Economics of Influenza Vaccine Development

By

Ayman Nassim Chit

A thesis submitted in conformity with the requirements for the degree of Doctorate of Philosophy

Faculty of Pharmaceutical Sciences
University of Toronto

© Copyright by Ayman Nassim Chit, 2013
Economics of Influenza Vaccine Development

Ayman Chit

Doctorate of Philosophy

Faculty of Pharmaceutical Sciences
University of Toronto

2013

Abstract

In this thesis we are particularly concerned about the development of new and improved influenza vaccines within the changing external economic environment. The thesis covers two major objectives:

1) Developing methods to estimate the costs of influenza vaccine development

The ability to calculate the development costs for specific medicines and vaccines are important to inform investments in innovation. Unfortunately, the literature is predominated by non-reproducible studies only measuring aggregate level drug research and development (R&D) costs. Further, the literature appears very scant on the development costs of new vaccines. In the first objective we therefore describe methodology that improves the transparency and reproducibility of primary indication expected R&D expenditures of influenza vaccines.

2) Developing methods to focus influenza vaccine R&D towards meeting cost-effectiveness targets

The second objective is focused on how to forecast evidence requirements for cost effectiveness analysis (CEA) of influenza vaccines. The guidance to manufacturers on what evidence would optimally support acceptable CEA is scant. The absence of such guidance and the increased emphasis on CEA can add significant risk to the vaccine development process. Thus we perform a Value of Information (VOI) analysis on the parameters of a cost effectiveness model designed to evaluate new influenza vaccines designed for use in elderly adults. The results of this study highlight what type of endpoints that should be studied in influenza vaccine R&D programs.

From our work on these objectives we are able to shed light on economics that should be considered while developing a new influenza vaccine. Though our contribution is mainly methodological, we conclude the thesis suggesting changes in the way the vaccine industry and HTA agencies work. These changes are in our view necessary to meet society’s demand for new vaccines that deliver high value for money.
"He, who learns for the sake of haughtiness, dies ignorant. He, who learns only to talk, rather than to act, dies a hypocrite. He, who learns for the mere sake of debating, dies irreligious. He, who learns only to accumulate wealth, dies an atheist. And he, who learns for the sake of action, dies a mystic."
Prophet Muhammad (S.A.W.)

Acknowledgment

Completing this thesis has been a true blessing from God and a testament to what can be accomplished by strategy, planning, focus, dedication and hard work.

There are several people that deserve my at most gratitude for the strength and resolve they provided me throughout this thesis. I will start by thanking my parents Khadije Nader, PhD and Nassim Chit, PhD whom always encouraged me and provided a commendable example through their life long achievements. Next would be my dear wife, Frances Lee; she has been a rock by my side throughout the demands of my career and this thesis. I have also been blessed with a loving work family, and would like to thank my managers at GlaxoSmithKline and Sanofi Pasteur: Shireen Khaliq, Diane Drolet, Reed Robson and Dion Neame for supporting me and allowing me the flexibility to achieve this degree. Of course none of this would be possible without the regular intellectual sparring sessions with my advisory committee; the quality of the discussions and debate we had has really borne everlasting fruits for me. And last but not least, I must take a bow to my supervisor Paul for shepherding me through the process, never restricting my creativity and always holding me to high standards.
# Contents

**LIST OF TABLES:** vi

**LIST OF FIGURES:** vii

**LIST OF APPENDICES:** viii

**INTRODUCTION** 1

**CHANGING ENVIRONMENT FOR MEDICAL TECHNOLOGY INNOVATION** .......................... 1

**INFLUENZA** ................................................................................................................. 2

**INFLUENZA VACCINES** .................................................................................................. 3

**THESIS OVERVIEW** ......................................................................................................... 4

1) **DEVELOPING METHODS TO ESTIMATE THE COSTS OF INFLUENZA VACCINE DEVELOPMENT** ............ 5

2) **DEVELOPING METHODS TO FOCUS INFLUENZA VACCINE R&D TOWARDS MEETING COST-EFFECTIVENESS TARGETS** .............................................................. 5

**REFERENCES** .................................................................................................................... 7

**CHAPTER 1** 10

**TOWARDS MORE SPECIFIC AND TRANSPARENT RESEARCH AND DEVELOPMENT COSTS: THE CASE OF SEASONAL INFLUENZA VACCINES** ................................................................. 10

**ABSTRACT** ....................................................................................................................... 11

**INTRODUCTION** ............................................................................................................. 12

**METHODS** .................................................................................................................... 13

**RESULTS** ....................................................................................................................... 16

**DISCUSSION** .................................................................................................................. 17

**REFERENCES** .................................................................................................................. 21

**TABLES** ......................................................................................................................... 24

**FIGURES** ....................................................................................................................... 28

**SUPPLEMENTARY MATERIAL** ....................................................................................... 29

**CHAPTER 2** 37

**NO FREE LUNCH: THE OPPORTUNITY COST OF DEVELOPING MEDICAL TECHNOLOGY** ......................... 37

**ABSTRACT** ....................................................................................................................... 38

**INTRODUCTION** ............................................................................................................. 38

**OPPORTUNITY COST OF INVESTORS IN MEDICAL TECHNOLOGY R&D** ........................................... 40

**CRITICAL APPRAISAL: THE COST OF CAPITAL & DRUG DEVELOPMENT** ........................................ 46

**CONCLUSION** ................................................................................................................ 50

**REFERENCES** ................................................................................................................ 51

**TABLES** ......................................................................................................................... 55

**FIGURES** ....................................................................................................................... 57

**SUPPLEMENTAL MATERIAL** ......................................................................................... 61

**CHAPTER 3** 65

**PRIORITIZING EVIDENCE GENERATION FOR THE DEVELOPMENT OF IMPROVED ELDERLY INFLUENZA VACCINES - A VALUE OF INFORMATION ANALYSIS** ................................................. 65

**ABSTRACT** ....................................................................................................................... 66

**INTRODUCTION** ............................................................................................................. 68
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHODS</td>
<td>70</td>
</tr>
<tr>
<td>RESULTS</td>
<td>76</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>78</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>81</td>
</tr>
<tr>
<td>TABLES</td>
<td>84</td>
</tr>
<tr>
<td>FIGURES</td>
<td>87</td>
</tr>
<tr>
<td>SUPPLEMENTAL MATERIAL</td>
<td>94</td>
</tr>
<tr>
<td>GENERAL DISCUSSION</td>
<td>99</td>
</tr>
<tr>
<td>VACCINE DEVELOPERS</td>
<td>100</td>
</tr>
<tr>
<td>HEALTH TECHNOLOGY ASSESSMENT (HTA) BODIES</td>
<td>102</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>104</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>106</td>
</tr>
</tbody>
</table>
List of Tables:

Chapter 1
Table 1: Successful transitions, abandonments and censored observations at each phase of development
Table 2: Number of trials, subjects per trial and phase length for VCs successfully transitioned from phase j to j+1
Table 3: Summary of mean un-capitalized clinical development costs in 2011 Canadian dollars
Table 4: Impact of the cost of capital on the cost of developing a new Vaccine Candidates
Table A: Time to event data for each of the 39 vaccine candidates in the study
Table B: Worked example that illustrates the Cumulative Incidence (CI) function calculation for 9 hypothetical VCs
Table C: Manufacturers and vaccine candidates included in the study
Table D: Extreme values of analysis reflecting estimate uncertainty

Chapter 2
Table 1: Beta values calculated by Scott Harrington for various segments of the healthcare technology industry [19]
Table 2: Cost of equity capital calculated by Scott Harrington for various segments of the healthcare technology industry [19]

Chapter 3
Table 1: A summary of the major model parameters
Table 2: Population level EVPPI estimates at various technology price premiums and levels of technology adoption. Calculations are based on forecasted product adoption in Canada.
List of Figures:

Chapter 1
Figure 1: Vaccine candidates developed by larg and small firms

Chapter 2
Figure 1: Historic rates of return from US government 10-year T-Bills
Figure 2: life cycle of a typical corporation
Figure 3: The historic performance of the Standards and Poors (S&P) 500 group of companies

Chapter 3
Figure 1: (A) A summary of the health states in our model and possible transitions. (B) Schematic of a summary structure of the Markov cost-utility model for the decision to vaccinate.
Figure 2: Detailed structure of the Markov model with all the possible health states, transitions and outcomes.
Figure 3: Sensitivity analysis on the incremental cost-effectiveness of varying the additional cost of new technology and vaccine efficacy (VE) of the new influenza vaccine. WTP was set at $50,000/QALY. A reduction of relative risk of 1 represents no added benefit of using the new vaccine over the SOC vaccine for the specified parameter, while reduction in relative risk of 0 represents 100% VE against the outcome. Panel A represents a 4-way sensitivity analysis where the new vaccine effectiveness against hospitalization and death are set to equal that of the SOC vaccine. Panels B, C and D represent 2-way sensitivity analysis where all other model variables take the values represented in table 1.
Figure 4: Acceptability curves from probabilistic sensitivity analysis for various additional new technology costs. Distributions and parameters for this analysis are presented in table 1.
Figure 5: EVPPI curves for new vaccine efficacy parameters (vaccine efficacy against GP visits, hospitalization and death) at various additional new technology costs.
Figure 6: EVPPI estimates for various model parameters at a WTP equal to the ICER and a WTP of $50,000/QALY. New technology price was set to $40.
Figure 7: EVPPI estimates for an aggregate of the model vaccine efficacy (VE) parameters and each of the VE parameters separately (VE against GP visits, hospitalizations and death). New technology price was set to $40.
List of Appendices:

Chapter 1
Appendix I: Vaccine candidate progress through various stages of development
Appendix II: Model for estimating phase transition probabilities
Appendix III: Model for estimating out of pocket costs
Appendix IV: Manufacturers and vaccine candidates
Appendix V: Uncertainty analysis

Chapter 2
Appendix I: Time Value of Money
Appendix II: Sample calculation of the Weighted Average Cost of Capital (WACC)
Appendix III: Incorporating Opportunity Cost into Business Management

Chapter 3
Appendix I: Value of Information (VOI)
Introduction

Changing Environment for Medical Technology Innovation

Currently the US federal deficit has reached its highest point since World War II, with a major driver being the pressure to increase spending rates without matching increases in revenue [1]. The largest component of this spending is dedicated to Social Security and Medicare/Medicaid programs [1]. While Social Security has historically been the largest share of this spending, today; in combination Medicare and Medicaid make up the largest share [1]. The current economic turmoil and weight of public spending on health care is by no means unique to the US. The majority of countries in the Economic Cooperation and Development (OECD) have experienced deficits highlighted during the last recession [2]. These countries have also seen healthcare expenditures increase at a higher rate than GDP for the past 30 years [3]. Today, the richest OECD countries have been shown to have quite comparable public spending per capita on health care as the US [4].

It is not surprising therefore to see the bolstering of health technology assessment (HTA) and particularly the use of economic evaluations such as cost-effectiveness analysis in OECD countries. Specific to the field of vaccines and immunization, a stark shift in U.S. HTA was observed over the past decade as the U.S. Advisory Committee on Immunization (ACIP) adopted economic reviews as part of their recommendation process [5]. This is in contrast to Medicare legislation that prohibits the use of cost-effectiveness analysis in coverage decisions [6]. Similarly in Canada, the National Advisory Committee on Immunization (NACI) has also recently started to use cost-effectiveness analysis as part of its recommendation process [7].

Concurrently, the pharmaceutical industry has been facing unprecedented challenges to deliver new medicines and vaccines. While R&D costs have been increasing, the industry has experienced severe loss of patent exclusivity as well as reduction of revenues from cost-constrained health care
systems [8]. Without doubt, the last decade has been transformational with society now not only expecting safe and effective medicines and vaccines, but demanding the products be cost-effective as well. While today R&D programs are designed to meet the safety and efficacy targets set by regulators, there now has to be careful adjustments to meet economic targets during the drug and vaccine development process.

In this work we study economic considerations that are relevant to the design of R&D programs for new drugs and vaccines. For the purpose of consistency and given the lead author’s profession as a research scientist focusing on infectious disease and vaccines, we use seasonal influenza vaccine development as a case study.

**Influenza**

The viruses that cause influenza belong to the *Orthomyxoviridae* family, with the name derived from the Greek *myxa* which means mucus given the affinity of these viruses to mucous membranes. The influenza family is subdivided into three genera influenza virus *A*, *B* and *C*. Antigenic variation particularly in the hemagglutinin (HA) and neuraminidase (NA) components of influenza is an important feature of the virus. The variation is caused by evolutionary pressure from immune and partially immune host populations. Influenza A is further subdivided into subtypes based on membrane surface antigens HA and NA. Studying the surface antigens (antigenic stability) of the influenza is one way to track the evolution of the viruses. To date there has been fifteen HA subtypes and nine NA subtypes of influenza A [9]. Influenza B appears to be antigenically more stable than A, with two distinct genetic lineages co-circulating (Victoria and Yamagata) over the past two decades [10]. All the influenza A and B subtypes and lineages mentioned have variation occurring within them.

The antigenic instability of influenza has made it a constant public health burden despite the use of influenza vaccination. Epidemics and outbreaks of influenza follow seasonal patterns and are
primarily driven by climate temperature and contact patterns between individuals; with the circulation of the virus being highest during the winter months of the year. For instance in the US and Canada the influenza season generally starts in the late fall and end in the spring with a peak in mid-winter [9].

Influenza is known to be a major cause of excess morbidity and mortality during the winter seasons [11]. The burden of influenza on the health care system is observed at a primary care level through general practitioner (GP) visits, as well as, hospitalizations and deaths [12]. The US Centers for Disease Control (CDC) estimates that the annual rate of hospitalization varies considerably for influenza ranging from 33 to 100 per 100,000 person years, with the highest rate of influenza hospitalizations occurring among elderly adults over the age of 65 (309 per 100,000) and children below one year of age (151 per 100,000) [13]. CDC also reports similar variation in the death rate ranging from a rate of 1.4 per 100,000 (in 1986-87) to 16.7 per 100,000 (in 2003-04), with the majority of the death toll occurring in elderly adults over the age of 65 [14]. Beyond the health care system influenza exerts further social distress in the form of work absenteeism and reduced quality of life. Overall the CDC estimates that the annual epidemic burden of seasonal influenza in the United States is a staggering $87.1 billion USD (C.I., $47.2, $149.5) [12].

**Influenza Vaccines**

Vaccination is considered the most effective preventative measure to protect against influenza infection [15]. The dominant majorities of influenza vaccines today use either a live attenuated form of the influenza virus or inactivates split subunit virus [16]. The vaccine manufacturing process involves growing viral strains in chicken eggs and then harvesting the virus for vaccine formulation [16]. Influenza vaccines have been manufactured in eggs since the 1940s when the first commercial influenza vaccines were approved based on studies in military recruits and college students [17,18]. Over the years the influenza vaccines has moved from crude formulations against
single strains of influenza to significantly more refined formulations covering as much as 4 strains of influenza today [9]. The recommendations on seasonal influenza vaccine are put forth by public health bodies such as US CDC’s ACIP and the Public Health Agency of Canada’s NACI. Both groups currently recommend annual immunization against influenza for the entire population over the age of 6 months [19, 20].

A cornerstone of these recommendations has been the well-documented efficacy of the influenza vaccine in protecting against influenza infection. This efficacy has been studied through randomized controlled trials (RCTs) as well as experimental field-based research. In a recent meta-analysis of RCTs conducted on influenza vaccines, DiazGranados and colleagues report that influenza vaccines can provide up to 65% protection against any strain of influenza, 78% against a matched strain and 55% against a mismatched strain [21]. Most of these RCTs measured outcomes of laboratory confirmed influenza infection. Field-based evaluations such as those by Talbott and colleagues provide further reassurance that influenza vaccines provide 61% protection to high-risk populations such as the elderly against severe influenza infection requiring hospitalization [22].

There is a vibrant influenza vaccine R&D community working on the development of improved influenza vaccines [16]. In a recent publication Lambert and colleagues summarized some of the future trends in influenza vaccine innovation [16]. The next few decades hold the promise of improvements on the manufacturing and protection front. Currently there are several vaccine candidates (VC) that look to move us away from egg-based production to what promise to be more efficient cell-based systems. Other VCs promise to improve the vaccine-induced immune responses. Several VC also hold the Holy Grail promise of a universally protective influenza vaccine that could eradicate the disease someday.

**Thesis Overview**
In this thesis we are particularly concerned about the development of new and improved influenza vaccines with in the changing external economic environment. The thesis covers two major objectives described below.

1) Developing methods to estimate the costs of influenza vaccine development

The ability to calculate the development costs for specific medicines and vaccines is important to inform investments in innovation. Unfortunately, the literature is predominated by non-reproducible studies only measuring aggregate level drug research and development (R&D) costs. Further, the literature appears very scant on the development costs of new vaccines. In the first objective we therefore describe methodology that improves the transparency and reproducibility of primary indication expected R&D expenditures of influenza vaccines.

2) Developing methods to focus influenza vaccine R&D towards meeting cost-effectiveness targets

The second objective is focused on how to forecast evidence requirements for cost effectiveness analysis (CEA) of influenza vaccines. The guidance to manufacturers on what evidence would optimally support acceptable CEA is scant. The absence of such guidance and the increased emphasis on CEA can add significant risk to the vaccine development process. Thus we perform a Value of Information (VOI) analysis on the parameters of a cost effectiveness model designed to evaluate new influenza vaccines designed for use in elderly adults. The results of this study highlight what type of endpoints should be studied in influenza vaccine R&D programs.

From our work on these objectives we are able to shed light on economics that should be considered while developing a new influenza vaccine. Though our contribution is mainly methodological, we conclude the thesis suggesting changes in the way the vaccine industry and
HTA agencies work. These changes are in our view necessary to meet society's demand for new vaccines that deliver high value for money.
References


[10] Belshe RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine. 2010; 28, 4: D45-D53


Chapter 1

Towards More Specific and Transparent Research and Development Costs: The Case of Seasonal Influenza Vaccines

Authors
Ayman Chit, Jayson Parker, Scott A. Halperin, Manny Papadimitropoulos, Murray Krahn, Paul Grootendorst.
University of Toronto, Toronto, Ontario, Canada
Sanofi Pasteur, Toronto, Ontario, Canada
Canadian Center for Vaccinology, Dalhousie University, Halifax, Nova Scotia, Canada
Eli Lilly Canada Inc, Scarborough, Ontario, Canada

Corresponding author
Ayman Chit
Leslie Dan Faculty of Pharmacy, University of Toronto,
144 College Street, Room 601,
Toronto, ON, M5S 3M2, Canada
Tel: +1-416-587-4651
Ayman.Chit@utoronto.ca

Competing Interest & Funding
At the time of writing, Ayman Chit was an employee of GlaxoSmithKline (GSK); currently he is with Sanofi Canada. Jayson Parker has worked in the pharmaceutical industry and advises a hedge fund which invests in life sciences. Scott Halperin has received research contracts and grants and has served on ad hoc advisory boards for vaccine manufacturers. Manny Papadimitropoulos is an employee of Eli Lilly & Company. Paul Grootendorst has provided expert testimony and/or reports on behalf of both generic and branded drug companies and has received financial and in-kind research support from both generic and branded drug companies.
Data base access to Trialtrove was provided through the GSK subscription. Other than Ayman Chit's direct contribution, GSK had no role in the study design, interpretation of results, or decision to publish. All opinions expressed are solely those of the authors.

Acknowledgment
We would like to thank Lesley Smeaton conducting the systematic review and Ryan McGuire for assisting in the conversion of trial data into a time to event format.

Word Count
Article excluding abstract, cover page, references and supplementary materials: 2,867
Abstract: 225
Abstract

**Background:** The ability to calculate the development costs for specific medicines and vaccines is important to inform investments in innovation. Unfortunately, the literature is predominated by non-reproducible studies only measuring aggregate level drug research and development (R&D) costs. We describe methodology that improves the transparency and reproducibility of primary indication expected R&D expenditures.

**Methods:** We used publically accessible clinical trial data to investigate the fate of all seasonal influenza vaccine candidates that entered clinical development post year 2000. We calculated development times and probabilities of success for these candidates through the various phases of clinical development. Clinical trial cost data obtained from university-based clinical researchers were used to estimate the costs of each phase of development. The cost of preclinical development was estimated using published literature.

**Results:** A vaccine candidate entering pre-clinical development in 2011 would be expected to achieve licensure in 2022; all costs are reported in 2022 Canadian dollars (CAD). After applying a 9% cost of capital, the capitalized total pre-tax R&D expenditure amounts to $474.88 Million CAD.

**Conclusion:** Clinical development costs for vaccines and drugs can be estimated with increased specificity and transparency using public sources of data. The robustness of these estimates will only increase over time due to public disclosure incentives first introduced in the late 1990s. However, preclinical development costs remain difficult to estimate from public data.

**Key Words**

Cost, Economics, Research and Development, Influenza, Vaccine, clinical trial, risk, biologic, drug development
Introduction

There has been polarizing debate in the literature regarding the “true” cost of developing new pharmaceutical drugs. In a much-publicized paper, Joseph DiMasi and colleagues estimate the cost of developing a new molecular entity (NME) in 2001 to be in the order of $800 million United States dollars (USD) [1]. More recently, Bill Paul and colleagues estimated the cost to be in the order of $1.8 billion USD [2]. Critics suggest that these estimates are vastly overstated. Donald Light and Rebecca Warburton estimate the cost of new drug development to be well under $100 million USD [3]. One reason for the controversy is that most cost-of-research and development (R&D) studies are not reproducible. Morgan and colleagues, in a recent review article, note that 10 of the 13 cost-of-R&D studies in the literature were based on self-reported, unaudited and confidential data from unnamed drug companies and unnamed products [4]. The non-reproducible aspect of these data raises questions about the representativeness of the R&D cost estimates. Critics also question the value of estimating average drug R&D costs given the substantial heterogeneity in development costs within a therapeutic area. For instance, Adams and Brantner report that the expected cost of developing an oncology medicine is $1.042 Billion USD while the cost of developing a medicine within this class – drugs that treat breast cancer – is $0.61 Billion USD [5]. The narrowly defined R&D cost in this case would more informative for decision making around new investments in breast cancer drugs.

In this paper, we use publicly available data to estimate the cost of development of seasonal influenza vaccines if the development was all conducted in Canada. In contrast to most other studies, our analysis is reproducible and confined to a specific therapeutic area. Although our primary contribution is methodological, we note that estimation of seasonal influenza vaccine R&D costs is of interest in its own right. Relative to drugs, estimates of vaccine development costs are limited. Moreover, influenza continues to impose a substantial burden of morbidity and mortality. Influenza vaccines are amongst the most effective means of protection against influenza infection. For instance, current vaccines can
prevent up to 62.1% of influenza related respiratory hospitalization [6]. Despite this, the US Centers for Disease Control estimates that the annual epidemic burden of seasonal influenza in the United States is $87.1 billion USD (C.I., $47.2, $149.5 billion) [7]. Given the residual high burden of disease improved influenza vaccines are a high development priority, and many are currently in development [8]. Knowledge of the cost of vaccine R&D can help guide public and private R&D investments in new vaccine development.

**Methods**

**Model and Data Sources**

The total, expected, uncapitalized, R&D cost $C_u$ required to bring a vaccine candidate (VC) to market is the sum of expected uncapitalized R&D expenditures during the pre-clinical phase $C_p$ and the clinical phase $C_c$.

\[ C_u = C_p + C_c \]

Following the methods developed by DiMasi et al [9], the expected clinical phase cost per approved vaccine, $C_c$, is defined as

\[ C_c = \frac{E(h)}{s} \]

$s$ is the probability that a VC emerging from pre-clinical development obtains market approval. $E(h)$ is the expected value of the clinical period costs $(h)$ and can be defined as:

\[ E(h) = p_I \mu_I + p_{II} \mu_{II} + p_{III} \mu_{III} + p_A \mu_A \]

$p_I, p_{II}$ and $p_{III}$ are the probabilities that a VC tested in humans will enter phase I, II and III, respectively, $p_A$ is the probability that long-term animal testing will be carried out. $\mu_I, \mu_{II}, \mu_{III}$ and $\mu_A$ are mean costs of developing a VC in phases I, II, III and long-term animal testing, respectively.

Firms are generally not able to allocate all pre-clinical costs to specific VCs, and there is very little publicly available information on these costs. The one notable exception is DiMasi et al [9] who
reported a general ratio of pre-clinical expenditures to total R&D expenditures, $\lambda$, of 30%. We used this same estimate to calculate $C_p$ using the following equation.

$$C_p = \left[ \frac{\lambda}{(1 - \lambda)} \right] C_u$$

We adjusted our cost estimates to account for the cost of capital using methods previously described by DiMasi and colleagues [9]. Harrington and colleagues in a recent working paper have updated the cost of capital for the pharmaceutical sector and estimate it to be 9% [10]. DiMasi in previous work estimated an 11% cost of capital [11]. Given the controversy around which rate to use, we employed 9% in this study and conducted sensitivity analysis using 5% and 11%. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends a 5% discount rate be used in health technology appraisals [12]. Light et al propose this rate as a substitute for the market-derived cost of capital [13].

Our model does not account for R&D tax incentives that are traditionally offered by the Canadian government to developers. The Canadian Scientific Research and Experimental Development (SR&ED) tax incentive program is used to reduce corporate tax owed on revenue [14]. Thus, while private corporations that engage in R&D are rewarded with tax payer subsidies, the social cost of developing the drugs remain the same.

In this study we used Trialtrove, a database held by Citeline intelligence solutions. This database is primarily built on data from clinicaltrials.gov and is supplemented through routine mining a broad range public domain sources [13].

Further, this approach allows us to exploit the disclosure mandates on human research that were first promulgated in 1997 by the US Food and Drug Administration Modernization Act, and which were bolstered by the 2004 decision by the International Committee of Medical Journal Editors to not publish results of clinical trials that had previously not been publicly registered [16]. The result is that a drug company cannot seek FDA approval for a new drug nor can it publish the results of its clinical trials in a reputable journal without having previously disclosed their clinical research. The new requirements
have led to the public disclosure of clinical research programs, including sponsorship, the identity of the investigational product and study design (phase, number of subjects, length of study, number of centers, primary endpoints, etc.). These data allow us to avoid selection biases that may have contaminated other cost of R&D studies, while also providing information on the quantity of the “inputs” used to conduct the R&D – the number of subjects, the number of measurements per subject, study duration, etc. These data are silent, however, on the unit costs of these inputs. For that, we obtained cost estimates from a well-known influenza research group in Canada known as the Canadian Center for Vaccinology (CCfV), at Dalhousie University in Halifax, Nova Scotia, Canada [17]. CCfV is a member site of the Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network (PCIRN) [18]. Cost data were provided in Canadian dollars which is has been close to parity with the U.S. dollar since 2007. No confidentiality agreements were required for this collaboration.

**Estimating Model Parameters**

We collected all the clinical trial records on seasonal influenza VCs that entered clinical development after the year 2000 until 2011. For each trial record we extracted information on the study design, a description of the underlying biotechnology, the name of the sponsor, the study phase (I, II, III), number of subjects enrolled, study start and end dates, as well as the most recent public reports on product development status. We organized the data to track the VCs’ development path. Once a VC entered a clinical development phase j, (j could be phase I, II or III), it could either successfully transition to phase j + 1 or to regulatory submission if it was already in phase j = III. Alternatively, the VC could be abandoned during development. The mean length of phase j was calculated by subtracting the start date of phase j from the start date of phase j+1 for the VCs that successfully made a transition. Any VC that did not transition to phase j+1 after being in phase j for longer than the upper bound of the 95% CI of the mean length of phase j were considered abandoned. VCs in phase j that did not transition to phase j+1 and had development times lower than the 95% CI of the mean phase j length were
considered right censored. In this manner our data set was organized as time to event data (abandonment or successful transition) that includes censored observations. The time to event data set is included in appendix I. These data were used to estimate \( p_j \), the probability over development time \( t \), that a VC will enter phase \( j \) of testing given that the previous phase was entered.

To estimate \( p_j \) we calculated the cumulative incidence (CI) function for successfully transitioning from phase \( j-1 \) to \( j \) of development [19]. This function estimates the probability that a VC transitions from phase \( j-1 \) to \( j \) before time \( t \) and that this occurs before the competing risk of abandonment. The function utilizes the Kaplan-Meier estimator that accounts for censored observations. Appendix II summarizes how this approach works. To calculate \( s \) (the probability of moving from phase I to market), we compute the CI for a transition from phase I to market using the same methods. The estimation of \( \mu_j \), the vaccine development costs for phases \( j \) where \( j \) could be I, II or III is described in appendix III. The cost of animal testing \( \mu_A \) was estimated from the literature as 4.5% of \( \sum_{j=1}^{3} \mu_j \) [20].

**Results**

Our data set contained information on 24 vaccine developers and 39 VCs. Large vaccine manufacturers developed 22 of the 39 VCs while small biotechnology firms developed the remaining 17 VCs (see appendix IV for list of companies and VCs). We observed a variety of biotechnologies in development. Some of these – such as preservative-free vaccines – were not very innovative, while others – such as vaccines that can protect against any influenza virus – were highly innovative. Three vaccines started development and were approved during the study period. These were an influenza vaccine made without the preservative thimerosal; as well as a high dose vaccine and an intradermal vaccine. Large firms developed all the approved vaccines; Figure 1 outlines development activity by firm size. Table 1 summarizes the VC transition status. Since all the VC we studied entered clinical development after the year 2000 we assigned 100% success rate for the transition from pre-clinical to Phase I. 40% (95% CI: 21-59%) of the VC transitioned from Phase I to II, while 74% (95% CI: 34-92%) and 69% (95% CI: 9-94 %)
successfully transitioned from Phase II to III and III to market respectively. Cumulatively, 20% (95% CI: 1-51%) successfully transitioned from Phase I to obtain market authorization.

Table 2 summarizes the number of trials, mean number of subjects per trial and mean phase length. The variable costs associated with conducting phase I, II and III trials are summarized in Table 3. For all studies a fixed cost of $70,385 (CAD) was required to conduct the trial. Total uncapsualized costs for each phase were calculated using the methods described earlier and the results are outlined in Table 3. Capitalized expected costs of development under different assumptions of cost of capital are reported in Table 4.

**Discussion**

We have demonstrated that the expected cost of developing a new influenza vaccine is in the order of $475 million (CAD) at a 9% cost of capital rate. Given different assumptions about the cost of capital this estimate ranges from $337 Million CAD to $570 Million CAD if a 5% or 11% cost of capital rate is applied respectively. The cost of capital adjustment is to account for opportunity cost since the money could have been used in a different investment with comparable or lower risk of failure. The cost of development will therefore be highly dependent on who pays for the work. While it is clear that the majority of the clinical development was paid for by corporations, it was not clear whom the funders of the pre-clinical activity were. A lower cost of capital indicates larger government support for R&D.

Our study offers methods to estimate R&D costs from public data sources. The methods we employ are most closely related to the work of Adams and Brantner who also used publicly available data to estimate the cost of drug R&D for multiple disorders and several primary indications [5]. We extend their work in several ways. First, we use publicly available and verifiable input pricing data from a national academic clinical trials network (PCIRN). Adams et al relied on DiMasi's confidential industry data to estimate R&D input costs. Second, despite Adams and Brantner’s use of publicly available data, there are questions about the representativeness of their data. The authors use data from 1989 to 2005;
these years are prior to the introduction of the aforementioned public disclosure mandates. This leads to concerns around truncation bias in this data set as firms had lower incentives to publically disclose development activities prior to the late 1990s. Third, Adams and Brantner did not appear to deal adequately with the possible censoring of the progression of drugs that were still in the midst of the development at the time that the data were collected. For instance, consider a drug that is known to have just recently completed a Phase II trial. The publicly available data can be silent on whether the sponsor will conduct more Phase II trials, will advance to Phase III, or will terminate development.

Our study has three major limitations. First, the cost of pre-clinical development continues to be unattainable from public data sources. Based on DiMasi and colleagues’ work, we assumed pre-clinical research accounts for 30% of total R&D expenditures [20]. This estimate is difficult to verify because manufacturers have no incentive to routinely disclose this activity, and even if the information were disclosed it is difficult to allocate to specific VC projects pre-clinical costs that are fixed or shared across a variety of VC projects. Secondly, publically disclosed datasets on human research are still fairly small. Estimates from these data sets therefore have a high degree of uncertainty. For instance, we did not observe any VCs being abandoned in phase III. Instead we observed 3 approvals and 7 censored VCs. The high degree of censorship resulted in wide confidence intervals to the transition probability between phase III and market (69%; 95% CI: 9 – 94%). The small number of trials also affected the precision of other model parameters such as mean trial length and mean number of subjects per trial. Appendix IV shows the high uncertainty associated with our current analysis. Over time these data sets will grow and researchers will be able to derive estimates with greater precision.

The third limitation is that all our unit price data are taken from a Canadian context. Canadian labor, material and overhead costs are on the high end globally and vaccine developers do take advantage of lower cost offered in other countries through multinational trials. This is likely imparts an upwards bias to our estimate. On the other hand there are a few points that clearly downward bias our estimate. We
do not capture the cost of any manufacturing costs a developer would incur such as building a production facility to supply clinical development. These costs are not expected to be very high for developers that already own an established influenza vaccine manufacturing facilities and aim to build technological developments based on their existing platform. However, the capital expenditures required to develop a technology based on a novel platform (e.g. non-egg based technologies) would be substantial. Moreover, our analysis only considers the R&D costs required to transition a product to its first market approval. We do not consider post licensure research such as safety and effectiveness monitoring which have significant costs.

In contrast to more recent analysis of drug development costs, our work shows that influenza vaccines appear relatively less expensive to develop than traditional small molecule pharmaceuticals. The systematic review by Morgan and colleagues reported capitalized drug development costs that ranged from $139 Million to $1800 Million, 2009 USD [4]. Their review was not restricted by time and the oldest study was conducted in the period 1963-1975. The systematic review, rather than individual studies, provides the best frame of reference as the field is characterized by polarized opinions on bias [21, 22]. These relatively low development costs are aligned to the work by André et al where they describe influenza vaccine development to be relatively simple compared to other vaccines [23]. Further, the output of the expected influenza vaccine development costs has been only re-formulations of existing vaccine technologies. The three new vaccines that have emerged are a higher dose vaccine (Fluzone® High-Dose, by Sanofi Pasteur), an intra-dermal vaccine (intanza®, by Sanofi Pasteur) and a preservative free vaccine (Thimerosal free FLULAVAL® by GlaxoSmithKline), all of which developed by large vaccine manufacturers. Thus, higher costs might be expected to develop novel technologies that don’t depend on classical egg-based antigens.
Recently, Parker and colleagues reported success rates of new drug clinical development for very specific indications: Crohn’s disease [24], HIV [25], Non-Hodgkin’s Lymphoma [26], but the researchers were not able to study costs. Our work provides these researchers methods to do so. New estimates will help reconcile some of the political debate around bias in the current cost of R&D literature. Further, quantifying development cost estimates for a vaccine or medicine can motivate investment in developing new ones, as it reduces the high uncertainty associated with such decisions. It will also be important to develop an appropriate analytical framework for decision makers. Such a framework should evaluate development costs, anticipated technology impact and overall burden of disease. Finally, further research should also focus on how development costs should inform pricing, especially that payers are moving towards the adoption of cost-effective medicines and vaccines that meet a price ceiling set by an incremental cost effectiveness ratio (ICER).
References


### Tables

**Table 1:** Successful transitions, abandonments and censored observations at each phase of development

<table>
<thead>
<tr>
<th>VC* Transition Status</th>
<th>Phase I to II</th>
<th>Phase II to III</th>
<th>Phase III to Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Transition</td>
<td>19</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Abandoned</td>
<td>14</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Censored</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

*VC: Vaccine Candidate*
Table 2: Number of trials, subjects per trial and phase length for VCs successfully transitioned from phase j to j+1

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th></th>
<th>Phase II</th>
<th></th>
<th>Phase III</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Number of Trials</td>
<td>2</td>
<td>1 - 5</td>
<td>5</td>
<td>1 - 12</td>
<td>3</td>
<td>2 – 4</td>
</tr>
<tr>
<td>Subjects per Trial</td>
<td>151</td>
<td>15 - 595</td>
<td>517</td>
<td>48 - 988</td>
<td>4,461</td>
<td>220 – 18,419</td>
</tr>
<tr>
<td>Phase Length (Months)</td>
<td>21</td>
<td>3 - 57</td>
<td>21</td>
<td>11 - 37</td>
<td>46</td>
<td>30 – 67</td>
</tr>
</tbody>
</table>
### Table 3: Summary of mean un-capitalized clinical development costs in 2011 Canadian dollars

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean number of subjects/trial</strong></td>
<td>151</td>
<td>517</td>
<td>4,461</td>
</tr>
<tr>
<td><strong>Mean number of trials/phase</strong></td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Variable cost/subject (CAD)</strong></td>
<td>6,821</td>
<td>4,369</td>
<td>3,442</td>
</tr>
<tr>
<td><strong>Fixed cost/trial (CAD)</strong></td>
<td>70,385</td>
<td>70,385</td>
<td>70,385</td>
</tr>
<tr>
<td><strong>Total uncapitalized cost/phase (CAD)</strong></td>
<td>1,919,944</td>
<td>10,485,647</td>
<td>51,368,604</td>
</tr>
<tr>
<td>Capitalized expected costs per approved new vaccines (Millions 2022 CAD)</td>
<td>5%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Pre-clinical expenditures</td>
<td>146.71</td>
<td>253.26</td>
<td>331.26</td>
</tr>
<tr>
<td>Clinical expenditures</td>
<td>190.44</td>
<td>221.62</td>
<td>239.14</td>
</tr>
<tr>
<td>Total R&amp;D expenditures</td>
<td>337.14</td>
<td>474.88</td>
<td>570.4</td>
</tr>
</tbody>
</table>

**Table 4**: Impact of the cost of capital on the cost of developing a new Vaccine Candidates
Figures

Figure 1: Vaccine candidates developed by large and small firms.
**Supplementary material**

**Appendix I**: Vaccine candidate progress through various stages of development

**Table A**: Time to event data for each of the 39 vaccine candidates in the study

<table>
<thead>
<tr>
<th>VC*</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VC*</td>
<td>Time (days)</td>
<td>Status</td>
<td>Time (days)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1331</td>
<td>2</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1722</td>
<td>414</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1310</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>2022</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>183</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2070</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>559</td>
<td>1</td>
<td>536</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>913</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>359</td>
<td>1</td>
<td>426</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>380</td>
<td>1</td>
<td>2009</td>
</tr>
<tr>
<td>12</td>
<td>92</td>
<td>1</td>
<td>334</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>244</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>1006</td>
<td>1</td>
<td>365</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>1522</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>77</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>461</td>
<td>1</td>
<td>456</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>1522</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>955</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>700</td>
<td>1</td>
<td>426</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>1</td>
<td>974</td>
<td>1</td>
</tr>
<tr>
<td>22</td>
<td>2497</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>791</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1</td>
<td>1050</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>1126</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>244</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>27</td>
<td>2526</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28</td>
<td>2891</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>0</td>
<td>1</td>
<td>699</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>638</td>
<td>1</td>
<td>1157</td>
<td>2</td>
</tr>
<tr>
<td>31</td>
<td>1233</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>32</td>
<td>0</td>
<td>1</td>
<td>1096</td>
<td>1</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
<td>1</td>
<td>426</td>
<td>0</td>
</tr>
<tr>
<td>34</td>
<td>0</td>
<td>1</td>
<td>548</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>2029</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>36</td>
<td>458</td>
<td>1</td>
<td>365</td>
<td>1</td>
</tr>
<tr>
<td>37</td>
<td>1249</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>38</td>
<td>1187</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>427</td>
<td>1</td>
<td>456</td>
<td>0</td>
</tr>
</tbody>
</table>

*VC: vaccine candidate

*0, 1 or 2 indicating censorship, successful transition or abandonment respectively
Appendix II: Model for estimating phase transition probabilities

The CI function of entering phase j can be defined as:

\[ CI(t)_j = \sum_{t_i \leq t} \hat{s}(t_{i-1}) \frac{r_i}{Y_i} \]

\( \hat{s}(t_{i-1}) \) is the Kaplan Meier estimator, evaluated just before time \( t_i \). \( r_i \) and \( Y_i \) represent the number of VCs that, successfully transitioned from phase j-1 to j at \( t_i \), and that are under development in a given phase j-1 at \( t_i \), respectively. The estimator treats both outcomes of transitioning out of phase j-1 due to a successful transition to phase j or abandonment as the same.

\[ \hat{s}(t_{i-1}) = \prod_{t_i \leq t} \left(1 - \frac{r_i + d_i}{Y_i} \right) \]

\( d_i \) represents the VC that are abandoned during phase j-1 at \( t_i \). \( r_i + d_i \) represents the number of VCs with an occurrence of any of the two competing outcomes (successful transition to j or abandonment).

Independent random censoring due to VCs that are still being actively developed are not counted as an event competing with successful transition to j or abandonment; thus only affecting the value of \( Y_i \). As such the cumulative incidence function estimates the probability that a VC transitions from phase j-1 to j before time \( t \) and that this occurs before the competing risk of abandonment. Below is a worked example that illustrates the Cumulative Incidence (CI) function calculation for 9 hypothetical VCs, 2 of which successfully transition from phase j-1 to j, 5 VCs are abandoned and 2 are censored.

Finally,

\[ p_j = CI(t)_j(CI(t)_{j-1}) \quad for \ j = 1,2,3 \]
Table B: Worked example that illustrates the Cumulative Incidence (CI) function calculation for 9 hypothetical VCs

<table>
<thead>
<tr>
<th>Time $t_i$</th>
<th>Events Transitioning VC out of Phase j-1</th>
<th>Censored VC VCs</th>
<th>Number of VCs in Development $Y_i$</th>
<th>$1 - \frac{(r_i + d_i)}{Y_i}$</th>
<th>Product-Limit Estimator $\hat{s}(t_{i-1}) = \prod_{t_i \leq t} (1 - \frac{(r_i + d_i)}{Y_i})$</th>
<th>$\frac{r_i}{Y_i}$</th>
<th>$\hat{s}(t_{i-1}) \frac{r_i}{Y_i}$</th>
<th>Cumulative Incidence Function $CI(t) = \sum_{t_i \leq t} \hat{s}(t_{i-1}) \frac{r_i}{Y_i}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Abandoned $d_i$</td>
<td>0</td>
<td>9</td>
<td>0.89</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>150</td>
<td>Successful $r_i$</td>
<td>0</td>
<td>8</td>
<td>0.88</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.13</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>175</td>
<td>Abandoned $d_i$</td>
<td>0</td>
<td>1</td>
<td>1.00</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
</tr>
<tr>
<td>200</td>
<td>Successful $r_i$</td>
<td>0</td>
<td>6</td>
<td>0.67</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
</tr>
<tr>
<td>250</td>
<td>Abandoned $d_i$</td>
<td>0</td>
<td>4</td>
<td>0.75</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
</tr>
<tr>
<td>350</td>
<td>Successful $r_i$</td>
<td>0</td>
<td>3</td>
<td>0.67</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.33</td>
<td>0.09</td>
<td>0.18</td>
</tr>
<tr>
<td>1000</td>
<td>Abandoned $d_i$</td>
<td>0</td>
<td>2</td>
<td>0.50</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.18</td>
</tr>
<tr>
<td>1500</td>
<td>Successful $r_i$</td>
<td>0</td>
<td>1</td>
<td>1.00</td>
<td>$\frac{r_i}{Y_i}$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Appendix III: Model for estimating out of pocket costs

\( \mu_j \), the vaccine development costs for phases \( j \) where \( j \) could be I, II or III is estimated using the following formula:

\[
\mu_j = n_{tj}(n_{sj}c_{sj} + C_{fj}) \quad \text{for} \quad j = 1, 2, 3
\]

\( n_{tj} \) and \( n_{sj} \) represent the total number of trials per phase \( j \) and the total number of subjects per trial in phase \( j \) respectively. \( c_{sj} \) is the variable per subject cost, while \( c_{fj} \) is the fixed costs of conducting a trial in phase \( j \). \( c_{sj} \) is computed using the following formula:

\[
c_{sj} = \frac{c_{mj} + c_{pj} + c_{lj} + c_{dj}}{n_{sj}}
\]

\( c_{mj}, c_{pj}, c_{lj} \) and \( c_{dj} \) are variable costs of conducting a given trial, they represent the cost of managing the trial \( (c_{mj}) \), cost related to clinical procedures performed on each subject \( (c_{pj}) \), the laboratory testing costs \( (c_{lj}) \), and the data management costs \( (c_{dj}) \).
**Appendix IV: Manufacturers and vaccine candidates**

**Table C: Manufacturers and vaccine candidates included in the study**

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine Candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>FluMist QIV</td>
</tr>
<tr>
<td>Pfizer</td>
<td>DNA Influenza Vaccine (PMED)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Adjuvanted vaccine - agatolimod sodium (CPG 7909)</td>
</tr>
<tr>
<td>Novartis</td>
<td>Optaflu</td>
</tr>
<tr>
<td>Novartis</td>
<td>EPI</td>
</tr>
<tr>
<td>Novartis</td>
<td>QIV (second B Strain)</td>
</tr>
<tr>
<td>Novartis</td>
<td>EPI</td>
</tr>
<tr>
<td>Novartis</td>
<td>QIV (second B Strain)</td>
</tr>
<tr>
<td>Merck</td>
<td>ISCOMATRIX adjuvant + M2 protein</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Flu Improved</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Cell culture</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>QIV (second B Strain)</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Fluarix TF</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>FluLaval TF</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Flu Improved Pediatric</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Flu Cell (cell culture)</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Universal Influenza Vaccine</td>
</tr>
<tr>
<td>Sanofi</td>
<td>intanza</td>
</tr>
<tr>
<td>Sanofi</td>
<td>QIV (second B Strain)</td>
</tr>
<tr>
<td>Sanofi</td>
<td>High Dose influenza vaccine</td>
</tr>
<tr>
<td>CSL</td>
<td>ISCOMATRIX® (CSL-412)</td>
</tr>
<tr>
<td>Solvay</td>
<td>Intranasal Flu Vaccine</td>
</tr>
<tr>
<td>Solvay</td>
<td>Influvac Cell Culture</td>
</tr>
<tr>
<td>AlphaVax x</td>
<td>VRP (Vaccine Replicon Particle) vaccine</td>
</tr>
<tr>
<td>Green Hills Biotech</td>
<td>DeltaFLU</td>
</tr>
<tr>
<td>Intercell</td>
<td>Iomai patch</td>
</tr>
<tr>
<td>Immune Targeting Systems (ITS) Limited (ITS)</td>
<td>Universal Influenza Vaccine (FP-01)</td>
</tr>
<tr>
<td>Juvaris</td>
<td>JVRS-100</td>
</tr>
<tr>
<td>NanoBio</td>
<td>NB-1008 using NanoStat adjuvant</td>
</tr>
<tr>
<td>NasVax</td>
<td>Influenza intramuscular</td>
</tr>
<tr>
<td>Omninvest</td>
<td>Fluval</td>
</tr>
<tr>
<td>PepTcell</td>
<td>Universal Influenza Vaccine</td>
</tr>
<tr>
<td>Protein Sciences</td>
<td>FluBlock</td>
</tr>
<tr>
<td>Vaxine</td>
<td>Advax(TM) – adjuvanted seasonal influenza vaccines</td>
</tr>
<tr>
<td>Vaxinnate</td>
<td>VAX102: M2e universal Influenza vaccine</td>
</tr>
<tr>
<td>Vaxinnate</td>
<td>VAX125: HA1 influenza vaccine</td>
</tr>
<tr>
<td>DelSite</td>
<td>GelVac powder</td>
</tr>
<tr>
<td>Company</td>
<td>Product</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Dynavax</td>
<td>Universal Flu Vaccine</td>
</tr>
<tr>
<td>Echo Therapeutics</td>
<td>SonoPrep device</td>
</tr>
<tr>
<td>BioDiem</td>
<td>LAIV Seasonal Vaccine</td>
</tr>
</tbody>
</table>
### Appendix V: Uncertainty analysis

**Table D**: Extreme values of analysis reflecting estimate uncertainty

<table>
<thead>
<tr>
<th></th>
<th>Least Expensive Scenario</th>
<th>Most Expensive Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase Length (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>0.25</td>
<td>4.75</td>
</tr>
<tr>
<td>Phase II</td>
<td>0.92</td>
<td>3.08</td>
</tr>
<tr>
<td>Phase III</td>
<td>2.48</td>
<td>5.58</td>
</tr>
<tr>
<td><strong>Number of Subjects per Trial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>15.00</td>
<td>595.00</td>
</tr>
<tr>
<td>Phase II</td>
<td>48.00</td>
<td>988.00</td>
</tr>
<tr>
<td>Phase III</td>
<td>220.00</td>
<td>18419.00</td>
</tr>
<tr>
<td><strong>Number of Studies per Phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Phase II</td>
<td>1.00</td>
<td>12.00</td>
</tr>
<tr>
<td>Phase III</td>
<td>2.00</td>
<td>4.00</td>
</tr>
<tr>
<td><strong>Transition Probability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I to II</td>
<td>59%</td>
<td>21%</td>
</tr>
<tr>
<td>Phase I to III</td>
<td>54%</td>
<td>7%</td>
</tr>
<tr>
<td>Phase I to Market</td>
<td>51%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Variable Clinical Development Cost/Subject (2010 CAD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>$5,101.34</td>
<td>$8,540.15</td>
</tr>
<tr>
<td>Phase II</td>
<td>$3,420.40</td>
<td>$5,318.54</td>
</tr>
<tr>
<td>Phase III</td>
<td>$2,323.32</td>
<td>$4,561.21</td>
</tr>
<tr>
<td><strong>Fixed Cost/Trial (2010 CAD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$70,385.00</td>
<td>$70,385.00</td>
</tr>
<tr>
<td><strong>Tax Return</strong></td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Cost of Capital</strong></td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Capitalized Expected Costs per Approved New Vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reporting Reference</td>
<td>Millions of 2018 CAD</td>
<td>Millions of 2028 CAD</td>
</tr>
<tr>
<td>Pre-Clinical Expenditures</td>
<td>1.69</td>
<td>19,161.12</td>
</tr>
<tr>
<td>Clinical Expenditures</td>
<td>1.76</td>
<td>7,395.34</td>
</tr>
<tr>
<td>Total R&amp;D Expenditures</td>
<td>3.46</td>
<td>26,556.46</td>
</tr>
<tr>
<td><strong>Capitalized Expected Total R&amp;D Costs per Approved New Vaccine in Millions of 2011 CAD</strong></td>
<td>2.80</td>
<td>15,822.76</td>
</tr>
</tbody>
</table>
Chapter 2

No Free Lunch: The Opportunity Cost of Developing Medical Technology

Authors
Ayman Chit\textsuperscript{1,2}, Ahmad Chit\textsuperscript{4}, Jayson Parker\textsuperscript{1}, Manny Papadimitropoulos\textsuperscript{1,4}, Murray Krahn\textsuperscript{1}, and Paul Grootendorst\textsuperscript{1}.

1. University of Toronto, Toronto, Ontario, Canada
2. Sanofi Pasteur, Toronto, Ontario, Canada
3. Rosen and Associates, Toronto, Ontario, Canada
4. Eli Lilly Canada Inc, Scarborough, Ontario, Canada

Corresponding author
Ayman Chit
Leslie Dan Faculty of Pharmacy, University of Toronto,
144 College Street, Room 601,
Toronto, ON, M5S 3M2, Canada
Tel: +1-647-406-0362
Ayman.Chit@utoronto.ca

Competing Interest & Funding
Ayman Chit is a former employee of GlaxoSmithKline (GSK) and a current employee of Sanofi Pasteur (SP). Ahmad Chit is an associate with Rosen and associates a firm that provides financial consulting services to the pharmaceutical industry. Jayson Parker has worked in the pharmaceutical industry and currently advises a hedge fund which invests in life sciences. Manny Papadimitropoulos is an employee of Eli Lilly & Company. Paul Grootendorst is an associate professor of Health Economics and has provided expert testimony and/or reports on behalf of both generic and branded drug companies and has received financial and in-kind research support from both generic and branded drug companies.
Other than Ayman Chit’s direct contribution, GSK and SP had no role in the conceiving the study, reviewing the findings, or decision to publish. All opinions expressed are solely those of the authors.

Word Count
Article excluding abstract, cover page, references and supplementary materials: 3,748
Abstract: 146
Abstract

The opportunity cost of the capital invested in medical technology R&D makes up a significant portion of the overall development cost, even as much as half in the case of pharmaceuticals, according to some reports. However, the literature on the cost of medical technology R&D is mixed in its opinion as to how, exactly, one should calculate this “hidden” cost. Some authors attempt to adopt models from the field of finance, while other prominent authors dismiss this practice as biased; arguing that it artificially inflates the R&D cost to justify higher prices for medical technology. In this article we examine the assumptions underpinning the cost of capital concept and describe in detail the various ways that it is currently being calculated in the field of finance. We then critique the estimation approaches used in the biomedical literature around the cost of medical technology R&D. Finally, we suggest an alternative standard based on pharmaceutical R&D cost calculations. Given the significant contribution of the cost of capital to the overall R&D cost, standardizing the calculation will be crucial in improving the utility of these estimates in the decision-making engaged in by R&D investors both in the public and private sector.

Introduction

Several prominent studies claim that costs associated with developing a new medicine have soared well beyond a billion dollars [28]. While in agreement about the soaring costs, the literature is mixed when it comes to identifying specific costs and their calculation. Not only does the literature present a wide range of overall cost estimates (from USD $161 million to USD $1.8 billion, in 2009 dollars) [1], but
there is heated debate over appropriate methods for estimating such costs [2,3,4,5]. One major point of disagreement is the so-called “cost of capital,” a specific form of “opportunity cost” relevant when describing the return that an enterprise must offer to entice monetary investments [2,5]. There is no question that accounting for such costs is warranted: pharmaceutical R&D is a lengthy and risky undertaking, using funds that might otherwise be used for other purposes. What appears to be under dispute is the manner and extent to which this “opportunity cost” should figure in the overall calculation. Indeed, this is an important dispute to resolve as the estimated value of medical technology R&D is highly dependent on the cost of capital, and it has been reported to account for 50% of DiMasi’s oft-cited $800 million cost of pharmaceutical R&D [6].

In economics, the total cost of an investment is calculated as the out-of-pocket cost plus the opportunity cost, where the opportunity cost refers to the value of the next highest valued alternate investment [29]. Consider a new graduate from a master’s program contemplating the cost of investing in a doctorate degree. The out-of-pocket costs are those paid to the university and could hypothetically add up to $40,000 over a four-year program. A major opportunity cost of the investment would equate to wages foregone by the new graduate by virtue of not working over those four years. Assuming an annual salary of $50,000 per year, the opportunity cost at $200,000 is staggeringly larger than the out-of-pocket costs alone. There is a further (smaller) opportunity cost the student experiences as a result of not investing the out of pocket costs. For instance, the $40,000 paid to the university could have been placed in a savings account earning a modest return. A total cost in
excess of $240,000 for a doctorate degree might still be well worth it; however, assuming the costs are only $40,000 when making the decision would be to significantly undervalue the activity.

Similarly, investors in the development of medical technologies face an out-of-pocket cost in the form of R&D expenditures as well as an opportunity cost in the form of profits foregone from not investing in the next highest value alternate. Hence, if the profits on the R&D investment are not sufficiently high to compensate investors on what the committed funds might have been earning elsewhere, then R&D investments will be re-allocated to other endeavors. Since investors don’t manage the R&D process directly, and only fund it, they are free to spend their time on other activities and thus one does not need to account for the opportunity cost of their labor.

It is important to walk through some key points to fully understand this more complex case of opportunity cost. In doing so, we will define who the investors in health technology R&D are and examine how opportunity cost is calculated from their perspective. In conclusion, we will review and assess the various methods used in the literature to account for opportunity cost in medical technology R&D estimates.

**Opportunity Cost of Investors in Medical Technology R&D**

An investor will always have multiple investment options other than simply depositing their funds in a savings account. These can range from investments in government bonds, which generally guarantee a specific interest rate and ensure
the security of the principal amount invested, to stock market investments, which can provide higher rates of return but also come with a higher risk of losing (sometimes considerable) value. The opportunity cost to investors in these options differs by virtue of the inherent risk and reward scenario of each.

There are two major types of R&D investors: government investors and corporate investors. Government investors tend to provide R&D funding at the early stages of technological discovery as well as, sometimes, research and commercialization grants to pharmaceutical firms during the later stages of technological development. The latter type of funding is less common than the discovery type of funding, which mainly goes to university-based researchers and to small startups. A recent review by Zhuang and colleagues review how governments around the world estimate their cost of capital [27]. The authors note that there are significant differences in how global governments estimate their cost of capital with developed countries estimating lower rates of 3-7% and developing countries estimating 8-15%. Of particular importance to R&D spending, the US Office of Management and Budget indicate that Treasury borrowing rates should be used as a cost of capital for internal government investments. Figure 2 shows the historic borrowing rates on 10 year US government Treasury Bills.

The opportunity cost of private corporate investors is more clear-cut; to explain this it is helpful to clarify the ownership structure of corporations. Figure 2 provides an overview of the typical life cycle and ownership structure of a publicly held company. After the Initial Public Offering (IPO), shareholders and bondholders own the company. A shareholder owns a stake in the company through the purchase of
shares, while a bondholder owns a portion of the company’s debt by loaning it money with a set interest rate and vesting period. These owners face different risks and reward structures. The difference in risk is most clear when one considers the bankruptcy situation: if a company is liquidated, bondholders are paid out first, followed by shareholders, who receive compensation only if any capital is left over. On the return side, bondholders receive a pre-set return on what they loan the company which is independent from short-term fluctuations in share price. In contrast, shareholder reward is directly tied to the financial performance of the company and its share price. Therefore, the opportunity cost to these two types of owners is different, because the value of the next highest value investment to them is different.

Both bondholders and shareholders experience different levels of overall risk; however, they both face a similar baseline level of risk because both their principal investments are not guaranteed in the same way they would be had they both purchased government bonds. Thus, the opportunity cost for investors in the stock market is higher than it is for those investing in the government bond market. The rate of return for investors in the government bond market is referred to as the risk-free rate of return (RFR). It is important to note that the term “risk free” is being challenged by the current financial turmoil in Europe, where several governments are contemplating default on their debt. In such a scenario, the principal of any government bond investment would no longer be guaranteed.¹ Nevertheless,

¹ As a result of the 2008 global economic recession, the notion of risk-free investments was deeply shaken when European governments such as Portugal, Ireland, Greece, Cyprus and Spain all contemplated defaulting on their national debt. Once the news was released, investors began to shy
government bonds are considered to be among the safest investment opportunities available and provide baseline rates associated with the time value of money (see Appendix 1 for a basic explanation of the time value of money). In contrast, stock market investments, which come with no guarantees on principal amounts, take on additional risk, which requires a higher rate of return than the RFR. This is commonly known as the risk premium. Hence, the risk premium required by a shareholder is different than that expected by a bondholder due to the different amount of risk they carry.

Next we turn to how the cost of capital for a given corporation is empirically estimated. This estimation is arrived at by considering the sources of a company’s capital and then calculating a weighted average of the returns from the next alternate investments for each source of capital. There are four steps to this estimation.

The first step is to quantify the inherent risk in a particular company relative to a diversified market portfolio. The diversified market portfolio is selected as a reference point because it is generally a combination of stocks that a portfolio manager can assemble to minimize risk to an investor from stock volatility. The idea is that stocks are selected such that short-term value declines in one stock will coincide with increases in another; hence, over time, the portfolio will have a

away from purchasing government bonds issued by these countries, which seriously constrained the ability of these governments to raise additional money through borrowing. To entice lenders, governments had to increase significantly the return on these government bonds (a reflection of the underlying risk of default). Simultaneously, the return on bonds issued by the few governments that appeared resilient in the face of the global recession, such as Germany and Canada, dropped to record lows.
smooth increasing return curve. Stock market indices exhibit this property, as can be seen in Figure 3.

Work by Beaver, Kettler and Scholes laid the foundation for assessing the relative risk of a given company to a well-diversified market portfolio [10,11,12]. They derive a statistic, Beta, which is now commonly used in the financial sector [13]. Beta is used as a measure of how a given stock moves relative to movements in the market. The value is mathematically defined as the covariance of a stock A with the market portfolio M, divided by the market portfolio M's variance. In other words, it evaluates the change in a stock's rate of return in relation to changes in the market's rate of return. If Beta is above 1, then the stock has higher risk than the market; if Beta is between 1 and zero, then the stock has lower risk than the market, and investors should not expect a return from it higher than that generated by the general market. Finally, in the rare case that a Beta is negative, the stock has returns in opposition to the stock market returns: low when the market is high, and vice versa.

Beta statistics can also be calculated by sector. Table 1 summarizes Beta values for the Pharmaceutical, Biotechnology and Device sectors. Beta values for public companies are routinely reviewed and updated for use by investment portfolio managers and others in the financial sector. These values are periodically published by various financial reporting companies such as Thomson Reuters [14], Morning star [15] and Bloomberg [16].

The second step in estimating the cost of capital is to determine how much of the company's operations are financed by debt vs. equity. Although the finances of
pharmaceutical companies predominantly come from equity, it is rarely the case that a sector or company depends entirely on equity financing. Generally, if a company does not have cash on hand through retained earnings it can obtain the necessary capital through borrowing by selling bonds. The relative amounts of debt and equity financing within a public company can be determined by reviewing public financial reports, which by law must disclose the relative amounts.

Since both sources of capital represent different opportunity costs to the respective investors, the third step is to estimate the opportunity cost of the debt and equity separately. The opportunity cost of debt is relatively straightforward: it is equal to the pre-set interest rate agreed to with the bondholders. Unlike lenders, shareholders do not enter into an agreement with the company on a set rate of interest for their investment. To help estimate the opportunity cost of financing projects through shareholder equity, the investment community turns to a few models. Chief amongst these is the Capital Asset Pricing Model (CAPM). CAPM was first suggested by William Sharp in 1964, and it has remained resilient as a dominant model until today [18]. CAPM defines the shareholder opportunity cost, also known as “cost of equity capital”, as the sum of the RFR and an adjusted difference between the market return and the RFR. The adjustment factor is the Beta for the particular stock. Mathematically, this can be represented as follows:

$$E(R_i) = R_{FR} + \beta_i (R_M - R_{FR})$$

where $E(R_i)$ is the expected cost of equity capital for investing in stock $i$, $\beta_i$ is the Beta value for stock $i$, and $R_M$ is the market rate of return.
Harrington has calculated cost of equity capital by health technology sector (see Table 3) [19].

The *fourth and final step* in estimating the cost of capital is to compute a weighted average cost for both sources of capital. This is known as the Weighted Average Cost of Capital (WACC) calculation (see Table 2). As with Beta values, WACC values are regularly calculated and published by financial reporting companies. A company's WACC value is utilized by management in financial evaluations of investment opportunities. Appendix 2 provides more insight into how WACC can influence business decision making.

**Critical Appraisal: The Cost of Capital & Drug Development**

A review of the cost of medical technology R&D literature reveals a variety of opinions regarding the opportunity cost accounting necessary to estimate overall costs of pharmaceutical R&D. Before we critique these, we will describe our recommendation on the most prudent way of approaching this calculation. To start, the R&D cash outlays over the time horizon of the R&D process need to be delineated. These should then be associated with the various funding sources, that is, government grants or corporate investments. Next, the cost of capital for each of these funding sources should be allocated over the appropriate investment period, which in the case of pharmaceutical R&D can be quite long. Once this is all in place, the cost of capital for the out-of-pocket R&D expenditure can be calculated for the corresponding development period. When looking back retrospectively to estimate R&D costs, cost of capital can be directly calculated. However, when one seeks to
forecast the cost of future R&D activity, careful consideration must be given to the
cost of capital estimates that are chosen. The choice should be informed by historic
opportunity costs and by forward-looking assumptions on the future economic state
of the funding institutions. For example, when retrospectively evaluating the cost of
R&D for a given technology, if Phases I to III were funded by public companies
between 1990 and 2010, then the cost of capital for those companies over that
specific time period would be used. Similarly, if pre-clinical development for the
project was funded by government grants, then the appropriate government
opportunity cost for that period would be used for that portion of the investment.
Accurate determination of the funding sources for various cash outlays can be
challenging; therefore, researchers should conduct thorough sensitivity analysis on
the cost of capital estimates they choose. This enables the reader to appreciate the
full range of possible, even if not likely, outcomes of the investment; it involves
calculating the range of R&D costs using a range of cost of capital estimates. Upper
and lower bounds of the sensitivity analysis should be restricted by the highest
WACC and the lowest RFR for the duration of the investment period.

DiMasi et al have published several estimates of R&D costs for the US
pharmaceutical sector [4,6,20]. Their first two major articles reported costs for the
periods 1970-1982 and 1980–1999 for “self-originating drugs” – these are drugs
that are developed entirely in-house. This allowed them to consider only the cost of
capital specific to these companies. Throughout their work, however, they rely
solely on the cost of equity capital. In justifying their methods, the authors state that
debt-to-equity ratios for pharmaceutical companies are predominated by equity.
Accordingly, the authors compute CAPM estimates of the cost of equity capital and apply it to R&D outlays over the entire period of development. This practice likely over estimates the costs since the authors assume, without providing clear supporting evidence, that the cost of debt capital is insignificant. Work by Pattikawa shows that the pharmaceutical sector has, indeed, carried less debt in recent years than in the past [21]. Nevertheless, debt-to-equity ratios of 0.36 and 0.16 for the periods 1970-1989 and 1989-2005, respectively, don’t appear negligible to the extent that they can be ignored, especially given that the cost of debt capital is generally significantly lower than the cost of equity capital [21,22].

Light and colleagues adopt a different approach in their recent publication on estimating the cost of Rotavirus vaccine development [5]. One of the major points underpinning Light et al’s position is that market-based costs of capital are fundamentally flawed, since returns from equity markets are unreliable [5]. They cite that in 2008 investors in the American Exchange Pharmaceutical Index of Stocks would have lost money on investments purchased in 1998 [5]. The group recommends that cost of capital adjustments be made based on either U.S. Government guideline rates of 7% or 3%; or on the Canadian Agency for Drugs and Technologies in Health’s (CADTH) discount rate of 5% [5]. These rates are used by the US and Canadian governments for internal decision making regarding, for example, health technology adoption. In our opinion, there are several reasons why Light’s approach under estimates the cost of drug development.

First, is their application of a single cost of capital rate for all three stages of drug development; in reality different funding sources contribute to drug development
and each has a unique cost of capital. Instead of specifically allocating costs of capital, Light et al use government rates to adjust R&D expenditures; this in effect employs the lowest cost of capital amongst any funding body and subsequently introduces downward bias. Secondly, the assumption that financial markets exhibit negative performance can also lead to under estimating R&D costs. This assumption was based on comparing two time points, 1998 and 2008. From an examination of Figure 3, it can be seen that the overall long-term trend in market performance is positive; however, 2008 is an anomaly in that it was the local minima of one of the most severe market recession of modern times.

Other authors such as Angell have also in our opinion under estimate the true cost of R&D [8]. In her book, Angell argues that R&D costs should not be subject to opportunity cost adjustments at all, the rationale being that pharmaceutical companies have no choice but to spend on R&D because they have no option but to stay in the pharmaceutical business [8]. It should be mentioned that Light and colleagues also adopt this position, but they still hold that a government risk-free rate should be applied to account for cost of capital [5]. Ferguson has rebutted Angell’s call to ignore the opportunity cost of R&D in a recent book review [22]. Ferguson refers to a publicized real life example to illustrate how opportunity cost changes the course of already specialized companies [22]. The example shows that if specialized companies encounter business opportunities that, relative to their core business, provide better returns for equal or less risk, they will diversify towards this activity. In this manner, the company moves towards higher value for their investors. Work by Hill and Hansen underscore this for the pharmaceutical
sector, summarizing empirical data on corporate development activities showing that, like other sectors, pharmaceutical companies also diversify [23]. Illustrative examples of this diversification include the over the counter drug business units in companies such as Johnson & Johnson and GlaxoSmithKline, and, more recently, the move by some pharmaceutical companies such as Sanofi towards acquiring generic business units [24, 25, 26]. These examples illustrate how companies currently engaged in R&D can exercise the option not to do so and divert their investments to other business when R&D returns become less attractive in comparison.

**Conclusion**

Accurate estimation of pharmaceutical R&D costs is important whenever an R&D investment decision is being made, be it by government agencies or industry. Because the resources invested in R&D can be large and spent over a long period of time, it is important to account for the opportunity cost of locking up these funds for the duration of the investment period. We have offered insight into how such an opportunity cost should be estimated. When estimating these costs, investors, analysts and researchers should use cost of capital rates that reflect both the Institutions funding the various R&D projects as well as the appropriate development time periods. Comprehensive sensitivity analysis is highly recommended in cases where funding contributions cannot be fully disentangled.
References


http://dx.doi.org/10.2139/ssrn.1512938


### Tables

**Table 1**: Beta values calculated by Scott Harrington for various segments of the healthcare technology industry [19]

<table>
<thead>
<tr>
<th></th>
<th>Beta 2001-2005</th>
<th>Beta for period 2006-2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharma</td>
<td>Biotech</td>
</tr>
<tr>
<td>Large</td>
<td>0.65</td>
<td>1.302</td>
</tr>
<tr>
<td>Small</td>
<td>0.795</td>
<td>1.35</td>
</tr>
</tbody>
</table>

*Table adapted from reference 19*
Table 2: Cost of equity capital calculated by Scott Harrington for various segments of the healthcare technology industry [19]

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharma</td>
<td>Biotech</td>
</tr>
<tr>
<td>Large</td>
<td>9.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Small</td>
<td>10.6</td>
<td>14.5</td>
</tr>
</tbody>
</table>

*Table adapted from reference 19*
Figures

Figure 1: Historic rates of return from US government 10-year T-Bills

Data obtained from Bloomberg Terminal (2013)
Figure 2: life cycle of a typical corporation
Overview of a public company’s creation, growth and bankruptcy. Before an initial public offering (IPO) the risk of a company’s failure lays with the entrepreneurs and Venture Capitalists (VCs). After an IPO the risk is transferred to the share holders. Lenders to a public company will also bare business failure risk, however, they normally bare less risk than share holders. This is illustrated by the bankruptcy process during which lenders are paid back with interest before share holders. The entrepreneur and the VCs are rewarded for their venture during the sale of the company through the IPO process. Share holders that purchase the company are rewarded over time as the share price increases and as management pays them dividend from sales revenue. Debt lenders are paid an interest rate agreed upon when the loan is issued.

Additional details:
- Funding: Venture Capital (VC)
- Ownership: Split between VC firm and entrepreneur, control dependent on funding deal
- Management: Entrepreneur and/or professional management

For a public company:
- Funding: Sales revenue and debt
- Ownership: Share holders and Lenders
- Management: Professional management reporting to shareholders

For a private company:
- Funding: Revenue from sale of shares
- Ownership: Share holders
- Management: Professional management reporting to shareholders

During bankruptcy the company’s assets are sold off. Lenders are paid off first, share holders are paid off from remaining funds.

Equity Ownership:
- Entrepreneur
- VC Firm
- Share Holders
- Lenders
**Figure 3:** The historic performance of the Standards and Poors (S&P) 500 group of companies

*Data obtained from Bloomberg Terminal (2013)*
Supplemental Material

Appendix I: Time Value of Money

The first building block in understanding an investor’s opportunity cost is a description of the time value of money. Any monetary-based decision we make takes into consideration the relevant period of time impacted by the decision. Decisions that affect our financial position in the short term are straightforward in nature. For example, let us assume we are heading up the development of a new vaccine in a Biotechnology company and are in need of a new Phase I Clinical trial. We have obtained offers from two Contract Research Organizations (CROs): CRO A offers $1,100,000, and CRO B offers $1,000,000. All things being equal, we would obviously choose to work with CRO B. In this case, only the direct monetary impact of the decision (savings of $100,000) matters.

Now, let’s assume that a third CRO (CRO C) also present us a bid of $1,000,000. But whereas CRO B will accept payment in 12 months, CRO C requires immediate payment. Our decision can no longer be attributed to the cost saving, since we would be paying the same amount to each of the CROs. All things being equal, our intrinsic decision would be to choose to conduct our Phase I trial with CRO B and pay in 12 months. Choosing to delay the payment is a result of us considering the time value of money: a dollar today is worth more to us than a dollar tomorrow.

Long-term decision making, therefore, requires more than just a simple monetary comparison of options. It must also take into account the time value of money. This value is not just an intrinsic notion: it can be quantified. Let’s assume that we are able to place the $1,000,000 in a savings account, which provides a 5% annual
return on deposits. The payment timetable for CRO B allows us to earn a year’s worth of interest on the $1,000,000 before using it to pay the CRO. This leaves us with $50,000 at the end of the year and our completed Phase I study. In comparison, CRO C’s immediate payment option would leave us with just the Phase I trial results at year’s end. Placing the $1,000,000 in a savings account is significantly less risky than investing it in R&D activity since the return is much more certain. If the savings account returning 5% annually met the definition of being the next highest valued alternate use of resources, then the opportunity costs, and thus the cost of that capital to our fictitious R&D investor, would be an annual interest rate of 5%.

**Appendix II: Sample calculation of the Weighted Average Cost of Capital (WACC)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
<th>Weight</th>
<th>Cost</th>
<th>WACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debt</td>
<td>$150</td>
<td>[A]</td>
<td>10%</td>
<td>6% [D]*[F]</td>
</tr>
<tr>
<td>Equity</td>
<td>$100</td>
<td>[B]</td>
<td>15%</td>
<td>6% [E]*[G]</td>
</tr>
<tr>
<td>Total</td>
<td>$250</td>
<td>[C]</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

**Appendix III: Incorporating Opportunity Cost into Business Management**

While exercising social and ethical responsibility, corporations are expected to engage in activity to maximize shareholder value. Projects that a company takes on must promise sufficient returns to compensate for investors’ out-of-pocket costs as well as opportunity costs. Net Present Value (NPV) analysis is one tool that is
commonly used by a company’s management to prioritize investments in various business projects based on their expected costs and returns. As an example, this type of analysis could aid in deciding if a Pharmaceutical company should continue to develop one of its home-grown drug candidates or if it should divert its investment to acquiring a promising drug from a startup company. NPV analysis involves first forecasting over time the expected out-of-pocket costs, and the returns, from a given project. In the aforementioned example, this would be all the costs related to commercializing the two options (R&D, licensing, manufacturing, sales, marketing, etc..) and the expected returns on them (sale revenue). The cash flows for each separate project are then discounted back to current time at an annual rate equal to the company’s opportunity cost. The discount rate is known as the cost of capital. The discounted cash flows for each project are then summed up individually and compared. The results of the analysis for each project could be either a positive or negative number.

Generally, businesses will have fiscal planning that allows them to compare and contrast projects with positive NPVs. The danger of overestimating a company’s cost of capital is that many stable business opportunities with lower rates of return, but higher probability of return, might be overlooked. This could force companies to accumulate a portfolio of very risky projects while at the same time leaving more stable opportunities available to competing companies. On the other hand, underestimating the cost of capital could move companies away from risk, in which case innovative, potentially transformational projects would likely not be considered. Management will make final investment decisions using additional
information beyond the NPV, such as the scale of the project as well as environmental risks that are difficult to quantify (political, social, economic and technological). Management will ultimately select projects based on a balanced assessment.
Chapter 3

Prioritizing Evidence Generation for the Development of Improved Elderly Influenza Vaccines - A Value of Information Analysis

Ayman Chit\textsuperscript{1,2}, Murray Krahn\textsuperscript{1}, Paul Grootendorst\textsuperscript{1}.

1. University of Toronto, Toronto, Ontario, Canada
2. Sanofi Pasteur, Toronto, Ontario, Canada

\textbf{Corresponding author}

Ayman Chit

Leslie Dan Faculty of Pharmacy, University of Toronto,
144 College Street, Room 601,
Toronto, ON, M5S 3M2, Canada
Tel: +1-416-587-4651
Ayman.Chit@utoronto.ca

\textbf{Competing Interest & Funding}

Ayman Chit was an employee of GlaxoSmithKline (GSK) and is currently an employee of Sanofi Pasteur (SP). Paul Grootendorst has provided expert testimony and/or reports on behalf of both generic and branded drug companies and has received financial and in-kind research support from pharmaceutical companies. Other than Ayman Chit’s direct contribution, SP and GSK had no role in the study design, interpretation of results, or decision to publish. All opinions expressed are solely those of the authors.

\textbf{Word Count}

Article excluding abstract, cover page, references and supplementary materials: 2,985
Abstract: 277
Abstract

**Background:** Health technology assessment (HTA) bodies have grown in influence over the past decade. These agencies require that drug developers provide evidence of the value for money offered by their products. To do so, drug developers routinely use cost effectiveness analysis (CEA). The guidance to manufacturers on what evidence would optimally support acceptable CEA is scant. The absence of such guidance and the increased emphasis on CEA can add significant risk to the vaccine development process.

**Methods:** We perform a Value of Information (VOI) analysis on the parameters of a cost effectiveness model designed to evaluate new influenza vaccines designed for use in elderly adults. In the base case the new influenza vaccine doubles protection against influenza infection requiring only a general practitioner visit. The VOI analysis allows us to isolate parameters that drive a CEA.

**Results:** The cost effectiveness of influenza vaccines with improved efficacy is highly sensitive to the vaccine’s ability to reduce severe outcomes. In the base case there was no value in further studying any other model parameters if price premiums for the new vaccine were below $40/dose. At a price premium above this, studies focused on providing new information on vaccine efficacy against hospitalization would be the most valuable to reducing decision uncertainty in a CEA.

**Conclusion:** In the absences of clear guidance to manufacturers from HTA agencies, VOI analysis can be a valuable tool to prioritize research agendas. Studying vaccine efficacy against severe outcomes such as hospitalization is an important research
target for assessing the cost effectiveness of new influenza vaccines. By incorporating this target into research programs, manufacturers stand a better chance at meeting the evidence needs of HTA agencies and payers.
Introduction

Regulators such as the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada have created comprehensive product development guidelines for vaccine manufacturers. Additionally, these regulators have offered formal opportunities to provide feedback on manufacturer development plans before hefty R&D investments are made. Despite this guidance, failure rates of medicines during development remain relatively high [1].

In contrast, Health Technology Assessment (HTA) agencies, such as the Advisory Committee on Immunization Practices (ACIP) in the US and the National Advisory Committee on Immunization (NACI) in Canada have significant influence over vaccine adoption. ACIP and NACI have recently bolstered their review process to included economic appraisals [2, 3]. Both ACIP and NACI, despite their growing influence on the commercial success of new vaccines, do not offer manufacturers guidance during the vaccine development process. For instance, ACIP working groups and committee deliberation do not start until a new vaccine submission is made to FDA [2]. The lack of communication between manufacturers and government recommending bodies on health economic considerations of new vaccines as they are being developed can add further risk to the already risky new vaccine development process. Evidence of this can be seen from the work of Anupam and Phillipson [4]. The authors report that a large number of market authorized products in Australia fail to achieve reimbursement by public payers due to negative HTA recommendations.
We are particularly concerned about the development of new and improved influenza vaccine. Influenza is known to be a major cause of excess morbidity and mortality during the winter seasons [5]. Vaccination is considered the most effective preventative measure to protect against influenza infection [6]. Various manufacturers can theoretically improve the protective effects of vaccination using several approaches that are currently under development [7]. From a traditional regulatory perspective, FDA requires that vaccine developers provide experimental (RCT) evidence of efficacy against clinical outcomes of influenza infection to qualify for regulatory review [8]. Accordingly, the most commonly used end point in influenza vaccine phase III efficacy studies, is the incidence of laboratory confirmed influenza like illness (ILI). However, it is not clear if this research design will be sufficient to provide the evidence required by HTA bodies to make a decision on the cost-effectiveness of new vaccine candidates. For instance, it is not clear if manufacturers should invest further R&D funds to power phase III trials to investigate the efficacy of new vaccines in preventing more severe complications of influenza that result in costly hospitalizations.

In the absence of clear HTA guidance to developers, Value of Information (VOI) analysis can be a powerful tool to guide manufacturers on how to incorporate health economic considerations into the design of their R&D programs. VOI analysis can provide the upper limit of what should be invested in R&D to further study specific outcomes that impact an adoption decision based on a cost effectiveness model. Today these methods are gaining popularity to help prioritize medical research [9, 10]. However, adoption in the vaccine literature is still very limited. In this paper
we use the dilemma around influenza vaccine development as a case example of how VOI can help inform the design of R&D agendas.

**Methods**

**Analysis Overview**

We constructed a Markov model that can compare the cost effectiveness of two influenza vaccines. Throughout the analysis we set one of the vaccines to be the standard of care trivalent inactivated influenza vaccine (TIV). As a base case, we set the comparator vaccine to be an improved influenza vaccine that doubles the protection against influenza infection requiring a general practitioner (GP) visit. The ability of the vaccine to provide additional protection against more severe infections was set to be unknown. This hypothetical base case was set up to allow the new influenza vaccine some minimal advantage that would be the basis for a price premium over TIV. From this base case we conducted a VOI to understand the influence of model parameters on cost effectiveness and research priorities.

**Model**

We used TreeAge Pro 2009 software to construct a Markov model. Figure 1 shows the 3 health states that our study cohort can occupy as well as an outline of the model structure. Our cycle length is 6 months, alternating between the influenza season (November to April) and the low transmission season (May to October), with the very first cycle starting in November. Individuals all start at 65 years of age living in the community. They are then all vaccinated against seasonal influenza
every other cycle with either the currently approved TIV or a new influenza vaccine. During each cycle individuals can contract influenza only once. Infected individuals may require hospitalization or a GP visit to manage their illness; alternatively they may require no intervention. Subsequent to these choices individuals may transition back into the community or could die. Individuals may transition into nursing homes only after hospitalization due to influenza and may subsequently be discharged back into the community.

We assigned transitional costs and utilities to influenza related hospitalizations, GP visits and deaths. Markov state utilities where assigned to each health state and costs were assigned only to the nursing home health state. Variables used in our model are summarized in table 1. We compared our results with the commonly cited threshold for WTP of $50,000/QALY. Future costs and effects are discounted at a 5% rate based on Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines [11].

**Modeling Assumptions**

We invoked the following assumptions. In our model we assume 100% subject compliance with yearly vaccination against seasonal influenza from the age of 65 until death. We also assume that influenza infection can only occur once every 6 months. Infected individuals only resort to hospitalization or GP visits as treatment for influenza and alternative interventions like emergency room visits are not taken into consideration. The severity of immunosenescence for all individuals is assumed to be constant from the age of 65 until death. We also did not take herd
immunity into consideration. We assumed that the new vaccine demonstrated non inferiority or superiority to the currently approved vaccine. Finally, we assumed the government would pay for all health care and nursing home costs in the model and will not renegotiate yearly vaccine prices with manufacturer.

**Vaccine Effectiveness**

During the influenza season (November – April) subjects are at highest risk for influenza infection [12]. In the off season (May to October) we estimated the base line risk of influenza infection to be substantially lower. In our model the individual’s base line risk of being infected with influenza was also varied based on living status. Once individuals transitioned into a nursing home, their relative risk of acquiring influenza was set at 1.33 times the base line risk of community dwellers [13].

To model the efficacy of the currently marketed TIVs we used efficacy estimates from the meta-analysis by Jefferson et al [14]. These values are summarized in Table 1. The equations below summarize how the new vaccine’s efficacy is modeled

\[
NVE_{GP} = 1 - (RR_{GP} \times \Omega_{GP})
\]

\[
NVE_{Hosp} = 1 - (RR_{Hosp} \times \Omega_{Hosp})
\]

\[
NVE_{Death} = 1 - (RR_{Death} \times \Omega_{Death})
\]

where: \(NVE_{GP}, NVE_{Hosp}, NVE_{Death}\) are the annual new vaccine efficacies against GP visits, hospitalization and death respectively. For recipients of the TIV, the relative risks of requiring a GP visit, hospitalization or experiencing death are represented by \(RR_{GP}, RR_{Hosp}, RR_{Death}\) respectively. To model the efficacy of the new vaccine we
multiplied the relative risks of infection for the TIV vaccine by a factor $\Omega$ ranging between 1 and 0. $\Omega_{GP}$, $\Omega_{Hosp}$ and $\Omega_{Death}$ facilitate modeling the improved efficacy of the new vaccine in reducing the relative risk of requiring a GP visit, hospitalization or experiencing death respectively. In doing so we assume that no new vaccine would be approved unless it was at least non-inferior to TIV. The multiplication factors and their assumed distributions are summarized in Table 1.

For the base case, uniform distributions between 0 and 1 were selected to represent $\Omega_{Hosp}$ and $\Omega_{Death}$. These distributions are selected as it is unlikely that new vaccines, at time of regulatory approval, will have data on their comparative vaccine efficacy against severe outcomes. However, implicitly we are assuming that no new vaccine would offer less protection against severe outcomes, as this will likely be a major safety issue. A gamma distribution with a mean of 0.5 and standard deviation (SD) of 0.14 was assumed for $\Omega_{GP}$. This distribution was based on the assumption that companies aspiring towards a price premium over the vaccines already on the market would need to demonstrate some added benefit over the SOC vaccine.

Utilities

Our model measures effectiveness in terms of quality adjusted life years. Utilities were obtained from published studies for the health states represented in the model for community dwelling elderly. It is expected that the values are lower for institutionalized population relative to community dwelling individuals. However, since data for institutionalized elderly is not published, we assigned the same utility values for both living in the community and in institutions. Utilities were then adjusted for the patients who experience transition states. Our model assigns a loss
of utility per day of 0.65 for influenza and 0.5 for hospitalization [15]. In each cycle, the average duration of influenza is considered 7 days and each hospitalization lasts 10 days [15].

**Costs**

Cost of TIV was assumed to be 7 Canadian dollars. A range of price premiums were then considered for new vaccines. The cost of outpatient visits and hospitalizations were obtained from an economic appraisal study of the Universal Mass Influenza Immunization Program in Ontario [16]. All costs are converted to $CAD 2010 values.

**Sensitivity Analysis**

We conducted multiple deterministic and probabilistic sensitivity analysis. The deterministic impacts of each of the components of new vaccine effectiveness (against GP visits, hospitalizations and death) were investigated at a range of new technology prices. We also conducted a probabilistic sensitivity analysis on all the model parameters at various new technology prices.

**Value of Information (VOI) Analysis**

In this work we used Expected Value of Perfect Information (EVPI) and Expected Value of Parameter Perfect Information (EVPPI) methods as described by Briggs, Claxton and Sculpher [17]. VOI is a Bayesian decision analytic approach, which acknowledges that the decision to adopt and reimburse the strategy with the highest expected NMB is based on the currently available information that is surrounded by uncertainty. Making a wrong decision will therefore have a cost
equal to the difference between the benefits of the correct decision and the lesser benefits of the wrong decision. In other words the expected cost of uncertainty is a function of i) the probability that a decision based on mean net benefit is wrong and ii) the size of the opportunity loss if the wrong decision is made. EVPI defines the most that should be paid for information to resolve all uncertainty associated with a decision. While EVPPI defines the most that should be paid to remove uncertainty associated with a specific model parameter.

We investigated the EVPPI for the aggregate vaccine efficacy parameters of the new vaccine at various WTP thresholds and various new technology prices. We also studied EVPPI of the separate vaccine efficacy parameters (against GP visits, hospitalization and death) at different WTP thresholds. Finally, we investigated the EVPPI of the aggregated natural history of disease parameters, the aggregate utility parameters and aggregate costs parameters. These final sets of EVPPIs were investigated at the incremental cost effectiveness ratio (ICER) and the societal WTP. Since we are adopting a Canadian perspective, we report the population EVPPI for eligible seniors in Canada. Given that our model is a cohort model that takes a lifetime perspective, the EVPPI estimates reported reflect a lifetime use (starting at the age of 65) of an improved vaccine compared to the SOC vaccine. We used an annual discount rate of 5%. Appendix 1 provides further detail on the EVPI and EVPPI methodology we used in our analysis.
Results

Sensitivity Analysis

We conducted various deterministic sensitivity analyses to investigate which vaccine efficacy components have the largest impact on the cost effectiveness of a new influenza vaccine. Figure 4 shows these results. Vaccine efficacy against mild outcomes has the lowest impact on cost effectiveness, followed by vaccine efficacy against death. Vaccine efficacy against hospitalizations demonstrates the highest impact on cost effectiveness. Further, in the presence of evidence that a new vaccine cannot provide additional protection against severe outcomes, the new vaccine will only be cost effective at modest price premiums.

We also conducted probabilistic sensitivity analysis (PSA) on the base case at different price premiums for the new vaccine. From this analysis, only when price premium exceeds $160 does the probability that the new vaccine is cost effective dips to below 50%.

Value of Information Analysis

To understand if the value of additional vaccine efficacy data under base case assumptions, we plotted population EVPPI curves for the aggregated new vaccine efficacy parameters at various new technology price premiums. Figure 5 summarizes these plots. From this analysis it can be seen that there is a value of
further studying vaccine efficacy only for vaccines prices at a $40/dose premium or higher. This is provided the societal WTP is $50,000/QALY.

In Figure 6 we investigate whether at a price premium of $40/dose there was any value in studying other model parameters. From this analysis we observe that there is no value in further studying other model parameters asides from the vaccine efficacy of the new vaccine. This is given a WTP of $50,000/QALY and a price premium of $40 or lower.

Subsequently we investigated which component of the vaccine efficacy was most valuable to study. In doing so we plotted population EVPPI against WTP for the aggregate vaccine efficacy parameters as well as for each vaccine efficacy parameter component (GP visits, hospitalizations and deaths) separately. The results are summarized in Figure 7. These data demonstrate that resulting uncertainty around vaccine efficacy against hospitalization provides the highest value, followed by vaccine efficacy against death. Further research to resolve uncertainty around vaccine efficacy against mild disease provides the least relative value.

Table 2 shows the value of information to a country like Canada. In this context it can be seen that population EVPPI can become quite substantial if the technology is expected to be used for a prolonged period of time. Given that such technology will likely be sold at a global scale, these results demonstrate that the EVPPI, if calculated at a global level, can be quite substantive.
Discussion

Recently, the cost-effectiveness of potentially improved seasonal influenza vaccines was estimated in a number of studies [15, 18, 19, 20]. A far larger number of studies have assessed the economic value of influenza vaccines in general [16, 21, 22, 23, 24, 25, 26, 27]. None of these studies have evaluated the VOI around parameter uncertainty. Therefore, our study is the first to systematically investigate this question and provide guidance to influenza vaccine developers. In our study it is clear that society most highly values an elderly flu vaccine that can prevent severe outcomes of influenza. Vaccine developers that can deliver new vaccines with these proven characteristics will be maximizing the social value of their product and in the process will have the opportunity to maximize their revenues.

Like any modeling study, our investigation has some limitations. First, we assumed that vaccine efficacies against disease requiring a GP visit, hospitalization, or resulting in death were independent from one another. However, in reality some severe influenza infections would first manifest in a mild form. Thus, preventing milder disease cases would have a downstream effect on reducing some severe infections. Secondly, we did not take transmission dynamics and herd effects into consideration. However, our analysis is limited to the elderly who, unlike children, are not major disease transmitters of influenza. Thus we don’t anticipate that herd effects would change our conclusions substantially. Under both limitations, we are likely overestimating the importance of investing further in R&D to study severe
outcomes of influenza infection. Further, this study was based on the assumption that manufacturers aim to design a vaccine that improves on efficacy. However, this will not always be the primary design objective. For instance, some manufacturers might be looking to develop products that are easier to administer, simpler to transport or cheaper to manufacture. Thus our study is meant to draw the research community to VOI analysis as a tool to help tailor R&D programs towards pertinent evidence generation to inform economic evaluations. Finally, VOI analysis we conducted was based on a WTP threshold of $50,000/QALY. Despite the fact that this willingness to pay threshold is commonly cited in the literature, ACIP and NACI do not adopt explicit WTP thresholds [2, 3]. Thus it is important for manufacturers to collaborate with HTA bodies to obtain guidance on WTP thresholds for specific vaccines.

In our review of the literature we noted the paucity of studies exploring vaccine efficacy against severe outcomes in the elderly. This could reflect the high cost of these studies and the uncertainty around the value of the information. Recent attempts to study vaccine efficacy against laboratory confirmed ILI in the elderly through an RCT required the enrollment of excess of 33,000 subjects [28]. Thus, given the relatively lower incidence of the more severe outcomes compared to laboratory confirmed ILI, the size of the RCTs required can be staggering. Other VOI methods, not explored in this article, such as expected value of sample information (EVSI) and expected net-benefit of sampling (ENBS) can be used to further inform the most efficient study designs in phase III and beyond. Researchers could explore
if less costly research designs than RCTs, such as case control studies post licensure, are adequate to resolve uncertainty around certain parameters.

Briggs, Claxton and Sculpher have described the operational implementation of VOI analysis into health technology development [16]. In summary, a decision model would need to be developed early on and it should be populated with existing data on the natural history of the disease, comparators and new intervention. VOI, cost effectiveness and net present value (NPV) should be evaluated, as new data is made available. If the expected cost effectiveness and NPV are positive then the development should continue. In situations where the cost effectiveness is unfavorable and the NPV is negative, developers should evaluate the VOI. If the VOI is high then further research and development should continue as there will be a chance that the technology could be cost effective. The development of a product should stop if the payoff is negative and the cost of conducting additional research exceeds the VOI, since this implies that the health technology is not cost effective, nor profitable, and further research is unlikely to change these conclusions.
References


### Tables

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>SD</th>
<th>Reference</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of infection during flu Season</td>
<td>0.09</td>
<td>0.02</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability of infection outside flu Season</td>
<td>0.01</td>
<td>0.02</td>
<td>Estimate from [29]</td>
<td>Beta</td>
</tr>
<tr>
<td>Assisted living residents relative risk of infection</td>
<td>1.33</td>
<td>n/a</td>
<td>[15]</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability of hospitalization per influenza infection (all risk)</td>
<td>0.04</td>
<td>0.01</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td>Probability of being a high risk elderly</td>
<td>0.52</td>
<td>0.73</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Probability of GP visit per influenza infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk elderly</td>
<td>0.82</td>
<td>0.09</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td>Non high risk elderly</td>
<td>0.62</td>
<td>0.03</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td>All risk elderly</td>
<td>0.72</td>
<td>n/a</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Probability of Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per influenza infection</td>
<td>0.01</td>
<td>0</td>
<td>[12]</td>
<td>Beta</td>
</tr>
<tr>
<td>Per influenza hospitalization in community</td>
<td>0.38</td>
<td>0.06</td>
<td>[15]</td>
<td>Beta</td>
</tr>
<tr>
<td>Per influenza hospitalization in assisted living</td>
<td>0.51</td>
<td>0.05</td>
<td>[15]</td>
<td>Beta</td>
</tr>
<tr>
<td>From all causes</td>
<td>Table</td>
<td>n/a</td>
<td>[30]</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Probability of transitioning to assisted living</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to influenza hospitalization</td>
<td>0.1</td>
<td>0.1</td>
<td>[31]</td>
<td>Beta</td>
</tr>
<tr>
<td>From all causes</td>
<td>Table</td>
<td>n/a</td>
<td>[32]</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Probability of transitioning to community</strong></td>
<td>Table</td>
<td>n/a</td>
<td>[33]</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Effectiveness of SOC Vaccine vs. No Vaccine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community living setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of a GP visits</td>
<td>0.42</td>
<td>0.14</td>
<td>[14]</td>
<td>Gamma</td>
</tr>
<tr>
<td>Relative risk of a hospitalizations</td>
<td>0.59</td>
<td>0.16</td>
<td>[14]</td>
<td>Gamma</td>
</tr>
<tr>
<td>Relative risk of death</td>
<td>0.74</td>
<td>0.04</td>
<td>[14]</td>
<td>Gamma</td>
</tr>
<tr>
<td>Assisted living setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of a GP visits</td>
<td>0.65</td>
<td>0.33</td>
<td>[14]</td>
<td>Gamma</td>
</tr>
<tr>
<td>Relative risk of a hospitalizations</td>
<td>0.51</td>
<td>0.15</td>
<td>[14]</td>
<td>Gamma</td>
</tr>
<tr>
<td>Relative risk of death</td>
<td>0.46</td>
<td>0.09</td>
<td>[14]</td>
<td>Gamma</td>
</tr>
<tr>
<td><strong>Effectiveness of New Vaccine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factors used to multiply the relative risk values above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of a GP visits</td>
<td>0.5</td>
<td>0.14</td>
<td>n/a</td>
<td>Gamma</td>
</tr>
<tr>
<td>Relative risk of a hospitalizations</td>
<td>0.5</td>
<td>=SQRT(1/12)</td>
<td>n/a</td>
<td>Uniform</td>
</tr>
<tr>
<td>Relative risk of death</td>
<td>0.5</td>
<td>=SQRT(1/12)</td>
<td>n/a</td>
<td>Uniform</td>
</tr>
<tr>
<td><strong>Cost (CAD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per dose SOC vaccine price</td>
<td>7</td>
<td>n/a</td>
<td>[34]</td>
<td>n/a</td>
</tr>
<tr>
<td>Per dose price premium for new vaccine technology</td>
<td>0-160</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Category</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Reference</td>
<td>Unit</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>Vaccine admin cost</td>
<td>3.59</td>
<td>n/a</td>
<td>[16]</td>
<td>n/a</td>
</tr>
<tr>
<td>Hospitalization episode</td>
<td>6418</td>
<td>7719</td>
<td>[16]</td>
<td>Gamma</td>
</tr>
<tr>
<td>GP visit</td>
<td>35</td>
<td>12.755</td>
<td>[16]</td>
<td>Gamma</td>
</tr>
<tr>
<td>Daily assisted living</td>
<td>150.8</td>
<td>n/a</td>
<td>[35]</td>
<td>n/a</td>
</tr>
<tr>
<td>Death</td>
<td>6418</td>
<td>n/a</td>
<td>Estimate</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Utilities**

<table>
<thead>
<tr>
<th>Category</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Reference</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily utility of symptomatic influenza (7 day episode)</td>
<td>0.65</td>
<td>0.09</td>
<td>[15]</td>
<td>Beta</td>
</tr>
<tr>
<td>Daily utility of serious influenza (10 day episode)</td>
<td>0.5</td>
<td>0.07</td>
<td>[15]</td>
<td>Beta</td>
</tr>
<tr>
<td>Living in the community</td>
<td>Table</td>
<td>n/a</td>
<td>[36]</td>
<td>n/a</td>
</tr>
<tr>
<td>Living in an institute</td>
<td>Table</td>
<td>n/a</td>
<td>[36]</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Table 1:** A summary of the major model parameters
Table 2: Population level EVPPI estimates at various technology price premiums and levels of technology adoption. Calculations are based on forecasted product adoption in Canada.

<table>
<thead>
<tr>
<th>Price Premium (CAD)</th>
<th>1, 50%</th>
<th>1, 75%</th>
<th>1, 100%</th>
<th>3, 50%</th>
<th>3, 75%</th>
<th>3, 100%</th>
<th>5, 50%</th>
<th>5, 75%</th>
<th>5, 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>$59,826</td>
<td>$89,739</td>
<td>$119,652</td>
<td>$171,067</td>
<td>$256,601</td>
<td>$342,134</td>
<td>$318,841</td>
<td>$478,262</td>
<td>$637,682</td>
</tr>
<tr>
<td>40</td>
<td>$736,320</td>
<td>$1,104,480</td>
<td>$1,472,640</td>
<td>$2,105,443</td>
<td>$3,158,160</td>
<td>$4,210,882</td>
<td>$3,924,202</td>
<td>$5,886,302</td>
<td>$7,848,398</td>
</tr>
<tr>
<td>80</td>
<td>$1,840,800</td>
<td>$2,761,200</td>
<td>$3,681,600</td>
<td>$5,263,608</td>
<td>$7,895,400</td>
<td>$10,527,204</td>
<td>$9,810,504</td>
<td>$14,715,756</td>
<td>$19,620,996</td>
</tr>
<tr>
<td>160</td>
<td>$29,696,706</td>
<td>$44,545,059</td>
<td>$59,393,412</td>
<td>$84,915,156</td>
<td>$127,372,541</td>
<td>$169,830,119</td>
<td>$158,267,956</td>
<td>$237,401,934</td>
<td>$316,535,718</td>
</tr>
</tbody>
</table>
Figure 1: (A) A summary of the health states in our model and possible transitions. (B) Schematic of a summary structure of the Markov cost-utility model for the decision to vaccinate.
Figure 2: Detailed structure of the Markov model with all the possible health states, transitions and outcomes.
Figure 3: Sensitivity analysis on the incremental cost-effectiveness of varying the additional cost of new technology and vaccine efficacy (VE) of the new influenza vaccine. WTP was set at $50,000/QALY. A reduction of relative risk of 1 represents no added benefit of using the new vaccine over the SOC vaccine for the specified parameter, while reduction in relative risk of 0 represents 100% VE against the outcome. Panel A represents a 4-way sensitivity analysis where the new vaccine effectiveness against hospitalization and death are set to equal that of the SOC vaccine. Panels B, C and D represent 2-way sensitivity analysis where all other model variables take the values represented in table 1.
Figure 4: Acceptability curves from probabilistic sensitivity analysis for various additional new technology costs. Distributions and parameters for this analysis are presented in table 1.
Figure 5: EVPPI curves for new vaccine efficacy parameters (vaccine efficacy against GP visits, hospitalization and death) at various additional new technology costs.
Figure 6: EVPPI estimates for various model parameters at a WTP equal to the ICER and a WTP of $50,000/QALY. New technology price was set to $40.
**Figure 7:** EVPPI estimates for an aggregate of the model vaccine efficacy (VE) parameters and each of the VE parameters separately (VE against GP visits, hospitalizations and death). New technology price was set to $40.
Supplemental Material

Appendix I: Value of Information (VOI)

The Net Monetary Benefit (NMB) is defined as:

$$NB = (NHB \times WTP) - NMC$$

Where, NHB is the Net Health Benefit (QALYs), WTP is the societal Willingness to Pay ($/QALY) and NMC is the Net Monetary Cost ($). In the context of a decision model such as our's with multiple uncertain parameters $\theta$, the expected NMB ($E_{\theta} NMB$) is the mean of the NMB across a large number of model runs. If there are multiple alternatives, $E_{\theta} NMB (j, \theta)$, is the mean NMB for each of $j$ alternatives.

VOI is a Bayesian decision analytic approach, which acknowledges that the decision to adopt and reimburse the strategy with the highest expected NMB is based on the currently available information that is surrounded by uncertainty. Making a wrong decision will therefore have a cost equal to the difference between the benefits of the correct decision and the lesser benefits of the wrong decision. In other words the expected cost of uncertainty is a function of i) the probability that a decision based on mean net benefit is wrong and ii) the size of the opportunity loss if the wrong decision is made.

Expected Value of Perfect Information (EVPI)

Under imperfect information we select the optimum alternative $j$, which has the highest mean NMB. This can be expressed as:
Max_j E_{\theta} NMB (j, \theta)

Under perfect information we would know the values of \theta. Therefore we would always be able to select j with the Max NMB. This can be expressed as:

Max_j NMB (j, \theta)

The mean of all the Max NMB values over all model runs can be expressed as

E_{\theta} Max_j NMB (j, \theta)

Erroneous decisions can be made using decision models with imperfect information. If such decisions are made there can be a loss of health benefit, resources or both. In the availability of perfect information there would be no chance of making the wrong decision. EVPI measures the cost of uncertainty given the societal WTP. EVPI can be expressed as:

EVPI = E_{\theta} Max_j NMB (j, \theta) - Max_j E_{\theta} NMB (j, \theta)

Table 3 provides a simple example of how EVPI is calculated.

EVPI estimates can be used to inform spending decisions on additional research. The EVPI value would constitute the upper bound of what additional research (to
resolve the uncertainty in θ) is worth, given the context of the decision problem at hand. It is important however, that EVPI is expressed for the total population that stands to benefit over the expected time of use. The population EVPI can be defined as follow:

\[ \text{Population EVPI} = \text{EVP.} \sum_{t=1,2,..,T} I_t/(1 - r)^t \]

Where \( I_t \) is the incident use of the alternative over the expected lifetime use \( t \). The discount rate \( r \) is applied to value future use appropriately.

**Expected Value of Partial Perfect Information (EVPPI)**

For the purposes of this paper we would like to divide θ into its components and study the uncertainty around specific components separately. Lets assume that θ is composed of two sets of parameters \( \varphi \) (which are of interest) and \( \psi \) (a grouping of the remaining parameters in the model). EVPPI is the difference in NMB between i) the expected value with perfect information around the parameters of interest \( \varphi \), and ii) the expected value with uncertainty around parameters θ.

To calculate i) we take a value of \( \varphi \) and calculate the expected net benefit over the remaining values of \( \psi \). This can be expressed as

\[ E_{\varphi|\psi} \text{NMB}(j,\psi,\varphi) \]
We then pick the alternative $j$ with the maximum NMB

$$\max_j E_{\psi|\varphi} NMB(j, \psi, \varphi)$$

This calculation is then repeated over the distribution of $\varphi$, and $\max_j$ values are averaged to compute the expected value with perfect information around the parameters of interest $\varphi$. This can be expressed as:

$$E_{\varphi} \max_j E_{\psi|\varphi} NMB(j, \psi, \varphi)$$

The expected value with uncertainty around parameters $\theta$ (ii) is calculated as before as per the following expression:

$$\max_j E_{\theta} NMB (j, \theta)$$

The expected value of perfect information around parameter $\varphi$ is then expressed as:

$$\text{EVPPI}_{\varphi} = E_{\varphi} \max_j E_{\psi|\varphi} NMB(j, \psi, \varphi) - \max_j E_{\theta} NMB (j, \theta)$$

Population level EVPPI$_{\varphi}$ is calculated in the same as described for EVPI but of course substituting the EVPI value for EVPPI$_{\varphi}$.

**Computation**
EVPPI calculations are computationally more intensive than EVPI. This is due to the two loops (inner and outer loops) of dependent sampling. The outer loop starts by selecting a value of \( \varphi \) from the parameters’ distribution. The inner loop then computes \( E_{\psi|\varphi} \text{NMB}(j, \psi, \varphi) \) by sampling the joint distribution of \( \psi \) for the value of \( \varphi \) selected by the outer loop. After the completion of the inner loop run, the algorithm stores a value for \( \text{Max}_j E_{\psi|\varphi} \text{NMB}(j, \psi, \varphi) \). The outer loop then selects another value of \( \varphi \) from the parameters’ distribution. This is then fed back into the inner loop to repeat and ultimately store another value of \( \text{Max}_j E_{\psi|\varphi} \text{NMB}(j, \psi, \varphi) \). The runs of the two loops are repeated to generate a sufficiently large number of samples to construct a stable estimate of \( E_{\varphi} \text{Max}_j E_{\psi|\varphi} \text{NMB}(j, \psi, \varphi) \). In this analysis we ran 1000 iterations of the inner loop for each of 250 iterations of the outer loop.

\[
\begin{array}{cccc}
\text{NMB (j, \theta)} & \text{A} & \text{B} & \text{Optimal Choice} \\
\hline
\text{Iteration 1} & 5 & 10 & \text{B} & 10 \\
\text{Iteration 2} & 2 & 4 & \text{B} & 4 \\
\text{Iteration 3} & 2 & 1 & \text{A} & 2 \\
\end{array}
\]

\[
\begin{align*}
\text{E}_\theta \text{NMB (j, \theta)} &= 3 \quad 5 \\
\text{Max}_j \text{E}_\theta \text{NMB (j, \theta)} &= 5 \\
\text{E}_\theta \text{Max}_j \text{NMB (j, \theta)} &= 5 \quad 1/3
\end{align*}
\]

\[
\text{EVPI} = \text{E}_\theta \text{Max}_j \text{NMB (j, \theta)} - \text{Max}_j \text{E}_\theta \text{NMB (j, \theta)}
\]

\[
= 5 \quad 1/3 - 5
\]

\[
= 1/3
\]

\textbf{Table 3: An example of how EVPI is calculated}
General Discussion

Through this dissertation we have implemented methods to aid influenza vaccine developers in gaining insight into economic aspects of R&D. In the first chapter we investigated methods to quantify and subsequently monitor the costs of influenza vaccine development. The second chapter provided clarity on the cost of capital, which has been shown to be a major cost driver in the R&D process. Finally in Chapter 3 we investigated how influenza vaccine developers can focus their R&D programs on outcomes that are of relevance to payers.

What was evident from our work was the scarcity of research on the economics of new vaccine R&D in general and influenza vaccines in particular. Most of the published literature is very general, and focused on economic evaluations of approved vaccines. Concurrently, we observed a growing trend with vaccine HTA bodies in the US and Canada both starting to conduct formal economic evaluations in their assessment of new vaccines and immunization programs. Thus, vaccine purchasers are increasingly assessing the value for money provided by new vaccines. While vaccine developers might not be accounting for these new demands when developing new vaccines.

We hope that our research can help industry and governments appreciate and hopefully utilize analytical methods to make decisions collaboratively around vaccine development targets, and the design of R&D programs. In the remainder of this discussion, we comment on how industry can examine economic considerations during development. We then suggest how HTA agencies can improve the way in which economic assessments of new vaccines are conducted.


**Vaccine Developers**

We have demonstrated that the expected cost of developing a new vaccine can be empirically estimated before starting on the vaccine development journey. For the case of the influenza vaccine we found costs to be in the order of $475 Million CAD at a 9% cost of capital rate. Given different assumptions around the cost of capital this estimate can range from $337 Million CAD to $570 Million CAD if a 5% or 11% cost of capital rate is applied respectively. These estimates are verifiable and derived from publically available sources of information.

We are hopeful that this work will pave the way to uncover the cost of developing other vaccines and medicines. Recently, Parker and colleagues reported on the success rate of new drug development in clinical trials for very specific indications: Crohn's disease [1], HIV [2], Non-Hodgkin's Lymphoma [3], and rheumatoid arthritis [*?4] but the researchers were not able to study costs. Our work provides researchers with methods to further study the economics of specific drug development. To fully leverage this information, however, it will be important to develop an appropriate analytical framework for decision makers. Such a framework should evaluate development costs, anticipated technology impact and overall burden of disease. This work should facilitate better recommendations on how R&D budgets should be spent.

Once a development target is selected, industry sponsors have to decide on the design of the clinical development program. An important component of this is selecting health outcomes and populations to study, as well as research methods and designs. However, there is little guidance provided in the literature; in particular we found no studies that used value of information (VOI) methods to select research targets or trial designs. Therefore, our study is the first VOI study in the influenza vaccine field and thus provides important guidance to influenza vaccine developers. In our study it is clear that society most
highly values an elderly influenza vaccine that can prevent severe outcomes of influenza. Vaccine developers that can deliver new vaccines with these proven characteristics will be maximizing the social value of their product and in the process will have the opportunity to maximize their producer surplus or revenues.

Other VOI methods, not explored in our study, such as expected value of sample information (EVSI) and expected net-benefit of sampling (ENBS) can be used to further inform the most efficient study designs in phase III and beyond [4]. Researchers could explore whether less costly research designs besides RCTs, such as case control studies post licensure, are adequate to resolve uncertainty around certain parameters [4]. Briggs, Claxton and Sculpher have described the operational implementation of VOI analysis into health technology development [4]. In summary, a decision model would need to be developed early on and it should be populated with existing data on the natural history of the disease, comparators and new intervention. VOI, cost effectiveness and net present value (NPV) should be evaluated, as new data are made available. If the expected cost effectiveness and NPV are favorable then the development should continue. In situations where the cost effectiveness is not favorable and the NPV is negative, developers should evaluate the VOI.

If the VOI is high then further research and development should continue as there will be a chance that the technology could be cost effective. The development of a product should stop if the payoff is negative and the cost of conducting additional research exceeds the VOI, since this implies that the health technology is not cost effective, nor profitable, and further research is unlikely to change these conclusions.

In summary, Briggs, Claxton and Sculpher provide industry a framework to incorporate VOI into vaccine development, and we suggested a method for evaluating expected costs of development. However, industry will not be successful in our opinion unless it can partner with governments and HTA agencies in making decisions using these tools. At the moment
there are no mechanisms for HTA agencies and industry to have such formally binding discussions.

**Health Technology Assessment (HTA) Bodies**

HTA assessments are influenced by three major paradigms: The relative clinical benefits and harms of the technology; the economic impact of the technology; and the ethical implications of the technology adoption decision [5, 6]. While different HTA agencies around the world vary in the way they weight these three parameters, these factors predominate committee deliberations.

In Canada, the National Advisory Committee on Immunization (NACI) is the body that conducts HTA for vaccines and makes recommendations on their proper use. In the US, the Advisory Committee on Immunization Practices (ACIP) plays the same advisory role to the Center of Disease Control (CDC). The committees act to advise the provinces in Canada in the case of NACI and the states in the USA. In their advisory role, both ACIP and NACI have recently been deliberating over health economic studies presented by various groups, including industry, to aid in making recommendations [7, 8]. However, to date there is no clear process for how ACIP and NACI conduct their reviews of economic data.

Unlike HTA agencies, major traditional regulators such as the Food and Drug Administration (FDA) in the US, the European Medicines Agency (EMA) and Health Canada have created comprehensive product development guidelines for vaccine manufacturers. Additionally, these regulators have offered formal opportunities to provide feedback on manufacturer development plans before substantial R&D investments are made. This guidance is likely a major factor in lowering development failure rates. However, despite these efforts failure rates remain relatively high [9].
In contrast, HTA agencies such as ACIP and NACI have significant influence over vaccine adoption. Both ACIP and NACI, despite their growing influence on the commercial success of new vaccines, do not offer manufacturers guidance during the vaccine development process. For instance, ACIP working groups and committee deliberations do not start until a new vaccine submission is made to FDA [10]. The lack of communication between manufacturers and government recommending bodies on health economic considerations of new vaccines as they are being developed can add further risk to the already risky new vaccine development process. Evidence of this can be seen from the work of Anupam and Phillipson [11]. The authors report that a large number of market authorized products in Australia fail to achieve reimbursement by public payers due to negative HTA recommendations based on cost effectiveness analysis (CEA).

Currently, only the UK’s NICE will hold formal discussions with manufacturers around development programs for new drugs [12]. And the only therapeutic-area specific economic evaluation guidelines are published in Canada for the field of oncology [25]. Despite this, the NICE pre-licensure discussions are not binding. Further the Oncology guidelines are not referenced by the pan Canadian Oncology Drug Review (pCODR). We see this as an opportunity for NACI and ACIP to take leadership and provide a mechanism to hold such discussions with vaccine manufacturers around the development of new vaccines and new indications. These discussions can be based on the VOI framework. Further, ACIP and NACI could develop specific guidelines for economic evaluations of vaccines and immunization programs.

Another opportunity for leadership within HTA lies in developing a framework for coverage with evidence generation. There are many situations where a vaccine’s efficacy against certain clinical outcomes cannot be fully established in RCTs required for regulatory approval. This can provide a serious challenge for economic evaluations, as they depend
highly on this type of evidence. Non-randomized observational studies using a surveillance system can provide a much more practical alternative. Thus, a framework for coverage with evidence generation would allow HTA recommendations to be revisited after real life effectiveness data are generated. This would minimize public access delays to new vaccines and indications.

It is important to give special consideration to willing to pay (WTP) thresholds. Under cost-effectiveness analysis technologies are deemed cost effective if they are below the society's WTP. Most HTA bodies around the world don’t declare an explicit WTP; instead implicit thresholds are observed from monitoring historic HTA recommendations. Some agencies such as NICE and Sweden’s Dental and Pharmaceutical Benefits Agency (TLV) declare in some situations, such as palliative care for end of life management, that WTP thresholds are higher than they would be under usual circumstances [13]. This will always be a major source of uncertainty for industry attempting to develop new vaccines. For instance, new vaccines might not be developed if industry does not believe they can obtain the required return on investment (ROI). The ROI calculations are heavily based on assumptions around WTP. It would be very helpful to the vaccine development process if HTA agencies can provide a clear and informative position on WTP. This can be in the form of explicit thresholds or criteria on how thresholds are set for different types of technology adoption decisions.

**Conclusion**

In summary, we have provided some examples of how vaccine developers can be more prudent about economic considerations during development. This starts at target selection and extends to the design of research programs and trials. These steps will only have a significant impact if manufacturers work through them closely with HTA agencies.
Currently there are no clear formal mechanisms for this. Substantial leadership is still needed from both manufacturers and HTA agencies to find ways to collaborate. Operationally, there is much to be learned from how manufacturers currently collaborate with regulators. Methodologically, our work provides good examples of the type of analytical exercises that can be used a framework for discussion. Formal collaborations between manufacturers and HTA bodies should be a priority topic of further research.
References


