—

* Odds ratios (adjusted and unadjusted) and relative risk reductions (adjusted and unadjusted) are given for the HHs or HHCs with an index patient in the baloxavir group as compared with those with an index patient in the placebo group.

† To meet the criteria for this end point, HHCs 12 years of age or older must have had either a body temperature of at least 38.0°C plus one respiratory symptom or one respiratory symptom plus one general systemic symptom with or without fever, and HHCs younger than 12 years of age must have had a body temperature of at least 38.0°C plus signs or symptoms of an upper respiratory tract infection. Symptoms could occur at any time and must have been new or, among HHCs with symptoms at baseline due to a preexisting medical complication, must have worsened since baseline.

‡ Transmission by day 9 includes transmission events by day 5, transmission events after day 5 that are limited to possible tertiary transmissions (from other HHCs who had a primary end-point event by day 5), and transmissions in which the HHC is infected with influenza bearing I38X or T20K substitutions.

§ The analysis was conducted with the use of a generalized-estimating-equation approach to account for clustering within households and the randomization stratification factors.

¶ Estimates of the adjusted relative risk reduction, a supportive summary measure, were derived from the adjusted odds ratio and incidence in the placebo group. The confidence interval was derived with the use of the bootstrap method.

‖ This end point was assessed as the proportion of HHCs who became RT-PCR–positive for influenza (confirmed by central laboratory) by day 9. The end point was used to evaluate the treatment effect on all influenza transmissions and not only transmissions in which the HHC had a virus subtype that matched the subtype in the index patient.

** This end point was assessed as the proportion of HHCs who became RT-PCR–positive for influenza (confirmed by central laboratory) by day 9 and met the clinical criteria as described for the end point "transmission of influenza virus by day 5 that resulted in symptoms."

In the current trial, the incidence of influenza transmission from an index patient to a household contact was significantly lower when baloxavir was administered to the index patient than when the index patient received placebo. The difference in the incidence of transmission of influenza virus by day 5 that resulted in symptoms was not significant; however, the incidence in the placebo group (7.6%) was lower than what was assumed in the sample-size calculations, possibly because of Covid-19 pandemic–related behavioral changes leading to fewer cases for evaluation. A difference in the incidence of transmission in favor of baloxavir over placebo was observed across age groups, seasons, influenza types (A[H1N1pdm09], A[H3N2], and B), times from symptom onset to receipt of baloxavir or placebo, and geographic regions. The matching of influenza subtype and the timing of the trial assessments mitigate the low likelihood of transmission from a nonhousehold source of infection during the follow-up period,[22,23] which would dilute the treatment effect. No new safety concerns were identified in the treated index patients.[13-15]

All influenza antiviral drugs exert a selective pressure on viruses, which can result in the emergence of drug-resistant variants.[24] In the CENTERSTONE trial, emergence of drug-resistant viruses during the follow-up period occurred in 7.2% of the index patients who received treatment with baloxavir, a finding consistent with previous reports in adults[13,14]; in the CAPSTONE-2 trial, clinical benefit with respect to the time to alleviation of influenza symptoms was still

Table 4. Development of Resistance in Baloxavir-Treated Index Patients.*

Patients and Substitution	Influenza A(H1N1pdm09)	Influenza A(H3N2)	Influenza B	Total†
All baloxavir-treated index patients — no.	69	88	53	208
Any PA I38X or T20K substitution at baseline — no. (%)	0	0	0	0
Any PA I38X or T20K substitution that emerged during follow-up — no. (%)‡	5 (7.2)	10 (11.4)	0	15 (7.2)
Baloxavir-treated index patients <12 yr of age — no.	4	18	3	25
Any PA I38X or T20K substitution that emerged during follow-up — no. (%)‡	1 (25.0)	3 (16.7)	0	4 (16.0)
PA I38N — no. (%)	1 (25.0)	0	0	1 (4.0)
PA I38T — no. (%)	0	3 (16.7)	0	3 (12.0)
PA I38T and I38I — no. (%)	0	1 (5.6)§	0	1 (4.0)
Baloxavir-treated index patients ≥12 yr of age — no.	65	70	50	183
Any PA I38X or T20K substitution that emerged during follow-up — no. (%)‡	4 (6.2)	7 (10.0)	0	11 (6.0)
PA I38M — no. (%)	0	1 (1.4)	0	1 (0.5)
PA I38T — no. (%)	3 (4.6)	6 (8.6)	0	9 (4.9)
PA I38T and I38I — no. (%)	1 (1.5)	0	0	1 (0.5)

* The index patients in this analysis include all of those who had samples that were obtained before and after administration of baloxavir for sequencing analysis. PA denotes polymerase acidic protein.
† The results for index patients with mixed influenza infection are presented within each influenza type and subtype but are only counted once in the overall summary and are only presented for the virus types for which paired samples are available for analysis.
‡ T20K substitutions were considered for influenza B only.
§ This index patient with influenza that involved a PA I38T and I38I substitution mix is also counted within the PA I38T row of the table.

observed in patients with baloxavir-resistant viruses.[14] Transmission of a resistant virus was not detected in any household contact in our trial, including the 27 household contacts of index patients who had resistant variants, although transmission of wild-type virus occurred; this may be due to influenza transmission from index patients occurring early in the course of infection when viral titers were higher, before the emergence of drug-resistant variants later in the follow-up period, although a low level of fitness of the resistant variants is also possible.

Most members of the households in this trial were mainly unvaccinated, and how previous vaccination may affect the incidence of transmission after baloxavir treatment remains unclear. Reduction of transmission would be an added benefit of antiviral treatment during seasonal influenza epidemics. Various modeling studies with assumed effect sizes similar to the effect size described here have shown that this could reduce the effect of the epidemic.[25-27] One study predicted that baloxavir treatment in 30% of patients with influenza within 48 hours after symptom onset could result in a 38% reduction in the number of cases, as compared with no antiviral treatment.[25]

In a pandemic, development of a vaccine would take time,[28] and the availability of an antiviral drug that reduces disease severity and person-to-person transmission could serve as a new element to combat such a pandemic. In the 2000s, concern about a potential influenza A(H5N1) pandemic led to the development of strategies to stop a pandemic at the source[29]; a drug with a dual effect on illness and transmission reduction would be valuable to achieve that aim.

Although vaccines will remain the primary control measure for influenza epidemics and pandemics, antiviral drugs play a complementary role, particularly in a pandemic scenario, as well as in persons who are not vaccinated seasonally. The availability of an antiviral drug for influenza A and B with dual treatment effects on illness and transmission is a welcome addition to the overall strategy for influenza control.

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