University of Alberta

Essays in Applied Vaccine Economics

by

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DEDICATION

I would like to dedicate this work to my mom, Patricia Hrynkiw, and dad, Michael Waye – they have always said that by taking one step at a time even the seemingly insurmountable is achievable. I am eternally grateful for their love and support each step of the way.

I would also like to dedicate my thesis with love to Terry McDonald, he has joined me on this journey and blessed me with love, strength, confidence, and life.

ABSTRACT

Objectives: This thesis consists of 3 partial vaccine economic evaluations. The objectives were to: 1) estimate the effectiveness of Canada's universal varicella childhood immunization strategy on varicella-related hospitalizations, 2) measure the economic impact of Alberta's universal childhood pneumococcal immunization program (Prevnar 7), and 3) generate a general model estimating the cost of vaccine research, development, and deployment (RDD).

Methods: For the first objective, rate ratios were calculated based on pre- and post- cases hospitalization across 10 provinces, and 6 age categories. For the second objective, an ex post cost analysis was conducted, comparing the costs associated with pneumococcal both before and after the introduction of universal Prevnar 7 immunization. The third objective was met by modifying cost models from the drug development literature.

Results: For the first objective, there was evidence of significant declines in varicella across all provinces in Canada, across most age categories less than 40, suggesting some evidence of herd immunity effect. For the second objective, the costs averted in Alberta as a result of decreased cases of pneumonia were $9.2 million and $1.8 million if serotype replacement is taken into account. For the third objective, Rotarix was used as a case example to demonstrate the vaccine costing model. It is found that it cost an estimated $2.7 billion to develop Rotarix vaccine, and $3.7 billion after consideration of risk premiums.

Conclusions: For objective one, the Canadian immunization strategy has been successful in reducing varicella-related hospitalizations across the country, and

across ages. For the second objective, costs have been averted in Alberta as a result of decreased cases of pneumonia due to PCV7. However, the relationship between the vaccine and serotype replacement could erode some of these benefits. For the third objective, a general model has been created that can estimate the cost of vaccine RDD. This model can be used to estimate cost of RDD for any vaccine in which the cost of clinical testing is known.

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CHAPTER 1: INTRODUCTION

1.1 Background

Vaccines have been recognized as being one of the most significant contributions to modern day science, and improvements to population health. It is estimated that worldwide more than 5.9 million deaths from infectious diseases are prevented each year as a result of diphtheria, tetanus, polio, measles, mumps, rubella, and influenza [1]. The impact of immunization on morbidity is also large. Morbidity from smallpox, diphtheria, polio, measles have decreased 100% since the start of the 20th century, meanwhile, measles, mumps, rubella, pertussis, and tetanus have declined 96-99% [2].

Cost savings resulting from the prevention of infectious diseases are significant, and one of the few health interventions that consistently generate considerably more public health benefits than costs [3]. Public Health Agency of Canada estimated that the DTaP (pertussis vaccine) will have cumulatively saved more than $370 million as of 2007 [4]. Similarly, the Haemophilius influenza type b vaccine provides an annual net savings is in the ballpark of $37 million [4]. Currently, vaccines have been produced to prevent more than 25 infectious diseases [5]. However, more than 40 infectious diseases are monitored in Canada [5], and many more non-infectious diseases exist for which therapeutic vaccines could help alleviate symptoms; there is much room for growth in vaccine development and deployment.

It is estimated that it takes at least 15-20 years and costs between $800 million and $1.5 billion USD to produce one pharmaceutical [6-10]. There is a

paucity of evidence regarding the cost of vaccine development. This study aims to fill this knowledge gap.

1.2 Economics of Vaccines and Allocative Efficiency

Most economic theory in the area of health economics fits under the umbrella of welfare economics [11]. Welfare economics is a basic framework that applies pieces of economic theory to allow us to answer specific questions such as: what is the optimal price for the vaccine to achieve a particular coverage rate or level of demand? Welfare economics represents the basic worldview of economists, allowing us to answer fundamental questions, which can be used to inform public policy and improve societal wellbeing [11].

The '*First Fundamental Theorem of Welfare Economics*' suggests that a competitive economy will achieve the most efficient allocation of societal resources in terms of consumption and production [11]. The primary tenets of this theorem are that individuals are rational actors, and that firms are perfectly competitive.[1] Given these assumptions, allocative efficiency is reached. This means that the marginal social benefit of consumption is equal to the marginal private benefit of consumption, and the marginal social cost equals the marginal private cost of production [11]. The point at which these curves intersect, results in a price that will allow the efficient exchange of private goods and services between the economic agents (producers and consumers) [11]. However, real economies generally do not meet these assumptions. As a result, prices are

[1] A rational actor is one in which more is: always preferred to less, respond to changes in price, consistent in choices, do not take into account the preferences of others when making decisions [11]. Competitive firms are ones which: have perfect information, have no barriers to entry, have no market power, and exhibit constant returns to scale [11]

distorted and the market fails to reach socially optimal allocations, which warrants government intervention to help the market to theoretically reach a more optimal allocation.

The market for vaccines exhibit market failures through violation the above assumptions in terms of: externalities in consumption, a public good characteristics in vaccine R&D. This means government intervention has an important role in correcting the market failures so as to achieve the price that represents the underlying value of the vaccine. Theoretically, in order for allocative efficiency to be established in the context of vaccines, governments must deal with market failures: *public goods in terms of positive vaccine consumption externalities*, and *non-excludability in their R&D* [12].

Private goods are those which only the purchaser benefits from consumption, as others can be excluded from consuming the good (excludability) and the consumption by one limits the consumption by others (rival consumption). However, when a good is non-excludability and/or non-rival, perfect competition leads to inefficient allocation.

Consumption of Vaccines

Goods that do not meet the conditions of excludability and rival consumption are referred to as *public goods* and vaccines are one such good. While vaccines meet the rival consumption condition, they do not meet the excludability condition since the consumption of vaccines by one person results in positive benefits to another (*positive consumption externality*). As a result, the benefits derived from vaccination are not only reaped by the individual

vaccinated, but also by others in close contact. In other words, fewer infectious individuals benefit society in terms of reduced circulation of disease (also known as herd immunity), which translates into improved health and ability to earn income and participate in leisure time.

Theoretically, demand for a vaccine is a function of the price and benefits derived from being vaccinated (healthy to earn income and participate in leisure time), and the disutility associated with the costs of being vaccinated (ie. out of pocket costs, time to be vaccinated, discomfort, possibility of side effects). Individual utility maximization will weigh the net benefits against the price and determine their demand for a vaccine. Notice that only private benefits are considered, the positive externality in consumption in terms of benefits derived by others through reduced circulation of disease are not considered. With this positive consumption externality, the marginal cost of producing a unit of the good is the same as the marginal social cost however, the marginal social benefit is higher than the marginal private benefit and therefore the private market allocation of the good is not optimal [12]. As a result, there is a role for governments to play in increasing individual demand by reducing the cost to consume vaccines. This policy will increase private demand toward the socially optimal level of consumption, a point which the market cannot reach on its own.

Production of Vaccines

The upfront financial cost associated with developing a vaccine is very high, as are the risks associated with its failure. The most recent estimated cost of developing a new drug is in excess of $1.5 billion [10], and it is estimated that

only *one of every 10,000* potential medicines are approved in the market [13]; of those who make it to clinical testing, roughly 1/5 (20%) succeed to market approval [6-9;14-17].

There are a number of market failures in the production of vaccines, one of which is the non-excludable nature of vaccine research. Knowledge is non-rival and non-excludable in that once it is produced others can consume the information and technology at no additional cost. This means that large upfront investments must be made for each potential vaccine, however, duplication of approved drugs and vaccines can occur at much lower costs and firms are therefore not guaranteed to derive all of the future market benefits [18; 19].

Theoretically, the result of this non-rival consumption in R&D is an incentive for firms to "free-ride" [18]; it is rational not to contribute to the provision of a public good, as no contribution is required to benefit. The result is a less than socially optimal investment in vaccine R&D. Governments tend to respond through policies such as investing in R&D, patent protection, as well as using "push" and "pull" incentives to stimulate pharmaceutical innovation in neglected diseases [18;20;21].

1.3 Research objectives and research questions

Governments will often respond (knowingly or unknowingly) to the distinctive economic characteristics of vaccines and the resulting deviations from allocative efficiency in the market. For example, in response to vaccine externalities, governments will often implement public universal immunization programs.

The objective of the first research paper is to examine the health benefits derived from positive externalities (herd immunity) derived from universal varicella vaccination in Canada. Specifically, the research questions to be examined include:

1) How effective was varicella vaccine at decreasing varicella-related hospitalizations in Canada?

2) Is there evidence in adults of decreased circulation (potential evidence of herd immunity), as measured by decreased varicella hospitalizations?

The objective of the second paper is to examine the magnitude of positive externalities (herd immunity) in terms of costs averted. The specific case example used is the universal Prevnar vaccination in Alberta. This policy evaluation examines 3 primary questions:

1) What is the economic impact of the implementation of PCV7 universal vaccination in Alberta?

2) Is there evidence of serotype replacement resulting from PCV7? If so, what are the associated costs?

3) What is the magnitude of the economic impact resulting of herd immunity?

The objective of the third paper is to provide a general costing model to help inform public policy discussions related to the financing of vaccines. In addition to generating a general model for estimating the cost of vaccine development, in this paper, I address three questions:

1) What is the current body of evidence for the cost of drug and vaccine research, development, and deployment?

2) Are the estimated drug and vaccine costs similar, if not, how do they differ?

3) Can we use drug development costs to approximate those of vaccines? If not, how can we estimate the cost of developing a vaccine?

1.4 Summary of thesis format

This thesis is written in a paper format. Chapters 2 through 4 are original manuscripts addressing the three objectives described above. Chapter 2 examines the effectiveness of varicella vaccine in relation to varicella-related hospitalizations across all ages in Canada between 1994 and 2010. In this ecological (aggregate level) study I compare the pre- and post- vaccination hospitalization rates to determine whether a significant decline in hospitalizations has occurred. Chapter 3 is original research assessing the costs averted in Alberta as a result of the universal immunization of infants with PCV7. This model is unique in that it takes into account costs incurred as a result of the potential increase in cases caused by non-PCV7 strains. Chapter 4 provides an overview of the current body of knowledge concerning the cost of producing a vaccine. I use this information to develop a model that serves to predict the cost of an individual or group of vaccines. I use Rotavirus vaccine to demonstrate the model. Chapter 5 summarizes the key findings of my research presented in Chapters 2 through 4 and concludes.

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CHAPTER 2: THE IMPACT OF THE UNIVERSAL INFANT VARICELLA IMMUNIZATION STRATEGY ON CANADIAN VARICELLA-RELATED HOSPITALIZATION RATES[1]

[1] A version of this chapter has been accepted for publication. Waye A, Jacobs P, Tan B. The Impact of the Universal Infant Varicella Immunization Strategy on Canadian Varicella-Related Hospitalization Rates. Vaccine 2013;31:4744-8.

2.1. Introduction

Varicella, commonly known as chicken pox, is a highly infectious disease caused by the varicella-zoster virus (VZV). Prior to the introduction of varicella vaccine, the Public Health Agency of Canada estimated the annual incidence of uncomplicated chickenpox to be 350,000 across all ages, and of these cases more than 1550 required hospitalization. Children are highly susceptible to varicella, with 50% of children contracting the disease by age five and 90% by age twelve [1]. Adults are more likely to have contracted the disease at a young age and are therefore immune to the disease. As a result, adult varicella incidence rates are estimated to be lower -- approximately 20 per 100,000 in adults aged less than 30, and 2 to 5 per 100,000 in adults over 40 prior to vaccine introduction [2].

The first vaccine to protect against varicella was approved in Canada in 1998. Since 2010, three vaccines have been available to protect against varicella: Merck's Varivax™-III and GlaxoSmithKline's (GSK's) univalent vaccine, Varilrix™ and quadrivalent (MMRV) vaccine, Priorix-Tetra™. In 1999, Canada's National Advisory Committee on Immunization (NACI) recommended single-dose routine varicella vaccination for children at 12-18 months, and catch-up immunizations for susceptible individuals, including a two-doses for people over the age of 12 years [3]. A one-dose varicella program for children was maintained in Canada until 2010, at which point NACI released a new 2-dose recommendation for children 12-18 months [3].

NACI's recommendations do not necessarily translate into publicly funded immunization programs. Therefore, at the time the varicella vaccines were

introduced, they were only acquired through private sale. Funding for universal vaccine programs is the responsibility of individual Canadian provinces and territories. The result of this autonomy has been a staggered introduction of universal varicella vaccination across the country. Two provinces and a territory introduced varicella vaccinations between 2000 and 2002 - Prince Edward Island (PEI), Alberta (AB), and the Northwest Territories (NWT).

The federal government provided $45 million in 2003 to develop the National Immunization Strategy to address the growing disparity in public immunization between Canadian provinces and territories [4]. In 2004, an additional per capita allocation of $400 million was delivered to the provinces under the Public Health Immunization Trust [4]. By 2007 all remaining provinces and territories have instituted public varicella programs.

The benefit of mass public immunizations such as varicella potentially extends beyond those who are immunized. Specifically, those not vaccinated will also be indirectly protected against the disease – a concept known as herd immunity [5;6]. Herd immunity has been theorized to eliminate varicella outbreaks [7], and prevent illness for individuals across all age groups and levels of susceptibility [8]. This public benefit is especially significant as it has been found that cases are more likely to be complicated among older cohorts [8-15]. In particular, adults over the age of 20 were found to be thirteen times more likely to be hospitalized and twenty five times more likely to die from VZV as compared to children under the age of 12 years [8].

Direct evidence of herd immunity is difficult to attain as it is necessary to provide individual-level coverage rates of vaccination, natural immunity from previous infection, and incidence rates. Nonetheless, a number of studies have gathered indirect evidence of herd immunity through the effect of varicella vaccination on disease prevalence and varicella-related hospitalizations. This evidence has been assessed in several countries with routine varicella vaccination programs [8;16;17]. These studies largely support the hypothesis that disease prevalence and varicella related hospitalizations will decline across the population following a public infant varicella immunization program. To date there has been limited published Canadian evidence of the impact of publicly funded varicella vaccination programs on varicella-related incidence or hospitalizations. A study of Canadian children examined the effect of varicella immunization programs on varicella-related hospitalizations and found that child hospitalizations have declined [18]. Similarly, a provincial study of the effect of a universal varicella immunization program on hospitalizations in Ontario has suggested decreased circulation of varicella, as evidenced by declines in varicella-related hospitalizations, ER, and doctor's visits across all ages [19]. The objective of this study is to determine the impact of Canada's publicly-funded varicella infant immunization programs on the entire population. Specifically, this research will examine whether there is evidence to suggest decreased circulation of varicella as indicated by decreased varicella-related hospitalization rates for all ages across Canada.

2.2. Methods:

This study is an ecological study examining the effects of varicella vaccine on varicella-related hospitalization rates in the 10 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Newfoundland, Prince Edward Island, Nova Scotia, and New Brunswick). Data from the three territories were not available for the time period studied.

Case Definition and Study Population:

The study population consisted of annual provincial cases hospitalized for varicella between 1994 and 2010. These were identified by searching the Canadian Institute of Health Information Discharge Abstract database [20;21]. Varicella hospitalization admissions are identified according to ICD-9 code 052, ICD-9CM code 052.X, and ICD-10 code B01 (Table 2-1).

Table 2-1: ICD9, ICD9CM and ICD10 Codes and Disease Classification Descriptions

Description	ICD9	ICD9CM	ICD10	Description
Postvaricella encephalitis	052	052.0	B011	Varicella encephalitis Postchickenpox encephalitis Varicella encephalomyelitis
Varicella (hemorrhagic) pneumonitis	052	052.1	B012	Varicella pneumonia
Chickenpox other specified complications	052	052.7	B018	Varicella with other complications
Chickenpox unspecified complication	052	052.8		

Varicella without complication	052	052.9	B019	Varicella without complication Varicella NOS
NOTES:	Used by Newfoundland, PEI, QU, ON, MB, SK, BC	Used by PEI, NS, NB, ON, MB, SK, AB, BC	Introduced in 2001 by MB, SK, PEI, NS, AB, BC Introduced in 2003 NB, 2006 in QU, and 2002 in ON	

Consistent with other analyses [19] dual codings for varicella and herpes zoster were excluded from this analysis, admissions were included only if varicella was listed as the most responsible diagnosis. This dataset has been validated elsewhere as containing detailed diagnostic data on all hospital admissions [22].

Statistical Analysis:

Varicella hospitalization rates for both years prior to universal vaccination program and years following the intervention were calculated using person-years of follow-up based on annual population estimates from Statistics Canada [23]. Due to the staggered introduction of vaccination across the provinces, the pre-vaccine and post-vaccine periods differ by province (Table 2-2). The calculation of person-years allowed for comparison of vaccine impacts across provinces. All provinces implemented a one-dose vaccination strategy up to 2010, and all except 2 provinces also implemented a catch-up program for susceptible children aged 12 and under (Table 2-2) [24].[2]

[2] Susceptible children are children healthy children who have not yet had natural chickenpox or received varicella vaccination.

Table 2-2: Provincial Program Information

Province	INTRO Vaccine Program	Age at Primary Immuni-zation for Healthy Children (1 dose) [1]	Catch-up Immunization of Susceptible Children (1 dose) [1]	Varicella Coverage Rates
Newfoundland	2005	12 months	At Preschool	92.8%-97.2%[2]
Prince Edward Island	2000	12 months	N/A	NA
Nova Scotia	2002	12 months	Between 1 & 6 yrs old	NA
New Brunswick	2004	12 months	N/A	NA
Quebec	2006	12 months	At Preschool & Gr. 4	NA
Ontario	2004	15 months	At Preschool	NA
Manitoba	2004	12 months	At Preschool & Gr. 4	80.1%[3]
Saskatchewan	2005	12 months	In Grade 6	71% [4]
Alberta	2001	12 months	At Preschool & Gr. 6	88%[5]
British Columbia	2004	12 months	At Preschool & Gr. 6	67%-89%[6]

[1]National Advisory Committee on Immunization (2010) [18].
[2]The coverage rates are based on data from 2006-2011, as discussed in the March 2013 Quarterly Communicable Disease Report: http://www.health.gov.nl.ca/health/publichealth/cdc/CDR%20Report%20March%202013.pdf, last accessed July 2013.
3 These data can be found at: http://www.gov.mb.ca/health/publichealth/surveillance/reports.html#mims, last accessed May 2013
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Rate ratios were calculated by province, year of hospitalization, and age. The year of vaccination is included in the pre-vaccination period. Patient's age was aggregated into 7 categories: less than 1 year; 1-4 years; 5-9 years; 10-19 years, 20-39 years, 40-59 years and 60+ years. Two-sided Chi-squared tests were performed at the 5% level of significance, and confidence intervals were calculated according to a Poisson distribution. I used SPSS v13.0 (2004) and Statsdirect 2.7.9 (2012) for this analysis.

2.3. Results:

This study included 10,762 hospitalizations over a 16 year period across 7 age categories.

Hospitalizations by period:

The analysis found evidence of significant declines in varicella-related hospitalizations in every studied Canadian province, across every age category. Table 2-3 presents the change in overall hospitalization rates of varicella for all ages across each of the 10 provinces. A gradient does appear to exist with age; the gains in terms of reduced hospitalizations are larger for younger populations within each province. However, older Canadian populations are experiencing declines in hospitalizations as well.

In each province, statistically significant declines in hospitalization were greatest for children aged 1-4, the vaccinated group. These declines in hospitalization ranged from a risk ratio (RR) of 0.06 in Quebec (95% CI, 0.04-0.09) to 0.30 in New Brunswick (95% CI, 0.16-0.52). Every province experienced significant declines in hospitalizations for the vaccinated age

group. Across Canada, the hospitalization RR for this group was 0.17 (95% CI, 0.16-0.20).

Table 2-3: Hospitalizations Rate Ratios by Age and Province								
	<1	1 to4	5 to 9	10 to 19	20-39	40-59	60+	**All Ages**
Newfoundland								
RR	0.28 (0.03-1.14)	0.07*** (0.00-0.43)	0.32*** (0.10-0.80)	0.18 (0.00-1.18)	0.00*** (0.00-0.55)	0.28 (0.01-2.07)	0.94 (0.15-4.41)	0.20*** (0.11-0.36)
Nova Scotia								
RR	0.26 *** (0.06-0.77)	0.12*** (0.04-0.31)	0.60 (0.32-1.06)	0.23*** (0.06-0.67)	0.34*** (0.15-0.70)	0.73 (0.21-2.39)	0.46 (0.04-3.22)	0.29*** (0.21-0.40)
New Brunswick								
RR	0.24** (0.06-0.67)	0.30*** (0.16-0.52)	0.68 (0.37-1.20)	0.50 (0.21-1.05)	0.26*** (0.12-0.53)	0.61 (0.10-2.56)	4.45 (0.80-45.11)	0.37** (0.27-0.48)
Prince Edward Island								
RR	0.00*** (0.00-0.79)	0.12** (0.00-0.97)	0.42 (0.04-2.95)	0.10*** (0.00-0.80)	0.00*** (0.00-0.86)	NA	NA	0.094*** (0.02-0.13)
Quebec								
RR	0.18*** (0.13-0.26)	0.06*** (0.04-0.09)	0.20*** (0.14-0.29)	0.20*** (0.09-0.40)	0.13*** (0.07-0.20)	0.34*** (0.17-0.62)	0.30*** (0.12-0.62)	0.12*** (0.10-0.14)
Ontario								
RR	0.36*** (0.28-0.47)	0.35*** (0.29-0.41)	0.42*** (0.35-0.51)	0.59*** (0.45-0.77)	0.45*** (0.36-0.56)	0.61*** (0.43-0.85)	0.73** (0.53-1.01)	0.39*** (0.36-0.44)
Manitoba								
RR	0.25*** (0.15-0.39)	0.23*** (0.15-0.34)	0.16*** (0.07-0.30)	0.49 (0.19-1.09)	0.22*** (0.08-0.52)	0.24*** (0.04-0.79)	0.32 (0.06-1.14)	0.22*** (0.17-0.27)
Saskatchewan								
RR	0.51*** (0.33-0.77)	0.28*** (0.17-0.44)	0.67 (0.38-1.13)	0.39 (0.07-1.32)	0.54 (0.22-1.18)	0.30** (0.06-1.01)	1.26 (0.27-4.96)	0.42*** (0.33-0.54)
Alberta								
RR	0.23*** (0.15-0.34)	0.14*** (0.10-0.20)	0.20*** (0.13-0.31)	0.31*** (0.16-0.56)	0.26*** (0.15-0.41)	0.54*** (0.29-0.97)	0.42*** (0.20-0.86)	0.21*** (0.18-0.26)
British Columbia								
RR	0.25*** (0.13-0.42)	0.18*** (0.12-0.27)	0.45*** (0.32-0.63)	0.36*** (0.18-0.66)	0.35*** (0.22-0.53)	0.60 (0.32-1.08)	0.81 (0.41-1.56)	0.30*** (0.25-0.37)
ALL Provinces								
RR	0.26*** (0.23-0.30)	0.17*** (0.16-0.20)	0.34*** (0.30-0.39)	0.39*** (0.32-0.47)	0.29*** (0.25-0.33)	0.52*** (0.42-0.65)	0.66*** (0.53-0.82)	0.26*** (0.24-0.27)
Note: Chi-Squared test of significance was conducted for the Rate Ratios								
*** significant at 0.05*			*** significant at 0.01*					

The next greatest declines in hospitalizations were experienced by the less than 1 age group, with a hospitalization RR of 0.26 (95% CI, 0.23-0.30). Every province experienced significant declines in hospitalizations for this age group. The statistically significant declines ranged from a RR of 0.00 in PEI (95% CI, 0.00-0.79) to 0.51 in Saskatchewan (95% CI, 0.33-0.77). This not yet vaccinated group experienced considerable benefit from decreased circulation of varicella.

Older children aged 5-12 and adolescence aged 10-19 also experienced significant declines, RR for ages 5-9 were 0.34 (95% CI, 0.30-0.39), and 0.39 (95% CI, 0.32-0.47) respectively. The greatest decline in hospitalization for ages 5-9 was in Manitoba with a RR of 0.16 (95% CI 0.07-0.30), and the smallest in British Columbia with a RR of 0.45 (95% CI, 0.32-0.62). The greatest decline in hospitalization for ages 10-19 was in PEI with a RR of 0.10 (95% CI 0.00-0.80), and the smallest in Ontario with a RR of 0.59 (95% CI, 0.45-0.77). However, unlike the younger age categories, the within province declines in hospitalization were less consistently significant for older children and adolescence. In particular, for ages 5 to 9, Nova Scotia, New Brunswick, PEI, and Saskatchewan did not observe significant declines in hospitalizations before and after vaccine program implementation. For ages 10-19, Newfoundland, New Brunswick, Manitoba, and Saskatchewan did not observe significant declines in hospitalizations.

Adults also benefited from the childhood immunization program as those aged 20-39 reported a statistically significant decline in RR of 0.00 in Newfoundland and PEI (95% CI, 0.00-0.55; 0.00-0.86 respectively) to 0.45 in

Ontario (95% CI, 0.36-0.56) (Table 2-3). The magnitude of reduced hospitalizations for ages 40+ was somewhat smaller than for younger populations. Alberta, Saskatchewan, Ontario Quebec, and Manitoba all experienced significant declines in this age category, ranging from a RR of 0.24 (95% CI, 0.04-0.79) to 0.61 (95% CI, 0.43-0.85). In the remaining provinces, declines are not found to be significant for the 40-59 age group (Nova Scotia, New Brunswick, Newfoundland, and British Columbia). There was a decline in hospitalization rates which did not reach statistical significance for ages 60+ in all provinces, except Quebec, Ontario, and Alberta, which reported rate ratios of 0.30 (0.12-0.62); 0.73 (0.53-1.01); and 0.42 (0.20-0.86) respectively.

Across each province, there are consistent declines, each with similar magnitudes. Saskatchewan had the lowest RR at 0.42 (95% CI, 0.33-0.53). PEI and Quebec experienced the largest decline with RRs of 0.09 (95% CI, 0.023-0.27) and 0.12 (95% CI, 0.10-0.14) respectively. All other provinces were in between this range, most of which centered around a RR of 0.20 (Newfoundland, Nova Scotia, Manitoba, and Alberta)

2.4. Discussion:

Varicella vaccine was available in Canada for private purchase prior to implementation of the publicly-funded immunization programs. Very modest declines were observed during the period of private availability, when hospitalizations declined by a modest 9% across all ages in Ontario [19]. Since the introduction of publicly-funded varicella vaccine for infants has resulted in

fewer varicella-related hospitalizations *for all ages* across Canada, which implies that there was a decrease in varicella circulation.

In the post-vaccination era, the largest decrease in hospitalizations was observed for children between the ages of 1 and 4, which includes the age group targeted by the immunization program. This group experienced highly significant declines in hospitalization for varicella, ranging from 65%-93% within provinces and 83% across provinces. Also, significantly large decreases were evidenced for infants, and children outside of the targeted group. For example, those less than 1 have experienced declines of 48%-100% within province, and 74% across provinces. Children aged 5-9 show significant declines of 58%-80% within province, and 66% across provinces. These findings are in agreement with other studies. Canadian data indicate that hospitalizations have declined by 78% in children <1 year, 90% for children aged 1-4 years, and 76% for children aged 5-9 years [18]. My data are also consistent with studies monitoring hospitalization rates in the United States. For example, Market Scan data indicates that there was a 100% decrease in hospitalization rates of children <12 months, and that a 91% decline for children under 10 years [25]. Similarly the National Hospital Discharge Survey (2006) revealed a 70%-72% reduction in hospitalization rates in children and young adults under 20 years of age [16]. This is in comparison with the US Vaccine Active Surveillance Project (2005), which showed a 75% decline for the same age groups [8;10], while the National Inpatient Sample (2002) noted an 88% decline in hospitalization rates [26].

My study on varicella-related hospitalization rates differs from other Canadian studies in that I have covered all Canadian provinces, and I have presented data on all adult age categories (as opposed to one or two age categories as is common in the literature). My study shows that adult age groups have benefited from reduced circulation of varicella. For example, the age group 20-40 experienced significant declines of 55%-100% within province and 77% across provinces in varicella-related hospitalizations. Meanwhile, the age group 40-59 showed a 48% decrease across provinces, and a 39%-76% decline in Alberta, Quebec, Ontario, Manitoba, and Saskatchewan. These results are consistent with other provincial and international studies. In the United States, Marin et al. (2008) & Reynolds et al. (2008) analyzed the Varicella Active Surveillance Project (VASP) in California and Pennsylvania [8;10]. They found a 60% decrease in varicella hospitalizations in adults aged 20 and over. Lopez et al. (2011) used the National Hospital Discharge Survey to indicate a decline of 65% for those older than 20 as of 2006 [16]. The MarketScan data note a 78% decrease for adults aged 20-49 as of 2002.

It would not be correct to attribute a decline in varicella-related hospitalizations to "herd immunity" without correlating it with vaccine coverage rates. However, coverage data is sparse in Canada (Table 2). To date only the National Childhood Immunization surveys can be used for analysis. In Canada, these surveys are generally conducted over 5 year intervals. The latest data from the Childhood National Immunization Coverage Survey (CNICS-2011) has yet to

be released.[4] The most recent survey (2006) for which data is available indicated that varicella coverage was low because most provinces (BC, ON, MB, NF, SK, QU, NB) implemented their own universal varicella immunization programs that same year, or later. Most provinces are in the early stages of developing vaccine registries.[5]

While vaccine coverage data from some provinces provide evidence that vaccine coverage has improved once publicly-funded programs were implemented, the absence of coverage data from most provinces makes it difficult to correlate with observed declining hospitalization rates. However, there is a definite temporal relationship between the introduction of the vaccine and the decline in hospitalizations across ages in Canada. These significant reductions in hospitalization rates for non-vaccinated groups, including adults and children under 12 months, indicate decreased circulation of the virus and suggests that "herd immunity" has occurred [18].

All provinces show evidence of significant declines in the circulation of varicella. Across all ages, each province experienced significant decline ranging from 60% (Ontario) to 90% (PEI). According to the objectives for varicella vaccination in Canada, derived at a national consensus conference on vaccine preventable diseases in Quebec in 2005, the goal has been to decrease varicella-related hospitalizations by 70% [24]. According to my data, this goal has been

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[4] Childhood National Immunization Coverage Survey (CNICS) 2011

[5] Manitoba does collect annual vaccine coverage data. Their data indicates that in 2010, varicella coverage reached 80.1% for children by age 2 years. Other Canadian provinces have only recently documented varicella coverage rates, for example, Saskatchewan has a provincial immunization record showing that varicella coverage rates were approximately 71% in 2006.

reached for the vaccinated age groups as well as infants, children, and adults aged 20 to 39. Other age categories including adolescence aged 10-19, as well as adults over 40 are approaching this goal. New NACI varicella vaccine recommendations call for a 2-dose regimen instead of the 1-dose previously employed. This new regimen should result in fewer hospitalizations among the 2-dose vaccinated population, as there was an average breakthrough rate of 3.1% per year in the 1-dose vaccinated cohort in Canada.

This study is limited by a number of factors. Firstly, hospitalization rates for infectious diseases may be affected by multiple factors, including: changing case management practices, demographic changes, and trends in the variety and virulence of the infectious diseases themselves. There may be additional variations in the ways in which physicians assign admission diagnoses, and hospitals code discharge diagnoses in different provinces.

Secondly, while varicella is a reportable disease, it is largely under-reported in Canada. Fifty five percent of the time, contraction of the disease does not warrant a physician visit [27], and patients are rarely formally tested for the disease when presented to a physician. As a result, there is active surveillance only for the most severe cases of varicella (those that are hospitalized), and the impact of vaccination on incidence rates has to be inferred from hospitalization rates.

Thirdly, varicella may occasionally be coded as zoster (and vice versa), which means that these data may under- or over-estimate the total number of cases.

Fourthly, the data used in this study only include cases whereby varicella is the primary reason for hospitalization. Other cases where varicella is present, but not primary, were excluded. Therefore, the total number of cases may be further under-reported. However, these last two factors would be unrelated to immunization patterns.

2.5. Conclusion

Following the implementation of Canada's National Immunization Strategy, varicella-related hospitalization rates declined in all age categories across Canada, including those in age groups falling outside age-groups not routinely recommended for immunization. In particular, declines in hospitalization were found to range from 34%-83% across all provinces. Within each province, declines were significant for the vaccinated cohort, as well as infants under one year old. The rest of the population under age 59 experienced significant declines in hospitalization across the majority of provinces. Despite the lack of vaccine coverage data, these findings are consistent with the herd immunity hypothesis, and suggest decreased circulation of varicella in the country following the introduction of vaccine programs.

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CHAPTER 3: ECONOMIC IMPACT OF ALBERTA'S PCV7 CHILDHOOD IMMUNIZATION PROGRAM

3.1. Introduction:

Acute respiratory tract infections caused by *Streptococcus pneumoniae* (SP) are a leading cause of morbidity and mortality in young children and the elderly. The burden of disease attributable to SP in the form of invasive pneumococcal disease (IPD), and other pneumococcal related disease (OPRD) is high. Rates of IPD in children range from 50 per 100,000 to 125 per 100,000 across Canada and the USA between 1998 and 2001, and 13.3 to 60.1 per 100,000 in adults and seniors [1-7].[1] IPD infection results when SP enter an individual's blood stream; clinical presentations include: invasive pneumonia, meningitis, or bacteremia; sequelae can include death. SP has proven to be fatal in up to 40% of cases in industrialized countries [8]. OPRD is a result of localized bacterial colonization and is often less severe than IPD and is generally presented as either Acute Otitis Media (in children only) (AOM), or localized pneumonia (where the bacteria has not yet entered the blood). The incidence of OPRD is less well known, and estimated to be 12/1000 in the United States [9]. Streptococcus pnuemoniae infections are costly; it is estimated that the Canadian societal costs of pneumococcal-related disease are between $155 million and $295 million annually [10].

Since 2002, a seven – valent conjugate vaccine (PCV7) (with serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), using a non-toxic mutant of diphtheria toxin as a carrier protein, has been provided publically in Alberta. Following the introduction of this vaccine, it has been shown that the 7-valent conjugate

[1] http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-3/

polysaccharide vaccine, administered to children, has been both clinically effective [11] and cost-effective at reducing the cases of pneumococcal disease via direct and indirect protection [12;13]. In particular, there is evidence that invasive disease caused by any one of the seven SP serotypes has dropped by 100% in areas with universal childhood immunization programs [1;2;6] (Appendix Table 3-1). However, some evidence has surfaced to suggest that non-PCV7 incidence rates have in fact increased following vaccine introduction -- a result of what is known as serotype replacement [2;11]. There has been no published research that has evaluated the cost impact of the policy decision to adopt PCV7 in Alberta's universal childhood immunization strategy.

3.2. Objective of Study

Using real world observational data, I will calculate the economic impact, from the perspective of the health system, resulting from Alberta's universal childhood PCV7 immunization strategy. Costs will be analyzed in terms of medical costs averted from direct and indirect (herd effects) vaccine protection.

3.3. Methods

3.3.1 Economic Evaluation:

A prospective population based surveillance program has tracked the incidence of IPD by serotype in Alberta, Canada since 2000 [3]. Using this serotype specific data, I develop a costing model to retrospectively estimate the costs saved by the health care system as a result of PCV7 between 2003 and 2008. Changes in the number of cases caused by PCV7 and non-PCV7 serotypes are taken into account in this economic evaluation.

3.3.2 Population and Study Perspective:

The model is based upon all residents of Alberta, and its age distribution between 2000 and 2008. It took a health ministry perspective, which accounts for the cost associated with all current and future medical and hospital services.

3.3.3 Costing Model:

The model is based on that of Meltzer et al. [14]. It is a model that in part estimates the economic impact of a vaccine intervention by calculating the savings from outcomes averted. The economic impact costing model developed calculates cost savings (from here on in referred to as *net costs*) associated with observed changes in cases of IPD, OPRD, and case fatalities.

The economic impact is calculated according to the distribution of outcomes within the population. The Alberta population is subdivided into seven age categories: <2, 2-4, 5-9, 10-14, 15-19, 20-64, 65+. All incidence rates are age standardized using Statistics Canada CANSIM Table 051-0001 [15].

Two direct medical cost measures are calculated, *PCV7 Costs Averted*, and *Net Costs*. Methods for calculating these measures are described below:

1) *PCV 7 Costs Averted*

To calculate costs averted, I tally the number of age standardized cases of IPD (by disease state), OPRD cases averted, as well as lives saved as a result of a decline in PCV7 strains. The cases averted were calculated by calculating the annual incremental difference in PCV7 cases (by disease state) from the baseline (pre vaccine period 2000-2002) is then calculated.

If the deviation from baseline shows an increase in cases in a particular year following vaccination, these costs are exempt from the PCV7 cost aversion calculation. This assumes that any increases in PCV7 strain incidence rates following vaccination are not caused by the vaccine, and are therefore not included in the calculation of costs.

Costs averted as a result of PCV7 are then calculated for each disease state by multiplying the average direct medical cost associated with that disease state by the number of incremental cases.

To then calculate the total cost averted for Alberta, the total cost per 100,000 was multiplied by the number of Albertans in that age category.

2) *Net Costs*

As mentioned briefly above, serotype replacement has been recognized as being associated with the introduction of PCV7. While there is some controversy concerning whether the vaccine is in fact responsible for serotype replacement and scientifically how this may occur [16-19], the majority of reports [11;20-23] suggest a causal relationship based on a temporal association between the vaccine and the redistribution of serotypes.

In this model, I account for the changes in serotype replacement by including the costs incurred as a result of non-serotypes in the calculation of cost impact. Net costs are the sum of costs averted as a result of PCV7 and costs incurred as a result of serotype replacement. The following decision rule has been applied to the serotype specific data to attribute changes in non-PCV7 serotypes to the introduction of PCV7:

i) Serotype incidence rates must be declining, constant, or variable prior to the introduction of the vaccine (2000-2002). If the serotype incidence rates were increasing prior to the vaccine introduction, then this serotype is excluded from the analysis.

ii) If condition (i) is satisfied, then at 2004, either:

a. The incidence rates monotonically increase after 2004, or

b. There is an inflection point in 2004, and incidence rates trend upwards (either monotonically, or with some variability) and the 2006-2008 incidence rates are greater than or equal to the 2000-2002 rates.

The non-PCV7 serotypes meeting the above criteria will be referred to as PCV7 serotype replacement (PCV7SR). The costs incurred as a result of PCV7SR will be calculated in the same way as PCV7 costs averted (see (i) above). If the deviation from baseline (2000-2002) is positive (PCV7SR costs are averted instead of incurred following vaccination), these costs are exempt from the PCV7SR calculation. This assumes that any decreases in PCV7SR strain incidence rates following vaccination are not caused by serotype replacement, and are therefore not included in the calculation of costs.

3.3.4 Clinical Presentation of Disease States:

The incidence of IPD was estimated using longitudinal data from a prospective surveillance program at the National Centre for Streptococcus. This passive surveillance program identifies about 93% of all IPD cases in Alberta each year. Details regarding the program are published elsewhere [3].

IPD is identified through a positive culture of Streptococcus Pneumoniae (SP) from normally sterile body fluid, usually blood or cerebrospinal fluid, and occasionally pleural fluid. Clinical presentation of IPD can either be invasive pneumonia, meningitis, or bacteremia (with or without the presentation of pneumonia). Sequelae for IPD pneumonia can include death. Sequelae for meningitis and bacteremia can include death, deafness, or neurological impairment. The distribution of the IPD disease states and rates of sequelae and death are taken from Morrow et al [10] and can be found in Table 3-A2 in the Appendix.

The remaining aetiologies of pneumonia are covered under OPRD, though only 20-30% of these cases are caused by SP [10]. Generally, cases of OPRD are detected either using a radiograph, or through lab analysis of fluid from a non-sterile site. Due to poor specificity and sensitivity, diagnostic tests are often ill equipped to correctly identify SP as the cause of OPRD.

OPRD is often less severe in terms of fatality and morbidity than IPD, though cases of OPRD can worsen into cases IPD. OPRD is generally presented as either Acute Otitis Media (in children only) (AOM), myringotomy with ventilation tube insertion (MVT), or localized pneumonia (invasion of pnumococci in the lungs that have not yet invaded the blood). A visual depiction of the clinical presentation of disease states can be found in Figure 3-1 in the Appendix. According to Morrow et al. (2007) proportion of OPRD cases are caused by SP, these estimates will be used in the present analysis [10].

3.3.5 Vaccine Effectiveness (Direct and Indirect Protection):

In 2002, at the time of universal inception, only children reaching 2 months of age were immunized. Children older than 2 months would not be offered the vaccine unless they belonged to a high risk group [24]. In this study, the measure of vaccine effectiveness against IPD and OPRD is measured by the incremental reduction in cases, by disease state, before and after vaccine introduction.

Indirect benefits are accrued to the non-vaccinated population is assumed to be indirectly protected as a result of the decreased circulation of the disease. Herd immunity will be calculated as the incremental difference between the number of cases, by disease state, before and after the introduction of PCV7. Only age categories 10+ will be considered.

3.3.6 Costs:

Direct medical costs include the cost of hospitalization and outpatient costs. Costs of medical care vary across age and disease presentations. The direct costs accounted for in this analysis will include: medical costs resulting from OPRD outpatient care, and any subsequent hospitalizations. Costs of treatment and sequelae for IPD and OPRD are taken from Table 3 in Morrow et al [10]. The present study will use the direct medical cost estimates of Morrow et al [10] (Table 3-1). Direct medical costs are applied to IPD, OPRD, and case fatalities for both PCV7 and PCV7SR cases.

Table 3-1: DIRECT MEDICAL COSTS 2008$ [10]							
Index	Menin-gitis	Hospit-alized bacter-emia	Non-Hospital bacteremia	Hospitalized pneumonia	Non-hospital pneumonia	OM	Myringotomy
0-4	$35,017	$6,553	$143	$2,686	$99	$69	$616
5-9	$32,981	$5,129	$143	$4,314	$99	$69	$616
10-19	$32,981	$5,129	$143	$7,165	$99	$0	$0
20-64	$14,170	$11,697	$143	$7,624	$99	$0	$0
65+	$11,304	$11,287	$143	$8,031	$99	$0	$0

The cost associated with a case fatality was $32,000 for any age [25].

All costs are adjusted to reflect 2009 Canadian dollars using the Canadian Consumer Price Index.

3.6.7 Model Analysis and Scenario Analysis:

The estimated cost impact following the introduction is calculated in Microsoft Excel 2003. The distribution of serotypes, categorized by age and year were analyzed using SPSS 2012.

A scenario analysis is conducted to determine the effects of model assumptions. Specifically, I will examine whether net costs are robust to fluctuations in incremental cases of PCV7 and PCV7SR post vaccination. In addition, I will describe costs averted following PCV7 introduction assuming there is no relationship between the vaccine and serotype replacement.

3.4. Results:

As mentioned above, it is assumed that serotype replacement exists due to PCV7 vaccine introduction. This paper examines the trajectory of each serotype to determine which serotypes in fact increase following vaccine introduction in 2002 that were not already increasing prior to vaccine introduction. Based on the

above criteria, I find serotypes that met the inclusion criteria, PCV7SR, include: 10A, 11A, 15A, 19A, 23A, 20, 34, 23B, 12F, 15B, 5, 38, and 22F. Serotypes excluded based on condition (ii) include: 10F, 11B, 16F, 18B, 28A, 33F, 33A, 35B, 6A, 7C, 7F, 9L, 1, 13, 38, 8, 35F, 15C, 3, 17F, 33F, 9N, 21, and 31.[2] More specifically, 51% of PCV7SR serotypes meet the inclusion criteria. In 2000 these serotypes contributed to 5% of all PCV7 and PCV7SR serotypes meeting inclusion criteria (this proportion excludes non-PCV7 strains that do not meet inclusion criteria). By 2008, this number increased to 58% of the same total.

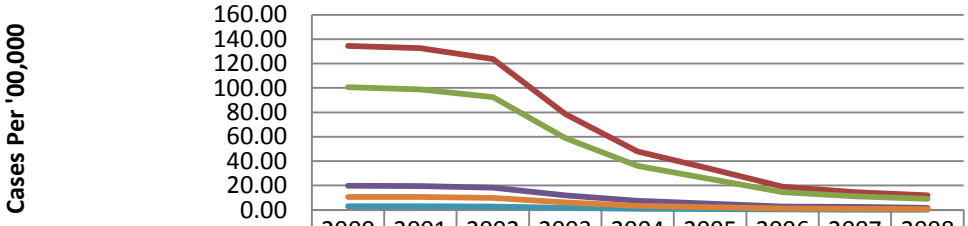
3.4.1 Changes in Incidence Rates of Streptococcus Pneumoniae:

This analysis shows that following the introduction of PCV7, the number of cases of IPD caused by vaccine serotypes declined significantly between 2000 and 2008 (Figure 3-1). PCV7SR cases on the other hand increased (Figure 3-2).

Along with the decrease in cases, an average of 1.6 lives were saved annually as a result of PCV7 (Table 3-2), and 1.37 lives once PCV7SR deaths are taken into account.

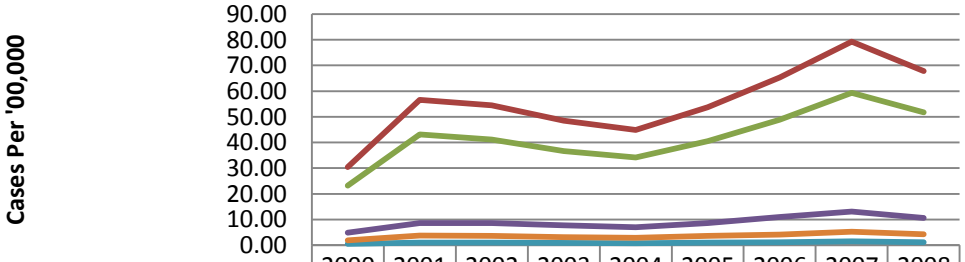
[2] Reasoning for exclusion can be found in Table 3-A3 of the Appendix.

Figure 3-1: Change in Number of PCV7 Incidences Per 100,000



	2000	2001	2002	2003	2004	2005	2006	2007	2008
All IPD combined	134.51	132.55	123.76	78.68	47.82	33.60	18.97	14.63	11.91
Pneumo	100.68	98.82	92.49	58.79	36.05	25.45	14.61	11.04	9.11
Bact	19.79	19.64	18.26	11.97	7.37	5.18	2.83	2.47	1.84
Mening	2.99	3.01	2.78	1.70	0.95	0.63	0.33	0.24	0.21
NonHosp bacteremia	10.71	10.76	9.92	6.05	3.38	2.28	1.18	0.86	0.74

Figure 3-2: Change in Number of PCV7 Incidences Per 100,000



	2000	2001	2002	2003	2004	2005	2006	2007	2008
All IPD combined	30.41	56.59	54.40	48.49	44.88	53.75	65.26	79.23	67.81
Pneumo	23.17	43.18	41.11	36.65	34.20	40.48	48.82	59.30	51.67
Bact	4.89	8.57	8.56	7.72	7.03	8.63	11.03	13.13	10.56
Mening	0.50	1.02	1.01	0.88	0.77	0.99	1.17	1.46	1.18
NonHosp bacteremia	1.82	3.73	3.63	3.16	2.82	3.56	4.15	5.21	4.30

Table 3-2: Average Annual PCV7 and PCV7SR Cases Per Hundred Thousand (2000-2008)							
	PCV7			*PCV7SR*			*TOTAL change following PCV7 introd-uction*
	Average PRE (2000-2002)	*Average POST (2003-2008)*	*Difference post vs pre PCV7*	*Average PRE (2000-2002)*	*Average POST (2003-2008)*	*Diff-erence post vs pre PCV7SR*	
Mortality	2.5	0.9	-1.6	1.8	2	0.2	-1.37
All IPD Combined	130	112	-18.6	47	53	6	-12.61
Pneumo	97	83	-14.0	36	40	4	-9.97
Bact	19	17	-2.6	7	8	1	-1.61
Mening	3	2	-0.4	1	1	0	-0.43
Nhbact	10	9	-1.6	3	4	1	-0.55
Nhbact get worse	1	1	-0.2	0	0	0	-0.16
OPRD caused by SP	4246	3639	-606.5	1563	1788	225	-381.45

3.4.2. Health ministry cost averted:

The direct medical costs saved by the health ministry as a result of the observed declines in PCV7 amount to over $5.2 million per 100,000 (Table 3-3). The direct medical costs incurred as a result of associated PCV7SR are over $900,000 per 100,000 people. Cost savings were greatest per hundred thousand in the vaccinated group (<2 year olds) with approximately $4.3 million in savings per hundred thousand. The next most significant savings were the elderly with more than $545 thousand per hundred thousand averted, and $314,934 saved on net.

In terms of costs incurred as a result of PCV7SR, incidence rates and related costs were greatest in the adult age categories. Specifically, on net, those aged 20-64 and 65+ incurred costs of $291,554 and $229,767 per hundred thousand respectively.

Given that the bulk of the population in Alberta is above the age of 20 (74% of the population), the net savings for the province are small relative to the

large savings per hundred thousand. In all, the costs averted from reducing PCV7 strains amounted to $9.4 million. However, the costs incurred as a result of PCV7SR were nearly $7.6 million. As a result, on net, the total cost savings for Alberta amounted to only about $1.846 million.

Table 3-3: PCV7 Costs Averted, PCV7SR Costs Incurred and Net Costs (in thousands $)

Age	PCV7 averted per hundred thousand	PCV7SR Incurred per hundred thousand	Net Cost per hundred Thousand	Pop Distri-bution (avg 2003-2008)	AB PCV7 averted	AB PCV7SR incurred	Net cost AB
<2	$4,561	($245)	$4,316	0.86	$3,923	($211)	$3,713
2-4	$884	($80)	$804	1.22	$1,083	($98)	$985
5-9	$46	($16)	$31	2.08	$96	($33)	$63
10-14	$35	($19)	$16	2.27	$80	($43)	$37
15-19	$27	($60)	($33)	2.44	$65	($146)	($81)
20-64	$106	($292)	($186)	21.42	$2,271	($6,244)	($3,973)
65+	$545	($230)	$315	3.50	$1,906	($804)	$1,102
Total	$6,204	($941)	$5,263	33.79	$9,425	($7,579)	$1,846

3.4.3. Herd immunity:

Herd immunity is a proportion of net costs calculated above. There is evidence of more than $700,000 costs averted per 100,000 as a result of PCV7. However, costs have increased by more than $600,000 per 100,000 as a result of costs incurred by related PCV7SR strains. As a result, the net herd immunity savings are found to be $112,562 per 100,000 population (Table 3-4).

Table 3-4: Herd Immunity -- PCV7 Costs Averted, PCV7SR Costs Incurred and Net Costs (Cost in thousands $)						
Age	**PCV7 averted per hundred thousand**	**PCV7SR Incurred per hundred thousand**	**Net Cost per hundred Thousand**	**AB PCV7 averted**	**AB PCV7SR incurred**	**Net cost AB**
10-14	$35	($19)	$16	$80	($43)	**$37**
15-19	$27	($60)	($33)	$65	($146)	**($81)**
20-64	$106	($292)	($186)	$2,271	($6,244)	**($3,973)**
65+	$545	($230)	$315	$1,906	($804)	**$1,102**
Total	**$713**	**($600)**	**$113**	**$4,322**	**($7,237)**	**($2,915)**

When taking into account the distribution of the Alberta population, the herd effects are actually larger for PCV7SR than they are for PCV7. Therefore, the net costs due to herd are negative. Implying that following the introduction of PCV7 in ages 10+, on net more than $3 million in costs were incurred in Alberta (Table 3-4). However, it should be noted that the number of cases of IPD in the 10-19 age groups were less than 5 in any given year. As original number of each serotype was likely small, any increase in absolute numbers would lead to a large percentage increase.

3.4.4. Scenario Analysis:

Table 3-5: Scenario Analysis -- Fluctuations in Incidence Rates Included in Analysis (Cost In thousands $)

Age	PCV7 averted per hundred thousand	PCV7SR Incurred per hundred thousand	Net Cost per hundred Thousand	Population distribution per hundred thousand (average 2003-2008)	AB PCV7 averted	AB PCV7SR incurred	Net cost AB
<2	$4,561	($243)	$4,318	0.86	$3,923	($209)	$3,714
2-4	$882	($70)	$812	1.22	$1,080	($86)	$994
5-9	$46	($14)	$32	2.08	$96	($30)	$66
10-14	$28	($5)	$23	2.27	$64	($12)	$52
15-19	$15	($47)	($32)	2.44	$36	($115)	($79)
20-64	$101	($292)	($190)	21.42	$2,169	($6,244)	($4,075)
65+	$545	($228)	$317	3.50	$1,906	($798)	$1,109
Total	$6,178	($900)	$5,278	33.79	$9,275	($7,494)	$1,781

As can be seen in Table 3-5, the fluctuations in incidence rates are minor, and have little effect on overall results. PCV7 costs per hundred thousand are 6.2 million as compared to 6.17 million when fluctuations are not included; PCV7SR costs incurred are roughly $900,000 as compared to $941,000 when fluctuations are excluded. Overall the difference in net effect is small, $15,248 per hundred thousand or $64,781 for Alberta.

3.5. Discussion:

The study results are very interesting as on net per hundred thousand, the PCV7 costs averted outweigh the costs incurred as a result of PCV7SR, saving more than $3.5 million per hundred thousand. However, overall Alberta saved on net roughly $1.846 million due to the PCV7 immunization program.

I estimate net costs to be in the range of $5.3 million in savings per hundred thousand. However, caution should be exercised when interpreting results. Nearly all of these cost savings are found to be for children, net costs are actually negative for ages 15-64. Therefore, calculating total cost for Alberta using the total net cost per 100,000 and adjusting it to calculate the cost savings in Alberta will lead to misleading conclusions ($177 million versus the correct amount of $1.845 million). Taking the population distribution and cost distributions into account was essential for this analysis.[1]

Herd Immunity:

There is evidence that indirect effects (herd immunity) have resulted from current child immunization programs. In addition to the direct protection resulting from immunization, vaccination also results in indirect effects, also known as herd immunity. Herd effects have been witnessed as a consequence of the universal PCV7 infant immunization programs [11;21;26-29]. In Canada, it has been found that adults have experienced a 34%-100% decrease in the incidence of IPD cases associated with serotypes specific to PCV7 for adults aged 65-85 [11]. In this study, I find that the economic impact resulting from the PCV7 immunization program are roughly 11% of total medical costs averted, or approximately $712,760 per 100,000. Without consideration of serotype replacement, herd effects are substantial and offer considerable cost savings to health systems. However, when taking PCV7SR strains into account, all herd

[1] Because most of the population is over the age of 20 (approximately 74% of the Alberta population), when examining the net costs for the province, the net costs are in fact negative – meaning more costs are incurred as a result of PCV7SR than are averted due to PCV7 for adults. However, the net costs for children are highly positive – resulting overall in small cost savings in Alberta.

effects are negated. In fact, the cost increases resulting from changes in serotype distribution more than offset the costs averted from PCV7 *in these age categories.*

The majority of reduction in cost was experienced by infants and seniors. Infant cost aversion was in the range of $4.6 million as a result of PCV7, and $4.3 million on net. Seniors on the other hand, per hundred thousand had a cost savings of $544,701 following the introduction of PCV7, and close to $315,000 on net. It is recognized that seniors are recommended to receive a 23-valent polysaccharide vaccine (PPV23). While it is not possible to show that the change in incidence rates is not a result of increased coverage of PPV23,[2] these data do show a clear temporal association between PCV7 childhood immunization and the decrease in incidences of SP in seniors.

A key implication of findings of herd immunity in older adults relates to recommendations of vaccination for these population subgroups. A follow-on vaccine to Prevnar 7, Prevnar 13-valent conjugate vaccine (PCV13), was recently approved for ages 50 and above. PPV23 has been shown to be less effective than PCV13, though it is yet to be determined whether it is cost-effective for these groups to be immunized. Much of the current evidence rests on whether the vaccine is effective against all-cause pneumonia, or OPRD [30]. In this study I find the effects of PCV7 on vaccine strains to be very striking, as incidence rates in all age categories declined to near zero. However, PCV7SR strains increased considerably, with differences in distribution across ages.

[2] There are no vaccine registries in Alberta

Serotype replacement (change in non-PCV7 serotypes):

It is questionable as to whether the total cost of health care as a result of SP has been reduced due to the introduction of PCV7. In particular, it can be seen that IPD increased in PCV7SR serotypes. Specifically, a 73%-140% increase in non-PCV7 strains of pneumococcal has been found [11;20].

Serotype 5 was most problematic for Albertans 15 and older, but not for children and youths. The incidence rate moved from 0 cases in the pre-vaccine period to more than 12 cases per 100,000 across all ages post vaccine period. The incidence rates were as high as 170 cases per 100,000 and 269 cases per 100,000 for people 20-39 and 40-64 respectively. This change in serotype incidence resulted in much lower net costs.

Other serotypes declined following the introduction of PCV7 (6A, 7F, 9L, 1 13, 18B, 16F). Still others remained constant (28A, 3), and were constant then spiked in 2007/2008 (9N, 21, 31, 33F, 8). There is no cited reason for these declines, and plateaus in serotype incidence.

There is little conclusive evidence fully explaining the causal relationship between PCV7 and serotype replacement. However, there is evidence of a strong temporal relationship, and scientific theoretical explanations for serotype replacement. As a result, serotype replacement was accounted for in this model. All increased costs resulting from serotype replacement were subtracted from the costs averted as a result of PCV7. In total, I find that medical cost savings still amount to $1.846 million in Alberta. Should serotype replacement be unrelated to

the introduction of PCV7, then the total medical cost averted in Alberta tops $9.2 million.

Many papers suggested cost effectiveness of PCV7 in childhood program:

Many cost effectiveness analyses have suggested that PCV7 was in fact cost effective [31-40]. With more than 10 years since the introduction of the vaccine, it is possible to retrospectively evaluate the program. The Alberta dataset was comprised of the first 6 years post universal immunization program. While this study only examines the costs averted as a result of a universal childhood immunization program, I do not examine the value of health gained. Therefore, the net impact of the program cannot be directly addressed. However, I do find cost savings of more than $4.3 million per 100,000 infants, and $300,000 per 100,000 seniors over the 6 years following introduction of PCV7.

3.6. Limitations of study

The analysis is limited by a few factors. First, the time period available before the vaccine (2 years) and the time observed following (6 years) may be inadequate for observing general trends in serotype natural history. Therefore, if specific serotypes do in fact meet the inclusion criteria given further surveillance, then costs incurred due to serotype replacement are underestimated. Similarly, if serotypes are episodic and increases are unrelated to the vaccine then costs averted are underestimated. Second, the analysis was primarily driven by actual epidemiologic surveillance data on IPD over time. Calculating the clinical and economic impact of OPRD used data (e.g., incidence and costs) from existing published studies as serotyping is not done for these cases. Third, there is no clear

understanding of cyclical patterns of disease by various serotypes. The original number of cases due to each serotype was small in some age categories (ie. less than 5 in any given year for ages 10-19). Therefore, any increase in absolute numbers would lead to a large percentage increase. The resulting cost estimates for these age ranges should be interpreted with caution.

3.7. Conclusion and looking forward

The childhood immunization program has been very successful in reducing the burden of disease among children immunized, as well as the rest of the population. Despite the rates of IPD caused by the 7 vaccine serotype declining by nearly 100% in most jurisdictions that have implemented a universal childhood immunization program [1;2;6], it is expert opinion that revoking this vaccine from the childhood immunization program at this point would result in a new surge of disease [41].

The economic impact of Alberta's PCV7 immunization program depends upon the relationship between the vaccine and serotype replacement. If serotype replacement is a result of PCV7, the economic impact of the program is roughly $1.846 million saved in terms of medical costs.

However, if the current change in the distribution of SP serotypes is unrelated to the vaccine, then the economic impact of PCV7 is much larger, at over $9.2 million in medical costs averted as a result of PCV7.

Further analyses concerning the health benefits derived from the program would be useful in a more comprehensive analysis of universal PCV7 childhood immunization. Specifically, a full economic analysis could be conducted by

calculating the incremental QALY's resulting from the immunization program. An ICER could then be generated in using the cost information from this study. In addition, future studies examining the impact of recently provided PCV13 would be similarly useful in understanding the economic impact of the new vaccine.

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CHAPTER 4: THE COST OF VACCINE RESEARCH, DEVELOPMENT, AND DEPLOYMENT[1]

[1] A version of this chapter has been submitted for publication. Waye, A., Jacobs, P., Schryvers T. Expert Reviews. 2013

4.1. Introduction

Pharmaceutical research and development (R&D) expenditure statistics have been used by government agencies and industry organizations to gauge a country's performance in drug development [1]. Recently, the related statistic "development cost of a new chemical entity" has emerged for use in a policy context [2]. A number of estimates for this statistic have been undertaken in the pharmaceutical industry [3-10;10-12], with a commonly cited estimate of the development cost of a new drug being in excess of $800 million [6]. However, there is a wide range of estimates in the pharmaceutical area, stemming both from the varying methods used to derive the statistic, from differences in the nature of the products, as well as from variations in the data that go into the formation of the estimate. There has been only one such study in the vaccine industry, on rotavirus vaccine [13], which cited a capitalized development cost of between $205 million and $878 million.

Vaccine development is an area which has bourgeoned economically since the turn of the new century. Prevnar, the vaccine for streptococcus pneumonia, was the first blockbuster vaccine with annual revenues over a billion dollars worldwide. After that, other vaccines have followed, opening up the vaccine field to a greater profitability. As a result, vaccine development today has become big business. And as vaccines have captured the public imagination as an alternative way of preventing and treating disease, new vaccine development has become a relevant policy issue in terms of financing, and attracting investment to further economic growth.

Canada, for example, has been providing tax and subsidy incentives to attract foreign investment in the biopharmaceutical industry [14]. In particular, the federal and provincial governments have reduced corporate income tax rates, provided generous tax credits against R&D costs, as well as developed subsidy programs to support health research, and innovative start-up companies [14].

If the information provided in the pharmaceutical policy arena is of any indication, costing statistics will need more careful scrutiny before being transplanted to the vaccine field for use as policy indicators for the monitoring of existing, or creation of new, financing or regulatory policy. The purpose of this paper is to review the concept of drug and vaccine research and development costs, to review the literature on the development of drugs and vaccines and to estimate the cost of vaccine development. The layout of this paper is as follows: Section 2 describes the objectives of study. Section 3 will describe the framework for understanding vaccine Research, Development and Deployment (RDD) costs. Section 4 will employ this framework to analyze the currently published total cost of vaccine estimates. Section 5 describes the methods for generating a model estimating the cost of vaccine RDD, using Rotarix as a specific case example. Section 6 presents estimated costs of RDD for Rotarix vaccine. Section 7 discusses the results and Section 8 concludes.

4.2. Objective of Study

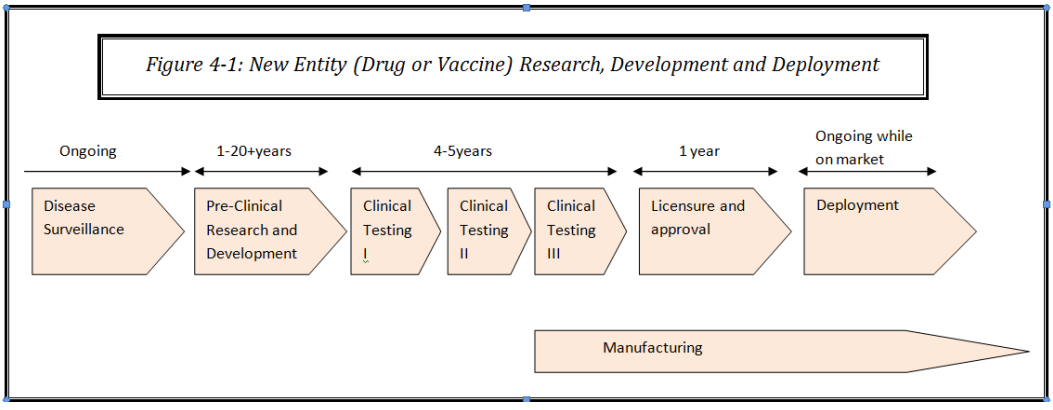
The objective of this study is to generate a general model to ex-post estimate the total societal costs of vaccine RDD for a given successful vaccine. A successful vaccine is one which has been licensed and approved in the marketplace. Societal costs of vaccine RDD include all resources expended internationally by companies, industry, governments, and the general public to develop a vaccine. Economic drug costing methodologies will be modified to create a general vaccine costing model. As a demonstration, I will use the model to calculate the cost of Rotarix vaccine RDD, using parameters drawn from leading studies in the area.

4.3. Framework for Assessing Vaccine RDD Costs

4.3.1. Five Phases of Vaccine RDD

A timeline of development needs to be defined when calculating the cost of vaccine RDD. In general, vaccine development can be broken down into 5 phases of development. These phases include: (i) Serotype surveillance, (ii) Pre-Clinical Research and Development (iii) Clinical Testing, including manufacturing (iv) Licensure, (v) Deployment. Figure 4-1 depicts the vaccine RDD pipeline.

Figure 4-1: New Entity (Drug or Vaccine) Research, Development and Deployment



i) **Serotype/Subtype Surveillance:**

Serotype surveillance is generally carried out by public health agencies, or academic institutions. During this phase, the distribution of the disease and its serotypes/subtypes are measured. In the case of Rotavirus, the 5 serotypes are monitored to determine the most prevalent strains of infection. This information is imperative in the development of a vaccine as these serotypes (or genotypes) are the target for the vaccine under development. Generally, the more strains covered, the more expensive the cost of manufacturing. There are no known estimates of the total cost of serotype surveillance for any given geographical region.

ii) Pre-Clinical Research and Development

Vaccine synthesis: The process of identifying new antigens with the potential to induce immune response and future immunity. The process may require: 1) research on the fundamental mechanisms of disease or biological process; 2) research on identified antigens and how they stimulate the immune system; 3) assay development. Vaccine design is a process whereby one or more antigen(s) is combined with an adjuvant, and a preservative. There are no known cost estimates of antigen discovery or vaccine synthesis for Rotavirus or any other vaccine.

Biological Screening and Pharmacological testing studies: explore the pharmacological activity and immunogenic potential of the vaccines. Generally, the process of designing a successful vaccine is iterative, meaning many antigens are considered, and vaccine designs tried, before one moving from pre-clinical to clinical research. Tests to determine candidate vaccines for clinical testing involve the use of animals, isolated cell cultures and tissues, as well as computer models. The chosen vaccine demonstrates the highest level of immunogenic promise with the smallest number of potentially harmful adverse effects. There are no known cost estimates of

vaccine biological screening and pharmacologic testing studies for Rotavirus or any other disease.

Pharmaceutical dosage formulation and stability testing: The process of determining vaccine form and dose that is suitable for humans. A vaccine can be of the intramuscular, oral, or intranasal form. The final antigen strength needs to be determined, as well as the final formulation containing an adjuvant, and a preservative. The impact of each on the human body must be tested. There are no known cost estimates of vaccine dosage formulation and stability testing.

Toxicology and safety testing: Determine the potential risk a vaccine poses to humans. These studies use animals, tissue cultures, and other tests to determine the relationship between the dose level, frequency of administration, and duration of exposure to the survival of the animals. The result of these tests is the toxic effect. There are no known cost estimates of toxicology and safety testing.

Regulatory review: An application must be filed with the government of each country for which the vaccine will be tested in humans. This application describes the clinical research plan for the vaccine and the specific protocol for phase I clinical testing.

iii) Clinical Testing, including manufacturing

Phase I clinical testing: The first testing of the vaccine in humans to determine the tolerance of healthy individuals at different doses. Phase I clinical trials are small in size (20-100 participants) and establish vaccine safety in healthy human subjects.

Phase II clinical trials: establish the vaccine's potential immunogenic response and its short term risks. Phase II trials are approximately 2 years long, and are also conducted in healthy participants (100-300 participants). Phase II trials establish the proof of concept of the vaccine.

Phase III clinical trials: determine safety and efficacy on a large scale. Generally, between 2,000 and 10,000 participants are required to generate evidence of vaccine

efficacy and safety over the course of 38-46 months. Phase III studies gather precise information on a broader range of adverse effects and immunogenicity than those in Phase I and II. These studies may also determine the best dosage of the vaccine and age of immunization. It is estimated that pharmaceutical companies spend between $300 and $880 million on these three clinical trials [5;6;13;15].

Process Development for Manufacturing and Quality: Engineering and manufacturing design activities determine the company's ability to produce the vaccine in large volume and develop procedures to ensure vaccine stability, uniformity from batch to batch, and overall product quality. The manufacturing facility may be built in conjunction with Phase II clinical testing (approximately 4-6 years prior to licensure) so that 'lots' can be produced, and shown to regulators to be pure. Pharmaceutical companies hold the expertise in process development and chemical engineering to develop and scale up manufacturing of vaccines [16]. The estimated cost of building a manufacturing facility ranges from $20-$26 million (15-20 million Euros) to $600 million USD [17].

The overall process of manufacturing may be similar for all vaccines; however, the fixed and operational costs of manufacturing differ considerably across vaccine classes and formulations.

Manufacturing costs can be decomposed into start-up costs, and operational costs. Start-up costs include all fixed costs associated with equipment and manufacturing facility. Operational costs can be described according to capital, labour, material, and consumables [17]. Start-up costs are all necessary expenditures on capital required for the commencement of manufacturing. Start-up costs include the facility and equipment necessary for the manufacturing of vaccines. Operational costs can be calculated according to 'cost of goods' accounting. The cost of goods measurements will include all costs involved in the production of the vaccine, including: material, labour, and allocated

overhead [18]. Douglas et al. estimates the cost of goods to be between $0.70 and $2.50 per dose [16]. These amounts are approximately 1%-20% of the vaccine sale price.

iv) Licensure: To successfully license a vaccine, a dossier must be prepared and distributed to the approving body based on information gathered throughout preclinical and clinical testing. Manufacturing facilities must also be approved and shown to produce a vaccine that is consistent and stable. Regulatory approval must be conducted in each country in which the product will be sold. The usual time required for approval is approximately 15 months in Canada and the USA [19].[1] The cost of applying for licensure in Canada is over $300,000 per application.[2]

v) Deployment: Reaching commercialization is the end of most vaccine development pipelines; a vaccine is considered successful upon reaching the deployment phase. However, costs are still incurred following commercialization of a vaccine. Specifically, the profitability of a new vaccine relies upon adequate deployment:

a) Marketing can be very costly, especially when government agencies decline to include a vaccine in their public immunization programs. For example, Merck spent an estimated $104 Million in 2007 on HPV vaccine advertisements.[3]

b) Some vaccines require a cold chain -- specific conditions for distribution as vaccine efficacy can be adversely affected if specific environmental conditions are not met.

c) Legal ramifications stemming from adverse events are an issue for vaccine manufacturers. In nearly all industrialized countries, governments have provided a form of insurance against adverse events caused by a vaccine that has been properly manufactured. Legal costs are of significant concern to all pharmaceutical companies.

[1] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm209349.htm
[2] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/fees-frais/fee_frais_guide-eng.php#a2.3.1
[3] http://www.fiercepharma.com/special-reports/merck-top-13-advertising-budgets

There were 3,625 adverse reactions to drugs and vaccines in 2004 in Canada.[4] Vaccines are of particular concern as they are administered to healthy individuals, and may, though very rarely, adversely affect the immunized individual. Most countries, with the exception of Canada, have a public insurance system to protect pharmaceuticals from legal repercussions of vaccination mishaps.[9] However, the province of Quebec did institute a public "No-Fault Vaccine Injury Compensation Program" in 1985. Between 1985 and 2000, this program awarded $2.7 million in benefits (approximately $180,000 per year) [16;20].[5]

d) Pharmaceutical companies are responsible for post-market surveillance in terms of safety monitoring and further evidence of vaccine efficacy. Patients, health professionals, manufacturers, and health product regulatory authorities (such as PHAC) together monitor adverse reactions and medical device incidents through spontaneous reporting from provincial and federal health departments.

4.3.2. Conceptualization of Vaccine Total Costs

In the literature, there are a number of different conceptualizations of total costs related to the development of a successful pharmaceutical. Light et al argue that the total cost is equivalent to the total cash outlays for development of the successfully approved pharmaceutical [13]. Young & Surrusco argue that the total cost is equal to the total cash outlays for not only the successful pharmaceutical but also the unsuccessful pharmaceuticals from which the successful pharmaceutical was derived [21]. In other words, the amount of

[4] According to PHAC, taken from Vaccine-Related Injuries: Why Canada Needs to Adopt a No-Fault Compensation Scheme in Light of the New H1N1 Vaccine In Dalhousie Journal of Legal Studies Online. 2010.
[5] http://www.cmaj.ca/content/183/5/E263.full.pdf+html

money companies required to finance the cash outlays of the successful and unsuccessful projects.

DiMasi et al., Young & Surrusco, Adams & Branter all suggest that the total cost of a successful pharmaceutical includes the *opportunity cost* of all cash outlays for both the successful and all unsuccessful projects [3-8;11;12;15;22;23]. The opportunity cost is the value of foregone returns on capital that could be earned elsewhere. Therefore, the opportunity cost of cash outlays will be greater than the actual expenditures; the present value of cash outlays is the amount necessary to entice investors to invest in a risky venture such as pharmaceutical research and development.

Perspective:

Economic costing analyses of RDD costs for a particular vaccine can be conducted from a number of different perspectives. A company perspective estimates the total costs incurred by a corporation across all projects related to a particular vaccine venture. A corporate perspective offers project level balance sheet, or net present value information. This is an important factor in the valuation of any company.

Similarly, an industry perspective examines the costs incurred by a set of firms within the vaccine industry to produce a particular vaccine. The industry perspective measures of R & D are oriented towards issues concerning industry profitability, measured as revenues less the firm's costs, *net of taxes and subsidies*. A cost statistic generated from an industry perspective would include after – tax and after – subsidy profits.

A societal perspective is more comprehensive than either the corporate, or industry perspective, as it includes all costs incurred in a vaccine's development by all corporations, as well as government and broader society (such as charities) are included. A societal perspective provides insight into how R&D costs have changed over time, and provides information about the relative contribution of the industry to the economy.

Scope

Geographic Location: The cost of economic inputs such as land, and labour vary across the world. Given that vaccine development is increasingly globalized, it is necessary to take into account differences in cost across the globe when calculating the cost of vaccine RDD. Indices such as those outlined in Love et al. (2003) can be used to for cost differences across countries [24].

Key components to Costing Vaccine RDD: The pharmaceutical pipeline

To capture all societal costs incurred in the vaccine RDD process, there are four key components that together are used to calculate the societal cost of vaccine RDD:

- Cash outlays: Cash outlays value the resources used in the development process. All land, labour, and capital, as well as any overhead costs across all 5 phase of development (Figure 4-1) should be included. Theoretically, these costs should add up the resources used and be valued at their opportunity cost. Practically speaking, estimates of cash outlays often reflect total expenditures paid for resources used at the market price.

- Cost of failure: The cost of failure in any given phase of development must be taken into account when determining the cost associated with vaccine RDD. Due to scarcity of data, this cost is often calculated based upon the likelihood of project failure.
- Subsidies and Tax breaks: Vaccine developers at different stages of development are privy to government subsidies and tax rebates for expenditures on research and development. These costs should only be taken into account when calculating costs from a corporate or industry perspective because taxes represent an expenditure of resources for the company/industry. At a societal level, taxes are a mere transfer of resources not an expenditure of wealth.
- Cost of capital investment: there must be an adequate return on a risky investment to entice an investor to invest in pharmaceutical research and development. The cost of capital represents the cost of funds to a company, or the rate that will entice investors to invest in the company and forego returns elsewhere on their capital. This measure is used by companies to calculate the viability of projects. Generally, the value of the cost of capital is the sum of the risk free interest rate that could be earned on a safe investment plus a risk premium. There are a number of ways to estimate the risk premium, including the capital asset pricing model (CAPM), as well as the weighted average cost of capital (WACC).

4.3.3. Method of Costing RDD

In general, there are two primary costing approaches used in economic evaluations: a top-down versus a bottom-up method of estimation. A top-down

method of estimation, also known as gross or aggregate costing, uses a defined metric to assign total costs to a project, set of projects, or company [25]. Detailed costs of resources used are not tallied, rather a general estimate of total cost is provided. Bottom-up method of estimation, also known as process based costing, generally uses microcosting techniques to generate detailed estimates of the resources used, and underlying value of these resources for each phase of a project. Phase costs are then aggregated to generate a total cost estimate for a particular drug or vaccine in development.

Each of these approaches can be employed to estimate costs ex-ante or ex-post. An ex-ante perspective will consider future costs incurred by a company, based on data from existing projects. Ex-post describes actual costs, or retrospectively value the costs incurred over a period of time.

4.4. Empirical Estimates of Vaccine and Pharmaceutical RDD Costs

In this section, literature on both the cost of vaccine and drug RDD is presented, and critically analyzed key articles based upon the key costing components listed above. Cost estimates are assessed to determine whether they are: a) methodologically sound, and b) generalizable to other vaccines. The section concludes by drawing the vaccine and drug costing literature together to explain why it does not appear as though drug costs can be applied to vaccines.

4.4.1. Estimated Cost of Vaccine RDD

Light et al. (2009) estimates the clinical and manufacturing cost of developing Rotarex and Rotarix, both licensed in 2006, to be between $205 and $878 million in 2008USD [13]. These vaccines were developed over a period of

16 years. Light et al [13] account for the cost of capital to be between 3% and 7%, but do not consider the costs associated with failures (stating that most vaccines do not fail after pre-clinical phase development). However, they do recognize that the high number of participants required for phase III clinical testing (more than 5 times the average number required) is a consequence of severe adverse events caused by a previously licensed (and subsequently withdrawn) Rotavirus vaccine. Clearly, Rotavirus vaccines did fail and resulted in not only added cash outlays, but also increased future costs of development.

Geographical differences in cost are assumed to be implicitly taken into account by the industry experts providing the per-patient clinical trial cost estimates as well as the cost of manufacturing facilities. The cost of capital employed by Light et al. is closer to those used in societal cost effectiveness analyses, ranging from 3% to 7%.

4.4.2. Estimated Cost of Drug RDD

Overview of Current Literature on the Cost of Drug RDD

Fifteen articles estimating the cost of drug development have been identified, estimating the cost of pharmaceutical development. Considerable variation exists across the estimates of drug development, ranging from $92 million in 1991 US$ ($161 million capitalized) to $888.3 million ($1.8 billion capitalized) in 2009 US$ (Figure 4-2) [26]. These studies have been conducted over a span of 5 decades. Most of these estimates only include the costs of clinical trials, though some also attempt to estimate preclinical costs.

Each of the 15 studies was conducted from an industry perspective. In other words, the average cost of drug development was estimated using data of successful and unsuccessful drugs across the industry. The cost of failure or success was not attributed to any one corporation, but to the industry as a whole. Costs incurred by the public sector including governments and charities or NGO's were not considered.

Three different methods of cost estimation were employed: retrospective costing analyses at the project level [2;3;14-17;22;23]; retrospective costing analyses at an aggregate level [11]; prospective costing analyses at the project level [27].

These 15 articles were written by 6 different research teams. DiMasi and his teams from Tufts University have published 8 articles retrospectively estimating the cost of drug development based on proprietary project level data [3-10]. Their original paper in 1991 was based upon Hansen and Chein [9] and Wiggins et al [28]. Of the remaining articles in the area, 3 modify or verify the results of DiMasi et al. [11-13], one estimates a model similar to DiMasi et al. using more recent data, and 2 use aggregate firm or industry level data to generate new estimates [11;19].

FIGURE 4-2 -- Empirical Estimates of Vaccine and Pharmaceutical RDD Costs

Study	Perspec-tive	Total Cost	Phases included	Method-ology	Type of molecule/ vaccine
DiMasi et al. (2003) [6]	Pharmac-eutical Industry	$800 Million Capitalized $400 Million Un-capitalized	Pre clinical drug synthesis to approval. Post market approval is estimated but not included.	Retrospec-tive project based cost analysis of expected total costs of development.	68 randomly selected new drugs from 10 pharmaceutical firms
Light et al. (2009) [13]	Corporate for one successfully produced Vaccine	Between $205 ($150) million and $878 ($507) million capitalized (un-capitalized).	Estimate clinical testing costs and mfg only.	Retrospective project level cost analysis Tally resources used at average unit cost for Rotarix and Rotateq	RotaTeq by merck and rotarix by gsk New vaccines for rotavirus
Adams and Brantner (2006) [11]	Pharmac-eutical Industry	$868 million per successful NME	Estimate clinical costs and add preclinical cost that DiMasi (2003) estimated.	Same methodology as DiMasi	3181 new formulations compounds (538 in DiMasi 2003)
DiMasi et al. (2007) [8]	Pharmac-eutical Industry	Total cost is roughly $1.2 billion for biopharmac-eutical NME	Same Preclinical and clinical costs as 2003 DiMasi article	Same methodology as DiMasi 2003	Compound specific costs for sample of 17 investigational biopharmaceutica l from 4 firms.

Young & Surrusco (2001) [21]	Pharmac-eutical Industry	Estimate the average total cost to be between $57 and $71 million per NME	Not clear what resources or phases are included in RD cost.	Retrospective aggregate level data of total RD expenditures and total number of drugs developed over a period of 7 years.	Based on industry level data on cost and number of new drugs approved. Estimate 57-71 million per new drug approved in 1990s.
Paul et al. (2010) [10]	Pharmac-eutical Industry	13 companies average total cost of 1.778 million per successful NME	PC and clinical costs only. PC starts at target selection	Retrospective project level cost analysis.	Based on 13 large pharmaceutical companies. Had small, large molecules and biologics.
OTA (1993) [12]	Pharmac-eutical Industry	Average after-tax RD cash outlay was $65 million. Capitalized cost was $194 million with linear cost of capital rate. In 1991$	Studies reviewed were for compounds that entered clinical testing in the 1960's and 1970s.	Used DiMasi 1991 estimates and 10-14% COC	Used DiMasi 1991

FIGURE 4-2 -- Empirical Estimates of Vaccine and Pharmaceutical RDD Costs (Continued)

Study	Risk calc.	Duration	Geography	Taxes and subsidy	Cost of Capital
DiMasi et al. (2003) [6]	Calculate the probab -ility of entering phase and of moving through the pipeline to approval.	Calculate for investigational compounds in their study	Unclear where any of the costs were incurred	Calculate out of pocket costs (resource used). Do not look at after tax/subsidy.	Use 11% as base estimate
Light et al. (2009) [13]	NA	Included 1987-2003 (16 years).	Mentioned important difference. Did not quantify	Not acknowledged for project	Include range of 3%-7%
Adams and Brantner (2006) [11]	Similar rate to DiMasi.	Similar duration to DiMasi, total durn	unclear	Not accounted for in their paper.	Used DiMasi's 11%
DiMasi et al. (2007) [8]	Same methods as 2003.	Same methods as 2003.	unclear	Calculate pre-tax R&D resource costs	11.50%
Young & Surrusco (2001) [21]	NA	7 year lag in cost and number of new drugs.	unclear	34%	Not included
Paul et al. (2010) [10]	11% biologics; 8%NMEs will succeed (data on successes going down since 2007)	13.5 years (ranged from 11.4 to 13.5	unclear	No	11%
OTA (1993) [12]	Adjusted DiMasi total costs – used DiMasi 1991 estimates	Adjusted DiMasi total costs –used DiMasi 1991 estimates	Adjusted DiMasi total costs – so used DiMasi 1991 sample	Used tax rate of 46%	Linear cost of capital of 14-10%

4.4.3 Key Article in Drug Costing Estimates – DiMasi et al. (2003) [4]

DiMasi et al. have published 6 articles retrospectively estimating the cost of drug development between 1970 and 2010 using project level data [3-8]. All of the DiMasi studies use the same costing methodology to examine: cost of drug development (over different time periods) [4;6], and variation in cost across therapeutic class or firm size [6;7;29]. Despite using the same methodology, the estimated costs of drug development have grown considerably over time. In one of the first studies of drug research and development costs, DiMasi et al (1991) it is estimated that the out of pocket cost per approved NCE was $114 million uncapitalized and $231 capitalized. DiMasi replicated their 1991 [12] study in 2003 [6] and 2007. In each of the subsequent studies, the cost of drug development was found to have increased, from $231 million in $1987, to $800 million in 2004. The study was again replicated in 2007 and the cost of drug development was predicted to be even higher at between $1.2 and $1.3 Billion [5]. Besides inflation, a couple of reasons are cited for this increase in cost: continually increasing costs of clinical trials, largely attributed to increasing trial complexity [6]; and increased employment costs as more scientific and professional staff have been added to pharmaceutical projects, and at higher salaries [6].

DiMasi et al.'s 2003 article is the most widely cited study conducted by this research team, calculating the average cost of phase development based on 68 successful and unsuccessful randomly selected new pharmaceuticals entering clinical testing 1992 and 2000 [6]; one of these pharmaceuticals was a vaccine. The study was based on a survey of 10 pharmaceutical firms in the US who created these 68 new

chemical entities (NCEs), as well as on data derived from Tufts CSDD database. DiMasi et al. (2003) imputed these data into a model generated in an earlier paper [4]. The estimated capitalized cost of development from compound synthesis to approval was $800 million in 2003.

4.4.4. Critical Analysis of DiMasi 2003 [4] Key Article.

The DiMasi et al. (2003) [4] estimates can be assessed based on the key costing components described above:

a) Not all cash outlays are considered. Only pre-clinical (from synthesis) and clinical phases of development are included in this study.[16] Pre-synthesis preclinical research costs are excluded, resulting in an underestimate of the total cost of research and development. Using CSDD data, preclinical costs were calculated as the ratio of average firm level un-capitalized preclinical to clinical expenditures (on new drugs only) multiplied by clinical expenditures to estimate the cost allocated to preclinical development. They use this aggregate method of calculation because they argue that many of the costs incurred during the preclinical period cannot be directly assigned to specific drugs.

b) Clinical costs are estimated using the average phase cost of the 68 compounds, adjusted for the probability of success and capitalized at a rate of 11%. Data on the average durations in each phase, as well as transition probabilities were taken from the CSDD dataset. The un-capitalized cost is roughly half the capitalized cost.

The paper has received criticism for capitalizing the costs of development [21]. However, as mentioned above, to entice investors to risk investing their money in drug

[16] Pre-Clinical is said to include: long term animal testing, regulatory animal testing approval submission costs, chemistry, manufacturing and control costs.

development, a rate of return must be provided. DiMasi et al. (2003) use the well known capital asset pricing model (CAPM), calculating the interest rate based on current returns to pharmaceutical market securities, to generate the 11% cost of capital. This means that it is assumed investors perceive investing in pharmaceuticals is more risky than investing in a well diversified pharmaceutical stock portfolio. It also assumes that the risk does not change over the course of RDD.

The DiMasi paper has been critiqued based on the use of an interest rate that is much higher than the risk free interest rate [13;27]. Meanwhile, others have suggested that the interest rate used by DiMasi for the period of study is low and should in fact be as high as 14% in pre-clinical development and 11% through clinical development [12]. Still others suggest the interest rate should be as low as 0% [27] or between 3 and 7% [13]. The appropriate rate used for calculating the cost of capital is highly contested.

c) Post approval costs were considered, but not included in the $800 million estimate. They estimate cost of post-approval, or deployment, to be an additional $140 million ($95 million capitalized to the date of approval). However, it is unclear what deployment activities are accounted for in this estimate.

d) The cost of drug development estimated by DiMasi et al. are pre-tax outlays, in other words, tax subsidies and deductions are not taken into account.

e) It is unclear whether differences in geography were considered in this study, as it depends upon how the pharmaceuticals reported the cost of clinical trials. Therefore, costs may be overestimated if many of the clinical trials were conducted in developing

countries and an average per patient cost was used to generate the NCE clinical trial estimates.

Others Replicating DiMasi Results

Many others have either modified the DiMasi findings [12], or replicated the methodology [11;15] to generate cost estimates that are mostly in agreement. A study by the Office of Technology Assessment (OTA) was conducted because of a long standing legal struggle between the US Congress and pharmaceutical companies to disclose R&D expenditure data [12]. This study was conducted in the late 1980's and questions the cost of drug development, and whether the highly publicized amount of $259 million estimated by DiMasi 1991 [12] was valid. The OTA determined that the methodology for calculation was indeed valid, and further adjusted the estimates to account for a greater cost of capital and for tax deductions of 46% [12]. Specifically, the OTA adjusted the DiMasi model by accounting for a linearly declining interest rate that is higher earlier in the research phase (14%-11% versus 9% in DiMasi), as well as for tax deductions on research spending. The tax rate of 46% was applied to every dollar expended on research and development, claiming that every dollar spent costs $0.54 because of corporate income deductions. The cost of drug development is an estimated capitalized $194 million capitalized and $65 million un-capitalized. Meanwhile DiMasi 1991 [4] estimated the capitalized costs to be $259 million ($127.2 million un-capitalized) in 1990 USD.

Others have similarly estimated the cost of drug development by replicating the DiMasi model using publically available data. Adams & Brantner [11], for example, apply the DiMasi model to data from Pharmaprojects. They calculate the average

phase costs, duration, and success rates from a sample of new molecular compounds developed after 1989. Their findings agree with Dimasi's (2003) suggesting the average capitalized cost of drug development is $868 million. In a more recent study, using firm-level cost data and the average number of approved drugs, Adams and Branter estimate that the average cost of drugs is higher at over $1 billion [15].

Each of these studies follows DiMasi's general methodology for calculating costs. Therefore, they do not account for all phases of development. However, each estimate does account for risk and the cost of capital using the same methodology as DiMasi [6]. It is generally the case that all costs, including those of failed attempts, are capitalized [3-12;15;29]. I argue that this method of calculation is unsound as the risk premium component of the capitalization rate should only be applied to successful projects (and not the failed attempts that led to each approved pharmaceutical). This is because a risk premium represents the payoff for risk assumed throughout the process of development. Each of the studies that capitalize the cost of drug development (studies using project level data) were estimated using data of successful *and* unsuccessful drugs across the industry [3-12;15;29]. The cost of failure or success was not attributed to any one corporation, but to the industry as a whole, which is somewhat misleading if the estimate is being interpreted as the cost incurred by a firm to develop a pharmaceutical.

It should be noted that none of these estimates are adjusted for tax deductions. In addition, it is unclear whether differences in geography were considered, as it depends upon how the pharmaceutical firms reported the cost of clinical trials.

Other Methodological Approaches to Calculating the Cost of Drug RDD

Young & Surrusco (2001) suggest that DiMasi et al. (1991) and OTA (1993) have over-estimated the cost of drug development [21]. Young & Surrusco (2001) use a retrospective industry level model to calculate the average cost of development. Seven years of PhRMA industry level R&D spending on development from the 1984-1990, and the number of drugs approved (563) between 1990 and 1996 are used to estimate the average total cost to be between $57 and $71 million per new drug (depending upon the 7 year period being analyzed). It is unclear what phases of development are included as R&D costs. Specifically, it is not specified whether pre-clinical costs are included in these estimates, or just clinical costs. Young & Surrusco (2001) do however include a tax rate in the same way as the OTA (1993), using a lower rate of 34%. No adjustment is made for the cost of capital or risk involved in the R&D process, or for geographic location of clinical trials or manufacturing.

Paul et al. (2010) conduct a firm level costing study on 13 pharmaceutical companies [10]. They use average cost data in a retrospective project-level costing model that was similar to DiMasi et al. (2003) accounting for risk, and cost of capital; calculating the cost per launched molecule by determining the expected cost per launch. They calculate the cost per new molecule entity (NME) to be roughly $1.78 billion in 2010 USD, and taking a period of more than 13 years. It is unclear whether this study sample includes vaccines. Like DiMasi et al. (2003), Paul et al. (2010) calculates pre-clinical (starting at target selection) and clinical costs. Risk is considered in this study in the form of overall success rates based on Eli Lilly data, and the same cost of capital as DiMasi et al. (2003) is applied (11%). Pre-clinical

costs related to target determination are not considered, nor are deployment costs, differences in cost across geography, or tax subsidies/deductions.

The Global Alliance for Tuberculosis (GAT) (2001) [27] disagree with the costs estimated by DiMasi (1991), suggesting that DiMasi's estimated costs are overstated. Based on a prospective aggregate industry level analysis to calculate the cost of developing a drug for Tuberculosis, GAT estimates that the expected cost is between $115 and $240 million in 2001 USD. GAT use a prospective costing methodology to estimate the cost of development based on a bottoms-up approach to estimating each phase cost. These costs account for risk associated with development, cost of capital, taxation, and geographic location. However, these costs are very specific to a modified drug for Tuberculosis. It is unclear how generalizable the results are to other classes of drugs, or vaccines.

4.4.5. Are drug costs representative of vaccine costs?

It is unclear whether the cost of drug development estimated by DiMasi et al. among others can be applied to vaccines [3-13;15;21;27;29]. Whether it is possible to apply the average cost of drug development, or the cost of an average drug, to vaccines depends upon whether the process of vaccine development is similar to that of drug development, and whether resources are used at similar intensities. Whether the resources used are similar depends upon the underlying process of development and similarities across each class of pharmaceutical.

Drug development, as examined by DiMasi et al., broadly includes both small molecules and biopharmaceuticals. However, biopharmaceuticals differ from small

molecule drugs in their general characteristics and development [30]. Vaccines are classified as a subtype of biopharmaceuticals.

Within each subclass of drugs, there is evidence of considerable cost variability. Specifically, DiMasi et al. (2004) estimate variations of up to 20% below and at least 10% above the average across therapeutic classes [7]. Similarly, Adams & Brantner estimate variation of 30% above (drugs for respiratory disease) and 50% below (drugs for parasites) the average capitalized cost of new drug development [15]. The study was only considered by therapeutic class; biopharmaceutical costs were not examined separately.

DiMasi & Grabowski (2007) is the only known article to examine whether the cost of biopharmaceuticals differs from that of small molecules [8]. They found that the overall cost of biopharmaceutical development was lower than that for small molecules. The mean cost for each phase was 14% higher than those found for pharmaceutical development (small molecule drugs). However, biopharmaceuticals had higher success rates; therefore there were lower expected costs through the development pipeline (includes synthesis through to approval phases). The capitalized costs are nearly the same due to the greater length of time required for biopharmaceutical development. Given that these data covered the first formulated biopharmaceuticals, the authors suggest that the probabilities of success will converge on those of small molecules.

Of critical importance to this review is whether vaccines differ significantly from biopharmaceuticals in development process and resulting cost. Vaccines and biopharmaceuticals are both manufactured from living organisms, whether the process

and related cost of their development is similar is unknown. We know that serotype and subtype surveillance are not particularly relevant to drug development, though critical to the development of many vaccines. Clinical phases are different in the resources required: biopharmaceutical trials are much smaller, requiring only 3000-5000 participants, while vaccine clinical trials require between 10,000 up to 100,000 participants [31]. The remaining phases of development are similar in process, though evidence of cost and resource use and intensity is limited.

Based on this evidence we can only speculate whether the average cost of certain phases of vaccine development might be more or less expensive than either small molecule, or biopharmaceutical development. More concrete evidence is necessary before applying drug development cost estimates to vaccines.

4.5. Methods

The total cost of vaccine development will be calculated as the opportunity cost of all cash outlays for both the successful and all unsuccessful projects across all 5 phases of development (serotype surveillance, pre-clinical research, clinical research, licensure, and deployment). These estimates can be used to describe ex-post the cost associated with producing a particular vaccine from a societal perspective. Cash outlays will include all expenditures for successful and unsuccessful projects in each phase of development. A model to retrospectively estimate the societal cost of vaccine RDD will be generated using a modified version of the DiMasi drug costing model. The costing methodology used in DiMasi et al [3-8] is applied to vaccines to calculate total expected societal costs *ex post*. DiMasi's model is as follows[17]:

[17] Note that deployment costs were estimated by DiMasi et al (2003), but not included in the $800 estimate of total drug development costs

DiMasi Eq1: Calculate the expected outlay per attempt <u>for each phase</u> of development

$$\boldsymbol{E[Total\ Cost\ Per\ Attempt]} = E[Clinical\ Phase\ Cost] + E[PreClinical\ Phase\ Cost] + E[Deployment\ Cost]$$

Where:

$$E[Clinical\ Phase\ Cost] = P_I * [\mu_{I|PC}] + P_{II} * [\mu_{II|I}] + P_{III} * [\mu_{III|II}]$$

$$E[Pre-Clinical\ Phase\ Cost] = \frac{Aggregate\ Industry\ Pre-Clinical\ outlays}{Aggregate\ Industry\ Clinical\ outlays} * E[Clinical\ Phase\ Cost]$$

=(0.3/0.7)*E[Clinical Phase Cost]

$$E[Deployment\ Phase\ Cost] = \frac{Aggregate\ Industry\ Deployment\ Outlays}{Aggregate\ Industry\ Clinical\ Outlays} * E[Clinical\ Phase\ Cost]$$

=(0.348/0.642)*E[Clinical Phase Cost]

Where:

$\mu_{i|i-1} = Mean\ cost\ for\ all\ attempts$ (all successful and unsuccessful vaccines)

$$P_i = Probability\ will\ enter\ phase\ i = \frac{Successful_{i-1}}{\sum(Successful_{i-1} + Fail_{i-1} + Incomplete_{i-1})}$$

DiMasi Eq2: Calculate the expected cost <u>per approved vaccine</u>

$$\boldsymbol{E[Cost\ Per\ APPROVED\ vaccine]} = \frac{E[Total\ Cost\ Per\ Attempt]}{P_i * P_{i+1} * P_{i+2} * \ldots * P_{i+n}}$$

DiMasi Eq3: Calculate the Capitalized cost <u>per approved vaccine</u>

$$\boldsymbol{Capitalized\ Cost} = [Pre\text{-}Clinical]*(1+r)^i + [Clinical]*(1+r)^i$$

Data

The purpose of this paper is to generate a general model to calculate the cost of vaccine RDD for any given successful vaccine. As a case example, the model is populated using vaccine cost information for Rotarix.[18] The model is populated using data drawn from the literature. Vaccine cost information for Rotarix is taken from Light [13], and success and duration estimates from Davis et al [22]. All data inputs are further discussed below.

[18] Rotarix is a vaccine developed by GSK and licensed in 2007 that protects against Rotavirus.

Cost of Vaccine RDD Model – Modified DiMasi Model

The total cost of vaccine RDD, from serotype surveillance through to deployment, can be estimated using a modified version of the DiMasi model described above [3-8].

The DiMasi model uses the expected cost per phase of a drug (successful and unsuccessful), phase-specific success rates, and development times to calculate an expected cost of drug development (see above *DiMasi Eq1* and *DiMasi Eq2*). My vaccine model assumes that the clinical costs of a particular successful vaccine have been realized and these actual costs can be used to retrospectively estimate the cost of vaccine development. The DiMasi model only populates the cost of clinical testing with project level data, and uses aggregate ratios to calculate the cost of pre-clinical, as well as deployment.

I modify the DiMasi model by imputing actual costs of clinical testing are instead of the expected costs, as seen below in *Waye Eq1*. The same ratios used for pre-clinical and deployment costs are used in this model. The vaccine probabilities of success are then used to account for all of the failed projects. These modifications to the DiMasi model are delineated below:

Waye Eq1: Calculate the actual cash outlays per attempt

[Total Societal Cost of Vaccine] = [Surveillance] + [Pre-Clinical] + [Clinical] + [Deployment]

Where:

$$[Clinical] = Clinical\ I + Clinical\ II + Clinical\ III$$

$$[PC] = \frac{Aggregate\ Industry\ Pre - Clinical\ outlays}{Aggregate\ Industry\ outlays} * [Clinical\ Phase\ Cost]$$

=(0.3/0.7)*[Clinical Phase Cost]

$$[Deployment] = \frac{Aggregate\ Industry\ Deployment\ Outlays}{Aggregate\ Industry\ Outlays} * [Clinical\ Phase\ Cost]$$

= (0.348/0.642)*[Clinical Phase Cost]

Waye Eq2: Calculate the total cash outlays for all attempts in Vaccine RDD

Total Cost of Vaccine RDD =
[[Surveillance] + [[Pre-Clinical] + [Clinical])/ P(S)]] + [Deployment]]

Where:

$$[P(S)] = P_i * P_{i+1} * P_{i+2} * \ldots * P_{i+n}$$

Note that the cost of failures are included, as the probability of successfully moving from pre-clinical through to approval is accounted in the term P(S).

Similar to DiMasi, the costs of RDD are then capitalized. However, in this model, only the cost of the successful project is capitalized, as described in *Waye Eq3* (as opposed to all expected costs in the DiMasi model).

Waye Eq3: Capitalized Cost of Total Cost of Vaccine

$\boldsymbol{Capitalized\ Cost}$ = *[Surveillance]+ [Pre-Clinical Successful]*(1+r)^i +[Pre-Clinical Successful attempts]+ [Clinical Successful]*(1+r)^i + [Clinical Attempts] + [Deployment]*

Where: $r = r_f + r_r$; $i = Phase\ duration$;
$r_f = risk\ free\ rate\ of\ return$; $r_r = risk\ premium$

Model Inputs:

The inputs into the model of cost estimation (described in the methods section above) are listed below.

Phase Cost Inputs:

i) Serotype Surveillance (Bacteria) or Genotype Epidemiology (Virus)

I acknowledge the cost of serotype and subtype surveillance, however, these costs are not included in this model because of the scale being considered – surveillance of OECD countries. Any estimate would be completely arbitrary because of the difficulty attributing the cost of a surveillance system to any one infectious disease.

ii) Pre-Clinical Research and Development

Little is known about the cost of antigen discovery and vaccine design. As a result, for the purposes of this analysis, the proportion of pre-clinical to clinical costs estimated by DiMasi [6] will be used to calculate clinical costs. DiMasi [6] use aggregate data based on survey data to calculate the ratio of clinical cost to pre-clinical costs, an estimated 43% of pre-clinical and clinical costs over a period of 52 months.

iii) Clinical Trial Phase I/II/III:

Rotarix clinical trial input costs are taken from Light et al. [13]. These estimates were derived using interview methods with leading developers of each Rotavirus vaccine to determine the average cost per patient enrolled in clinical trials, determined to be approximately $3000 per patient. These costs were combined with the total number of participants in the clinical trials, over all clinical trials performed, to estimate the total clinical testing costs.

Manufacturing Costs

Manufacturing costs can be decomposed into start-up costs, and operational costs.

Startup costs include all scale-up costs and fixed costs associated with equipment and the manufacturing facility. Light et al. published data concerning Rotarix facility costs, these data will be imputed into the model.

Operational costs can be described according to capital, labour, material, and consumables [17]. The per unit operational costs, also known as 'cost of goods sold', are derived from Douglas et al., and assumed to range from 1% to 20% of price [16]. Health Canada and the FDA recommend 2 doses of Rotarix, at a price of $106 for both doses.

iv) Licensure Costs:

The cost of developing a dossier is assumed to be similar to that of developing a research paper over the span of a year. Dossiers are approximately 100,000 pages in length [32]. At a cost per page of $50, it is assumed that the cost of generating a dossier is $5,000,000. A country specific dossier is required, assuming a vaccine is licensed in all OECD countries (in addition to the EU), more than 20 dossiers would need to be generated. If the additional cost of composing a dossier for a different country is $100,000, then an added cost of $2,000,000 would be required in gaining licensure.

v) Deployment Costs:

Deployment costs include costs associated with marketing, phase IV clinical testing, adverse event reporting systems, and distribution. The costs associated with

marketing and phase IV clinical testing are derived from DiMasi [6]. Here DiMasi [6] use aggregate data based on survey data to calculate the ratio of pre-clinical and clinical cost to post approval, an estimated 54%. These costs are said to include phase IV testing and marketing. Legal costs and distribution costs do not appear to be considered.

This model will consider the legal costs of adverse events only, as costs associated with negligence are random and very difficult to predict. However, according to above, the Canadian Immunization Guide expects 40/100,000 to experience an adverse event and one per million doses to cause a serious adverse event [33]. It is assumed that all of these children received compensation of $120,000 (average compensation awarded in Quebec) [20].

Cold chain and distribution costs are paid for by pharmaceutical companies, distribution centres, pharmacies, and physician's offices. These costs are difficult to estimate as each depends upon distances shipped, and number of doses. Therefore, these costs are recognized to exist, but will not be estimated in this model.

Duration of RDD and Probability of Success Inputs:

Serotype and genotype surveillance define the beginning of vaccine RDD, and one year of deployment is considered the end of RDD. The cost of developing a successful vaccine will be estimated, including all costs of past failures -- whereby a successful vaccine is one that is approved by regulatory authorities to enter the market.

The time it takes for Rotarix vaccine to move through the clinical testing is taken from Light et al. [13]. It is assumed that the time in pre-clinical development is

the same as for drugs; estimates of pre-clinical duration are taken from DiMasi et al. 2003 [6].

Given the high rates of failure in developing a vaccine, the cumulative probability of one vaccine successfully navigating the development pipeline must be considered. To account for these failures, we take the estimated cost of the successful vaccine, and divide by the probability of success (see Waye Eq2 above).[19]Success probabilities are taken from Davis et al.'s (2011), which are based on Pharmaproject data for 132 vaccines from 1995-2011.

The probability of success is only applied to phases in which a vaccine may fail (pre-clinical and clinical testing). Manufacturing phase costs do not include the cost of failure; this assumes that the manufacturing facility is built only for successful vaccines. Deployment phase costs are only incurred for approved vaccines, therefore a probability of success should not be applied to them.

Cost of Capital Inputs

The cost of capital is the sum of the risk free interest rate plus a risk premium. The value of time, the base interest rate, is 7% and 11% to make the results comparable with those of Light et al. [13] and DiMasi et al. [6]. However, a range of 3% to 11% will be employed and results examined. As mentioned above, the risk premium component of the capitalization rate should only be applied to successful projects (and not the failed attempts that led to each approved pharmaceutical). This is because a risk premium represents the payoff for risk assumed throughout the process of development.

[19] In the drug models, the cost of failure is accounted for by calculating the expected value of each phase of production; in this model, the expected value is calculated as a measure aimed to capture the average expected cost of development at that phase of the vaccine pipeline.

Costs are capitalized to the end of the first year of approval.

Geographic Indices:

There are known global differences in the cost of clinical testing, as well as manufacturing. Indices have been developed to estimate the differences across countries [24].

The model cost estimates for Rotavirus were taken from Light et al. [13]. Clinical trials for Rotarix and Rotateq were conducted in Latin America, Finland and the USA. Manufacturing facilities are located internationally. Because estimates were drawn from industry experts, it is assumed that the per patient clinical costs, and manufacturing fixed costs provided by industry representatives accounted for the geographic trial cost differences. Therefore, an index such as that in Love et al. (2003) is not required for adjustment [24]. The following table (Table 4-1) lists each of the model inputs described above.

Table 4-1: Model Inputs

Model Input	Rotarix Phase Cost	Probability of Success	Duration	Interest Rate
Serotype surveillance	NA	NA	NA	
Antigen Discovery Vaccine Design & Animal Testing	$82,374,086	48%	4.33	11%
Clinical Trial Cost I Light High Estimate 2008$	$150,400	74%	8	11%
Clinical Trial Cost II Light High Estimate 2008$	$2,380,800	58%	5	11%
Clinical Trial Cost III Light High Estimate 2008$	$189,675,000	61%	4	11%
Licensing Costs	$7,000,000	100%	1	11%
Manufacturing Fixed Costs 2008$	$240,000,000	100%	1	11%

Manufacturing Operating Costs (variable cost assuming price=106.57 and Cost of goods sold=1%)	$53,285,000	100%	Current	11%
Legal Costs (1% adverse events with average payout of 50,000)	$68,750,000	100%	Current	11%
Deployment Costs (Transportation Cold Chain, post market surveillance)	$102,588,585	100%	Current	11%
TOTAL	$763,203,871			

4.6. Results – Total Societal Cost of Rotarix Vaccine RDD

A general model has been created to estimate the cost of vaccine RDD using a modified methodology developed by DiMasi et al [6]. As a case example, I use Rotarix to demonstrate. The model was populated using rotavirus clinical and manufacturing cost estimates from Light et al. (2009) [13], and pre- and post- market activities are derived from DiMasi et al. (2003) estimates [6]. The probabilities of success and duration in the pipeline are drawn from Davis et al. (2001) [22]. The total societal cost of vaccine RDD measures the cash outlays that society is expected to have spent on developing Rotarix vaccine, accounting for all of the failed attempts.

Given a 1% COGs these data suggest that without the cost of serotype surveillance, the total societal cost of Rotarix RDD is $2.7 billion when the cost of failure is taken into account (Table 4-2). The capitalized cost of Rotarix RDD is closer to $3.7 billion using a cost of capital of 11%. The duration of Rotarix vaccine development is found to be approximately 22 years with a success rate of only 12.6%.

Table 4-2: Total Societal Cost of Rotarix Vaccine RDD (1% COGs)			
Model Input	**Un-Capitalized Cost**	**Capitalized Cost WAYE formula**	**Capitalized Cost DIMASI formula**
Serotype surveillance	$0	$0	$0
Antigen Discovery Vaccine Design & Animal Testing	$655,480,568	$1,202,958,530	$6,739,410,930
Clinical Trial Cost I Light High Estimate 2008$	$1,196,788	$1,988,036	$7,831,242
Clinical Trial Cost II Light High Estimate 2008$	$18,944,892	$27,086,614	$53,792,523
Clinical Trial Cost III Light High Estimate 2008$	$1,509,312,980	$2,005,219,622	$2,543,280,146
Licensing Costs	$7,000,000	$14,420,000	$7,770,000
Manufacturing Fixed Costs 2008$	$240,000,000	$252,000,000	$266,400,000
Manufacturing Operating Costs (variable cost assuming price=106.57 and Cost of goods sold=1%)	$53,285,000	$53,285,000	$59,146,350
Legal Costs (1% adverse events with average payout of 50,000)	$68,750,000	$68,750,000	$68,750,000
Deployment Costs (Transportation Cold Chain, post market surveillance)	$102,588,585	$102,588,585	$102,588,585
TOTAL	$2,656,558,813	$3,728,296,387	$9,848,969,777

The main drivers of these findings include the costs associated with building a new manufacturing facility ($240 million and over $500 million capitalized), as well as the costs associated with phase III clinical testing and deployment costs.

Model sensitivity to input parameters are examined in Table 4-3. As can be seen, the model is fairly robust. Model output is slightly variable with differing values of cost of capital. At a rate of 3% and 7%, the assumed cost of capital reduces the capitalized cost to $3.3-$3.5 billion respectively. If the number of participants in Phase III is reduced from 58,000 to 10,000, assuming a $3000 cost per participant, then the

cost of Rotarix RDD declines considerably. With only 10,000 phase III participants, costs decline to $750 million including the cost of failure, and roughly $840 million capitalized. Results do, however, seem to be robust to changes in cost of goods sold; a higher cost of goods sold increases the cost of RDD to $4.7 billion.

Table 4-3: Sensitivity to Model Inputs

	Total Cost with Failures ($Billions)	Total Capitalized Cost Waye formula ($Billions)	Total Capitalized Cost Dimasi formula ($Billions)
Base Model	**$2.657**	**$3.728**	**$9.849**
Sensitivity to Parameters			
COGs 20%	**$3.669**	**$4.734**	**$10.973**
Cost of Capital 3%	**$2.657**	**$3.321**	**$3.526**
Cost of Capital 7%	**$2.657**	**$3.501**	**$5.620**
No new manufacturing facility	**$2.184**	**$2.823**	**$7.525**
Average number of Phase III participants (10,000)	**$0.748**	**$0.841**	**$2.015**

Using the DiMasi formula of capitalization, we do see far more variability in results. This is due to the fact that all costs are capitalized over a long period of time (over 20 years). As a result, any small change in cost of capital will result in very different estimates. The results from the DiMasi formula are then also relatively sensitive to key cost drivers such as number of trial participants in phase III, as with only 10,000 participants costs drop to $2 billion.

Table 4-4 shows that the cost of Rotarix vaccine, assuming the average phase costs of drugs from DiMasi et al. (2003) is $1.9 billion with the cost of failures, and $2.6 billion capitalized. If only the probability and duration of drugs as estimated by DiMasi et al. (2003) are imputed into the original model, the cost of Rotarix RDD ranges from $1.749 (uncapitalized) to $2.6 billion (capitalized). Evidently, the model

is also sensitive to timing and magnitude of expenditures, and estimates of phase transition.

Table 4-4: Comparative Results to DiMasi et al 2003			
	Total Cost with Failures ($Billions)	Total Capitalized Cost Waye formula ($Billions)	Total Capitalized Cost DiMasi ($Billions)
Base Model	**$2.657**	**$3.728**	**$9.849**
Sensitivity to Parameters			
DiMasi Cash outlays	**$1.857**	**$2.611**	**$7.331**
DiMasi Durations	**$2.657**	**$3.484**	**$5.029**
DiMasi Probabilities	**$1.749**	**$2.814**	**$5.967**
DiMasi Durations and Probabilities	**$1.749**	**$2.576**	**$3.190**

4.7. Discussion

It is found that without the cost of serotype surveillance, the total societal cost of Rotarix vaccine RDD is $2.7 Billion when the cost of failure is taken into account. This uncapitalized cost does not include the return on capital, including the risk premium assumed to be paid to investors on successfully approved pharmaceuticals. We might also use the capitalized valuation, which would then reflect private sector profits (the risk premium component of the capitalization rate). According to my model, the capitalized cost of Rotarix RDD is closer to $3.7 billion using a cost of capital of 11%.

These estimated costs are in line with those estimated by Light et al. (2009). In particular, Light et al. (2009) find that clinical costs for the one successful Rotavirus vaccine were between $128 and $200 million. Given a success rate of 12%, accounting for all successful and unsuccessful clinical costs we would expect the clinical costs alone to cost between $1.6 and $2 billion. Pre-clinical costs of

development are not yet included, nor are deployment costs. Therefore, an estimated cost of $2.7 billion for Rotarix vaccine seems reasonable.

Key Cost Drivers of Non-Capitalized Costs

The primary driver of the total societal cost associated Rotarix RDD is the cost of phase III clinical testing. These phase III costs for Rotarix are based upon the largest phase III clinical trials ever conducted. The abnormally large Phase III clinical trials were required by regulators as a result of past complications of intussusceptions with another Rotavirus vaccine introduced by Wyeth half a decade prior. Wyeth had successfully licensed their vaccine following a phase III clinical trial of 10,000. As mentioned above, the average number of participants traditionally in phase III clinical testing is roughly 10,000. Should the model be based on fewer participants assumed to be immunized in phase III, the cost of vaccine RDD declines to approximately $840 million capitalized.

The next major cost driver is the building of a new manufacturing facility for the manufacturing of a new vaccine (with a cost of $240 million). The possibility of failure is not included in this number because it is assumed in the model that a manufacturing facility is not built for a vaccine that failed in Phase III testing. Therefore, it is assumed that an old facility was modified for the production of the Rotarix vaccine in Phase III testing. It should be noted that the cost of the facility is not subject to the probability of approval – it is assumed that only one facility is built for each of the vaccines that succeeds.

Should this assumption not be true, and a facility is built for phase III testing (and is subsequently closed or sold if the vaccine fails), then the net cost of building

this manufacturing facility should be accounted for. Should each vaccine (successful and failed) require its own facility be built for phase III clinical testing (as is suggested by Berndt [31]), the costs would be astronomically higher.

Cost of Vaccine Compared to Drugs

The cost of Rotarix RDD appears to be higher than the average cost of drug development as estimated by DiMasi and others. To identify whether the phase cost or model parameters are driving these results, I reproduce the model with the phase costs of DiMasi, as well as the drug success probabilities and durations.

The expected costs calculated by DiMasi for drug development are somewhat similar to those estimated by Light for Rotavirus with the exception of the phase III clinical trials. The cost of Rotarix phase III trials was $189 million, whereas the average cost of phase III clinical trials was $86 million. This difference can be attributed to the fact that vaccines require more participants than drug trials to determine efficacy of the vaccine (especially for low incidence diseases), as well as for more rigorous safety information.

Using the average drug duration for each stage of development, the estimated cost of Rotarix RDD is roughly the same as using the actual development time. This is largely because the costs are more concentrated towards the end and not the beginning of the period. The time it takes to bring a vaccine to market impacts costs because of the time value of money. Specifically, there is an opportunity cost associated with investing money [18], here the investment is made in developing a vaccine. The estimated total time required to research and develop a vaccine (up to the point of approval) was 22 years based on Light's data on the timing of Rotarix development.

This time to approval is considerably higher than that described elsewhere for vaccines and drugs. Specifically, the average total time for drugs seems to be between 11.9 and 12.5 years [6;8;11;23]. Davis et al has suggested that the average time to develop a successful vaccine is 14.3 years [22]. These averages include the time spent on failed vaccines in each stage of the development process, therefore, the average will be lower for all projects than for a successful project. Others have estimated the time to approval for successful vaccines and found: varicella vaccine to have taken between 25-30 years to develop; 25-30 years to develop Flumist; 14-16 years to develop HPV [16]. Based on these data, it appears as though vaccines require a longer time to develop and therefore partially explain the higher capitalized costs of development.

Some of the transition probabilities are also lower for vaccines, as is the overall probability of approval (12.6% as compared to 21.5% for drugs). Therefore, when using the drug probability of success, the cost of vaccine development is lower at $1.7 billion uncapitalized and roughly $2.8 billion capitalized.

In general, it appears as though the cost of vaccine RDD would be expected to be higher than for drugs. This is because of the higher expected cash outlays, resulting from increased numbers of participants required for Phase III clinical testing, and the expenses related to manufacturing. Second, the time to approval appears to be higher for vaccines than drugs, and the probability of success lower. More work could be done in this area, using this model with different phase cost inputs, probabilities, and durations.

Societal perspective

There are many partners that contribute to pharmaceutical RDD worldwide: Pharmaceutical companies (large and small); biotech companies; governments (usually in the form of grants); academics (often subsidized by industry or governments); as well as charity organizations such as the Bill and Melinda Gates Foundation. The total societal cost estimated in this study aims to take into account the Rotarix RDD expenditures from each of these partners.

The model is not designed to quantify any one partner's contributions. However, if a different perspective is adopted in estimating the total costs of vaccine development, for example an industry perspective, the estimated total costs will change. Theoretically, given an industry perspective, the costs of surveillance are not accounted for. In addition, the total cash outlays are reduced because of considerable tax breaks and research grants, especially in the early stages of development (from a societal perspective this transfer of funds cancels out). Young & Surrusco (2001) suggested that the total tax break to pharmaceutical corporations for research and development was roughly 46%, claiming that every dollar spent costs 0.54$ because of corporate income deductions. Applying a tax break of 46% to every dollar expended on research and development, the total industry cost of Rotavirus RDD is less, around $1.7 billion and $2.7 billion capitalized.

Generalizability of the Model to other Vaccines and Scenarios

Extension to other vaccines

The degree of variation in the cost of vaccine RDD across different types of vaccines is unclear, especially based upon the number of participants required for testing, and the amount of time spent in pre-clinical research. Therefore, it is uncertain how generalizable results are to other vaccines. However, this model can be applied to any other vaccine for which clinical phase costs can be estimated.

New Versus Modified Vaccines and their Cost of Development

It is suggested that modified drugs (generic drugs) costs less to develop and manufacture than a new chemical entity [10]. This difference forms the basis of many patent laws aimed at protecting innovators, allowing founding companies to recuperate some of the costs of research and development prior to competition from generic follow-ons.

It is unclear as to whether the manufacturing and licensure of generic follow-on vaccines is a consideration, as very few generic follow-ons exist. It seems highly likely that the cost associated with modifying a serotype specific vaccine such as Rotavirus to contain two serotypes as opposed to one would be less expensive than developing the initial vaccine. However, this may only be true for the founding company, as the manufacturing regulations are more stringent, and intellectual property related to vaccines is more sophisticated. Little research has been conducted in the area to test this hypothesis. Given data regarding success rates, duration, and cash outlays, this model could be repopulated to determine the cost of follow-on vaccines.

4.8 Limitations of Study

This study is limited by a number of data gaps. First, the project level cost data used in this model were assumed based upon clinical trial averages. These estimates were derived at an aggregate project level. Therefore, the accuracy of the underlying phase cost estimates is uncertain. Second, preclinical and deployment cost estimates are based upon a ratio derived by DiMasi et al. [6]. This ratio is more of a rule of thumb and is used because we do not know these particular costs for rotavirus or any other vaccine. Likely, the average cost of pre-clinical research varies considerably from one vaccine (or drug) to another. For example, it took only 3 years to discover an antigen for the AIDS virus – the first AIDS vaccine entered clinical trials in 1987. To date, the successful antigen has yet to be discovered, or recognized as being successful. Similarly, Hepatitis C was discovered in 1989 and a vaccine candidate is now in the process of entering clinical testing [34]. Meanwhile, vaccines discovered in the early 19^{th} century such as small pox was stumbled upon using very basic technology. Third, the degree of knowledge sharing during preclinical phases of development is unknown. As a result, this model assumes each venture is independent, as the expenditures associated with each failed attempt in the preclinical phase is accounted for. Therefore, costs associated with pre-clinical development may be over-estimated. Fourth, the societal cost of rotavirus development is not comprehensive as the cost of serotype surveillance is unknown. Surveillance is performed to various degrees within many countries. However, there is no global database for surveillance information. Fifth, the length of the deployment phase is

assumed to be one year. This may overstate costs as deployment likely lasts longer than 1 year, and costs would be discounted back to time to approval.

4.9. Conclusion

The Rotarix RDD model suggests that the total uncapitalized cost of $2.7 billion ($3.7 billion capitalized). The main drivers of this result are the number of participants required in phase III clinical testing, as well as the fixed cost of a manufacturing facility. It is expected that these same drivers will similarly impact the estimated cost of other new vaccines.

Countries such as Canada have invested considerable amounts in attracting investment from the Biopharmaceutical Industry, which includes vaccines [14]. To adequately evaluate these new policies, a reliable measure of the cost of biopharmaceutical and vaccine development is necessary. The model generated in this study is of value as this project level retrospective vaccine R&D expenditure statistic can contribute to the monitoring and evaluation of benefits of existing policies, as well as to inform the creation of new financial and regulatory public policies.

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CHAPTER 5: THESIS CONCLUSIONS

I have used economic methods to examine the impact of specific government interventions that have been initiated in response to market failures within the market for vaccines. Specifically, markets do not allocate vaccines efficiently as a result of the lack of exclusivity in the consumption of vaccines, and non-rival consumption and non-excludability in vaccine R&D. Canadian Federal and Provincial governments have responded to both of these market failures to achieve a more efficient allocation.

In response to the lack of exclusivity of vaccines, or the public benefits derived from the positive externalities of consumption, governments have made it nearly costless to be vaccinated. This significant reduction in price encourages individuals to be immunized, therefore increasing the coverage rates of vaccines. In this thesis, I study the impact of public universal immunization policies from both a health and cost perspective.

Prior to universal provision, according to the Childhood National Immunization Coverage Survey (2006), uptake was very low in Canada. Reaching more socially optimal rates of vaccination (demand) resulted in decreased hospitalizations, which suggests herd immunity. This analysis provides evidence of success of the Canadian Immunization Strategy in decreasing circulation of varicella amongst not only children immunized, but amongst the entire Canadian population. Specifically, declines in hospitalization were found for children aged 1-4 (ranges from 65%-93%), and children less than 1 (ranges from 48%-100%). Adults aged 20-39 and 40-59 also experienced statistically significant declines (55%-100%, and 39-76% respectively).

My third chapter demonstrated the economic benefits of public universal immunization policy in Alberta. In 2002, the Alberta government implemented a universal immunization program against *Streptococcus pneumoniae*. Prevnar 7 (PCV7) was used to immunize infants against the disease. Public health benefits were observed for not only the immunized group, but also for the non-immunized groups. In particular, the reduced costs as a result of PCV7 for ages 10 and above were in the range of $712,000 per 100,000 population. When translating these values to the Alberta population, the economic impact was $9.2 million in medical costs averted as a result of PCV7. However, the economic impact of Alberta's PCV7 immunization program depends upon the relationship between the vaccine and serotype replacement. If serotype replacement is a result of PCV7, the economic impact of the program is roughly $1.846 million.

There are also market failures in the production of vaccines, which can result in inefficient allocations of vaccines. The high capital investment and high risk associated with early stages of vaccine research and development are said to deter investors, in addition, difficulties appropriating return on initial R&D investments lead to less than socially optimal development of vaccines. As a result, governments have intervened by providing subsidies, and other financial aids. There are many policies in place to attract investment and support development. My general model helps to inform new financial or regulatory vaccine RDD policies, as well as assist in the monitoring of existing policies.

APPENDICES

Appendix 3-1: Observed Incidence Rates and Pneumococcal Epidemiology

Figure 3-A: Disease Presentations of Streptococcus Pneumoniae

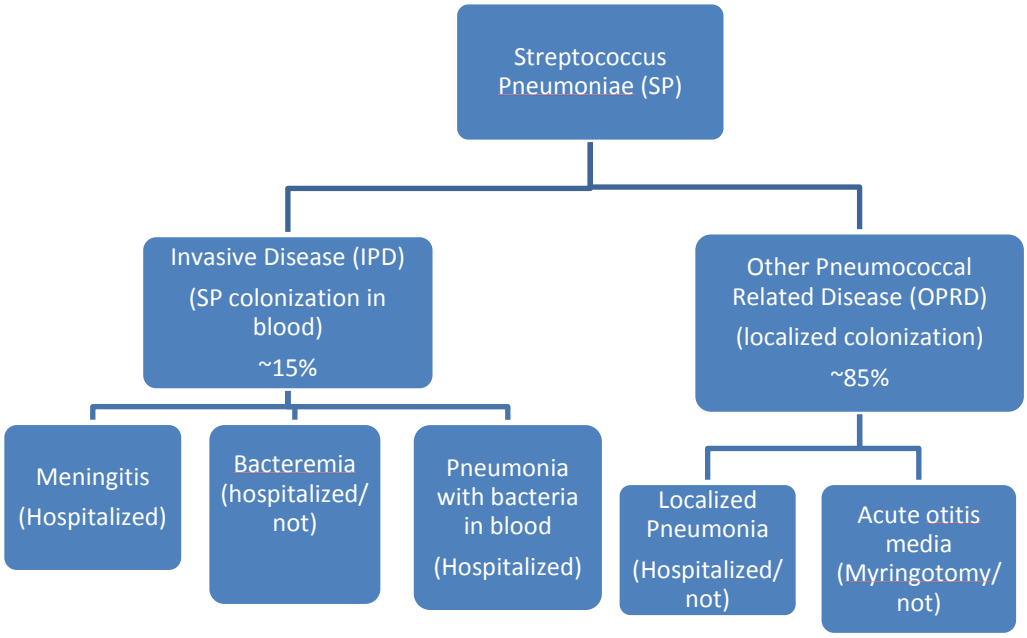

Table 3-A1: Observed Incidence Rates

Study	Geographic Region	Date of universal vaccine introduction	Dates	Age	PCV7 Incidence rate Percentage Chage	Non PCV7 Serotype IPD Change
Tyrell [3]	Alberta	2002	2000 vs 2006	All	-61%	Not significant when exclude serotype 5
Kellner (2009) [11]	Calgary, Alberta	2002	1998-2001 vs. 2007	<2 65+	-94% -63%	183% (ages 16-64)
Paulus et al [5]	Vancouver	2003	2002 vs 2005	<5 years	-68%	Not significant
Pishivili [2]	USA	2000	1998-1999 vs 2007	<5 All ages	-100% -94%	30% (increase of 6.1-7.9 per 100,000)

Table 3-A2: EPIDEMIOLOGY Chuck et al [12]								
	<2	2-4	5-9	10-14	15-19	20-39	40-64	65+
IPD/'000000	2.23	2.88	2.55	0.33	0.88	2.25	4.11	5.28
Distribution								
Hosp pneumo	74.0 %	74.0 %	88.2 %	62.4 %	62.4 %	66.9 %	66.9 %	81.5 %
Hosp bact	14.3 %	14.3 %	6.7%	24.8 %	24.8 %	26.3 %	26.3 %	15.0 %
Non hospitalized bacteremia	8.9%	8.9%	4.1%	9.6%	9.6%	5.1%	5.1%	2.9%
Meningitis	2.5%	2.5%	1.0%	3.2%	3.2%	1.7%	1.7%	0.6%
Distribution of NIPD								
Non-hosp pneumo	3%	3%	3%	100%	100%	100%	100%	100%
OM	97%	97%	97%					
Mortality								
Hosp pneumo	1%	1%	1%	2%	2%	2%	2%	2%
Bact	2%	2%	2%	2%	15%	15%	15%	31%
Meningitis	7%	7%	7%	7%	28%	28%	28%	28%
Sequelae								
Deafness	13%	13%	13%	13%	26%	26%	26%	26%
Neurological	7%	7%	7%	7%	19%	19%	19%	19%
Myringotomy	4%	4%						

Table 3-A3: Non-PCV7 Serotypes Included and Excluded		
Non-PCV7 Included	Non PCV7 Excluded	EXPLANATION For Exclusion
10A	10F	FLAT
11A	11B	DECREASING TREND Prior to 2002, FLAT UNTIL 2007/8
15A	16F	2000-2001 INCREASED THEN DECLINED
12F	18B	STEADY DECREASE
15B	28A	FLAT
19A	33F	DECREASING TREND
23A	33A	FLAT
5	35B	DECREASING TREND
20	6A	DECREASING TREND, Increasing prior
34	7C	Flat WITH STEADY INCREASE 2007/8
23B	7F	DECREASING TREND, Increasing prior
38	9L	DECREASING TREND, Increasing prior
22F	1	DECREASING TREND, Increasing prior
	13	DECREASING TREND, Increasing prior
	33F	FLAT UNTIL 2007/8
	8	FLAT UNTIL 2007/8
	35F	Increasing prior to immunization
	15C	Increasing prior
	3	Constant
	17F	Increasing prior
	9N	Constant until 2007
	21	Constant until 2008
	31	Constant until 2008