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INVESTMENT IN ANTIVIRAL DRUGS: A REAL OPTIONS APPROACH

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SUMMARY

Real options analysis is a promising approach to model investment under uncertainty. We employ this approach to value stockpiling of antiviral drugs as a precautionary measure against a possible influenza pandemic. Modifications of the real options approach to include risk attitude and deviations from expected utility are presented. We show that risk aversion counteracts the tendency to delay investment for this case of precautionary investment, which is in contrast to earlier applications of risk aversion to real options analysis. Moreover, we provide a numerical example using real world data and discuss the implications of real options analysis for health policy. Suggestions for further extensions of the model and a comparison with the expected value of information analysis are put forward. Copyright © 2009 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Uncertainty plays a crucial role for many investment decisions, and investments in health care are no exception. The traditional ways to account for uncertainty in health economics are by means of (probabilistic) sensitivity analyses and confidence intervals, using cost-effectiveness acceptability curves to present the outcomes (Briggs and Gray, 1999; Fenwick *et al.*, 2006). A problem with this kind of analyses, however, is that investments are considered as 'now-or-never' decisions, whereas in reality deferral is one of the most frequent decisions taken, to enable the decision maker to assemble more information (Claxton, 1999). In investment theory at large, real options theory has gained interest as a tool to analyze investment decisions (e.g. Dixit and Pindyck, 1994; Trigeorgis, 1996). The real options approach stems from the financial literature and was proposed as a more realistic alternative to neoclassical investment theory. In essence, the latter states that an investment should be undertaken when expected discounted benefits exceed a critical value: the expected discounted costs of some project. Again, decisions are considered as having a 'now-or-never' character. In contrast, real options theory explicitly recognizes the option to postpone an investment. Valuing this option implies including the

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related opportunity costs of an investment, so that the critical value of expected discounted benefits of a project is higher using real options analysis than using neoclassical analysis.

A real option framework is most suitable when three key characteristics are present. These are irreversibility of the investment, uncertainty about the reward and the ability to defer the investment. *Irreversibility* means that once an investment has been made, it is not possible to recover the investment or at least not without large cost. *Uncertainty* means that the net benefits of an investment project follow a stochastic process (over time). Finally, the investment can be *deferred* in the sense that the investor may delay the investment for some time in order to await new information or better values of the stochastic benefits.

These characteristics are present in many health care decisions, so that it is worthwhile investigating the role of the real options framework in understanding health care decision making. Still, although applications of real options theory have been intensively investigated in several economic disciplines,[1] examples in the health economics literature are scarce. In fact, we found only three studies applying real options analysis in a medical context. Palmer and Smith (2000) showed how the adoption of an unspecified new health technology may be modeled as an options problem and explored possibly fruitful areas of application within health economics. Driffield and Smith (2007) showed by means of a numerical example how real options analysis can be used to inform decisions about the treatment of individual patients with abdominal aortic aneurysm. Finally, Eckermann and Willan (2008) extended the Expected Value of Perfect Information (EVPI) approach (Claxton, 1999) to the case of partial irreversibility. That is, the case where reversion is costly but not prohibitively so, creating the option of trialing the effectiveness of some project even when one has already invested in that project.

The current paper extends this small literature by looking at an important type of decision in public health: precautionary investment to prevent large public health problems, for instance, an influenza pandemic. Specifically, we consider decisions by a government on stockpiling antiviral drugs to prepare for an influenza pandemic. This investment problem is suitable for the real options approach because the aforementioned three key characteristics are present. Irreversibility is a realistic assumption, since antiviral drugs cannot easily be resold in the market. Uncertainty is present in many aspects of the problem, especially the unknown probability of outbreak and the uncertain benefits of the drug after an outbreak, about which more information becomes available over time. Finally, the investment can be deferred in the sense that the government may delay the investment for some time in order to await new information about, for example, the probability of outbreak. Delaying investment, however, of course bears the risk of an outbreak during the deferral period. Furthermore, we analyze modifications of the real options approach, including risk attitude and prospect theory, since risk plays a crucial role for decision makers facing the threat of a pandemic.

The threat of a new influenza pandemic has become evident since the World Health Organization raised the pandemic alert due to the spread of the new influenza A/H1N1 in April 2009. Moreover, the worldwide spread of avian influenza A/H5N1, and the occasional, often fatal, cross-species transmission to humans are serious candidates for another human influenza pandemic. During the last century there have been three pandemics, of which the 1918–1919 'Spanish flu' (A/H1N1) was the most severe causing at least 40–50 million deaths worldwide (Johnson and Mueller, 2002; Nguyen-Van-Tam and Hampson, 2003). The 1957–1958 'Asian flu' (A/H2N2) and the 1968–1969 'Hong Kong flu' (A/H3N2) were relatively mild with probably less than 1 million deaths (Dunn, 1958; Nguyen-Van-Tam and Hampson, 2003). Pandemic contingency planning is key to mounting an adequate response to the morbidity, mortality and the corresponding demand on health care, if a new pandemic would occur (Webby and Webster, 2003; WHO, 2005). Lacking an effective vaccine, therapeutic treatment with antiviral drugs is

[1]For example, Ekern (1988) for petroleum projects, Pennings and Lint (1997) for research and development, Kelly (1998) for a mine property, Bollen (1999) for the dependence of capacity changes on product life cycles, and Fenichel *et al.* (2008) for precautionary fisheries management.

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a realistic alternative (Health Council of the Netherlands, 2005). To be able to provide the population with these drugs on time, stockpiling is necessary, and currently there is much attention on investment decisions in stockpiling antiviral drugs (Balicer *et al.*, 2005; Lee *et al.*, 2006; Siddiqui and Edmunds, 2008).

To sum up, the present paper is the first to apply real options theory in a public health perspective, by investigating the decision of a country to invest in antiviral drugs for emergency treatment in case of an influenza pandemic. We derive the theoretical solution to this problem in Section 2 and subsequently present the application to antiviral drugs in Section 3, comparing our solution to the solution under neoclassical investment theory. In Section 4 we extend the example to include risk aversion and show that risk aversion and the option to defer investment have opposing effects on the optimal timing of investment. Section 5 analyzes the incorporation of prospect theory. Finally, Section 6 provides a discussion and Section 7 concludes.

2. MODEL

Suppose a country is contemplating whether to invest in antiviral drugs. We assume, in accordance with most applications of real options analysis, that the decision maker (i.e. the government) has the objective to maximize the expected net present value of benefits. This is equivalent to *risk neutrality* with respect to monetary outcomes, meaning that an individual is indifferent between choosing a gamble and a certain outcome with the same expected payoff.

The benefits of having sufficient antiviral drugs are taken to be the reduced losses in health and productivity when a pandemic occurs: H. We express these in monetary terms. We assume a pandemic can occur in each quarter of a year. In addition, the decision maker uses an evaluation period, depending on the shelf life of the antiviral drugs, as is explained further in Section 3. Since we do not know beforehand in which quarter, if ever, a pandemic outbreak will take place, we multiply H by the discount factor (D) corresponding to half the evaluation period. Such a discount factor corresponds to our assumption of a uniform distribution with regard to the probability of when an outbreak would occur. As a result, we obtain the discounted benefits in case of outbreak, $R(O) = D*H$. In case of no outbreak (N), no benefits are obtained, so $R(N) = 0$. It is uncertain whether a pandemic will occur, and we have to model this uncertainty. The occurrence of a pandemic outbreak in a particular evaluation period (consisting of a predetermined number of quarters) is assumed to be binomially distributed, with hazard rate p (which depends on the quarterly probability (q) of outbreak). Hence:

- No Outbreak (N) with hazard rate $1 - p$ in any evaluation period (1)
- Outbreak (O) with hazard rate p in any evaluation period

The discounted expected benefits (i.e. the avoided health costs) over the considered time horizon are given by $\varphi = E(R) = p*D*H$. Furthermore, uncertainty exists about the hazard rate and the benefits in case of outbreak. These sources of uncertainty cause the option to delay to be valuable, which will be shown below. In the remainder, we focus on uncertainty concerning the hazard rate, because adding uncertainty around the benefits will not change the qualitative nature of the results. The value of the hazard rate is described by a stochastic variable that is assumed to follow a Brownian motion: $dp = \sigma p dz$, with σ the standard deviation and dz a Wiener process, that is, a continuous-time stochastic process, related to the random walk process. It depends on scientific progress concerning the elicitation of the true value of the hazard rate (Gollier and Treich, 2003). The expected benefits therefore also follow a Brownian motion: $d\varphi = \sigma\varphi dz$.

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The price of the drugs (P) and the quantity of antiviral drugs to be bought (Q), which depends on the size of the population, are taken as exogenous variables. Therefore, total purchase costs are given by $P*Q$. Finally, there are stockpiling costs ($S(Q)$) of the drugs, so that total costs amount to $C = P*Q+S(Q)$.

According to the option value approach, it is optimal for the government to choose the time of investment so as to maximize the value of the investment opportunity $F(\varphi)$:

$$F(\varphi) = \max E[(\varphi_t - C)e^{-rt}] \quad \text{subject to } d\varphi = \sigma\varphi dz \tag{2}$$

where E is the expectation, t is the unknown future time point at which the investment is made, and r is the risk-free interest rate. For comparison, according to standard cost-benefit analysis, it is optimal for the government to choose between investment at time t or no investment in order to maximize the expected net present value: $\max E[(\varphi_t - C)e^{-rt}]$ with $\varphi_t = pDH$ having a fixed rather than a stochastic value as defined in (2). The critical value of φ, φ^*, that is, the expected discounted benefit above which it is optimal to invest, equals C.

The critical value of φ using the option value approach may be determined using Bellman's principle of optimality. This principle breaks a multi-period planning problem into simpler steps (subproblems) at different points in time. In terms of a decision tree model, each node may be considered a subproblem. The optimality principle then starts from the idea that an optimal solution to the entire problem cannot contain suboptimal solutions to any of its subproblems. If a suboptimal solution to some subproblem was included, the solution could be improved by improving the solution to this subproblem. In other words, an optimal policy has the property that, whatever the initial action, the remaining actions are optimal with respect to the subproblem starting at the state that result from the initial action (Bertsekas, 1976). Or again in terms of decision trees: for each node, the strategy from this node onwards must be optimal. For problems in discrete time, backward reasoning may then be used to derive an optimal policy. For problems in continuous time, like the one at hand, the principle may be used to derive the so-called Bellman equation that characterizes an optimal solution, using subproblems over very small periods of time, dt. The Bellman equation is given by:

$$rFdt = E(dF) \tag{3}$$

As shown in the Appendix, we can subsequently derive the following results:

$$F(\varphi) = B_1(\varphi)^{\alpha_1} \tag{4}$$

$$\varphi^* = \frac{\alpha_1}{(\alpha_1 - 1)} C \tag{5}$$

with

$$B_1 = \frac{(\alpha_1 - 1)^{\alpha_1 - 1}}{\alpha_1^{\alpha_1} C^{\alpha_1 - 1}} \tag{6}$$

and

$$\alpha_1 = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{2r}{\sigma^2}} > 1 \tag{7}$$

From these formulas it can be seen that it is optimal to invest only when the costs of investment *plus an additional amount* are lower than the expected revenues (i.e. the product of the hazard rate and the averted costs in case of a pandemic outbreak). Hence, compared to standard cost-benefit analysis, the critical value is larger. This additional amount reflects the option value of delaying the investment in antiviral drugs and being able to profit from new information about the hazard rate. The higher is the value of α_1, the lower the required wedge between expected benefits and costs (Equation (5)) and the lower is the option value.

The parameter α_1 is decreasing in σ indicating that greater outbreak uncertainty leads to a higher option value, a higher critical value, φ^*, and hence a higher return on investment that is needed to make

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the investment profitable. α_I increases in r, indicating that heavier discounting of future outcomes leads to a lower return on investment that is needed to make the investment profitable.

The option value of delaying the investment in stockpiling therefore essentially grows with increases in epidemiological uncertainty and reductions in the interest rate, as we will see more clearly in the next section.

3. NUMERICAL EXAMPLE/APPLICATION

We illustrate how the model of Section 2 can be applied in a real world context by using available data for the Netherlands on the potential costs of an influenza pandemic (Lugnér *et al.*, 2009). We assume a conventional annual discount rate r of 4%, or $1.04^{1/4}-1 = 0.009853 = 0.9853\%$ per quarter (CvZ, 2006).

3.1. Costs

At present, the most popular medicine for dealing with influenza is Tamiflu. We estimate price per defined daily dose (DDD) by dividing total costs by quantity used, which is available in the SFK database (www.SFK.nl). We take the most recently available price per DDD of Tamiflu as the current purchase costs per unit (P). This is the average price of the fourth quarter of 2007, which was $P = 4.12$ Euros per DDD.

In addition to purchase costs, several other costs are associated with an investment in antiviral drugs. First, when there is no pandemic outbreak, the drugs have to be stored, causing stockpiling costs. Second, in case of an outbreak, a patient can only collect a prescription at the pharmacy after a telephone consultation with the general practitioner, and, hence, prescription costs are generated (Lugnér *et al.*, 2009). We treat the latter as negative benefits, however, because they only occur when there is a pandemic, whereas the purchase and stockpiling costs occur regardless of an outbreak. Tamiflu tablets have a shelf life of approximately five years. Thereafter, the drug ceases to be effective and has to be destroyed and the decision maker has to make a new decision (buying a new stock or waiting). During a five-year period, we assume that the probability of two or more outbreaks is small enough to ignore.[2] Thus, a single purchase of antiviral drugs will be sufficient for this period. Hence, the decision maker views a time horizon of at most five years (i.e. the evaluation period) after the moment of investment, and shorter in case a pandemic actually occurs.

A deterministic compartmental dynamic model was constructed to evaluate the effect of antiviral therapy (Lugnér *et al.*, 2009; Mylius *et al.*, 2008). The whole population was assumed to be susceptible to a new pandemic virus. Individuals started out being susceptible, and upon infection they progressed through a succession of stages: being infected but not infectious (latent); being infected and infectious; recovering; and finally, immune (removed). The model included key epidemiological parameters such as contact rates among and within age groups, the length of infectious period, and the probability of transmission of the virus during a contact. The use of antiviral drugs affects the recovery rate and infectivity of a person with symptomatic influenza, if treatment starts within 48 h of onset of symptoms. In the calculations it was assumed that the pandemic virus behaves as a seasonal influenza virus in the sense that risk of symptoms, risk of illness, risk of death upon infection are similar to the risk observed for seasonal influenza. The Dutch population consists of approximately 16.4 million people. The dynamic model predicts that 10.4 million would be infected with the influenza virus if no intervention was offered. Treating 80% of the individuals who would have had influenza-like illness with antiviral drugs would reduce the transmission among the population, and as a result, 8.6 million people would be

[2]For a yearly probability of 0.03, changes of no outbreak, one outbreak and more than one outbreak are 0.86, 0.13 and 0.01, respectively.

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infected. Of these, 60% would have had influenza-like illness (5.2 million) and 4.1 million would use antiviral drugs.

We assume further that each patient needs 10 DDD's of Tamiflu, so that $Q = 41$ million doses of Tamiflu have to be bought, costing in total about €169 million. Stockpiling costs for this amount are €50 thousand per year (Lugnér and Postma, 2009), resulting in a present value of €220 thousand for an annual discount rate of 4% and a five year horizon. Total costs (C) then amount to almost €170 million.

3.2. Benefits

We use the estimates of the benefits of Lugnér *et al.* (2009), which we convert from 2005 prices to 2007 prices using harmonized consumer price indices (CBS, 2008). Three different effects are distinguished. One is discounted life years saved due to the use of antiviral drugs. These are estimated to be around 38 900 (Lugnér *et al.*, 2009). Taking a conservative estimate of the willingness to pay per life year saved of €20 000 (Casparie *et al.*, 1998), this translates into savings in life years in case of a pandemic with a value of about €778 million.

In addition, considerable savings in production losses due to fewer illnesses and fewer deaths are expected. These savings are estimated by means of the friction cost method (Koopmanschap *et al.*, 1995) and the assumptions of Oostenbrink *et al.* (2004) and Postma *et al.* (2005), at about €1.8 billion.

The third kind of effects is costs saved with antiviral drugs, because of lower health care consumption caused by influenza complications. Reductions in health care consumption are obtained in several areas: fewer general practitioner (GP) visits due to fewer complications, fewer antibiotics, less consumption of over-the-counter drugs, and less hospitalization (Lugnér *et al.*, 2009). As mentioned before, negative benefits also exist: the GP consultation and prescription costs for antiviral drugs.

Total net savings in case of a pandemic and presence of antiviral drugs are then obtained by subtracting the costs from gross savings, yielding an amount of €2.638 billion. Using a 4% yearly discount rate, and taking the discount factor corresponding to the midpoint of the five year period, that is, 10 quarters, we obtain an estimate of D of 0.907, and, hence, the present value of net savings is equal to $D{*}H = €2.392$ billion. Table I lists the details for these estimates.

3.3. Hazard rate

There is no clear consensus in the literature concerning the probability of outbreak. Therefore, like Balicer *et al.* (2005), we consider the number of pandemic outbreaks with a high impact during the last century.[3] In this period, three of such outbreaks have taken place, resulting in a probability of 0.75% ($q = 0.0075$) per quarter. The probability of at least one outbreak within 5 years is then equal to 14%, which we treat as the probability of one outbreak for convenience (i.e. the hazard rate $p = 0.14$). In this case, the expected discounted net savings are $\varphi = pDH = 0.14{*}€2.392$ billion = €335 million. Further, we assume this hazard rate to evolve according to a Brownian motion without drift (i.e. a Brownian motion process without an upward or downward trend), and a volatility of 0.05 per 5-year period: $\mathrm{d}p = 0.05\,p\mathrm{d}z$.

3.4. Optimal timing of investment

The estimate of the variance and the assumed value of the discount rate allow us to estimate Equation (7), giving a value for α_1 of 3.35. Applying Equation (5) then results in a wedge between benefits and costs of about 42.5%, indicating a sizeable influence of the inclusion of the option value of waiting. The critical value φ^* (see Equation (5)) is equal to €243 million, again indicating that the option value of deferral implies a considerable wedge between expected costs ($C = €170$ million) and the required value of expected benefits. The expected benefits ($\varphi = €335$ million) are above the critical value in this example;

[3]That is, excluding the recent outbreak of the new influenza A/H1N1.

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Table I. Estimated savings of antiviral drugs in case of an influenza pandemic (Lugnér *et al.* 2009)

Area	Savings in millions of Euros
Value of life years saved	778
GP-consultations for influenza	16.8
Antibiotics (for influenza)	3.1
OTC drugs	5.4
Hospitalizations	43.1
Production losses	1862
Gross savings	2708
GP consultations for antiviral drugs	44.3 −/−
Pharmacy costs for antiviral drugs	26.0 −/−
Net savings (H)	2638

Price level 2007.

Table II. Parameter estimates

α_1	3.35
σ	0.05
r	0.0098
B_1 (Equation (A16))	5.7041E-21
φ^*(Equation (A13))	€243 mln
$S(Q)$	€0.22 mln
C	€170 mln
φ	€335 mln
p	0.14
H	€2638 mln
D	0.907
Q	41 mln

however, so it is still optimal to invest immediately. An overview of the parameter estimates is given in Table II.

Using the estimated benefits of €335 million, and the parameter estimates above, we can also calculate at what value for p a value for the critical value φ^* of €335 million or over will be reached. The critical hazard rate equals 10.1% per 5-year period, that is, 0.533% per quarter. Waiting is recommended when the hazard rate is lower than this critical value.

In comparison, the critical hazard rate under net present value analysis is only 7.1% per 5-year period (0.368% per quarter). Hence, only for very low probabilities of an outbreak the investment will be cancelled. Real options analysis prescribes a more precautionary investment strategy in order to profit from the potentially valuable option of waiting for more information.

4. ANALYSIS UNDER RISK AVERSION

Empirical evidence suggests that many individuals are not risk neutral but instead *risk averse* (Abdellaoui, 2000; Holt and Laury, 2002), which means that individuals are reluctant to choose a gamble rather than a certain outcome with the same, but possibly lower, expected payoff. Van den Goorbergh *et al.* (2003) and Hugonnier and Morellec (2007) have therefore extended real options theory to take account of risk aversion. They found that risk aversion reinforced the tendency to postpone the decision implied by valuing the option of deferral. Because investment in antiviral drugs concerns precluding losses instead of seeking gains, however, this finding does not hold in our situation.

Suppose that instead of maximizing net present benefits, the decision maker is risk averse and maximizes expected utility. Expected utility theory considers utility over wealth levels ($U = U(W)$). The

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decision maker will invest whenever the expected utility of wealth after investing is higher than the expected utility of wealth when not investing. Let $R(O) = \eta = DH$, and let C and p be as defined above. In addition, let Z be the loss caused by a pandemic and X the present wealth level. The expected utility from investing will then be given by $pU(X-Z+\eta_t-C)+(1-p)U(X-C)$. The expected utility from not investing is $pU(X-Z)+(1-p)U(X)$. According to traditional cost-utility analysis, it is therefore optimal to invest whenever:

$$pU(X - Z + \eta_t - C) + (1 - p)U(X - C) > pU(X - Z) + (1 - p)U(X) \tag{8}$$

Because we can set $U(0) = 0$ and normalize X so that $X = Z$, (8) simplifies to:

$$pU(\eta_t - C) + (1 - p)U(Z - C) > (1 - p)U(Z) \tag{9}$$

Rearranging gives:

$$p[U(\eta_t - C) + U(Z) - U(Z - C)] > U(Z) - U(Z - C) \tag{10}$$

Then we define $\chi_t = p(U(\eta_t - C) + U(Z) - U(Z - C))$ and $\delta = U(Z) - U(Z - C)$, so that the similarity with the risk neutral case becomes clear. Accounting for the option value of delay now implies an optimization problem given by:

$$F(\chi) = \max E[(\chi_t - \delta)\mathrm{e}^{-rt}] \quad \text{subject to } \mathrm{d}\chi = \sigma\chi \mathrm{d}z \tag{11}$$

The remainder of the analysis can then be finished by replacing φ and C in the Appendix by χ and δ, respectively. We end up with:

$$\chi^* = \frac{\alpha_1}{\alpha_1 - 1}\delta \tag{12}$$

After replacing χ and δ by their full expressions, this becomes:

$$p(U(\eta^* - C) + U(Z) - U(Z - C)) = \frac{\alpha_1}{(\alpha_1 - 1)}(U(Z) - U(Z - C)) \tag{13}$$

which after solving for η^* gives:

$$\eta^* = U^{-1}\left\{\left(\frac{\alpha_1}{p(\alpha_1 - 1)} - 1\right)(U(Z) - U(Z - C))\right\} + C \tag{14}$$

In addition, we have:

$$B_1 = \frac{(\alpha_1 - 1)^{\alpha_1 - 1}}{\alpha_1^{\alpha_1}\delta^{\alpha_1 - 1}} = \frac{(\alpha_1 - 1)^{\alpha_1 - 1}}{\alpha_1^{\alpha_1}(U(Z) - U(Z - C))^{\alpha_1 - 1}} \tag{15}$$

We now have η^* and B_1 expressed in terms of α_1, the parameters p, C, and Z, given some utility function $U(W)$.

Investigating the consequences of this extension is interesting. In particular, it is of interest how the optimal decision rule changes when we assume a concave instead of a linear utility function (i.e. a utility function corresponding to risk aversion over wealth instead of one corresponding to risk neutrality). The power utility function $U = W^\gamma$ is often used in economic applications (Wakker, 2008). The case of $\gamma < 1$ corresponds to risk aversion, whereas $\gamma > 1$ implies risk proneness and $\gamma = 1$ means risk neutrality. For a power utility function, the derivative of η^* with respect to γ in (14) is given by:

$$\frac{\partial \eta^*}{\partial \gamma} = \left(\left(\frac{a_1}{p(\alpha_1 - 1)} - 1\right)(Z^\gamma - (Z - C)^\gamma)\right)^{1/\gamma} \times \left(-\frac{1}{\gamma^2}\ln\left(\left(\frac{a_1}{p(\alpha_1 - 1)} - 1\right)(Z^\gamma - (Z - C)^\gamma)\right) + \frac{(Z^\gamma \ln Z - (Z - C)^\gamma \ln(Z - C))}{\gamma(Z^\gamma - (Z - C)^\gamma)}\right) \tag{16}$$

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Since $a_1/p(\alpha_1 - 1) > 1$ and $Z > C$ in virtually all real-world examples, this derivative is positive whenever:

$$(Z^\gamma - (Z-C)^\gamma)\ln\left(\left(\frac{\alpha_1}{p(\alpha_1-1)} - 1\right)(Z^\gamma - (Z-C)^\gamma)\right) < \gamma(Z^\gamma \ln Z - (Z-C)^\gamma \ln(Z-C)) \qquad (17)$$

This holds true for $\gamma > 0$ for reasonable values of Z. A higher degree of risk aversion, therefore, lowers the critical value of η and leads a decision maker to invest sooner than if he would be risk neutral. A similar reasoning holds for risk proneness and results in an incentive to wait longer before investing.

If we repeat our numerical example with risk neutrality replaced by risk aversion, where risk aversion is captured by the power utility function $U = W^{0.9}$, we find that η^* is lowered substantially (from about €1.7 billion to about €1.5 billion for a value of Z of €3 billion). In our example, while the critical value changes considerably, this does not matter much, since the optimal decision to invest immediately is not altered.

5. EXTENSION TO PROSPECT THEORY

The above analysis used an expected utility framework. Although this framework can be very useful for prescriptive purposes, there is evidence that expected utility lacks descriptive validity (Starmer, 2000). Therefore, we extend our analysis to investigate how conclusions change when we incorporate prospect theory into the analysis. Prospect theory (Kahneman and Tversky, 1979; Tversky and Kahneman, 1992) has become the most important alternative to expected utility.

The above model can readily be extended to include behavior according to prospect theory. Preferences depend on a reference point in prospect theory and outcomes better than the reference point are considered as gains, whereas worse outcomes are considered as losses. Two major effects are included in prospect theory. First, decision makers are loss averse, meaning that losses loom larger than gains. This is modeled by including a loss aversion parameter with a value higher than 1, which is multiplied by the value of the loss. Second, decision makers do not evaluate probabilities linearly but transform probabilities. That is, probabilities are given a decision weight, which is not necessarily equal to the probability itself. In particular, small probabilities tend to receive more weight and large probabilities less weight.

A conventional reference point in this example seems to be the case of no pandemic outbreak. The outbreak of an influenza pandemic is then considered a loss, and this loss gets additional weight. It turns out that loss aversion is not relevant in our example, however, since losses occur in any scenario so the loss aversion parameter drops out of the equation (see the Appendix for a proof). We assume the following well-known probability weighting function (Tversky and Kahneman, 1992):

$$w^-(p) = \frac{p^\gamma}{(p^\gamma + (1-p)^\gamma)^{1/\gamma}} \qquad (18)$$

with $w^-(p)$ the weight given to the probability of outbreak.[4] γ is a behavioral parameter describing the nonlinear transformation of probabilities. It was estimated to be 0.69 (Tversky and Kahneman, 1992). This corresponds to the usual case where small probabilities are given more weight and large probabilities are given less weight.

The remainder of the analysis is similar to that of Section 2, with the only modification that the hazard rate p should be replaced by the decision weight $w^-(p)$ given to that probability. In our example, the probability is quite small so we obtain a decision weight that is higher than the probability itself

[4]We only need the probability weighting function for losses here because there are no gains present in this example.

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($w^{-}(0.14) = 0.2080$). That is, the government is pessimistic in this case, overestimating the probability of a pandemic outbreak. The subjective expected benefits now are €514 million, considerably higher than the objective expected benefits of €335 million. Probability weighting therefore induces the policy maker to invest in antiviral drugs sooner in our numerical example.

6. DISCUSSION

Most of the literature on option values in health care is purely theoretical (Eckermann and Willan, 2008; Palmer and Smith, 2000). The only application considered in the literature (Driffield and Smith, 2007) concerned decisions for individuals. We have now shown an application of the theory in public health.

In agreement with the standard real options problem, the option value causes the critical value of benefits to increase in our example, making waiting more attractive. On the other hand, the introduction of risk aversion diminishes this critical value in our problem. This is in contrast with the findings of van den Goorbergh *et al.* (2003) and Hugonnier and Morellec (2007), who show that, in the common real option investment problem, risk aversion will reinforce the option effect and increase the critical value of benefits further, since the variability in the expected benefits can cause more harm under concave utility functions. The finding of risk aversion causing a countervailing force against the incentive to wait due to the option value may be important in other cases.

An explanation for our opposite findings is that we investigated the opposite of standard investment problems. In studying the preparation for a possible influenza pandemic, there is no benefit (in monetary terms) to be gained for the decision maker. The purpose of the decision maker is to somehow manage the losses. Under expected utility and risk neutrality, this does not matter since the optimal decision is not changed. When risk aversion is taken into account, the optimization problem does change though. All possible outcomes in our example are losses. The decision maker wants to minimize the utility lost by these outcomes. The government faces a lottery, with a probability p of a large loss (in case of an outbreak) and a probability $1-p$ of no loss (i.e. no outbreak and a preservation of the status quo). By investing, the government can reduce the loss during the outbreak, although the amount of loss reduction is uncertain. The uncertainty causes the option of delaying the investment to be valuable.

Investigating the impact of using the framework of prospect theory shows that the expected benefits will be considerably higher than in an expected utility framework. In other words, we find that under prospect theory, investment in antiviral drugs to reduce the losses of a pandemic is considered beneficial at lower critical values of the benefits than under expected utility. Prospect theory seems to be a more realistic framework, since governments frequently do not behave according to expected utility, by giving too much weight to rare events, due to, for instance, pressure by interest groups. It should be kept in mind, however, that this is only a descriptive analysis and we do not attempt to suggest the use of prospect theory for prescriptive purposes.

The above analysis can also be conducted when both benefits and costs are stochastic. The only thing we need is an estimate of the variance of the costs. Modeling both stochastic costs and benefits will be more complex, though, as pointed out by Dixit and Pindyck (1994, Section 6.5).

It is important to notice the large percentage of benefits that is generated by productivity gains. These gains cover more than half of total benefits, and make the difference between investing immediately and postponing the investment. That is, taking a more narrow health care perspective in which productivity gains are neglected changes the conclusion in our example. On the other hand, we have, by using the friction cost method, provided a rather cautious estimate of production gains. One could also take a broader perspective than we did, by for example using the human capital method. In that case production gains would be even higher than estimated in this study. Indeed, infectious disease emergencies may violate the assumptions of partial equilibrium, and the presence of a health threat can have an impact far beyond the direct resolution in productivity from sick patients (Beutels *et al.*, 2008).

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Results may also differ depending on the population considered, for example, if only key workers are included in the target population for receiving antiviral drugs.

The standard problems where the real options approach is being used consider benefits and costs measured in monetary terms. An important difference with the health domain is that health benefits are usually not directly measured in terms of money. An interesting extension of this theory would therefore be to investigate how things change when effects are measured in other terms. In the health economics area, in particular, effects are usually valued in quality adjusted life years without explicitly converting these to monetary values.

The analogy of real options analysis with EVPI analysis is also worth mentioning. EVPI analysis was discussed by Claxton (1999) as an alternative to the usual approach to model uncertainty in health economic evaluations. Both types of analyses share the premise that there is an extra option in addition to investing and not investing. Although the option of waiting has a value in real options analysis, the option of assembling additional information has a value in EVPI analysis. In EVPI analysis, net benefits are stochastic and the expected costs of uncertainty consist of the probability that a decision based on mean net benefit is wrong multiplied by the size of the opportunity loss if the wrong decision is made. By waiting, however, we can lower this probability, in the same way as acquiring more information does in EVPI. The option value is the maximum value that can be placed on additional waiting for new information and the costs are the opportunity costs of foregone benefits, whereas in EVPI analysis, these are the costs of additional sampling. Hence, the two approaches are complementary and do not replace each other. The one considers the value of waiting for more information, while the other considers the value of explicitly investing in more knowledge.

We have assumed that the price and quantity of the antiviral drugs are exogenous. The price of the drugs may depend on the quantity purchased, for example, if a quantum discount can be arranged. This does not however change the qualitative nature of the problem, in which the emphasis lies on the benefits. The quantity needed seems to depend to a great extent on epidemiological and demographic characteristics, so the assumption of exogenous quantity seems to be appropriate.

7. CONCLUSION

This paper contributes to the real options literature by providing an example in the public health domain where real options analysis seems to be a useful new tool. We showed how the problem of investment in the case of antiviral drugs can be modeled in a real options setting, and we applied this model using real cost data and estimates of benefits. We have confirmed the findings of Driffield and Smith (2007) that the option value can be large and lead to important policy changes in health care.

Moreover, we have extended the analysis to take into account risk aversion and probability weighting. Both are relevant issues in the case of decision making on catastrophic occurrences with a small probability, like an influenza pandemic. It was shown that risk aversion and overweighting of small probabilities have a tendency to neutralize the delaying effect of the possession of the option on investment. The reason that these effects are of opposing signs was that the main purpose of the decision problem was control of losses, rather than maximization of gains. We recommend a more thorough development of option pricing techniques in health economics and the investigation into more refined parameter estimates.

The empirical results in this paper indicate strong evidence favoring investment in antiviral drugs in the Netherlands. The inclusion of the option value of waiting does not change this conclusion. Therefore, our analysis supports the decision by the Dutch government in the past to invest in a large stock of Tamiflu, part of which is being used at the moment to treat patients infected by the new influenza A/H1N1. When this stock has been run down or destroyed, a new investment decision has to be made. This decision should take into account the option value of waiting for more information,

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because the present study indicates that this option can be of high value. In our example the investment is so beneficial that even taking loss of option value into account, it would be optimal to invest in antiviral drugs. However, taking a narrower health care perspective and excluding production losses, the option value makes the difference between investing immediately and waiting.

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APPENDIX A: PROOFS

A.1. Derivation of the results of Section 2

We expand dF using Ito's lemma:

$$dF = F'(\varphi)d\varphi + \tfrac{1}{2}F''(\varphi)(d\varphi)^2 \tag{A1}$$

Substitute $d\varphi = \sigma\varphi dz$ into (A1) and noting that $E(dz) = 0$, we obtain:

$$E[dF] = \tfrac{1}{2}F''(\varphi)\sigma^2\varphi^2 dt \tag{A2}$$

The Bellman equation then becomes:

$$\tfrac{1}{2}F''(\varphi)\sigma^2\varphi^2 - rF = 0 \tag{A3}$$

Equation (A3) is linear in F and its derivatives, so that its general solution can be expressed as a linear combination of any two independent solutions (Dixit and Pindyck, 1994). The general solution can therefore be written as $F(\varphi) = B_1\varphi^{\alpha_1} + B_2\varphi^{\alpha_2}$, with B_1 and B_2 constants to be determined.

In addition, the underneath boundary conditions must be satisfied by $F(\varphi)$ in the optimum.

$$F(0) = 0 \tag{A4}$$

$$F(\varphi^*) = \varphi^* - C \tag{A5}$$

$$F'(\varphi^*) = 1 \tag{A6}$$

Hence, we have to solve for (A3) subject to (A4), (A5), and (A6).

Trying the function $F(\varphi) = B_1(\varphi)^{\alpha_1} + B_2(\varphi)^{\alpha_2}$ we see by substitution that it satisfies (A3) as long as α is a root of the quadratic equation:

$$\tfrac{1}{2}\sigma^2\alpha(\alpha - 1) - r = 0 \tag{A7}$$

This equation has two solutions:

$$\alpha_1 = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{2r}{\sigma^2}} \tag{A8}$$

and

$$\alpha_2 = \frac{1}{2} - \sqrt{\frac{1}{4} + \frac{2r}{\sigma^2}} \tag{A9}$$

with $\alpha_1 > 1$ and $\alpha_2 < 0$. Since $\alpha_2 < 0$ and (A4) has to hold, $B_2 = 0$. Hence, we are only interested in α_1, which is a known constant whose value depends on the parameters σ and r (Dixit and Pindyck, 1994).

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To solve for the remaining unknowns B_1 and φ^*, the critical value of the expected benefits at which it is optimal to invest, we use the other boundary conditions (A5) and (A6). Substituting the general form into Equation (A5) yields:

$$\varphi * (1 - B_1(\varphi*)^{(\alpha_1-1)}) = C \tag{A10}$$

Subsequently, we take the derivative of $F(\varphi)$, substitute it into (A6) and rearrange:

$$\varphi^{(\alpha_1-1)} = \frac{1}{B_1\alpha_1} \tag{A11}$$

Substituting (A11) into (A10) then gives:

$$\varphi * \left(1 - \frac{1}{\alpha_1}\right) = C, \text{ or} \tag{A12}$$

$$\varphi* = \frac{\alpha_1}{\alpha_1 - 1} C \tag{A13}$$

so

$$DH* = \frac{\alpha_1}{p(\alpha_1 - 1)} C \tag{A14}$$

In addition, we have:

$$B_1 = \frac{F(\varphi)}{\varphi^{\alpha_1}} \tag{A15}$$

Combining this with boundary condition (A5) and using (A13) yields:

$$B_1 = \frac{\varphi - C}{\varphi^{\alpha_1}} = \frac{\frac{\alpha_1}{\alpha_1 - 1} C - C}{\left(\frac{\alpha_1}{\alpha_1 - 1} C\right)^{\alpha_1}} = \frac{(\alpha_1 - 1)^{\alpha_1 - 1}}{\alpha_1^{\alpha_1} C^{\alpha_1 - 1}} \tag{A16}$$

We now have B_1 and φ^* expressed in terms of α_1 and the given parameter C.

A.2. Proof that loss aversion is not relevant in our example

Prospect theory considers preferences that depend on some reference point r. Outcomes better than the reference point are gains and outcomes worse than this point are losses. In addition, decision makers are loss averse, that is, losses loom larger than gains. This loss aversion is captured by a loss aversion parameter λ (Tversky and Kahneman, 1992). Finally, prospect theory assumes that probabilities are not evaluated linearly but are transformed instead, as explained in the main text. Our example includes no gains and can therefore be considered a loss prospect (p:g; h), with a probability p of the outcome g and probability ($1-p$) of the outcome h. This is evaluated as follows (e.g. Bleichrodt *et al.*, 2001):

$$U(r) - \lambda(1 - w^-(p))(U(r) - U(h)) - \lambda w^-(p)(U(r) - U(g)) \tag{A17}$$

For $r \geq h \geq g$. The reference point is given by the status quo in most cases, so $r = X$ in our example. g is the worst outcome, that is, the case of a pandemic outbreak, whereas h is the best outcome, that is, no outbreak. Therefore, with no investment, $g = X-Z$ and $h = X$. With investment, we have $g = X-Z+\eta-C$ and $h = X-C$. For convenience and without loss of generality we can set $U(X) = 0$, so we are left with:

$$-\lambda w^-(p)(U(X) - U(X - Z)) \tag{A18}$$

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for not investing, which becomes 0 for $X = Z$. Hence, the only relevant expression is the one for investing, which is given by:

$$-\lambda(1 - w^{-}(p))(-U(X - C)) - \lambda w^{-}(p)(-U(\eta - C)) \tag{A19}$$

Investment is optimal under standard cost benefit analysis when (A19) is positive, that is:

$$(1 - w^{-}(p))U(X - C) > -w^{-}(p)U(\eta - C) \tag{A20}$$

After rearranging, this expression gives:

$$w^{-}(p)(U(\eta - C) - U(X - C)) > -U(X - C) \tag{A21}$$

which is similar to (10), so the real options analysis becomes similar to the real options analysis under expected utility, except for the replacement of p with $w^{-}(p)$, and the value of λ does not matter.

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