Pertussis Persistence in Ontario

by

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

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Abstract

Pertussis, or whooping cough, is a vaccine preventable disease. However, despite having a robust childhood, adolescent, and adult immunization program in Ontario, we continue to see hundreds of reported pertussis cases each year. The goal of this dissertation is to explore the gaps in current immunization programs. By developing a well calibrated transmission model to predict the spread of pertussis in the community, I estimated the underlying burden of pertussis in adolescents and adults and estimated the degree to which pertussis is under-identified in different age groups. I estimated that there are a considerable number of under-identified patients who contribute to the force of infection of pertussis and silently transmit the disease to others. Using a systematic review and meta-analysis, I estimated that the pertussis vaccine, DTaP, is associated with a much shorter duration of immunity than previously thought. This level of waning immunity allows for pertussis to spread amongst previously vaccinated individuals contributing to the persistence of the disease. Finally, using a microsimulation model, I estimated the agespecific costs and health burden associated with pertussis in Ontario. Using these values, I estimated the substantial health and economic impact that pertussis has in both Ontario and Canada. Individually, these findings provide critical insight into the persistence of pertussis in Ontario, but together the results of this dissertation can be integrated into cost-effectiveness analyses to evaluate new immunization schedules and strategies to contain the spread of pertussis.

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1 Chapter One: Introduction

Pertussis, or whooping cough, is an upper respiratory infection caused by the gram-negative *Bordetella pertussis* bacteria. While pertussis is a vaccine preventable disease, it continues to circulate in Canada, with a national incidence of approximately 13.9 per 100,000 population in 2012.¹ There has been substantial Canadian research surrounding pertussis and the dynamics of transmission; however, many questions remain unanswered. Several of these, including the role of pertussis under-identification and under-diagnosis in adults and adolescents and the associated contribution to the force of infection, the duration of protective immunity conferred from the childhood immunization series, and the health and economic burden of pertussis are addressed in this dissertation.

1.1 Pertussis Background

1.1.1 Natural History

Pertussis is a highly transmissible infection with three distinct phases of illness preceded by an incubation period of approximately 7 days.^{2,3} The first clinical phase is called the catarrhal phase and lasts around 1-2 weeks.^{4,5} During this phase, symptoms gradually become more prominent and include a mild cough, low grade fever, and a runny nose.⁴ The catarrhal phase is easily missed and often mistaken as a common cold.^{4,6} The next phase, the paroxysmal phase, is characterized by a violent cough which is often accompanied by post-tussive vomiting and inspiratory whooping.⁴ This phase can last from 1 to 6 weeks and it is often during this phase that pertussis is suspected and diagnostic tests are performed.⁴⁻⁶ As symptoms slowly start to improve, the patient enters the convalescent phase of disease which can last 1-3 weeks.^{4,5} While recovery is gradual, symptoms eventually disappear.

1.1.2 Spectrum of Clinical Severity

Clinical severity of pertussis can vary greatly by a number of key factors including age, previous immunization status, and previous disease history. Children tend to exhibit the classic symptoms of pertussis, making diagnosis in this age group relatively straightforward.⁵ Infants, who may not be strong enough for "whooping", may present with apnea or respiratory failure.⁶ In one study of infants admitted to intensive care units with respiratory failure, apnea and/or bradycardia, or an acute life-threatening episode, 25 out of 126 infants with nasopharyngeal swab specimens were diagnosed with pertussis (19.8%, 95% confidence interval (CI): 12.9%-26.8%). However, of these 25 infants, only 7 presented with symptoms suspect of pertussis.⁷ With atypical symptoms, infant pertussis cases can be challenging to identify while childhood pertussis cases are much more clinically recognizable and straightforward to diagnose.

Infants and children have the highest pertussis morbidity, hospitalization, and mortality rates of any age group. Complications of infant and childhood pertussis disease include pneumonia, seizures, encephalopathy, hernias, failure to thrive, and death.^{6,8} Mortality is highest in infants, with one nationally representative surveillance study finding case-fatality rates of 0.9% in Canadian infants less than two years of age and 1.0% in infants less than 6 months of age.⁸ More recent data from this surveillance network estimated a case-fatality rate of 1.2% in infants under 2 years of age, with the majority (78%) under 2 months of age.¹ Hospitalizations for pertussis tend to occur more frequently for infants than any other age group. On average, 69% of pertussis-related hospitalizations in Canada from 1995-2010 were among infants <1 year of age, with the majority (72%) less than 3 months of age.¹ The consequences of pertussis are most severe for infants and children.

Adolescents and adults tend to exhibit less severe and more general symptoms⁴⁻⁶. A prolonged cough may be the only clinical symptom, so adolescents and adults may not seek medical care or may be misdiagnosed if they do.⁹ There is evidence that adolescents and adults do experience classic pertussis symptoms with 82-83% of adolescents and 33-

100% of adults experiencing paroxysms and 30-47% of adolescents and 7-82% of adults experiencing "whooping".⁹ Yet, the disease remains under-diagnosed by clinicians even though adolescents and adults have been found to be emerging risk groups in Canada.¹⁰

Complications of pertussis in adolescents and adults include sinusitis, otitis media, urinary incontinence, pneumonia, weight loss, rib fracture, and fainting.¹¹ During a 1998 outbreak of pertussis in Quebec, the hospitalization rates for these age groups were found to be fairly low (1% for adolescents, 2% for adults, and 6% for adults \geq 50 years old).¹¹ Mortality rates are low in these age groups, with a US surveillance study estimating a case-fatality rate less than 0.1% for adults at least 20 years old.¹² Pertussis morbidity among adolescents and adults tends to be less severe than among infants and children, but remains present.

In addition to the effects of age, vaccination status has also been associated with pertussis clinical severity. Vaccinated individuals have been found to have both less severe clinical disease and a shorter duration of illness.¹³ In a study of pertussis in Oregon from 2010-2012, patients who had ever been vaccinated against pertussis were found to have 0.2 times the odds of pertussis hospitalization compared to those who had never been vaccinated, adjusting for age (95%CI 0.1-0.8). Similarly, those who had ever been vaccinated had 0.4 times the odds of severe pertussis disease compared to those who had never been vaccinated, adjusting for age (95%CI 0.2-0.9).¹³ As well, the authors found that both individuals who were up-to-date with their pertussis vaccines and those who had been previously vaccinated against pertussis but not up to date had a shorter cough duration than those who were unvaccinated, hazard ratio (HR) = 1.7 (95%CI: 1.3-2.2) and HR=1.5 (95%CI: 1.1-1.9) respectively.¹³ Independent of age, individuals who have previously been vaccinated but develop pertussis are likely to have a less severe form of the disease and shorter cough duration.

Age and vaccine related factors both contribute to the under-diagnosis and underreporting of pertussis in adolescents and adults. A recent systematic review of the pertussis literature estimated that between 13% and 20% of prolonged coughs in adolescents and adults were attributable to pertussis, suggesting that the incidence rate of pertussis infection may be closer to 370-1,500 cases per 100,000 population¹⁴. Because the epidemiology of pertussis disease (reported pertussis cases) is different from the epidemiology of pertussis infections (pertussis caused by *Bordetella pertussis* that may or may not be recognized clinically but has been determined through serologic testing), the review authors delineated between these when summarizing the epidemiologic trends¹⁴. This distinction will remain throughout this dissertation.

1.1.3 Transmission of Pertussis

Pertussis is highly transmissible through respiratory droplets spread from infectious to susceptible individuals. The infectious period of pertussis is about 3 weeks long starting from the beginning of the catarrhal phase.⁶ As the catarrhal phase is non-specific, many patients do not realize they have pertussis and silently transmit the disease to others. The reproductive number (R_0) of pertussis has been estimated to be between 12 and 17,¹⁵ although one European study estimated it to be much lower (5.5).¹⁶ With a reproductive number this high, pertussis is easily spread through a population.

Individuals who are asymptomatic or mildly symptomatic are still able to transmit the infection to others. In a 2013 review of studies examining the source of infection for infants with pertussis, the authors found 55% (95%CI: 52-58%) were from parents and 5% (95%CI: 2-10%) were from grandparents, suggesting that household exposure is a key source of pertussis. Additionally, the authors estimated that between 16-43% of infections were from siblings and 4-22% were from non-household contacts, but couldn't pool the estimates due to heterogeneity. Interestingly, they found no identified source of infection for 32-52% of cases and asymptomatic infection in 8-13% of contacts.¹⁷ A 2015 study suggested that the most commonly cited source of infection for infants is siblings (35.5%), surpassing mothers (20.6%) and fathers (10%).¹⁸ Thus, the transmission of pertussis from asymptomatic and mildly symptomatic individuals is concerning, and suggests that immunization strategies to reduce infection in adolescents and adults are necessary to control the spread of pertussis.

1.1.4 Diagnosing Pertussis

Diagnosis of pertussis relies on both clinical suspicion and laboratory tests. According to the Public Health Agency of Canada, there are three classifications of pertussis cases: confirmed case (either through laboratory confirmation or epidemiologic link), probable case, and suspect case (**Table 1.1**).¹⁹ Due to the wide range of possible clinical symptoms, clinical suspicion is not always present. The changing sensitivity and specificity of laboratory tests over the course of the disease also complicates diagnosis.⁵

Case Classification	Definition			
Confirmed Case (Lab	Isolation of <i>B. pertussis</i>			
Confirmation)	OR			
	Detection of <i>B. pertussis</i> DNA plus at least one of:			
	- Cough of at least 2 weeks			
	- Paroxysmal cough			
	- Inspiratory "whoop" cough			
	 Cough involving vomiting or gagging, or apnea 			
Confirmed Case	Epidemiologic link to a lab-confirmed case and at least one of:			
(Epidemiologic Link) - Paroxysmal cough				
	- Inspiratory "whoop" cough			
	 Cough involving vomiting or gagging, or apnea 			
Probable Case	Cough of at least 2 weeks without lab tests not epidemiologically linked to a			
	lab-confirmed test and at least one of:			
	- Paroxysmal cough			
	- Inspiratory "whoop" cough			
	 Cough involving vomiting or gagging, or apnea 			
Suspect Case	At least one of the following:			
	- Paroxysmal cough			
	 Inspiratory "whoop" cough 			
	- Cough involving vomiting or gagging, or apnea			

Table 1.1. Case definitions of pertussis in Canada.

While culture is generally accepted as the "gold standard" for laboratory pertussis confirmation, the sensitivity of the test is low and varies according to the natural history

of the disease. Sensitivity estimates in the early symptomatic phases vary between 37% and 54.1% in infants and children,²⁰⁻²² but can be as low as 15% among adults.²⁰ However, the sensitivity of culture decreases to 0-3% three weeks after the onset of cough.²³ Culture is highly specific, with one study estimating 100% specificity of cultures from nasopharyngeal aspirates of patients with suspected pertussis, assuming "true positives" had both positive cultures and a fourfold increase in antibody titres.²² The other benefit of culture is the ability to type the strain of pertussis and test for antibiotic resistance.⁶

Polymerase chain reaction (PCR) is a much more sensitive test used to diagnose pertussis. Similar to culture, PCR performs best during the first 3 weeks after cough onset and sensitivity tends to decrease as the disease progresses.⁶ Sensitivity estimates have been shown to be between 73% and 100% while the specificity is thought to be close to 100%,^{6,24,25} though some oversensitive assays may have resulted in identification of "pseudo-outbreaks".²⁶

Serology is another way to detect pertussis. Lab tests to evaluate the levels of antibodies to pertussis antigens (pertussis toxin (PT), pertactin (PRN), and filamentous haemagglutinin (FHA)) that develop after natural infection with pertussis can be helpful in evaluating pertussis in individuals who present after 3 weeks of cough onset.⁵ However, the sensitivity of serologic tests can vary dramatically (between 20%-90%),^{27,28} in part because there is no standard cut-off value for seropositivity.⁵

In Ontario, both PCR and culture are approved tests for the diagnosis of pertussis in the presence of clinical signs and symptoms.²⁹ Because infants and children tend to present with classic pertussis symptoms, PCR and/or culture are generally used to diagnose pertussis in these age groups. However, as adolescents and adults may only present with a prolonged cough, PCR and culture may be insensitive to pertussis diagnosis, contributing to the under-diagnosis of pertussis in these age groups. While not

an approved test for pertussis in Ontario, serology may be a more appropriate method to diagnose infection in adults and adolescents.⁶

1.1.5 Treatment of Pertussis

Treatment of pertussis mainly includes supportive care but antibiotics are commonly prescribed to limit communicability.⁴⁻⁶ While antibiotics have not been found to reduce the clinical severity of disease or change the course of illness unless given very early, they are effective in shortening the infectious period, thereby reducing the potential for spread of the disease.³⁰ Recommended antibiotics in Canada include erythromycin for 10 days or cotrimoxazole if erythromycin is contra-indicated.³¹ Post-exposure prophylaxis of high-risk contacts of pertussis cases is also recommended in Canada, although according to a 2007 Cochrane Review, there is insufficient evidence to evaluate the benefits of such chemoprophylaxis.^{30,32}

1.2 Pertussis Trends

1.2.1 Historical Trends

Pertussis has been a nationally notifiable disease in Canada since 1924, but vaccines were not introduced until the 1940s. In 1924, there were 6,377 cases of pertussis disease reported in Canada with an incidence of 70.50 per 100,000 population.³³ Pertussis incidence continued to climb through the 1930s, and in the five years before the vaccine was introduced incidence of pertussis disease averaged 156 cases per 100,000 population annually.^{1,33} During this time, pertussis demonstrated a cyclic pattern with peaks every 2-5 years (**Figures 1.1 & 1.2**).^{1,14} After the vaccine was introduced, pertussis rates decreased, and by the mid 1980s, pertussis rates in Canada appeared stable and low with a mean incidence of 7 cases per 100,000 from 1984 to 1988 (**Figure 1.1**).¹ However, by the late 1980s, incidence of pertussis began to increase. These trends are comparable in Ontario (**Figure 1.2**).



Figure 1.1. Historical trends of reported pertussis disease in Canada from 1924-2013. Number of cases of pertussis are shown in blue, and the rate of pertussis disease per 100,000 population is shown in red. Data obtained from the Public Health Agency of Canada's Notifiable Diseases Online Database.³³



Figure 1.2. Historical trends of reported pertussis disease in Ontario from 1904-1989. Number of cases of pertussis are shown in blue, and the rate of pertussis disease per 100,000 population is shown in red. Years for which data are unavailable are shaded in grey. Data obtained from the International Infectious Disease Data Archive at McMaster University.³⁴

1.2.2 Current Trends

Despite having a robust immunization program and considerable vaccine uptake, pertussis persists in Canada. While we continue to see a cyclic pattern associated with pertussis disease, the peaks have become smaller and less pronounced (**Figure 1.1**).¹ In addition, as pertussis dynamics vary geographically, each province demonstrates peaks in different years, leading to dilution of periodicity at the national level.¹ Similarly, outbreaks in particular provinces can drive the increase of cases at a national level, making it appear as though there was a widespread pertussis outbreak where the actual increase of cases could have been localized.

Pertussis has been associated with sex, with incidence and hospitalization rates consistently higher among females than males. The annual median female-to-male incidence rate of reported pertussis disease was 1.15:1 for all ages during 1990-2012.¹ In an outbreak of pertussis in Quebec, 55% of adolescent cases were female and 70% of adult cases were female.¹¹ Between 1995 and 2010, the median female-to-male ratio for pertussis hospitalization was 1.12:1.¹ Among hospitalized infants under 2 years of age, the female-to-male ratio was found to be 1.16:1.⁸

The most recent peak year for which Canadian data is available was 2012 (**Figure 1.1**). During this year, the national incidence of pertussis disease was 13.9 per 100,000 population for all ages, but was highest among infants less than one year (120.8 per 100,000) and adolescents aged 10-14 (64.1 per 100,000).¹ This year was associated with 3 infant pertussis-related deaths and was considered a peak year for pertussis in Canada. Similarly, 2006 was a peak year for reported pertussis disease in Toronto, although the magnitude of the peak was magnified by increased clinician awareness and improved diagnostic sensitivity,³⁵ as described in Section 1.2.3 (**Figure 1.3**). The persistence of pertussis and the peaks every few years demonstrate that the disease is not well controlled by current immunization programs.



Figure 1.3. Historical trends of reported pertussis disease in Toronto from 1990-2011. Number of cases of pertussis are shown in blue, and the rate of pertussis disease per 100,000 population is shown in red. Data obtained from the Public Health Laboratory of Toronto.

1.2.3 Pertussis Persistence

Current trends demonstrate that pertussis persists in the community despite routine administration of pertussis vaccines. Proposed reasons for the persistence of reported pertussis disease include genetic mutation of *B. pertussis*, decreased immunogenicity of vaccines, changing testing methodologies, more awareness of pertussis, and waning of vaccine-induced immunity.¹⁴

Genetic mutation of *B. pertussis* may contribute to the increased number of pertussis cases reported in recent years. Studies in Europe have documented genetic changes to *B. pertussis* over the past three decades.³⁶⁻³⁸ From 1998 to 2007-2009, the predominant circulating strain of *B. pertussis* decreased in prevalence from 30% to 13%.³⁷ In addition, two key pertussis antigens (pertactin and pertussis toxin) have been found to have variants, although the frequency of the variants was relatively stable prior

to 1988. Changes in the frequency of these variants occurred from 1989-1996, the last year of the study, with the authors suggesting the vaccine may have selected for different variants.³⁸ These changes to the genetic makeup of circulating *B. pertussis* strains is thought to make the vaccines less effective.³⁹ However, more recent work suggests that these genetic changes are a contributing factor to the reduced duration of immunity conferred by these vaccines.³⁶ Regardless of the mode of action, genetic changes of *B. pertussis* may be contributing to pertussis persistence.

While it has not been proven globally, there is evidence to suggest that decreased immunogenicity of vaccines may also be partly responsible for the persistence of pertussis. In fact, it is believed that the resurgence of pertussis in the early 1990s in Canada was largely due to a cohort effect as a result of changing vaccine preparations to an adsorbed vaccine with a low effectiveness (48-69%).⁴⁰ The vaccine preparation has since been changed and adolescent and adult boosters have been added to the routine immunization programs (see Section 1.3.2 and Table 1.2), but under-protected adults and adolescents likely contribute to the force of infection driving the persistence of pertussis.

Similarly, both changing diagnostic testing methodologies and greater awareness of pertussis have contributed to the increased number of pertussis cases in Canada. In a 2003 editorial, Cherry argued that while some of the increase in pertussis was attributable to vaccine-induced waning immunity and lessened potency of pertussis vaccines, the large "resurgence" of cases was mainly due to the greater awareness of pertussis by clinicians.³⁹ In fact, he argued that more clinicians were aware of the atypical symptoms in adolescents and adults and were more likely to test for it and thus more likely to report it.³⁹ A study of the 2005-2006 outbreak of pertussis in Toronto confirmed that clinician awareness was an important factor driving the increased pertussis cases. The authors found that while the surge in pertussis incidence reflected a true increase in disease circulation, it was magnified by increased diagnostic test sensitivity and better clinician awareness.³⁵ Thus, clinician awareness plays an important role in explaining the increased number of reported pertussis cases in Canada.

However, in 2012-13 four distinct studies demonstrated waning immunity after childhood immunization with the acellular pertussis vaccine, DTaP (Diphtheria-Tetanus-acellular Pertussis)⁴¹⁻⁴⁴. Similarly, a 2015 study on the effectiveness of the adolescent Tdap (Tetatnus-diphtheria-acellular Pertussis) vaccine found that vaccine effectiveness was 73% (95%CI: 60-82%) one year after vaccination but dropped to 34% (95%CI: -0.03-58%) two to four years after vaccine administration,⁴⁵ suggesting that pertussis protection from Tdap wanes in a similar fashion to DTaP. Together, these studies provide compelling evidence that the duration of protective immunity conferred by acellular pertussis vaccines is shorter than previously thought, suggesting that this may be the most important factor explaining the persistence of pertussis.¹⁵

1.3 Pertussis Vaccines

Currently, there are 9 pertussis-containing vaccines authorized for use in Canada.⁴⁶ These products are manufactured by Sanofi Pasteur Ltd. and GlaxoSmithKline Inc. and are grouped into two main product types: DTaP and Tdap. Both products contain antigens for diphtheria, tetanus, and acellular pertussis, but Tdap contains lower concentrations of diphtheria and acellular pertussis antigens than DTaP. Preparations have been developed to combine DTaP and Tdap with inactivated polio virus vaccine (Tdap-IPV, DTaP-IPV), *Haemophilus influenza* type B vaccine (DTaP-IPV-Hib), and hepatitis B vaccine (DTaP-HB-IPV-Hib). Typically, infants and children are immunized with DTaP and adolescents and adults are immunized with Tdap.⁴⁶

1.3.1 Vaccine History

Widespread Canadian immunization campaigns with whole-cell pertussis vaccine began in the 1940s, with subsequent introduction of the adsorbed whole cell vaccine (DTwP) in the 1980s, and acellular preparations (DTaP) in 1997-98.⁴⁷ Concerns about adverse events after immunization with DTwP precipitated the development of a new acellular vaccine,⁴⁸ and this vaccine, DTaP, has been shown to have fewer side effects than the DTwP preparation.⁴⁹⁻⁵¹ Acellular pertussis vaccines are designed to prevent pertussis but where breakthrough disease does occur, patients tend to have less severe and

reduced duration of disease potentially leading to lower infectivity compared to pertussis in unvaccinated individuals.¹³

1.3.2 Current Vaccine Recommendations

The National Advisory Committee on Immunization (NACI) provides recommendations for the use of immunizations in Canada. However, each province is responsible for their own immunization program, and so each province follows a slightly different childhood immunization schedule. For the purpose of this dissertation, where the work is primarily done in the Ontario context, I will focus on the Ontario immunization program, recommendations, and guidelines.

With the original Ontario DTaP vaccine program, infants and children received pertussis vaccines at 2, 4, 6, and 18 months of age and again between 4 and 6 years of age.⁵² Due to a shortage of Quadracel (a DTaP product), in 2014 NACI recommended that either DTaP-IPV or Tdap-IPV be given to 4-6 year olds for the pre-school booster and Ontario adopted this recommendation.⁵³ In 2000, the National Advisory Committee on Immunization (NACI) recommended that Tdap be administered to adolescents at age 14-16 and in 2003, Ontario included this vaccine in the Publicly Funded Immunization Schedule.^{52,54} In 2011, the Ontario Publicly Funded Immunization Schedule was expanded once again to include a one-time adult Tdap booster, recommended to replace the next tetanus-diphtheria (Td) vaccine.⁵² The recommended Ontario schedule can be found in **Table 1.2**.

Table 1.2. Publicly funded immunization schedule for pertussis in Ontario (as of October 2015).⁵⁵

				18	4-6	14-16	≥18
	2 Months	4 Months	6 Months	Months	years ^a	years	years ^b
DTaP-IPV-Hib	~	~	~	~			
Tdap-IPV					~		
Tdap						~	~

^a Preferably given at 4 years of age.

^b Adults ≥ 18 years of age receive Tdap instead of Td when next Td vaccine is needed and then receive Td every 10 years after that.

DTaP-IPV-Hib = Diphtheria, Tetanus, Pertussis, Polio, Haemophilus influenzae type b

Tdap-IPV = Tetanus, Diphtheria, Pertussis, Polio

Tdap = Tetanus, Diphtheria, Pertussis

1.3.3 Proposed Changes to Vaccine Recommendations

Given evidence of pertussis persistence and waning immunity after immunization with acellular pertussis vaccines, current immunization programs are not succeeding at controlling the spread of pertussis in the community. Leading vaccinologists have proposed competing strategies which are focused on either yielding levels of protection that are high enough to achieve herd immunity or preventing transmission to vulnerable young infants. In addition to current strategies already recommended by NACI, these include "cocooning" by immunization of contacts of newborns, immunization during pregnancy, immunization of healthcare workers, immunization of childcare workers, and routine repeated adult immunization.⁵⁶

Prior to recommending one or more of these immunization strategies in the Canadian context, it is helpful to compare the relative costs and outcomes through economic analysis and mathematical modeling. While mathematical models are not a substitute for epidemiologic data, they serve as platforms for synthesis of data from multiple sources, performance of realistic cost-effectiveness analyses that incorporate the effects of interventions (such as vaccines) on recipients and non-recipients, and provide a means for identifying uncertainty and prioritizing future research.⁵⁷ The use of models to evaluate the effectiveness and cost-effectiveness of different immunization programs in Ontario would allow for economic comparison that includes both the direct effects of the vaccination program as well as the indirect, or herd effects of the program.

1.4 Key Areas of Uncertainty

While the pertussis literature is large and fairly comprehensive, many questions remain unanswered. The persistence of pertussis despite routine childhood, adolescent, and adult immunization programs in Canada highlights the need to examine new immunization strategies. Cost-effectiveness analysis provides a platform to evaluate the potential costs and benefits of competing immunization programs. However, before reliable cost-effectiveness models can be built and analyzed, there are several key parameters which must be addressed. The role of pertussis under-diagnosis and underreporting in adults and adolescents and the associated contribution to the force of infection, the duration of protective immunity conferred from the childhood immunization series, and the health and economic burden of pertussis cases will be addressed in this dissertation.

1.5 Specific Aims

Given the uncertainty in the literature about pertussis, this dissertation will be comprised of three independent but complementary aims that seek to inform the gaps in current pertussis immunization programs in Ontario. These aims are outlined below:

Aim 1. To estimate the underlying burden of pertussis infection in adolescents and adults in Ontario.

Objective 1.1. To create a well calibrated transmission model to accurately reflect pertussis dynamics in Ontario.

Objective 1.2. To derive credible age-specific estimates of the burden of underdiagnosis and under-reporting of pertussis infection in Ontario.

Aim 2. To summarize the current literature on duration of protective immunity conferred from childhood immunization with DTaP.

Objective 2.1. To qualitatively synthesize the current literature on pertussis waning immunity after immunization with 3 and 5 doses of childhood DTaP.Objective 2.2. To use meta-analysis to quantitatively estimate the duration of protective immunity conferred after 3 and 5 doses of DTaP.

Aim 3. To evaluate the health and economic impact of pertussis in Ontario.

Objective 3.1. To estimate the age-specific life years lost, quality-adjusted life years lost, and costs associated with pertussis in Ontario.

Objective 3.2. To evaluate the budget impact and net monetary impact of pertussis in both Ontario and Canada.

1.6 Format of the Dissertation

This dissertation is an exploration of the gaps in current immunization programs in Ontario. It is written in the journal format where Chapters 2-4 are stand-alone manuscripts composed of their own abstract, introduction, methods, results, and discussion. Each chapter is introduced with a reader's note. The discussion in Chapter 5 summarizes the research, ties the results of Chapter 2-4 together, and provides directions for future research. Supplementary information is presented in Chapter 6. References can be found at the end of each chapter.

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2 Chapter Two: Estimation of the Underlying Burden of Pertussis in Adolescents and Adults in Southern Ontario, Canada

2.1 Reader's Note

Here I present evidence that the underlying burden of pertussis in adolescents and adults in Ontario is considerable and likely contributing to the force of infection. I developed and calibrated a transmission model and validated it to ensure validity. I compared the model incidence to reported pertussis incidence data to estimate the age-specific under-identification ratios of pertussis. A version of the work described in this chapter has been published in *PLoS ONE*, but some editorial changes have been made to keep the terminology consistent throughout this dissertation.

Reference:

McGirr AA, Tuite AR, Fisman DN. Estimation of the Underlying Burden of Pertussis in Adolescents and Adults in Southern Ontario, Canada. Plos One. 2013;8(12).

2.2 Abstract

Despite highly successful vaccination programs and high vaccine uptake, both endemic pertussis and periodic pertussis outbreaks continue to occur. The underrecognized role of adolescents and adults in disease transmission, due to waning immunity following natural infection and vaccination, and reduced likelihood of correct diagnosis, may contribute to pertussis persistence. We constructed a mathematical model to describe the transmission of pertussis in Southern Ontario in both pre-vaccine and vaccine eras, to estimate the underlying burden of pertussis in the population. The model was well calibrated using the best available data on pertussis in the pre-vaccination (1880-1929) and vaccination (1993-2004) eras in Ontario. Pertussis under-identification by age group was estimated by comparing model-projected incidence to reported laboratory-confirmed cases for Greater Toronto. Best-fit model estimates gave a basic reproductive number of approximately 10.6, (seasonal range 9.9 to 11.5). Underidentification increased with age, and approximately >95% of infections in children were caused by infections in persons with waning immunity to pertussis following prior infection or vaccination. A well-calibrated model suggests that under-recognized cases of pertussis in older individuals are likely to be an important driver of ongoing pertussis outbreaks in children. Model projections strongly support enhancement of booster vaccination efforts in adults.

2.3 Introduction

Pertussis is a highly contagious respiratory tract infection caused by the gram negative bacterium *Bordetella pertussis*, or less commonly by *B. parapertussis*.¹ While children and adults of any age may develop pertussis, severe sequelae (including encephalopathy and pneumonia) are most common in young infants.²⁻⁴ The disease remains one of the leading causes of infant mortality, causing 300,000 deaths and 50 million cases per year, mostly in countries lacking the resources to support widespread immunization.^{3,5}

With introduction of pertussis immunization in Canada in the 1940s, annual pertussis incidence decreased dramatically (from over 140 cases per 100,000 to fewer than 20 cases per 100,000 by the 1970s).⁶ However, despite high levels of vaccine uptake in Canada, the disease has not been eliminated. Periodic pertussis outbreaks continue to present a challenge,^{7,8} with recent large outbreaks or increases in pertussis incidence occurring in infants in high income countries including United States, Canada, Norway, Ireland, Australia and the United Kingdom, ⁶⁻¹¹ though in middle income countries with longstanding vaccine programs, such as Thailand, resurgences have been absent.¹² Disease incidence also appears to be increasing,^{2,13,14} a phenomenon variously attributed to changing vaccine preparations, aging of under-vaccinated cohorts, bacterial mutation, and more sensitive laboratory testing.^{1,3,6,13,15-20}

Another proposed explanation for the persistence of pertussis is the underrecognized role of adolescents and adults in disease transmission,²¹ due to waning immunity following natural infection and vaccination,^{3,13,22} and decreased likelihood of diagnosis, due to different disease manifestation in these groups, compared to that observed in infants and children.²³ Furthermore, widespread adoption of vaccination, but at a level insufficient to result in disease elimination, could eliminate natural "boosting" through interactions between previously infected individuals and infectious cases, further contributing to loss of immunity in older individuals.^{24,25} Indeed, a recent communitybased study of cough illness performed in Poland suggested that pertussis in older adults might be under-detected by a factor of 167, in contrast to 4-fold under-detection in children aged 3 to 5.²⁶ Given the apparent importance of adolescents and adults in disease spread, several countries have advocated implementing a booster dose of pertussis vaccine, ^{27,28} though others have suggested that age-assortative mixing would mean that boosting in adolescents might have little impact on disease impact in infants.¹¹

To better understand how under-recognition of pertussis in adolescents and adults may contribute to observed disease patterns, we constructed a mathematical model to describe the transmission of pertussis in the Canadian province of Ontario. We used this model to estimate the underlying burden of pertussis in the population, and to derive credible estimates of the likely degree of under-identification of pertussis in older individuals that would be necessary to explain current observed epidemiological trends.

2.4 Methods

2.4.1 Pertussis Model Construction

We used Berkeley Madonna²⁹ to construct an age-structured compartmental model that included births and deaths, and the introduction of the pertussis vaccine, in order to examine multi-year pertussis dynamics (see Section 6.1.1-6.1.3 for additional model details). The basic model structure is presented in detail in Figure 2.1. Natural history parameters (Table 2.1) were derived from epidemiologic studies and by model calibration. The population was divided into eight different disease states: susceptible (S), vaccinated (V), exposed (E, infected but not infectious), infectious (I), recovered (R), resusceptible (S_R), re-exposed (E_R), and re-infectious (I_R). Transmission of infection occurred through contact between susceptible or re-susceptible and infectious individuals. As individuals lost naturally-acquired or vaccine-induced immunity over time, they became re-susceptible to infection; we assumed that these individuals were equally susceptible as pertussis-naïve individuals, but were one-fifth as infectious (i.e., less likely to spread infection to others as assumed in previous models).³⁰ This decrease in

infectiousness incorporates both the hypothetical vaccine efficacy for infectiousness³¹ and the reduced duration of cough observed in partially immunized individuals.³²



Figure 2.1. Model overview. The population was divided into eight different disease states: susceptible (S), vaccinated (V), exposed (E, infected but not infectious), infectious (I), recovered (R), re-susceptible (S_R), re-exposed (E_R), and re-infectious (I_R). Each vaccination compartment ($V_1...V_5$) represents a different level of conferred immunity as children progress through the 5 recommended childhood pertussis vaccines. For complete model details refer to **Section 6.1.1-6.1.3**.

Parameter	Best-fit value (plausible range for	Source
	sensitivity analysis)	Name and Data 2009 ³³
Latent period (days)	8	Nguyen and Rohani, 2008
Infectious period (days)	15	Nguyen and Rohani, 2008 ³³
Duration of immunity following infection (years)	17.84 (10 – 50)	Assumption; Wendelboe <i>et al.</i> , 2005 ³⁴ ; Wearing and Rohani, 2009 ³⁵
Duration of immunity following complete immunization (years)	27.11 (2 – 30)	Model calibration; Wendelboe <i>et al.</i> , 2005 ³⁴
Relative infectiousness of individuals re-challenged with pertussis (following loss of naturally-acquired or vaccine- induced immunity)	0.2	Assumption, similar to van Boven <i>et al.</i> , 2000 ³⁰
β_1 , base transmission parameter	11.33 (9 – 12)	Model calibration
β_2 , relative amplitude of annual forcing	0.05 (0.005 – 0.1)	Model calibration
β_3 , relative amplitude of seasonal forcing	0.029 (0.01-0.05)	Model calibration
Life expectancy pre-vaccine era (years)	66	Assumption
Life expectancy in vaccine era (years)	75	Assumption
Vaccine Efficacy	0.9	Schmitt <i>et al.</i> , 1996 ³⁶ , Preziosi and Halloran, 2003 ³¹ , Ward <i>et al.</i> , 2005 ³⁷

Table 2.1. Parameter values used in model. Parameters used in the sensitivity analysis were drawn from uniform distributions with the plausible ranges indicated.

To model existing pertussis vaccination schedules and to enable the representation of more realistic contact patterns within and between age groups, our model was agestructured, with ten age classes based in part on vaccine recommendations (<2 months, 2–4 months, 4-6 months, 6 months–2 years, 2-7 years, 7-10 years, 10-15 years, 15-20 years, 20-65 years and 65+ years). Mixing within and between age strata was based on the best available survey data for high-income countries.³⁸ The original survey was conducted in Great Britain with a nationally representative sample of participants who maintained diaries of the age and gender of all contacts with which they had a two-way conversation consisting of more than 3 words per day. The results from Great Britain echoed similar findings from Belgium, Germany, Finland, Italy, Luxembourg, The Netherlands, and Poland in terms of the age-specific contact patterns, suggesting that this contact matrix is robust. The contact matrix used in the present analysis was modified from Mossong and colleagues³⁸ to capture the age categories specific to the ten age classes used in the model. The full contact matrix can be found in the **Section 6.1.4**.

The birth rate was set equal to the death rate to maintain a constant population size and population distribution among age classes. Deaths occurred only in the oldest age group, with continuous aging through the age cohorts. Loss of immunity following immunization or natural infection was incorporated using existing estimates and model calibration. While the vaccine preparation offered in Ontario changed from adsorbed whole cell vaccine to an acellular preparation in 1997-98, the two preparations exhibited similar levels of efficacy so were treated as such in the model.³⁹ Latent and infectious periods were assumed to follow a gamma distribution.³³ Additional information on model parameter values is presented in **Table 2.1**.

Periodicity of pertussis epidemics was simulated by forcing the effective contact rate (β) to oscillate through time. This was done by incorporating two cosine terms into the base model transmission parameter (β_1) to represent annual outbreaks (β_2) and epidemics every 4 years (β_3),⁴⁰ such that:

$$(t) = {}_{1}*1 + {}_{2}\cos\frac{2t}{365} + {}_{3}\cos\frac{2t}{4*365}$$

Vaccination was modeled as a continuous process whereby individuals were moved into different vaccination compartments as they entered the different age classes at which pertussis vaccine is typically administered (i.e., as they enter the 2 month, 4
month, 6 month, 2 years, or 7 years of age categories), resulting in a total of 5 vaccinated compartments. Upon administration of the first dose at 2 months, a susceptible individual was moved into the V_1 compartment, and with each subsequent dose moved up to the next vaccination compartment (V_2 to V_5). The final distribution of individuals among the 5 vaccination compartments in the 7-10 age category (i.e., after administration of the final possible vaccine dose) was specifically designed using age-specific probabilities of vaccination to reflect existing Canadian pertussis vaccine coverage estimates (**Table 2.2**).⁴¹ We assumed that the individuals in the vaccinated compartments were fully protected against pertussis infection, with the remaining fraction receiving no protection. Receipt of each vaccine dose was assumed to boost immunity to infection, and with loss of vaccine-induced immunity, an individual was moved to a lower vaccine compartment and ultimately returned to the re-susceptible class (i.e., from V_k to V_{k-1} or V_1 to S_R).

Number of doses	Recommended age at vaccination	Reported (PHAC) ^a	Model
0		0.04	0.034
1	2 months	0.02	0.022
2	4 months	0.04	0.043
3	6 months	0.06	0.067
4	1.5 years	0.19	0.183
5	4-6 years	0.65	0.652

Table 2.2. Estimated pertussis vaccine coverage at 7 years of age.

^aMcWha L, MacArthur A, Badiani T, Schouten H, Tam T, et al. (2004) Measuring up: results from the National Immunization Coverage Survey, 2002. Can Commun Dis Rep 30: 37-50

2.4.2 Model Calibration

In order to credibly calibrate our model, we used a two-step procedure, first calibrating pertussis incidence in an unvaccinated population to the best available data on pre-vaccination pertussis incidence in Ontario (1880-1929), and subsequently calibrating vaccine effectiveness and durability estimates using more recent time series data (1993-2004). Specifically, we used reported proportionate mortality by age group⁴² and applied age-specific case-fatality ratios (estimated in 32 U.S. cities over a ten-year period)⁴³ to calculate expected pertussis incidence between 1880 and 1929. The time series data for pertussis incidence in the vaccine-era was obtained from the two pertussis testing laboratories in the Greater Toronto Area (GTA): the Public Health Laboratory- Toronto (PHLT) and the Hospital for Sick Children (HSC). This dataset contains laboratory confirmed pertussis cases (by culture and PCR) from 1993 to 2004. Calibration was performed using Berkeley Madonna modeling software, which determines the best fitting estimates based on minimizing the root mean square deviation between the dataset and the predicted outputs from each run.^{29,44} Full details on the model calibration procedure can be found in the **Section 6.1.5**.

2.4.3 Model Validation

In order to validate the model, the secondary model outputs including the estimated reproductive number and duration of vaccine-induced immunity were compared with previously cited literature values.

2.4.4 Estimation of Pertussis Under-identification

To determine the degree of pertussis under-identification, we compared model projected age-specific annual incidence to the 1993-2004 time series. The underidentification ratio of projected to reported cases was estimated using the mean daily cumulative incidence over this time period. The contribution of infection in persons previously exposed to pertussis, either through natural infection or vaccination, to the force of infection (the rate at which susceptible individuals become infected), was calculated as:

$$\frac{FOI_{previous \exp osed}}{FOI_{all \inf ected}} \div = \frac{\prod_{m=1}^{10} (t)rrIR_m}{\prod_{m=1}^{10} (t)(I_m + rrIR_m)}$$

where *j* is the age group of the susceptible population, *m* is the age group of the infectious contacts, I_m is the number of previously pertussis-naïve infectious individuals of age *m*, IR_m is the number of previously exposed or vaccinated infectious individuals of age group *m*, *rr* is the relative infectiousness of previously exposed individuals, and $\phi_{j,m}\beta(t)$ is the probability of effective infectious contact between an infectious and susceptible individual.

2.4.5 Estimation of Vaccine-Induced Immunity Among Older Individuals

In order to estimate the proportion of individuals in each age group with vaccineinduced immunity to pertussis, we calculated the model predicted distribution of individuals in each of the vaccination compartments, V_1 to V_5 , for each of the age groups at the end of the 2012 calendar year. We then used the derived probabilities of vaccination for each age group to calculate the estimated proportion of individuals who had received at least one pertussis vaccination within each of the age groups.

2.4.6 Sensitivity Analyses

Given the uncertainty around parameters describing the natural history and epidemiology of pertussis, we conducted a multi-way sensitivity analysis. Parameters were drawn from uniform distributions, with the ranges outlined in **Table 2.1**, for 1000 simulations. Age-specific probabilities of under-identification were calculated for each model run and summarized with parametric confidence limits.

2.5 Results

2.5.1 Calibration

Through model calibration in the pre-vaccine era, we found the basic reproductive number (R_0) of pertussis to be between 9.87 and 11.47 in Southern Ontario between 1880 and 1929. Assuming a 16% identification rate of pertussis at the time and a duration of immunity of approximately 18 years, best-fit estimates yielded β_1 =11.334, β_2 =0.050, β_2 =0.029 (**Figure 2.2**).

Using these best-fit estimates of natural history parameters, we used data from the vaccine era to derive estimates of duration of vaccine-induced immunity. The best-fit value was 5.42 years per vaccine dose received or 27.11 years for fully vaccinated individuals, assuming age specific case identification rates. In particular, the best-fitting model had case-identification values of 4.4%, 17.38%, 7.6%, and 0.55% for children under 2 months old, between 2 and 4 months old, between 4 and 6 months old, and between 6 months and 2 years old, respectively (**Figure 2.3**).



Figure 2.2. Model calibration to pertussis incidence in the pre-vaccine era. Modelprojected (a) cumulative pertussis incidence and (b) annual pertussis incidence in the population under 2 years old (bars) were fit to a time-series of pertussis incidence between 1880 and 1929 (line). Best-fit parameter estimates were: β_1 of 11.335, β_2 of 0.050, and β_3 or 0.029 assuming duration of immunity following infection of approximately 18 years.



Figure 2.3. Model calibration to cumulative and annual pertussis incidence in the 1993-2004 vaccine era. Cases confirmed by the Public Health Laboratory --Toronto and the Hospital for Sick Children are shown in black and model predicted incidence of identified cases for the four age groups (under 2 months old, 2-4 months old, 4-6 months old, 6-24 months old) is shown in grey.

2.5.2 Validation

The secondary outputs derived from the model were consistent with previously cited literature values. At 5.42 years per vaccine dose received, the estimated duration of vaccine-induced immunity was towards the shorter, rather than longer, end of previously reported ranges.^{11,34,35} Our estimated reproduction number of 10.63 (seasonal range from 9.9 to 11.5), is a bit lower than previously cited reproduction numbers;^{45,46} however, this difference is likely due to heterogeneity between communities.

2.5.3 Degree of Under-identification of Pertussis and Age-specific Effects

We used the model to estimate the annual age-specific incidence of pertussis and compared these rates to reported rates for the period between 1993 and 2004, to ascertain the likely degree of pertussis under-identification. Pertussis under-identification was found to vary dramatically with age: in the 2-7 year old age group, we projected that there were approximately 597 un-identified pertussis cases per reported case, with this ratio increasing to a maximum of approximately 33,302 un-identified cases per reported cases per reported case in the 20 to 64 year age group (**Figure 2.4**).

We also assessed the contribution of infections in persons with loss of immunity to the rate at which susceptible individuals become infected (i.e., the force of infection). Using best-fit model parameters, we estimated that approximately 97% of infections in the <2 age group were attributable to infection from persons re-susceptible to infection through loss of naturally-acquired or vaccine-induced immunity. The high burden of disease caused by previously exposed individuals occurred despite our assumption that these individuals were one-fifth as infectious as individuals without prior immunity.



Figure 2.4. Estimated under-identification of pertussis by age group. The model predicted ratio of underlying pertussis cases per laboratory-confirmed case was calculated based on reported cases for the Greater Toronto Area between 1993 and 2004. Results are presented on a logarithmic scale. For each age group, the minimum, mean, and maximum number of model predicted un-identified cases for every reported case are displayed.

2.5.4 Estimation of Vaccine-Induced Immunity Among Older Individuals

We used the model predicted distribution of individuals in each of the vaccination compartments at the end of the year 2012 to ascertain the levels of vaccine-induced immunity in adolescents and adults of Southern Ontario (**Figure 2.5**). While we found high vaccination coverage rates among the older populations, less than 10% of individuals over age 20 were found to have immunity against pertussis. Infants and children were found to have the highest levels of immunity, with this value decreasing substantially in the older age groups.



Figure 2.5. Model predicted vaccine induced immunity and vaccine coverage by age group, at end of 2012. Proportion immune represents the proportion of individuals who remain immune to pertussis due to vaccine-induced immunity. Proportion vaccinated represents the proportion of individuals who received at least one pertussis immunization.

2.5.5 Impact of Uncertainty

Given the wide range of reported values for parameters describing the natural history of pertussis, we conducted wide-ranging sensitivity analyses to determine the impact of uncertainty on our estimates of pertussis under-identification. Results are presented in **Figure 2.6**. Although variation of input parameters across plausible ranges resulted in some variability in the estimated ratio of total pertussis cases to reported pertussis cases, there was no qualitative difference between results from sensitivity analyses and those derived in the base case.



Figure 2.6. Multi-way sensitivity analysis. Probability of under-identification for each age group. Confidence limits are based on the mean and standard deviation of the results from the sensitivity analysis.

2.6 Discussion

The ongoing morbidity associated with pertussis even in the face of widespread pediatric immunization simultaneously highlights gaps in our knowledge regarding the epidemiology of this disease, and the importance of these very gaps. In both Canada and the United States, national immunization recommendations have evolved and now advocate boosting of adolescents and young adults against pertussis,^{27,28} but whether such policy changes will result in further progress towards disease elimination remains to be seen. Some authors have expressed skepticism regarding this strategy, suggesting that the limited interactions between adolescents and infants and young children at a population level make it unlikely that interventions targeted at the former group would result in large reductions in risk in the latter.¹¹ A further element of complexity relates to the question of whether reduced force of infection resulting from immunization could paradoxically

increase the pool of potentially infectable adolescents and adults by eliminating natural boosting.²⁵

The decrease in pertussis severity in older individuals (who presumably have partial immunity to the disease via prior exposure or vaccination) has been well described^{47,48} and a recent community-based study performed in Poland suggested that there is an age-related decrease in the likelihood that pertussis is reported to public health authorities.²⁶ This creates an obstacle for the formulation of optimal disease control policy, as adults with mild disease are unlikely to modify their behavior in a way that prevents disease transmission, are less likely to present for clinical care and diagnostic testing, and as such are likely to be absent from surveillance records. We sought to create a mathematical model of pertussis in Southern Ontario, Canada to approximate the degree of under-identification of pertussis in older individuals that would be expected based on reported pertussis epidemiology by age group.

The creation of well-calibrated disease dynamic models for pertussis is known to be challenging. By incorporating age-structure and limiting the duration of effective immunity following natural infection,³⁸ we were able to calibrate our model such that it fit well to pre-vaccination time-series. Calibration of the model to reflect reported case counts in infants was greatly facilitated by assuming the existence of a partially immune state in which individuals with prior infection or vaccination were less infectious than individuals with first infection in the absence of prior immunity; this finding is similar to that previously reported by Broutin et al.,⁴⁹ and consistent with the milder course of pertussis in older individuals.⁵⁰ Nonetheless, even assuming marked reductions in infectious in infectious in our model.

In estimating the degree of under-identification of pertussis in older age groups, we projected that age-related patterns of under-identification are inverse to patterns of reported incidence, with pertussis under-identified by several orders of magnitude in adults. Again, this echoes the suggestion by others that pertussis is markedly under-recognized in adults ^{26,51,52} and provides a credible explanation as to why high rates of vaccination coverage have failed to eliminate pertussis.^{6,53}

Our model has important policy implications; in particular, that optimal control of pertussis may depend on repeated boosting of adults (as with diphtheria and tetanus). Our best-fit model also implies that the duration of protection through immunization is toward the shorter, rather than longer, end of reported ranges.^{34,35} With our estimated reproductive number of 10.63 and some seasonal variability in occurrence, we estimate the critical fraction vaccinated for herd immunity to be 90-92%, which would be impossible in the absence of adult boosting. Fortunately, a safe combined vaccine preparation of diphtheria, tetanus, and pertussis, appropriate for use in adults, is now available, but the challenges associated with immunization of adults are well described.⁵⁴ Like any model, ours has limitations, and when data or parameters were sparse or absent we were forced to make some simplifying assumptions. However, our model outputs were robust over a wide range of possible parameter values, and in the face of alternate assumptions. As further data on the natural history and epidemiology of this disease become available, it will become possible to further refine the estimates presented here.

In conclusion, we were able to create a well-calibrated population dynamic model of pertussis that reproduced the reported epidemiology of this disease in children in Southern Ontario, Canada, both before the advent of immunization, and after immunization became widespread. Our model implies that maintenance of pertussis endemicity in the face of high rates of vaccine coverage depends on relatively short duration of immune protection from *both* natural infection and immunization, as well as continued susceptibility to infection (albeit with diminished infectiousness) in adults. While areas of uncertainty in our model suggest promising avenues for future research, our findings support the suggestion that ongoing pertussis boosting in adults may be necessary for optimal control of this disease in children.

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3 Chapter Three: Duration of Pertussis Immunity Following DTaP Immunization: A Meta-Analysis

3.1 Reader's Note:

In this chapter, I present evidence that the DTaP vaccine is associated with a relatively short duration of protective immunity. Through systematic review of the literature and meta-analysis and meta-regression, I estimate the waning effects of DTaP. The work described in this chapter has been published in *Pediatrics*. It has been reproduced here with permission from Journal Pediatrics, Vol. 135(2), Page(s)331 – 343, Copyright @ 2015 by the AAP.

Reference:

McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. Pediatrics. 2015;135(2):331-343.

3.2 Abstract

Background and Objectives: Pertussis incidence is increasing, possibly due to the introduction of acellular vaccines, which may have decreased durability of immune response. We sought to evaluate and compare the duration of protective immunity conferred by a childhood immunization series with three or five doses of DTaP.

Methods: We searched Medline and Embase for articles published before October 10, 2013. Included studies contained a measure of long-term immunity to pertussis after 3 or 5 doses of DTaP. 12 articles were eligible for inclusion, 11 of these were included in the meta-analysis. We assessed study quality and used meta-regression models to evaluate the relationship between the odds of pertussis and time since last dose of DTaP and to estimate the probability of vaccine failure through time.

Results: We found no significant difference between the annual odds of pertussis for the three versus five dose DTaP regimens. For every additional year after the last dose of DTaP, the odds of pertussis increased by 1.33 times (95%CI: 1.23–1.43). Assuming 85% initial vaccine efficacy, we estimate vaccinated children would have 10% protection 8.5 years after the last dose of DTaP. Limitations included the statistical model extrapolated from data and the different study designs included, most of which were observational study designs.

Conclusions: While acellular pertussis vaccines are considered safer, the adoption of these vaccines may necessitate earlier booster vaccination and repeated boosting strategies to achieve necessary 'herd effects' to control the spread of pertussis.

3.3 Introduction

Pertussis, a highly contagious upper respiratory infection caused by *Bordetella pertussis*, is a poorly controlled vaccine-preventable disease in Canada, despite relatively high vaccine coverage rates.^{1,2} Disease incidence is highest in infants, with mortality rates greatest in infants younger than 3 months;³ however, the burden of disease among adolescents and adults has recently increased considerably.³ While this increase has been attributed to a multitude of factors including aging of under-vaccinated cohorts⁴ and more sensitive laboratory testing methods,⁵ recent reports have suggested that waning immunity of vaccinated individuals may also contribute to the resurgence of pertussis.⁶⁻¹⁰

Vaccination against pertussis was introduced in Canada in 1943,¹ and was associated with a marked decline in the incidence of pertussis.³ However, small outbreaks of pertussis continued to persist with predictable seasonality.⁴ In 1997/98, an acellular preparation of pertussis vaccine (DTaP) was introduced in Canada. This combination vaccine was associated with fewer side effects and had a better safety profile than the previously used whole cell vaccine (DTwP).^{11,12} There are currently two types of acellular preparations licensed for use in Canada. The children's preparation, DTaP, contains high concentrations of antigens for diphtheria, tetanus, and acellular pertussis while the adolescent/adult formulation, Tdap, contains high concentrations of antigens for tetanus, but lower concentrations of antigens for diphtheria and acellular pertussis.¹ Recommendations in Canada call for DTaP immunizations at 2 months, 4 months, 6 months, and between 12-23 months of age. A childhood booster vaccine (of either DTaP or Tdap) is recommended between ages 4 and 6.^{1,13} Additional boosters for adolescents and adults are recommended between ages 14 to 16 and once again as an adult.^{1,14} While a similar five dose DTaP vaccine series is used in Canada and the United States, globally there are a wide variety of DTaP vaccination schedules that are recommended. In many European countries, a three dose DTaP vaccine series is offered, often in conjunction with a booster vaccine for school-age children aged 4-9.¹⁵ The three dose schedule typically recommends vaccination at 2, 3, 4 months, 2, 4, 6 months, or 3, 5, and 11 months of age.¹⁵ However, despite widespread implementation of these different immunization programs and associated levels of uptake, pertussis persists.

A previous review by Wendelboe and colleagues summarized several studies relating to the duration of protective immunity conferred by natural infection with pertussis, with DTwP, and with DTaP.¹⁶ However, this study was published in 2005, well before the existence of much of the current literature. In addition, the review did not include a meta-analysis of the key results. Thus, we believe there is a critical need for a systematic literature review and meta-analysis to evaluate the weight of evidence about waning pertussis immunity from available studies, and to synthesize this evidence.

Understanding waning immunity and its impact on the disease burden of pertussis in different age groups is critical to designing vaccination programs to control the spread of pertussis in the community. While ethical issues surround the feasibility of a randomized controlled trial to evaluate vaccine-induced waning immunity, decisions still need to be made on optimal vaccine strategies, and systematic review and meta-analysis provides a mechanism whereby such decisions can be informed by the best available data. Our objectives were to 1) synthesize the current literature surrounding waning immunity to pertussis after vaccination with three and five childhood doses of DTaP, and 2) estimate the duration of protective immunity to pertussis following three and five doses of DTaP using meta-analytic techniques.

3.4 Methods

3.4.1 Search Criteria

A literature search was conducted using both Medline and Embase databases. In consultation with a research librarian at the University of Toronto, the search strategy consisted of key words and medical subject headings. Similar terms and synonyms were combined with an "OR" operator, and these distinct components were linked together with an "AND" operator. Search terms included, "whooping cough", "pertussis", "diphtheria-tetanus-acellular pertussis vaccine", "time-factors", "follow-up studies", "drug efficacy", "outcome assessment", and "treatment duration". The search strategies were carried out without limits on October 10th, 2013. The unique search strategies for each database can be found in **Table 3.1**. To ensure completeness, the reference lists of

the included studies were searched to identify any studies that had not been captured by the original literature search.

	Ta	ab	le	3	.1	. Sear	ch	strateg	ies	used	in	the	two	diff	erent	data	abase	es.
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Database	Search Terms
Medline	"exp Whooping Cough/ep, im, pc [Epidemiology, Immunology, Prevention & Control]"
	AND "exp Child/ OR exp Adolescent/" AND "exp Follow-Up Studies/ OR exp Time
	Factors/ OR exp Immunization Schedule/" AND "exp Diphtheria-Tetanus-Pertussis
	Vaccine/ad, im, st [Administration & dosage, Immunology, Standards] OR exp
	Diphtheria-Tetanus-acellular Pertussis Vaccines/ad, im, st [Administration & Dosage,
	Immunology, Standards] OR exp Pertussis Vaccine/ad, im [Administration& Dosage]"
Embase	"exp pertussis/dt, ep, pc [Drug Therapy, Epidemiology, Prevention]" AND "exp
	diphtheria pertussis tetanus vaccine/dt [Drug Therapy] OR exp pertussis vaccine/dt [Drug
	Therapy" AND "exp drug efficacy/ OR exp follow up/ OR exp risk assessment/ or exp
	outcome assessment/ or exp treatment duration/" AND "child/ OR adolescent"

3.4.2 Study Selection

Relevancy Screen: Ashleigh McGirr (AM) and David Fisman (DF) reviewed the titles and abstracts of the retrieved articles to assess for relevancy. All primary research articles, not including modeling studies, that assessed a measure of long-term immunity (>18 months of follow-up) were included. Studies where pertussis immunity was not an outcome, studies about DTP or DTwP, studies about strategies to improve vaccine uptake, and studies about adverse events following vaccination were excluded at this stage. Abstracts published in languages other than English were translated using Google Translate to assess relevancy.¹⁷ Agreement between the two reviewers was assessed using the kappa statistic, and where discrepancies on the study inclusion criteria existed, they were resolved by discussion and consensus.

Full-Text Review: The full-texts of the studies screened for inclusion were read by AM and included in the review if they met the pre-defined full-text inclusion criteria. Specifically, studies that utilized either three or five childhood doses of DTaP and that included a measure of time since vaccination were included. To ensure completeness of the literature search, the references of the included studies were scanned and relevant articles were included in the systematic review.

3.4.3 Quality Assessment

A modified version of the Downs and Black critical appraisal tool for randomized and non-randomized studies was used to evaluate the quality of the included studies.¹⁸ This validated and widely used instrument contains 27 questions pertaining to reporting, external validity, internal validity (bias and confounding), and power.^{18,19} Each question was scored as a 0 or 1, except for one question (reporting of confounders) that was scored from 0 to 2. For the purpose of this study, the instrument was modified by removing the question about power as the different study designs each have their own sample size requirement (**Section 6.2.1**). AM analyzed the quality of the included studies. Study quality categories were assigned based on the following modified Downs and Black scores: excellent (25-27), good (19-24), fair (14-18), and poor (\leq 13).

3.4.4 Data Abstraction

Data from the relevant articles was abstracted in order to calculate odds ratios and standard errors comparing the odds of pertussis for each year since the last dose of DTaP, where available. One year after the last dose of DTaP was chosen as the referent since the majority of articles presented the results this way. When available, measures of association and standard errors were taken directly from the articles, and where tabular data existed, measures of association and corresponding standard errors were calculated manually. In one case, the referent data was obtained from a previously published article from the same research study.²⁰ When the odds ratios were presented using a continuous predictor of time since last dose of DTaP, the logistic model was extrapolated to calculate odds ratios and standard errors for each year. Risk ratios for the serological studies were calculated by comparing the risk of vaccine failure at the given time period compared to the risk of vaccine failure 1 year post-vaccine administration (assumed to be 18.8% for the five dose series and 17.7% for the three dose series, as per previous studies of the same cohorts of subjects^{21,22}). Risk ratios and incident rate ratios were assumed to approximate odds ratios according to the rare disease assumption.²³ These odds ratios and corresponding standard errors were entered manually into a spreadsheet for analysis.

3.4.5 Statistical Analysis

All data analysis and statistical modeling was performed using the *metafor* package in R Statistical Software.^{24,25} Publication bias was assessed using Funnel plots with asymmetry between the measures of association and standard errors quantified using Egger's test.²⁶ Random effects models using the DerSimonian-Laird estimator were used to pool the results between the included studies once the heterogeneity, as assessed using Higgins' I² statistic, among the effect estimates was considered.^{27,28} A meta-regression model using the DerSimonian-Laird estimator was fit to the data to evaluate the relationship between the odds ratio of pertussis and time since last DTaP vaccination.²⁷ To evaluate the importance of the number of doses and the type of pertussis 'diagnosis' (ie. clinical vs. serological), we included these variables in the meta-regression model and evaluated the change in the estimate of the main effect. Using a point estimate of 85% from a Cochrane review of vaccine efficacy estimates, with a range between 80 and 90% of vaccine efficacy estimates from the US and Canada, we were able to anchor the probability of vaccine failure for the first year since DTaP series completion (either 3 or 5 doses).^{1,29,30} We assumed that the probability of vaccine failure followed an exponential distribution, where the probability of immunity at some time t was $P(I)_t = VE(exp(-\lambda t))$, with VE being the efficacy of vaccination during the initial period following series completion, and λ representing the rate of vaccine failure. Under this scheme, the mean duration of immunity among those who initially respond to the vaccine is $1/\lambda$. With the rare disease assumption, the predicted odds ratios from the meta-regression were assumed to approximate risk ratios, allowing for the creation of functions of probability of vaccine failure through time.

3.5 Results

3.5.1 Included Studies in Review

Of the 389 potentially relevant articles identified through the literature search, $33^{9,10,31-61}$ underwent full text review. Agreement between the independent reviewers with respect to the title/abstract scan was fair (κ =0.61). Six^{9,10,47,59-61} of these studies fit the five-dose eligibility criterion to be included in this review and six^{38,39,41,44,51,55} met the

three-dose criterion (**Figure 3.1**). None of the articles published in languages other than English met inclusion criteria. No additional articles were identified through hand-searches of reference lists.

Of the included studies, two were case-control studies,^{10,47} two were cohort studies,^{9,59} three were follow-up studies from previously performed randomized controlled trials,^{44,55,61} two were surveillance studies,^{41,51} two were serum antibody studies,^{38,39} and one was a double blind crossover study⁶⁰ (**Table 3.2**). Despite searching without limits on publication dates, the included studies with five doses of DTaP were all published between 2010 and 2013 and the included studies with three doses of DTaP were all published between 2001 and 2006. The majority of the five dose included studies were performed in the United States (California,^{10,47,59} Minnesota,⁹ and Oregon⁹) with the remaining five dose studies performed in cities across Germany.^{60,61} Almost all of the three dose studies were performed in Europe (Italy^{38,39,55} and Sweden^{41,51}), although one study was conducted in Senegal.⁴⁴

The studies included in the analysis differed in terms of defining loss of immunity. The clinical studies compared the incidence of pertussis for every year since the vaccine was administered, using various case definitions of pertussis. Two of the studies used polymerase chain reaction (PCR) laboratory methods only,^{10,59} two of the studies used culture or PCR methods regardless of symptoms,^{41,51} one used a cough lasting >20 days with bacteriologic or serologic confirmation or link to documented case,⁴⁴ and one used laboratory confirmed pertussis infection and spasmodic cough lasting \geq 14 days or cough lasting \geq 21 days.⁵⁵ The remaining two studies used the Council of State and Territorial Epidemiologists confirmed case definition⁹ and confirmed/probable case definition in conjunction with the suspected case definition from the California Department of Public Health.⁴⁷

The serological studies compared the number of individuals who had levels of immunological markers above a certain threshold for every year since the vaccine was administered. Two of the studies explicitly defined seropositivity as anti-PT (\geq 5 EL

U/mL),^{60,61} while two defined seropositivity as positivity using an enzyme-linked immunosorbent assay (ELISA) without clear description of cut-off.^{38,39} These varying clinical and serological case definitions of pertussis likely contributed to the observed heterogeneity between the studies (**Table 3.2**).



Figure 3.1. Flow chart of studies included in the review and meta-analysis.

Table 3.2. The characteristics of the included studies.

Study	Location	Study Design	Data Source(s)	Study Period	Study Population	Vaccine Schedule	Loss of Immunity "Case Definition"	Control Selection	Statistical Technique	Covariates
Tartof et al. 2013	Minnesota/Oregon, USA	Cohort	National Notifiable Diseases Surveillance System and Immunization Information Systems	2000 - 2010	Children born between 1998 and 2003 with 5 recorded doses of DTaP with last between ages 4-6	2, 4, 6, and 15-18 months, 4-6 years	Confirmed cases as Council of State and Territorial Epidemiologists	Age specific populations of Minnesota and Oregon	Log binomial model of calculated incidence rates	Examined age at receipt of fifth dose but found no difference
Klein et al. 2012	Northern California, USA	Case-Control	Kaiser Permanente Northern California Databases	Jan. 2006 – Jun. 2011	Kaiser Permanente Northern California members born after 1999 without Tdap or any pertussis vaccine between 5th dose and PCR test date	2, 4, 6, and 15-18 months, 4-6 years	PCR Positive for Pertussis and PCR negative for parapertussis	PCR negative for pertussis and PCR negative for parapertussis	Conditional Logistic Regression (conditioned on calendar time)	Age (4 to <7, 7 to <10, and 10 to 12), sex, medical clinic, race/ ethnicity
Misegades et al. 2012	California, USA	Case-Control	Reports to local health departments and medical records	Jan. 2010 – Dec. 2010	Children aged 4 to 10 from 15 California Counties (Alameda, Del Norte, El Dorado, Fresno, Madera, Marin, Merced, Orange, Riverside, San Diego, San Luis Obispo, Santa Clara, Santa Cruz, Sonoma, and Stanislaus)	2, 4, 6, and 15-18 months, 4-6 years	Probable and confirmed cases as defined by Council of State and Territorial Epidemiologists, suspected cases as defined by the California Department of Public Health	3 controls per case, selected through reporting clinicians	Logistic Regression accounting for clustering by county and physician	Sex, age at enrollment, and age at fifth dose were assessed as potential confounders, but none found to be
Witt <i>et al.</i> 2012	Marin County, California, USA	Retrospective Cohort	Kaiser Permanente electronic medical records	Mar. 2010 – Oct. 2010	Children and adolescent members of Kaiser Permanente Medical Center in San Rafael, California	2, 4, 6, and 15-18 months, 4-6 years of age	PCR Positive for Pertussis	Kaiser Permanente Medical Center population as a whole	Stratification (Vaccine Effectiveness via Screening Method)	None
Zinke <i>et al.</i> 2010	Germany	Serologic Follow-Up Study of RCT	According to Protocol (ATP) Cohort from earlier RCT, Study B (Zinke <i>et al.</i> 2009)	Jul. 2006 – Dec. 2006	Healthy German children between 7 and 9 years of age who had been immunized with DTPa-HBV-IPV- Hib vaccine in previous RCT	3, 4, 5, and 12-18 months of age, 4-6 years of age	Anti-PT≥5 EL U/mL	NA	Seropositivity rates	None

Table 3.2. The characteristics of the included studies.

Study	Location	Study Design	Data Source(s)	Study Period	Study Population	Vaccine Schedule	Loss of Immunity "Case Definition"	Control Selection	Statistical Technique	Covariates
Zepp <i>et al.</i> 2007	Germany	Double Blind Cross-over Study	According to Protocol (ATP) Cohort from earlier RCT (Knuf <i>et al.</i> 2006)	Not Specified	German adolescents who were enrolled and complied with the protocol of a previous RCT who had available immunogenicity data	3, 4, 5, and 12-18 months of age, 4-6 years of age	Anti-PT ≥5 EL U/mL	Crossover design	Seropositivity rates	None
Gustafsson et al. 2006	Sweden (except Gothenburg and area)	Surveillance Study	Swedish Institute for Infectious Disease Control, Statistics Sweden, clinical chart review	Oct. 1997 – Sept. 2004	Swedish children	3, 5, and 12 months of age	Culture or PCR confirmed pertussis, regardless of symptoms	NA	Incidence Rates	None
Lacombe et al. 2004	Niakhar, Senegal	Follow-up of Previous RCT	Patients previously enrolled in RCT (Simondon <i>et al.</i> 1997)	Patients Enrolled 1990-1995	Newborn infants enrolled in original RCT	2, 4, and 6 months of age	Cough lasting >20 days with bacteriologic or serologic confirmation or link to documented case	NA	Logistic regression	Intensity of exposure, birth-rank, height-for-age index at 7 months
Olin <i>et al.</i> 2003	Sweden (except Gothenburg and area)	Surveillance Study	Swedish Institute for Infectious Disease Control, Statistics Sweden, clinical chart review	Oct. 1997 – Sept. 2000	Swedish children born between January 1996 and September 2000	3, 5, and 12 months of age	Culture or PCR confirmed pertussis, regardless of symptoms	NA	Incidence Rates	None
Esposito et al. 2002	Italy	Serum antibody study	Patients enrolled in clinic at University of Bologna	Dec. 1999	Healthy Italian children 5 and 6 years old who were born premature and given 3 doses of DTaP as an infant	3, 5, and 11 months of age	Positive ELISA (EU/mL) for anti- PT, cutoff value not specified	NA	Seropositivity rates	None
Salmaso et al. 2001	Piemonte, Veneto, Friuli-Venezia Giulia, and Puglia Italy	Follow-up of Previous RCT	Patients remaining under surveillance at stage 3 of RCT (Greco <i>et al.</i> 1996)	Oct. 1995 – Oct. 1998	Newborn infants enrolled in original RCT	2, 4, and 6 months of age	Laboratory confirmed pertussis infection and spasmodic cough lasting \geq 14 days or cough lasting \geq 21 days	NA	Vaccine Efficacy using person-time incidence density	None

Table 3.2. The characteristics of the included studies.

Study	Location	Study Design	Data Source(s)	Study Period	Study Population	Vaccine Schedule	Loss of Immunity "Case Definition"	Control Selection	Statistical Technique	Covariates
Esposito et al. 2001	Italy	Serum antibody study	Patients enrolled in clinics at the University of Palermo and the University of Bologna	Dec. 1999 – Jan. 2000	Healthy Italian children 5 and 6 years old either given 3 doses of DTaP as an infant or had clinical pertussis as an infant	3, 5, and 11 months of age	Positive ELISA (EU/mL) for anti- PT, cutoff value not specified	NA	Seropositivity rates	None

* Knuf et al. 2006⁶², Zinke et al. 2009⁶³, Greco et al. 1996⁶⁴, Simondon et al. 1997⁶⁵

3.5.2 Quality Assessment

The included studies had a diverse range of quality. Two studies were assessed as 'good' quality,^{10,44} 9 studies were assessed as 'fair' quality,^{9,38,39,41,47,51,55,59,60} and one study was assessed as 'poor' quality⁶¹ (**Table 3.3**). Of the four categories assessed with the modified Downs and Black rating scale, reporting showed the biggest variability of scores. Most commonly, studies scored poorly because of undefined study aims, vague or no description of the study participant characteristics, and no mention of participants lost to follow-up.

3.5.3 Included Studies in Meta-Analysis

One study (Witt *et al.*) was excluded from the meta-analysis because of contamination of the measure of association.⁵⁹ The study participants were classified as being up to date for age of immunization according the US Centers for Disease Control and Prevention (CDC) Guidelines, but were grouped into age categories of 2-7 years of age, 8-12 years of age, and 13-18 years of age. Since the CDC recommends a booster immunization at 10-12 years of age, some of the participants in the 8-12 age category and most of the participants in the 13-18 age category would have had the adolescent booster vaccine already. The authors highlighted this as a potential reason for the lower attack rates of pertussis in the older age groups. To ensure comparability of the estimates, the results from this study were removed from the meta-analysis.

The study by Klein *et al.* contained two control groups (PCR-negative controls and matched controls) and used them to calculate two different odds ratios for pertussis.¹⁰ Because the two control groups were compared to the same case group, we used only the estimates for the PCR-negative controls because the authors believed this measure contained the least amount of bias. The study by Tartof *et al.* contained two distinct study populations (Minnesota and Oregon) with separate measures of association.⁹ Similarly, the study by Salmaso *et al.* contained two study populations: one which was vaccinated with a DTaP vaccine made by SmithKline Beecham and the other which was vaccinated with a DTaP vaccine made by Chiron-Biocine.⁵⁵ As such, we included both sets of results from each of these studies in the analysis, for a total of 13 distinct estimates. All data included in the meta-analysis can be found in **Section 6.2.2**.

Table 3.3. Quality assessment of the included studies.

Downs and Black Criteria	Possible Points	Esposito <i>et al.</i> 2001	Esposito et al. 2002	Gustafsson et al.	Klein <i>et al.</i>	Lacombe et al.	Misegades et al.	Olin <i>et al.</i>	Salmaso <i>et</i> <i>al.</i>	Tartof <i>et</i> <i>al</i> .	Witt <i>et al.</i>	Zepp et al.	Zinke <i>et</i> al.
Reporting	11	8	7	6	10	10	9	5	7	6	4	4	7
External Validity	3	1	1	3	2	2	1	3	1	1	3	1	1
Internal Validity - Bias	7	6	5	4	5	4	4	3	4	5	5	5	3
Internal Validity - Confounding	6	3	3	3	4	5	3	3	3	4	3	4	2
Total	27	18	16	16	21	21	17	14	15	16	15	14	13
Quality Rating		Fair	Fair	Fair	Good	Good	Fair	Fair	Fair	Fair	Fair	Fair	Poor

3.5.4 Meta-Analysis Results

Publication Bias: There was no evidence of publication bias for any of the years since the last DTaP vaccine, with all funnel plots demonstrating symmetry between the measure of association and the standard error according to Egger's test (**Figure 3.2**).



Figure 3.2. Funnel plots and p-values from Egger's test evaluating the risk of publication bias for the odds ratios of pertussis for years 2-6 after the last dose of DTaP.

Pooled Effects: Summary measures of association along with the observed Higgin's I^2 measure of heterogeneity for every year since the last dose of DTaP are shown in **Figure 3.3**. The pooled odds ratios of pertussis were found to increase with the time since the last dose of DTaP, suggesting considerable waning immunity. Between-study heterogeneity was also found to increase for every year since the last dose of DTaP, with year 2 showing moderate heterogeneity and years 3 to 6 demonstrating substantial heterogeneity (**Figure 3.4**). This increasing heterogeneity in effect estimates as the time since last DTaP vaccine increases is likely due to a compounding effect of the heterogeneity in the study designs.

12=40.70%

12=77.16%



Figure 3.3. Forest plots demonstrating the pooled odds ratio of pertussis for years 2-6 versus year 1 after the last dose of DTaP. Pooled odds ratio calculated using random effects models with the DerSimonian-Laird estimator. I2=Higgins' I^2 measure of heterogeneity.



Figure 3.4. The relationship between heterogeneity between studies (as measured with Higgins' I^2) and time since last DTaP. Higgins' I^2 is a measure of the total variation between studies that is due to heterogeneity.²⁸

Meta-Regression: The results from the final meta-regression model suggest the odds of pertussis for every year since the last dose of DTaP was estimated to increase by a multiple of 1.33 (95% CI: 1.23 - 1.43) (**Table 3.4, Figure 3.5**). As the odds ratio associated with the years since last DTaP variable did not change appreciably when the number of doses variable was included, there is evidence to suggest that the duration of protective immunity from DTaP is the same for those given 3 or 5 doses of the vaccine (**Table 3.4**). Similarly, when the definition of loss of immunity variable was included, the odds ratio again did not change appreciably, suggesting that the duration of protective immunity from DTaP is the same for the studies measuring clinical markers of pertussis and those measuring serological markers (**Table 3.4**). However, the addition of these variables changes the absolute risk of pertussis, with a higher risk of pertussis in the studies examining the 5 dose vaccine series and a lower risk of pertussis in the studies using serological outcomes (**Table 3.4**).

Table 3.4. Beta coefficients and corresponding standard errors (in parentheses) for the 3 different meta-regression models. Beta coefficients represent the log of the odds ratio for every unit increase in the predictor variable.

	Intercept	Years Since Last DTaP	5 Doses	Serological Study
	0.321	0.289		
Model 1	(0.14)	(0.06)		
	-0.053	0.26	0.719	
Model 2	(0.14)	(0.05)	(0.14)	
	-0.003		0.695	-0.728
Model 3	(0.11)	0.2862 (0.04)	(0.11)	(0.16)



Figure 3.5. The odds ratio of pertussis for each year since the last dose of DTaP. The circles, inversely weighted by study variability, represent the odds ratios calculated from each of the studies examining 5 doses of DTaP while the inverted triangles represent the odds ratios from the studies examining 3 doses of DTaP included in the meta-analysis. The black line represents the fitted meta-regression curve accounting for the effects of time. In this meta-regression curve, dose type was assumed to be constant at 5 doses and the diagnosis type was assumed to be constant at "clinical".

Using the above estimated odds ratio of 1.33, we created curves of the predicted probability of vaccine failure through time (**Figure 3.6**). From this analysis, the average duration of vaccine protection from DTaP is approximately 3 years, assuming 85% initial vaccine efficacy. With this loss of protection, we predict that vaccinated children would only have 10% protection against pertussis 8.5 years after the last DTaP dose, but this could be higher or lower with alternate assumptions regarding vaccine efficacy.



Figure 3.6. Estimated probability of vaccine failure for different levels of vaccine efficacy.

3.6 Discussion

Understanding the duration of protective immunity conferred by a vaccine is critical to the development of immunization guidelines and programs. To our knowledge, this is the first systematic review and meta-analysis of the duration of protective immunity to pertussis following routine childhood immunization with DTaP. Our findings suggest that the odds of pertussis increase by 1.33 times (95%CI: 1.23 - 1.43) for every additional year since the last dose of DTaP. With this loss of protection, we predict that VE would only be 10% for children

vaccinated with DTaP 8.5 years after the last dose, assuming an initial vaccine efficacy of 85%.^{1,30}

While we found that the odds of pertussis for every year since the last dose of DTaP did not depend on the number of doses, we did find that there was a greater absolute risk of pertussis in the studies examining 5 doses of DTaP and a lower absolute risk of pertussis in the serologic studies. As the participants in the five dose studies were older on average than the participants in the three dose studies, this may highlight the increased risk of pertussis in older age groups. While infants under the age of 1 remain at highest risk for pertussis, recent surveillance reports from the US and Canada indicate that age groups with the next highest incidence of pertussis include the 7-10 year olds (US) and 10-14 year olds (Canada).^{66,67} The lower absolute risk of pertussis in the studies examining serologic outcomes may be due to the sensitivity of these testing methodologies and their corresponding anti-PT cutoff levels.

It is important to highlight the limitations of studies included in this review. Most studies were observational in nature^{9,10,38,39,41,47,51,59} allowing for biases and confounding to distort measures of association. While three studies adjusted for potential confounders of interest (age, sex, race/ethnicity, age at fifth dose of DTaP, medical clinic (**Table 3.2**)) ^{9,10,47} others did not, which may have contributed to over- or under-estimates of the duration of protective immunity. Case-ascertainment bias could have affected individual study results: where nasopharyngeal swabs were necessary for confirmation of the case-definition of pertussis,^{9,10,41,44,47,51,59} physicians may have been more likely to test sicker or more medically complex patients due to the invasive nature of the procedure, which could alter estimates of effect. One of the studies specifically addressed this concern and implemented standardized procedures for collecting nasopharyngeal swabs for ongoing coughs, regardless of other clinical characteristics.⁵⁵ Serological follow-up studies^{38,39,60,61} would not be affected by this type of case-ascertainment bias but all serological follow-up studies^{38,39,60,61} were funded by vaccine companies producing DTaP, potentially inducing biases of another nature.

As with all systematic reviews, this study had a number of limitations. Primarily, the follow-up periods for the studies included in the meta-analysis ranged from 2 to 6 years, limiting
estimates to this relatively brief period. We extrapolated meta-regression results as longerduration studies were not identified. While we believe this was a necessary assumption, it nonetheless presents a limitation in the interpretation of the results. In addition, we found considerable between-study heterogeneity, possibly an artifact of varying case definitions, study designs, and study populations. Thirdly, the three- and five-dose series each included different dosing schedules (**Table 3.2**), which may have added to the observed heterogeneity. Lastly, by constraining the literature search to published research articles only, we did not search the grey literature so have not included results from governmental reports, dissertations, or other unpublished documents.

However, this systematic review and meta-analysis is the first of its kind to synthesize the information and provide a credible estimate on the duration of vaccine-induced immunity to pertussis. The review methods were robust and captured a wide range of studies in multiple languages and countries of publication. Although translation using Google Translate is imperfect, it allowed us to determine citation relevance for non-English studies, thereby reducing the potential for publication bias.²⁶ By searching multiple databases and the references of included studies, we are confident that the search captured all relevant published studies, and we found no evidence for publication bias using Egger's test and analysis of the funnel plots (**Figure 3.2**).

The results from this meta-analysis have important policy implications, mainly surrounding boosting strategies for adolescents to ensure 'herd effects' of pertussis are maintained. While an adolescent Tdap booster is offered in Canada, it is recommended for teenagers aged 14-16¹ which may be too late and leave those aged 10-14 susceptible to pertussis. The adolescent Tdap booster is recommended for youth between 10 and 12 years of age in the United States and many European countries,^{15,68} which may represent more appropriate timing.

In addition, the results from this analysis have implications for repeated pertussis vaccinations in adults. Previous research has highlighted the importance of repeat Tdap immunization for each pregnancy.⁶⁹ It has also been suggested that a decennial booster strategy with Tdap may be an effective and cost-effective way to control the spread of pertussis among

adults.⁷⁰⁻⁷² While the risk of pertussis infection may be lower in adults, assuming waning immunity to Tdap is similar to waning immunity to DTaP, repeated booster vaccines will be necessary to maintain a population with high levels of vaccine coverage for pertussis.

Our findings will also provide epidemiologists, mathematical modelers, and health economists with credible data inputs for modeling studies. The weight of the evidence suggests that the average duration of protective immunity to pertussis after the fifth dose of DTaP is approximately three to four years, a key parameter in many studies evaluating vaccination strategies and their economic impact. However, this estimate of the probability of vaccine failure is sensitive to the initial vaccine efficacy. The parameterization of the function can be modified to generate predictive values of duration of protection for different levels of vaccine efficacy.

In summary, we performed a systematic literature review to understand the relationship between risk of pertussis and time since pertussis vaccination. We found evidence of waning immunity and estimated the average duration of vaccine protection from DTaP is approximately 3 years, assuming 85% initial vaccine efficacy. With this loss of protection, we predict that children vaccinated with DTaP would only have 10% protection against pertussis 8.5 years after the last dose. With a pre-school booster offered for children age 4-6, our findings suggest that very few children over age 10 would be protected against pertussis, signaling the need for an earlier adolescent Tdap booster in Canada.

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4 Chapter Four: The Health and Economic Burden of Pertussis in Canada: A Microsimulation Study

4.1 Reader's Note

Here I present evidence of the sizeable health and economic impact of pertussis persistence in Ontario and Canada. Through microsimulation modeling, I estimate the age-specific life years lost, QALYs lost, and costs associated with pertussis and use these to evaluate the economic impact of pertussis as well as the net monetary impact.

4.2 Abstract

Background: This study estimates age-specific life years (LYs) lost, quality-adjusted life years (QALYs) lost, and costs associated with pertussis to evaluate the health and economic burden of pertussis in Canada and it's most populated province, Ontario.

Methods: A microsimulation model was designed to simulate disease progression through a pertussis natural history model and outcomes were compared to those from a model with no pertussis health states. Daily probabilities of pertussis complications, hospitalizations, and disease sequelae as well as utilities and costs for the health states were derived from the literature. A healthcare payer perspective was used with a lifetime time horizon. LYs lost, QALYs lost, and costs were discounted at 5% per annum. Probabilistic sensitivity analysis with 100,000 model realizations per age group was used to generate distributions for the estimates. Economic burden was assessed by multiplying average case cost estimates by annual age-specific incidence. Using 1-3 times gross domestic product (GDP) per capita for a willingness to pay range, we quantified the QALY loss to assess the net monetary impact of pertussis.

Results: Pertussis associated LYs lost per case declined with age (0.051 LYs lost for infants and 0.007 LYs lost for adults). Infants showed the greatest mean QALY loss per case (0.123 QALYs). QALY loss was smallest in seniors (0.018 QALYs). Age-specific costs generally declined with age with infants having a mean (sd) cost per case of \$8,946 (\$25,886) and seniors costing \$2,479 (\$10,087). Based on current age-specific incidence, pertussis costs the Ontario healthcare system approximately \$5.0 - \$16.9M annually and costs the Canadian healthcare system approximately \$20.4M-\$66.4M annually. When QALYs were included at 1xGDP (3xGDP) per capita, the net monetary impact of pertussis in Ontario was estimated at \$11.0M - \$38.6M annually (\$22.8M - \$82.0M). For all of Canada, these values were assessed at \$46.5M - \$158.6M (\$98.6M - \$342.8M) annually.

Interpretation: The health and economic consequences of pertussis persistence in Canada are substantial and highlight the need for either improved strategies for the use of existing vaccines or development of new vaccines.

4.3 Introduction

Despite a robust immunization program in Canada, pertussis, commonly called whooping cough, persists in Canada. In the pertussis outbreak year of 2012, the national incidence of pertussis was approximately 13.08 per 100,000 population; but even in non-outbreak years incidence is non-negligible (e.g. 3.63 per 100,000 in 2013).¹ However, while disease burden of reported pertussis is quite well characterized, the full health and economic impact of pertussis and its sequelae have not been examined in the Canadian context.

Classic symptoms of pertussis include a violent cough which is often accompanied by an inspiratory whooping noise and/or vomiting,² although there is a range of clinical severity. Infants and children tend to have more severe disease than adolescents and adults, and the mortality is highest in infants.³ Complications can include pneumonia, seizures, hernias, failure to thrive, sinusitis, otitis media, weight loss, rib fracture, fainting, and urinary incontinence.^{3,4} In rare instances, encephalopathy or death can occur.³

Understanding the health and economic burden of pertussis helps identify key public health priorities, allocate necessary resources, and inform health policy. It forms the basis of cost-effectiveness analysis of interventions and strategies that may prevent pertussis. While there have been previous cost-effectiveness studies of different pertussis immunization programs or outbreak response programs in Canada,⁵⁻⁹ these studies have not calculated an estimate of the total costs associated with having pertussis. They all rely on the Ontario Case Costing Initiative which can be used to estimate the costs associated with pertussis in Ontario; however, this unique data source evaluates the direct short-term hospitalization and ambulatory care costs.¹⁰ It does not take into consideration the costs from cases seen by a family physician or a walk-in clinic and does not include costs associated with follow-up visits, or long term sequelae of disease, which are particularly important for pertussis given the broad spectrum of clinical illness and potential complications. Outside Canada, other studies have estimated costs of pertussis,¹¹⁻¹³ but again tend to focus on one component of the disease (e.g. only clearly defined clinical cases or only hospitalized cases) and do not incorporate the full range of outcomes, long-term sequelae, or treatment options.

As adolescents and adults tend to have less severe and non-specific symptoms of pertussis,^{14,15} their infection tends not to be diagnosed as easily, leading to under-identification and under-detection in these age groups.¹⁶ Compounding this issue is the fact that complications and disease sequelae for infants and young children are considerably different from the complications among adults and adolescents. With more severe disease, infants and young children are more likely to be hospitalized with pertussis,^{4,17} have more severe complications,^{3,4} and have a higher mortality rate than adolescents and adults.^{3,18} The Ontario Burden of Infectious Disease Study estimated the overall health burden of pertussis in Ontario implicitly incorporating age effects, but did not explicitly report the impact within age groups. In order to accurately describe the health impact and costs associated with pertussis, analysis must be conducted across different age groups.

To address these gaps, we estimated the age-specific life years lost (LYs), quality-adjusted life years (QALYs) lost, and costs associated with pertussis cases in Ontario. We aim to characterize the economic burden on the healthcare system for both Ontario and Canada using these estimates and the most recently available incidence data.^{1,19,20}

4.4 Methods

4.4.1 Model Overview

We designed a microsimulation model in TreeAge Pro²¹ to reflect the natural history of pertussis and its sequelae. The disease model is comprised of the pertussis health states (susceptible, prodromal, catarrhal, paroxysmal, convalescent, and recovered) with additional states for pertussis-related complications, hospitalizations, and death (**Figure 4.1**). Complications of interest included both age-specific inpatient and outpatient complications derived from observational studies of pertussis patients in Canada.^{3,4} These complications included pulmonary complications (pneumonia, atelectasis, and pneumothorax), neurological complications (seizures, encephalopathy, and long term sequelae), hernias, sinusitis, otitis media, rib fracture, fainting, urinary incontinence, and weight loss. The counterfactual model represents the scenario which may occur if individuals do not contract pertussis so it consists of susceptible and dead states only. Because of the age-specific distribution of pertussis manifestations and

complications, we examined 5 distinct age groups: infants (<6 months of age), children (6 months to 4 years of age), youth (5-17 years of age), adults (18-64 years of age), and seniors (65+ years of age).



Figure 4.1. The schematic of the microsimulation model used. Health states shaded in grey are present in both the pertussis and counterfactual models. Solid arrows represent pertussis related transitions while the dashed arrows represent the underlying mortality rate in the population.

4.4.2 Model Analysis

We used a lifetime time horizon with a time step of one day to account for the relatively short duration of pertussis illness and the relatively long duration of pertussis complications. Outcomes of interest included age-specific per patient LYs lost, QALYs lost, and costs. All health outcomes and costs were discounted at 5% per annum. Probabilistic sensitivity analyses over 100,000 model realizations were performed for each age group to generate the distribution of outcomes.

4.4.3 Health State Transitions

Transitions between health states were based upon both length of stay "rules" and daily probabilities. We used tracker variables to evaluate the length of stay in the different compartments. Every time-step, the length of stay was compared to the expected length of stay in that compartment, and if it was longer, a transition to the next state was initiated. In addition, a daily probability of a complication or death could signal a transition from one health state to the next. The transition probabilities and the duration of stay for the different health states can be found in **Table 4.1, Table 4.2, and Table 4.3**.

We obtained expected length of stay values from the literature and expert opinion, where necessary. In terms of pertussis natural history health states, duration of stay reflected routinely described length of pertussis illness phases.^{2,15,22} For outpatient pertussis-related complications, the length of each complication was based on expert opinion and literature where available. The Ontario Case Costing Initiative was used to estimate the duration of hospitalization for inpatient complications and duration of hospitalization from uncomplicated pertussis was obtained from the two observational studies described below.^{3,4,10}

We estimated the age-specific probabilities for different pertussis-related complications primarily from two observational studies. The first study examined the epidemiology of hospitalized children in pediatric tertiary care centers from across Canada³ and the second study examined the morbidity of adolescents and adults during a pertussis outbreak in Quebec.⁴ Probabilities of hospitalization and pertussis-related death were also derived from the literature (**Table 4.3**). The model also incorporated competing mortality from Canadian life tables.²³ All probabilities were converted to daily probabilities in the model due to the daily time steps.

Clinical Name	Symptoms	Duration, Mean	Utility Values, Mean (SD)	Cost, Mean (SD)	
0		214	L 0 0 04 (0 074) ²⁴		
Susceptible	• NA	NA	1: β =0.94 (0.074) ^{a24} C: β =0.94 (0.074) ^{a24}	NA	
			Y: $\beta = 0.94 (0.074)^{24}$		
			A: $\beta=0.93 (0.08)^{24}$ S: $\beta=0.91 (0.09)^{24}$		
Prodromal	• Non-specific, easily missed stage ¹⁵	$e=7 \text{ days}^{15}$	Same as susceptible	NA	
Catarrhal	• Cold-like symptoms ²	e=7 days ^{2,22}	I: $\beta = 0.40 (0.30)^{b}$	NA	
	• Low grade fever • Rhinorrhea ²²		C. β =0.43 (0.34) Y: β =0.51 (0.39) ^{c25}		
	• Lacrimation ²²		A: $\beta = 0.67 (0.38)^{c25}$		
	 Malaise²² Mild and unproductive cough²² 		S: p=0.07 (0.38)		
Paroxysmal	 Severe coughing spells²² Inspiratory whooping²² Posttussive vomiting²² Cyanosis²² 	<i>e</i> =21 days	I: β=0.27 (0.36) ^{c25} C: β=0.30 (0.37) ^b Y: β=0.35 (0.38) ^{c25} A: β=0.58 (0.42) ^{c25}	Hospitalized All Ages: $\gamma = \$1,799$ $(\$2,662)^{d10}$	
	• Apnea ²²		S: $\beta = 0.58 (0.42)^{c25}$	daily	
				Non- Hospitalized All Ages: \$80.88°	
Convalescent	• Less frequent and forceful cough ²²	e=14 days	Same as catarrhal	NA	
	• Recovery is gradual ²				

Table 4.1. Pertussis natural history parameters. Distributions for sensitivity analysis shown with mean and standard deviation (shown in parentheses).

I: Infants, C: Children, Y: Youth, A: Adults, S: Seniors

^a Extrapolated from age groups used in Mittmann *et al.* 1999^{24}

^b Extrapolated from age groups used in Withinam *et al.* 1999 ^b Extrapolated from age groups used in Lee *et al.* 2005²⁵ ^c Based of Short-Term TTO methods, undiscounted ^d Based off ICD-10 codes A37.0 (whooping cough due to *Bordetella pertussis*) and A37.9 (whooping cough unspecified). Adjusted to \$2016 CAD.

^e Based off \$33.70 cost per medical visit²⁶ with mean of 2.4^4 (sd=0.25) visits (See Section 6.3.1 for details).

Complication	Probability Per	Utility Values,	Cost Per Day of	Duration of		
	Episode ^{a,b,c,d}	Mean (SD)	Treatment Cost,	Complication in		
	-		Mean (SD)	Davs, Mean (SD)		
				(~)		
Pulmonary ^e	I: 0.136 ³	I: $\beta = 0.27 (0.36)^{25}$	I: \$1.950 ¹⁰	I: $\gamma = 3.9 (4.8)^{10}$		
	$C: 0.083^3$	C: $\beta = 0.27 (0.36)^{25}$	C: \$1,950 ¹⁰	C: $\gamma = 3.9 (4.8)^{10}$		
Hernia ^f	I: 0.01^3	I: $\beta = 0.27 (0.30)^{h}$	I: \$2,725 ¹⁰	I: $\gamma = 1.9 (2.2)^{10}$		
	C: 0.005^3	C: $\beta = 0.27 (0.30)^{h}$	C: \$2,725 ¹⁰	C: $\gamma = 1.9 (2.2)^{10}$		
Neurological ^g	I: 0.042^3	I: $\beta = 0.21 (0.33)^{25}$	I: \$2,724 ¹⁰	I: $\gamma = 5.2 (16.9)^{10}$		
-	C: 0.033^3	C: $\beta = 0.21 (0.33)^{25}$	C: \$2,724 ¹⁰	C: $\gamma = 5.2 (16.9)^{10}$		
Long-term	I: 0.33 of infants	I: $\beta = 0.21 (0.33)^{25}$	Median (IQR)	Lifetime		
Neurological	with neurological		annually:			
	complication ^{5,27}		\$18,136 (\$5,343-			
			\$50,954) ⁱ²⁸			
Weight Loss >5%	I: 0.014^3	I: $\beta = 0.70 (0.30)^{\Box}$	I: \$1,062 ¹⁰	I: $\gamma = 4.6 (4.4)^{10}$		
	C: 0.01^{3}	C: $\beta = 0.70 (0.30)^{h}$	C: $$1,062^{10}$	C: $\gamma = 4.6 (4.4)^{10}$		
	$Y: 0.03^4$	Y: $\beta = 0.85 (0.30)^{h}$	Y: \$33.70 ²⁶	Y: $\gamma = 4.6 (4.4)^{h}$		
	A: 0.03 ⁴	A: $\beta = 0.85 (0.30)^{h}$	A: \$33.70 ²⁶	A: $\gamma = 4.6 (4.4)^{h}$		
	S: 0.03 ⁴	S: $\beta = 0.85 (0.30)^{h}$	S: \$33.70 ²⁶	S: $\gamma = 4.6 (4.4)^{h}$		
Sinusitis	Y: 0.11 ⁴	Y: $\beta = 0.56 (0.30^{h})^{29}$	Y: \$33.70 ²⁶	Y: $\gamma = 7 (3^{h})^{32}$		
	A: 0.148 ⁴	A: $\beta = 0.56 (0.30^{h})^{29}$	A: \$33.70 ²⁶	A: $\gamma = 7 (3^{h})^{32}$		
	S: 0.17 ⁴	S: $\beta = 0.56 (0.30^{h})^{29}$	S: $33.70^{26} +$	S: $\gamma = 7 (3^{h})^{32}$		
			\$16.02			
Pneumonia	$Y: 0.02^4$	Y: $\beta = 0.35 (0.37)^{25}$	Y: \$43.81 ²⁶	Y: $\gamma = 7 (3)^{n}_{1}$		
	A: 0.047 ⁴	A: $\beta = 0.62 (0.40)^{25}$	A: \$43.81 ²⁶	A: $\gamma = 7 (3)^{n}$		
	S: 0.09 ⁴	S: $\beta = 0.62 (0.40)^{25}$	S: $43.81^{26} +$	S: $\gamma = 7 (3)^{h}$		
			\$6.54 31,33			
Otitis Media	Y: 0.04^{4}	Y: $\beta = 0.79 (0.04)^{34}$	Y: \$33.70 ²⁶	Y: $\gamma = 7 (3)^{h}_{h}$		
	A: 0.04 ⁴	A: $\beta = 0.79 (0.04)^{34}$	A: \$33.70 ²⁶	A: $\gamma = 7 (3)^{n}$		
	S: 0.04 ⁴	S: $\beta = 0.79 (0.04)^{34}$	S: $33.70^{26} +$	S: $\gamma = 7 (3)^{h}$		
			\$20.50 ¹³¹			
Rib Fracture	Y: 0.01 ⁴	Y: $\beta = 0.69 (0.3)^{35}$	Y: \$59.50 ²⁶	Y: $\gamma = 14 (5)^{h}$		
	A: 0.04 ⁴	A: $\beta = 0.69 (0.3)^{35}$	A: \$59.50 ²⁶	A: $\gamma = 14 (5)^{n}$		
	S: 0.04 ⁴	S: $\beta = 0.69 (0.3)^{35}$	S: \$59.50 ²⁶	S: $\gamma = 14 (5)^{h}$		
Fainting	A: 0.02 ⁴	A: $\beta = 0.90 (0.29)^{h}$	A: \$33.70 ²⁶	A: While coughing		
	S: 0.02 ⁴	S: $\beta = 0.90 (0.29)^{h}$	S: \$33.70 ²⁶	S: While coughing		
Urinary	A: 0.093 ⁴	A: $\beta = 0.8 (0.3^{h})^{36}$	A: \$33.70 ²⁶	A: While coughing		
incontinence	$S: 0.34^4$	S: $\beta = 0.8 (0.3^{h})^{36}$	S: \$33.70 ⁻²⁶	S: while coughing		
(females only)						

Table 4.2. Parameter values for pertussis-related complications. Distributions for sensitivity analysis shown with mean and standard deviation (in parentheses).

I: Infants, C: Children, Y: Youth, A: Adults, S: Seniors

^a Infant and children values extrapolated from age groups used in Halperin *et al.* 1999,³ converted to daily probabilities.

^b Youth probabilities extrapolated from 12-17 year olds non-hospitalized adolescents in De Serres *et al.* 2000.⁴ Converted to daily probabilities.

^c Adult probabilities are weighted average of probabilities from 18-29yo, 30-39yo, 40-49yo, and 50+yo non-hospitalized patients in De Serres *et al.* 2000.⁴ Converted to daily probabilities.

^d Senior probabilities extrapolated from 50+ year old non-hospitalized patients from De Serres *et al.* 2000.⁴ Converted to daily probabilities.

^e Includes pneumonia, atelectasis, and pneumothorax

f Includes both inguinal and umbilical hernias.

^g Includes seizures, encephalopathy, and other neurological complications

Assumption

[®] Converted to \$2016 CAD by adjusting for inflation

Expert opinion

2			,
Age	Probability of Hospitalization per episode [*] , Mean (SD)	Duration of Hospitalization, Mean	Probability of Death per episode [*] , Mean (SD)
Infant	$\beta = 0.631 (0.006)^{37}$	$e=9.3 \text{ days}^3$	$\beta = 0.01 (0.004)^3$
Child	$\beta = 0.148 (0.005)^{37}$	$e=4.9 \text{ days}^3$	$\beta = 0.005 (0.005)^3$
Youth	$\beta = 0.01 (0.006)^4$	e=3 days ⁴	$\beta = 0.0003 (0.0003)^{37}$

e=3 days

 $e=17 \text{ davs}^4$

Table 4.3. Probability of hospitalization and death for Pertussis. Distributions for sensitivity analysis shown with mean and standard deviation (in parentheses).

 $\beta = 0.0003 (0.0003)$

 $\beta = 0.0003 (0.0003)^3$

Converted to daily probabilities in model

 $\beta = 0.02 (0.008)^{\circ}$

β=0.06 (0.033)

4.4.4 Utilities

Adult

Senior

The utility weights used to calculate the QALYs were obtained from the only study examining the quality of life associated with the different health states of pertussis.²⁵ The study used a short-term time trade-off method to estimate utilities to better differentiate the severity of these short-term health states. Because our model incorporated a 5% annual discount rate, we used the undiscounted mean and standard deviations for the pertussis- and vaccine-related health states for infants, adolescents, and adults. Although children were not explicitly examined in this study, we were able to interpolate utilities by assuming intermediate disease severity between that experienced by infants and adolescents (**Table 4.1**).

Utility values for "susceptible" and "prodromal" phases of illness were obtained from a study which used responses from the National Population Health Survey (NPHS) to estimate utilities.²⁴ We used age-specific utility scores from the individuals with no chronic condition to represent the underlying health of the population. As infants and children are not included in the NPHS, we assumed they would have the same underlying health distribution as the youths. Utility values for pertussis-related sequelae were also derived from the published literature (**Table 4.2**).

4.4.5 Cost Parameters

Costs were assessed from the perspective of the healthcare payer and were adjusted to \$2016 CAD. Hospitalization costs were extracted from the Ontario Case Costing Initiative (OCCI), an online database of person-level costs from ambulatory and acute inpatient care.¹⁰ The OCCI data includes direct and indirect costs associated with provision of patient care and running the hospital. Similar to cost-effectiveness studies involving OCCI data, we included a 5% premium to represent physician costs not included in the OCCI.^{38,39} The mean cost per hospitalized day for each of the pertussis-related complications was extracted with the mean and standard deviation of the length of stay (**Section 6.3.2**). The sensitivity analysis allowed the length of stay to vary according to the probability distribution, driving the costs of hospitalization for each patient.

Costs associated with outpatient physician visits were obtained from the Schedule of Benefits for Physician Services under the Health Insurance Act.²⁶ The average number of physician visits for each pertussis-related complication was estimated from the literature and expert opinion to create a distribution of physician costs (Section 6.3.1). While outpatient prescription drugs age generally paid for by healthcare consumers in Ontario, drug costs for seniors are covered by the Ontario Drug Benefit Program and were included. Antibiotic choice and dosages were obtained from the literature and costs were retrieved from the Ontario Drug Benefit Formulary (Section 6.3.3).³¹

We estimated the long-term costs of neurologic sequelae of pertussis-related encephalitis from a study of the costs of complex medical care for children in Ontario.²⁸ The median direct cost of caring for a child with neurological impairment was estimated at \$36,272 (\$2016CAD) for the two years after the initial hospitalization, not including the costs of this first hospitalization.²⁸ We assumed the costs were distributed equally over the two years and would remain approximately the same each year over the child's lifetime.

4.4.6 Sensitivity Analysis

Probabilistic sensitivity analyses over 100,000 model realizations per age group were used to generate the distribution of outcomes. Model parameters were drawn from the distributions as described in **Tables 4.1-4.3**.

4.4.7 Economic Burden and Net Monetary Impact

Economic burden was assessed by multiplying mean case cost estimates by annual agespecific incidence in Canada¹ and it's most populated province, Ontario.^{19,20} We adjusted the reported incidence estimates by a factor of 5.63 to account for the previously cited underdetection of pertussis in Ontario, and taking into consideration the improved sensitivity of diagnostic testing.^{40,41} At the time of analysis, 2013 was the most recently available data so we used data from 2013 to represent a current "average" pertussis year and data from 2012 to represent an "outbreak" year.⁴² Based on benchmarks from the World Health Organization, we used gross domestic product (GDP) per capita, and three times GDP per capita, as a range of plausible cost-effectiveness thresholds for a single QALY. These calculations were performed to estimate the net monetary impact of pertussis which allows for costs and QALY loss to be monetized into a single cost metric. In 2015, the Canadian GDP per capita was assessed by the World Bank at \$55,560.⁴³

4.5 Results

4.5.1 Health Burden

In terms of life years lost, infants experienced the greatest losses per case (0.051 LYs) followed by children (0.015 LYs), youth (0.010 LYs), and adults (0.007 LYs) (**Figure 4.2**). The mean number of life years lost in the seniors group was -0.014 per case, suggesting that pertussis had a protective effect on life expectancy, but the credible interval overlapped zero suggesting this finding was a result of stochastic variation combined with a small effect size (95%CI: -0.038 - 0.01 LYs).

Infants showed the greatest QALY loss per case (0.123 QALYs or 44.93 quality-adjusted life days (QALDs)). QALY loss per case was smallest in the seniors (0.018 QALYs or 6.57

QALDs) followed by the adults (0.041 QALYs or 14.98 QALDs). Children and youth had similar QALY loss per case (0.065 and 0.068 QALYs respectively) (**Figure 4.2**). Assuming the age-specific annual incidence derived in **Table 4.4**, total QALY loss in Ontario was estimated to be 165.31 QALYs annually and as much as 539.70 QALYs in an outbreak year. For all of Canada, the total QALY loss was estimated at 636.87 QALYs annually and as much as 2,041.41 QALYs in an outbreak year.

4.5.2 Economic Burden

As expected, infants less than 6 months of age had the highest mean (sd) cost per case at \$8,946 (\$25,886). In general, the costs were found to decline with age with cases among children, youth, and adults costing approximately \$2,895 (\$7,514), \$1,697 (\$2,172), \$1,617 (\$2,399) respectively. Pertussis cases among seniors, with higher probabilities of complications as well as more expensive health care costs, were found to cost \$2,479 (\$10,087) on average (**Figure 4.2**).

Based on estimated age-specific incidence accounting for under-detection in **Table 4.4**, pertussis costs the Ontario healthcare system approximately \$5.0M annually and as much as \$16.9M in an outbreak year. The net monetary impact of pertussis during a typical year in Ontario was estimated to be between \$11.0M and \$22.8M when QALYs were valued at 1 and 3 times GDP per capita. During an outbreak year, this could be as much as \$38.6M to \$82.0M (**Figure 4.3 and Section 6.3.4**).

At a national (Canadian) level, pertussis costs approximately \$20.4M annually and \$66.4M in an outbreak year. The net monetary impact of pertussis during a typical year in Canada was estimated to be between \$46.5M and \$98.6M when QALYs were valued at 1 and 3 times GDP per capita. During an outbreak year, this could be as much as \$158.6M to \$342.8M (**Figure 4.3 and Section 6.3.4**).



Figure 4.2. The mean LYs lost, QALYs lost, and costs per case for the different age groups in the model. The error bars represent the 95% confidence intervals. QALYs = quality-adjusted life years, LY= life years.



Figure 4.3. Economic burden and net monetary impact of pertussis in Ontario and Canada.

	Ont	ario	Canada			
Age Group	2012	2013	2012	2013		
<6 mo	799	293	2,528	951		
6 mo to 4y	997	282	3,693	1,013		
5 to 17 y	2,342	529	12,504	2,967		
18 to 64 y	1,605	372	5,782	1,909		
65+ y	113	45	1,025	332		
Total	5,855	1,520	25,532	7,173		

Table 4.4. Estimated age-specific number of pertussis cases in Ontario and Canada during 2012-2013. Data obtained from Public Health Ontario and Canadian National Notifiable Disease Database, corrected for under-detection.^{1,20,44}

4.5.3 Sensitivity Analysis

Probabilistic sensitivity analyses (PSA) incorporating both stochasticity and parameter uncertainty were used to generate the distributions for the age-specific LYs lost, QALYs lost, and costs. Full distributions of age-specific outcomes are presented in **Sections 6.3.5-6.3.7**. At the Ontario level, the results of the PSA suggest the economic burden could range between \$670 and \$550M during an average year, although the 95% confidence interval (CI) is between \$4.97M and \$5.12M. Similarly, for all of Canada, the range of potential values for the economic burden of pertussis range from \$11,200 to \$7.3B, although the 95%CI is between \$65.5M and \$67.3M.

In terms of discounting, we allowed the annual discount factor to vary between 0%, 3%, and 5%. For infants, the estimated LYs lost ranged from 0.051 to 0.226 when the discount factor was decreased from 5% to 0%. Similarly, QALYs lost ranged from 0.123 to 0.33 and costs increased from \$8,946 to \$10,337 as the discount factor decreased from 5% to 0%. Full results for LYs lost, QALYs lost, costs for each discount factor are shown in **Table 4.5**.

	LYs Lost			QALYs Lost			Costs		
	0%	3%	5%	0%	3%	5%	0%	3%	5%
Infants	0.226	0.077	0.051	0.333	0.154	0.123	\$10,337	\$9,195	\$8,946
Children	0.050	0.020	0.015	0.096	0.069	0.065	\$2,910	\$2,901	\$2,895
Youth	-0.012	0.006	0.010	0.048	0.065	0.068	\$1,706	\$1,701	\$1,697
Adults	0.008	0.007	0.007	0.039	0.040	0.041	\$1,624	\$1,620	\$1,617
Seniors	-0.019	-0.015	-0.014	0.013	0.017	0.018	\$2,492	\$2,484	\$2,479

Table 4.5. Sensitivity analysis for discount rate. Age-specific per patient mean LYs lost, QALYs lost, and costs associated with pertussis are shown in the table.

4.6 Discussion

We estimated the age-specific quality of life and costs associated with pertussis in Ontario to evaluate the annual health and economic impact at both a provincial and national level. Cases among infants and children were found to have the greatest impact on health and be the most expensive. This is not surprising considering pertussis cases among infants and children tend to be associated with the highest levels of morbidity and mortality.¹⁵ We estimate that pertussis remains an important source of lost health and healthcare costs in Ontario and Canada as a whole.

It is important to note that while our model estimates life years lost due to pertussis in all age groups except the seniors, there were actually no reported pertussis deaths in Ontario in 2012 and 2013.^{45,46} However, given that surveillance in Canada between 1991 and 2012 reported between 0 and 4 infant deaths per year,⁴⁷ the Ontario mortality numbers are likely an artifact of under-recognition of pertussis combined with small samples.

In 2012, the Institute for Clinical Evaluative Sciences and the Ontario Agency for Health Protection and Promotion evaluated the morbidity and mortality burden of infectious diseases in Ontario.⁴⁰ They estimated that pertussis was associated with 220 year-equivalents of reduced functioning (undiscounted) and 220 total health-adjusted life years (HALYs, undiscounted).⁴⁰ As the HALYs calculated were a hybrid measure of disability-adjusted life years (DALYs) and QALYs, they are not directly comparable to our undiscounted estimate of 165.31 QALYs lost

annually and 539.70 QALYs lost in an outbreak year in Ontario. However, the similarity between these HALYs and our calculated QALY loss is reassuring.

The Economic Burden of Illness in Canada (EBIC) study estimates that respiratory infections cost Canadians approximately \$2.59B in 2008. Within Ontario, this number was estimated at \$1.04B. In Ontario, pneumonia and the common cold were the most expensive respiratory infections at \$260M and \$217M respectively and influenza was estimated at \$22M.⁴⁸ Our pertussis economic impact estimates (\$5M-\$17M annually) were lower than influenza, as expected, but were within range, adding credibility to our estimates.

While there have been other studies examining the costs of pertussis,^{11-13,49} our study is the first to evaluate the age-specific costs of pertussis and pertussis-related complications. In 2000, Lee and Pichichero used a prospective survey to evaluate the costs of pertussis morbidity in Rochester NY.¹¹ They estimated that average costs of pertussis among infants, children, adolescents, and adults to be \$2,822, \$308, \$254, and \$181 (\$1996 USD) respectively. In another study, Lee and colleagues used Massachusetts surveillance data linked with health service utilization data to estimate that pertussis-related costs among adolescents and adults were \$242 and \$326 (\$2002 USD) respectively.¹² Additionally, O'Brien and Caro used hospital discharge data to evaluate pertussis-related hospitalization costs across 4 US states. They found that infants, children, and adolescents/adults had a mean cost of \$9,580, \$4,729 and \$5,683 (\$2002 USD) respectively per hospitalization.¹³ These studies all had small sample sizes and have lacked power to demonstrate infrequent sequelae of pertussis that contribute significant costs. In addition, they did not account for the follow-up costs associated with pertussis-related sequelae, which is likely why our estimates are generally higher.

Our microsimulation study has several limitations. First, the economic burden and net monetary impact of pertussis in Ontario and Canada were estimated using reportable disease data from the provincial and national levels.^{1,20,44} This surveillance data relies on physicians identifying potential cases, testing these cases, and the laboratories reporting positive cases. We used a factor of 5.63 times to account for the under-detection of pertussis, modified from Deeks and colleagues⁴¹ in a similar fashion to the Ontario Burden of Infectious Disease Study.⁴⁰

However, such adjustment does not account for the phenomenon of under-identification of mild cases. We have previously estimated under-identification ratios for Southern Ontario.¹⁶ Under-identified cases can either be asymptomatic or mildly symptomatic infections, with only clinical infections contributing to health and economic burden. Thus, our economic impact represents a conservative estimate. Other limitations are common to all models, including simplifying assumptions and data input quality. For example, while studies have shown that multiple complications of pertussis in an individual are possible,^{3,4} we assumed that the health and economic consequences would largely be driven by the worst single complication in a given individual. Again, such simplifying assumptions would cause our estimates to represent lower-bound estimates.

Despite these limitations, our study is the first of its kind to address the impact of pertussis within Ontario and Canada. The health and economic consequences of pertussis persistence in Canada are substantial and highlight the need for improved strategies for the use of existing vaccines. Our estimates can be incorporated into future analyses that attempt to evaluate the effectiveness and cost-effectiveness of emerging pertussis prevention strategies, including immunization during pregnancy, "cocoon" immunization of all contacts of newborns, earlier boosters for adolescents, and decennial adult boosters.^{50,51} Such analyses will help policy makers and public health officials make informed decisions about optimal immunization programs to maximize health benefits, at a reasonable cost.

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5 Chapter Five: Discussion

5.1 Summary of Findings

Together, the results of this dissertation address gaps in current pertussis immunization programs in Ontario. Through three distinct research questions, explored using three unique analytical approaches, I have examined key reasons why we continue to see cases of pertussis, and how much these cases contribute to our healthcare system, both financially and in terms of health impact. The results of this dissertation can be integrated into cost-effectiveness analyses to create a framework for policy makers and public health officials to make informed decisions that optimize the efficiency and effectiveness of immunization programs and assist in strategic health planning.

In Chapter 2, I used a compartmental model to simulate the transmission of pertussis in Ontario. The model incorporated age-structure and age-dependent mixing patterns and was well calibrated to incidence data from both the pre-vaccine and vaccine eras. By comparing model predicted incidence to reported pertussis disease incidence, pertussis under-identification ratios were found to vary with age. In the 2-7 year olds, I estimated that for every case of reported pertussis, there were approximately 600 un-identified cases. In the 20 to 64 year olds, this value increased to over 33,000 un-identified cases for every reported case. In addition, I estimated that over 95% of pertussis in children was caused by infections in individuals with waning vaccine-induced immunity. The results from this study suggest that unidentified pertussis cases are abundant among adults and adolescents in Ontario and these asymptomatic and mildly symptomatic pertussis cases contribute substantially to the overall force of infection.

In Chapter 3, I used a systematic review and meta-analysis to estimate the duration of immunity conferred by the childhood pertussis vaccine, DTaP. Meta-regression results combining estimates from eleven studies showed that the odds of pertussis increased by 1.33-fold for every additional year after the last dose of DTaP (95%CI: 1.23-1.43), suggesting that the

mean duration of immunity from DTaP is approximately 3 years. With immunity waning at this rate, I estimated that children vaccinated with DTaP would have 10% protection against pertussis 8.5 years after the last dose (assuming an initial vaccine efficacy of 85%), such that whole cohorts of adolescents would be susceptible to pertussis before their scheduled Tdap booster at 14-16 years of age. This finding highlights the need to re-evaluate the current pertussis immunization schedule in Ontario as well as all of Canada.

In Chapter 4, I described a microsimulation model used to estimate the age-specific impact of pertussis on health and healthcare costs in Ontario and Canada. I found that LY loss, QALY loss, and pertussis costs in Ontario generally decline with age (0.051 LYs lost, 0.123 QALYs lost, and \$8,946 for infants, -0.014 LYs lost, 0.018 QALYs lost, and \$2,479 for seniors). Using these age-specific estimates, I estimated the cost of pertussis to the Ontario healthcare system to be \$5.0M per year (\$20.4M across Canada) and as much as \$16.9M in an outbreak year (\$66.4M across Canada), although these estimates are much higher when I calculated the net monetary costs taking into account health outcomes. The results from this aim suggest that both the health and economic impact of pertussis persistence are sizable, underscoring the need to examine alternative immunization strategies to control pertussis in Ontario.

5.2 Methodological Considerations

Methodological strengths and limitations pertaining to each individual aim are discussed in the previous chapters. Here, I describe the methodological considerations that span multiple components of the dissertation including defining pertussis immunity, pertussis reporting completeness, and use of mathematical models.

5.2.1 Defining Immunity

Pertussis immunity is not lifelong, regardless of whether naturally acquired or vaccineinduced.¹ Defining pertussis immunity is a complex issue, particularly because there is no recognized serologic correlate associated with clinical protection. Diagnostic confirmation via serology is equally complex, again because cut-off values differ by jurisdiction.² Without the involvement of clinical symptoms, serology results cannot distinguish between immune response from infection and immune response from vaccination.² Additionally, mathematical modeling of infectious diseases allows for entirely different definitions of immunity. Defining pertussis immunity was particularly important in both Chapters 2 and 3 of this dissertation, and methodological considerations for the relevant decisions made are described below.

In Chapter 2, the mathematical model incorporated both natural and vaccine-induced immunity to pertussis. Since immunity was modeled as protection from pertussis derived from being in a "vaccinated" or "recovered" compartment of the model, the definition of immunity relied on a mathematical, as opposed to clinical or serologic, definition. Mathematically, immunity from a vaccine can be integrated into a compartmental model in two ways: a "leaky" vaccine assumes that everyone who receives the vaccine has partial protection whereas an "all-or-nothing" vaccine assumes that a proportion of the population has complete protection while another proportion has no protection.^{3,4} Vaccine efficacy was incorporated as "all-or-nothing" where 90% of individuals were assumed to have 100% protection against pertussis and 10% were assumed to have 0% protection. This mathematical definition of pertussis immunity is subject to the assumptions of compartmental models; that is, the "individuals" in the vaccination compartments are infinitely divisible and exit each compartment according to an exponential distribution.⁵ While these properties may not reflect a perfect representation of immunization programs at the population level.⁵

The duration of vaccine immunity for Chapter 2 was modeled as an exponential process with a mean duration estimated through model calibration. The calibration procedure aimed to minimize the root mean square deviation between the model predicted output and the cumulative incidence data over different values for the mean duration of vaccine-induced immunity. The best fitting model estimate was found to be 27.11 years for complete immunization (or 5.42 years per dose received). Although this value is much longer than the duration of vaccine induced immunity estimated in Chapter 3, the model dynamics were found to be a good representation of the reported disease data (**Figure 2.3**), suggesting a good fit. Although the

vaccine preparation changed from whole cell to acellular in 1997/98, to reduce model complexity, I modeled the two vaccines as interchangeable given their similar effectiveness estimates. Since the population modeled would have had various combinations of whole cell and acellular primary series and booster immunizations, this is a reasonable assumption, but the longer duration of immunity estimated via model calibration likely reflects this decision, as whole cell pertussis vaccines have been shown to have longer immunity than acellular vaccines.¹

The definition of pertussis immunity was also important in Chapter 3. The studies included in the systematic review operationalized pertussis immunity in various ways. For some the definition was purely clinical, while for others a serologic correlate was used to indicate immunity. To capture as much literature as possible, I included both types of studies in the systematic review; however, I examined the effect of the definition of pertussis immunity using meta-regression.

In total, there were four studies that used serologic correlates of pertussis infection.⁶⁻⁹ While acellular pertussis vaccines contain at least one pertussis antigen (PT, FHA, PRN, FIM 2, and FIM3), PT is the only pertussis specific antigen.¹⁰ To ensure comparability of the estimates used in the meta-analysis, I chose to extract anti-PT IgG as a correlate of protection in this study. In addition, I used the unique thresholds of seropositivity as given in each of the studies. For two, this was defined as anti-PT levels of at least 5 EL U/mL,^{8,9} while the other two did not specify their cut-off value.^{6,7} Because these seropositivity values were not a perfect measure, I investigated the impact of including serologic studies by controlling for the different types of pertussis immunity definitions (clinical and serologic) in the meta-regression analysis and found no appreciable difference in the odds ratio. Thus, while there may be no reliable serologic correlate of protection for anti-PT, the seropositivity values used in the different studies included in the meta-analysis had no effect on the estimated duration of protective immunity conferred by DTaP.

The definition of pertussis immunity posed particular challenges for Chapters 2 and 3 of this dissertation. While I chose to operationalize immunity in different ways due to the distinct research aims, available data, and the complexity of the analysis, this methodological consideration was critical throughout the entire research process.

5.2.2 Pertussis Reporting Completeness

Another critical methodological issue present throughout this dissertation is the completeness of reported pertussis case data. To evaluate the true burden of pertussis from the reported case data, one must examine the under-reporting, under-detection, and under-identification of pertussis. While there is considerable discrepancy in the literature about the different definitions of these key terms, I have used the definitions described below to ensure consistency throughout my dissertation. These definitions are presented graphically in **Figure 5.1**.



Figure 5.1. The epidemiologic "iceberg" of pertussis and classification of reporting completeness. Figure modified and adapted from Gibbons *et al.* 2014.¹¹
Under-identified (or *under-ascertained*) cases refer to pertussis cases that are not diagnosed or reported because they do not seek health care.^{11,12} Often, these cases are asymptomatic or mildly symptomatic but can carry the pathogen and contribute to the force of infection. While the term "under-reporting" in the literature can refer to pertussis cases that are not reported to the appropriate health authorities after seeking medical care,¹¹ for the purpose of this dissertation, I have chosen to delineate between true under-reported to refer to pertussis cases and under-detected (or under-diagnosed) cases. I have used the term *under-reported* to refer to pertussis in Canada (**Table 1.1**),¹³ but have not been reported to the appropriate health authority.¹⁴ I have used the *under-detected* (or *under-diagnosed*) cases to refer to pertussis cases that are not diagnosed properly after seeking medical care.

In Ontario, the completeness of pertussis case reporting for patients seeking medical care is more heavily influenced by under-detection than under-reporting. While both probable and confirmed cases are reportable to local health authorities, only confirmed cases are reported at a national level.^{13,15} Confirmed cases are diagnosed either by laboratory confirmation or via an epidemiologic link to a laboratory confirmed case in the presence of pertussis symptoms (**Table 1.1**). As two of the three definitions for "confirmed" cases in Ontario require laboratory tests that occur in licensed laboratories, including provincial laboratories, these cases tend to be well reported to health authorities. The case definitions involving an epidemiologic link and/or symptomatic assessment may leave more room for under-reporting to occur, but far more influential to the completeness of reporting is under-detection of cases. Often, under-detection occurs because the clinician does not consider pertussis in the differential diagnosis, typically because symptoms are considered atypical, the patient is immunized, or because the clinician does not test for it, often because they do not have the nasopharyngeal swab testing kits.¹⁶

The completeness of pertussis reporting in Ontario as well as Canada was an important methodological consideration for this dissertation. Because the reported cases of pertussis only represent the tip of the epidemiologic iceberg (**Figure 5.1**), I used different techniques to estimate the burden of pertussis at different clinical levels for aims 1 and 3 of this dissertation.

To evaluate the underlying burden of pertussis infections in Ontario, I calculated agespecific under-identification ratios in Chapter 2. Quantifying the size of the pertussis epidemiologic iceberg is critical to understanding the force of infection of pertussis and the persistence of disease despite routine immunization programs. By comparing the number of reported cases to model predicted incidence of pertussis infections, I was able to estimate the age-specific under-identification ratios for pertussis in Ontario between 1993-2004. These agespecific under-identification ratios varied between 597:1 in the 2-7 year age group to 33,302:1 in the 20-64 year are group (**Figure 2.4**). These ratios intrinsically incorporate both under-reporting and under-detection in their calculation, although the relative contribution of each for the different ages is unknown.

In Chapter 4 of this dissertation, I used under-detection ratios to estimate the true incidence of clinical pertussis cases in Ontario and Canada. As the objective of this aim was to evaluate the health and economic burden of pertussis, I accounted for under-detection of cases to incorporate the life-years lost, QALYs lost, and costs associated with cases that sought health care with pertussis-associated symptoms. The under-detection ratio used in the analysis was obtained from a 1999 study of clinician awareness and reporting of pertussis in Ontario. The authors estimated an under-detection ratio of 16.9:1 (33 diagnosed cases of pertussis within 558 patients seeking medical care) and modified under-detection ratio of 28.5:1 (33 diagnosed cases of pertussis within 941 individuals meeting the clinical case definition of pertussis but not necessarily seeking medical care).¹⁶ However, with improved sensitivity of PCR testing methodologies, similar to the Ontario Burden of Infectious Diseases Study, I estimated a three fold better rate of detection for an under-detection ratio of 5.63:1.¹⁷ This is likely a conservative estimate of the under-detection of pertussis in Ontario, especially in adolescents and adults as atypical symptoms may not prompt suspicion of pertussis. However, using a conservative estimate for the under-detection of pertussis allows for a conservative estimate of the health and economic burden of pertussis.

Incomplete pertussis reporting in Ontario and Canada posed methodological problems in this dissertation. As cases can fail to be reported at different levels along the clinical spectrum of disease (**Figure 5.1**), incomplete reporting is a function of under-identification, under-detection, and under-reporting. These were incorporated throughout this dissertation to evaluate the true burden of pertussis.

5.2.3 Use of Models

Another key methodological consideration that spans this dissertation is the use of mathematical models. While models are often a simplification of reality, they can be useful for predicting outcomes in the absence of epidemiologic data. They allow users to examine the effects of an intervention and the counterfactual scenario if the intervention had not been introduced.¹⁸ There are many types of mathematical models including state-transition models, discrete event simulations, dynamic transmission models, and agent-based models. This dissertation includes two very different types of models, each uniquely chosen to address the particular research question.

In Chapter 2, to estimate the underlying burden of pertussis in Ontario, I used an agestructured compartmental model. To capture the transmissibility of pertussis and the indirect effects of vaccination, it was necessary to use a dynamic model.¹⁹ While either a compartmental model or an agent-based model would have been appropriate for the research question, the added complexity of an agent-based model was unnecessary. An agent-based model incorporates interindividual variation in contact patterns, decisions to self-quarantine, and other self-protection methods that can affect how a disease may transmit in a population; however, as I was interested in the macro-level disease dynamics that affect the burden of pertussis, the less computationally intensive compartmental model was chosen.

I used a microsimulation model to evaluate the health and economic burden of pertussis in Chapter 4. As the model reflected the natural history of pertussis compared to the natural history of remaining disease free, the transmissibility of pertussis was not necessary to include and so a static model was used. As opposed to Markov or cohort models, microsimulation models simulate a population of individuals at the person-level and allow for memory of previous health states.²⁰ As such, they allow for the calculation of accumulated costs and health effects. Thus, a microsimulation model was chosen as the most appropriate model for this research question.

Parameter uncertainty is a challenge for all types of models. Unfortunately, mathematical models are subject to the "garbage in, garbage out" principle - a model's output is only as reliable as the parameters it is built upon. While obtaining credible parameter estimates was the goal for both of these models, sometimes there was no literature value available. Where this occurred, calibration techniques were used to estimate parameters. Sensitivity analyses were also used to explore the uncertainty around parameters and evaluate the model results under different scenarios.^{19,20} In both Chapter 2 and Chapter 4, robust sensitivity analyses were undertaken to evaluate the impact of different parameter values.

Mathematical models allow researchers to estimate and predict outcomes under a variety of different conditions. Where epidemiologic data does not exist or cannot be obtained, they are an important tool to help policy makers and public health officials make informed decisions. They have the flexibility to be as simple or as complex as desired, and to integrate as much uncertainty or variation as required.^{18,19} Their great strength is the ability to represent the counterfactual and predict outcomes without intervening on a population. While mathematical models are not a substitute for epidemiologic data, they are increasingly viewed as credible platforms to synthesize information for optimizing health policy and for the identification of important areas of uncertainty that should be prioritized for future research.¹⁸

5.3 Contribution to the Literature and Future Directions

The results of this dissertation have important policy implications. I found that pertussis in adolescents and adults is a contributing factor to pertussis persistence. Combined with the relatively short duration of protective immunity conferred by DTaP that I found in Chapter 3, it appears as though the current Ontario immunization program will not achieve levels of immunity high enough for disease elimination. Given the considerable health and economic burden of pertussis found in Chapter 4, it is important to examine new immunization strategies for pertussis.

Cost-effectiveness analyses have been performed to evaluate the relative impact of different acellular pertussis immunization strategies. There have been two systematic reviews focusing on the economic impact of different pertussis immunization strategies.^{21,22} In a 2012 systematic review of 13 cost-effectiveness analyses of pertussis booster strategies, strategies considered included booster immunizations for pre-school age, adolescents, and adults (one time and decennial), immunization at birth, "cocooning", maternal immunization, post-partum immunization, and immunization of healthcare workers.²² A 2014 systematic review focusing on immunization strategies specifically for reduction of morbidity and mortality in children retrieved 8 economic evaluation articles.²¹ Between these two reviews, only three articles were written in the Canadian context and they evaluated immunization of health care workers²³ and adolescent boosters (**Table 5.1**).^{24,25} A specific search strategy was not outlined in Rivero-Santana *et al.* 2014, but an updated search using the strategy in Millier *et al.* 2012,²² revealed no additional Canadian studies.

Study Authors and Year	Strategies Compared	Under- Identification/Under -Detection/Under- Reporting	Duration of Vaccine Immunity	Pertussis Associated Costs and QALYs
Iskedjian, Walker, and Hemels, 2004 ²⁵	Introduction of adolescent acellular vaccine at age 12 in Ontario compared to "current" practice of Td vaccination at age 14.	Adjusted incidence rates by under- detection factor of 9 (from Halperin 1989 ²⁶).	Children given DTaP at age 5 were assumed to remain protected until at least age 12 and adolescents given Tdap had at least 10 years of protection.	Costs: Outpatient and ER treatment costs, diagnostic tests, pneumonia and sinusitis co- morbidities, and productivity losses. QALYs: Not explicitly modeled.
Iskedjian, Walker, De Serres, and Einarson, 2005 ²⁴	Introduction of adolescent acellular vaccine at age 14 in Quebec compared to "current" practice of Td vaccination at age 14.	Adjusted incidence rates by under- detection factor of 9 (from Halperin 1989 ²⁶).	Children given DTaP at age 5 were assumed to remain protected until at least age 14 and adolescents given Tdap had at least 10 years of protection.	Costs: Outpatient and ER treatment costs, diagnostic tests, pneumonia and sinusitis co- morbidities, and productivity losses. QALYs: Not explicitly modeled.
Greer and Fisman, 2011 ²³	Vaccination of healthcare workers at different coverage rates (25-95%) compared to no Tdap vaccine.	Under-identification ratio of 2.5 (40% of adults with pertussis assumed to be symptomatic).	Not explicitly modeled.	Costs: Contact tracing, missed work for healthcare provider, diagnostic test, daily NICU costs, costs associated with moderate and severe neurologic impairment, and hospital case management costs. QALYs: Utilities associated with childhood neurologic disability and moderate and severe infant neurologic disability.

 Table 5.1.
 Summary of Canadian economic evaluations of pertussis immunization programs.

The three cost-effectiveness models performed in the Canadian context are described in **Table 5.1**. While all input parameters are important in the construction of an economic evaluation model, I have chosen to highlight the three parameters that are addressed in this dissertation. The underlying burden of pertussis was incorporated into all three models; however, with slightly different research questions, the authors incorporated under-estimation of pertussis at different levels (under-identification and under-detection), making comparisons difficult. The age-specific under-identification ratios estimated in Chapter 2 could be incorporated into models such as these to account for the silent transmission of asymptomatic or mildly symptomatic adolescents and adults and their contribution to the force of infection.

None of the studies incorporated waning immunity into their models. As waning immunity would affect the number of susceptible individuals in the population and therefore effective reproduction number of disease, it would likely affect the cost-effectiveness of different immunization strategies. The probability of vaccine failure curves in **Figure 3.6** could be used in future analyses to parameterize vaccine failure over time.

While all three studies examined costs of pertussis disease, only one examined QALYs associated with pertussis. Pertussis diagnosis and outpatient/inpatient treatment were incorporated into the models, but complications and sequelae were limited. The pertussis-attributable age-specific per case costs, QALY losses, and life-year losses that were estimated in Chapter 4 can be used to parameterize future health economic models and cost-effectiveness analyses.

With the persistence of pertussis and evidence suggesting that current immunization programs are not sufficient to stop the spread of pertussis in the community, alternative strategies must be considered. Further Canadian cost-effectiveness research on alternative immunization strategies, including "cocooning" by immunizing contacts of newborns, immunization during pregnancy, immunization of childcare workers, and routine repeated adult immunization, is

needed.²⁷ The results from this dissertation provide credible input parameters necessary for the construction of such models.

5.4 Conclusions

The persistence of pertussis in Ontario, despite routine childhood immunization programs, remains a significant public health concern. Through three distinct research aims, the overall goal of this dissertation is to address the gaps in current immunization programs in Ontario. The key results from this dissertation including the significant contribution of under-identified adults and adolescents to the force of infection of pertussis, the relatively short duration of protective immunity conferred from the DTaP vaccine, and the considerable health and economic impact of pertussis highlight the need to examine new immunization strategies to control pertussis. Together, these results can be integrated into cost-effectiveness models to help public health officials and policy makers evaluate the relative benefits and costs associated with different immunization strategies.

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6 Chapter Six: Appendix

6.1 Supplementary Information for Aim #1

6.1.1 Model Description

To model the transmission dynamics of pertussis in the presence of vaccination, we built an age-structured SEIR-type model that included heterogeneity in contact patterns by age. A schematic overview of the model is given in Figure 2.1, where $S_i(t)$, $E_i(t)$, $I_i(t)$, and $R_i(t)$ represent the respective number of susceptible, exposed, infectious, and recovered individuals in age groups j=1,2,...,10. SR_i(t), ER_i(t), and IR_i(t) represent the number of susceptible, exposed, and infectious individuals who have been previously exposed to pertussis through infection or vaccination and whose immunity to infection has waned. Where applicable, $V_{i,k}(t)$ represents the number of individuals in each age group that have received k doses of vaccine with k=1,2,...,5. There are a total of five possible vaccinated compartments, representing receipt of between one and five total doses of vaccine. Vaccination was implemented according to the current immunization schedule, with a proportion of individuals receiving the vaccine as they enter an age category for which pertussis vaccination is recommended (i.e., as they enter the 2 month, 4 month, 6month, 2 years, or 7 years of age categories). The exposed and infected classes were divided into 2 and 4 compartments, respectively, to change the amount of time spent in each class from and exponential to a more realistic gamma distribution. We allowed the model to run for 145 years before implementation of vaccination.

The age groups are defined as follows:

1: 0-2 months 2: 2-4 months 3: 4-6 months 4: 6-24 months 5: 2-7 years 6: 7-10 years 7: 10-15 years 8: 15-20 years 9: 20-65 years 10: ≥65 years

6.1.2 Model Equations

$$\begin{aligned} \frac{dS_{j}}{dt} &= {}_{j}N {}_{j}S_{j} + \left(1 {}_{c_{j-1,1}}\right) {}_{j-1}S_{j-1} {}_{j-1}S_{j-1} {}_{j}S_{j} \\ \frac{dV_{2,6,1}}{dt} &= c_{j-1,1-j-1}S_{j-1} + \left(1 {}_{c_{j-1,k+1}}\right) {}_{j-1}V_{j-1,1} + {}_{v}V_{j,2} {}_{v}V_{j,1} {}_{j}V_{j,1} {}_{u_{j}}V_{j,1} \\ \frac{dV_{2,6,2,5}}{dt} &= \left(1 {}_{c_{j-1,k+1}}\right) {}_{j-1}V_{j-1,k} + c_{j-1,k-j-1}V_{j-1,k-1} + {}_{v}V_{j,k-1} {}_{v}V_{j,k} {}_{j}V_{j,k} \right] \\ \frac{dV_{7,10,1,5}}{dt} &= {}_{j-1}V_{j-1,k} + {}_{v}V_{j,k+1} {}_{v}V_{j,k} {}_{j}V_{j,k} {}_{j}V_{j,k} \\ \frac{dE_{j}}{dt} &= {}_{j}S_{j} {}_{j}E_{j} {}_{j}F_{j} + {}_{j-1}E_{j-1} {}_{j}E_{j} \\ \frac{dI_{j}}{dt} &= E_{j} {}_{j}I_{j} {}_{j}F_{j} + {}_{j-1}I_{j-1} {}_{j}I_{j} \\ \frac{dR_{j}}{dt} &= \left(I_{j} + IR_{j}\right) {}_{k}R_{j} {}_{j}R_{j} + {}_{j-1}R_{j-1} {}_{j}SR_{j} \\ \frac{dSR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}ER_{j} {}_{j}R_{j} + {}_{j-1}ER_{j-1} {}_{j}ER_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}ER_{j} {}_{j}R_{j} {}_{j}F_{j} {}_{j}F_{j-1} {}_{j}ER_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}ER_{j} {}_{j}R_{j} {}_{j}F_{j-1} {}_{j}R_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}ER_{j} {}_{j}R_{j} {}_{j}F_{j-1} {}_{j}R_{j} {}_{j}R_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}ER_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}ER_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} {}_{j}R_{j} \\ \frac{dIR_{j}}{dt} &= {}_{j}SR_{j} {}_{j}R_{j} {}_{j$$

Parameter	Description
$\lambda_{\mathbb{Z}}^*$	Force of infection
Е	Rate of transition from exposed to infectious
γ	Rate of recovery from infection
Ø	Rate of loss of immunity following infection
ω_{v}	Rate of loss of immunity following vaccination
rr	Relative infectiousness of for individuals with previous
	exposure to pertussis
C _{j,k}	Vaccine coverage
$ ho_{j}$	Aging rate
μ _j	Mortality rate
ni	Birth rate

6.1.3 Model Parameters

 $\frac{\eta_j}{\text{Subscript j indicates age group, k indicates vaccine dose number.}}$

*Force of infection is given by:

$$_{j} = \frac{_{jm} (t)(I_{m} + rrIR_{m})}{N}$$

where ϕ_{jm} is the contact rate for infective individuals of age group m (I_m and IR_m) with susceptible individuals of age group j (based on a population-based prospective study of contact patterns in eight European countries), rr is the reduction in infectiousness for individuals with previous exposure to pertussis, N is the total population size, and $\beta \Box \Box \Box$ is the probability of transmission given contact (assumed to be independent of age):

$$(t) = {}_{1}*1 + {}_{2}\cos\frac{2t}{365} + {}_{3}\cos\frac{2t}{4*365} + {}_{3}$$

6.1.4 Contact Matrix

Below is the contact matrix used in simulations, adapted from a prospective study of contact patterns in Great Britain.¹ The values represent the average number of contacts in each column age group that an individual in each row age group meets per day. In this study, a 'contact' is defined as either a two-way conversation involving an exchange of at least 3 words (non-physical contact) or an interaction with skin-to-skin contact (physical contact).

	0-2mo	2-4mo	4-6 mo	6mo- 2y	2-7y	7-10y	10-15y	15-20y	20-65y	65+ y
0-2mos	0.002	0.002	0.002	0.019	0.047	0.013	0.014	0.008	0.130	0.013
2-4mos	0.002	0.002	0.002	0.019	0.047	0.013	0.014	0.008	0.130	0.013
4-6mos	0.002	0.002	0.002	0.019	0.047	0.013	0.014	0.008	0.130	0.013
6mos-2y	0.019	0.019	0.019	0.173	0.424	0.117	0.123	0.072	1.173	0.117
2-7y	0.051	0.051	0.051	0.460	2.138	1.828	0.682	0.436	4.658	0.506
7-10y	0.019	0.019	0.019	0.171	1.936	2.390	0.654	0.438	3.468	0.408
10-15y	0.016	0.016	0.016	0.144	0.812	0.786	6.850	1.520	4.540	0.740
15-20y	0.011	0.011	0.011	0.099	0.334	0.204	1.030	6.710	6.500	1.110
20-65y	0.166	0.166	0.166	1.491	5.138	3.234	5.090	5.950	70.490	10.330
65+ y	0.008	0.008	0.008	0.069	0.242	0.156	0.330	0.300	5.990	3.510

6.1.5 Model Calibration

For calibration of the base model without vaccination, a time series of pertussis mortality in Ontario between 1880 and 1929² was used to derive estimates of pertussis. Specifically, we used reported proportionate mortality by age group² and applied age-specific case-fatality ratios (estimated in 32 U.S. cities over a ten-year period)³ to calculate expected pertussis incidence. In the absence of vaccination we assigned a duration of immunity after natural infection of approximately 18 years based on the best available data.⁴ We used an annual forcing term (β_2), a seasonal forcing term (β_3), and a base transmission parameter (β_1) to encapsulate the underlying dynamics of the effective contact rate (β). β_1 , β_2 , and β_3 were varied to achieve the optimal fit between model predicted incidence and the data for the under 2 years of age cohort. Pertussis is known to be under-diagnosed, and based on best available data we assumed a 16% probability of case-detection.⁵

In order to calibrate estimates of duration of vaccine-induced immunity, we added vaccination to the best calibrated model derived based on natural history data as above. We then calibrated the model, incorporating vaccination, to a previously described time series including all data on laboratory-confirmed pertussis cases for the Greater Toronto Area (GTA), covering the period 1993 to 2004.⁶ We varied age-specific case-report probabilities and duration of vaccine-induced immunity to achieve an optimal model fit to the data on individuals less than 2 years old. We used data on the under 2 age group for both model calibration steps because we assumed case-detection would be most complete for younger children, given more typical and more severe disease manifestations in this group.

6.2 Supplementary Information for Aim #2

6.2.1 Modified Downs and Black Checklist for Measuring Study Quality.⁷

Reporting

1. Is the hypothesis/aim/objective of the study clearly described?

yes no 0

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no.

> yes no

> > 0

0

3. Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. yes

4. Are the interventions of interest clearly de- scribed? Treatments and placebo (where relevant) that are to be compared should be clearly described. ves 1

no

no

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.

> yes 2 partially 1 no

6. Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below). yes 1 0

7. Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes 0 no

no

8. Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

yes 0 no

9. Have the characteristics of patients lost to follow-up been described? This should be answered ves where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

yes 1 no

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

yes 1 0 no

External validitv

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

```
yes
         1
no
         0
unable to determine 0
```

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes No 0 unable to determine 0

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

```
yes
no
         0
unable to determine 0
```

Internal validity - Bias

14. Was an attempt made to blind study subjects to the intervention they have received?

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

```
yes 1
no 0
unable to determine 0
```

16. If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

```
Yes 1
no 0
unable to determine 0
```

18. Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example non- parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

```
yes 1
no 0
unable to determine 0
```

19. Was compliance with the intervention/s reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

```
yes 1
no 0
unable to determine 0
```

20. Were the main outcome measures used accurate (valid and reliable)?

For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

```
yes 1
no 0
unable to determine 0
```

Internal validity - Confounding (Selection Bias)

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case- control studies where there is no information concerning the source of patients included in the study.

```
yes 1
no 0
unable to determine 0
```

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

```
yes 1
no 0
unable to determine 0
```

23. Were study subjects randomized to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no be- cause it is predictable.

```
yes 1
no 0
unable to determine 0
```

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes 1 no 0 unable to determine 0

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or con- founding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

```
yes 1
no 0
unable to determine 0
```

26. Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

```
yes 1
no 0
unable to determine 0
```

6.2.2 Data abstraction for Meta-Analysis

Below is the table summarizing the data-abstraction for the studies included in the systematic review.

Study	Measure of Association Calculated in Study	Odds Ratio Conversion ^a	Type of Pertussis Definition	Number of Vaccines
Tartof <i>et al</i> . 2013 ⁸	Risk Ratio	$\begin{array}{c} {\rm OR}_2({\rm MN}){=}1.9(95\%{\rm CI:}1.3-2.9)\\ {\rm OR}_3({\rm MN}){=}2.6(95\%{\rm CI:}1.7-3.8)\\ {\rm OR}_4({\rm MN}){=}3.2(95\%{\rm CI:}2.1-4.8)\\ {\rm OR}_5({\rm MN}){=}6.1(95\%{\rm CI:}4.1-8.9)\\ {\rm OR}_6({\rm MN}){=}8.9(95\%{\rm CI:}6.0-13.0)\\ {\rm OR}_2({\rm OR}){=}1.3(95\%{\rm CI:}0.6-2.8)\\ {\rm OR}_3({\rm OR}){=}1.5(95\%{\rm CI:}0.7-3.7)\\ {\rm OR}_4({\rm OR}){=}1.7(95\%{\rm CI:}0.8-3.7)\\ {\rm OR}_5({\rm OR}){=}2.6(95\%{\rm CI:}1.2{-}5.6)\\ {\rm OR}_6({\rm OR}){=}4.0(95\%{\rm CI:}1.2-5.6)\\ \end{array}$	Clinical	5
Klein <i>et al.</i> 2012 ⁹	Odds Ratio	$\begin{array}{c} OR_2 = 1.42 \; (95\% CI:\; 1.21 - 1.66) \\ OR_3 = 2.02 \; (95\% CI:\; 1.72 - 2.36) \\ OR_4 = 2.86 \; (95\% CI:\; 2.45 - 3.35) \\ OR_5 = 4.07 \; (95\% CI:\; 3.48 - 4.75) \\ OR_6 = 5.77 \; (95\% CI:\; 4.93 - 6.75) \end{array}$	Clinical	5
Misegades <i>et al</i> . 2012 ¹⁰	Odds Ratio	$\begin{array}{c} OR_2 = 2.43 \; (05\% CI:\; 1.41 - 4.20) \\ OR_3 = 4.02 \; (95\% CI:\; 2.39 - 6.77) \\ OR_4 = 6.62 \; (95\% CI:\; 3.97 - 11.04) \\ OR_5 = 8.95 \; (95\% CI:\; 5.40 - 14.78) \\ OR_6 = 14.94 \; (95\% CI:\; 9.13 - 24.46) \end{array}$	Clinical	5
Witt <i>et al</i> . 2012 ¹¹	Vaccine Effectiveness	NA	NA	NA
Zinke <i>et al</i> . 2010 ¹²	Seropositivity	OR ₂ =1.59 (95%CI: 1.21 - 2.08)	Serologic	5
Zepp et al. 2007 ¹³	Seropositivity	OR ₆ =2.23 (95%CI: 1.88 - 2.70)	Serologic	5
Gustafsson <i>et al.</i> 2006 ¹⁴	Rate Ratio	$\begin{array}{c} OR_2 = 1.15 \; (95\% CI: \; 0.84 - 1.57) \\ OR_3 = 1.19 \; (95\% CI: \; 0.86 - 1.65) \\ OR_4 = 1.31 \; (95\% CI: \; 0.92 - 1.85) \\ OR_5 = 1.92 \; (95\% CI: \; 1.36 - 2.69) \\ OR_6 = 2.85 \; (95\% CI: \; 1.96 - 4.09) \end{array}$	Clinical	3
Lacombe et al. 2004 ¹⁵	Risk Ratio	OR ₂ =2.24 (95%CI: 1.21 - 4.12)	Clinical	3
Olin <i>et al</i> . 2003 ¹⁶	Rate Ratio	OR ₂ =0.99 (95%CI: 0.65 - 1.48)	Clinical	3
Esposito et al. 2002 ¹⁷	Seropositivity	OR ₅ =0.97 (95%CI: 0.50 - 1.72)	Serologic	3
Salmaso <i>et al.</i> 2001 ¹⁸ Rate Ratio		$\begin{array}{c} \text{OR}_{2.5}(\text{SB}) = 1.22 \; (95\%\text{CI:}\; 0.73 - 2.03) \\ \text{OR}_{3.5} \; (\text{SB}) = 1.22 \; (95\%\text{CI:}\; 0.71 - 2.07) \\ \text{OR}_{4.5} \; (\text{SB}) = 3.19 \; (95\%\text{CI:}\; 2.08 - 4.95) \\ \text{OR}_{2.5} \; (\text{CB}) = 1.00 \; (95\%\text{CI:}\; 0.57 - 1.72) \\ \text{OR}_{3.5} \; (\text{CB}) = 1.05 \; (95\%\text{CI:}\; 0.59 - 1.84) \\ \text{OR}_{4.5} \; (\text{CB}) = 3.12 \; (95\%\text{CI:}\; 2.02 - 4.88) \\ \end{array}$	Clinical	3
Esposito et al. 2001 ¹⁹	Seropositivity	OR ₅ =1.06 (95%CI: 0.83 - 1.37)	Serologic	3

^a Subscript represents number of years after last dose of DTaP. Reference category is one year after last DTaP vaccine.

6.3 Supplementary Information for Aim #3

6.3.1 Outpatient Complication Costs

Below is the breakdown of costs included in complications. Distributions for sensitivity analysis shown with mean and standard deviation (in parentheses).

Complication	Cost per Visit	Number of Visits	Total
Weight Loss >5%	\$33.70 ²⁰	γ=1 (0.25)	\$33.70
Sinusitis	\$33.70 ²⁰	γ=1 (0.25)	\$33.70
Pneumonia	\$33.70 ²⁰	$\gamma = 1.3 (0.25)^*$	\$43.81
Otitis Media	\$33.70 ²⁰	γ=1 (0.25)	\$33.70
Rib Fracture	\$33.70 ²⁰ GP Visit \$17.05 ²⁰ X Pass (technical	γ=1 (0.25)	\$59.50
	\$17.95 A-Kay (lecinical		
	\$7.85 ²⁰ X-Ray (professional		
	component)		
Fainting	\$33.70 ²⁰	γ=1 (0.25)	\$33.70
Urinary Incontinence	\$33.70 ²⁰	γ=1 (0.25)	\$33.70
Pertussis no	\$33.70 ²⁰	$\gamma = 2.4 (0.25)^{21}$	\$80.88
complications			

*Expert opinion

6.3.2 Inpatient Complication Costs

Below is the breakdown of inpatient costs included in model. Data were obtained from the Ontario Case Costing Initiative.²²

	ICD-10 Codes	2011 Cost,	2016 Cost,	Length of	Daily Costs,
		Mean (SD)	Mean (SD)	Stay, Mean	Mean (SD)
			w/ 5%	(SD)	
			Physician		
			Costs		
Paroxysmal	A37.0, A37.9	\$12,160	\$13,674	7.6 (10.8)	\$1,799
Pertussis		(\$17,990)	(\$20,230)	days	(\$2,662)
Weight Loss	R63.4	\$4,346	\$4,887	4.6 (4.4)	\$1,062
>5%		(\$10,294)	(\$11,576)	days	(\$2,516)
Neurological	G04.0, G40.1,	\$12,595	\$14,163	5.2 (16.9)	\$2,724
Complications	G40.2, G40.3,	(\$58,989)	(\$66,333)	days	(\$12,756)
	G40.4, G40.6,				
	G40.7, G40.8,				
	G40.9, G41.0,				
	G41.1, G41.2,				
	G41.8, G41.9,				
	G93.4, R56.8				
Pulmonary	J13.0, J14.0,	\$6,763	\$7,605	3.9 (4.8)	\$1,950
Complications	J15.0, J15.1,	(\$12,614)	(\$14,184)	days	(\$3,637)
	J15.2, J15.3,				
	J15.4, J15.5,				
	J15.6, J15.7,				
	J15.8, J15.9,				
	J17.0, J18.9,				
	J93.0, J93.1,				
	J93.8, J93.9,				
	J98.1, P28.0,				
	P28.1				
Hernia	K40.0, K40.1,	\$4,605	\$5,178	1.9 (2.2)	\$2,725
Complications	K40.2, K40.3,	(\$5,480)	(\$6,162)	days	(\$3,243)
-	K40.4, K40.9,			-	
	K42.0, K42.1,				
	K42.9, K46.0,				
	K46.1, K46.9				

6.3.3 Antibiotic Costs

Complication	Drug	Dosing	Number of	Cost per tab	Total cost
			Tabs		
Uncomplicated	Erythromycin	2g per day in 4	112	0.1828^{24}	\$20.47
pertussis	(250mg)	doses for 14			
		days ²³			
	Azithromycin	500mg on day	6	\$1.3070 ²⁴	\$7.842
	(250mg)	one, 250mg for			
		days $2-5^{23}$			
Sinusitis	Amoxicillin-	1000/62.5mg 2	20-28	\$0.6673 ²⁴	\$16.0152
	Clavulanate	tabs or			
	(500mg / 125	2000/125mg 1			
	mg)	tab, twice daily			
		for 5-7 days ²⁵			
Otitis Media	Amoxicillin	1000mg three	60	\$0.3417 ²⁴	\$20.502
	(500mg)	times daily for 10			
		days [*]			
Pneumonia	Azithromycin	500mg on day	5	\$1.3070 ²⁴	\$6.535
	(250mg)	one, 250mg for 4			
		days ²⁶			

Below are the adult antibiotic treatment costs included in model.

*Expert opinion

6.3.4 Age Specific Economic Burden and Net Monetary Impact

	Ont	Ontario		ada
	2012	2013	2012	2013
Budget Impact				
<6 mo	\$7,152,113	\$2,619,084	\$22,614,780	\$8,512,022
6 mo to 4y	\$2,885,166	\$815,019	\$10,693,043	\$2,934,067
5 to 17 y	\$3,975,243	\$898,252	\$21,223,592	\$5,035,945
18 to 64 y	\$2,593,949	\$600,704	\$9,347,319	\$3,085,434
65+ y	\$279,179	\$111,671	\$2,540,526	\$823,577
Total	\$16,885,649	\$5,044,730	\$66,419,259	\$20,391,044
Net Monetary				
Impact (1GDP/capita)				
<6 mo	\$12,596,240	\$4,612,708	\$39,828,958	\$14,991,300
6 mo to 4y	\$6,493,279	\$1,834,260	\$24,065,485	\$6,603,334
5 to 17 y	\$12,834,004	\$2,899,991	\$68,520,006	\$16,258,462
18 to 64 y	\$6,262,439	\$1,450,249	\$22,566,755	\$7,449,007
65+ y	\$393,318	\$157,327	\$3,579,197	\$1,160,289
Total	\$38,579,281	\$10,954,535	\$158,560,400	\$46,462,392
Net Monetary Impact (3GDP/capita)				
<6 mo	\$23,484,495	\$8,599,956	\$74,257,313	\$27,949,857
6 mo to 4y	\$13,709,505	\$3,872,742	\$50,810,369	\$13,941,870
5 to 17 y	\$30,551,526	\$6,903,470	\$163,112,833	\$38,703,495
18 to 64 y	\$13,599,419	\$3,149,339	\$49,005,626	\$16,176,151
65+ y	\$621,598	\$248,639	\$5,656,541	\$1,833,714
Total	\$81.966.543	\$22.774.146	\$342,842,682	\$98 605 087

Below are the age-specific estimates of the economic burden and net monetary impact of pertussis in Ontario and Canada for 2012 and 2013.

6.3.5 Outcome Distributions for Costs

Below are the outcome distributions for the probabilistic sensitivity analyses for costs.



6.3.6 Outcome Distributions for QALYs Lost

Below are the outcome distributions for the probabilistic sensitivity analyses for QALYs lost.



6.3.7 Outcome Distributions for Life Years Lost

Below are the outcome distributions for the probabilistic sensitivity analyses for life years lost.



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