Impact of adding oseltamivir to usual care on quality-adjusted life-years during influenza-like illness

Manuscript Title: Impact of adding oseltamivir to usual care on quality-adjusted life years during influenza-like illness

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Abstract

Objectives The ALIC^{4}E trial has shown that oseltamivir reduces recovery time while increasing the risk of nausea. The aim of this secondary analysis of the ALIC^{4}E trial was to determine the gain in Quality-Adjusted Life Years (QALYs) associated with adding oseltamivir to usual primary care in patients presenting with influenza-like illness (ILI).

Methods ILI patients were recruited during influenza season (2015-2018) in 15 European countries. Patients were assigned to usual care with or without oseltamivir through stratified randomization (age, severity, comorbidities and symptom onset). Patients' health status was valued with the EuroQol questionnaire and visual analogue scale (VAS) for up to 28 days. Average EQ-5D and VAS scores over time were estimated for both treatment groups using one-inflated beta regression in children (<13years) and adults (≥13years). QALY gain was calculated as the difference between the groups. Sensitivity analysis considered the value set to convert EQ-5D answers to summary scores, and the follow-up period.

Results In adults, oseltamivir gained 0.0006 (95% confidence interval (CI): [0.0002, 0.0010]) QALYs, while no statistically significant gain was found in children (14 days follow-up, EQ-5D). QALY gains were statistically significant in patients aged ≥65 years, patients without relevant comorbidities, or experiencing symptoms for ≤48h. Using VAS and accounting for 28 days follow-up resulted in higher QALY gain.

Conclusion QALY gain due to oseltamivir is limited compared to other diseases, and its clinical meaningfulness remains to be determined. Further analysis is needed to evaluate if QALY gain and its impact on ILI treatment cost renders oseltamivir cost-effective.

Introduction

Influenza is an infectious disease that occurs in winter epidemics. Every year, 11.5% of lower respiratory tract infection related hospitalisations are attributable to influenza.[1] In addition, and of greater economic impact, influenza and influenza-like illnesses (ILI) cause a large number of mild to moderate cases leading to increased health and social service costs.[2,3] Recommended treatment of ILI in high-risk individuals consists of neuraminidase inhibitors such as oseltamivir consumed as early as possible after symptom onset.[4] Oseltamivir treatment for other ILI patients can be considered if initiated within 48 hours of symptom onset.[5]

Meta-analyses demonstrated that oseltamivir (when compared to placebo) reduces the median time to alleviation of clinical symptoms in adults with 25.2h (95% CI -36.2, -16.0) and the median time to first alleviation of symptoms with 16.8h (95% CI 8.4, 25.1), while it increases the risk of nausea with 3.7% (95% CI 1.8, 6.1).[6,7] In the primary analysis of the ALIC^{4}E trial, Butler *et al.* recently demonstrated that oseltamivir (when compared to usual care alone) reduces time to recovery by 1.02 days (95% CI 0.74, 1.31). This reduction ranged from 0.70 days (95% CI 0.30, 1.20) in children below 13y with less severe symptoms, no comorbidities and shorter previous illness duration to 3.20 days (95% CI 1.00, 5.50) in patients aged 65 years or older who had more severe symptoms, comorbidities and longer previous illness duration.[8] But, while these results all demonstrate a reduction in duration of illness, insight into the impact of oseltamivir treatment on QALY gain is vital for decision making on treatment of ILI in the community.

The aim of this secondary analysis of the ALIC^{4}E trial data was to determine whether adding antiviral treatment to usual primary care for ILI patients is effective in reducing their QALY loss, which would provide insights for future cost-effectiveness analysis to inform decision making.

Methods

The trial protocol[9] and primary analysis[8] of this investigator-initiated, open-label, pragmatic, response-adaptive, platform, randomised controlled trial were published elsewhere.

Participants

The trial recruited 3259 patients from 21 primary care networks covering 209 practices in 15 European countries. Recruitment took place over three consecutive influenza seasons (2015-2018) with the recruitment period based on national incidence of ILI raising (falling) above (below) country-specific thresholds.[8]

Eligible subjects were patients of at least one year of age presenting with ILI symptoms that started no longer than 72 hours earlier, for whom written informed consent was provided, who could comply with study requirements, and who agreed to take an antiviral drug as assigned.

Exclusion criteria included: chronic kidney failure, impaired immunity, requiring immediate antiviral treatment or hospitalisation (assessed by the clinician), allergy to oseltamivir, scheduled procedures requiring general anaesthesia in the subsequent two weeks, life expectancy below six months, liver impairment, randomisation not possible ≤72 hours after symptom onset, requiring a live vaccine in the next seven days, pregnancy, lactation or breastfeeding.[8]

Study design

Patients were randomised to either usual care (i.e. according to the clinicians' regular preferences) or usual care plus oseltamivir in a 1:1 ratio. Randomisation was stratified by age (<12, 12-65, and >65 years), severity of ILI rated by the clinician (mild, moderate, and severe), relevant comorbidities (yes or no) and duration of symptoms since onset (≤48 or >48-72 hours).

For adults and children ≥13 years (adults/adolescents) oseltamivir was given as 75mg capsules twice daily for five days. For children <13 years oseltamivir was given as oral suspension according to weight twice daily for five days (30mg for 10-15kg, 45mg for >15-23kg, 60mg for >23-40 kg, and 75mg for >40kg).

Patients were asked to complete a symptom diary for 14 days to evaluate symptom duration and severity, consumption of medication, cost of care and health status. The diary was supplemented with child-specific questions for children <13 years. After 28 days a telephone interview was conducted to inquire on secondary infections, side effects, cost of care and health status.

At the end of the study period, 3059 (93.9%) patients remained. No notable differences in demographic or clinical characteristics were noted between the treatment arms. No participant in the usual care group was prescribed oseltamivir as part of their usual care.[8]

Outcome measures

Patients valued their health status with the five-dimensional EuroQol questionnaire (EQ-5D) and a vertical visual analogue scale (VAS). EQ-5D is a standardised instrument measuring the generic health status in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated using a three-level (EQ-5D-3L and EQ-5D-Y) or five-level (EQ-5D-5L) scale.[10] The EQ-5D-5L was used for adults and children ≥13 years while the child-specific EQ-5D-Y was used for children <13 years.[11] Children under 13 years self-completed as much as possible assisted by a caregiver. The EQ-5D questionnaire was completed on days 1, 7, 14 (in writing) and 28 (orally by phone).

Statistical analysis

The five dimensions of EQ-5D were converted to a single summary EQ-5D score using the UK value set (EQ-5D-3L for children, EQ-5D-5L for adults).[13–15] The resulting EQ-5D scores are situated on a scale with full health scored as 1 and death scored as 0, allowing for negative EQ-5D scores to represent health states evaluated worse than death. Because a large part of the respondents rated their health as perfect, one-inflated beta regression was used to model both EQ-5D and VAS scores. This implies that both the probability to be in perfect health (score '1' for EQ-5D and '100' for VAS) and the score if not in perfect health (non-one scores) are modelled as a function of important covariates, which were included regardless of significance.[16,17] To account for the correlation between repeated measurements for the same patient, a random intercept was included in the model.[18]

One-inflated beta regression requires all scores to fall within the]0,1[interval (excluding 0 and 1).[19] Therefore, the non-one EQ-5D scores were first normalized to fall within the [0,1] interval (as they can be negative):

$$\text{EQ-5Dnorm}_i = \frac{\left[\text{EQ-5D}_i - \min(\text{EQ-5D})\right]}{\left[\max(\text{EQ-5D}) - \min(\text{EQ-5D})\right]}$$

The VAS scores were normalized by dividing by 100, assuming worst health you can imagine (score 0) is valued the same as death, as no separate valuation of the state of death on the VAS was done during the trial.

Afterwards, the normalized non-one EQ-5D and VAS scores were shrunk to fall in the]0,1[interval:[19]

$$\text{Score\_new}_i = \frac{\left(\text{Score\_norm}_i \times (N-1) + 0.5\right)}{N}$$

for $i = 1, \ldots, N$ with N=number of patients

Because different questionnaires were used for children (<13 years) and adults (13-64 or ≥65 years), their scores were modelled separately. Predicted values of final models were transformed back to original scores (i.e. allowing for zero and negative scores). Because the health status for day 28 was assessed orally (by phone) while the health status up to day 14 was assessed in writing, we considered 14 days of follow-up, but performed a sensitivity analysis using 28 days of follow-up. The gain in Quality-Adjusted Life Years (QALYs) from adding oseltamivir to usual care was obtained by taking the difference between predicted score for a patient treated with usual care + oseltamivir and predicted score for a patient treated with usual care alone at each time-point, and weighting these differences over the duration they persisted relative to a full year (e.g. one day equals 1/365 or 0.0027 years).

All analyses were conducted in R version 3.4.2 using the R package 'gamlss'.[20]

Model selection

The starting model contained fixed effects for time, treatment (usual care or usual care + oseltamivir), season (1, 2 or 3), presence of comorbidities (yes or no), baseline symptom severity (mild, moderate or severe) and duration of symptoms before consultation (≤48h or 48-72h). The model for adults (≥13 years) included a fixed effect for age (13-64 or ≥65 years), due to age stratification at randomisation. In addition, the starting model contained all two-way interactions with time and with treatment. Because the time needed to reach convergence increased with decreasing convergence criteria, convergence criteria of 0.1 were selected while allowing for 150 iterations in the outer iteration, the inner iteration and the backfitting algorithm (for more information see documentation for R package 'gamlss'[20]).

From this starting model, the final model was obtained in two steps. In a first step, the mean structure was optimized by allowing for splines to capture the curvature in the evolution over time when modelling the probability to be in perfect health and/or the health score if not in perfect health. Because our primary focus was on the impact of treatment, treatment-specific splines were included. Taking into account the complexity of the starting model and the difficulties in reaching convergence, other subgroup-specific splines were not included. In a second step, the variance structure was optimized by including a random intercept that accounts for the

dependency of EQ-5D scores within a patient with or without correcting for clustering of patients within countries. Taking into account the complexity of the model and the difficulties in reaching convergence, random slopes were not included.

Goodness-of-fit for all optional models was compared using the Akaike information criterion (AIC; lower is better).[21] The significance of treatment was assessed using a likelihood ratio test. Confidence intervals for predicted EQ-5D scores were obtained by stratified bootstrapping (n=1000).

Sensitivity analysis

Value sets for the EQ-5D-5L questionnaire were available for France[22], Ireland[23], the Netherlands[24], Poland[25], Spain[26] and England[13]. Value sets for the EQ-5D-3L questionnaire were available for Belgium[27], France[28], the Netherlands[29], Poland[30], Spain[31], Sweden[32] and the UK[14]. We performed sensitivity analysis using different value sets as recommended by EuroQol when country-specific value sets were not available.

Initially, the study aim was to use countries' own value sets when available to convert the EQ-5D score to a single summary score, and the average of the participating countries' value sets otherwise ('CS approach'). However, the use of multiple value sets resulted in convergence issues for the children's data (see further). As a result, the UK value set was used in the main analysis, and the CS approach in sensitivity analysis for adults. In addition, the average of the available value sets for participating countries was used for all participating countries, regardless of availability of their own value set ('AV approach').

Additional analyses using VAS as outcome measure to estimate QALY gain were performed. VAS is a scale running from 0 (worst health you can imagine) to 100 (best health you can imagine), which is seen as a continuum of possible scores by the patients.[12] The VAS was completed on days 1 to 14 (in writing) and on day 28 (orally by phone). VAS scores were modeled in the same way as EQ-5D scores (one-inflated beta regression models), and hence needed to be normalized and shrunken to fall between the]0,1[interval. VAS scores were normalized by dividing by 100, assuming worst health you can imagine (score 0) is valued the same as death, as no separate valuation of the state of death on the VAS was done during the trial. Model selection was done in the same way as for EQ-5D scores.

No formal correction for multiple comparisons was made, because all comparisons were predefined (i.e. fixed effects to be included, EQ-5D value sets to be used, 14- and 28-day follow-up, and using VAS and EQ-5D as

outcome measures) and because our interest lies in having a P(type 1 error) < 0.05 for each of these separate analyses rather than a joint P(type 1 error).

Results

Diaries were returned by 2234 adults (≥13 years) and 363 children (<13 years). At least one VAS measurement was reported for 2213 adults (99.1%) and 363 children (100%), while 2213 adults (99.1%) and 361 children (99.4%) reported at least one EQ-5D measurement. Distribution of patients across countries is shown in Table 1 (for one child from France and one from Sweden a VAS, but not an EQ-5D measurement was reported), and detailed patients' clinical and demographic characteristics are described in the primary analysis.[8] Out of these patients, 1970 adults (89.0%) and 311 children (85.6%) delivered complete VAS profiles (i.e. a score for all measurement occasions), while 1945 adults (87.9%) and 288 children (79.8%) delivered complete EQ-5D profiles. Negative EQ-5D values were reported by 30 adults (1.4%) and 95 children (26.3%). Note that the odds of having a negative EQ-5D score was not associated with age (children: p=0.9307; adults: p=0.8898).

EQ-5D

The best fitting mean structure contained splines to model both the probability to have an EQ-5D score of 1 ('perfect health') and the score if not in perfect health (Model 4; Supplementary material Table A1). For adults, the best fitting variance structure included a random intercept for both subject and country (Model 4B; Supplementary material Table A1). For children, the AIC values were comparable. Therefore, the simpler model including only a random intercept for subject was selected (Model 4A; Supplementary material Table A1).

Based on EQ-5D, the addition of oseltamivir to usual care reduced ILI-related QALY loss when compared to usual care alone in adults (p=0.0005 and p=0.0024 for 14 and 28 day follow-up, respectively). Adding oseltamivir to usual care adult ILI patients gained 0.0006 [0.0002, 0.0010] QALYs when considering 14 days follow-up and 0.0008 [0.0002, 0.0013] QALYs when considering 28 days follow-up (Table 2 and Figure 1). In children, oseltamivir did not reduce QALY loss (p=0.3478 and p=0.7395 for the 14 and 28 day follow-up, respectively).

Subgroup-specific QALY gain for adults when measuring QALYs with EQ-5D are reported in Supplementary material Table A3. Based on this evaluation, QALY gains were statistically significant in patients aged ≥65 years, for patients without relevant comorbidities, or experiencing symptoms for ≤48h (Table 2).

Sensitivity analysis: EQ-5D value sets

For adults, both CS and AV approaches selected the same final model as when using the UK value set (Model 4B; Supplementary material Tables A2). Using the CS approach, the reduction of loss in EQ-5D score was statistically significant for a 14 day follow-up (p=0.0001), while it was not statistically significant for a 28 day follow-up (p=0.0767). Adding oseltamivir to usual care resulted in 0.0005 [0.0001, 0.0009] QALYs gained for the 14 follow-up (Supplementary material Figure A1). Using the AV approach, adding oseltamivir to usual care resulted in a reduction of loss in EQ-5D score (p=0.0008 and p=0.0032 for the 14 and 28 day follow-up periods, respectively). Adding oseltamivir to usual care gained 0.0005 [0.0001, 0.0008] QALYs and 0.0007 [0.0002, 0.0011] QALYs for the 14- and 28-day follow-up, respectively (Supplementary material Figure A2).

For children, the CS-approach resulted in convergence issues. The AV-approach delivered comparable AIC values resulting in the selection of the simpler model including only a random intercept for subject as when using the UK value set (Model 4A; Supplementary material Tables A2). The loss reduction in EQ-5D score for children was not statistically significant (p=0.1440 and p=0.6742 for 14- and 28-day follow-up, respectively).

Sensitivity analysis*: VAS*

The addition of oseltamivir to usual care reduced the loss in VAS score due to influenza when compared to usual care alone in adults (p<0.0001 for the 14- and 28-day follow-up). Adding oseltamivir to usual care gained 0.0015 [0.0011, 0.0019] QALYs when follow-up was 14 days and 0.0020 [0.0014, 0.0027] QALYs when follow-up was 28 days (Supplementary material Text A1 and Figure A3).

Subgroup-specific QALY gains in VAS score were statistically significant in all adults except for the subgroup aged ≥65 years (Supplementary material Table A4). In children, oseltamivir reduced the loss in VAS score (p<0.0001 for the 14 and 28 day follow-up). Adding oseltamivir to usual care gained 0.0025 [0.0015, 0.0036] QALY when follow-up was 14 days and 0.0034 [0.0018, 0.0051] QALY when follow-up was 28 days (Supplementary material Figure A4). Subgroup-specific QALY gains in VAS score were statistically significant in all children except for the subgroup with ILI severity rated by the clinician as mild (Supplementary material Figure A4).

Discussion

This manuscript presents a secondary analysis of the ALIC^{4}E trial, a large-scale international randomised controlled trial investigating the effectiveness of adding oseltamivir to usual primary care in influenza-like illness powered to detect effects in key clinical subgroups.

To our knowledge, this is the first study to assess the evolution of the patients' health status after adding oseltamivir to usual care for patients with ILI. The reduction in QALY loss in ILI patients receiving oseltamivir is estimated between no statistically significant reduction for children, and a reduction of 0.0008 [0.0002, 0.0013] QALYs when following up adults' EQ-5D-5L scores for 28 days. This is a relatively low per-patient QALY gain achieved by an intervention compared to other interventions with follow-up of less than a year (mean 0.02, interquartile range 0.01-0.04)[33], and its clinical meaningfulness remains to be determined. However, one has to keep in mind that ILIs are an annually recurring burden to millions of people worldwide with a mean illness duration of about one week.[34] Potential reductions in transmission through the use of an antiviral cannot be accounted for in this study, as it focuses only on trial participants, and not on their contacts or the community to which they belong.

In the ALIC^{4}E trial, health status was assessed using the EuroQol questionnaires, that contain five questions with three (EQ-5D-Y) or five (EQ-5D-5L) optional answers, and a visual analogue scale (VAS), that ranges from worst health to best health one can imagine. In adults, analyses on both measures found a statistically significant improvement in health status by adding oseltamivir to usual care, albeit that the estimated difference was orders of magnitude larger when valued by VAS than by EQ-5D-5L. In children, the analysis based on EQ-5D-Y found no statistically significant effect, while the reduction in VAS score was statistically significant.

The difference between results based on EQ-5D and VAS may be due to a difference in how the health state 'death' is valued. Especially for children, a substantial proportion indicated combinations of dimension levels resulting in negative EQ-5D scores which represent health states valued worse than death. Because the participants were not asked to rate death on the VAS scale, we assumed that all respondents implicitly valued death as the worst imaginable health state on the VAS scale and inter-respondent variability on this issue cannot be accounted for.[35] Because some health states might be implicitly considered worse than death on these health outcome instruments, the VAS scores may have been slightly overestimated. To inform health economic evaluations, EQ-5D remains the preferred measurement instrument. However, VAS and EQ-5D for children was

completed by proxy (usually a parent), and estimating disutility from health impacts in small children remains an area under development.[36] Clearly, our findings for children should be interpreted with care.

The difference between children's and adults' EQ-5D scores may be due to higher sensitivity of five level response categories per dimension on the EQ-5D-5L versus three on the EQ-5D-Y, and the fact that children's responses were obtained partially or completely through the aid of a proxy (a parent or caregiver). The elicitation of children's health status for economic evaluation remains difficult, especially for common mild transient illness episodes,[36] with childhood infectious diseases being a classic case in point.[37] While the EQ-5D questionnaire is well-studied, the concepts of the five included dimensions might be hard to grasp especially for the younger children.[38,39] In order to overcome this, child-specific EQ-5D questionnaires (intended for use in 8-15y olds) have been developed (EQ-5D-Y), and this is indeed the version that was used for patients aged younger than 13 years recruited in the ALIC^{4}E trial.[32,40] However, with a protocol to develop value sets only just published, the EQ-5D-3L was chosen to obtain EQ-5D index scores in this study.[41] It has been shown that parents answering the EQ-5D-3L on behalf of their children provides a good proxy.[42] However, the application of adult EQ-5D-3L values to evaluate children's health status is disputable.[43] This is supported by the high proportion of children reporting negative EQ-5D scores (26.3% versus 1.4% of adults). Therefore, the findings based on EQ-5D values for children should be interpreted with care. However, as children have been shown to be capable of assessing their own health status from the age of five years onwards,[44,45] the VAS could provide some insight into the impact of oseltamivir on children's health status.

In the ALIC^{4}E trial, health status was assessed at fixed time-points (1-14 and 28 for VAS, or 1, 7, 14 and 28 for EQ-5D). This is suboptimal compared to assessing the patient's health status until resolution of symptoms. However, symptoms caused by ILI typically resolve after 3-7 days for the majority of the population, which is only a quarter of the foreseen follow-up window. Hence, for future analysis, shorter follow-up but with more frequent health status measurements might provide more precise insight in how (fast) QALY gain changes over time for ILI without complications. The last assessment was conducted orally (by phone) rather than in writing because of practical reasons. Even though previous research has proven equivalence of written and interactive voice response EQ-5D scorings, telephone interviews conducted at day 28 were conducted by the trial team, potentially hindering this equivalence.[46,47] Therefore, analyses were conducted for 14-day and for 28-day

follow-up. In general, similar conclusions were reached for both scenarios with slightly higher QALY gained based on 28 days of follow-up instead of 14 days of follow-up.

The choice of value set to obtain single summary EQ-5D scores had a limited impact on the results. Only when using the CS approach, no statistically significant QALY gain was found for adults when considering 28 days of follow-up. While the UK value set and the AV approach use the same value set regardless of the patients' origin, the CS approach uses country-specific value sets, when available, resulting in seven different value sets being used. Although country-specific value sets might reflect the countries' idea on the importance of the five EQ-5D dimensions better, the differences in methodologies to obtain single summary EQ-5D scores might add one too many complexity when combining data from multiple countries.[48,49] Data were too few to do country-specific analyses. This explanation is supported by the numerous convergence issues encountered when applying the CS approach to the children's EQ-5D scores. Therefore, our findings through the CS approach should be interpreted with great care, and more weight should be placed on the consistent findings from the UK and AV approaches.

We used one-inflated beta regression models because they appropriately capture the non-symmetrical distribution of EQ-5D and VAS index scores. Nevertheless, they are limited in how correlation between time-points can be accounted for. Our results should be interpreted in light of this.

In conclusion, this analysis demonstrates that adding oseltamivir to usual care results in statistically significant QALY gain in adolescent and adult ILI patients, but not in children (when measured with EQ-5D). However, the clinical meaningfulness of this QALY gain remains to be determined, as well as the cost-effectiveness of providing oseltamivir to all ILI patients, or to specific subgroups.[50]

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Impact of adding oseltamivir to usual care on quality-adjusted life years during influenza-like illness: Supplementary Material

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Table A1. Akaike Information Criterion values for models including splines to model the probability to have a perfect EQ-5D score (υ) and for the score if not in perfect health (μ), and including random intercept(s). Final models for adults and children are highlighted in bold.

	Spline		Random effect	Adults		Children	
	μ	υ		14d	28d	14d	28d
Model 1	0	0	none	-482.03	1517.23	715.63	1082.72
Model 2	0	1	none	-633.96	795.49	664.47	906.22
Model 3	1	0	none	-634.50	1050.17	693.28	1024.01
Model 4	1	1	none	-786.42	328.43	641.12	847.07
Model 4A	1	1	subject	-2543.89	-1480.96	**517.63**	**719.08**
Model 4B	1	1	subject + country	**-2637.79**	**-1563.97**	517.53	718.80

Table A2. Akaike Information Criterion values for models including splines to model the probability to have an EQ-5D score of 1 ('perfect health', υ) and for the score if not in perfect health (μ), and including random intercept(s), with EQ-5D obtained through alternative value sets. Final models for adults and children are highlighted in bold.

	Spline			Adults				Children			
				14d		28d		14d		28d	
	μ	υ		CS	AV	CS	AV	CS	AV	CS	AV
Model 1	0			-9552.95	-2242.06	-11870.94	-437.10	-1864.64	721.07	-2803.06	1085.20
Model 2	0	1		-9667.73	-2393.97	-12310.14	-1158.84	-1863.98	669.92	-2804.38	908.71
Model 3	1	0		-9727.19	-2397.99	-12884.63	-913.66	-1969.80	697.86	-3155.74	1026.05
Model 4	1	1		-9841.97	-2549.90	-13323.83	-1635.40	-1969.15	646.70	-3157.06	849.55
Model 4A	1	1	Subject	-11871.39	-4249.96	-17028.28	-3387.61	**-1762.65**	**508.56**	FC	**707.53**
Model 4B	1	1	Subject + country	**-13389.33**	**-4338.27**	**-18805.49**	**-3465.96**	FC	508.55	FC	707.27

CS: using the countries' own value set when available, and the average of the participating countries' value sets otherwise; AV: using the average of available value sets for participating countries; FC: false convergence

obtained, results not trustworthy.

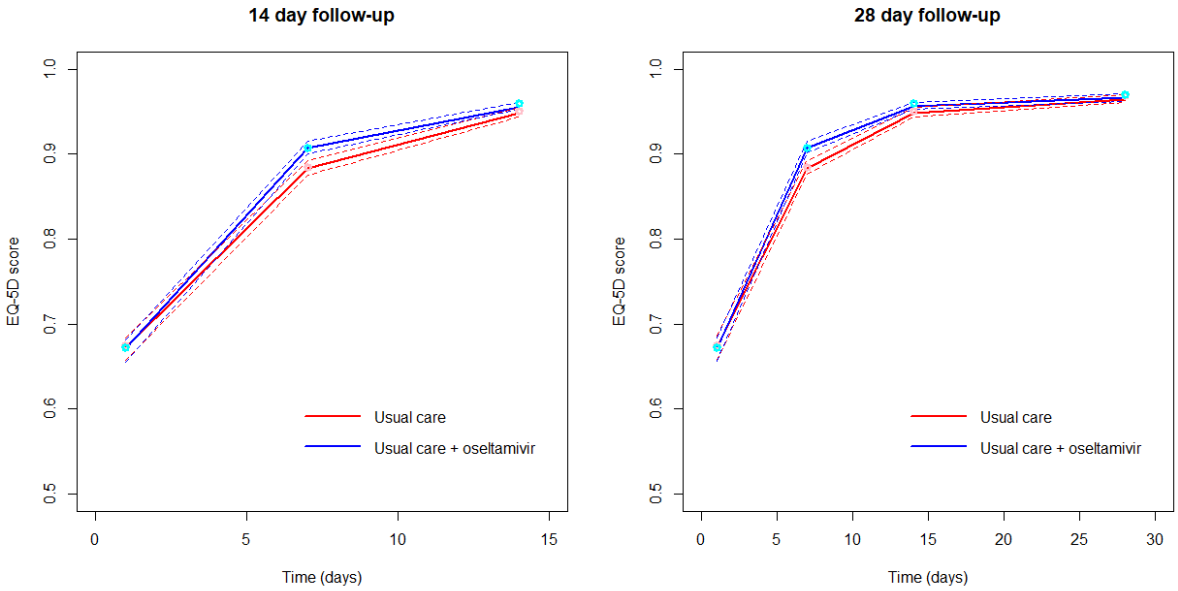

Figure A1. Estimated EQ-5D scores using the country-specific value sets when available and the average of available country-specific value sets otherwise) for adults in 14 (left) and 28 (right) day follow-up. Note that data-points for day 28 for usual care and usual care + oseltamivir overlap

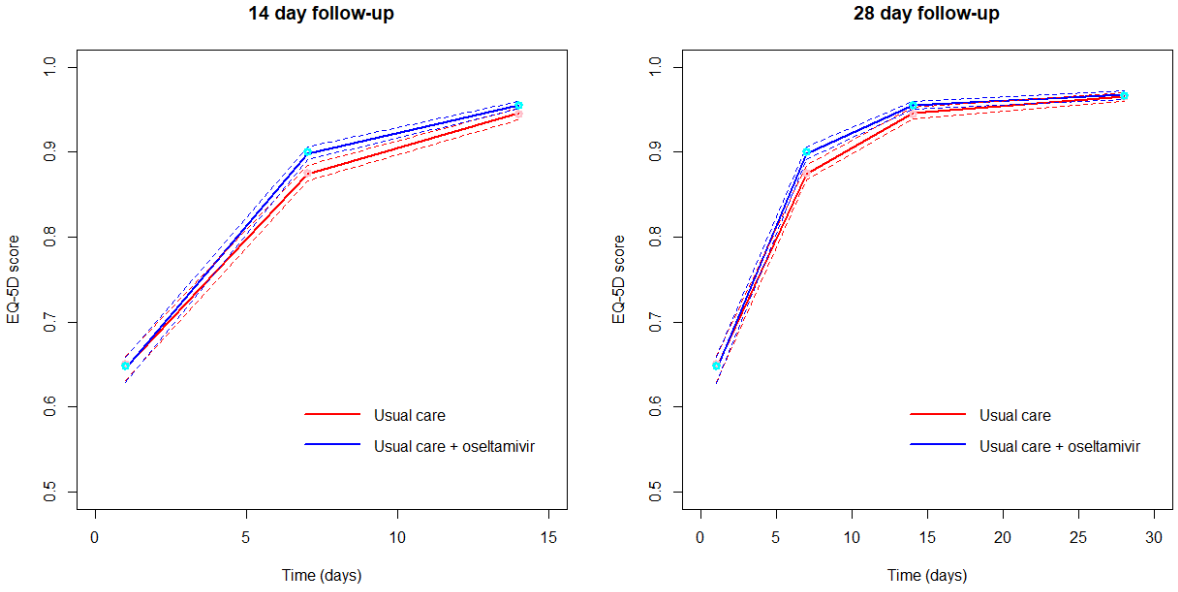

Figure A2. Estimated EQ-5D scores using the average of available country-specific value sets) for adults in 14 (left) and 28 (right) day follow-up. Note that data-points for day 28 for usual care and usual care + oseltamivir overlap

Text A1. VAS analyses

The best fitting mean structure contained splines to model both the probability to have a VAS score of 100 ('perfect health') and the score if not in perfect health (Model 4; Table A3). For adults, finding an optimal variance structure resulted in convergence issues. When considering 14 days of follow-up, the model did converge while using a random intercept for subject and country (Model 4B; Table A3). When considering 28 days of follow-up, the model did converge while using a random intercept for subject alone (Model 4A; Table A3). For children, the AIC values were comparable. Therefore, the simpler model including only a random intercept for subject was selected (Model 4A; Table A3).

Table A3. Akaike Information Criterion values for models including splines to model the probability to have a perfect VAS score (υ) and for the score if not in perfect health (μ), and including random intercept(s). Final models for adults and children are highlighted in bold.

	Spline		**Random effect**	**Adults**		**Children**	
	μ	**υ**		**14d**	**28d**	**14d**	**28d**
Model 1	0	0	none	-3376.13	1770.61	1428.37	2503.66
Model 2	0	1	none	-3707.63	-370.20	1335.81	1965.72
Model 3	1	0	none	-4407.74	-2215.86	1265.34	1953.65
Model 4	1	1	none	-4739.44	-4356.69	1172.42	1415.48
Model 4A	1	1	subject	FC	**-38437.76**	**-3910.99**	**-3562.86**
Model 4B	1	1	subject + country	**-38714.24**	FC	-3909.37	-3562.91

FC: false convergence obtained, results not trustworthy

Table A4. Overall and subgroup-specific estimates for gain in influenza-related quality of life when treating with usual care + oseltamivir compared to treating with usual care alone. Estimates are expressed in Quality-Adjusted Life Years (QALYs). Confidence intervals obtained using stratified bootstrapping (n=1000).

	Number of included patients: usual care + oseltamivir – usual care alone	**Follow-up 14 days**	**Follow-up 28 days**
VAS CHILDREN			
Overall	191 – 192	0.0025 [0.0015, 0.0036]	0.0034 [0.0018, 0.0051]
Duration of symptoms: ≤48h	122 – 128	0.0018 [0.0004, 0.0031]	0.0024 [0.0002, 0.0046]

Duration of symptoms: >48h	69 – 64	0.0039 [0.0023, 0.0057]	0.0059 [0.0032, 0.0089]
Comorbidities: absent	173 – 165	0.0023 [0.0012, 0.0034]	0.0031 [0.0015, 0.0049]
Comorbidities: present	18 – 27	0.0048 [0.0005, 0.0093]	0.0080 [0.0002,0.0174]
Severity at baseline: mild	67 – 62	0.0010 [-0.0011, 0.0030]	0.0013 [-0.0018, 0.0049]
Severity at baseline: moderate	104 – 110	0.0034 [0.0021, 0.0048]	0.0048 [0.0028, 0.0072]
Severity at baseline: severe	20 – 20	0.0032 [0.0004, 0.0059]	0.0048 [0.0007, 0.0101]
VAS ADULTS			
Overall	1098 – 1114	0.0015 [0.0011, 0.0019]	0.0020 [0.0014, 0.0027]
Age: 13-64 years	997 – 1014	0.0016 [0.0012, 0.0020]	0.0023 [0.0016, 0.0030]
Age: ≥65 years	101 – 100	0.0006 [-0.0012, 0.0024]	0.0006 [-0.0026, 0.0037]
Duration of symptoms: ≤48h	735 – 733	0.0016 [0.0010, 0.0021]	0.0021 [0.0013, 0.0029]
Duration of symptoms: >48h	363 – 381	0.0015 [0.0007, 0.0022]	0.0022 [0.0008, 0.0035]
Comorbidities: absent	917 – 931	0.0015 [0.0010, 0.0019]	0.0021 [0.0014, 0.0028]
Comorbidities: present	181 – 183	0.0017 [0.0004, 0.0029]	0.0023 [0.0000,0.0044]
Severity at baseline: mild	214 – 213	0.0013 [0.0002, 0.0023]	0.0018 [0.0001, 0.0034]
Severity at baseline: moderate	666 – 684	0.0015 [0.0009, 0.0021]	0.0021 [0.0011, 0.0030]
Severity at baseline: severe	218 – 217	0.0019 [0.0009, 0.0029]	0.0027 [0.0011, 0.0043]

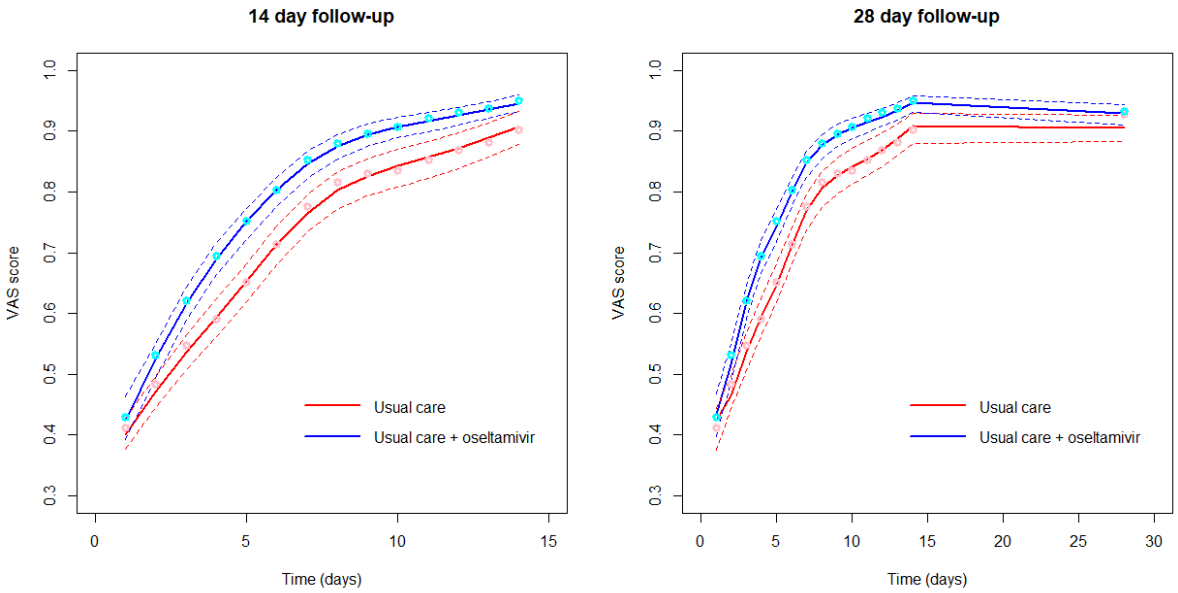

Figure A3. Observed (dots, at day 1-14 and day 28) and predicted (lines) VAS scores + 95%CI on original scale for adults in 14 (left) and 28 (right) days of follow-up. Note that data-points for day 28 for usual care and usual care + oseltamivir overlap.

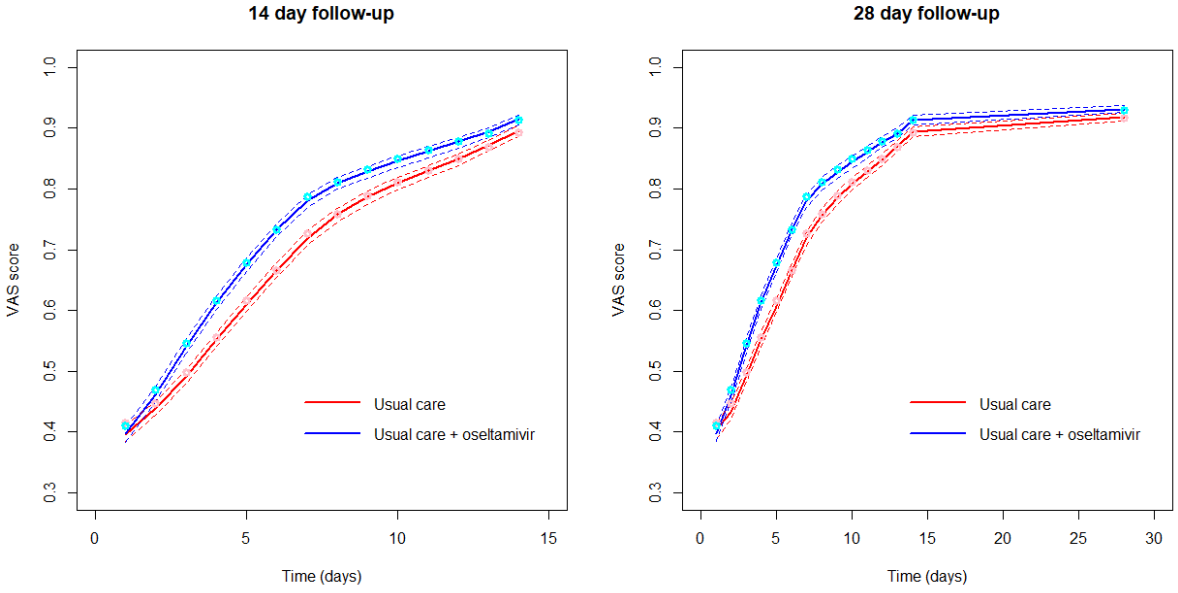

Figure A4. Observed (dots, at day 1-14 and day 28) and predicted (lines) VAS scores + 95%CI on original scale for children in 14 (left) and 28 (right) days of follow-up. Note that data-points for day 28 for usual care and usual care + oseltamivir overlap.