PUBLIC HEALTH

What are Bayesian Models? How do They Compare with Traditional Models for Economic Evaluations in Health Care? A Review

Waseem Sharieff, MD, Ph.D.
George Tomlinson, Ph.D.

ABSTRACT
Models are frequently used in economic evaluations to estimate outcomes and the associated costs, in a group of people after interaction with an agent, the 'health intervention'. Traditionally, mathematical, regression or decision tree models have been used. Bayesian models are a new addition. We reviewed Bayesian methodology and application in relation to traditional models. Bayesian models have several advantages over traditional models. However, given that each model has its own merits and demerits, we conclude that for a specific application, the most appropriate model would be the one which reasonably presents the real life situations under investigation. When a single model is either too simple (leaves out well understood interactions) or too complex (includes vague interactions), a hybrid approach may be appropriate.

WHAT IS A MODEL?

A model represents our understanding of how things work in real life. We use models to describe a phenomenon. In real life, complex interactions can occur between several variables that influence an outcome. Using one model, we may understand some of these interactions, and using another model we may understand other interactions. Thus, we may understand a complex phenomenon by breaking it down into simpler models. Models are used in all disciplines to understand a phenomenon or to predict an outcome. For example, models are used to forecast weather, to set an insurance premium for a customer, and in economic evaluations to facilitate decision making for priority setting and resource allocation.

Nowadays, Bayesian models are being increasingly used to estimate a health outcome.[1,2,3,4] They are also being used to determine cost effectiveness of interventions in relation to their effects on health outcomes. Traditionally, mathematical, regression or decision tree models have been used for this purpose. Thus general medical readers usually lack a basic understanding of Bayesian methods – there is a need to familiarize general readers with Bayesian models[5] in relation to traditional models. Thus, we describe the methodology of traditional and Bayesian models in the context of the cost effectiveness of automated external defibrillators (AEDs) in improving survival in patients who experienced an out-of-hospital cardiac arrest (a leading cause of death) on the basis of findings from the Ontario Prehospital Advanced Life Support (OPALS) study.[6]

MATHEMATICAL MODELS

Simple Model

A simple mathematical model uses arithmetic and algebra. Such a model is commonly used in health economics, for example, to estimate the cost effectiveness of a new intervention in a group of patients in relation to a control intervention in a similar group of patients.

Let ΔC be the difference in costs, and ΔE the difference in effect, between the intervention and control groups. Cost effectiveness of the intervention is determined by calculating the incremental cost effectiveness ratio (ICER), which is the ratio of the difference in costs and difference in effects ($ICER = \Delta C/\Delta E$). Uncertainty around this estimate is captured by sensitivity analyses which could require re-calculation of the ratio for the worst (pessimistic) and best (optimistic) scenarios.

For example, the OPALS investigators estimated that the rate of out-of-hospital cardiac arrest was 59 per 100,000 people (mean age = 70 years) in Ontario.[7] They also estimated that 3.9% (183/4690) of cardiac arrest patients survived to hospital discharge, but after the implementation of the AED program in which responders to the '911' system carried AEDs and helped in resuscitating cardiac arrest patients, the survival rate was 5.2% (85/1641).[8] The odds ratio (OR) was 1.33 (95% confidence interval = 1.05, 1.70) for survival after implementation of the AED program in relation to survival before implementation. In addition, the OPALS investigators estimated that the ongoing annual costs for continuing the AED program in Ontario would be $2,000 per 100,000 residents, or $2,400 per life saved.

This estimate of cost effectiveness is based on simple arithmetic. That is, in a population of approximately 13 million people in Ontario, there would be 7,670 annual cardiac arrests (59 arrests/100,000 people × 13 million people), and thus approximately 100 additional lives (0.052-0.039 × 7670) could be annually saved by the ongoing AED program – this would correspond to $2,600 per life saved ($260,000/100 lives), which is approximately equal to what OPALS investigators estimated.

Let's assume that the cost would vary from $1,000 to $3,000 per 100,000 residents, and effectiveness would vary from 50 to 150 additional lives saved. Thus, cost per life saved would range from $800 to $7,200 per life saved in the best and worst case scenarios, respectively.

A variation in this approach is what is called the cost utility analysis that takes both the quantity and quality of life into consideration when measuring the health effect. This is because life expectancy and functional level of an older person is less than those of a younger person. Thus, the effect is expressed as the gain in quality adjusted life years (QALYs). Let's assume that the life expectancy at the age of 70 years is 15 years, and the person is expected to function at 80% of the level that the person could function at a younger age (say at 25 years of age). Under this assumption, on average, each life saved among cardiac arrest patients would correspond to a gain of 12 QALYs (15 life years × 0.8 utility). Thus, the mean cost per QALY gained by the ongoing AED program would be $200 ($2,400/12 QALYs).

The advantage of this model is it relays an otherwise complex phenomenon through simple and easily understandable arithmetic. The major disadvantage is that this model does not capture the effect of response time on survival which is the key to improving survival through early cardiorespiratory resuscitation and defibrillation.[9]

Complex Models

A complex implementation of mathematical models uses advanced mathematics (such as, calculus and differential/difference equations). These may capture the motion and change that occur over time.

For example, Eddy and colleagues used difference equations to capture events that occur in a cohort over a given time period. That is, at the starting point the cohort comprised of prevalent cases of diabetes mellitus – the patients could transit from one health state to another (say, 'non-stroke' state to 'stroke' state), and in the same time period incident cases of diabetes mellitus could join the cohort, and could be followed up.[10] They composed software they call 'Archimedes', which has modeled diabetes outcomes and has replicated several trial results.[11,12] However, due to the complex equations at the heart of their model, they could not transparently describe their methodology; this limits the acceptance of their work.[13] Nevertheless, Archimedes was used to estimate the cost effectiveness of diabetes interventions.[14] It was felt that more transparency was needed for the model to be useful for informing policy decisions.

Another example of the use of advanced mathematics in economic modeling is the calculation of disability adjusted life years (DALYs), a measure of the amount of life years lost due to premature disability or death. The DALY approach assigns higher value to life at young age in relation to extremes of age (when people are economically more productive). Thus, the death of an infant or elderly person is valued less than that of a young adult.[16] This approach captures loss of productivity due to irreversible disability. Homedes has described the derivation of DALY,[17] in which the parameter values are arbitrarily chosen. Nevertheless, in Figure 1, we graphically illustrate the motion and change produced by the DALY equation in an age interval of 0–80 years; DALYs lost for an individual who dies at the age of 10 years are higher compared to an individual who dies at one year of age or 70 years of age.

Figure 1. Motion and change produced by a complex mathematical model
DALY has five components: duration of time lost due to a death at each age; disability weights (0 = perfect health, 1 = dead); age-weighting function; discounting function; and cumulative value of health. These components are integrated in the DALY equation which produces the motion and change shown above.

Applying the DALY approach to the ongoing AED program would save 6.35 DALYs for averting death of a 70-year-old patient. Thus, the mean cost per DALY saved would be $378 ($2,400/6.35 DALYs).

The advantage of complex models is that they capture longitudinal changes that may be non-linear. However, this advantage is offset by their complexity, which makes it difficult to transparently describe them. This is a major limitation of these models.

Regression Models

Regression models are generally used in analyses of data from observational and experimental studies to estimate or predict the effect of one or more variables on an outcome of interest. Using gathered data which contain values of predictors '*x*' and values of an outcome '*y*', all available observations are used to estimate the coefficients (α, β) in the regression model ($y = \alpha$ + I). Since, these models relate some function of the mean of an outcome of interest to one or more predictor variables through regression coefficients, mean of I can be estimated for any given set of values of α, β and x.

When the outcome is a binary variable, for example survival status (dead = 0, alive = 1), a form of regression called logistic regression is used. The OPALS investigators used this model to study the effect on survival of response time in cardiac arrest patients.[18] In their multivariable logistic regression model with vital status at the time of hospital discharge as the outcome, the reported β coefficient was -0.262 for the variable measuring defibrillation response in minutes (predictor). The antilog of β yields the OR of 0.77, which means that for each minute delay in defibrillation from the onset of a cardiac arrest, the probability that the patient would survive to hospital discharge decreases by 23%. Conversely, it can be said that for each minute improvement in defibrillation response, the survival increases by 29% (1/0.77 = 1.29). These estimates can be used to estimate the mean cost per life saved or mean cost per QALY gained as previously described.

For example if the current survival rate following cardiac arrest is 5.2%, and if the mean response time is reduced by 2 minutes, the survival rate would increase to 8.6% (5.2 × 1.29 × 1.29). This would correspond to 244 lives saved at a mean cost of $983 per life saved, or mean cost of $82 per QALY gained (based on the previous cost estimate of $2,000 per 100,000 residents, and a total population of 13 million people).

The advantages of using regression models are that they are built directly from data that they employ standard and well-understood techniques, that there is a huge body of knowledge on model estimation and validation, and that easy-to-use software for many types of regression models are readily available. Thus, descriptions of these models are easily communicated and they are widely accepted. Perhaps their main disadvantage is related to the potential 'abuse' of the current software packages that have automatic procedures for model selection. This tempts a novice to build a model without considering issues of model selection, model fit and validation. Such a model may not have any clinical utility.

Decision-tree Models

A Decision-tree model portrays the branching cascade of consequences that could arise from a decision, each leading to one of several clinical scenarios.[19] At each level of the tree, the uncertainty around whether one branch or the other is taken is represented by a probability.[20] Associated with each clinical scenario is a utility, a global measure of health status expressed on a scale of 0 to 1, where 1 represents the best possible outcome (usually full health) and 0 represents the worst possible outcome (usually death).[21] Typically, values for probabilities and utilities are based on estimates (proportions, means, relative risks) from the literature.[22] The rational decision is the one that gives the maximum expected utility. [23] The strength of this modeling approach is that it can take into account the numerous potential benefits and harms resulting from each choice and thereby facilitate choice of the best decision.

Let's suppose a 71-year-old man considers buying an AED for home use in the event of a cardiac arrest. His spouse agrees to acquire training in CPR and the use of AED. In the event of a cardiac arrest at home, the patient's spouse would call 911, start CPR and use AED. The EMS personnel would take over the patient's management upon arrival. Now suppose, that in the event of an arrest, the use of home AED would reduce defibrillation response time by 6 minutes – that is there would be a 4.6 fold (1.29 × 1.29 × 1.29 × 1.29 × 1.29 × 1.29) increase in the chance of survival. However, suppose there is a 57% risk of developing neurological impairment when CPR is performed by a lay person compared to 5% risk when CPR is performed by an EMS responder (inadequate CPR may not prevent hypoperfusion of the brain during a cardiac arrest, and lead to neurological impairment). Now, the person has two options: buy an AED for home use in which case there is a 23% (0.05 × 4.6) chance of survival associated with 43% chance of full functional recovery; or continue relying on the EMS alone in which case there is a 5% chance of survival associated with 95% chance of full functional recovery. Figure 2 presents these scenarios as a decision tree, where the person assigns a utility of 0 to death, 0.5 to being alive with neurological impairment, and 1 to being alive with full functional status.[24] The expected value (EV) of the utility for a decision can be calculated by taking the product of the probabilities and utilities for each branch for that decision and summing them up. Thus, the EV of choosing home AED is 0.16 ([0 × 0.77] + [1 × 0.43 × 0.23] + [0.5 × 0.57 × 0.23]) and the EV

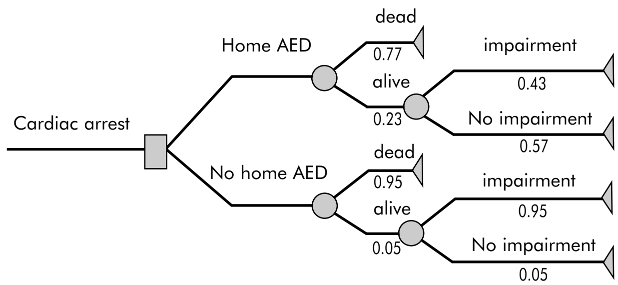

Figure 2. A simple decision tree
- A square indicates a decision node – the point where one decides which path to follow.
- A circle represents a chance node – the point where one may experience one of the two outcomes to the right of the node – the associated outcomes and probabilities are also shown.
- A triangle represents a terminal node – an end-point.
- Utility is 0 for death, 0.5 for neurological impairment and 1 for no impairment.

of not choosing home AED is 0.05 ([0 × 0.95] + [1 × 0.95 × 0.05] + [0.5 × 0.05 × 0.05]). Using this approach, the decision is in favor of the option that yields higher EV which in this case is buying AED for home use.

This approach can be extended to carry out cost utility analysis from a health systems perspective. For example, a decision maker may consider deployment of AEDs in the homes of all individuals > 70 years in Ontario. In this context, the cost of device is $2,500/AED, the cost of training is $200/person, the number of people > 70 years is 1.2 million, and the number of target homes is 600,000 (assuming each person > 70 years has a spouse of similar age). Using the difference of EVs to calculate the gain in utility, we estimated a gain in QALYs in the event of arrest to be 1.73 QALYs (15 life years × 0.11 unit gain in utility). The estimated annual number of cardiac arrests in this population is 3,260 – 50% of the 7,670 annual arrests occur in persons > 70 years, of which 85% occur in the home.[7] Thus, in this population annually 5,640 QALYs (3,260 arrests × 1.73 QALYs gained per arrest) would be gained. As the life span of the AED is 5 years, 28,199 QALYs would be cumulatively gained (assuming all cardiac arrests occurred in different individuals). The estimated total cost of deploying AEDs in homes is $1.6 billion ($2,700 × 600,000 homes), and thus, the cost per QALY is estimated to be $57,449; this is an undiscounted estimate – most health economists would discount costs incurred in the future as well as future QALYs at 3% to 5% annual rate. The decision is based on affordability and cost-effectiveness.

However, there is always uncertainty in the probability value assigned to a branch or utility value assigned to a health state. For example, a probability of 0.165 in published data will be known only to a certain level of precision. This uncertainty is addressed by carrying out sensitivity analyses using several plausible values for one or more components of the tree. For example, if the lower and upper bounds of the 95% confidence interval for the probability correspond to 0.10 and 0.23 respectively, sensitivity analyses will involve two recalculations of EVs, replacing the value of the probability once with 0.10 and once with 0.23. If the optimal decision is the same for each of these analyses, the choice of best decision does not depend on knowing the exact value of the probability. If the two analyses give rise to different optimal decisions, then the best decision requires more precise knowledge of that probability. An extension of this approach is to recalculate EVs many times for probabilities throughout their likely range. For example, values for the probability could be simulated from a normal distribution with mean 0.165 and standard deviation 0.0325, a so-called Monte Carlo simulation. For some of the simulated probabilities, the EV for one decision may be better and for others, the EV for the other decision may be better. If there is uncertainty for more than one component of the tree, this Monte Carlo simulation can be done simultaneously for all of them, and the results summarized by computing the means (and their 95% intervals) for each option. The rational decision would be the one that has the largest mean with the narrowest interval.

However, probabilities may change over time and thus standard decision tree models are not suited for modeling scenarios with long time horizons. For such applications, decision tree models are built as **Markov discrete-state** models.[25,26,27] A Markov Chain is a process that consists of a finite number of states and some known probabilities; the current status determines the probability of moving from one state to another in the next time cycle of the chain. The accompanying appendix provides a working example of a Markov process using matrix multiplication.

Markov models make it possible to model health outcomes over a long time horizon, using for example cumulative QALYs over a lifetime, while accounting for time-dependent changes in probabilities. Again, to better account for variation in the estimates of proportions and means, Monte Carlo simulations may be used upon a Markov model.

One disadvantage of decision-tree models is that they may overestimate the effects on quality of life measures when there are several co-existing conditions. Typically, in a decision tree, decrements in the utility value assigned to a given health state are the sum of individual decrements for components of that health state: if a final health state consisted of four co-morbidities each associated with a 0.1 decrease in utility when compared to full health, the utility assigned to that health state would be 0.6 (1.0 – 0.4); in practice, these deficits in health do not simply "add up". But it is difficult to know all the complex interactions among several variables that happen in the real world, which also influence outcomes; simplification is needed to allow modeling.

Bayesian Models

The essence of a Bayesian model is that it provides a formal way for updating current beliefs (the prior) when data are observed and arriving at a new set of beliefs (the posterior). The Bayesian paradigm is well established in the setting of diagnostic testing where pre-test probabilities are converted to post-test probabilities based on new data (observed outcomes of diagnostic tests). For example, Sharieff and Tevaarwerk found similar results for the positive predictive value (PPV) of alpha feto-protein to diagnose hepatocellular carcinoma (HCC) in Saudi Arabia – they calculated PPV equal to 66% from their own data and when they ‘plugged’ their prior belief into Bayes’ theorem to extrapolate evidence from a study in the US, they calculated PPV equal to 62%.[28]

Let’s extrapolate Sharieff and Tevaarwerk’s data to four settings: (a) institutional setting comprising of primary and tertiary care services, where the chance of having a positive (HCC) or negative (no HCC) outcome is equally likely; (b) similar setting; (c) tertiary care setting with high disease prevalence; and (d) primary care setting with low disease prevalence.

For modeling these beliefs about the distribution of disease prevalence in the four settings, let’s assume that the prior probability follows a beta distribution with two parameters a and b. Using different combinations of weights for a and b, we obtained four different prior distributions from the beta family[29,30] corresponding to each of the four settings: (a) beta (1,1)[31], the flat prior which gives equal prior weight to both positive and negative outcomes; (b) beta (½,½), Jeffreys’ prior[32] considered a good reference prior[33,34] which gives equal prior weight to both positive and negative outcomes, but more weight on the extreme low and high ends; (c) beta (10, ½), an optimistic prior that gives more prior weight to the positive outcome; (d) and beta (½, 10), a pessimistic prior that gives more prior weight to the negative outcome. A plot of the prior probability distribution from these four beta priors is shown in Figure 3. Applying these priors to the data, we obtained posterior distribution of the estimated PPV (Table 1) which is also shown in Figure 4.

With the use of Jeffreys’ prior, PPV varied from 0.38 to 0.87 with a median of 0.66 in a setting of mixed cases. If prior probability (prevalence) is very high and there are other conditions that favor high true positive rates, then PPV would vary from 0.61 to 0.93 with a median of 0.8, while on the contrary it would vary from 0.19 to 0.58 with a median of 0.37. Thus, starting with some belief or evidence about the probability that a patient has HCC (the prevalence in a population), we observe data (that a patient had a positive test) and update our belief that the patient has HCC.

Bayesian models extend this approach to estimation of such unknowns as intervention effects (relative risks, odds ratios), prevalence and parameters in regression models

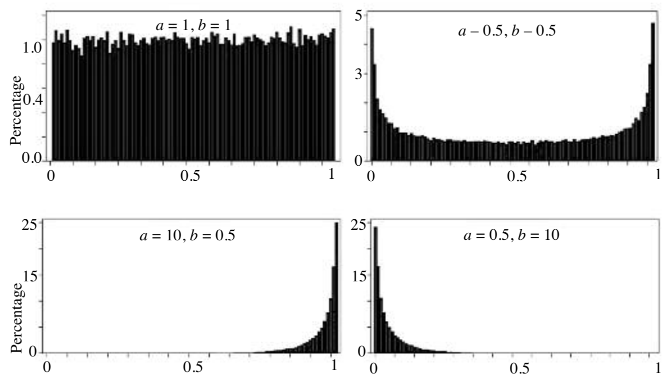

Figure 3. Samples from the four priors of beta distribution (a,b)
Flat (a = 1, b = 1) and Jeffreys’ (a = 0.5, b = 0.5) priors assign equal weight on both sides
Other two priors assign more weight on one of the two sides

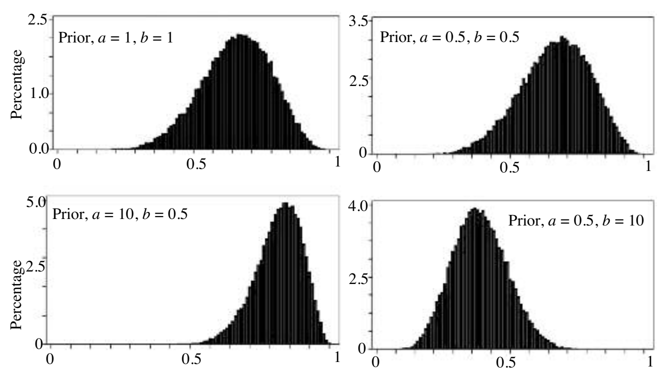

Figure 4. Samples from the posterior distributions
Note the posterior distribution does not shift much when switching from the flat prior to Jeffrey’s prior; however, it shifts from the left to the right when switching from the optimistic to the pessimistic prior.

using simulation techniques; observed outcomes of the interventions may be discrete or continuous.

Let’s consider the regression model ($y = \alpha + \beta x$) in the Bayesian paradigm. The model starts with an expression of what is believed about β for example, before data on x and y are observed. This expression of belief is formalized as a prior distribution. If there is prior ignorance, the prior distribution for β might be expressed as a normal distribution with mean zero and standard deviation 50, which says that there is a 95% probability that β lies in the wide range of -98 to +98. This represents a weak prior (also called ‘vague’ or ‘non-informative prior’). Strong prior belief that β is near zero could be incorporated by choosing a standard deviation of 0.5, which puts 95% probability in the range -0.98 to 0.98. Next, the information from the prior and from the pairs of observations x and y in the regression model are combined to compute the likely values of β. This produces a posterior

Table 1. Median and 95% credible regions (CR) of prevalence of HCC and positive predictive value of alpha feto-protein using four different beta priors

Parameter	Neutral setting (Flat prior)	Neutral setting (Jeffreys' prior)	Favorable setting (Optimistic prior)	Unfavorable setting (Pessimistic prior)
	Median (95% CR)	Median (95% CR)	Median (95% CR)	Median (95% CR)
Prevalence	0.2 (0.12, 0.33)	0.2 (0.11, 0.33)	0.32 (0.2, 0.45)	0.17 (0.09, 0.28)
PPV	0.65(0.38, 0.86)	0.66 (0.38, 0.87)	0.80 (0.61, 0.93)	0.37 (0.19, 0.58)

Table 2. Summary of models

Model	**Application**	**Relevance**	**Limitations**
Simple mathematical	Estimation	Easy to understand	Not useful for complex problems
Complex mathematical	Estimation/Prediction	Useful for complex problems	Not easy to understand
Regression	Explanation/Prediction	Easy to build	May not be clinically meaningful
Decision tree	Decision analysis	Weighs benefit versus harm	May overestimate effects
Bayesian	Multi-purpose	Portrays real life situations	Difficult to build

distribution. Since it is a distribution, the posterior allows calculations such as the probability that the true value of β is greater than zero, or a range which with 95% probability contains the true value of β. With the weak prior, most information in the posterior would come from the data on x and y. These results would be similar to results from a classical regression model. With the strong prior, relatively more information would be from the prior – the results may be different when data are scanty in relation to the strength of the prior.

To elaborate this further, let's return to the example from the section on simple model. Suppose before the OPALS study was done, we had no beliefs in the effectiveness (positive or negative) of the AED program. We could represent our belief as vague priors with normal distributions having means equal to 0 for α and β, and standard deviations equal to 1000, in a Bayesian model that combined our belief with the observed data (183 out of 4,690 patients survived before the AED program, and 85 out of 1641 patients survived after the AED program), to produce a posterior distribution. From the posterior distribution, we calculated that OR was 1.35 (95% CR = 1.03, 1.74) which corresponded to 90 (7, 179) lives saved. This in turn corresponded to mean cost of $2,282 per life saved ($1,295, $15,300), and $133 per QALY gained ($66, $1394). The probability that the AED program would be effective (lives saved > 0) was 98%.

Now suppose, in another setting (total population = 10 million), 10,000 cardiac arrests annually occur. In a sample of 100 cardiac arrest patients, 5 patients survived. The setting is similar to Ontario (in terms of patient demographics and EMS system) and thus, we strongly believe that after implementation of the AED program, a similar effect would be observed. That is the OR would equal to 1.33 ($\beta = 0.29$). However, after the implementation of the program, we observed that 6 out of 100 patients survived. Using the previous model, which replaced the vague prior for β with a strong prior (mean = 0.29, standard deviation = 0.5), and replaced data from OPALS study with data from the current setting, we could combine our belief (based on OPALS study) with data in hand to produce a posterior distribution. From the posterior distribution, we calculated that OR was 1.48 (0.4, 4.0) which corresponded to 107 (-469, 704) lives saved. This in turn corresponded to mean cost of $779 per life saved (-$11,240, $11,070), and $48 per QALY gained (-$863, $911). The probability that the AED program would be effective (lives saved > 0) was 64%.

The advantages of a Bayesian approach are: information from other studies can be borrowed; prediction about future trials can be made; and inference regarding non-standard functions of the parameters is quite simple.[35,36,37,38,39] However, some level of training is required to carry out the technical aspects of model fitting and checking given that the modeler already has a sound background in clinical epidemiology and bio-statistics.

In summary, Bayesian models have a wide range of applications. However, each model has its own objectives and associated advantages and disadvantages (Table 2). To maximize advantages and minimize disadvantages for a given application, one might consider using a hybrid approach, piecing together smaller, well-understood models that each most appropriately treats a particular component of the system being modeled. With the objective of replacing RCTs with a computer model, we used a hybrid approach and simulated the physiology of iron absorption and regulation based on observations from two RCTs that evaluated supplementation with micronutrients including iron in children in Ghana.[40] When baseline mean hemoglobin of Chinese children from a third RCT was fed into the model, the model accurately predicted end-of-study hemoglobin concentrations for that population. Thus, we recommend that for a specific question a variety of models should be considered and when a single type of model does not meet the needs, a hybrid approach be used.

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Author Biographies

Waseem Sharieff is a resident physician in the Radiation Oncology Program at McMaster University, Hamilton. He also holds an adjunct faculty appointment at the Department of Health Policy, Management and Evaluation, University of Toronto. His research interests lie in randomized clinical trials, Bayesian methods, computer simulations, and health economics.

George Tomlinson is an Associate Professor in the Department of Public Health Sciences, University of Toronto, where he teaches Biostatistics and Bayesian methods. He is also affiliated with the Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto. His research interests lie in Bayesian methods, meta-analysis, and longitudinal data analysis.