British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 1580–1594 1580

PHARMACOECONOMICS

Interdisciplinary pharmacometrics linking oseltamivir pharmacology, influenza epidemiology and health economics to inform antiviral use in pandemics

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Received 23 February 2016; **Revised** 6 December 2016; **Accepted** 7 December 2016

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Keywords epidemiology, health economics, influenza, interdisciplinary pharmacometrics, oseltamivir, pharmacokinetics/pharmacodynamics

AIMS

A modular interdisciplinary platform was developed to investigate the economic impact of oseltamivir treatment by dosage regimen under simulated influenza pandemic scenarios.

METHODS

The pharmacology module consisted of a pharmacokinetic distribution of oseltamivir carboxylate daily area under the concentration–time curve at steady state (simulated for 75 mg and 150 mg twice daily regimens for 5 days) and a pharmacodynamic distribution of viral shedding duration obtained from phase II influenza inoculation data. The epidemiological module comprised a susceptible, exposed, infected, recovered (SEIR) model to which drug effect on the basic reproductive number (R_0), a measure of transmissibility, was linked by reduction of viral shedding duration. The number of infected patients per population of 100 000 susceptible individuals was simulated for a series of pandemic scenarios, varying oseltamivir dose, R_0 (1.9 *vs.* 2.7), and drug uptake (25%, 50%, and 80%). The number of infected patients for each scenario was entered into the health economics module, a decision analytic model populated with branch probabilities, disease utility, costs of hospitalized patients developing complications, and case-fatality rates. Change in quality-adjusted life years was determined relative to base case.

DOI:10.1111/bcp.13229

RESULTS

Oseltamivir 75 mg relative to no treatment reduced the median number of infected patients, increased change in quality-adjusted life years by deaths averted, and was cost-saving under all scenarios; 150 mg relative to 75 mg was not cost effective in low transmissibility scenarios but was cost saving in high transmissibility scenarios.

CONCLUSION

This methodological study demonstrates proof of concept that the disciplines of pharmacology, disease epidemiology and health economics can be linked in a single quantitative framework.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- To date, modelling of influenza has been conducted in discrete discipline areas.
- The discrete pharmacology, epidemiology and health economic models are not linked and make assumptions about the adjacent disciplines that are inappropriate.
- There are no epidemiological or health economic models which have taken into account between subject variability in the pharmacology of influenza treatments.

WHAT THIS STUDY ADDS

- This study provides the first integrated interdisciplinary framework to understand the cost-utility of antiviral therapy under various influenza pandemic scenarios linking drug pharmacokinetics/pharmacodynamics, epidemiological and health economics endpoints.
- This quantitative framework was able to show that oseltamivir reduced the median number of infected individuals, increased quality-adjusted life years by deaths averted, and was cost-saving under most pandemic scenarios.
- Given the growing need to justify pricing of medicines to society and payer, the methodology of interdisciplinary pharmacometrics can be applied across all disease areas where the pharmacokinetics/pharmacodynamics, clinical or epidemiological endpoints of interest can eventually be linked to health economic value.

Introduction

Influenza is a common transmissible viral respiratory illness that, in susceptible individuals, can be associated with substantial morbidity and mortality due to complications such as pneumonia and bronchitis. Influenza tends to spread rapidly in seasonal epidemics and in some cases extensive spread results in a pandemic.

A very relevant and essential public health topic is influenza pandemic containment and how to apply strategies to mitigate the impact of a pandemic in a timely manner [1, 2]. To date, however, even the most sophisticated mathematical modelling approaches, which are important for informing influenza pandemic planning, do not consider basic features of antiviral pharmacology. These approaches consider drug effect as either *on* or *off* in terms of altering transmission [1, 2]. There has been very little consideration of variability in pharmacokinetics (PK) or drug response/pharmacodynamics (PD) [1, 2]. Furthermore, such models have not linked drug PK/PD to epidemiological or health economics endpoints. An integrated framework linking these modules is required to better understand the cost-utility of current and emerging antiviral therapies, and their application and optimal deployment to manage influenza pandemics.

The current antiviral cornerstone of influenza pandemic preparedness is the neuraminidase inhibitor oseltamivir [3]. Oseltamivir is an oral prodrug that is extensively metabolized by hepatic carboxylesterase 1A1 to oseltamivir carboxylate (OC). Once in circulation, OC is predominately cleared by the kidney via glomerular filtration and renal secretion. Following oral dosing, plasma oseltamivir concentrations decline rapidly with an apparent elimination half-life ($t_{1/2}$) of 1–3 h, while OC has a $t_{1/2}$ of 6–10 h [4]. OC inhibits the production of influenza virus (viral shedding) from infected host cells [4] thereby reducing the duration of infection and hastening resolution of signs and symptoms of infection.

Whilst there is general agreement that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, there are divergent views expressed in the literature on whether oseltamivir reduces risk of lower respiratory tract complications, and admittance to hospital [5, 6].

Recently, Rayner and colleagues have identified the PK/PD determinants of oseltamivir efficacy, showing an area under the concentration–time curve (AUC) relationship with time to cessation of viral shedding and time to resolution of influenza symptoms [7]. The AUC breakpoints were similar for virological and clinical endpoints, indicating that the PD effects of oseltamivir on viral shedding and symptoms were synchronized by drug exposure.

In epidemiology, the basic reproductive number (R_0) is a fundamental concept describing transmissibility of an infectious disease in a given population. Qualitatively, R_0 is defined as the number of secondary infections produced from a primary infective source [8]. Quantitatively, R_0 can be captured implicitly within a simple transmission model called the susceptibility, infectivity and recovered model, which describes the progression of an epidemic/pandemic over time in a population [9].

Modelling approaches, such as decision analytic models, are commonly employed in health economic studies to estimate the cost-utility of various interventions and health outcomes. The cost-utility analysis is a specific type of cost-effectiveness analysis in which effectiveness is measured in terms of quality-adjusted life-years (QALY). The QALY is calculated by using utility values to adjust the duration of time in a particular health state for the quality of an individual's life in that health state. A recent review reported that most antiviral economic studies used static models, which are incapable of incorporating the dynamic nature of the viral transmission process [10].

The current work describes a modular approach to link oseltamivir PK/PD [7], influenza epidemiology via a variant of the susceptibility, infectivity and recovered model, and a health economic decision analytic model. Our motivation was driven by: (i) public health considerations: to understand the impact of oseltamivir pharmacological variability on patient outcomes, health utilization and economics under different simulated pandemic scenarios; and (ii) production of a proof of concept framework: to integrate drug PK/PD, dynamic disease transmission, and health economic data. To our knowledge, linking of the adjacent disciplines of pharmacology, epidemiology and health economics has not to date been successfully implemented in a single quantitative framework.

Methods

Pharmacology (PK/PD) module

The PK/PD relationships were previously generated based on data from 140 subjects collected from two phase II inoculation studies; each study was approved by an ethics committee and conducted in accordance with the Declaration of Helsinki; all participants gave their informed consent prior to inclusion. For a full description of the study designs, population, and PK/PD analysis see [7, 11]. A three-group (placebo, low and high exposure) OC AUC relationship with time to cessation of viral shedding (Figure 1A) and resolution of composite symptoms (Figure 1B) have been reported. An AUC breakpoint of >14 180 ng.h ml^{-1} was identified as a common PK/PD threshold of interest [5] based on enhanced cessation of viral shedding and resolution of influenza symptoms (Figure 1A,B). A previously published oseltamivir population PK model of 390 healthy and infected subjects ranging from 1–78 years across a dose range of 20–1000 mg was used to describe OC exposure. The final covariate model from this population PK analysis included a relationship between weight and creatinine clearance on OC clearance and weight on the OC central volume of distribution. All covariates had a fitted allometric exponent [11]. From this final covariate model, we simulated oseltamivir PK parameter profiles in 5000 70-kg adult patients aged 18–65 with normal renal function receiving the standard 75 mg twice daily (BID) and 150 mg BID oseltamivir for 5 days. The population pharmacokinetic model structure consisted of a two-compartment model with first-order absorption of oseltamivir and first-order conversion of oseltamivir to OC and a one-compartment model with first-order elimination of OC. The AUCs for each patient were quantified and the proportion of patients with OC AUCs above the identified PK/PD viral shedding threshold (14 180 ng.h ml^{-1}) was calculated for each dosing regimen. Additional Monte Carlo simulations were conducted for each dosage regimen, sampling from the oseltamivir population AUC distributions (Figure 1C) to construct a density distribution of the population fraction achieving target attainment for each regimen. For each patient at a given oseltamivir dose, an individual duration of viral shedding (T_{shed}; Υ) value was assigned from a log-normal T_{shed} distribution based on inoculation study data [7] (see Table 1).

Epidemiology module

To link oseltamivir PK/PD to influenza epidemiology, we used a stochastic susceptible, exposed, infected, recovered (SEIR) epidemiological model [12], adapted to incorporate the impact of antiviral therapy (Figure 2A).

The differential equations describing the SEIR model are:

$$\frac{dS}{dt} = -\left(\frac{\beta}{N}\right)SI \tag{1}$$

$$\frac{dE}{dt} = \left(\frac{\beta}{N}\right)SI - E\kappa \tag{2}$$

$$\frac{dI}{dt} = E\kappa - F_0\gamma_0 I - F_{AUChigh} \times \gamma_{high} I - F_{AUClow} \times \gamma_{low} I \tag{3}$$

$$\frac{dR}{dt} = F_0\gamma I + F_{AUChigh} \times \gamma_{high} I + F_{AUClow} \times \gamma_{low} I \tag{4}$$

where S is the number of individuals in the population who are susceptible to influenza, E represents the number of individuals exposed and in the latent stage of influenza infection, I represents the number of infected individuals, and R represents individuals who have recovered from infection and are immune to re-infection. The parameter β governs infectivity, and is a composite of both frequency of individual interactions (population density and social behaviours), and the probability that an interaction will result in a successful influenza infection in a susceptible individual (infectiousness). κ represents the transit time from E to I (delay time between influenza exposure and development of symptoms), which is assumed to be 1 day [13] while γ governs the disease recovery rate in the population. F_0 represents the fraction of the simulated population not receiving therapy, F_{AUClow} is the fraction of the population receiving oseltamivir with an AUC ≤ 14 180 ng.h ml^{-1}, and $F_{AUChigh}$ is the fraction of the population receiving oseltamivir with an AUC > 14 180 ng.h ml^{-1}, obtained from the pharmacology module. N equals the total population (assumed to be 100 000). Because each simulation was limited to a single influenza season (1 year), population birth and death rates were not incorporated into the model. Initial conditions for each compartment were as follows: S = 100 000; E = 0; I = 1; R = 0.

As oseltamivir acts to reduce duration of illness by inhibiting T_{shed}, the recovery rate γ in the SEIR model is inversely related to T_{shed} ($T_{shed} = 1/\gamma$). The R_0 or transmissibility can be expressed in approximate terms [12] as

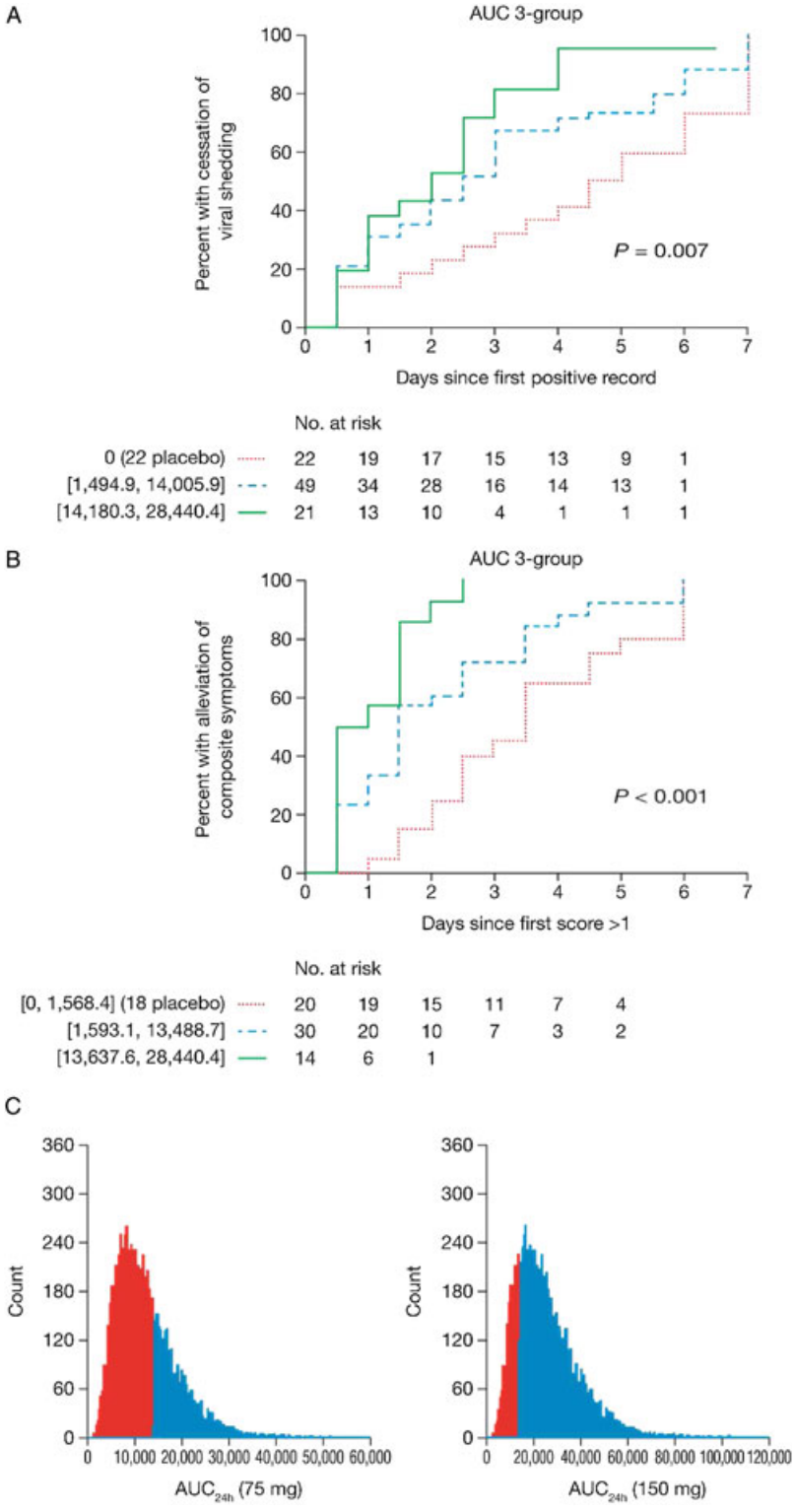

Figure 1

Pharmacology (pharmacokinetics/pharmacodynamics) module. Figure 1A and B were adopted from Rayner *et al.* [7] and show the relationship between oseltamivir area under the concentration-time curve (AUC) and time to cessation of viral shedding and resolution of symptoms, respectively, from phase II data. A cut-off AUC of 14 180 ng.h ml^{-1} separated low (blue dashed line) and high oseltamivir exposed (green solid line) patients in the three-group relationship (AUC breakpoints are shown in brackets next to number of patients carrying over); red dotted line shows unexposed patients (placebo). Figure 1C shows the proportion simulated above and below the cut-off AUC at two dosage regimens (75 and 150 mg twice daily for 5 days) using an established pop pharmacokinetic (PK) model (Kamal *et al.* [9]). Dark red = 'low' AUC group; light blue = high 'AUC' group

Table 1

Input parameters used in the pharmacology–epidemiology modules

Descriptor	Value
Population size (In)	100 000 cases
Latency period (1/κ)	1 day
$F_{AUChigh}$ (150 mg BID)	0.795 (0.095)
$F_{AUChigh}$ (75 mg BID)	0.326 (0.048)
$T_{shed(0)}$ (No treatment)	6 (2.5) days
$T_{shed(low)}$ (AUC 0–14 180 ng.h ml^{-1})	3 (0.58) days
$T_{shed(high)}$ (AUC > 14 180 ng.h ml^{-1})	1.9 (0.51) days
β, Moderate infectivity	0.21 days^{-1}
β, High infectivity	0.41 days^{-1}

κ, the delay rate between exposure to influenza and symptom development; $F_{AUChigh}$, the mean (SD) fraction of the simulated population receiving oseltamivir with an AUC >14 180 ng.h ml^{-1}; $T_{shed(0)}$, the duration of viral shedding under no treatment; $T_{shed(low)}$, the mean (SD) duration of viral shedding if OC AUC is <14 180 ng.h ml^{-1}; $T_{shed(high)}$, the mean (SD) duration of viral shedding if OC AUC is greater than 14 180 ng.h ml^{-1} β, the rate of infectivity; AUC, area under the concentration–time curve; BID, twice daily

$R_0 \approx$ infectivity rate/rate of recovery $\approx \beta/\gamma \approx \beta \times T_{shed}$ and hence empirically by reducing T_{shed}, oseltamivir reduces R_0.

To confirm that the SEIR model provided results that were in general agreement with prior experience, the SEIR model (without incorporation of antiviral therapy) was validated using data from a previous influenza outbreak in the Midwestern USA (2007–2008 seasons) extracted from the Centers for Disease Control and Prevention influenza seasonal summary database (http://www.cdc.gov/flu/weekly/pastreports.htm). In the Midwestern USA, 20 263 patients were tested for influenza, with 4970 confirmed with an influenza infection. The structural model validation was achieved by loading the SEIR structural model (without antiviral therapy) and the data from the Midwestern influenza outbreak into Berkeley Madonna Software. Using the model fitting procedure available in Berkeley Madonna, which uses a weighted sum of squared differences approach to achieve minimization, the attack rate and viral shedding rate was estimated. These values were consistent with those used in our simulations and provided a satisfactory fit with the original data set.

Using the model, simulations were then undertaken to evaluate the impact of oseltamivir treatment regimens under a number of pandemic scenarios; input parameters used in the simulations are provided in Table 1. The simulation scenarios evaluated were stratified by: treatment (no treatment, oseltamivir 75 mg and 150 mg BID for 5 days); the percent drug uptake, i.e., percentage of the infected population who had an uptake of oseltamivir (25%, 50%, and 80%); and transmissibility (R_0 of approximately 1.9 and 2.7) [14]. For each update scenario, 100% adherence to therapy was assumed. Parameters for β were adjusted to achieve the requisite R_0 number as outlined in Table 1. For each of the above, 1000 Monte Carlo simulations (pandemics) were conducted to provide the median attack rate (number of infected cases per total population of 100 000). Each simulation was run across a period of 1 year i.e. an entire flu season. All pharmacometric and epidemiological simulations were conducted in Berkley Madonna version 8.3.18.

Health economics module

The number of infected individuals obtained from each simulated pandemic scenario, from the epidemiology module (SEIR model), were entered into a decision analytic model, i.e. a decision tree (See Figure 3). Each branch of the decision model represents a possible decision or occurrence which is mutually exclusive. A cost-utility analysis was undertaken based on the US population of healthy adults, aged 18–64 years, from both a payer and societal perspective. The payer perspective included only direct costs, whereas the societal perspective included both direct and indirect costs. Total costs and QALYs were determined over a 1-year time period. These two outcomes were combined to calculate incremental cost-effectiveness ratios (ICERs), a commonly used metric in cost-utility analysis that is constructed by dividing the difference in cost between two interventions by the difference in effectiveness between two interventions. ICERs are a useful way of describing the increased cost required to yield one more unit of effectiveness when implementing one strategy over another. QALYs were calculated by multiplying the life-years (LY) by a utility, a value that describes the patient's quality of life in a certain health state ranging from 0 to 1 with 0 being death and 1 being perfect health. The number of LYs gained by a therapeutic intervention was determined by the number of deaths averted (one LY was lost per death from a population of 100 000 individuals). The expected value of utility was determined from the utility of all the health state events in Figure 3.

While there is no consensus as to the optimal ICER threshold in the USA, experts in a recent commentary advocated for a threshold of $100 000 to $150 000 per QALY. For the purpose of this study, we assumed that a gain of one QALY was valued at 100 000 USD [15]. Therefore, an ICER >100 000 USD per QALY indicated the new intervention was not cost-effective. Because of the difficulty in interpreting an ICER <0 ($\Delta C < 0$ and $\Delta E > 0$), in these instances we simply indicate that cost-saving has occurred.

An infected individual entered the health economics (HE) model either as an outpatient or inpatient (Figure 3). Inpatients admitted into a general ward or an intensive care unit could experience pneumonia, sepsis, or acute respiratory distress syndrome (ARDS) [16–18]. We assumed that patients could only experience one influenza-related complication within 1 year. The infected patient either recovered from the infection or died. It was also assumed that all patients were 100% adherent to treatment received, and that oseltamivir reduced the time of symptom alleviation by 21 hours and had no direct effects on influenza complications or hospitalization rate [19–21].

Data inputs for the HE model (Table 2) such as branch probabilities, direct medical costs (medication and hospitalization), direct nonmedical costs (transportation to and from hospital), length of hospitalization, case-fatality rates from

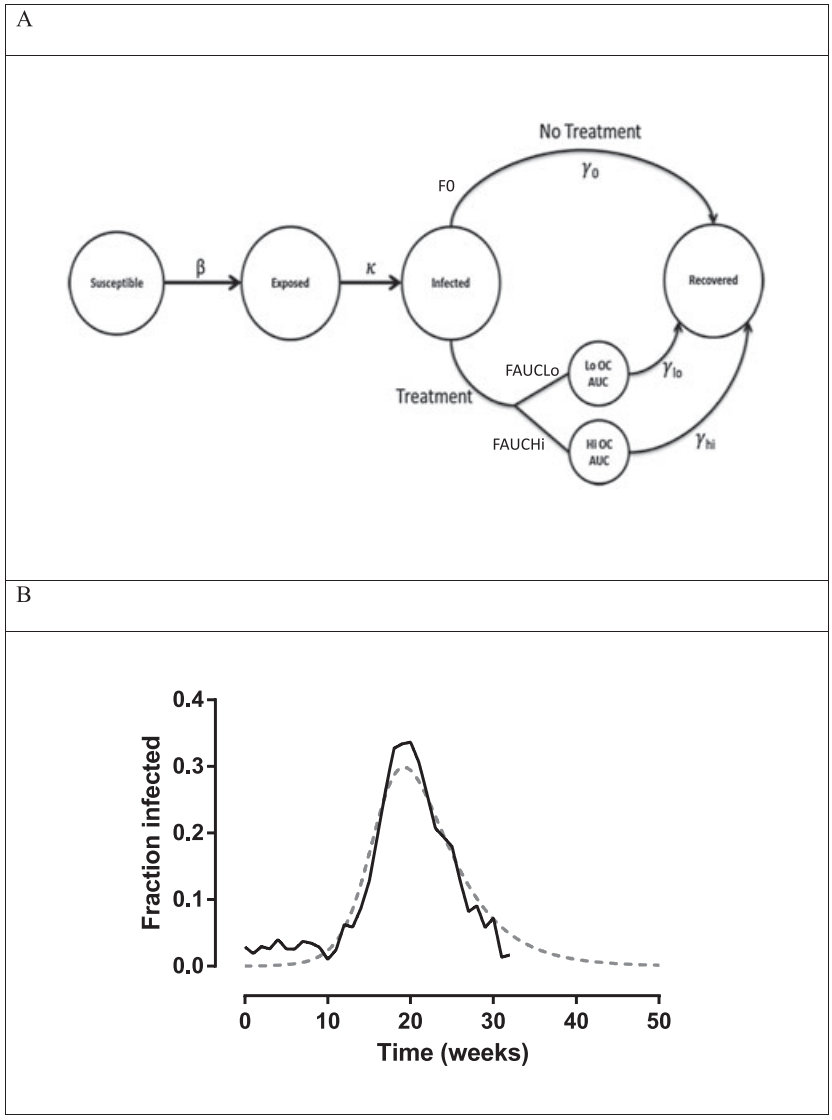

Figure 2

Epidemiology module. Figure 2A shows the SEIR (susceptible, exposed, infected, recovered) influenza epidemiology model adapted to account for oseltamivir treatment effect. Figure 2B shows fit of the SEIR model to 2007–2008 Influenza Epidemic Data from the Midwestern USA (http://www.cdc.gov/flu/weekly/pastreports.htm). The fitting produced parameter values of $\beta = 0.73$, $\gamma = 4.1$ day, and $1/\kappa = 1$ day. The grey dotted line represents model fitted function; the solid black line represents actual data. AUC, area under the concentration-time curve; OC, oseltamivir carboxylate

influenza complications and health state utilities (which are used in the construction of the QALY) were obtained from the published literature [22–42] and Healthcare Cost and Utilization Project Nationwide Inpatient Sample database. Where possible, data related to the 2009 pandemic H1N1 influenza was used. All costs were converted to 2013 USD using the Consumer Price Index [43]. Indirect costs, defined as the costs attributed to daily work productivity loss by age, were determined by the approach of Meltzer *et al.* [36].

Four pandemic scenarios were assessed in the HE model: (i) high transmissibility and high severity; (ii) low transmissibility and low severity; (iii) high transmissibility and low severity; and (iv) low transmissibility and high severity. Within each scenario, three interventions were assessed (no treatment, oseltamivir 75 mg and oseltamivir 150 mg BID for 5 days). Drug uptake was varied as described in the epidemiological module (25%, 50%, and 80%). The β values for transmissibility were obtained from the epidemiological module (Table 1) whereas severity of illness (proxy for virulence of disease) was based on health care utilization; low severity was based on 2009 H1N1 pandemic experience [44]; and the high severity scenario involved doubling the probability of hospitalization [45] for the low severity scenario. All HE modelling was performed using Microsoft Excel and R (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, http://www.R-project.org._)

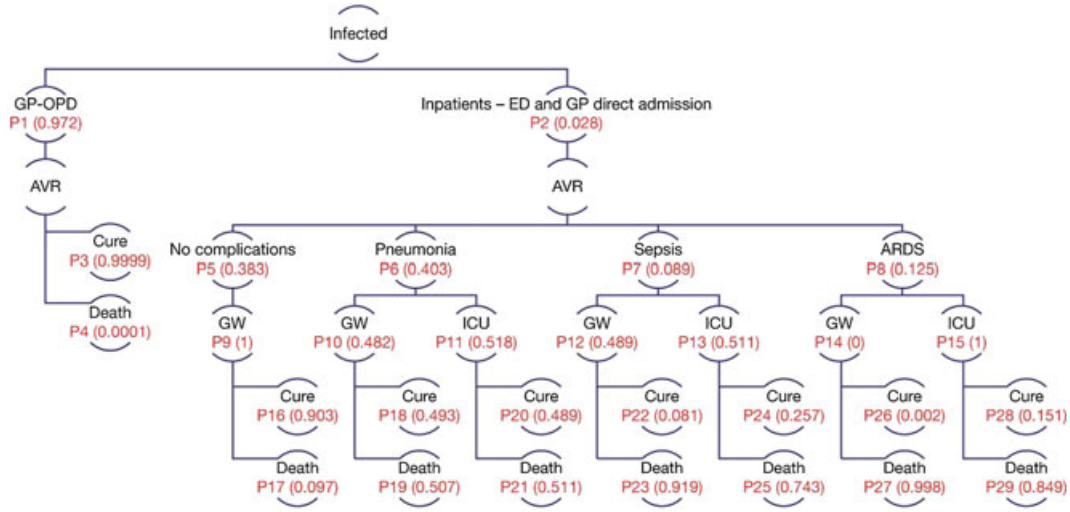

Figure 3

Health economics module. The number of infected-influenza patients per population of 100 000 (calculated from the epidemiology module) entered a decision analytic model. Patients received treatment in an outpatient or inpatient setting. Inpatients admitted into a general ward (GW), or an intensive care unit (ICU) may experience pneumonia, sepsis, or acute respiratory distress syndrome (ARDS). The branch probabilities (P1-P29) are shown for the base case (see Table 2 for data source). AVR, antiviral treatment; ED, emergency department; GP-OPD, general practice or outpatient department

Sensitivity analysis

As the magnitude and effect of the outcome of this proof of concept quantitative framework is dependent on the point estimate of T_{shed} used in our simulations, a sensitivity analysis around the change in viral shedding in terms of infected patients and the subsequent impact on the HE model was warranted. Using the data provided by Rayner *et al.* [7], the 25th and 75th percentiles of viral shedding in each of the OC AUC exposure groups defined by the classification and regression analysis were calculated. All dosing scenarios described above were then repeated, using these upper and lower bounds of viral shedding to provide upper and lower bounds on number of patients infected (see Table 2). The number of infected patient at 25% T_{shed}, 50% T_{shed} and 75% T_{shed} were then used as inputs into the current HE model for comparison.

Results

Pharmacology (PK/PD) module

The PK/PD target threshold, which separated low and high oseltamivir exposure groups in the time to event relationships [7] between OC AUC and cessation of influenza viral shedding (Figure 1A) and resolution of influenza symptoms (Figure 1B) was 14 180 ng.h ml^{-1} [7]. The simulated AUC density distributions for the 75 mg and 150 mg BID dosing regimens are shown in Figure 1C. Simulation results determined that the proportion of patients in a population with OC AUCs above the PK/PD threshold was 0.326 and 0.795 when treated with 75 mg and 150 mg BID regimens, respectively (Table 1). As shown in Table 1, the distribution of duration of viral shedding (T_{shed}) data obtained from the influenza inoculation studies [7] was as follows: for patients above the PK/PD threshold, the T_{shed} distribution with mean (standard deviation; SD) Υ_{high} was 1.9 (0.51) days, for those less than the PK/PD target the mean (SD) Υ_{low} was 3 (0.58) days, and for patients not receiving drug the mean (SD) Υ_0 was 6 (2.5) days.

Epidemiology module

A schematic of the epidemiological SEIR model adapted to incorporate oseltamivir PK/PD is shown in Figure 2A (see Methods). Results of the SEIR model external validation to epidemic data gathered from a previous influenza outbreak in the Midwestern USA (2007–2008 seasons) is shown in Figure 2B. As shown, the model was adequately fitted to the extracted data, capturing the fraction of the population infected over the duration of the influenza outbreak.

The SEIR model was then used to simulate the median number of individuals infected (per population of 100 000) under different pandemic and treatment intervention scenarios. Results of these simulations are shown in Table 3. A pandemic, by definition, requires an $R_0 > 1$ [8, 12]. As shown, in the low transmissibility scenario ($R_0 = 1.9$), under no antiviral treatment, approximately 37 000 individuals would be infected, with that number decreasing to ~5000 under oseltamivir 75 mg BID treatment and 25% drug uptake. As expected, increasing the proportion of the infected population receiving antiviral treatment (drug uptake) had a significant impact on the incidence of infection in the population in both low and high (R_0 = 2.7) transmissibility pandemic scenarios. A higher dose of oseltamivir, 150 mg BID, demonstrated a greater improvement in reducing the number of infected individuals as the percentage of the population treated increased, particularly in the high transmissibility scenario.

Table 2

Input parameters, values and data sources used in the health economics module

Parameters	Base–case value	Source(s)
Probabilities		
Medical care received		
Outpatient visit	0.972	[22]
Inpatient	0.028	[22]
Channels of inpatient admission		
Through ED visit	0.778	[23]
Through outpatient visit	0.222	[23]
Complication associated with influenza		
No complications	0.383	
Pneumonia	0.403	[16–18]
Sepsis	0.089	[17, 18]
ARDS	0.125	[17, 18]
Type of hospitalization		
No complication		
ICU	0	
GW	1	Assumed
Pneumonia		
ICU	0.518	[16]
GW	0.482	
Sepsis		
ICU	0.511	[24]
GW	0.489	
ARDS		
ICU	1	[18]
GW	0	
Probable outcome from the medical care received		
GP		
Cure	0.9999	
Death	0.0001	[25]
No complication		
In GW		
Cure	0.903	
Death	0.097	[17, 18]
Pneumonia		
In GW		
Cure	0.493	[17, 18]
Death	0.507	
In ICU		
Cure	0.489	

(*continues*)

Table 2

(Continued)

Parameters	Base–case value	Source(s)
Death	0.511	[17, 18]
Sepsis		
In GW		
Cure	0.081	[17, 18]
Death	0.919	
In ICU		
Cure	0.257	
Death	0.743	[17, 18]
ARDS		
In GW		
Cure	0.002	[17, 18]
Death	0.998	
In ICU		
Cure	0.151	
Death	0.849	[17, 18]
Costs (USD, year of costing: 2013)		
Direct medical care costs		
Oseltamivir	132.77	[26]
Over the counter medications	16.95	[27]
GP visit	169~	[22]
ED visit	551	[28]
Hospitalization		
GW		
No complication	17 260	[29]
Pneumonia	18 966	[29]
Sepsis	23 771	[29]
ARDS	45 330	[30]
ICU		
Pneumonia	22 771	[31]
Sepsis	44 958	[32]
ARDS	128 860	[30]
Direct nonmedical care cost		
Transportation (per visit)	2.83	[33, 34]
Indirect costs (daily productivity loss by age)		
Age 18–64	146.04	[35]
Productivity loss (days lost) = length of stay plus days of convalescence		
GP visit	2.0	[22, 36]
Hospitalization		

(*continues*)

Table 2

(Continued)

Parameters	Base–case value		Source(s)
GW			
No complication	7.4		[29, 36]
Pneumonia	8.4		[29, 36]
Sepsis	10.5		[29, 36]
ARDS	13.0		[29, 36]
ICU			
Pneumonia	9.7		[31, 36]
Sepsis	14.4		[32, 36]
ARDS	17.0		[30, 36]
Length of stay (days)			
GP visit	1.0	NA	[22]
Hospitalization			
GW			
No complication	6.4		[29]
Pneumonia	7.4		[29]
Sepsis	9.5		[29]
ARDS	12.0		[30]
ICU			
Pneumonia	8.7		[31]
Sepsis	13.4		[32]
ARDS	16.0		[30]
Utilities (95% CI)			
Baseline average quality of life	0.96	(0.92–1.00)	[37–39]
Quality of life during illness with influenza	0.81	(0.70–0.90)	[37, 40]
Pneumonia	0.63		[41]
Sepsis in hospital ward	0.59		[42]
Sepsis in ICU	0.10	(0.08–0.15)	[39–42]
ARDS in hospital ward	0.59		[42]
ARDS intubated in ICU	0.10	(0.08–0.15)	[42]
Recovery from severe influenza, for patients who received inpatient ICU care	0.90	(0.85–0.95)	[37]

HE module

The median number of infected individuals (per population of 100 000) for each pandemic scenario (Table 3) was entered into a decision analytic model and became part of the economic analysis. The final HE decision analytic model is shown in Figure 3. Data inputs (and literature sources) for the HE model such as branch probabilities, direct medical costs (medication and hospitalization), direct nonmedical costs (transportation to and from hospital), length of hospitalization, case-fatality rates from influenza complications, and health state utilities are shown in Table 2. As shown in the table, the vast majority of influenza-infected patients in a population present as outpatients (>97%), and of the 3% who present as inpatients, 40% present with pneumonia as an influenza complication followed by (ARDS; 12%) and sepsis (8%).

HE simulation scenarios and treatment comparison

Results of the HE analysis are shown in Table 4. As shown, across all pandemic scenarios, 75 mg BID oseltamivir was cost-saving relative to no treatment, i.e., ΔC (incremental cost) <0 and ΔE (incremental effectiveness) >0 (see Methods, Equation 5).

The decrease in costs (ΔC) was driven by savings from direct medical and nonmedical costs and indirect nonmedical costs (through fewer work days lost) which offset the increased drug costs. As shown in Table 4, and using the low transmissibility and low severity pandemic scenario as an example, when comparing oseltamivir 75 mg *vs*. no treatment, costs from the payer perspective (which include direct costs only) were substantially lower (9.2 million US dollars [USD] *vs*. 42.6 million USD at baseline). From the societal perspective, which includes indirect costs in addition to direct costs, there was also a large decrease in costs (13 million USD *vs*. 107 million USD at baseline). The increase in QALYs (ΔE) for the 75 mg oseltamivir treatment strategy relative to no treatment was primarily driven by a reduction in mortality. As shown in Table 4, again using the low transmissibility and low severity scenario, a gain in QALYs (ΔQALY) of 430 was seen with the oseltamivir 75 mg intervention relative to no treatment. This value was driven by the number of deaths averted downstream in Figure 3 by the 75 mg BID intervention (Δ Death = 412 for this scenario). As shown in Table 4, the total number of deaths per population of 100 000 was dependent on the intervention, and ranged from as low as 16 to as high as 1591 deaths, equivalent to mortality rates of approximately ~0.016% and 1.6% respectively, and is consistent with the reported range of mortality of known influenza pandemics [46]. In the base case under no treatment low transmissibility and low severity), death due to hospitalization with pneumonia constituted the highest percentage (47%) of total deaths from complications of influenza, followed by ARDS (27%) and sepsis (15.5%).

When compared with oseltamivir 75 mg at 50% drug uptake (Table 4), the new intervention using 150 mg was not cost-effective in low transmissibility scenarios; however, it was cost-saving in the high transmissibility scenarios.

Sensitivity analysis

The simulations from the sensitivity analysis using the 25th or 75th percentile of viral shedding on the epidemiological model are presented in Table 3. When the epidemiological data were linked to the HE model, only minimal changes in

Table 3

Output of the combined pharmacology–epidemiology modules. Median number of infected individuals per population of 100 000 by therapeutic intervention, transmissibility (R_0), and % of infected individuals treated with oseltamivir[a]

% treated	No treatment	75 mg BID	150 mg BID
Low transmissibility (R_0 = 1.9)			
	37 068		
25%	--	7846 (7846–20 354)	5311 (5311–1,6303)
50%	--	2252 (2252–12 279)	1357 (1357–7202)
80%	--	1349 (1349–8504)	741 (741–4891)
High transmissibility (R_0 = 2.7)			
	67 512		
25%	--	60 397 (60397–71 149)	53 032 (53032–59 498)
50%	--	41 331 (41331–55 660)	31 700 (31700–37 024)
80%	--	20 941(20941–40 616)	12 881 (12881–14 665)

BID, twice daily; R_0, the basic reproductive number.
[a]median (25^{th} and 75^{th} % of viral shed) simulation are reported in this table. Note: 25^{th} and 50^{th} percentile identical given right skewed distribution.

the overall HE conclusions were observed. The only significant change was with the 75^{th} percentile viral shedding in the low transmissibility and high severity scenario. All HE outcomes were the same, except for the 150 mg dose compared to the 75 mg dose in the low transmissibility and high severity scenario, which now achieved *cost-savings* from a payer and societal perspective (data not shown). This demonstrates that our quantitative framework is robust to possible intrinsic variability in viral shedding, yet is able to detect and translate meaningful antiviral exposure response without impacting the health economic conclusions.

Discussion

We developed a modular interdisciplinary pharmacometric platform that was able to show that oseltamivir reduced the median number of infected individuals, increased QALYs by preventing deaths, and was cost-saving under most pandemic scenarios. The pharmacology–epidemiology modules aimed to translate variability in the exposure (PK)–response (PD) effect of oseltamivir on influenza viral shedding and then demonstrate the indirect benefits achieved by altering disease transmissibility at a population level. The individual and population outcomes were translated into improvements in the QALY and cost-utility (captured by the ICER) allowing insight into the health economic impact of various interventions under pandemic scenarios.

The positive economic impact of oseltamivir was mostly driven by reducing the number of infected patients (per 100 000 population) entering the decision analytic model (Figure 3), thereby reducing the number of individuals who otherwise may have gone forward to develop influenza complications and hence averting deaths downstream (increased QALY). From a payer perspective, direct medical costs were decreased through less health care use (Figure 3), and from a societal perspective, the decrease in indirect costs was driven mainly by fewer days lost from work. As shown in Table 4, increased dose (150 mg) relative to standard dose (75 mg) may have some economic impact in high transmissibility scenarios, but not low transmissibility at 50% drug uptake (drug uptake is a proxy for the ability to stockpile and distribute drug to susceptible individuals). The exception is at 25% drug uptake (data not shown) where the 150 mg dose may have a favourable ICER, suggesting that in low transmissibility scenarios, treatment of a smaller portion of infected individuals with a higher dose may have some economic value.

The integrated platform developed in the current study may also be used to investigate the health economic impact of other antivirals under development once a PK/PD readout has been achieved in early development. This would allow early consideration of novel antiviral compounds for pandemic planning, such as a haemagglutinin monoclonal antibody that inhibits viral entry into the host cell [47]. Such a therapeutic modality is being developed by different organizations to treat severe influenza, and hence may potentially act on the lower (distal) parts of the decision analytic model by reducing hospitalization duration once admitted to the intensive care unit, where oseltamivir acts proximally by reducing the number of infected individuals that enter the decision analytic model (Figure 3). As such, combining therapeutic modalities may be complementary from a health economic and pandemic perspective by addressing both transmissibility and severity (virulence). Other applications of the platform include conducting threshold analysis on drug pricing, which would lead to a desired ICER.

Certain competing factors may have confounded our estimation of the economic impact of oseltamivir. Factors leading to underestimation include: (i) capturing only treatment effect of oseltamivir on recovery rate (γ) and not the effect on the rate of infectivity, β (Figure 2A), via its documented effects on prophylaxis [48]; and (ii) employing a conservative assumption of oseltamivir having no effect on reducing influenza complications, despite some evidence suggesting positive effects [5]. By contrast, factors that may have led to

Table 4

Health economics module output: Effect of oseltamivir treatment intervention at 50% drug uptake on cost, life-years (LY) and quality-adjusted LY (QALY) by pandemic scenario. A cost per QALY gained of <0 indicates the new intervention is cost-saving, a cost per QALY gained of >0 and <100 000 USD indicates the new intervention is cost effective, and a cost per QALY gained >100 000 USD indicates the new intervention is not cost effective

										Payer perspective		Societal perspective	
Comparators (Treatment *vs.* baseline)	**Costs (A) (payer)**	**Costs (B) (payer – Baseline)**	**Costs (A) (societal)**	**Costs (B) (societal - Baseline)**	**Death (A)**	**Death (B)**	**Δ Death (A–B)**	**Δ LYs (A–B)**	**Δ QALYs (A–B)**	**Cost per LY gained**	**Cost per QALY gained**	**Cost per LY gained**	**Cost per QALY gained**
Low transmissibility and low severity													
75 mg (A) *vs.* no treatment (B)	9 225 251	42 578 018	12 998 947	106 995 703	27	439	–412	399	430	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 (B) mg	14 835 713	9 225 251	17 109 649	12 998 947	16	27	–11	10	11	546 753	515 260	400 598	377 524
High transmissibility and high severity													
75 mg (A) *vs.* no treatment (B)	94 961 869	144 271 547	171 053 550	272 957 742	974	1591	–617	598	629	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 mg(B)	81 019 150	94 961 869	139 379 855	171 053 550	747	974	–227	220	227	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Low transmissibility and high severity													
75 mg (A) *vs.* no treatment (B)	11 450 971	79 213 439	15 596 974	149 869 617	53	874	–821	795	828	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 mg (B)	16 176 877	11 450 971	18 675 157	15 596 974	32	53	–21	20	21	231 280	223 797	150 642	145 768
High transmissibility and low severity													
75 mg (A) *vs.* no treatment (B)	54 113 197	77 547 403	123 371 900	194 871 423	489	799	–310	300	330	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) *vs.* 75 mg (B)	49 689 085	54 113 197	102 809 041	123 371 900	375	489	–114	110	117	Cost-saving	Cost-saving	Cost-saving	Cost-saving

All costs are expressed in 2013 USD.

A, the alternative intervention; B, the baseline intervention.

overestimation include: (i) the univariate nature of our analysis with respect to intervention, where only the antiviral effect was considered without incorporation of other pandemic mitigating factors such as school/airport closure, social distancing, mask wearing and vaccination; and (ii) use of inoculation data that involved administration of drug immediately after infection, thereby lacking consideration of the effect of time to treatment [49] (the effectiveness of oseltamivir is highest at early treatment times relative to infection). We sourced PK/PD data from phase II inoculation studies because they employed the widest range of oseltamivir doses and had well characterized PK/PD relationships [7], although emerging work [50] is also showing some PK/PD relationships from phase III data (seasonal influenza), where significant differences could not be revealed by comparing dose groups alone. It is important to also note that different opinions exist on the potential effect of doubling an oseltamivir dose [7, 51–56]; some have also noted improved viral shedding in hospitalized adults infected with influenza B with higher doses [51], whereas others have failed to identify the superiority of double dosing in avian and severe influenza [52]

Numerous oseltamivir population PK models have been developed to evaluate PK for specific purposes including impact of obesity, pregnancy, end-stage renal dysfunction, ontogeny in infants younger than 1 year and the impact of probenecid to incite a drug–drug interaction [11, 57–62]. Whilst fit for their specific purpose, such models were too narrow for application in this program. The population PK model used in this framework had the greatest patient number, and age, weight, creatinine clearance and dose range. Thus enabling suitable populations of interest to be robustly simulated to evaluate OC exposure in this framework.

The situation of administering drug immediately after infection is an ideal scenario, and is likely to deviate from the reality of a pandemic. In the current methodological study, linkage of the pharmacoepidemiology and HE modules is demonstrated deterministically, i.e. median predictions of the number of infected individuals (Table 2) from the pharmacoepidemiological modules form the input into the HE module. This approach was undertaken because currently available epidemiological models are not able to provide the full variance–covariance matrix between parameters due to paucity of observational data of influenza seasons to build such models robustly. Nevertheless, it was reassuring that our model was able to more than adequately describe the previous influenza outbreak in the Midwestern USA (2007–2008 seasons) extracted from the Centers for Disease Control.

To address some of these limitations in future work, this iteration is amenable to improvement due to the modular nature of the platform. For example, to overcome the limitations of the SEIR model, which is well stirred with regards to susceptibility and infectiousness of influenza, an agent-based epidemiology model (ABM) could be used instead. The ABM would account for the unique contact structures in a population [1, 12] allowing for more heterogeneous representation of infectiousness (β in Figure 2A). Some of the present authors have begun steps towards the integration of an ABM [63]. Future efforts may also involve exploring the potential health economic impact of alternate dosing scenarios (e.g. half-dose, triple dose). It is worth noting that considering adverse events and disease complications brings the HE model closer to clinical reality. However, it should be highlighted that the focus of the current study is the demonstration of proof-of-concept of linking PK/PD information to the HE model through the epidemiological model. However, those factors will be considered in our future work along with the use of the more sophisticated ABM model.

The model also did not consider emergence of resistance during an influenza season, which might result in decreased viral clearance, and therefore potentially reduced impact of oseltamivir. Neither did it consider the acquisition of resistance mutations that may also result in a cost to infectivity that may reduce the potential for transmission. There is a paucity of data to support or describe the rate and extent of resistance emergence within an influenza season to support assumptions for such scenarios. The spatial and time aspects of emergence of resistance (e.g. arising in a specific geography mid-way through an epidemic) are more appropriately explored using ABM approaches.

Despite these limitations, we have successfully demonstrated proof of concept that relevant endpoints can be linked across adjacent disciplines (in this case drug AUC, viral shedding, and their respective variabilities, R_0 and ICER). Many have, through use of meta-analysis of randomized clinical trial data or retrospective analysis of pandemic data, advocated use of neuraminidase inhibitors as one of several strategies to contain a pandemic [5, 64], and this is reflected in current guidelines [3]. While we recognize that further work is needed to quantify the health economic impact of oseltamivir more rigorously in a given pandemic scenario, the potential utility of interdisciplinary pharmacometric methodology in beginning to solve multilayered problems should not be understated. Given the growing need to justify pricing of medicines to society and payer, the authors favour greater application of interdisciplinary techniques across all disease areas where the PK/PD, clinical, or epidemiological endpoints of interest can eventually be linked to health economic value. We advocate that this approach will bring together the developer, payer and regulator earlier in the drug development process to facilitate accelerated access to affordable medicines.

Conclusion

Oseltamivir 75 mg relative to no treatment reduced the median number of infected patients, increased ΔQALY by deaths averted, and was cost-saving under all simulated pandemic scenarios, while 150 mg relative to 75 mg was not cost effective in low transmissibility scenarios but was cost saving in high transmissibility scenarios. This methodological study demonstrates proof of concept that the disciplines of pharmacology, disease epidemiology and health economics can be linked in a single quantitative framework.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on

request from the corresponding author) and declare: M.A.K., P.F.S., K.N., G.D., S.T. and C.R.R. all had support from Roche for the submitted work; M.A.K. was an employee of Roche in the previous 3 years; P.S., K.N., G.D., S.T. and C.R. are employees of d3 Medicine, which is a strategic advisory company in drug development and advised multiple pharmaceutical and biotechnology companies, including Roche in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

This work was supported by funding from F. Hoffmann-La Roche Ltd. Support for third-party writing assistance for this manuscript was provided by F. Hoffmann-La Roche Ltd.

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[Correction note: This article was first published online on the 20th of February 2017. Minor grammatical corrections were made in the abstract, Introduction and Methods sections on the 22nd of March 2017 prior to issue publication.]