Efficacy of Influenza Antivirals in Prophylaxis

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Topics to be covered

- Influenza only Has a long history and can be used as a template for other respiratory viruses
- History of prophylactic studies Remember that vaccine is the first prophylactic agent
- Seasonal and outbreak prophylaxis. Not really different Start and stopping rules may be different but no effort to follow an exposure
- Post exposure prophylaxis Will follow an exposure for a variable amount of time. Often studied in households to confirm success.
- Prevention of transmission usually not the intent Successful antiviral treatment may reduce spread. If clinical infection is prevented, there will be reduced or no transmission

March 9, 1979

Prevention of Russian Influenza by Amantadine

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JAMA. 1979;241(10):1003-1007. doi:10.1001/jama.1979.03290360019018

Abstract

We tested the effectiveness of amantadine hydrochloride in prevention of illness and infection caused by Russian (H1N1) influenza. The trial lasted seven weeks and was double-blind and placebo controlled. The dosage used was 200 mg daily. Efficacy in prevention of serologically confirmed clinical influenza was 70.7%. Efficacy in prevention of infection, symptomatic or asymptomatic, was 39.4%. Side effects seen were all mild, began within two days of the start of the trial, and terminated rapidly on cessation of prophylaxis. The withdrawal rate attributable to use of amantadine was 6.2%. Those who continued to receive prophylaxis for the remainder of the trial did not exhibit excess side effects. It is concluded that amantadine is safe and effective in prophylaxis of H1N1 strains, as has been shown previously for other subtypes of A influenza.

(*JAMA* 241:1003-1007, 1979)

Neuraminidase Inhibitors (NAIs)

- **Active *in vitro* and in animal models against both influenza A and B viruses**
- **Active against neuraminidases of all influenza A viruses tested (N1-N9)**
- **Given twice daily for 5 days in therapy, once daily for prophylaxis**
- **Zanamivir (GG167) *Relenza***
  - topically applied sialic acid analog
- **Oseltamivir (GS4104, Ro 04-0796) *Tamiflu***
  - oral prodrug of GS4071, transition state analog

Zanamivir in the Prevention of Influenza Among Healthy Adults

A Randomized Controlled Trial

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Context The neuraminidase inhibitor zanamivir, a sialic acid analog administered directly to the respiratory tract, has been demonstrated in clinical studies to be effective in treatment of type A and B influenza. It has also been shown to prevent influenza infection and disease in an experimental model.

Objective To examine the efficacy of zanamivir, administered once daily, in the prevention of influenza infection and disease.

Design Double-blind, randomized, placebo-controlled trial.

Setting Two midwestern university communities.

Participants A total of 1107 healthy adults (mean age [range], 29 [18-69] years) were recruited in November 1997, before the influenza season.

Intervention At the start of the influenza outbreak, 554 subjects were randomized to receive placebo and 553 to receive zanamivir. The drug, 10 mg once per day, or identical placebo was administered by oral inhalation for a 4-week period.

Main Outcome Measures Illness occurrence was recorded by participants daily and records were evaluated weekly. Specimens were collected for viral isolation when symptoms were reported within 3 days of illness onset. Infection was also identified by testing paired serum samples for rise in antibody titer against the circulating influenza viruses.

Results Zanamivir was 67% efficacious (95% confidence interval [CI], 39%-83%; $P<.001$) in preventing laboratory-confirmed clinical influenza meeting the case definition and 84% efficacious (95% CI, 55%-94%; $P=.001$) in preventing laboratory-confirmed illnesses with fever. All influenza infections occurring during the season, with or without symptoms, were prevented with an efficacy of 31% (95% CI, 4%-50%; $P=.03$). The nature and incidence of adverse events in the zanamivir group did not differ from placebo. Compliance with the once-daily dosage was high.

Conclusions Zanamivir administered once daily is efficacious and well tolerated in the prevention of influenza for a 4-week period in healthy adults.

JAMA. 1999;282:31-35 www.jama.com

TWENTY YEARS AGO, THE ANTIVIral drug amantadine was reported to be 70% efficacious in prevention of symptomatic influenza during an epidemic associated with the reappearance of type A(H1N1) virus.[1] A few years later, amantadine and the related compound rimantadine were demonstrated to be efficacious in preventing illnesses associated with type A(H3N2) and type A(H1N1) viruses.[2] However, while clearly effective, there has been a longstanding controversy about appropriate use of these drugs dating to the 1960s.[3,4] Concerns raised include the lack of effectiveness against type B viruses, occurrence of adverse effects mainly related to amantadine, and the rapid development of resistance to both agents.[5-7]

Table 2. Efficacy of Zanamivir in Prevention of Influenza Infection and Disease*

Outcome	Frequencies in Study Groups, No. (%)		Odds Ratio (95% CI)	Estimated Risk Ratio (95% CI)	Efficacy, 1 – Risk Ratio (95% CI), %
	Placebo (n = 554)	Zanamivir (n = 553)			
Laboratory-confirmed clinical influenza	34 (6)	11 (2)	0.31 (0.14-0.64)†	0.33 (0.17-0.61)	67 (39-83)
Laboratory-confirmed influenza with fever	19 (3)	3 (<1)	0.15 (0.03-0.53)†	0.16 (0.06-0.45)	84 (55-94)
All febrile illnesses	58 (10)	33 (6)	0.54 (0.34-0.86)‡	0.57 (0.38-0.86)	43 (14-62)
Influenza infection with or without illness	77 (14)	53 (10)	0.66 (0.44-0.97)§	0.69 (0.50-0.96)	31 (4-50)

*CI indicates confidence interval.
†$P \leq .001$.
‡$P = .009$.
§$P = .03$.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of the Selective Oral Neuraminidase Inhibitor Oseltamivir to Prevent Influenza

Authors: Frederick G. Hayden, M.D., Robert L. Atmar, M.D., Margo Schilling, M.D., Casey Johnson, D.O., Donald Poretz, M.D., David Paar, M.D., Les Huson, Ph.D., Penelope Ward, M.D., Roger G. Mills, M.D., and the Oseltamivir Study Group* Author Info & Affiliations

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Abstract

TABLE 3. INCIDENCE OF INFLUENZA AND INFLUENZA-LIKE ILLNESS IN THE OSELTAMIVIR AND PLACEBO GROUPS.*

INFECTION OR ILLNESS	OSELTAMIVIR			PLACEBO (N=519)
	ONCE DAILY (N=520)	TWICE DAILY (N=520)	COMBINED GROUPS (N=1040)	
Culture-proved influenza-like illness — no. of subjects (%)	0	4 (0.8)	4 (0.4)	15 (2.9)
Protective efficacy — % (95% CI)	100†	73 (29 to 93)	87 (65 to 96)	
P value	<0.001	0.011	<0.001	
Laboratory-confirmed influenza with fever ≥37.8°C — no. of subjects (%)	2 (0.4)	5 (1.0)	7 (0.7)	19 (3.7)
Protective efficacy — % (95% CI)	90 (61 to 98)	74 (37 to 91)	82 (60 to 93)	
P value	<0.001	0.004	<0.001	
Laboratory-confirmed infection (symptomatic or asymptomatic) — no. of subjects (%)	28 (5.4)	27 (5.2)	55 (5.3)	55 (10.6)
Protective efficacy — % (95% CI)	49 (24 to 69)	51 (26 to 70)	50 (31 to 67)	
P value	0.002	0.001	<0.001	
Influenza-like illness without laboratory evidence of infection — no. of subjects (%)	5 (1.0)	6 (1.2)	11 (1.1)	7 (1.3)
Protective efficacy — % (95% CI)	29 (−83 to 87)	15 (−108 to 84)	22 (−67 to 83)	
P value	0.58	0.79		

*P values are for the comparison with placebo. CI denotes confidence interval.

†The 95 percent confidence interval could not be estimated.

Influenza Prevention in Household Studies with NAIs: Involves Post-exposure Prophylaxis

Antiviral (Study)	Season (Virus)	Reduction in Secondary Cases %	Resistance Transmission
No Treatment of Index			
Zanamivir (Monto et al, 2002)	2000-01 (A/H3N2, B)	81%	—
Oseltamivir (Welliver et al, 2001)	1998-99 (A/H3N2, B)	89%	—
With Treatment of Index			
Zanamivir* (Hayden et al, 2000)	1998-99 (A/H3N2, A/H1N1)	79%	No
†Oseltamivir (Hayden et al, 2004)	2000-01 (A/H3N2, B)	85%	No

*Prophylaxis is given ≥ 5 years.
†Excludes contacts positive for influenza prior to prophylaxis.

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Original Contribution

Antiviral Effects on Influenza Viral Transmission and Pathogenicity: Observations from Household-based Trials

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Four household-based, randomized clinical trials, two each of zanamivir and oseltamivir, were designed primarily to estimate the effect of postexposure prophylaxis on preventing influenza illness in household contacts. However, the effect of influenza antivirals on infectiousness as well as on the ability of the virus to cause disease—the pathogenicity—have important public health consequences. The authors show how such studies can provide estimates of pathogenicity, antiviral efficacy for pathogenicity, and the antiviral effect on infectiousness. Analysis of the four studies confirmed the high prophylactic efficacy against illness of both zanamivir (75%, 95% confidence interval (CI): 54, 86) and oseltamivir (81%, 95% CI: 35, 94). The effect on reducing infectiousness was 19% (95% CI: −160, 75) for zanamivir and 80% (95% CI: 43, 93) for oseltamivir. Pathogenicity in controls ranged from 44% (95% CI: 33, 55) to 66% (95% CI: 48, 72). Efficacy in reducing pathogenicity for zanamivir was 52% (95% CI: 19, 72) and 56% (95% CI: 14, 77) in the two studies; for oseltamivir, it was 56% (95% CI: 10, 73) and 79% (95% CI: 45, 92). Studies of influenza antivirals in transmission units would be improved if randomization schemes were used that allow estimation of the antiviral effect on infectiousness from individual studies.

antiviral agents; disease transmission; family characteristics; influenza, human; randomized controlled trials; treatment outcome

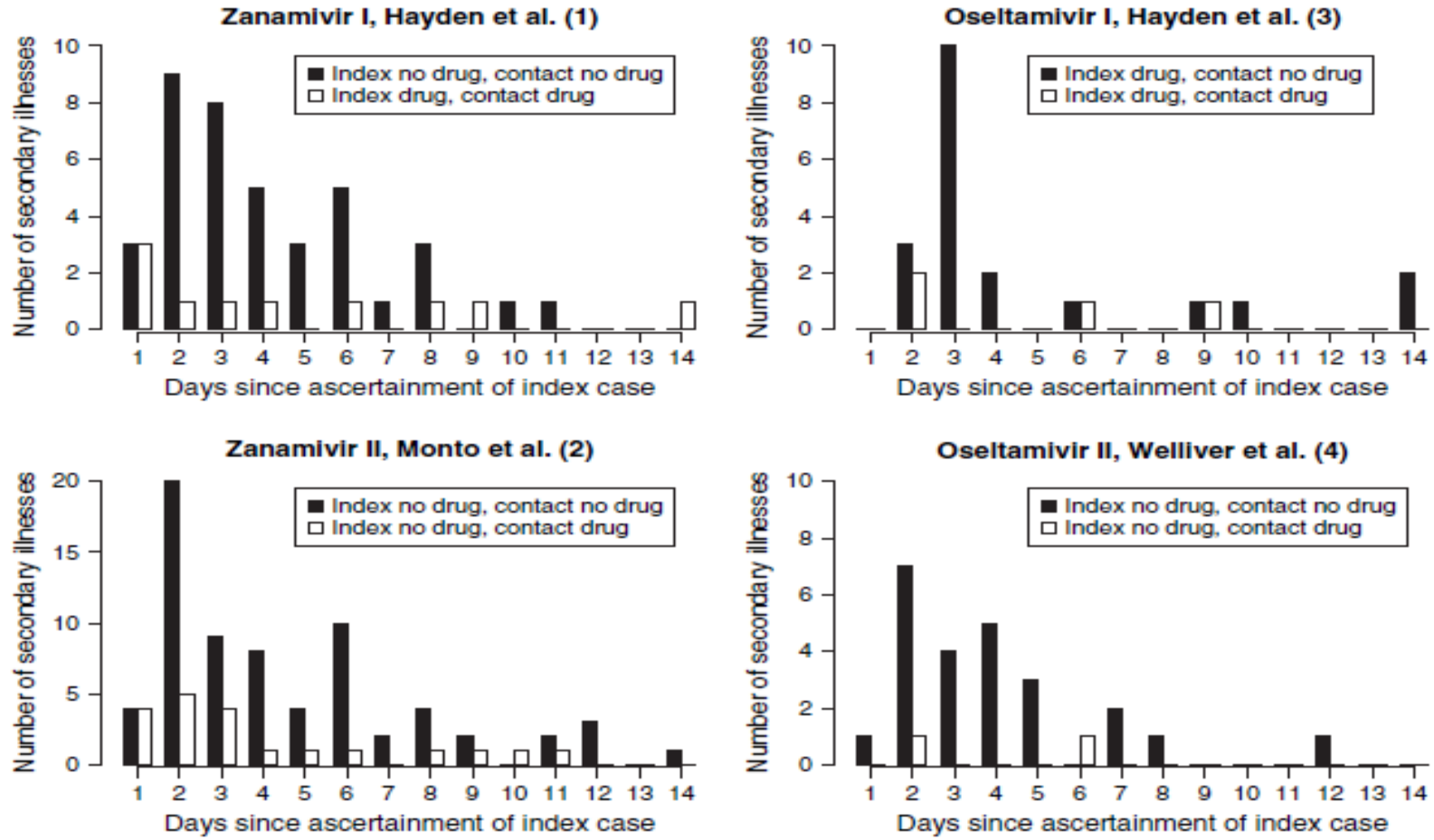

FIGURE 1. Distribution of the number of secondary cases of influenza in contacts by day since ascertainment of the index case according to antiviral agent status of the index cases and contacts.

Effects of oseltamivir treatment of index patients with influenza on secondary household illness in an urban setting in Bangladesh: secondary analysis of a randomised, placebo-controlled trial

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See Comment page 617

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Summary

Background Antiviral drugs are a proposed medical intervention to reduce household transmission of influenza viruses. In a previously described randomised, placebo-controlled trial in Dhaka, Bangladesh, we showed that oseltamivir treatment of index patients was able to reduce influenza symptom duration and virus shedding. In a further analysis that is part of the same study, we aimed to assess efficacy of oseltamivir to reduce secondary household illnesses in the same cohort.

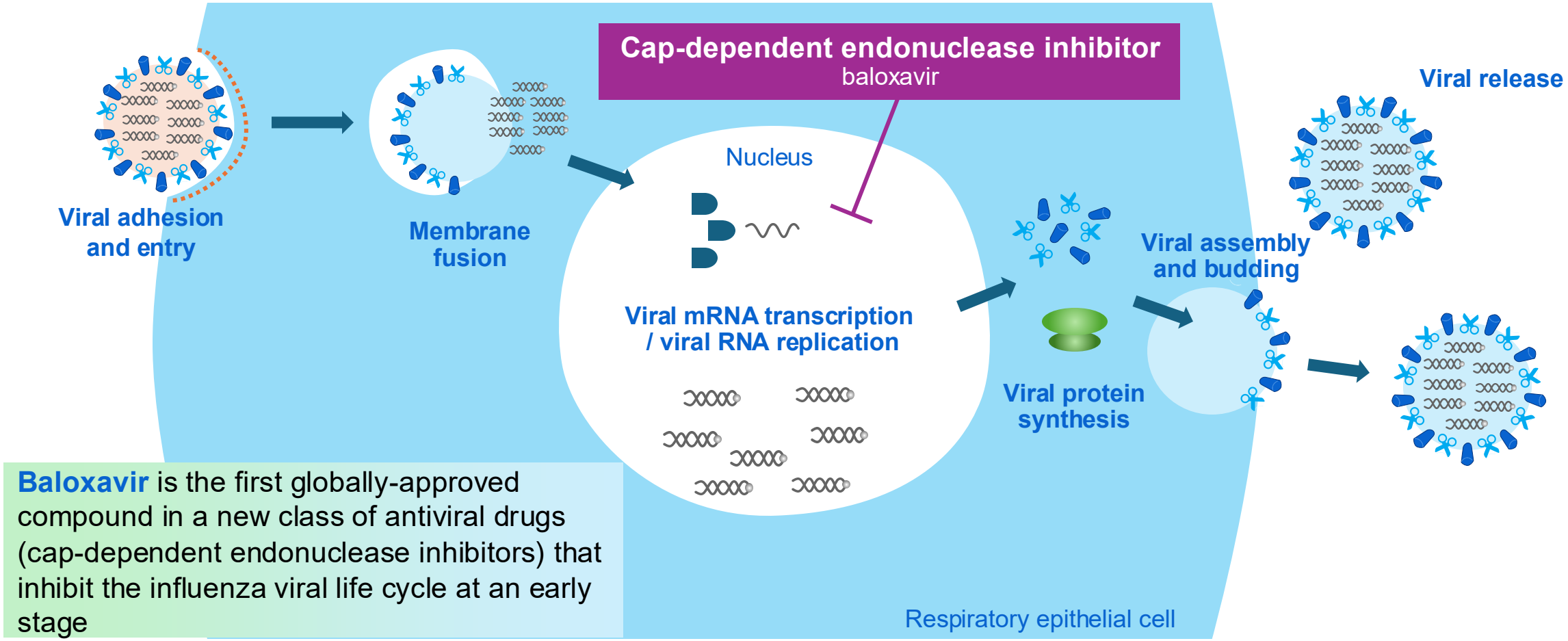
Methods In this double-blind oseltamivir efficacy trial, we identified index patients aged older than 1 year through surveillance of households in Dhaka, Bangladesh. We randomly allocated eligible patients (1:1) to receive oseltamivir or placebo twice-daily for 5 days, and we stratified them by enrolment 48 h versus 48–120 h since illness onset. Participants provided nasal wash specimens at enrolment and 2, 4, and 7 days after enrolment and were visited daily by a research assistant to record symptoms, both in index patients and in household members. For this part of the study, household members were asked to give respiratory specimens for influenza PCR testing. Our primary outcomes were household secondary illness and PCR-confirmed influenza virus infection, assessed in household members of all randomly allocated index patients. This trial is registered with ClinicalTrials.gov, number NCT00707941.

Findings From May 11, 2008, to Dec 31, 2010, we enrolled 1190 index patients with 4694 household members. 592 patients were allocated to placebo (2292 household members) and 598 to oseltamivir (2402 household members). Household secondary illness was lower in the oseltamivir group (196 [8%] influenza cases) than in the placebo group (233 [10%]; odds ratio [OR] 0·77, 95% CI 0·60–0·98, p=0·031). PCR-confirmed influenza virus infection did not differ between the placebo (103 [5%]) and oseltamivir groups (92 [4%]; 0·84, 0·59–1·19, p=0·319); however, only 243 (57%) of ill household members gave a specimen for analysis.

Interpretation In a crowded, low income setting, oseltamivir treatment of index patients resulted in a small reduction of secondary influenza in their households. Even this slight reduction, in the setting of widespread antiviral use during a community influenza outbreak, might result in reductions in overall disease burden.

Funding Centers for Disease Control and Prevention (in an agreement with the International Centre for Diarrhoeal

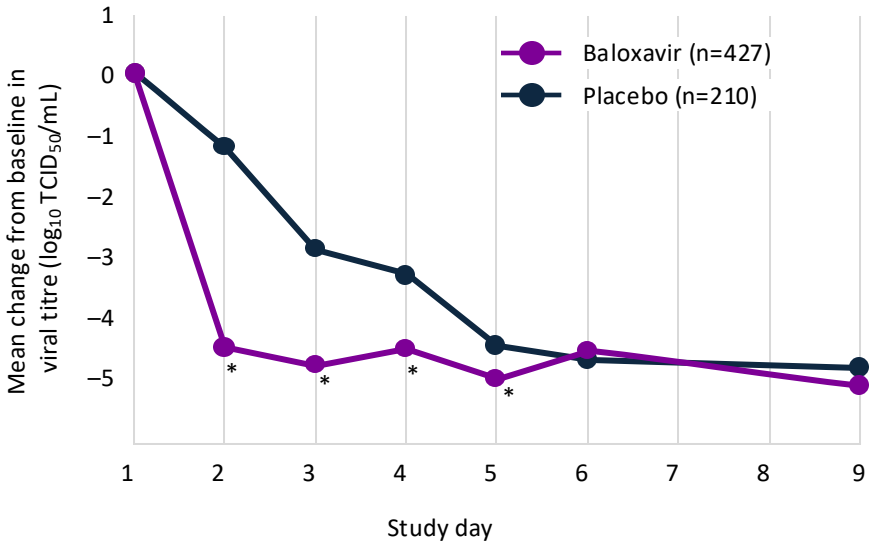
Baloxavir is a new antiviral treatment option for influenza



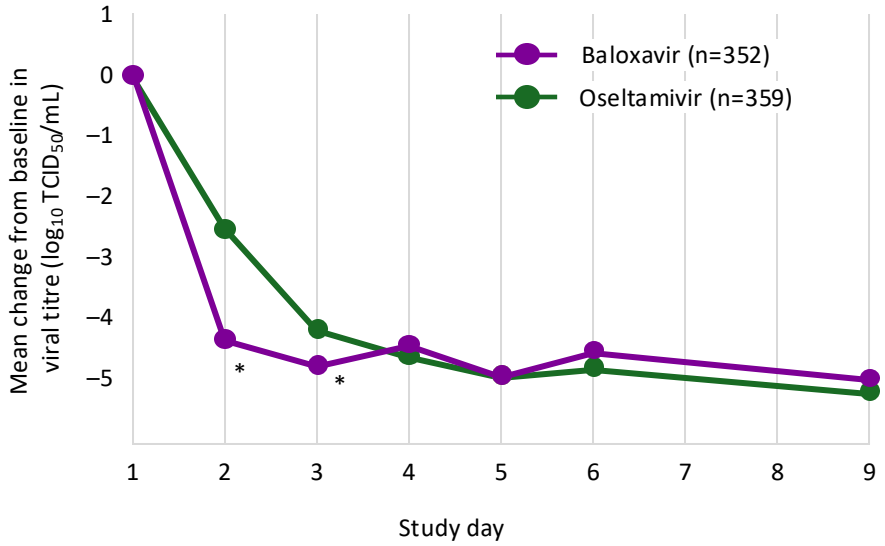
Baloxavir is the first globally-approved compound in a new class of antiviral drugs (cap-dependent endonuclease inhibitors) that inhibit the influenza viral life cycle at an early stage

Impact of baloxavir and oseltamivir on viral load

Change in viral titres: baloxavir vs placebo



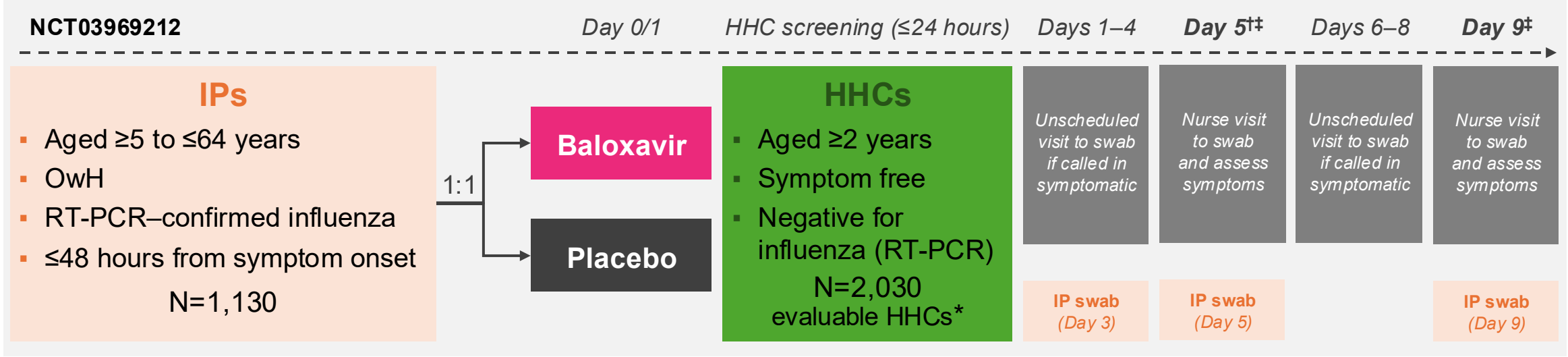
Change in viral titres: baloxavir vs oseltamivir†



In the CAPSTONE-1 study of otherwise-healthy adults with uncomplicated influenza, baloxavir substantially reduced viral loads as measured by $TCID_{50}$, faster than with placebo and oseltamivir

Secondary endpoint. ITTI population. First dose given on study day 1
*p<0.05 vs placebo or oseltamivir; †Adults aged 20–64 years
Baloxavir marboxil is authorised in the European Union. Not marketed in Spain.
ITTI, intention-to-treat infected; $TCID_{50}$, tissue culture infectious dose

CENTERSTONE: a Phase IIIb, randomised, placebo-controlled transmission trial in OwH IPs



Key exclusion criteria (IPs)

- Severe influenza virus infection requiring hospitalisation
- SARS-CoV-2 infection
- Pregnant or breastfeeding
- Lives with any HHCs who meet HHC exclusion criteria

Key exclusion criteria (HHCs)

- Immunocompromised
- SARS-CoV-2 infection
- Pregnant or within 2 weeks post-partum

*Primary analysis population (PAS-HHC), defined as all full trial unvaccinated HHCs associated with an IP who was RT-PCR–positive for influenza and received trial drug, with all HHCs in the household RT-PCR–negative for influenza at baseline; †Primary endpoint and key secondary efficacy endpoint; ‡Additional secondary efficacy endpoints
HHC, household contact; IP, index patient; OwH, otherwise healthy; PAS-HHC, primary household contacts analysis set
RT-PCR, reverse transcription polymerase chain reaction

The primary endpoint was transmission of influenza virus by Day 5

Primary endpoint: transmission of influenza virus by Day 5

Proportion of RT-PCR–positive HHCs by Day 5 following IP treatment, with a virus subtype consistent with that of the IP

Secondary efficacy endpoints*

Transmission of influenza virus resulting in symptoms by Day 5†

Transmission of influenza virus by Day 9‡¶

Safety endpoints

Frequency, severity and timing of AEs and SAEs in IPs

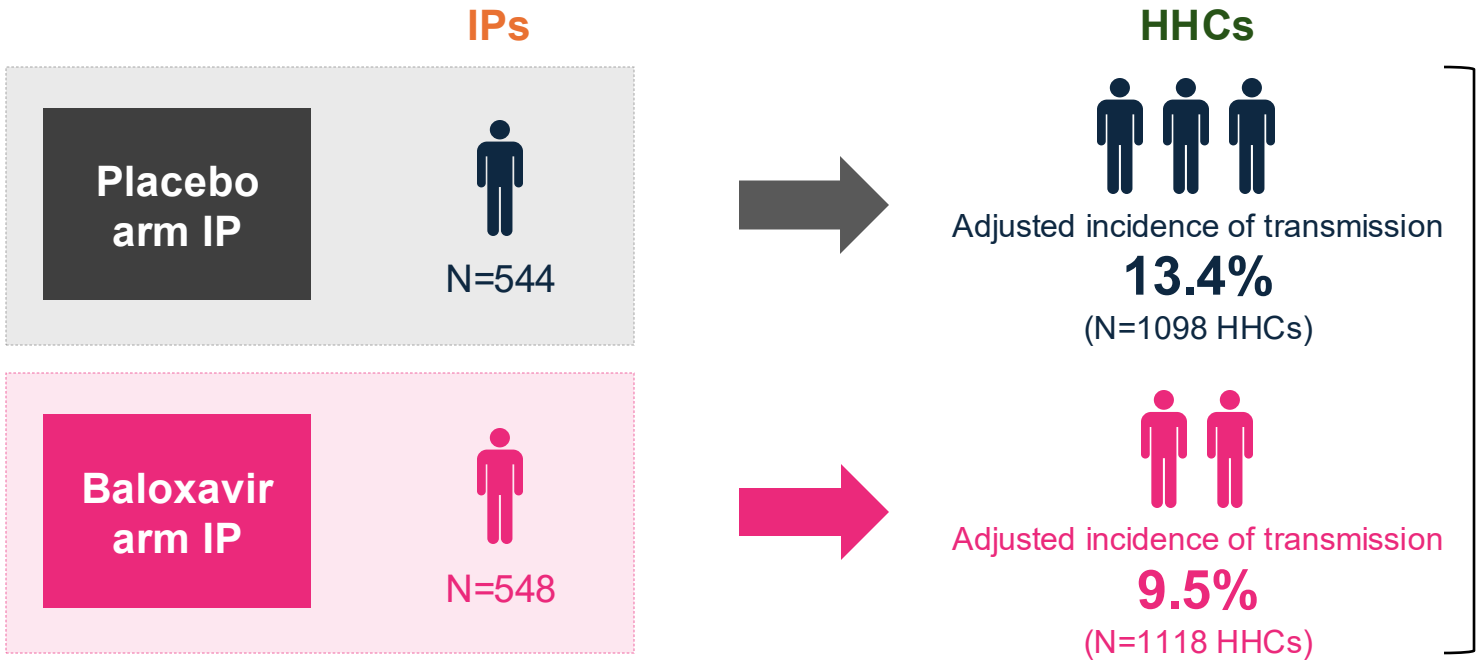
Exploratory endpoint

Proportion of IPs and HHCs with viruses harbouring RAS

*Additional secondary efficacy endpoints were evaluated, including transmission of influenza virus by household
†Key secondary efficacy endpoint, defined as the proportion of HHCs meeting the primary endpoint AND either: temperature ≥38.0 °C plus one respiratory symptom, or one respiratory symptom plus one general systemic symptom, with or without fever (in HHCs aged ≥12 years); or temperature ≥38.0 °C plus signs or symptoms of a URTI (in HHCs aged <12 years)
‡Day 9 transmission includes transmission events by Day 5 and transmission events after Day 5 that are limited to possible tertiary transmissions (with other HHCs positive for the primary endpoint by Day 5) or transmissions with the HHC influenza virus bearing a PA/I38X or PA/T20K substitution
¶Assessed as the fourth of nine secondary efficacy endpoints in the hierarchical testing sequence
AE, adverse event; HHC, household contact; IP, index patient; PA, polymerase acidic; RAS, resistance-associated substitutions; RT-PCR, reverse transcription polymerase chain reaction
SAE, serious adverse event; URTI, upper respiratory tract infection

Baloxavir showed a statistically significant and clinically meaningful reduction in transmission of influenza virus by Day 5 compared with placebo

Transmission of influenza virus by Day 5*



29% aRRR with baloxavir (95.38% CI, 12–45%)

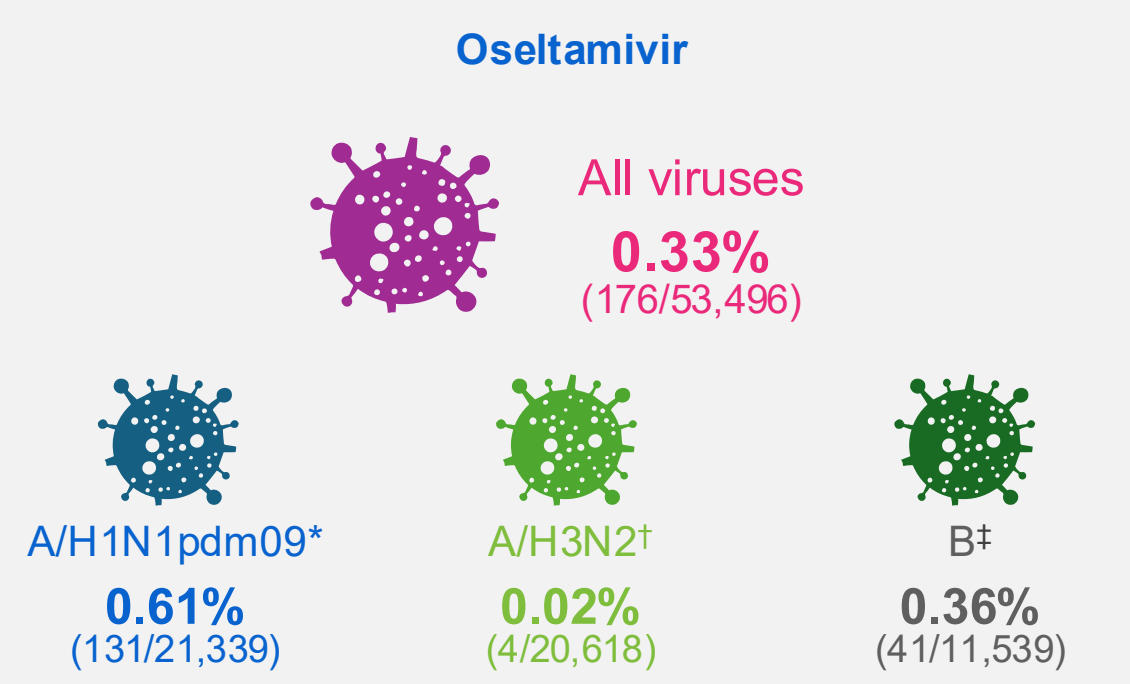
aOR: 0.68 (95.38% CI, 0.50–0.93), p=0.013†

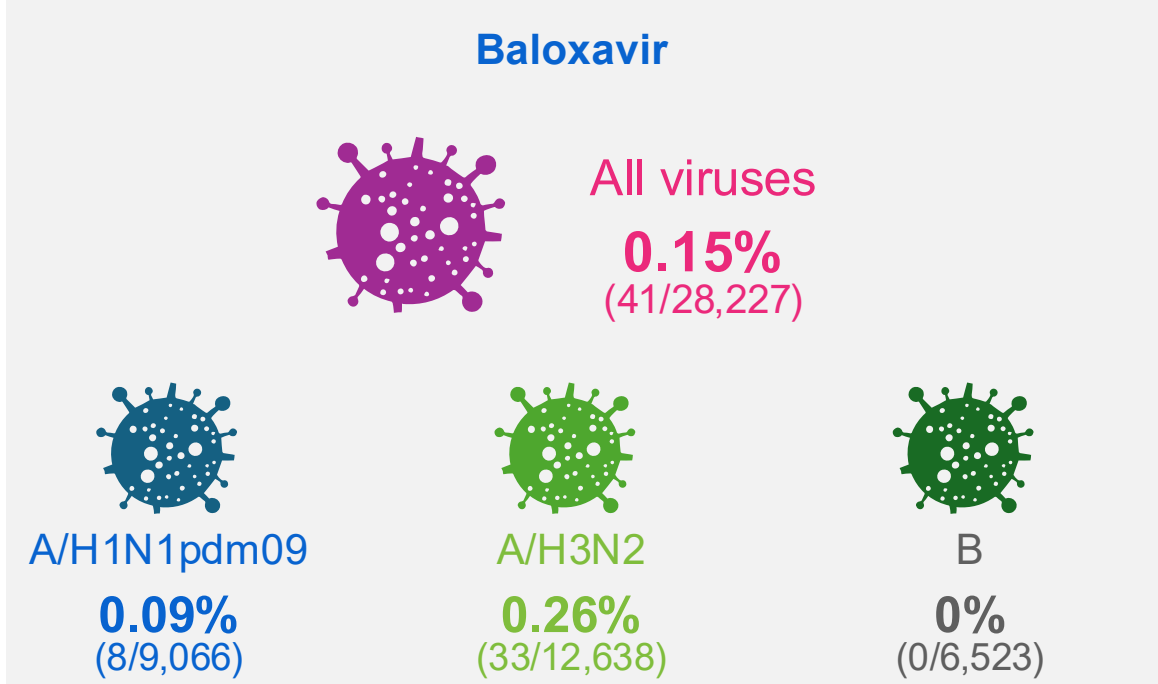
- A **clinically meaningful reduction** was also observed with baloxavir by **Day 9**‡
  - Adjusted incidence of transmission: placebo, 15.4% (N=1038 HHCs) vs baloxavir, 10.8% (N=1081 HHCs)
  - **30% aRRR** with baloxavir (95.38% CI, 12–44%); aOR: 0.66 (95.38% CI, 0.48–0.91)¶

PAS-HHC population
*Proportion of RT-PCR–positive HHCs by Day 5 following IP treatment, with a virus subtype consistent with that of the IP. Analysis based on a generalised estimating equations (GEE) approach, accounting for clustering within households and the randomisation stratification factors; †An adjusted significance level of 0.0462 was used to account for the efficacy interim analysis. Confidence intervals were also adjusted; ‡Assessed as the fourth of nine secondary efficacy endpoints in the hierarchical testing sequence
¶Not statistically significant as a preceding endpoint in the testing hierarchy did not reach statistical significance; the confidence intervals may not be used in place of hypothesis testing
aOR, adjusted odds ratio; aRRR, adjusted relative risk reduction; CI, confidence interval; HHC, household contact; IP, index patient
PAS-HHC, primary household contacts analysis set; RT-PCR, reverse transcription polymerase chain reaction

Occurrence of oseltamivir and baloxavir resistance among surveillance samples is extremely low

WHO GISRS: frequency of resistance among circulating viruses between September 2018 and August 2024





*Between January and September 2022, 5 viruses were found to have the H275Y mutation, which usually confers oseltamivir resistance; however, only 4 of these viruses were available for phenotypic analysis; †The WHO does not specify the number of oseltamivir-resistant A/H3N2 viruses for the period between February and September 2019;
‡For the periods September 2019–January 2020, September 2021–January 2022 and September 2022–August 2023 the number of viruses resistant to NAIs is used; the WHO does not provide figures specifically for oseltamivir for this period

No cases of resistance-associated substitutions (RAS) were observed in HHCs

- No viruses with RAS were detected in IPs at baseline
- The rate of treatment-emergent RAS in IPs was **7.2%** (95% CI, 4.1–11.6%), consistent with previous trials,
  and transmission of viruses with RAS was not detected in any of the 27 associated HHCs (0%; 95% CI, 0.0–12.8%)

Treatment-emergent RAS in IPs*	Virus type/subtype, n (%) [95% CI]			
	A(H1N1)pdm09 (N=69)	A(H3N2) (N=88)	B (N=53)	Total (N=208)
PA/I38X	5 (7.2) [2.4–16.1]	10 (11.4) [5.6–19.9]	0 (0) [0–6.7]	15 (7.2) [4.1–11.6]

- No RAS was detected in the 1268 HHCs exposed to baloxavir-treated IPs, including 13 IPs† who were shedding viruses with RAS

*IPs with paired baseline and post-baseline sequences
†Two of the IPs with treatment-emergent RAS did not enrol any HHCs into the trial
CI, confidence interval; HHC, household contact; IP, index patient; PA, polymerase acidic
RAS, resistance-associated substitutions