# Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial

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See Comment page 4

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## Summary

**Background** Antivirals are infrequently prescribed in European primary care for influenza-like illness, mostly because of perceived ineffectiveness in real world primary care and because individuals who will especially benefit have not been identified in independent trials. We aimed to determine whether adding antiviral treatment to usual primary care for patients with influenza-like illness reduces time to recovery overall and in key subgroups.

**Methods** We did an open-label, pragmatic, adaptive, randomised controlled trial of adding oseltamivir to usual care in patients aged 1 year and older presenting with influenza-like illness in primary care. The primary endpoint was time to recovery, defined as return to usual activities, with fever, headache, and muscle ache minor or absent. The trial was designed and powered to assess oseltamivir benefit overall and in 36 prespecified subgroups defined by age, comorbidity, previous symptom duration, and symptom severity, using a Bayesian piece-wise exponential primary analysis model. The trial is registered with the ISRCTN Registry, number ISRCTN 27908921.

**Findings** Between Jan 15, 2016, and April 12, 2018, we recruited 3266 participants in 15 European countries during three seasonal influenza seasons, allocated 1629 to usual care plus oseltamivir and 1637 to usual care, and ascertained the primary outcome in 1533 (94%) and 1526 (93%). 1590 (52%) of 3059 participants had PCR-confirmed influenza infection. Time to recovery was shorter in participants randomly assigned to oseltamivir (hazard ratio 1·29, 95% Bayesian credible interval [BCrI] 1·20–1·39) overall and in 30 of the 36 prespecified subgroups, with estimated hazard ratios ranging from 1·13 to 1·72. The estimated absolute mean benefit from oseltamivir was 1·02 days (95% [BCrI] 0·74–1·31) overall, and in the prespecified subgroups, ranged from 0·70 (95% BCrI 0·30–1·20) in patients younger than 12 years, with less severe symptoms, no comorbidities, and shorter previous illness duration to 3·20 (95% BCrI 1·00–5·50) in patients aged 65 years or older who had more severe illness, comorbidities, and longer previous illness duration. Regarding harms, an increased burden of vomiting or nausea was observed in the oseltamivir group.

**Interpretation** Primary care patients with influenza-like illness treated with oseltamivir recovered one day sooner on average than those managed by usual care alone. Older, sicker patients with comorbidities and longer previous symptom duration recovered 2–3 days sooner.

**Funding** European Commission's Seventh Framework Programme.



## Introduction

Guidelines recommend antiviral treatment for individuals presenting with suspected or confirmed influenza who have high-risk features.[1,2] However, antivirals are not often prescribed in primary care in many European countries,[3] partly because of clinical and cost-effectiveness, because of potential side-effects, such as nausea and vomiting, and because individuals who will especially benefit have not been identified in prospective, non-industry-funded, and pragmatic studies.[4] Whether treatment should be initiated only after a positive test for influenza or whether it should be based on syndromic presentation alone is unclear. Oseltamivir treatment is recommended by the Centers for Disease Control and Prevention as early as possible for patients with confirmed or suspected influenza who are hospitalised, severely ill, or have higher risk for influenza complications, and treatment can be considered for symptomatic outpatients with suspected influenza if treatment can be initiated within 48 h of illness onset, which is similar to European recommendations.[1,2,5]

Meta-analyses have found that oseltamivir improves the median time to alleviation of symptoms over placebo among adults by 17·8 h (95% CI 27·1–9·3),[6] and time to

## Research in context

### Evidence before this study

At the conception of this trial on Jan 15, 2015, we searched PubMed for systematic reviews in any language using the following MEDLINE subject heading keywords: "neuraminidase inhibitors" and "influenza". A systematic review of placebo-controlled randomised trials found that oseltamivir reduced the median time to alleviation of symptoms over placebo by 17·8 h (95% CI 27·1 to 9·3), and a Cochrane systematic review found oseltamivir reduced time to first alleviation of symptoms by 16·8 h (95% CI 21·8 to 8·4), both in intention-to-treat populations with influenza-like illness. A systematic review and meta-analysis of published and unpublished placebo-controlled trials in adults with suspected or confirmed influenza found a mean reduction in duration of symptoms from oseltamivir of 20·7 h (95% CI 13·3–28·0) in five studies that included 3833 participants in an intention-to-treat population, and a mean reduction of 25·4 h (95% CI 17·2–33·5) in the intention-to-treat infected population (7 studies, 2690 patients), a difference of about 5 h. Trials have found relatively greater benefits in individuals treated within 24 h of symptom onset, and guidelines recommend initiating oseltamivir within 48 h of symptom onset. Some of the trials included in the systematic reviews have been criticised for under-recruiting, selective reporting of outcomes, not including sufficient children or older people, and recruiting in a single season. Additionally, the effects of antiviral treatment on return to daily activities, quality of life, and care-seeking in key subgroups is largely unknown.

### Added value of this study

In an open-label, pragmatic, randomised controlled trial that included 3266 adults and children presenting in primary care with influenza-like illness, patients treated with oseltamivir recovered sooner, irrespective of influenza virus test results. Older, sicker, patients with comorbidities and longer previous symptom duration showed greater absolute benefit. Our overall estimate of benefit is similar to effects found in placebo-controlled trials, but we identified additional benefit in those with certain risk factors. Previous trials have found relatively greater benefit in those treated within 24 h of symptom onset, but additional benefit from earlier treatment was not apparent in our trial. Similarly, unlike some trials, benefit in our trial was similar regardless of influenza test results.

### Implications of all the available evidence

Adding oseltamivir to usual primary care for patients with influenza-like illness accelerates recovery by a mean of about one day, and slightly longer in individuals with risk factors, irrespective of influenza status. Initiating oseltamivir 48–72 h after illness onset appears to give similar benefit to earlier initiation. Clinicians might consider treatment in patients who are sicker or older, who have comorbidities, and who have been unwell for longer, because oseltamivir might reduce their illness by as much as 2–3 days.

first alleviation of symptoms by 16·8 h (21·8–8·4).[7] Some of the included trials have been criticised for under-recruiting, selective reporting of outcomes, not including sufficient children or older people, and recruiting in a single season.[7,8] Additionally, the effect of antiviral treatment on return to daily activities, quality of life, and care-seeking is largely unknown, which is pivotal to assessing cost-effectiveness. We therefore aimed to determine whether adding antiviral treatment to usual primary care for patients with influenza-like illness is effective in reducing time to recovery both overall and in key subgroups.

## Methods

### Study design and participants

ALIC⁴E was an investigator-initiated, open-label, pragmatic, response-adaptive, platform, randomised controlled trial. The trial protocol has been published previously.[9]

Independent trial steering, data monitoring, and ethics committees provided study oversight. The funder (European Commission's Seventh Framework Programme) had no influence on the design or conduct of the trial. The trial protocol, available online, was approved by National Research Ethics Service Committee South Central—Oxford B. Clinical trial authority approval was obtained from the UK Medicines and Healthcare products Regulatory Agency. All participating countries gained national research ethics committees and clinical trial authority approval as required.

Potential participants were identified when they presented with symptoms of influenza-like illness, or when they telephoned for an appointment or advice about their symptoms, to medical practices that were part of primary care research networks that had agreed to participate in the trial. Influenza-like illness was defined as a sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, or running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills, or tiredness), with symptom duration of 72 h or less during a seasonal influenza epidemic.[10] Participants with influenza-like illness of at least 1 year of age, for whom written informed consent was provided, who could comply with study requirements, and who agreed to take an antiviral drug according to assignment were eligible.

Exclusion criteria included: chronic renal failure; substantial impaired immunity (eg, long-term oral steroids, chemotherapy, or immune disorder); patients who should be prescribed immediate antiviral treatment or immediate hospitalisation in the opinion of the responsible clinician; allergy to oseltamivir; scheduled elective surgery or other procedures requiring general

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See Online for appendix

anaesthesia during the subsequent 2 weeks; life expectancy estimate of less than 6 months; severe hepatic impairment; unable to be randomised within 72 h after onset of symptoms; requirement for any live viral vaccine in the next 7 days; and, in some jurisdictions, pregnant, lactating, or breastfeeding women.

### Randomisation and masking

Participants were randomly assigned at the point of care, using a remote online electronic data capture system (Research Online 2), to either usual primary care according to general practitioners' normal preferences or oseltamivir plus usual care in a 1:1 ratio. The prespecified design required that response adaptive randomisation be activated at an interim timepoint if either of the following prespecified criteria were met (appendix p 2): an interim conclusion of super-superiority within a subgroup or the addition of a second antiviral group. Neither criterion was met, so a 1:1 randomisation ratio was maintained throughout the trial. The trial design did not contain any adaptive stopping rules (eg, early success or futility); rather the trial sought to enrol as many patients as possible across three consecutive winters (targeting between 2500 and 4500 participants). Stratified block randomisation was implemented, with random blocks of two, four, and six participants and stratification by age (<12, 12–<65, and ≥65 years), overall severity of influenza-like illness (rated by the responsible clinician as mild, moderate, or severe), any relevant comorbidity (yes or no for heart disease, diabetes, chronic respiratory condition, hepatic, haematological, neurological, or neurodevelopmental condition, stroke or transient ischaemic attack, or overnight hospital stay in previous year), and previous duration of symptoms since onset (≤48 h or >48–72 h, based on recommendations that oseltamivir should be started within 48 h of symptom onset). This was an open-label study, so no placebo was used and drugs were not masked.

### Procedures

Adults and children weighing more than 40 kg who were assigned to the usual care plus oseltamivir and able to swallow capsules were given 75 mg oral oseltamivir twice daily for 5 days. For children younger than 13 years, oseltamivir was given in oral suspension according to weight (children weighing 10–15 kg received 30 mg, >15–23 kg received 45 mg, >23–40 kg received 60 mg, and >40 kg received 75 mg).

A baseline case report form was completed covering overall clinician-rated severity of influenza-like illness (general practitioners' global impression of mild, moderate, or severe illness without provided, predefined criteria), duration of symptoms, comorbidity, temperature, pulse, individual influenza-like-illness symptom severities (patient-reported at inclusion), and usual care advice (registered by general practitioner). Oropharyngeal and nasal swabs (COPAN, Bresica, Italy) were taken from participants younger than 16 years of age and nasopharyngeal swabs (COPAN, Bresica, Italy) from those aged 16 years or older. Clinicians were trained in swabbing techniques using face-to-face and online video methods. The Fast Track Diagnostics Respiratory Pathogens 21 plus real-time PCR assay (Fast Track Diagnostics, Luxembourg) was used to determine the aetiology, including influenza A and B status after each season, or after study completion, but results were not available for clinicians to inform management.[11]

Patients were asked to complete a symptom diary for 14 days to indicate when they had returned to their usual daily activities and to evaluate fever, running or congested nose, sore throat, headache, cough, shortness of breath (adults only), muscle ache, sweats or chills (adults only), diarrhoea, nausea or vomiting, abdominal pain, low energy or tired, not sleeping well, dizziness, and feeling generally unwell were recorded as no, minor, moderate, or major problems. These diaries were supplemented with child-specific questions, so that the Canadian Acute Respiratory Illness Flu Scale was completed for children 12 years of age or younger.[12] Patients were contacted by telephone between days 2 and 4, days 14 and 28, and after 28 days to support study participation and diary completion, monitor intervention adherence, and ascertain a minimal outcome dataset.

### Outcomes

The primary outcome was patient-reported time to recovery, defined as having returned to usual daily activity and fever, headache, and muscle ache rated as minor or no problem in key subgroups. For non-verbal children, clinginess replaced headache and muscle ache when both were unanswered. Secondary outcomes were cost-effectiveness of adding antiviral treatment to usual primary care (to be reported separately), incidence of hospital admissions, complications related to influenza-like illness, repeat attendance in general practice, time to alleviation of symptoms of influenza-like illness, incidence of new or worsening symptoms, time to initial reduction in severity of symptoms, use of additional symptomatic and prescribed medication, including antibiotic, transmission of infection within household, and self-management of symptoms of influenza-like illness. These outcomes, together with reports of individual symptoms, such as nausea and vomiting, that might be side-effects of oseltamivir and symptoms of influenza, were also considered in relation to possible harms from the intervention.[9]

### Statistical analysis

Full details and explanation of the statistical design are provided in the appendix (pp 2–4). Given the platform trial design,[13] the statistical analysis explicitly addressed the estimation of a treatment effect in multiple prespecified subgroups and allowed for an additional treatment during trial, although this was not implemented, because no suitable drug became available for inclusion in the

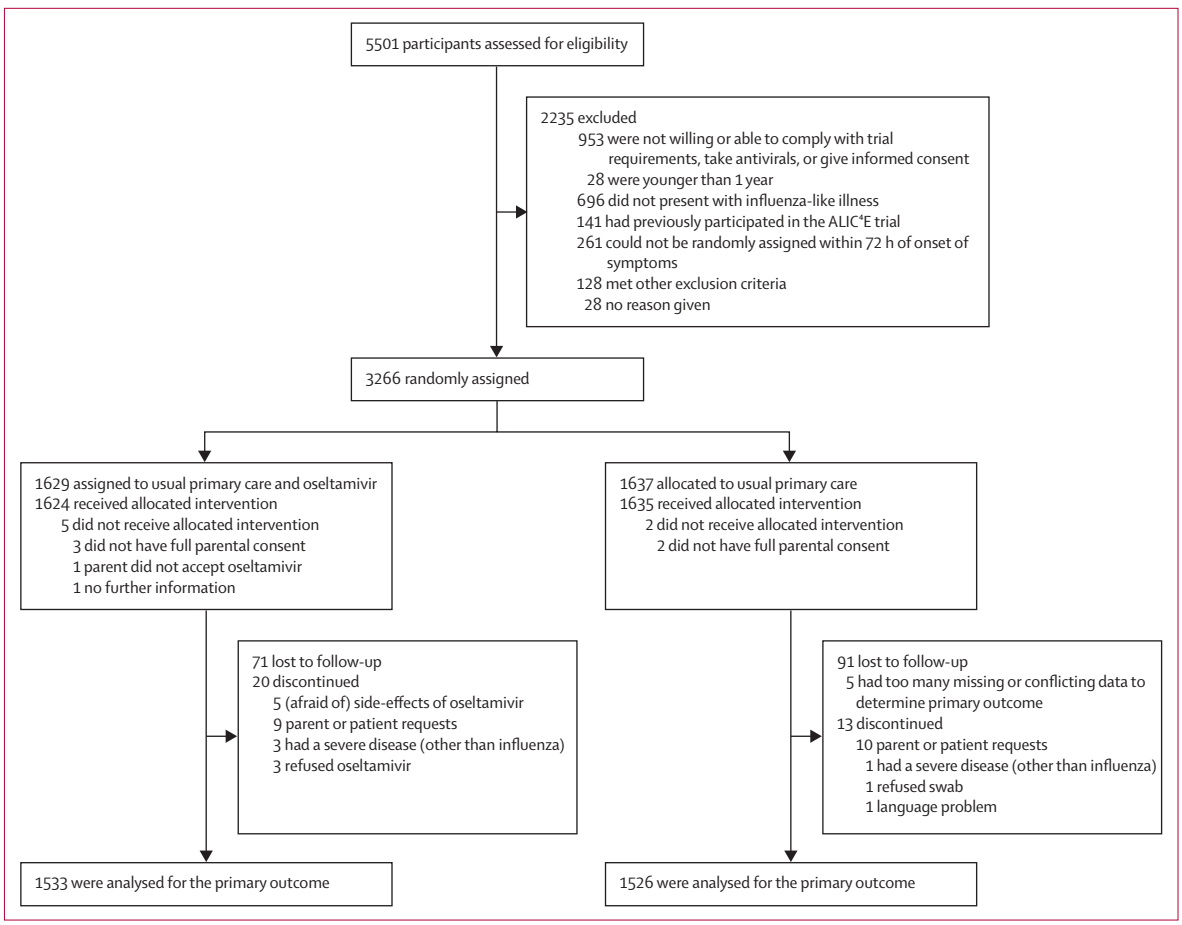


***Figure 1:*** **Study profile**

trial. The trial aimed to recruit between 2500 and 4500 participants over three consecutive winters. Simulations in the design stage ensured this sample size was sufficient to provide at least 80% power for detecting a mean 1–2-day oseltamivir benefit in each of the subgroups.

The prespecified primary analysis was based on a Bayesian piece-wise exponential time-to-event model. The intention-to-treat population included all randomly assigned patients regardless of treatment received. For the primary endpoint, where diary data were unavailable, data from the day 14–28 telephone calls was used, and if that was unavailable, data from the calls after 28 days. When data were incomplete, participants were censored at their last contact date or at 28 days.

Per the prespecified design, the model evaluated the benefit of oseltamivir in the overall study population, within each marginal subgroup by each stratification factor, and within each of the 36 stratification factor subgroup combinations. The model included parameters for season, intervention group, age, severity, any comorbidity, symptom duration, and the corresponding two-way interaction terms between the intervention and each of the four stratification variables. On the basis of prespecified design, the usual care plus oseltamivir group was declared superior for a specific population if the Bayesian posterior probability exceeded 0·975 for that population. To protect against false positives, the model used previous distributions that favour homogeneity in response between the various subgroups, unless data suggested otherwise. For subgroups with a small sample size, estimates of treatment benefit were driven by the observed results in similar subgroups and the overall study population. Extensive simulations were done in the trial design phase to ensure adequate control of false positive conclusions; the simulated type I error was between 0·001 and 0·04 for each of the hypotheses in the global null setting (ie, when no oseltamivir benefit in all populations). Complete details are provided in the appendix (p 3). Estimates in the primary analysis were not adjusted for any interim analyses, because there was no evidence of bias resulting from adaptations in trial design simulations.

An exploratory analysis not specified in our original statistical analysis plan evaluated the interaction between the intervention and PCR-confirmed influenza status with respect to the primary outcome. These analyses

| | Usual care (control), n=1635* | Usual care plus oseltamivir (intervention), n=1624* |
|---|---|---|
| Sex | | |
| Male | 731 (45%) | 707 (44%) |
| Female | 904 (55%) | 917 (56%) |
| Age | | |
| <12 years | 223 (14%) | 225 (14%) |
| 12–65 years | 1306 (80%) | 1296 (80%) |
| >65 years | 106 (6%) | 103 (6%) |
| Comorbidity | 239 (15%) | 251 (15%) |
| Heart disease | 76 (5%) | 71 (4%) |
| Diabetes | 42 (3%) | 40 (2%) |
| Chronic respiratory condition | 92 (6%) | 104 (6%) |
| Hepatic, haematological, neurological, or neurodevelopmental condition | 11 (1%) | 21 (1%) |
| Stroke or transient ischaemic attack | 9 (1%) | 4 (<1%) |
| Overnight hospital stay in preceding year | 45 (3%) | 51 (3%) |
| Severity of influenza-like illness | | |
| Mild | 353 (22%) | 340 (21%) |
| Moderate | 985 (60%) | 983 (61%) |
| Severe | 297 (18%) | 301 (19%) |
| Previous symptom duration | | |
| ≤24 h | 454 (28%) | 448 (28%) |
| >24–48 h | 633 (39%) | 616 (38%) |
| >48–72 h | 548 (34%) | 560 (34%) |
| Signs and symptoms (major or moderate) | | |
| Fever | 1264 (77%) | 1287 (79%) |
| Running or congested nose | 990 (61%) | 1001 (62%) |
| Sore throat | 968 (59%) | 946 (58%) |
| Headache | 1190 (73%) | 1189 (73%) |
| Cough | 1134 (69%) | 1093 (67%) |
| Shortness of breath† | 387 (24%) | 381 (23%) |
| Muscle ache and pains | 1147 (70%) | 1139 (70%) |
| Sweats or chills† | 1109 (68%) | 1103 (68%) |
| Diarrhoea | 97 (6%) | 73 (4%) |
| Nausea or vomiting | 171 (10%) | 154 (9%) |
| Abdominal pain† | 161 (10%) | 149 (9%) |
| Low energy or tired | 1334 (82%) | 1336 (82%) |
| Not sleeping well | 881 (54%) | 852 (52%) |
| Dizziness† | 362 (22%) | 417 (26%) |
| Feeling generally unwell | 1428 (87%) | 1413 (87%) |
| Poor appetite‡ | 143 (60%) | 144 (60%) |
| Crying more‡ | 81 (34%) | 84 (35%) |
| Needing extra care‡ | 121 (51%) | 135 (56%) |
| Clinginess‡ | 121 (51%) | 120 (50%) |
| Not playing well‡ | 102 (43%) | 119 (49%) |
| Irritable, cranky, fuzzy‡ | 105 (44%) | 114 (47%) |
| Not interested in what is going on‡ | 73 (31%) | 76 (32%) |
| Unable to get out of bed‡ | 36 (15%) | 49 (20%) |
| Temperature, Celsius, mean (SD) | 37·5 (0·89) | 37·6 (0·91) |
| Pulse, beats per minute, mean (SD) | 87·4 (15·1) | 87·7 (16·1) |
| Smoker, yes + occasionally (%) | 257 + 65 (20%) | 240 + 78 (20%) |
| Flu vaccination | 156 (10%) | 151 (9%) |
| Pneumococcal vaccination | 86 (5%) | 86 (5%) |
| PCR evidence of influenza | 820 (50%) | 852 (52%) |
| Influenza A | 452 (28%) | 496 (31%) |
| Influenza B | 369 (23%) | 357 (22%) |

Data are n (%), unless otherwise specified. Missing data were no more than 3% for any variable, except for the symptom variables, which were only answered by children, where missing was not more than 12%. *7 patients withdrew before any data collection or data had to be deleted (2 in the usual care group and 5 in the usual care plus oseltamivir group). †Symptoms answered by participants older than 12 years. ‡Symptoms answered by participants 12 years of age or younger (n=238 for control and n=241 for intervention).

***Table 1:*** **Baseline demographic and clinical characteristics in the intention-to-treat population**

were based on complete case analyses, in which patients with unknown influenza status were ignored.

The trial is registered with the ISRCTN Registry, number ISRCTN 27908921.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Jan 15, 2016, and April 12, 2018, 3266 participants (data from 7 patients needed to be deleted) were recruited from 21 networks covering 209 primary care practices in 15 European countries over three consecutive influenza seasons: 495 in 2015–16, 1225 in 2016–17, and 1546 in 2017–18 (figure 1; appendix p 5). Each season's recruitment period was based on reports of national incidences of influenza-like-illness presentation rising above or falling below country-specific thresholds, using information from the European Centre of Disease Prevention and Control[14] and regional sources for each network. 1672 (51%) of 3259 of participants had confirmed influenza, and randomisation occurred within 48 h of symptom onset for 2151 (66%) of 3259.

After randomisation, 33 participants withdrew, 162 were lost to follow-up, and 5 had too many missing or conflicting data to determine the composite primary outcome. The primary outcome was ascertained for 3059 (94%) of 3259 participants (figure 1). No relevant

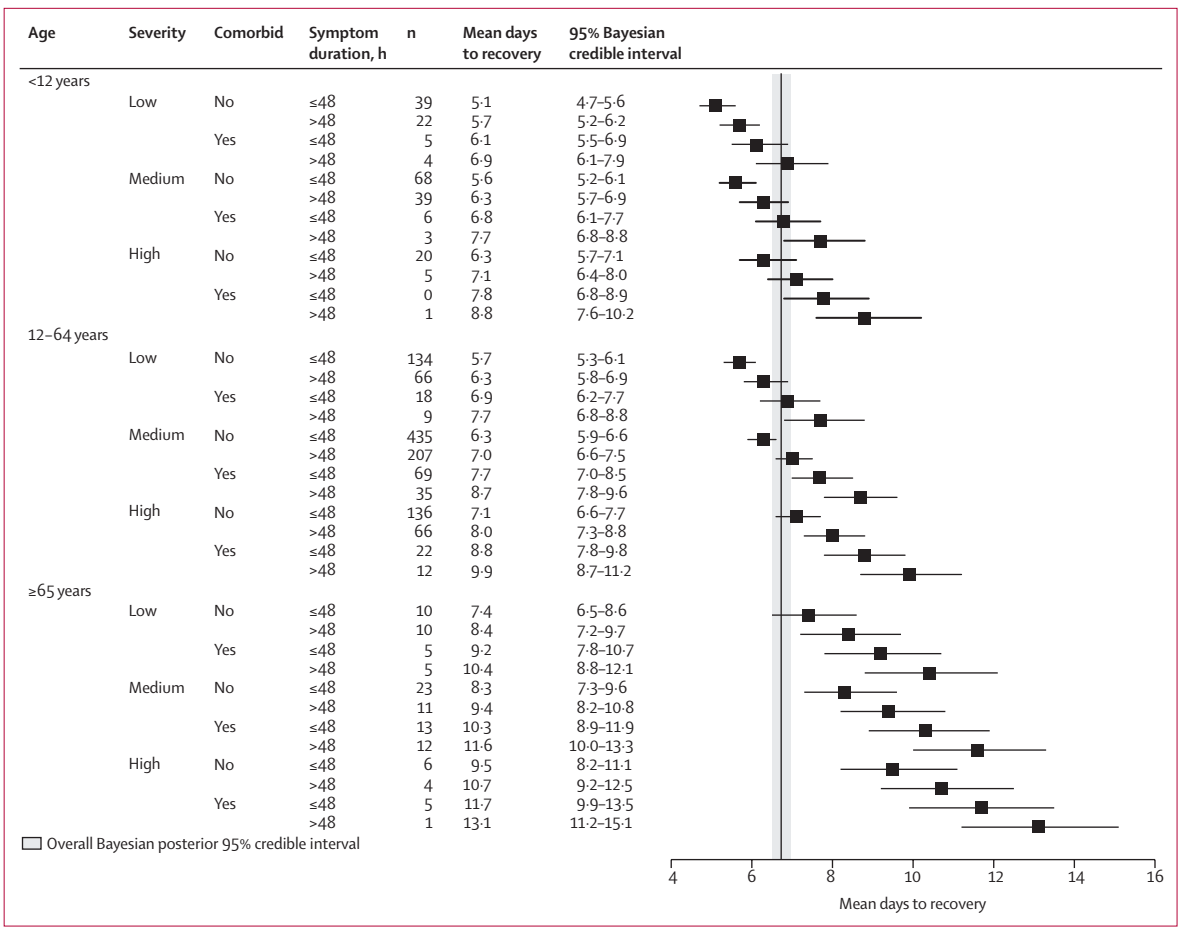


***Figure 2:*** **Estimated mean days to recovery for all subgroups in the usual care intention-to-treat population**

differences in demographic or clinical characteristics were noted between the groups (table 1) or between flu seasons (appendix pp 6–9). The low vaccination rate reflects recommendations in European countries that seasonal vaccination be given to individuals at risk for complications, for example children with asthma and adults older than 65 years with comorbidity. Regarding adherence, 1477 (96%) of participants assigned to usual care plus oseltamivir and included in the primary outcome analysis reported having initiated treatment, and 1232 (80%) reported having used the complete course; 657 (80%) of 818 of those with confirmed influenza infection reported completing the course. No participant in the usual care group was prescribed oseltamivir.

The model-based estimated mean number of days to recovery for patients in the intention-to-treat usual care group was 6·73 days (95% Bayesian credible interval [BCrI] 6·50-6·96) for those with longer previous symptom duration; recovery took longer for patients who were older, for patients with a comorbid condition, for patients with longer previous symptom duration, and for patients with severe symptoms (figure 2). The estimated mean oseltamivir benefit was 1·02 days (BCrI 0·74–1·31), corresponding to an estimated mean of 5·71 days to recovery in the intention-to-treat usual care plus oseltamivir population.

The corresponding hazard ratio (HR) for all patients was 1·29 (95% BCrI 1·20–1·39), indicating faster recovery with oseltamivir (a Kaplan-Meier plot is provided in the appendix [p 13]). Estimated HRs for each marginal subgroup within the four stratification factors (eg, stratification group age has three marginal subgroups) showed similar oseltamivir benefit, with estimated HRs ranging from 1·26 to 1·41. For each of these ten marginal subgroups, the Bayesian posterior probability that adding oseltamivir was superior to usual care alone exceeded the 0·975 predetermined threshold to declare superiority (appendix p 14). In addition, the primary analysis model showed relatively similar HRs across the 36 subgroup combinations (all possible combinations of the 4 stratification factors), with estimated HRs ranging from 1·13 to 1·72. The Bayesian posterior probability of superiority exceeded the 0·975 threshold for 30 of the 36 subgroups (appendix p 15).

These estimated HRs indicate similar proportionate benefits of oseltamivir, and when applied to the varying absolute numbers of days to recovery in the usual care

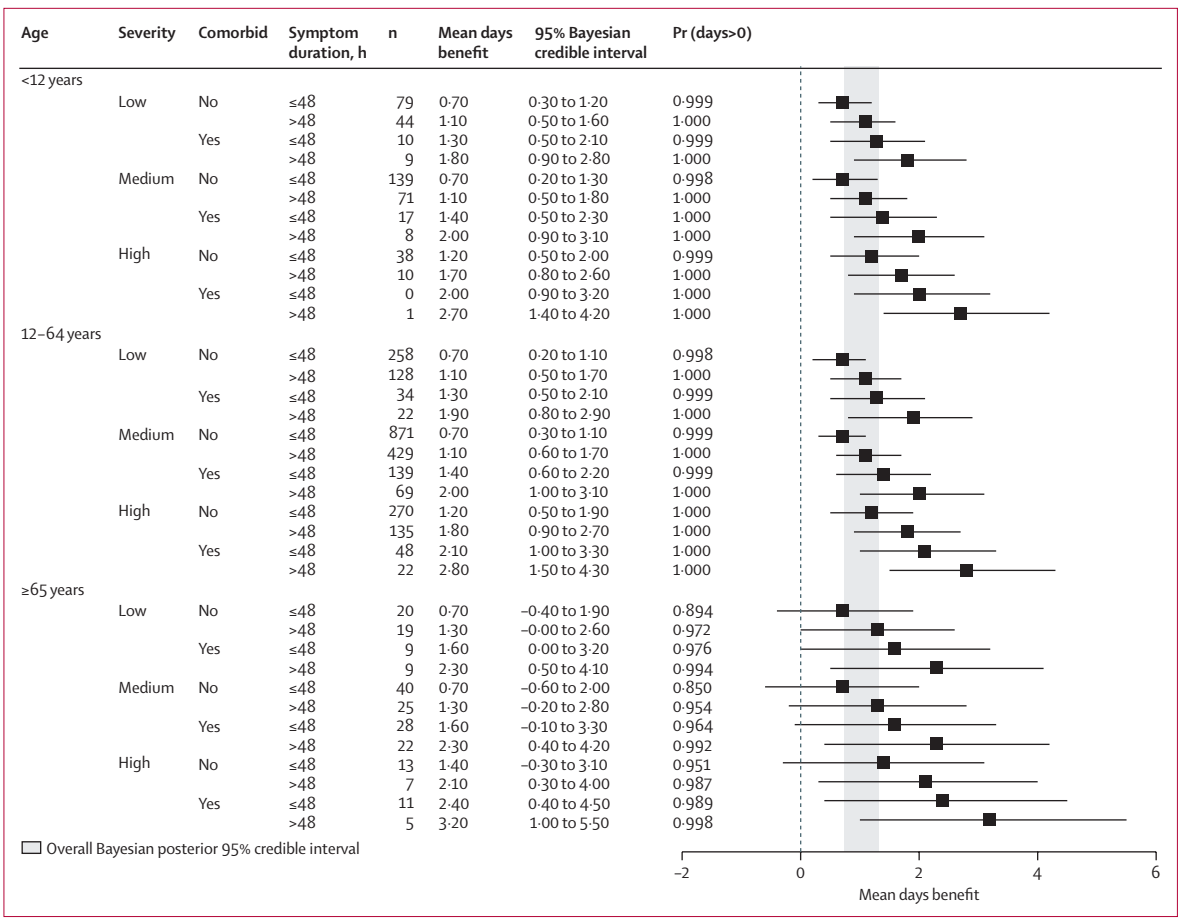


***Figure 3:*** **Estimated mean days of oseltamivir benefit for all subgroups in the intention-to-treat population**
Pr (days>0)=Bayesian posterior probability mean days benefit is greater than 0.

subgroups (figure 2), might translate to meaningful differences in the estimated absolute numbers of days of oseltamivir benefit between the 36 subgroups (figure 3). For instance, in patients younger than 12 years, without comorbidities and with low severity symptoms at inclusion and previous symptom duration of 48 h or less, a HR of 1·31 gives an oseltamivir benefit of 0·70 days over the usual 5·1 days to recovery (figure 3). However, in patients aged 65 years or older, with comorbidities, moderate to severe symptoms at inclusion, and previous symptom duration of more than 48 h, HRs of 1·38–1·52 give an oseltamivir benefit of 2·30–3·20 days over the usual 11–13 days to recovery (figure 3). In general, more absolute benefit of oseltamivir was observed with increasing age, more severe illness, comorbidity, and when presenting after 48 h (appendix p 16).

Additionally, the estimated HR for oseltamivir benefit in patients with influenza infection was 1·27 (95% BCrI 1·15–1·41), compared with 1·31 (1·18–1·46) for patients negative for influenza (figure 4), indicating a similar oseltamivir benefit regardless of influenza status. Additional sensitivity analyses, some of which were not prespecified, were done to evaluate the robustness of the primary analysis findings, with similar conclusions: no evidence of differential benefit between individuals infected with influenza A versus influenza B, no evidence of differential benefit by season, and no evidence of differential benefit by infection with influenza versus any other confirmed viral infection (figure 4; appendix p 4). For example, the estimated benefit of oseltamivir versus usual care was around 1·2 days for season 1, 0·9 days for season 2, and 1·1 days for season 3 with overlapping credible intervals.

Antibiotics were used by a slightly smaller proportion of patients in the usual care plus oseltamivir group than in the usual care group, and a lower proportion reported new household infections (table 2).

Secondary analyses did not identify differences in patient-reported repeat visits with health-care services, hospitalisations, x-ray confirmed pneumonia, or over-the-counter use of medication containing acetaminophen or ibuprofen (table 2). Incidence of new or worsening symptoms of vomiting or nausea occurred in more participants in the usual care plus oseltamivir group than in the usual care group (325 [21%] of 1535 *vs* 248 [16%] of 1529; appendix pp 10–11), and lasted longer in the usual

care plus oseltamivir group (HR for time to symptom alleviation 0·94, 95% CI 0·86–1·01). All other symptoms resolved faster in the usual care plus oseltamivir group (appendix p 17). The number of patients missing usual activities and the number of hours of usual activities missed was similar in both groups (appendix p 12).

Of the 29 serious adverse events reported, 17 were in the usual care group and 12 in the usual care plus oseltamivir group. Of the 12 events in the usual care plus oseltamivir group, one was assessed as a serious adverse reaction (known adverse reaction related to oseltamivir)—urticaria—and one, which occurred in a patient who tested positive for influenza, was assessed as a suspected unexpected serious adverse reaction (thought to be possibly related to oseltamivir because of a temporal relationship, but not expected from current information)—ischaemic left leg requiring below knee amputation. The remaining ten serious adverse events in the usual care plus oseltamivir group were assessed as unrelated to oseltamivir—three were reported as pneumonia, one suspected meningitis, one acute tonsillitis, one hip fracture, one hypertension, one ovarian cyst, one planned hospitalisation, and one shortness of breath and chest pain.

In the usual care group, five serious adverse events were pneumonia, two were influenza, two were asthma, one was a broken leg, one was Guillain-Barré syndrome, one was laryngospasms causing breathing difficulty, one was leukocytoclastic vasculitis, one was lung carcinoma, one was paracetamol overdose, one was peritonsillar abscess, and one was viral meningitis.

No serious breaches were reported, although 74 protocol deviations occurred. The most common reasons for deviation were medication storage temperature excursions (n=13), issues with lost or incorrectly labelled swabs (n=9), back-up randomisations being done (n=9), incorrect participant identifiers being used for randomisation (n=7), and issues with consent (n=6)—some countries required both parents to provide consent for their child and one parent gave consent at the time of the baseline visit.

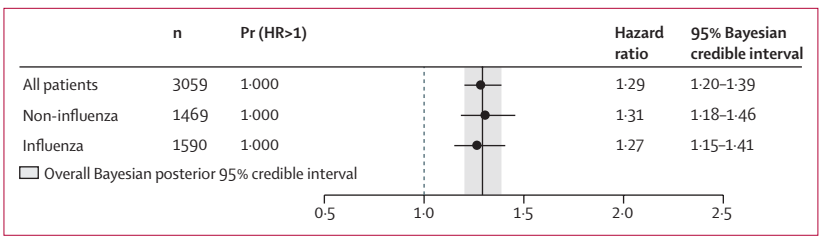


***Figure 4:*** **Modelled oseltamivir benefit by influenza status in the intention-to-treat population**
Pr (HR>1)=Bayesian posterior probability hazard ratio is greater than 1.

| | Usual care (control), n=1529* | Usual care plus oseltamivir (intervention), n=1535* | Difference (95% CI) |
|---|---|---|---|
| Week 1–2 | | | |
| Hospital attendance | 52/1462 (4%) | 43/1469 (3%) | 0·6% (–0·7 to 2·0) |
| Hospital overnight stay | 14/51 (27%) | 8/42 (19%) | 8·4% (–10·8 to 27·6) |
| X-ray confirmed pneumonia | 12/21 (57%) | 7/15 (47%) | 10·5% (–28·2 to 49·1) |
| Week 3–4 | | | |
| Hospital attendance | 22/1393 (2%) | 19/1426 (1%) | 0·2% (–0·7 to 1·2) |
| Hospital overnight stay | 4/22 (18%) | 4/17 (24%) | –5·3% (–36·4 to 25·7) |
| X-ray confirmed pneumonia | 3/5 (60%) | 0/0 (0%) | .. |
| Repeat attendances with health-care services (except hospital)† | 805/1529 (53%) | 796/1535 (52%) | 0·8% (–2·8 to 4·4) |
| Took over-the-counter or other medication† | 1258/1529 (82%) | 1254/1535 (82%) | 0·6% (–2·2 to 3·4) |
| Use of antibiotics† | 202/1529 (13%) | 142/1535 (9%) | 4·0% (1·7 to 6·3) |
| Median days on antibiotics (IQR) | 7 (5–8) | 5 (3–7) | .. |
| Use of acetaminophen containing medicine† | 974/1529 (64%) | 924/1535 (60%) | 3·5% (0·0 to 7·0) |
| Use of ibuprofen containing medicine† | 621/1529 (41%) | 594/1535 (38%) | 1·9% (–1·6 to 5·4) |
| Reports of new infections within the household | 553/1222 (45%) | 485/1237 (39%) | 6·0% (2·1 to 10·0) |

Data are n/N (%) unless otherwise specified. *For the calculation of secondary outcomes, denominator and percentages are those with information from patients' diaries; for hospital admission or overnight stay and pneumonia, data is from phone data too. Overnight hospital stay was calculated for those who attended the hospital and x-ray confirmed pneumonia for those who had an x-ray in the hospital. †If patients did not give an answer to the questions for repeat attendances, over-the-counter or other medication, and antibiotic use it was assumed the answer to the question was no. From over-the-counter medication, acetaminophen and ibuprofen (containing medication) use is shown separately.

***Table 2:*** **Secondary outcomes**

## Discussion

The ALIC⁴E trial was a large-scale, international, publicly-funded, pragmatic, randomised controlled trial of the effectiveness of adding oseltamivir to usual primary care for people with influenza-like illness over three influenza seasons powered to detect effects in key clinical subgroups. Overall, these patients returned to their usual activities with mild residual symptoms minimally interfering after about 6·5 days, and about one day earlier with oseltamivir addition, which is consistent with previous placebo-controlled evidence in adults and children.[6,7,15,16] Moreover, we found that participants at higher risk of adverse outcome—older, sicker, with comorbid conditions, or longer previous symptom duration—might expect to return 2–3 days earlier with oseltamivir.

Participants with confirmed influenza did not benefit more than those testing negative in our study. Furthermore, we found no evidence of a differential effect between participants who were positive for influenza and those positive for other viruses or between those infected with influenza A or B. A systematic review and meta-analysis of published and unpublished placebo-controlled studies of oseltamivir for influenza-like illness found a clinically unimportant difference of less than 5 h in the mean reduction of symptom duration between individuals in the intention-to-treat population (5 studies, 3833 patients) and individuals with confirmed influenza infection (7 studies, 2690 patients).[15] Because we asked participants to complete the symptom diary once a day, we might not have detected such a small

difference. Another explanation might be that oseltamivir's mode of action might include some generalised non-specific mechanisms, or an action on a wider range of viruses.[6] We might also have missed cases of influenza infection due to variable virus shedding over time. The Flu Watch study[17] found that only a quarter of people with serologically confirmed influenza had PCR confirmed disease, and a study in intensive care units[18] found that nucleic acid testing underestimated pandemic (H1Na) influenza when compared with paired serology by about a third. Other possible explanations include inconsistent swabbing techniques (which seems unlikely given data from the recruiting Network[11]), that our primary outcome captured a range of factors (eg, deterioration after initial recovery) and social influences (eg, thresholds for returning to work) that might be less affected by antiviral activity earlier in the illness, or that we found a placebo effect. However, there was no evidence of a differential relative benefit in subgroups such as those with lower illness severity where systematic reviews suggest a more marked placebo response.[19] Moreover, our overall estimate is similar to effects found in placebo-controlled trials.[6,7,15,16] The inclusion criterion of fever means we have not been able to document benefit in some elderly individuals where the febrile response can be less marked. Predicting the effect in a more highly vaccinated population is difficult. There could be a lesser effect due to partial protection, but it could also plausibly be greater, because individuals presenting with influenza-like illness would be more likely to be vulnerable individuals with a poor vaccine response.

Some might consider the absence of a placebo control as a limitation. We deliberately chose to do an open-label trial in the context of everyday practice, because effect sizes identified by placebo-controlled, efficacy studies with tight inclusion criteria might not be reproduced in routine care. We also wished to estimate time to patient-reported recovery from the addition of an antiviral agent to usual care rather than benefit from oseltamivir treatment compared with placebo.[20] This pragmatic, open trial design makes our findings likely to reflect real-world effects in primary care, because knowledge of what medication one is taking could affect subsequent help seeking and health behaviour and use of symptomatic medications.[21,22] However, the design did not allow us to be sure of mechanisms or how much of the observed effect can be attributed to specific oseltamivir or other possible effects, and the relative contribution of such possible effects which might differ for the various subgroups.

Previous trials have found relatively greater benefits in individuals treated within 24 h of symptom onset.[5,23] Additional benefit from earlier treatment was not apparent in our trial, but it was specifically powered to detect subgroup effects in a representative primary care population. A community-based trial[24] of oseltamivir for uncomplicated influenza found a similar effect to our study overall and observed reductions in the duration of symptoms and virus shedding even when treatment was started more than 48 h after illness onset. An open, randomised trial[25] of oseltamivir added to usual care in adults hospitalised with influenza-associated lower respiratory tract infections with a median time to oseltamivir initiation of 6 days found no reductions in terms of clinical failures. In our population, individuals presenting with longer previous duration (>48 h) had a longer natural history, so although relative benefit did not differ, the absolute benefit was greater. In individuals with a shorter natural course of influenza-like illness, a ceiling effect might also exist, so that the effect on viral replication might be too brief for benefit to become apparent, especially in a largely healthy primary care population. A possible explanation for the observation of the greatest effect in subgroups who were older and at higher risk,[26] is that viral replication continues for longer, with a longer natural history of the illness in such individuals.

Meta-analyses have found that oseltamivir reduced the risk of self-reported pneumonia but not of clinically diagnosed pneumonia,[6,7] and that treatment with oseltamivir might reduce the risk of complications and hospitalisation in patients tested positive for influenza.[6] Although our study was not powered on secondary outcomes, we found no evidence of an effect on pneumonia or hospitalisation, although oseltamivir was associated with slightly lower antibiotic use and reported new infections in household members.

Regarding harms, we did not identify meaningful differences in patient-reported repeat visits with health care services, hospitalisations, or serious adverse events, but found evidence for increased burden of vomiting or nausea in the usual care plus oseltamivir group, which is a common side-effect of oseltamivir. One participant who tested positive for influenza had a below knee amputation following arterial occlusion after having started oseltamivir 5 days previously. A search by the study team and also by an independent medicines information service did not find reports of arterial thrombosis linked with oseltamivir, although we did find reports of thrombotic events related to influenza. We decided to err on the side of caution by classifying this event as a possible suspected unexpected serious adverse reaction owing to the temporal relationship between oseltamivir and the thrombosis. One serious adverse event (urticaria) was considered related, and a further ten unrelated.

Previous trials have generally reported either time to first alleviation of symptoms or return to usual activities as their primary outcome. Our composite outcome captured both specific symptoms of influenza-like illness and return to usual activities. Baseline body temperature was lower in our participants than reported in hospital-based studies, suggesting applicability to a typical primary care population. As in many other studies,

children and older people were under-represented, but this might reflect consulting behaviour.

In conclusion, adding oseltamivir to usual primary care for influenza-like illness is likely to accelerate recovery by about a day in patients with influenza-like illness and slightly more in those with risk factors. The effect does not appear to be mediated by influenza virus status, as measured using PCR analysis of swabs, and is unlikely to be due to a placebo effect alone. Although the reason for this effect is unclear, the real-world estimates are what patients and clinicians can anticipate will occur in daily practice. Furthermore, oseltamivir started more than 48 h after symptom onset has a similar effect. Although the average benefit for many patients is modest, and advocation of widespread use of oseltamivir is difficult owing to concerns about possible side effects and the medicalisation of a largely self-limiting illness, clinicians and patients might wish to consider adding oseltamivir to routine treatment where a day less of illness is particularly important for patients. Clinicians might especially want to consider treatment in patients who are sicker or older, who have comorbidities, and who have been unwell for longer, in whom the absolute benefit might decrease recovery time by as much as 2–3 days.

#### Contributors

CCB and TJV were co-chief investigators of this trial and act as guarantors of the study in its entirety. CCB and TJV led the development of the research question, study design, and obtaining the funding with AWvdV, JC, PL, PO, MDdJ, and HG. AWvdV, EB, and JC managed the trial and coordinated the operational delivery of the study protocol to the networks coordinating centres. SCo and NAF, members of the trial management group, provided scientific and practical input. BRS, JH, RJL, and JTC were the trial statisticians. VM and MI led the microbiological analysis. MG-C, CLl, SCh, CLi, BS, P-DS, AC, RA, LB, NJH, ML, DG, HCB, BK, RRJ, PTL, AWM, and ADS represented the collaborating coordinating centres responsible for their network's participation in the trial. CCB led and produced the first draft of this manuscript. All authors provided critical review and final approval of the manuscript.

#### Declaration of interests

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#### Data sharing

After publication of the full trial report, formal requests for study data should be made to the corresponding author (CCB) using a bespoke data request form delineating research aims, methods, and the variables needed. Such requests will be considered by the core ALIC⁴E team (CCB, TV, BS, AWV, and EB) and the PREPARE coordinator (HG). If research questions and methods are considered relevant and valid, the Data Management Department of the Julius Center, UMC Utrecht, will securely transfer the requested, fully anonymised data in the desired format to the party under data transfer agreements. The ALIC⁴E team will decide about co-authorships, after discussion with the interested party about this. The study protocol, statistical analysis plan, and informed consent form will be made available.

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