Evaluating pertussis vaccine effectiveness in Manitoba using administrative and public health surveillance data

By

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Abstract

Objective: Pertussis persists in Manitoba despite a long-standing universal vaccine program; however, little is known provincially about the impact of this program on disease rates or about the effectiveness of the different pertussis vaccines used over time. Estimates of provincial pertussis vaccine coverage are lower than the national herd immunity target of 95%, but it is unclear whether periodic increases in cases are driven by an under-vaccinated cohort or if resurgences are due to low pertussis vaccine effectiveness or waning vaccine protection. This study aims to address these gaps in knowledge.

Methods: We linked several administrative datasets housed at the Manitoba Centre for Health Policy to public health surveillance data to identify laboratory-confirmed cases of pertussis between 1992 and 2017. We used age-period-cohort models to investigate population-level trends in pertussis incidence over the study period and conducted a nested case-control study to measure whole-cell and acellular pertussis vaccine effectiveness and duration of protection.

Results: The whole-cell pertussis vaccine used in Manitoba from 1981 to 1996 had low vaccine effectiveness and contributed to a large outbreak of pertussis in the mid-1990s. The acellular pertussis vaccine in use from 1997 to the present provided high early protection, which appeared to wane over time. Most hospitalizations were in children under the age of one across the study period.

Conclusion: Changes in the pertussis vaccine program contributed to outbreaks of disease many years later, highlighting the importance of ongoing disease surveillance and vaccine effectiveness estimation. Severe outcomes were almost exclusively observed in young children, making this cohort an appropriate target for future research and interventions.

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The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living or other data providers is intended or should be inferred.

Dedication

To Michel, Henri, and Madeleine

Love and a cough cannot be hid – *George Herbert*

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List of Abbreviations

aP	Acellular pertussis vaccine
APC	Age, period, cohort
CDS	Communicable disease surveillance
CI	Confidence interval
cNICS	Childhood National Immunization Coverage Survey
DAG	Directed acyclic graph
DPIN	Drug Programs Information Network
DTaP	Diphtheria tetanus acellular pertussis vaccine
HAD	Hospital Abstracts Database
HIPC	Health Information Privacy Committee
HREB	University of Manitoba Health Research Ethics Board
ICD	International classification of diseases
LC	Laboratory-confirmed
MCHP	Manitoba Centre for Health Policy
MH	Manitoba Health
MHR	Manitoba Health Insurance Registry
MIMS	Manitoba Immunizations Monitoring System
MSD	Medical Services Database
NACI	National Advisory Committee on Immunization
OP	Outpatient
OR	Odds ratio
PHIMS	Public Health Information Management System
PHIN	Personal health identification number
PT	Pertussis toxin
RCT	Randomized clinical trial
RR	Risk ratio
Tdap	Tetanus diphtheria acellular pertussis vaccine
VE	Vaccine effectiveness
wP	Whole cell pertussis vaccine

Authorship Declaration

This is a “sandwich” or grouped manuscript thesis that consists of a collection of papers that have already been or are soon to be published in peer-reviewed journals. All studies in this dissertation were conceptualized and executed by the PhD candidate (Krista Wilkinson) in collaboration with her thesis advisor and thesis advisory committee: Dr. Salaheddin Mahmud, Dr. Sergio Fanella, and Dr. Lawrence Elliott. Additional collaborators were Dr. Christiaan Righolt, Dr. Jeff Kwong, Dr. Kevin Schwartz, Dr. Margaret Russell, and Dr. Natasha Crowcroft.

Krista Wilkinson takes full responsibility for the accuracy of this thesis and was responsible for statistical analyses and interpretations. All authors listed on the published studies participated in the interpretation of results and assisted with preparation of manuscript drafts. All authors approved final manuscripts.

Chapter 1. Introduction

Overview

Pertussis (whooping cough) is a highly contagious bacterial respiratory disease caused by *Bordetella pertussis*. One of the characteristic symptoms of pertussis is a burst of rapid coughing followed by an inspiratory whoop, although this symptom is often lacking in very young or adult/geriatric patients [1]. Most pertussis-related complications occur among young infants, and the cause of most pertussis-related deaths is secondary bacterial pneumonia [2].

Following a long period of good pertussis control, there was an increase of pertussis in Manitoba and other Canadian provinces in 2012 [3-5]. Although low vaccine coverage was one of the hypotheses proposed to explain the resurgence of disease [6, 7], it was also observed that cases were occurring among individuals considered fully-vaccinated against pertussis [4, 8, 9]. Canada had moved from whole-cell pertussis (wP) vaccines to acellular pertussis (aP) vaccines in the late 1990s and accumulating evidence suggested a waning of protection of the aP vaccine over time [10].

Public information about pertussis in Manitoba is limited to separate annual reports providing population-level estimates of disease incidence and vaccine coverage. No single report provides details on long-term disease trends. Compiling several annual reports gives a broad overview of pertussis incidence; however, information is not available prior to 2013. Estimates of Manitoba's pertussis vaccine coverage from various sources have consistently been lower than the national target of 95% recommended to achieve herd immunity [11-13]. With sub-optimal vaccine coverage, no information on the impact of the pertussis vaccine program on pertussis rates in Manitoba, and no estimates of vaccine effectiveness, the specific drivers of sporadic provincial increases in cases remain unclear.

This research describes the disease burden of pertussis (incidence of pertussis-related hospitalizations, outpatient medical visits, and laboratory-confirmed pertussis cases) and measures product-specific vaccine effectiveness in Manitoba over several decades spanning both

the wP and aP vaccine periods. Manitoba data are needed to guide vaccine policy and local public health and clinical practice.

Background

Pertussis disease

Pertussis disease is a two-stage process with respiratory colonization followed by toxin-mediated disease; bacteria adhere to the cilia of respiratory epithelial cells, multiply extracellularly in the airways, and release several toxins which have a variety of effects on the host [14]. Predominant among these toxins is pertussis toxin (PT), a multi-subunit protein toxin which is the main contributor to severe disease. At the site of infection, toxins paralyze the cilia and cause inflammation of the respiratory tract, which then interferes with clearing of pulmonary secretions, contributing to the characteristic pertussis cough [1].

Pertussis toxin activity has also been linked with severe and lethal pertussis disease in young infants. Severe pertussis complications include pneumonia, apnea, leukocytosis, pulmonary hypertension, seizures, and encephalopathy [1]. Leukocytosis and hypertension are associated with PT-mediated dysfunction outside the airways, suggesting bacteria or toxins can disseminate beyond the primary site of infection [14].

Infant immune responses differ from older individuals, with an emphasis on a disease tolerance strategy rather than a disease resistance strategy; it is likely that insufficient immune response of the infant provides an opportunity for enhanced *B. pertussis* colonization, which can lead to exacerbated PT-mediated pathologies [14].

Pertussis vaccines

There are two types of pertussis vaccines. Whole-cell pertussis vaccines are suspensions of the whole cells of one or more strains of killed *Bordetella pertussis* which have been appropriately treated to minimize toxicity and retain potency [15]. Instead of containing the whole bacterium, acellular pertussis vaccines consist of a few selected antigens; generally pertussis toxin, filamentous haemagglutinin, 69kDa outer-membrane protein (pertactin), and fimbrial-2 and fimbrial-3 antigens [1]. There is considerable variety in acellular pertussis vaccines available

from different manufacturers as a result not only of the differing concentrations of antigen and different purification methods, but also as a result of potentially using different strains of *B. pertussis* [16].

Pertussis in Canada

Pertussis has been under national surveillance in Canada since 1924, allowing for broad temporal associations to be shown between vaccination programs and trends in disease incidence [3]. In the five years before the introduction of the first whole-cell (wP) pertussis vaccines (1938-1942), the annual incidence of pertussis in Canada was an average of 156 cases per 100,000 people. Incidence subsequently steadily declined, reaching an average of 7 cases per 100,000 people by the mid-1980s [3]. However, this pattern changed in the 1990s, with a rise in incidence and a periodicity of approximately four years [17]. This increase was largely attributed to the low efficacy of the adsorbed wP vaccine being used in Canada during this period [18].

Along with this low efficacy, concerns around adverse events associated with the wP vaccine had been gaining prominence [19, 20]; although it had long been recognized that the wP vaccine had more local and systemic adverse events than most other vaccines, it wasn't until the 1970s that concerns regarding a connection between pertussis vaccines and permanent brain damage became widespread [18, 21]. Although follow-up studies ultimately showed this association was unfounded, wP vaccines were still removed from use in countries such as Sweden (1979) and Japan (for a short period in 1975, replaced by aP in 1981) [22, 23]. In 1997, the Canadian National Advisory Committee on Immunization (NACI) strongly endorsed the newly approved aP vaccine, citing the lower number of vaccine-associated adverse events and the possibility the aP vaccine might be more efficacious (based on short-term efficacy studies) as the basis for this preference [24]. By 1998, the aP vaccine was being used throughout the country [3].

Following the introduction of the aP vaccine, pertussis incidence further declined to a low of 2 cases per 100,000 people by 2011. However, in 2012, the national incidence in Canada increased seven-fold, with outbreaks occurring in several areas among older, vaccinated individuals [3].

Evidence has accumulated over the past several years suggesting that waning protection of the aP vaccine contributed to the increase in disease.

Currently, in Canada, pertussis vaccine is only available as an acellular preparation in combination vaccines [2]; the two types used are the children's formulation (DTaP) that contains high concentrations of pertussis antigens and the adolescent and adult formulation (Tdap) that contains lower concentrations of pertussis antigens [10]. DTaP is recommended at 2,4,6 months and between 12 and 23 months of age, a childhood booster of either DTaP or Tdap is recommended between 4 and 6 years of age, and boosters of Tdap are recommended between 14 and 16 years of age and once again as an adult. NACI further recommends that Tdap vaccine should be offered in every pregnancy, regardless of previous pertussis vaccination history [25].

Pertussis in Manitoba

The epidemiology of pertussis disease is not well understood in Manitoba and information is limited to annual reports available for the years 2013 to 2017 [26]. Over this period, incidence rates varied considerably by region, with Southern Health having incidence rates higher than the provincial estimates from 2013 to 2015 and in 2017 (Table 1). The Northern Health Region had the highest incidence rate in 2016 (28.8 cases per 100,000 people). The highest incidence rates reported across all years were consistently observed in the under one year old age group.

Table 1 Confirmed cases of pertussis in Manitoba by Regional Health Authority and year

Regional Health Authority	2013		2014		2015		2016		2017	
	Count	IR	Count	IR	Count	IR	Count	IR	Count	IR
Manitoba	7	0.5	13	1.0	56	4.2	116	8.7	75	5.5
Winnipeg	2	0.3	5	0.7	6	0.8	37	4.8	15	1.9
Southern Health	3	1.6	6	3.1	47	24.2	47	23.8	42	20.9
Interlake-Eastern	1	0.8	2	1.6	0	0.0	4	3.1	4	3.1
Prairie Mountain	0	0.0	0	0.0	1	0.6	6	3.5	2	1.2
Northern Health	1	1.3	0	0.0	2	2.6	22	28.8	12	15.6

IR – Incidence rate (cases per 100,000 people)
Note: Adapted from *Manitoba Annual Summary of Communicable Diseases* by Manitoba Health, reports for 2013 through 2017, available at https://www.gov.mb.ca/health/publichealth/surveillance/cds/index.html

Available information on pertussis vaccination uptake in Manitoba suggests that the proportion of the population considered fully vaccinated against pertussis has been consistently lower than the 95% required for herd immunity [27]. A study using Manitoba Immunization Monitoring System (MIMS) data estimated that pertussis vaccine coverage for two year-olds was 74% in the period between 2000 and 2007 [12]. The Manitoba Annual Immunization Surveillance Reports produced by Manitoba Health (MH) covering the same period reported slightly lower proportions of two year-olds being complete for age (with a low of 68% in 2005 and a high of 73% in 2007) [28]. Recent MIMS reports indicate that there is regional variation in uptake with coverage consistently lowest in the Southern and Northern Health Regions (Table 2). Using parental interview and healthcare provider chart review, the 2013 Childhood National Immunization Coverage Survey (cNICS) estimated Manitoba's pertussis vaccine coverage for two year-olds at 67.5% [13]. Although they vary slightly due to methodology, data source, and time-period, estimates of pertussis vaccine coverage have been consistently low in the province, potentially resulting in a large and vulnerable under-vaccinated cohort.

Table 2 Percentage (%) of 2-year old population with up-to-date pertussis vaccine status by Regional Health Authority and year, Manitoba

Regional Health Authority	2013	2014	2015	2016	2017
Manitoba	69.6	70.9	73.8	71.7	72.4
Winnipeg	71.4	73.0	75.0	73.6	73.9
Southern Health	61.2	62.6	64.9	62.7	64.7
Interlake-Eastern	71.6	72.0	75.0	72.8	75.4
Prairie Mountain	72.9	75.4	79.1	79.2	79.5
Northern Health	69.8	69.6	76.6	68.6	66.9

Note: Adapted from *Annual Report of Immunization Surveillance* by Manitoba Health, reports for 2013 through 2017, available at https://www.gov.mb.ca/health/publichealth/surveillance/immunization/index.html

Purpose of the study

There are differences between the timing, magnitude, and overall trends of pertussis activity across the Canadian provinces and territories. As well, vaccine schedules, products, and uptake vary by province and territory, making application of national data to local patterns of limited value.

There is a significant knowledge gap around the burden of pertussis in Manitoba. Several sources have shown that pertussis vaccination coverage is well below the national target of 95%, but there is no information about whether incident cases of pertussis in Manitoba are reflective of this low coverage rate, or an indicator of waning immunity. This research provides a comprehensive understanding of pertussis in Manitoba that will be of particular value to provincial decision-makers. The following research questions were examined:

> Question 1 (Chapter 2): What are the effects of age, period, and vaccine birth cohort on pertussis disease incidence in Manitoba?
> Question 2 (Chapter 3): What is already known about pertussis vaccine effectiveness and duration of protection, from the scientific literature?
> Question 3 (Chapter 4): What is the pertussis vaccine effectiveness and duration of protection in Manitoba?

Methods

Data sources

Manitoba Health provides comprehensive health insurance, including coverage for laboratory, hospital, and ambulatory care services, to the province's 1.3 million residents. Coverage is universal, without regard to age or income [29]. For administrative purposes, MH maintains several centralized electronic databases that can be linked using a unique health services number (PHIN). Known for their completeness and accuracy [30, 31], these databases have been used extensively in studies of infectious disease surveillance and vaccine safety and effectiveness [29, 32] [33-35].

Data used in this study were obtained from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy (MCHP), University of Manitoba; MCHP is a research unit within the Department of Community Health Sciences that develops and maintains a population-based data repository on behalf of the Province of Manitoba.

We obtained data from six MH administrative databases (specific database descriptions in methods sections of Chapters 2 and 4) to establish the study cohort, identify individuals diagnosed with pertussis, and describe case and control characteristics.

Case definitions

We included all cases of pertussis diagnosed in the study cohort between April 1, 1992, and March 31, 2017 using the following case definitions:

i) Laboratory-confirmed cases: any individual with a positive pertussis laboratory result reported to MH and recorded in the MH Communicable Disease surveillance database.

ii) Clinical cases: any individual with a clinical report of pertussis reported to MH and recorded in the MH Communicable Disease surveillance database without laboratory confirmation. These cases represent individuals epi-linked to confirmed cases as well as individuals reported to MH on the basis of clinical symptoms.

iii) Hospitalized cases: any individual with a separation diagnosis of pertussis as recorded in the Hospital Abstracts database; ICD9 codes with the first three digits 033 and ICD10 codes starting with A37 (Table A.1).

iv) Outpatient cases: any individual with a pertussis-related ICD9 diagnosis starting with 033 as recorded in the Medical Claims/Medical Services database.

We considered all diagnoses within 6o days as the same episode for an individual and kept the earliest episode; an individual could meet more than one case definition in the same episode and episode date (index date) was the earliest date by any case definition. For example, an individual might have an OP visit followed by a subsequent hospitalization with a LC result during the

same episode and would meet all three case definitions with the episode date based on the medical service date.

Research design in vaccine effectiveness studies

The classical hierarchy of research design places randomized control trials (RCTs) at the pinnacle due to their ability to deal with confounding and bias. However, there are several factors that impact estimates of vaccine effectiveness that may not be easily studied in an RCT including: host factors (e.g., age, comorbidity, prior exposure to disease and vaccine, adherence to recommended vaccine schedule, and time since vaccination) and vaccine factors (e.g., vaccine composition and match between vaccine strain and circulating disease). Although RCTs can provide high quality evaluation of short-term vaccine effectiveness under rigid parameters, it is arguably more important to establish how pertussis vaccines perform in real-world settings.

Observational studies are designed to show how a vaccine (often already proven efficacious in an RCT) performs under natural field conditions. However, although these studies allow us to measure the messy real-world effectiveness of vaccines, they are also subject to multiple complex challenges. Of particular concern in observational vaccine effectiveness studies are biases resulting from misclassification of pertussis disease, misclassification of pertussis vaccine status, confounding, and selection bias. However, a carefully designed and executed observational study with attention to possible sources of confounding and bias can yield high quality evidence regardless of its relative position on the hierarchy of evidence.

Ethics approvals

The study was approved by the University of Manitoba Health Research Ethics Board (HREB file: H2018:013) and by the Health Information Privacy Committee (HIPC project: 2017/18-59) at Manitoba Health, Seniors and Active Living. The required annual renewals of the HREB approval were completed, as was the annual accreditation through MCHP (MCHP project: 2018-016). Data providers were notified of all presentations and manuscripts submitted for publication.

Knowledge translation

The findings from these studies have been disseminated through various mechanisms. This research has been published in peer-reviewed academic journals and findings were also presented at the European Society for Pediatric Infectious Diseases (May 2019) and at the Canada Student Health Research Forum (June 2019).

Chapter 2. Age-period-cohort analysis of pertussis disease incidence in Manitoba

Preface

The first objective of this dissertation was to describe the age, period, and birth cohort-specific trends in pertussis disease incidence over a 25-year period in Manitoba. In the introduction, we saw that broad changes in vaccine products were associated temporally with changes in disease incidence nationally. Using administrative data, we performed an age-period-cohort analysis to explore the impact of major changes in Manitoba's vaccine program on pertussis disease between 1992 and 2017, spanning both the whole-cell and acellular pertussis vaccine periods. This is the first study we are aware of that examines the effects of age, period, and cohort on pertussis incidence. The availability of multiple administrative databases allowed us to identify cases from various data sources, providing important insights into the role of case definition on estimates of disease.

Manuscript

Wilkinson K, Righolt CH, Elliott L, Fanella S, Mahmud SM (2022). The impact of pertussis vaccine program changes on pertussis disease burden in Manitoba, 1992-2017 – An age-period-cohort analysis. *International Journal of Epidemiology*, Epub ahead of print doi: 10.1093/ije/dyac001

Abstract

Background: Changes to pertussis vaccination programs can have long-term impacts on disease burden at the population level. These impacts should be estimated independently from other factors such as age and period-related trends. We linked public health and administrative databases and used age-period-cohort (APC) models to explore pertussis incidence in Manitoba over a 25-year period.

Methods: We identified all laboratory-confirmed cases of pertussis between 1992 and 2017 from Manitoba's Communicable Diseases Database and calculated age-standardized incidence rates. We used APC models to investigate trends in pertussis incidence.

Results: During the study period, 2,479 cases were reported. Age-standardized rates were highest during a large outbreak in 1994 (55 cases/100,000 person-years), with much lower peaks in 1998, 2012, and 2016. We saw strong age and cohort effects in the APC models, with a steady decrease in incidence with increasing age and increased risk in the cohort born between 1980 and 1995.

Discussion: The highest risk for pertussis was consistently in young children, regardless of birth cohort or time-period. The 1981 program change to an adsorbed whole-cell pertussis vaccine with low effectiveness resulted in reduced protection in the 1981-1995 birth cohort and contributed to the largest outbreak of disease during the 25-year study period.

Introduction

Pertussis, a highly contagious bacterial respiratory disease, remains a common vaccine-preventable disease in Canada, despite the availability of a vaccine since the 1940s [36]. The purpose of pertussis vaccine programs is to reduce disease burden; evaluation of these programs is necessary to determine whether they are achieving this objective [37]. At the national level, temporal associations between changes in the vaccine program and incidence of pertussis have been observed [3]. In Manitoba (a Canadian province with 1.3 million residents), both pertussis vaccine products and vaccine schedules have changed over time [38]. The whole-cell pertussis (wP) vaccine used since the 1940s was replaced by the adsorbed wP vaccine in the 1980s. Concerns about the effectiveness and safety of the wP vaccine led to the switch to acellular pertussis (aP) vaccines in the late 1990s [12, 39]. Although provincial pertussis incidence rates have been reported [40], the influence of program changes on rates has not been estimated independently from other important influences such as age-related trends.

Age-period-cohort (APC) models permit estimating the independent effects of age, period, and cohort on disease incidence [41-43]. In these models, age effects are the variations with age that influence all periods and cohorts similarly; period effects are the variations over time periods that influence all age groups and cohorts simultaneously; and cohort effects are the variations across groups of individuals who experience an initial event: birth in the same year in this case [44].

Using APC models, we explored the impact of major changes in the pertussis vaccine program in Manitoba on provincial disease burden over a 25-year period while accounting for possible period and age effects.

Methods

We examined changes in pertussis trends between 1992 and 2017 (the earliest and most recent years with full data availability) through linking public health surveillance with several Manitoba Health (MH) hospital, physician, and prescription claims databases. This study was approved by the University of Manitoba Research Ethics Board and by MH's Health Information Privacy Committee.

Data sources

MH is a government agency that provides universal publicly funded health care to the province's residents; insured services include hospital, physician, and preventive services such as vaccinations. We used a unique lifetime personal health identification number (PHIN) to link electronic administrative and public health databases. The Manitoba Health Insurance Registry (MHR) tracks addresses and dates of birth, insurance coverage, and death for all insured persons in the province. The Communicable Disease Surveillance Database (CDS) records all cases of notifiable diseases reported by clinicians and laboratories to MH since 1992. Under *The Manitoba Public Health Act*, clinicians must report all cases and deaths due to pertussis and laboratories must report any positive pertussis tests. The CDS database stores information on laboratory specimen type, collection date, and test results.

Study cohort

We defined an eligible participant as any individual who was born after 1988 and was continuously registered in the MHR within two months of birth at any time between April 1, 1992, and March 31, 2017 (the study period). Participants entered the study cohort at the start of the study period (if born between 1988 and March 31, 1992) or at birth (if born after April 1, 1992) and exited the study cohort on earliest of the date they lost MH coverage for any reason, the end of the study period, or the date of pertussis diagnosis (see below).

Case definition

We included all individuals with a positive laboratory test for *Bordetella pertussis* between April 1, 1992 and March 30, 2017 as recorded in the CDS. We considered all diagnoses within 6o days as the same episode for an individual and kept the earliest episode. A case's index date (date of diagnosis) was specimen collection date, or laboratory report date where specimen collection date was not available.

Covariates

Age groups used in stratified analyses were created to align with the current publicly-funded pertussis vaccine schedule in Manitoba; the combined diphtheria, tetanus, aP, polio, *Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccine at 2, 4, 6, and 18 months (since 1997), the combined tetanus, diphtheria, aP vaccine , and polio (Tdap-IPV) vaccine at 4-6 years of age (replacing DTaP-IPV in 2012), and the Tdap vaccine once in adolescence (since 2003), and once in adulthood (since 2012) (Supplementary Table 1) [12, 39, 45, 46].

Birth cohorts were created according to the vaccine product and schedule in use at the patient's birth. The wP vaccine birth cohort was born between 1975 and 1980; the adsorbed wP vaccine birth cohort was born between 1981 and 1996; and the aP vaccine birth cohort was born after 1997.

Analysis

We calculated age-standardized incidence rates per 100,000 person-years using the end-of-year population data from the MHR as the denominator and the 2016 Canadian Census population as the reference population.

Age-period-cohort models

We modelled age, period, and cohort as continuous variables through the use of spline functions [47]. To account for the identifiability problem in APC models (i.e., cohort=period-age) we forced a constraint (average risk ratios [RR] of 0 on the log scale) on the period effects in our primary analysis; period effects were detrended and the drift term was added to the cohort effects.

Cohort analyses were limited to individuals born after 1975 (the earliest year population data were available). In all models, the reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of

the cases (1989); age effects were rates per 100,000 person-years for the reference cohort and cohort effects were risk ratios (RR) relative to the reference cohort.

Results

We identified a total of 2,479 newly diagnosed laboratory-confirmed cases between 1992 and 2017, for an overall incidence rate of 7.9 cases per 100,000 person-years. Age-standardized rates were highest in 1994 at 55 cases per 100,000 person-years (Figure 1, Table B.2) with much lower peaks occurring in 1998, 2012, and 2016. The graph of age-specific incidence rates by period of diagnosis in Figure 2A provides some evidence of period effects with roughly parallel lines across the study period.

Figure 1. Age-standardized rates of pertussis cases per 100,000 person-years in Manitoba by index year

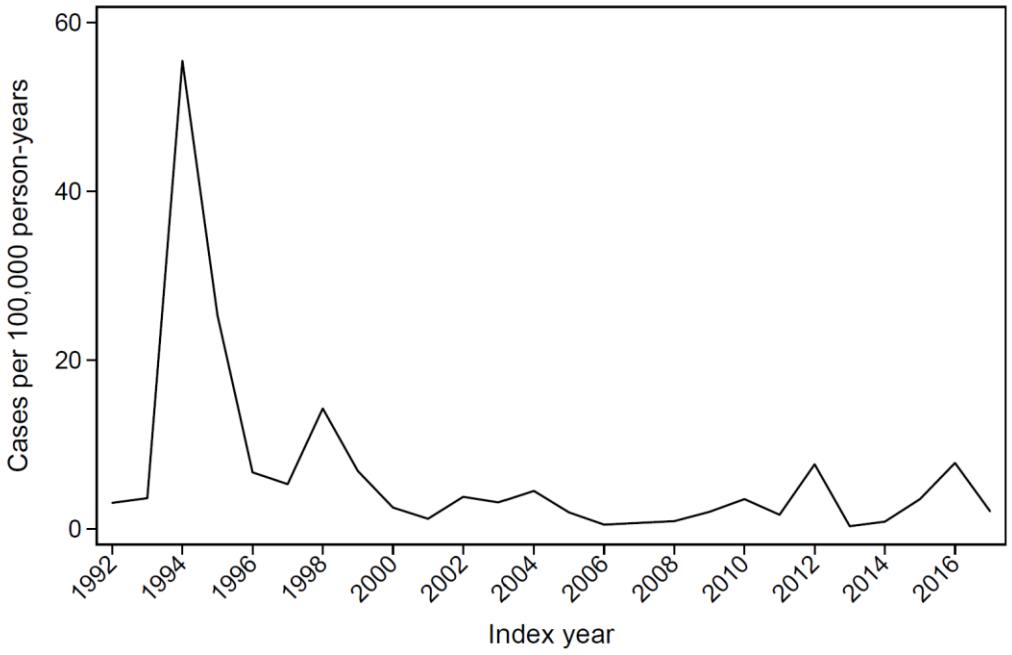


Figure 2B shows incidence rates within age groups by vaccine birth cohort; although limited to the three later cohorts, the pattern is suggestive of cohort effects. In the adsorbed wP vaccine birth cohort (born 1981-1996), incidence was highest in 1-11 year olds compared to the aP

vaccine birth cohort (born >1997) which had the highest age-specific rates in the <1 year olds. Incidence was low and linear for cases 18 years and older across all birth cohorts.

Figure 2 A) Cases of pertussis per 100,000 person-years in Manitoba, 1992-2017, stratified by age at index date B) Cases of pertussis per 100,000 person-years by vaccine birth cohort, stratified by age at index date. Lines correspond to each age group.

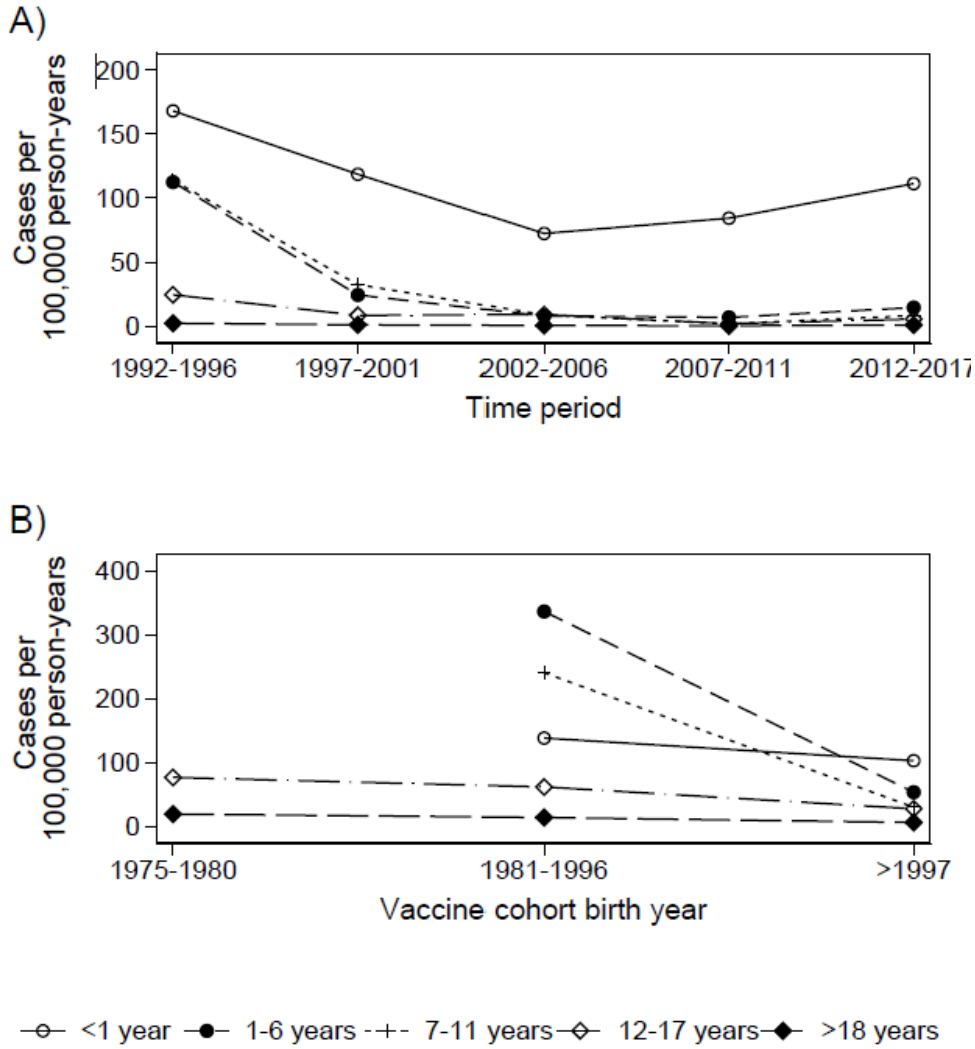


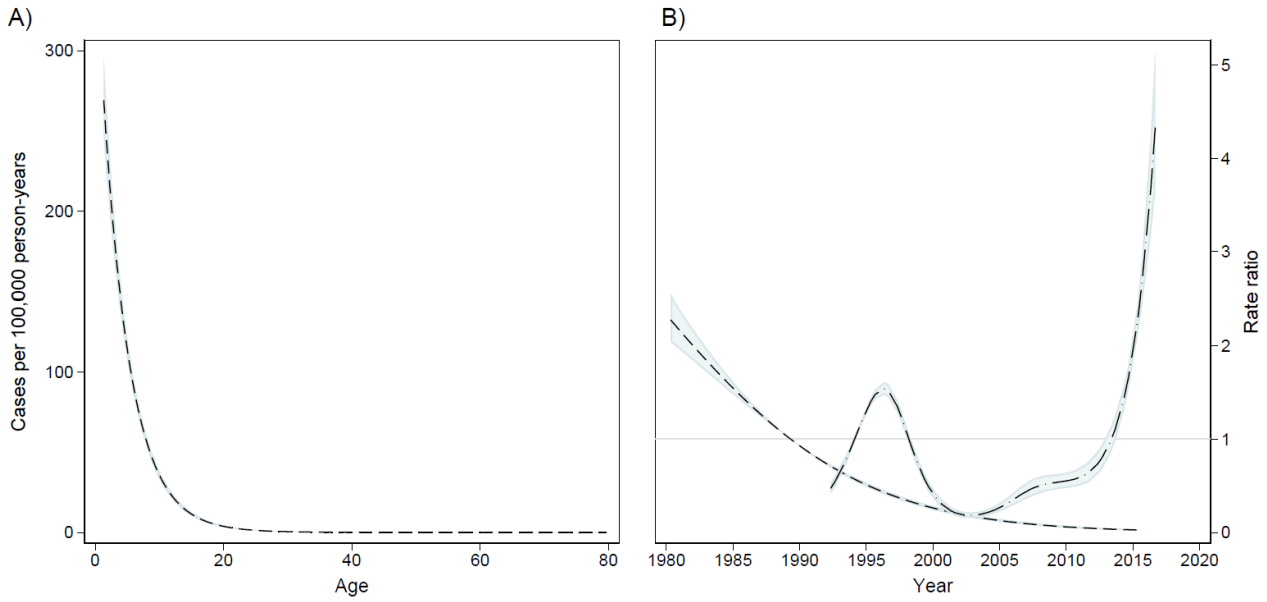
Figure 3 shows the age, period, and cohort effects estimated from the APC model. Figure 3A shows strong age effects, with a steady decrease in pertussis incidence with increasing age. This

follows the same age pattern as seen in Figure 1, with the highest rates of disease observed in young children and very little disease seen in adults across the study period.

Figure 3 Age-period-cohort model of pertussis incidence in Manitoba, 1992-2017, with average period effect constrained to be zero

A) Estimated age effect.

B) Cohort effect (dashed) and period effect (dashed-dot) rate ratios. The reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of the cases (1989).



Period was constrained in this model, so the function on the right in Figure 3B is the period function relative to 1996 and the function on the left is a cohort function representing residual effects. The period function in Figure 3B (the shorter graph on the right) shows deviation from linearity in the mid-90s and again around 2012 where increased risk was observed relative to the reference year of 1996 suggesting period effects. This result corresponded to the pattern suggested in the age-period plot (Figure 2A).

The graph on the left in Figure 3B shows a cohort effect characterized by a rapid deceleration of risk from the earlier birth cohorts relative to the 1989 reference cohort. Risk continued to decelerate in later cohorts, although the decrease was slightly slower for those born after 2005.

When we constrained the cohort effect (instead of the period effect), we continued to see an increased risk in the cohort born between 1980 and 1995 (Figure B.1). In this figure, the function on the left is the cohort function relative to individuals born in 1989 and the function on the right is a period function representing residual effects. With this reparameterization, period effects were less important than in the model with the period effect constrained.

Discussion

Our APC models indicate that the changes in pertussis incidence in Manitoba had a birth cohort component with increased risk in individuals born between 1980 and 1995. Our results further suggest that period effects were less important in explaining trends in pertussis disease burden over time. Our models show strong age effects with the highest pertussis incidence consistently in young children.

The age-specific rate changes we observed in the mid-1990s were consistent with a cohort effect resulting from a change in the provincial vaccine program. In 1981, Manitoba moved from the wP vaccine used since the 1940s to an adsorbed wP vaccine. A large outbreak occurred in 1994/1995 in older children born after 1981 (i.e., had received the adsorbed wP vaccine). This outbreak was largely attributable to the low vaccine effectiveness (VE) of the Canadian adsorbed wP vaccine (estimates of the wP vaccine used in Canada during this period ranged from 20-60% [18]). A study that looked at trends of pertussis incidence in the Canadian province of Quebec identified a similar cohort effect, although that study did not include an APC analysis [48]. In Manitoba, the low protection in the adsorbed wP pertussis vaccine cohort likely contributed to the increase of pertussis disease in the mid-90s.

Due to concerns about effectiveness and safety, the adsorbed wP vaccine was replaced by aP vaccine in 1997 [24]. Manitoba then experienced a long period of low pertussis activity until an increase in disease occurred in 2012. Laboratory-confirmed cases in 2012 occurred mostly in

individuals born after 1997 who would have received the aP vaccine and approximately 40% of cases occurred in individuals over 7 years old. This shift towards an older age group aligned with previous studies showing waning protection for the aP vaccine [10, 49]. Manitoba-specific estimates showed that although short-term VE for the aP vaccine was high, protection may have waned by 8 years post-vaccination [50]. In the presence of waning immunity, we would expect to see an increase in incidence rates in the older age groups as the aP vaccine cohort moved across time. Although we did not see an aP vaccine birth cohort effect in our APC model, this may have been due to the relatively short period of time this cohort contributed (20 years) compared to the adsorbed wP vaccine (about 40 years) as well as to the magnitude of the large adsorbed wP cohort outbreak in 1994/95.

Waning vaccine-induced protection combined with a vulnerable cohort of adolescents vaccinated with only the low VE adsorbed wP vaccine prompted the National Advisory Committee on Immunizations (NACI) to recommend an adolescent booster in 2003 [51] and Manitoba added an adolescent booster to its school vaccination program for grade 8/9 students that year. However, this still left almost a decade-long birth cohort with declining protection (those born between 1981 and 1989) and no efforts were made to catch-up this group.

Although individuals belonging to this cohort have increased risk relative to the reference cohort, pertussis has largely remained a childhood disease in Manitoba with the highest annual rates consistently in the <1 year old age group, making reduction of infant illness an important focus of the pertussis vaccination program. MH added primary caregivers of newborns to the provincially funded program in 2012 and pregnant women with no history of adult pertussis vaccinations were added in 2015. Although evidence from other jurisdictions has shown that adding a maternal booster during pregnancy was effective in interrupting pertussis incidence [52], it has only been recommended for every mother during every pregnancy in Manitoba since 2019, so we were not able to assess the impact of this vaccine program change on infant pertussis hospitalizations in this analysis.

Changing constraints in APC models can result in very different results; although the choice of constraining either the period or the cohort effect doesn’t affect the model fit, it does affect both

the estimates and their graphical interpretations [53]. Exploring whether period or cohort was responsible for changes in pertussis rates is important for targeting possible interventions [54]. The strong assumption in our primary analysis – when constraining period effect to 0 - was that the period trend was flat; this allowed for estimation of discrete period effects but couldn't identify long periods of increasing or declining trends [55]. Although both model parameterizations in our analyses supported a cohort effect, only the model with period constrained strongly suggested discrete period effects. Given the weak evidence from the age-specific rates by time period graph as well as the limited support for period effects in the APC model with the cohort effect constrained, we concluded that period effects were less important in explaining pertussis trends in Manitoba compared to both age and cohort effects. It is also possible that changes in the vaccine program led to both period and cohort effects i.e., the vulnerable adsorbed wP cohort contributed to the large outbreak in 1994/95 that also saw increased pertussis rates across other age groups. This highlights the importance of interpreting the results of APC models cautiously; although changes in Manitoba's vaccine program appeared to drive changes in pertussis rates, it is still challenging to determine which of age, period, or cohort was the main driver of that change [55].

Although other studies have explored the impact of specific changes in vaccine programs on incidence in in specific age groups [52, 56], this is the first analysis we are aware of that attempts to disentangle the effects of age, period, and cohort on the burden of pertussis disease.

Limitations

We were interested in whether changes in vaccine coverage rates may have contributed to provincial pertussis disease patterns but estimates of pertussis vaccination coverage were not available for Manitoba across the entire study period. Estimates have suggested that pertussis vaccine coverage in Manitoba is consistently below the national target of 95%; the most recent provincial estimate from 2017 reported that the percentage of two-year olds considered up-to-date for pertussis vaccination was 75.8% [11-13]. Previous models have suggested that the resurgence of pertussis among adolescents and adults may have been the result of historically

inadequate vaccine coverage with an imperfect vaccine [57]. We were unable to assess the impact of low vaccination coverage on pertussis rates in Manitoba in this analysis.

Although we were interested in looking at four vaccine cohorts (pre-vaccine, wP, adsorbed wP, and aP cohorts), our analyses were limited to individuals born after 1975 due to availability of population data. As a result, the pre-vaccine cohort was excluded and the wP cohort did not contain any individual younger than 12. However, retaining the partial wP cohort allowed for assessment of waning adolescent immunity and helped reinforce the finding that pertussis was rare in individuals over the age of 18, regardless of vaccine birth cohort.

Period effects should be interpreted cautiously as the availability of pertussis diagnosis status (about 25 years) is much shorter than the time span for the cohorts (about 40 years). In addition, our vaccine birth cohorts were broad and contained multiple age groups. For example, in the outbreak year 1994, members of the adsorbed wP vaccine cohort could have been newborn up to 13 years old and thus would have been subject to different age effects although their cohort and period effects would be similar. However, our APC models treated age and cohort as continuous variables, and strong age and cohort effects were seen showing this overlap in the derived categories didn’t change results.

Conclusion

Disentangling age, period, and cohort effects is important when evaluating vaccine programs at the population level over time. In Manitoba, the switch to the low VE adsorbed wP vaccine resulted in reduced protection in the 1980-1995 vaccine birth cohort and may have contributed to the largest outbreak of disease in the 25 years of the study period. Our results suggested that period effects, such as changes in laboratory testing, did not explain trends in disease burden. We observed strong age effects with the highest pertussis incidence consistently in young children. Additional research is needed to determine the long-term impacts of the recommended adolescent and maternal pertussis boosters on the burden of pertussis disease in the province.

Additional analyses

The focus of the publication was laboratory-confirmed pertussis; we repeated APC analyses for hospitalized and outpatient pertussis cases to assess the impact of case definition on estimates of disease burden over time.

Methods

Case definitions

We included all cases of pertussis diagnosed between April 1, 1992 and March 30, 2017 using the following case definitions: i) *Laboratory-confirmed (LC) cases*: any individual with a positive laboratory test for *Bordetella pertussis* as recorded in the CDS, ii) *Hospitalized cases*: any individual with a separation diagnosis of pertussis as recorded in the HAD (Table A.1), iii) *Outpatient (OP) cases*: any individual with a pertussis-related ICD-9 diagnosis of 033 as recorded in the MSD. We considered all diagnoses within 6o days as the same episode for an individual and kept the earliest episode; an individual could meet more than one case definition in the same episode and episode date (index date) was the earliest date by any case definition. For example, an individual might have an OP visit followed by a subsequent hospitalization with a LC result during the same episode and would meet all three case definitions with the episode date based on the medical service date.

Results

We identified 2,479 LC, 482 hospitalized, and 13,837 OP cases between 1992 and 2017 Table 3). Hospitalized cases were younger, more likely to live in a rural area, and more likely to live in a neighborhood in the lower 40% income quintile; OP cases were more likely to be older and have chronic conditions, be immunocompromised, and have more prescriptions in the year prior to their index date; and LC cases were less likely to have four or more physician visits in the year prior to their index date.

Table 3 Number (%) of pertussis cases by certain socio-economic and clinical characteristics by case definition

	Lab-confirmed (N=2,479)	Hospitalized (N=482)	Outpatient (N=13.837)
Female	1,327 (54%)	254 (53%)	7,372 (53%)
Age group (years)			
<1	450 (18%)	372 (77%)	1,752 (13%)
1-2	236 (10%)	36 (7%)	1,934 (14%)
3-5	454 (18%)	13 (3%)	2,774 (20%)
6-8	476 (19%)	12 (2%)	2,142 (15%)
9-13	517 (21%)	24 (5%)	1,891 (14%)
>=14	346 (14%)	25 (5%)	3,344 (24%)
Rural residence	1, 086 (44%)	278 (58%)	4, 982 (36%)
Income in lower 40%	1, 010 (41%)	325 (67%)	5, 967 (43%)
Has chronic condition	246 (10%)	56 (12%)	1, 552 (18%)
Immunocompromised	164 (7%)	17 (4%)	1,439 (10%)
Four or more physician visits	1,224 (49%)	308 (64%)	9,021 (65%)
One or more hospitalizations	128 (5%)	195 (40%)	734 (5%)
Two or more prescriptions	490 (20%)	74 (15%)	5,437 (39%)

Age-standardized rates were highest in 1994 at 55, 5, and 260 cases per 100,000 person-years for LC, hospitalized cases, and OP cases respectively (Table 4). Incidence rates were slightly higher (compared to the few years before and after) in 1998, 2012, and 2016 for LC cases and in 1998 and 2010-11 for OP cases. Incidence rates have been steady around 1 case per 100,000 person-years for hospitalized cases since 2000.

Table 4 Incidence rates of pertussis cases per 100,000 person-years in Manitoba by index year and case definition

Index year	Lab-confirmed		Hospitalized		Outpatient	
	Crude (95%CI)	Age-standardized (95%CI)	Crude (95%CI)	Age-standardized (95%CI)	Crude (95%CI)	Age-standardized (95%CI)
1992	4 (2-4)	3 (2-4)	2 (1-2)	2 (1-2)	52 (36-43)	40 (36-43)
1993	5 (3-5)	4 (3-5)	3 (1-3)	2 (1-3)	60 (43-50)	46 (43-50)
1994	72 (52-59)	55 (52-59)	7 (4-7)	5 (4-7)	336 (252-269)	260 (252-269)
1995	33 (23-28)	25 (23-28)	3 (2-3)	2 (2-3)	147 (108-119)	114 (108-119)
1996	9 (5-8)	7 (5-8)	2 (1-2)	1 (1-2)	55 (41-48)	44 (41-48)
1997	7 (4-7)	5 (4-7)	3 (1-3)	2 (1-3)	32 (23-28)	25 (23-28)
1998	18 (12-16)	14 (12-16)	3 (2-4)	3 (2-4)	80 (61-69)	65 (61-69)
1999	8 (6-8)	7 (6-8)	2 (1-3)	2 (1-3)	58 (45-52)	48 (45-52)
2000	3 (2-4)	3 (2-4)	1 (0-2)	1 (0-2)	28 (22-27)	24 (22-27)
2001	1 (1-2)	1 (1-2)	1 (0-1)	1 (0-1)	21 (16-20)	18 (16-20)
2002	5 (3-5)	4 (3-5)	1 (0-1)	1 (0-1)	38 (30-37)	33 (30-37)
2003	4 (2-4)	3 (2-4)	1 (1-2)	1 (1-2)	28 (21-27)	24 (21-27)
2004	5 (3-6)	5 (3-6)	1 (1-2)	1 (1-2)	31 (24-30)	27 (24-30)
2005	2 (1-3)	2 (1-3)	1 (1-2)	1 (1-2)	20 (16-21)	18 (16-21)
2006	1 (0-1)	1 (0-1)	0 (0-1)	0 (0-1)	11 (8-11)	9 (8-11)
2007	1 (0-1)	1 (0-1)	1 (0-1)	0 (0-1)	7 (5-8)	6 (5-8)
2008	1 (0-2)	1 (0-2)	1 (0-1)	0 (0-1)	8 (7-10)	8 (7-10)
2009	2 (1-3)	2 (1-3)	1 (1-2)	1 (1-2)	6 (4-6)	5 (4-6)
2010	4 (3-5)	4 (3-5)	2 (1-2)	1 (1-2)	51 (45-53)	49 (45-53)
2011	2 (1-3)	2 (1-3)	2 (1-2)	1 (1-2)	51 (46-54)	50 (46-54)
2012	9 (6-9)	8 (6-9)	2 (1-2)	1 (1-2)	22 (18-22)	20 (18-22)
2013	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	7 (5-8)	6 (5-8)
2014	1 (0-2)	1 (0-2)	0 (0-0)	0 (0-0)	6 (4-7)	6 (4-7)
2015	4 (3-5)	4 (3-5)	1 (0-1)	0 (0-1)	10 (8-11)	9 (8-11)
2016	9 (6-9)	8 (6-9)	1 (1-2)	1 (1-2)	17 (14-18)	16 (14-18)
2017	2 (1-3)	2 (1-3)	0 (0-1)	0 (0-1)	5 (3-6)	4 (3-6)

Hospitalized cases

The graph of age-specific hospitalization rates by period of diagnosis in Figure 4A suggest little evidence of period effects, although there is a decline in incidence in the <1 year olds over time. Figure 4B shows hospitalization rates within age groups by vaccine birth cohort. In the adsorbed wP birth cohort (born 1981-1996), incidence was highest in the <6 year olds compared to the aP vaccine birth cohort (born >1997). Hospitalization rates could not be estimated for all age groups and vaccine birth cohorts due to the low number of older hospitalized cases.

Figure 4 A) Hospitalized cases of pertussis per 100,000 person-years in Manitoba, 1992-2017, stratified by age at index date B) Hospitalized cases of pertussis per 100,000 person-years by vaccine birth cohort, stratified by age at index date. Lines correspond to each age group.

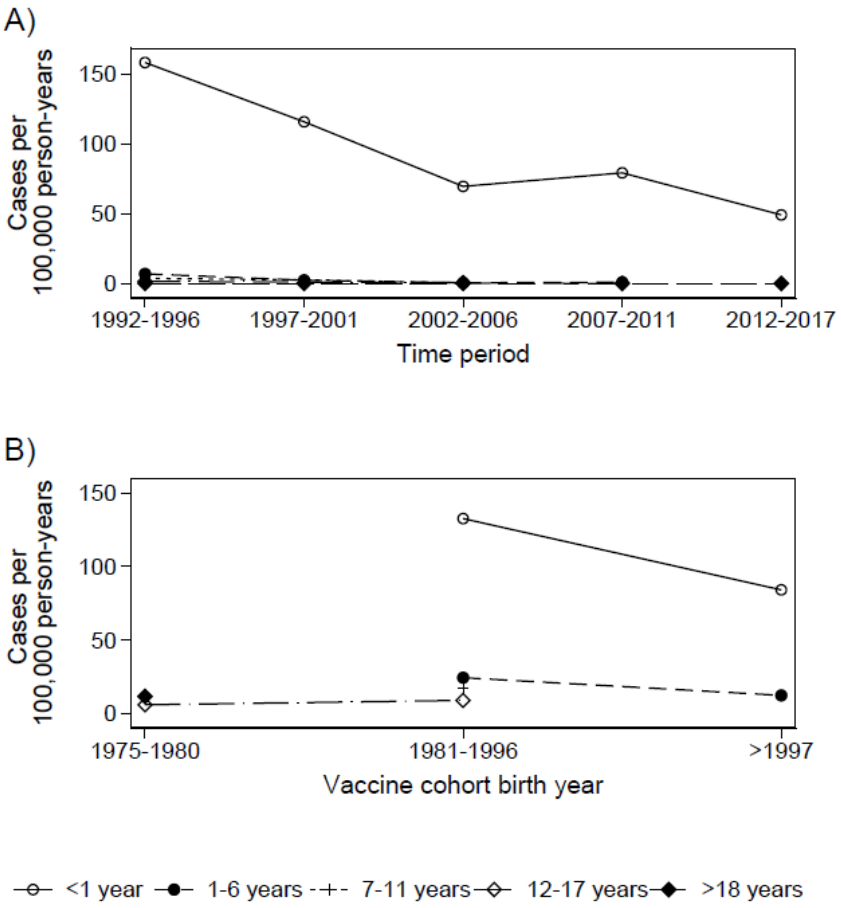
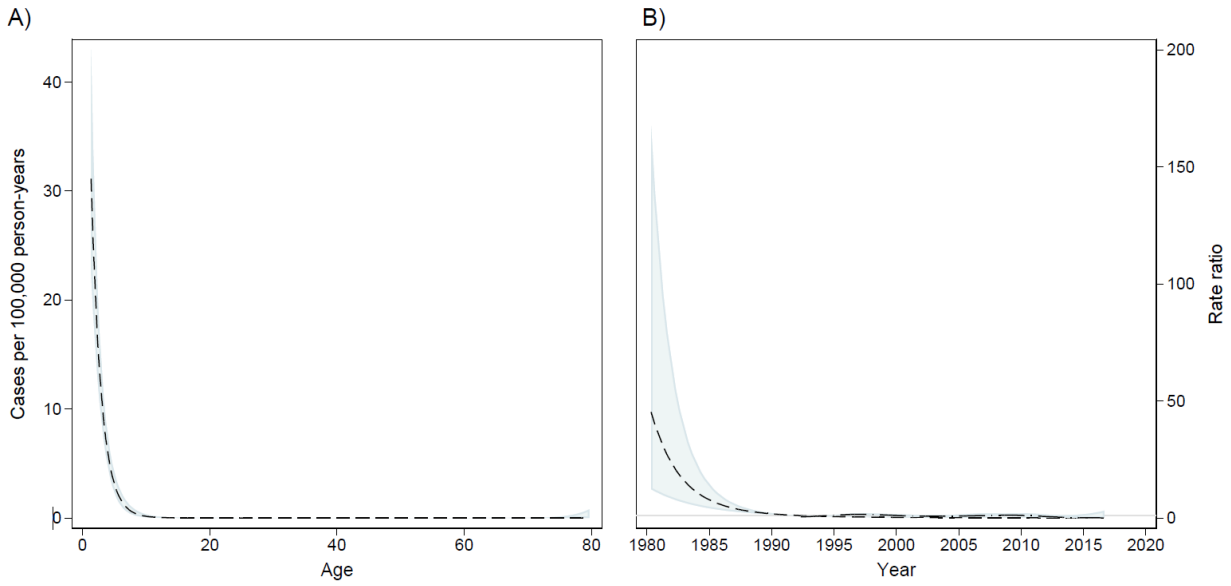


Figure 5 shows the age, period, and cohort effects estimated from the APC model for hospitalized cases. Figure 5A shows strong age effects, with the highest burden in the youngest ages. This follows the same age pattern as seen in Figure 4, with the highest rates of hospitalization observed in young children and very few hospitalizations observed in older children and adults.

Figure 5 Age-period-cohort model of pertussis hospitalization rates in Manitoba, 1992-2017, with average period effect constrained to be zero

A) Estimated age effect.

B) Cohort effect (dashed) and period effect (dashed-dot) rate ratios. The reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of the cases (1989).



Period was constrained in this model, so the function on the right in Figure 5B is the period function relative to 1996 and the function on the left is a cohort function representing residual effects. The period function in Figure 5B (the shorter graph on the right) shows no deviation

from linearity suggesting no period effects. This result corresponded to the pattern suggested in the age-period plot (Figure 4A).

The graph on the left in Figure 5B shows a cohort effect characterized by a deceleration of risk from the earlier birth cohorts relative to the 1989 reference cohort. Risk remained stable in cohorts born after 1990.

When we constrained the cohort effect (instead of the period effect), we continued to see an increased risk in the cohort born before 1985 as well as an increasing risk starting around 2009 relative to the reference cohort (Figure B.2). With this reparameterization, period effects were still not observed.

Outpatient cases

The graph of age-specific incidence by period of diagnosis in Figure 6A suggests evidence of period effects, with roughly parallel lines between age groups over time. Figure 6B shows incidence rates within age groups by vaccine birth cohort; although limited to the three later cohorts, the pattern is suggestive of cohort effects. In the adsorbed wP vaccine birth cohort (born 1981-1996), incidence was higher across all age groups compared to the aP vaccine birth cohort (born >1997).

Figure 6 A) Outpatient cases of pertussis per 100,000 person-years in Manitoba, 1992-2017, stratified by age at index date B) Outpatient cases of pertussis per 100,000 person-years by vaccine birth cohort, stratified by age at index date. Lines correspond to each age group.

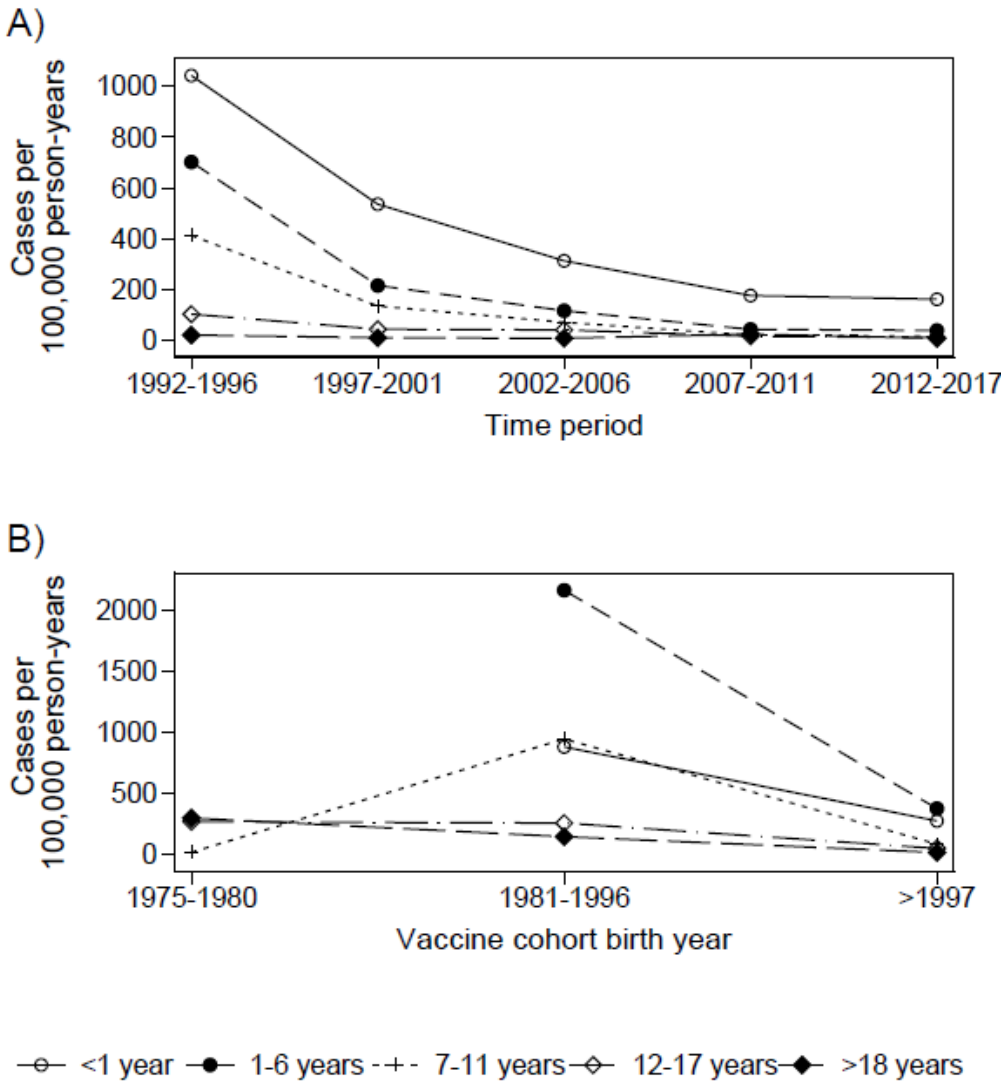
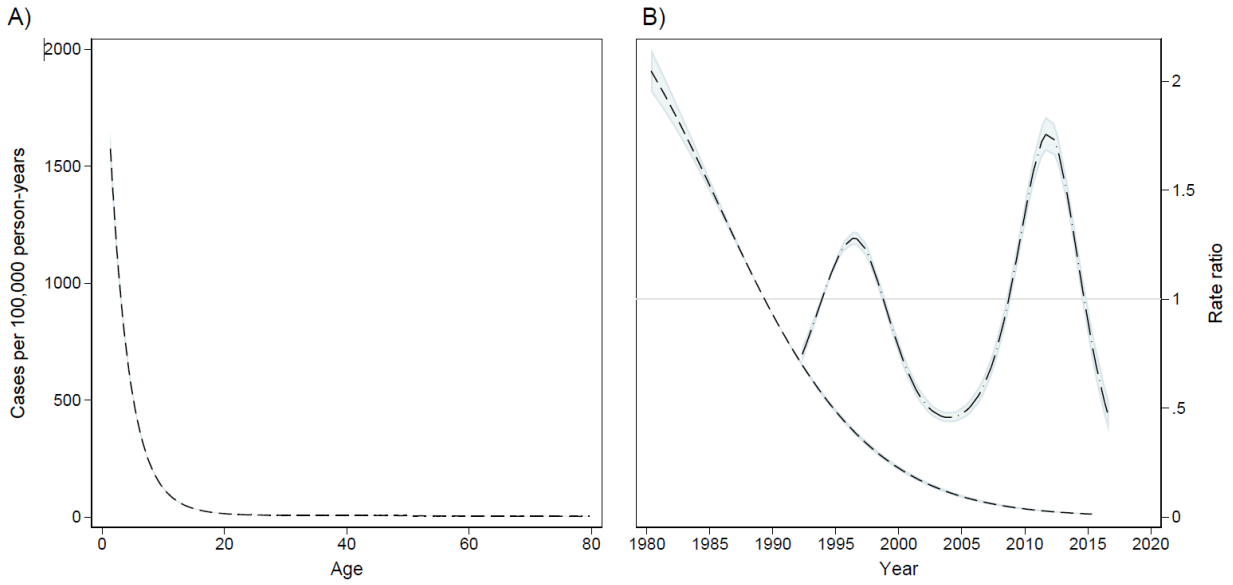


Figure 7 shows the age, period, and cohort effects estimated from the APC model for outpatient cases. Figure 7A shows strong age effects, with a steady decrease in pertussis incidence with increasing age. This follows the same age pattern as seen in Figure 6, with the highest rates of disease observed in young children and very little disease seen in adults across the study period.

Figure 7 Age-period-cohort model of pertussis outpatient rates in Manitoba, 1992-2017, with average period effect constrained to be zero

A) Estimated age effect.

B) Cohort effect (dashed) and period effect (dashed-dot) rate ratios. The reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of the cases (1989).



Period was constrained in this model, so the function on the right in Figure 7B is the period function relative to 1996 and the function on the left is a cohort function representing residual effects. The period function in Figure 7B (the shorter graph on the right) shows deviation from linearity in the mid-90s and again around 2012 where increased risk was observed relative to the reference year of 1996 suggesting period effects. This result corresponded to the pattern suggested in the age-period plot (Figure 6A).

The graph on the left in Figure 7B shows a cohort effect characterized by a rapid deceleration of risk from the earlier birth cohorts relative to the 1989 reference cohort. Risk continued to decelerate in later cohorts, although the decrease was slightly slower for those born after 2000.

When we constrained the cohort effect (instead of the period effect), we continued to see an increased risk in the cohort born between 1980 and 1995 (Figure B.3). In this figure, the function on the left is the cohort function relative to individuals born in 1989 and the function on the right is a period function representing residual effects. With this reparameterization, period effects were less important than in the model with the period effect constrained.

Discussion

Our APC models show strong age effects in Manitoba with the highest pertussis incidence in young children, especially among hospitalized cases. We observed birth cohort effects characterized by decreasing risk in individuals born after 1995 (hospitalized cases) and 1990 (LC and OP cases).

Case definition was an important consideration when describing the burden of pertussis in Manitoba over time. We observed differences in both demographics and incidence patterns. Our analyses were restricted to individuals with a healthcare encounter that resulted in a diagnosis of pertussis. A national survey in the US suggested that many primary care physicians were not able to recognize the clinical signs of pertussis in adolescents and that many did not test adolescents as part of their clinical practice [58]. However, it has also been previously suggested that the increased incidence of pertussis in the 2010s was not attributed to a real increase in infection, but due to improved diagnostic awareness and physician testing behavior as a result of several large, well-publicized outbreaks [59]. We observed a shift towards a greater proportion of older outpatient cases in later years; in 2011/12 approximately 40% of cases were more than 12 years old as compared to approximately 15% in 1992/93 and the mean age of outpatient cases increased from 7 years old in 1992 to 19 years old in 2017 (data not shown). The outpatient group represents individuals who were diagnosed with pertussis during a physician visit and the shift to the older age group may suggest a change in diagnostic awareness. This change in testing behavior may also partially explain the slight period effects in the lab-confirmed and outpatient APC models that were not seen for the younger, hospitalized cases.

Along with diagnostic awareness, it has also been suggested that changes in diagnostic testing methods, such as the increased use of PCR, may partially account for the rise in pertussis incidence [59]. Diagnostic tests have different sensitivity and specificity and are also highly dependent on the timing of specimen collection [60]. In Manitoba, culture was the prevalent diagnostic method identified throughout the study period until about 2012 when PCR became more common (Table B.3). Although 100% specific, culture has low sensitivity and requires viable bacteria for isolation compared to PCR which is more sensitive and doesn't require viable bacteria [60]. Since the laboratory-confirmed and outpatient cases followed the same patterns over the study period, we concluded that the impact of changes in diagnostic testing on the incidence of laboratory-confirmed cases was minimal in Manitoba.

Limitations:

Our laboratory-confirmed cases were obtained from public health surveillance data and we did not have access to negative test results. This meant we were unable to validate physician testing practices (i.e., we could not differentiate between outpatient cases that were not tested and outpatient cases that were tested but had negative results). Having access to negative results would have given us further insights into changes in physician's testing practices over the 25-year study period.

Conclusion

We observed differences in demographics and incidence based on case definition, especially for the hospitalized cases, highlighting the importance of not collapsing pertussis case counts from different sources in a single analysis. Including multiple case definitions allowed for a more complete understanding of the burden of disease.

Chapter 3. Systematic review and meta-analysis

Preface

In the previous chapter, we saw that major changes in Manitoba's pertussis vaccine program were consistent with impacts on disease incidence at the population-level years later; findings suggested that pertussis vaccine birth cohort effects, possibly due to the low efficacy of the adsorbed whole-cell pertussis vaccine and potential waning immunity of the acellular pertussis vaccine, contributed to periodic increases in pertussis incidence in the province. In this next study, we conducted a systematic review and meta-analysis of pertussis vaccine effectiveness and duration of protection for both the whole-cell and acellular pertussis vaccines. The design and conduct of observational pertussis vaccine effectiveness studies contributes to substantial heterogeneity in pooled analyses, which is important to consider when designing and interpreting VE studies.

Manuscript

Wilkinson K, Righolt CH, Elliott, LJ, Fanella, S, Mahmud SM (2021). Pertussis vaccine effectiveness and duration of protection – A systematic review and meta-analysis. *Vaccine,* 39(23): 3120-3130.

Abstract

A comprehensive review of observational pertussis vaccine effectiveness (VE) studies was needed to update gaps from previous reviews. We conducted a systematic review of VE and duration of protection studies for the whole-cell (wP) and acellular (aP) pertussis vaccines and conducted a formal meta-analysis using random effects models. Evidence continues to suggest that receipt of any pertussis vaccine confers protection in the short-term against disease although this protection wanes rapidly for aP vaccine. We detected significant heterogeneity in pooled estimates due, in part, to factors such as bias and confounding which may be mitigated by study design. Our review of possible sources of heterogeneity may help interpretation of other VE studies and aid design decisions in future pertussis VE research.

Introduction

Although pertussis vaccines have been available for more than a century [61], pertussis remains one of the most common vaccine-preventable diseases globally [62]. Pertussis vaccines are available in whole-cell (wP) or acellular (aP) formulations, and are often included in combination vaccines [1]. Due to concerns about vaccine safety and efficacy, aP vaccine replaced wP vaccine in the vaccine programs of most developed and many middle-income countries in the late 1990s [61]. Neither infection nor vaccination provides life-long immunity; outbreaks in older, vaccinated individuals in the 2000s [8-10] highlighted concerns about the effectiveness of pertussis vaccines over time [10, 49, 63, 64].

Previous systematic reviews and meta-analyses (SRMA) estimating pertussis vaccine effectiveness (VE) and waning immunity varied in both inclusion criteria and measured outcomes. A 2003 systematic review of short-term pertussis VE included few studies and reported varied wP estimates (from 37-92%) and a pooled aP estimate of 73% [65]. In 2016, a SRMA of short-term contemporary pertussis VE following the childhood priming series included two aP efficacy studies 84% (81-87%) and three wP studies 94% (88-97%) [66]. Neither of these SRMAs included duration of protection. A 2015 SRMA measuring duration of immunity following the childhood priming series estimated that for every year after the last dose, the odds of pertussis increased by 1.33 times (95% CI 1.23-1.43) [10]. The most recent SRMA (2019) focused on adolescent and adult aP boosters was restricted to clinical trials, of which only one included a VE estimate of 89% after 2.5 years of follow-up [67]. A meta-regression modeling study using discrete time points since vaccination to estimate the duration of protection of the aP vaccine estimated that VE for the childhood and adolescent series declined 10% and 12% annually [68].

Our SRMA includes studies published since the earlier reviews and provides a comprehensive look at pertussis VE and duration of protection for both wP and aP vaccines. This is the first SRMA that includes VE against severe disease as an outcome. The inclusion of observational studies allows for a thorough analysis of heterogeneity which may help interpretation of other VE studies and aid design decisions in future pertussis VE research.

Methods

We followed the Cochrane Handbook for Systematic Reviews of Interventions approach [69] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Table C.1) [70].

Populations, interventions, comparators, outcome measures, and study designs

Our primary research question was "What is the vaccine effectiveness and duration of protection of pertussis vaccines?" We included vaccinations with any pertussis vaccine in any age group. There were no restrictions on study design and study/publication year. We excluded modelling studies, secondary prevention studies (e.g., the impact of maternal vaccination on infant pertussis), and studies that measured only immunogenicity.

Our main outcomes were pertussis vaccine effectiveness against disease and duration of protection. Our secondary outcome was pertussis vaccine effectiveness against severe disease, defined as hospitalization or death.

Search strategy for identification of studies

We searched Medline (Ovid), EMBASE (Ovid), and Cochrane Library (Wiley) from inception to November 26, 2019 using database-specific search strategies (e.g., Table C.2 for Medline). We hand-searched the reference lists of narrative and systematic reviews and included studies for relevant citations. We performed reference management in EndNote (version X7.2.1, Thomson Reuters).

Study selection

We used a 2-stage process for study screening and selection using standardized screening forms. Two reviewers independently screened titles and abstracts to determine whether a citation met inclusion criteria. Discrepancies between reviewers were resolved through consensus.

Data abstraction and management

One reviewer extracted data (study information and characteristics, pertussis vaccine type and comparator details, and results) using a standardized template. Data management was performed using Microsoft Excel (v14, Microsoft).

Data analysis

We analyzed data using Stata (v16, StataCorp), including a formal meta-analysis to evaluate statistical and clinical heterogeneity. We estimated pooled vaccine effectiveness (VE=1-OR) with 95% confidence intervals using random effects models. For studies that measured VE for multiple vaccine products, control groups, or study designs, individual VE estimates were given a short description and treated as separate studies.

For duration of protection analyses, we derived the *elapsed time since last pertussis vaccine dose* based on the maximum number of years according to the study. Derived variables are defined in Table C.3.

We explored and quantified statistical heterogeneity of the data using the I^2 test [71]. We used funnel plot analysis to explore if there were publication or related biases [72].

Subgroup analyses

We determined clinical and methodological subgroup analyses *a priori*. Subgroup analyses were dependent on the number of studies and the availability of appropriate outcomes and covariates.

Results

Of the 5,342 unique citations identified, we excluded 773 duplicate and 4,447 irrelevant publications (Figure 8). We assessed 92 full-text articles and excluded 22 based on inclusion criteria, leaving 70 studies for review. All studies were published in English in peer-reviewed journals between 1979 and 2019; 47 studies measured VE against disease (9 clinical trials, 38

observational), 6 observational studies measured VE against severe outcomes, and 15 (2 clinical trials, 13 observational) measured duration of protection (Table 5 & Table 6).

Figure 8 Study flow diagram of pertussis vaccine effectiveness and duration

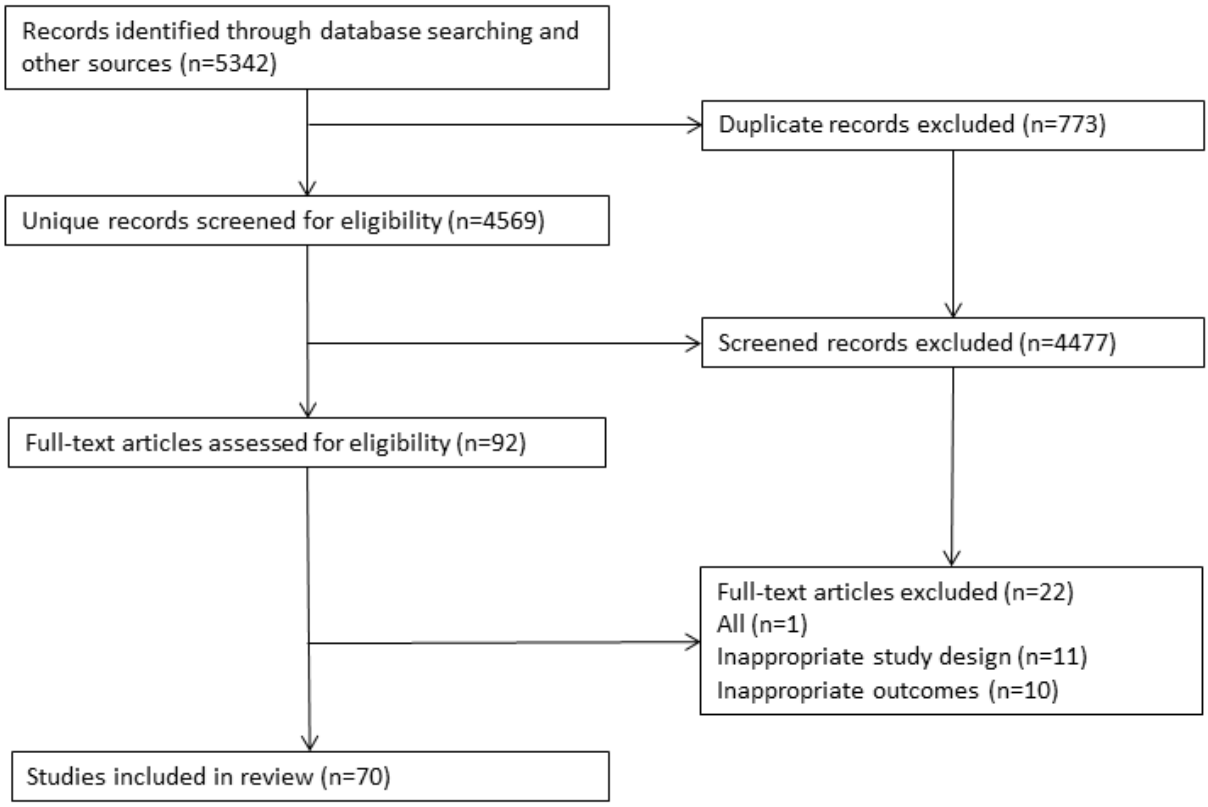


Table 5 Characteristics of included studies measuring pertussis vaccine effectiveness

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
Vaccine effectiveness against disease								
Acosta [Acellular priming series], 2015 [73]	2012	Case-control	Matched	11 to 19 years	Acellular	No booster	OR	63.9 (49.7-74.1)
Acosta [Mixed vaccine priming series], 2015 [73]	2012	Case-control	Matched	11 to 19 years	Any/Not specified	No booster	OR	51.5 (26.1-68.1)
Baxter [Nested case control], 2013 [74]	2006-2011	Case-control	Nested	>11 years	Acellular	No vaccine	OR	64 (55.5-70.9)
Baxter [Test negative], 2013 [74]	2006-2011	Case-control	Test-negative	>11 years	Acellular	No vaccine	OR	53 (41.9-62)
Bentsi-Enchill [Dose 5 at 4 years], 1997 [75]	1994	Case-control	Frequency matched	<10 years	Whole-cell	Incomplete vaccine	OR	57 (23-77)
Bentsi-Enchill [Dose 5 at 6 years], 1997 [75]	1994	Case-control	Frequency matched	<10 years	Whole-cell	Incomplete vaccine	OR	40 (-11-67)
Berger, 2010 [76]	2006	Case-control	Matched	15 to 24 years	Any/Not specified	Incomplete vaccine	OR	0 (0-69)
Bisgard, 2005 [77]	1998-2001	Case-control	Nested	6 to 59 months	Any/Not specified	No vaccine	OR	97.1 (93.7-98.6)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
Blennow, 1988 [78]	1982-83	Clinical trial	Unblinded	6 to 23 months	Whole-cell	No vaccine	RR	80.1 (58.2-90.5)
Breakwell [11-19 year olds], 2016 [79]	2011-2013	Case-control	Matched	11-19 years	Acellular	No booster	OR	70 (54-81)
Breakwell [4-10 year olds], 2016 [79]	2011-2013	Case-control	Matched	4-10 years	Acellular	No vaccine	OR	84 (58-94)
Briere, 2018 [80]	2005-2012	Cohort	Retrospective	11-18 years old	Acellular	No booster	RR	59 (39-73)
Broome, 1981 [81]	1979	Cohort	Household contact	<5 years	Whole-cell	No vaccine	RR	94 (75-99)
D'Argenio, 1998 [82]	1995-1996	Cohort	Screening method	Not specified	Any/Not specified	Not stated	RR	92 (77-98)
De Serres [Child care centre], 1996 [83]	1992-1993	Cohort	Retrospective	mean/median 36 months	Whole-cell	Incomplete vaccine	RR	61 (44-72)
De Serres [Schools], 1996 [83]	1992-1993	Cohort	Retrospective	4 to 10	Whole-cell	Incomplete vaccine	RR	60 (10-82)
De Serres [Mixed vaccine], 2001 [84]	1998	Case-control	Matched	Not specified	Any/Not specified	No vaccine	OR	81 (50-90)
De Serres [wP], 2001 [84]	1998	Case-control	Matched	Not specified	Whole-cell	No vaccine	OR	87 (60-90)
Greco [Whole-cell], 1996 [85]	1992/93	Clinical	Double blind	<3 years	Whole-cell	DT	RR	36.1 (14.2-52.1)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
		trial						
Greco [aP, Biocine], 1996 [85]	1992/93	Clinical trial	Double blind	<3 years	Acellular	DT	RR	84.2 (76.2-89.7)
Greco [aP, SmithKline], 1996 [85]	1992/93	Clinical trial	Double blind	<3 years	Acellular	DT	RR	83.9 (75.8-89.4)
Guris [19-47 months old], 1997 [86]Guris	1992-1994	Cohort	Screening method	19-47 months	Any/Not specified	No vaccine	RR	92 (90-93)
Guris [7-18 months old], 1997 [86]Guris	1992-1994	Cohort	Screening method	7 to 18 months	Any/Not specified	No vaccine	RR	82 (79-85)
Gustafsson [aP, 2 component], 1996 [87]	1992-1995	Clinical trial	Double blind	mean 2.5 years	Acellular	DT	HR	58.9 (50.9-65.9)
Gustafsson [aP, 5 component], 1996 [87]	1992-1995	Clinical trial	Double blind	mean 2.5 years	Acellular	DT	HR	85.2 (80.6-88.8)
Gustafsson [wP], 1996 [87]	1992-1995	Clinical trial	Double blind	mean 2.5 years	Whole-cell	DT	HR	48.3 (37-57.6)
Haller [15-16 year olds], 2015 [88]	2002-2012	Cohort	Screening method	15 to 16 years	Any/Not specified	No booster	RR	96.5 (88.3-98.7)
Haller [2-3 year olds], 2015 [88]	2002-2012	Cohort	Screening method	2 to 3 years	Any/Not specified	No vaccine	RR	96.9 (77.2-99.3)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
Haller [5-7 year olds], 2015 [88]	2002-2012	Cohort	Screening method	5 to 7 years	Any/Not specified	No vaccine	RR	92.8 (86.7-96.1)
Hara, 2015 [89]	2010	Cohort	Retrospective	Unspecified	Acellular	Incomplete vaccine	RR	52 (3-76)
Heininger [aP],1998 [90]		Cohort	Household contact	18 month-3.5 years	Acellular	DT	RR	75 (42-89)
Heininger [wP], 1998 [90]		Cohort	Household contact	18 month-3.5 years	Whole-cell	DT	RR	91 (66-98)
Hviid, 2004 [91]	1995-2001	Cohort	Retrospective	<2 years	Acellular	No vaccine	RR	78 (59-88)
Kenyon, 1996 [92]	1993-1994	Cohort	Screening method	19 to 47 months	Whole-cell	No vaccine	RR	76 (28.6-91.9)
Khetsuriani, 2001 [93]	1997	Cohort	Retrospective	median age 10	Any/Not specified	Incomplete vaccine	RR	80 (66-88)
Liese [aP], 1997 [94]	1993-1995	Unclear	Unclear	<2 years	Acellular	No vaccine	OR	80 (63-89)
Liese [wP], 1997 [94]	1993-1995	Unclear	Unclear	<2 years	Whole-cell	No vaccine	OR	95 (81-99)
Liu, 2019 [95]		Case-control	Nested	>=45 years	Acellular	No booster	OR	52 (15-73)
Lugauer [aP], 2002 [96]	1995-2000	Clinical trial	Unblinded	<14 years old	Acellular	DT	RR	89 (79-94)
Lugauer [wP], 2002 [96]	1995-2000	Clinical trial	Unblinded	<14 years old	Whole-cell	DT	RR	92 (84-96)
Misegades, 2012 [97]	2010	Case-	Matched	4-10 years	Acellular	No vaccine	OR	88.7 (79.4-93.8)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
		control						
Mortimer, 1990 [98]		Cohort	Household contact	Unspecified	Acellular	No vaccine	RR	81 (64-90)
Ohfuji, 2015 [99]	2009-2012	Case-control	Matched	<30 years	Acellular	No vaccine	OR	80 (-373-99)
Okada, 2009 [100]	1999-2001	Case-control	Matched	<6 years	Acellular	No vaccine	OR	95.9 (46.1-99.7)
Onorato, 1992 [101]	1984-1986	Cohort	Household contact	1-4 years	Whole-cell	No vaccine	RR	85 (59-94)
Palmer [Direct estimates], 1991 [102]	1987	Cohort	Retrospective	<15 years	Whole-cell	No vaccine	RR	88 (68-95)
Palmer [Screening method], 1991 [102]	1987	Cohort	Screening method	<15 years	Whole-cell	No vaccine	RR	90 (83-93)
Ramsay [Epidemic], 1993 [103]	1989-90	Cohort	Screening method	<9 years	Whole-cell	No vaccine	RR	89 (85-92)
Ramsay [Non-epidemic], 1993 [103]	1989-90	Cohort	Screening method	<9 years	Whole-cell	No vaccine	RR	94 (91-96)
Rank, 2009 [104]	2005	Cohort	Screening method	12-19 years	Acellular	No booster	OR	78 (60.7-87.6)
Salmaso [aP, Chiron Biocine], 2001 [105]	1992-93	Clinical trial	Unblinded	<6 years	Acellular	DT	RR	86 (79-91)
Salmaso [ap, SmithKline Beecham], 2001 [105]	1992-93	Clinical trial	Unblinded	<6 years	Acellular	DT	RR	86 (79-91)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
Salmaso [aP, SmithKline Beecham], 1998 [106]	1992-93	Clinical trial	Unblinded	<33 months	Acellular	DT	RR	77.7 (62.2-86.7)
Salmaso [ap, Chiron Biocine], 1998 [106]	1992-93	Clinical trial	Unblinded	<33 months	Acellular	DT	RR	88.8 (79.1-94.1)
Schmitt, 1996 [107]	1992-1994	Cohort	Household contact	6 to 48 months	Acellular	DT	RR	88.7 (76.6-94.6)
Stehr [aP], 1998 [108]	1992-1993	Clinical trial	Double blind	<2 years	Acellular	DT		83 (76-88)
Stehr [wP], 1998 [108]	1992-1993	Clinical trial	Double blind	<2 years	Whole-cell	DT		93 (89-96)
Storsaeter [Mono-component], 1992 [109]	1986-87	Cohort	Household contact	<2 years	Acellular	Placebo	RR	79 (32-95)
Storsaeter [Two-component], 1992 [109]	1986-87	Cohort	Household contact	<2 years	Acellular	Placebo	RR	53 (-25-83)
Tafuri [12 year olds], 2013 [110]	2009	Cohort	Retrospective	about 12 years	Any/Not specified	No booster	RR	42.8 (-36-74.5)
Tafuri [9 year olds], 2013 [110]	2009	Cohort	Retrospective	about 9 years	Any/Not specified	No booster	RR	28.5 (-41.1-96.3)
Terranella, 2016 [111]	2011	Cohort	Retrospective	11 to 19 years	Acellular	No booster	RR	68.5 (32.7-86.2)
Torm, 2005 [112]	2003	Cohort	Retrospective	7-16 years	Whole-cell	Incomplete	RR	53 (31.8-67.2)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
						vaccine		
Trollfors , 1996 [113]	1992-1994	Clinical trial	Unblinded	Unspecified	Acellular	DT	RR	73 (61-83)
Ward, 2005 [114]	1997-1999	Clinical trial	Double blind	15-65 years	Acellular	Hepatitis A	RR	92 (32-99)
Wei, 2010 [115]	2007	Cohort	Prospective	11 to 18	Acellular	No booster	RR	70.6 (-10.3-95.9)
Wilkinson [Non-outbreak], 2019 [50]	1992-2015	Case-control	Nested	2 months-27 years	Whole-cell	No vaccine	OR	54 (32-69)
Wilkinson [Outbreak], 2019 [50]	1992-2015	Case-control	Nested	2 months-27 years	Whole-cell	No vaccine	OR	28 (4-47)
Wilkinson, 2019 [50]	1992-2015	Case-control	Nested	2 months-27 years	Acellular	No vaccine	OR	85 (79-90)
Wolff, 2015 [116]	2011-2013	Case-control	Test-negative	2 mo - <12 years	Acellular	No vaccine	OR	78.3 (48.6-90.8)
Zamir, 2015 [117]	1998-2011	Case-control	Nested	2 to 12 months	Any/Not specified	No vaccine	OR	84.4 (72.2-91.3)
Zerbo, 2019 [63]	2006-2017	Cohort	Retrospective	3 months-11 years	Acellular	No vaccine	OR	93 (91-94)

	Study period	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*	*Estimate type*	*VE % (95% CI)*
Vaccine effectiveness against severity								
Guris [19-47 months old], 1997 [86]	1992-1994	Cohort	Screening method	19-47 months	Any/Not specified	No vaccine	RR	93 (89-95)
Guris [7-18 months old], 1997 [86]	1992-1994	Cohort	Screening method	7 to 18 months	Any/Not specified	No vaccine	RR	87 (84-90)
Hviid [aP], 2009 [118]	1990-2004	Cohort	Retrospective	<2 years	Acellular	No vaccine	RR	96 (93-98)
Hviid [wP], 2009 [118]	1990-2004	Cohort	Retrospective	<2 years	Whole-cell	No vaccine	RR	87 (80-91)
Hviid, 2004 [91]	1995-2001	Cohort	Retrospective	<2 years	Acellular	No vaccine	RR	93 (78-98)
Juretzko, 2002 [119]	1997-2000	Cohort	Screening method	2 to 32 months	Acellular	No vaccine	OR	98.6 (91.4-99.9)
Preziosi [Mildest], 2003 [120]	1993	Cohort	Longitudinal/prospective	<15 years	Any/Not specified	No vaccine	RR	11 (8-15)
Preziosi [Most severe], 2003 [120]	1993	Cohort	Longitudinal/prospective	<15 years	Any/Not specified	No vaccine	RR	83 (60-93)
Sheridan [2009], 2014 [121]	2009-2010	Cohort	Screening method	1 to 12 years	Acellular	No vaccine	OR	87.1 (65.6-95.3)
Sheridan [2010], 2014 [121]	2009-2010	Cohort	Screening method	1 to 12 years	Acellular	No vaccine	OR	85.6 (30.9-97)

VE=Vaccine effectiveness; OR=Odds ratio; RR=Risk ratio; aP=Acellular pertussis vaccine; wP = Whole-cell pertussis vaccine; DT=Diphtheria and tetanus vaccine

Table 6 Characteristics of included studies measuring pertussis duration of protection

Study	*Study period*	*Study design*	*Design details*	*Age of participants*	*Vaccine type*	*Comparator*
Acosta, 2015 [73]	2012	Case-control	Matched	11 to 19 years	Acellular	No booster
Acosta, 2015 [73]	2012	Case-control	Matched	11 to 19 years	Any/Not specified	No booster
Bell, 2019 [122]	2010-2015	Case-control	Test-negative	3 months->65 years	Acellular	No vaccine
Berger, 2010 [76]	2006	Case-control	Matched	15 to 24 years	Any/Not specified	Incomplete vaccine
Breakwell, 2016 [79]	2011-2013	Case-control	Matched	4-10 years	Acellular	No vaccine
Briere, 2018 [80]	2005-2012	Cohort	Retrospective	11-18 years old	Acellular	No booster
Crowcroft, 2019 [123]	2009-2015	Case-control	Frequency matched	3 months-22 years	Acellular	No vaccine
Klein, 2015 [124]	2006-2015	Cohort	Retrospective	10 to 19 years	Acellular	No vaccine
Koepke, 2014 [125]	2012	Cohort	Retrospective	12-14 years	Acellular	No vaccine
Latasa, 2018 [126]	2001-2015	Cohort	Screening method	< 5 years old	Acellular	Unclear
Lugauer [aP], 2002 [96]	1995-2000	Clinical trial	Unblinded	<14 years old	Acellular	DT
Lugauer [wP], 2002 [96]	1995-2000	Clinical trial	Unblinded	<14 years old	Whole-cell	DT

Misegades, 2012 [97]	2010	Case-control	Matched	4-10 years	Acellular	No vaccine
Ohfuji, 2015 [99]	2009-2012	Case-control	Matched	<30 years	Acellular	No vaccine
Schwartz, 2016 [46]	2009-2013	Case-control	Test-negative	3 mo-21 years	Any/Not specified	No vaccine
Taranger, 1997 [127]	1992-1995	Clinical trial	Unblinded	3 years	Acellular	DT
Wilkinson, 2019 [47]	1992-2015	Case-control	Nested	2 months-27 years	Acellular	No vaccine
Acosta, 2015 [73]	2012	Case-control	Matched	11 to 19 years	Acellular	No booster
Acosta, 2015 [73]	2012	Case-control	Matched	11 to 19 years	Any/Not specified	No booster
Bell, 2019 [122]	2010-2015	Case-control	Test-negative	3 months->65 years	Acellular	No vaccine
Berger, 2010 [76]	2006	Case-control	Matched	15 to 24 years	Any/Not specified	Incomplete vaccine
Breakwell, 2016 [79]	2011-2013	Case-control	Matched	4-10 years	Acellular	No vaccine
Briere, 2018 [80]	2005-2012	Cohort	Retrospective	11-18 years old	Acellular	No booster
Crowcroft, 2019 [123]	2009-2015	Case-control	Frequency matched	3 months-22 years	Acellular	No vaccine
Klein, 2015 [124]	2006-2015	Cohort	Retrospective	10 to 19 years	Acellular	No vaccine
Koepke, 2014 [125]	2012	Cohort	Retrospective	12-14 years	Acellular	No vaccine
Latasa, 2018 [126]	2001-2015	Cohort	Screening method	< 5 years old	Acellular	Unclear

Lugauer [aP], 2002 [96]	1995-2000	Clinical trial	Unblinded	<14 years old	Acellular	DT
Lugauer [wP], 2002 [96]	1995-2000	Clinical trial	Unblinded	<14 years old	Whole-cell	DT
Misegades, 2012 [97]	2010	Case-control	Matched	4-10 years	Acellular	No vaccine
Ohfuji, 2015 [99]	2009-2012	Case-control	Matched	<30 years	Acellular	No vaccine
Schwartz, 2016 [46]	2009-2013	Case-control	Test-negative	3 mo-21 years	Any/Not specified	No vaccine
Taranger, 1997 [127]	1992-1995	Clinical trial	Unblinded	3 years	Acellular	DT
Wilkinson, 2019	1992-2015	Case-control	Nested	2 months-27 years	Acellular	No vaccine

aP=Acellular pertussis vaccine; wP = Whole-cell pertussis vaccine; DT=Diphtheria and tetanus vaccine

Forty-seven studies reported pertussis VE against disease; the pooled VE for the 36 aP, 22 wP, and 14 mixed vaccines studies were 79% (95% CI, 73-83; I^2=89%), 79% (69-86; I^2=93%), and 84% (75-90; I^2=92%) respectively (Table 7, Figure C.1-C.3).

Table 7 Subgroup analyses for pertussis vaccine effectiveness by vaccine type

	Acellular			Whole-cell			Any/mixed		
Outcome	Studies	VE Estimate (95%CI)	I^2	Studies	VE Estimate (95%CI)	I^2	Studies	VE Estimate (95%CI)	I^2
Overall	36	79 (73-83)	89	22	79 (69-86)	93	14	84 (75-90)	92
Study design									
Case control	12	74 (65-81)	79	6	65 (39-80)	84	5	78 (37-93)	94
Frequency matched				2	49 (22-67)	0			
Matched	6	79 (64-87)	65	1	87 (74-93)		3	53 (-4-79)	82
Nested	3	71 (45-85)	89	2	41 (9-62)	69	2	93 (64-99)	92
Test-negative	2	64 (26-83)	66						
Unclear	1	80 (63-89)		1	95 (78-99)				
Clinical trial	12	83 (76-87)	86	5	79 (52-91)	95			
Double blind	6	81 (69-89)	91	3	71 (23-89)	97			
Unblinded	6	84 (78-88)	54	2	88 (69-95)	68			
Cohort	12	77 (61-86)	89	11	84 (72-90)	90	9	87 (79-92)	89
Household contact	5	79 (68-87)	27	3	89 (78-95)	0			
Prospective	1	71 (-52-94)							
Retrospective	5	76 (36-91)	95	4	65 (46-77)	58	3	64 (13-85)	63
Screening method	1	78 (61-88)		4	90 (86-93)	65	6	92 (86-95)	90
Comparison type									
Placebo	16	82 (76-86)	82	5	81 (55-92)	95			
Incomplete series	1	52 (4-76)		5	56 (45-64)	0	2	56 (-115-91)	94
No vaccine	12	82 (69-89)	95	12	85 (72-92)	93	7	91 (85-94)	90
No booster	7	65 (58-71)	0				4	72 (7-91)	86
Not specified							1	92 (73-98)	
Source of pertussis outcome									
Active case finding by physician	3	80 (67-87)	0	2	93 (81-98)	0	3	69 (-24-92)	73
Active case finding in outbreak	3	75 (29-91)	75				1	0 (-80-44)	
Administrative database	1	93 (91-94)							
Clinical trial	14	82 (75-86)	84	4	78 (45-91)	96			

	Acellular			Whole-cell			Any/mixed		
Outcome	Studies	VE Estimate (95%CI)	I^2	Studies	VE Estimate (95%CI)	I^2	Studies	VE Estimate (95%CI)	I^2
Disease surveillance system	10	75 (66-81)	71	10	84 (69-92)	94	10	89 (82-93)	92
Hospital database	1	80 (-335-99)							
Laboratory records	3	61 (49-71)	61	3	62 (30-79)	61			
Parental questionnaire				2	61 (46-72)	0			
Unclear				1	53 (32-67)				
Case definition category									
Clinical	3	79 (51-91)	79	9	86 (77-92)	87	2	86 (69-94)	26
Lab	7	74 (49-87)	97	4	43 (26-56)	31	1	0 (-80-44)	
Lab & clinical	13	83 (79-86)	26	2	73 (-83-96)	86	3	66 (-0-88)	74
Lab & clinical OR clinical							2	88 (73-95)	98
Lab & clinical OR epi-link	10	80 (69-86)	84	4	80 (48-92)	95	4	96 (93-97)	24
Lab OR clinical OR epi-link	2	70 (52-81)	53	2	79 (61-89)	0	2	68 (25-87)	85
Lab or clinical				1	94 (70-99)				
Unclear	1	78 (59-88)							
Source of vaccine status									
Administrative database	4	74 (30-90)	99						
Clinical trial	16	82 (76-86)	82	6	81 (58-91)	94			
Disease surveillance system							5	92 (85-96)	92
Health authority records	1	52 (4-76)		2	90 (85-93)	0			
Mixed	8	74 (63-82)	59	6	69 (49-81)	71	5	86 (63-95)	91
Parental questionnaire	1	80 (-335-99)							
Physician charts	1	80 (63-89)		3	92 (87-95)	66			
Registry	3	83 (77-87)	0	2	41 (9-62)	69	3	66 (-0-88)	74
School records	1	78 (61-88)							
Unclear	1	96 (45-100)		3	70 (38-86)	60	1	0 (-80-44)	
Confounding									
Adjusted for confounding	20	75 (65-83)	92	6	61 (36-77)	76	5	86 (43-97)	94
Not adjusted for confounding	2	77 (50-89)	0	4	76 (52-88)	76	2	80 (69-87)	0
Not applicable	12	83 (76-87)	86	4	78 (45-91)	96			
Epidemic									
Both	5	63 (53-70)	51						

	Acellular			Whole-cell			Any/mixed		
Outcome	Studies	VE Estimate (95%CI)	I^2	Studies	VE Estimate (95%CI)	I^2	Studies	VE Estimate (95%CI)	I^2
Endemic	2	85 (79-90)	0	2	83 (-22-98)	98			
Epidemic	5	72 (51-84)	69	9	75 (53-86)	93	6	58 (25-76)	76
Unspecified	24	82 (75-86)	88	11	81 (68-89)	91	8	92 (87-95)	89
Age group									
0-10	18	82 (77-86)	80	15	80 (67-88)	93	8	89 (83-93)	90
11-19	6	67 (59-73)	0				3	77 (7-94)	90
20+	1	52 (15-73)							
Other	11	79 (64-88)	95	7	78 (56-89)	93	3	74 (-18-94)	90
Country									
Australia	2	67 (30-85)	72						
Austria							3	94 (90-97)	0
Canada	1	85 (78-90)		7	58 (39-70)	74	1	81 (58-92)	
Denmark	1	78 (59-88)							
Estonia				1	53 (32-67)				
France							1	0 (-80-44)	
Germany	5	84 (79-87)	0	4	93 (89-95)	0			
Israel							1	84 (72-91)	
Italy	6	85 (82-87)	0	1	36 (14-52)		3	69 (-24-92)	73
Japan	4	75 (45-89)	49						
Sweden	5	73 (52-84)	90	2	66 (13-86)	83			
United Kingdom				4	91 (87-93)	50			
United States	12	76 (61-86)	95	3	85 (71-92)	0	5	86 (73-93)	96

Estimates from clinical trials (83% [76-87; I^2=86%]) were higher than from cohort (77% [61-86; I^2= 89%]) or case-control studies (74% [65-81; I^2=79%]) for aP vaccines, although confidence intervals were wide and overlapped (Table 7). Test-negative designs (TND) had lower VE estimates (64% [26-83; I^2=66%]) compared to matched case-control studies (79% [64-87; I^2=65%]).

The aP studies with stricter case definitions (clinical and laboratory confirmation) had higher VE estimates than those with looser case definitions (including epidemiologically-linked cases) (83% [79-86; I^2=26%] versus 80% [69-86; I^2=84%] respectively) (Table 7). Case definitions

based on clinical symptoms, lab results, or of any lab, clinical, or epi-linked criteria had lower aP VE estimates (79% [51-91; I^2=79%], 74% [49-87; I^2=97], and 70% [52-81; I^2=53] respectively).

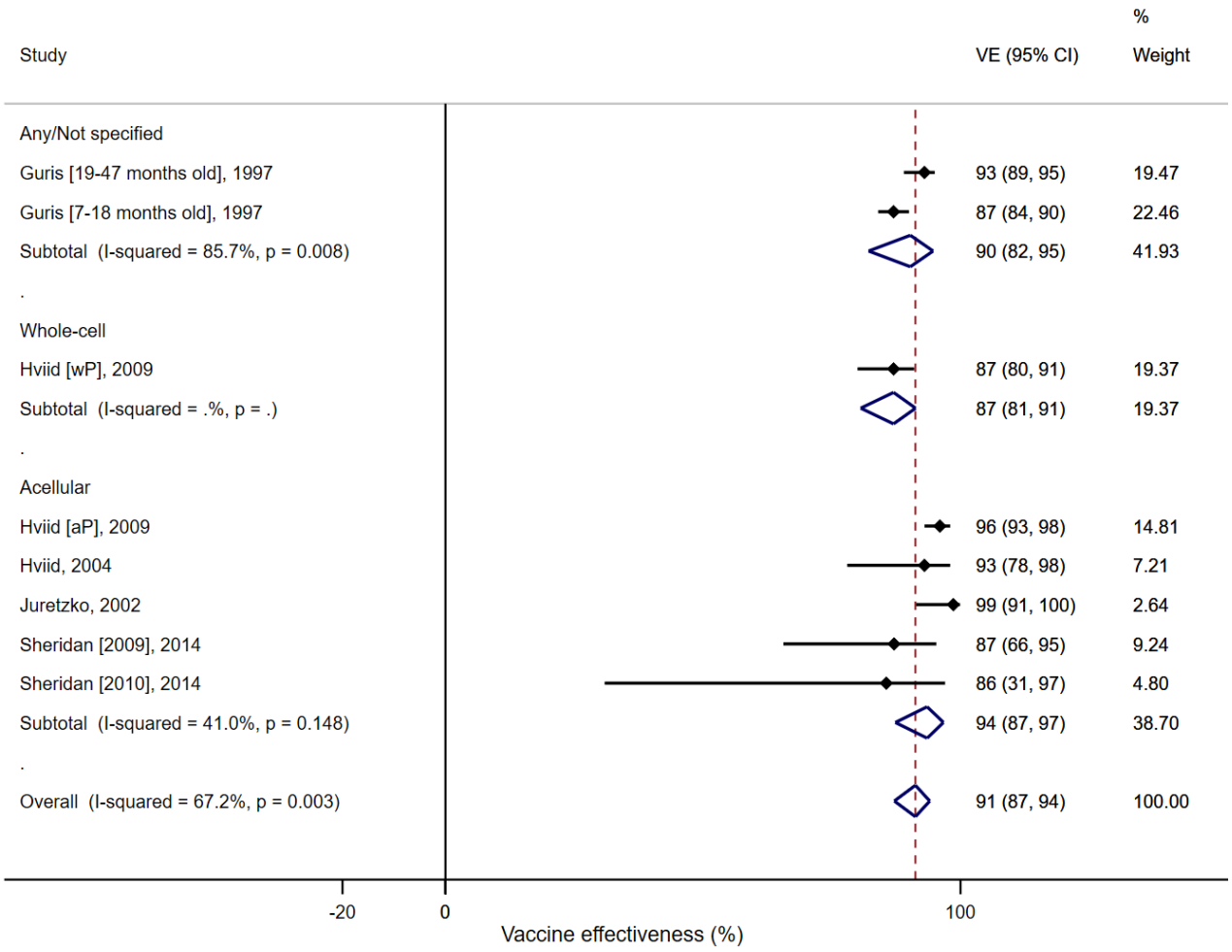
The aP estimates with vaccine status obtained from clinical trials (82% [76-86; I^2=82] or vaccine registries (83% [77-87; I^2=0]) were higher than estimates from administrative databases (74% [30-90; I^2=99%]) (Table 7).

We detected high statistical heterogeneity (I^2>50%) in VE estimates against disease for all vaccine types which persisted despite stratification by *study design*, *case definition*, *source of data on pertussis outcome*, or *source of data on vaccine status.*

Studies comparing vaccinated individuals against unvaccinated individuals or those who received placebo had higher VE estimates than studies using incomplete series (Table 7). For the aP vaccine, VE estimates decreased from 82% (77-86; I^2=80%) in the 0-10 year-old age group to 52% (15-73; n=1) in the over 20 year-old age group. VE estimates from epidemic periods were lower than endemic periods; 72% (51-84; I^2=69%) versus 85% (79-90; I^2=0%) for aP vaccines and 75% (53-86; I^2=93%) versus 83% (-22-98; I^2=98%) for wP vaccines. Estimates for countries with more than one study ranged from 67% (30-85; I^2=72%) in Australia to 85% (82-87; I^2=0) in Italy for aP vaccines. Estimates for wP vaccines ranged from 58% (39-70; I^2=74) in Canada to 93% (89-95; I^2=0) in Germany.

Six studies reported pertussis VE in preventing severe disease; the pooled estimate for five studies that measured VE against hospitalization was 91% (87-94; I^2=67%; Figure 9). One study reporting a range of VE estimates in reducing severity of disease (from mildest to most severe) was excluded from the meta-analysis as it did not include hospitalization [120].

Figure 9 Pertussis vaccine effectiveness against hospitalization by vaccine type



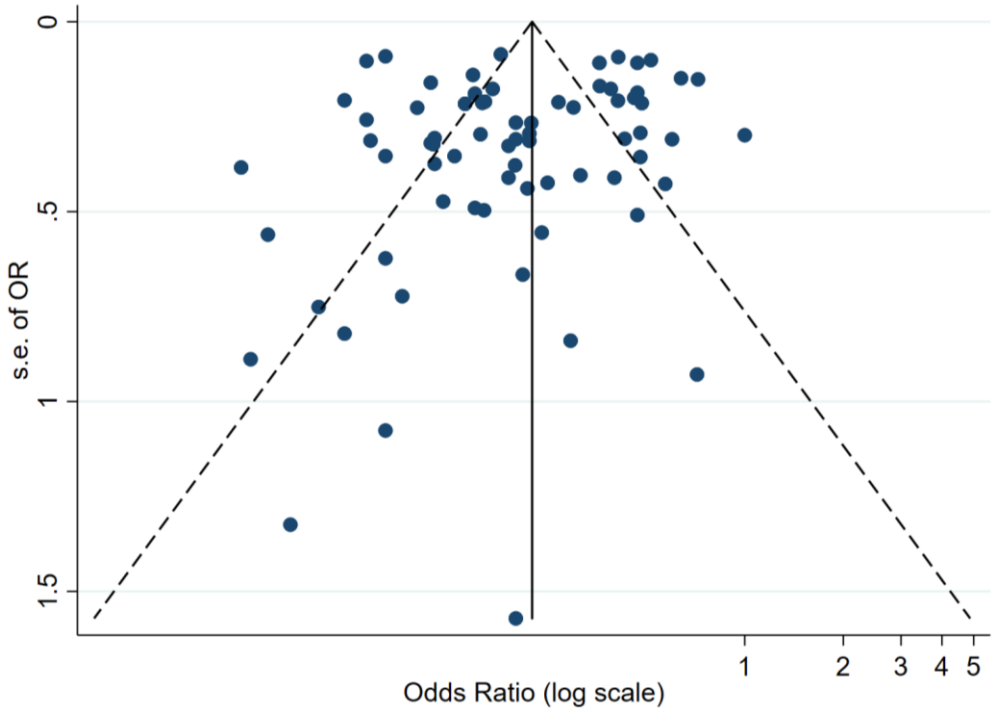
Fifteen studies (13 aP, 1 wP, and 3 mixed) reported duration of vaccine protection. We excluded Riffelmann [128] from the meta-analysis as the study did not measure VE at discrete time-points. Vaccine effectiveness for 0-10 year-old cohorts declined from 98% (90-100; I^2=94%) in the first year to 81% (69-89; I^2=0%) by five years post-vaccination (Table 8). In 11-20 year-old cohorts, VE declined from 72% (66-76; I^2=0%) in the first year to 42% (16-60; I^2=2%) at four years post-vaccination. Figure C.4 shows the forest plot of aP VE by both age category and specific age. Subgroup analyses were not done for the duration of protection or VE against severity outcomes due to the low number of included studies.

Table 8 Duration of acellular pertussis vaccine protection by maximum years since last dose by age-group cohorts

	0-10 year olds			11-19 year olds			Other ages		
	Studies	VE (95% CI)	I^2	Studies	VE (95% CI)	I^2	Studies	VE (95% CI)	I^2
Elapsed years									
1	3	98 (90-100)	94	4	72 (66-76)	0	3	87 (82-90)	67
2	5	84 (70-91)	87	5	64 (58-69)	0			
3	2	92 (87-95)	0	2	32 (19-43)	0	3	86 (80-91)	75
4	2	87 (78-92)	0	2	42 (16-60)	2	1	77 (13-94)	100
5	2	81 (69-89)	0	1	12 (-11-30)	100	1	74 (4-93)	100
6	1	68 (12-88)	100				2	90 (41-98)	54
7							3	76 (71-80)	0
8							1	75 (-23-95)	100
9							1	86 (8-98)	100
11	1	79 (75-83)	100						
24							1	89 (-11-99)	100

We observed no asymmetry in the funnel plot of studies estimating pertussis VE against disease although there was a suggestion of missing studies in the lower right-hand area where we would expect to observe smaller studies reporting lower VE (Figure 10). We did not include a funnel plot for VE against hospitalization due to the low number of included studies or for the duration of protection studies as there were multiple and varying time points per study.

Figure 10 Funnel plot of included pertussis vaccine effectiveness studies



Discussion

Estimation of pertussis VE is subject to many complex potential confounders and biases, making estimating effectiveness challenging. In addition to vaccine potency, factors ranging from study design to the sociodemographic, behavioural, environmental, and epidemiological characteristics of the examined populations impact measured estimates [129, 130]. A lack of consistency between pertussis VE studies in this SRMA contributed to the substantial heterogeneity in pooled estimates and precluded most head-to-head comparisons. A single estimate of pertussis VE would not be relevant, so we evaluated the included studies to demonstrate areas where insufficient evidence created knowledge gaps.

Vaccine Potency and Dosage

Vaccine potency varies by type and between products. The difference in potency between wP vaccine preparations is partially due to different manufacturing processes [131], making pooled

estimates of wP VE of limited value [65]. Variability in number and concentrations of pertussis antigens, in purification methods, and potentially in the choice of *B. pertussis* strain [16] in aP vaccines also influence estimates [24]. Differences in efficacy between wP and aP vaccines may be due to differing mechanisms of action likely involving both humoral and cellular adaptive immunity [132]. Vaccine administration factors, e.g., number and timing of doses, might contribute to heterogeneity but this information was not available from all reviewed studies. Although the pooled estimates for both the wP and aP vaccines had high heterogeneity, we were unable to explain how much of this heterogeneity may have been due to vaccine factors.

Study Design

In general, there is little difference between results from randomized control trials (RCT) and those from observational studies [133]. However, a carefully-designed observational study permits evaluation of VE under real-world conditions and can provide insight into clinical end-points not easily measured in an RCT (e.g., duration of protection). In our review, pooled aP estimates from clinical trials were higher than those for observational studies, although confidence intervals over-lapped. The higher point estimates from clinical trials may be attributed to the more favorable conditions (e.g., increased compliance) and possibly to the relatively shorter duration of follow-up which is supported by our duration of protection estimates showing high VE in the first two years after vaccination. The effects of waning immunity are less likely to be observed in shorter studies, yielding higher VE estimates. We further observed lower VE estimates for TNDs compared to matched and nested case-control studies which was consistent with previous findings [134], however we were unable to assess the net bias in our estimates.

A distinction not explicitly specified in most studies we reviewed was whether the study period included endemic and/or epidemic periods. In the studies that specified endemicity, estimates from epidemic periods were lower than those from endemic periods. These differences in VE estimates may be attributed to testing bias; since VE estimates are higher for typical/severe cases, heightened physician awareness and enhanced testing and reporting of cases with atypical/milder disease during outbreaks could result in lower VE estimates [86]. It is also

possible that the pertussis vaccine offers less protection during periods of intense exposure, which may contribute to the lower VE seen in outbreak periods [86, 103].

Outcomes

Case definition is an important source of methodological heterogeneity. In this review, studies with stricter case definitions had higher aP VE estimates than studies with looser case definitions. In one efficacy study [101], the addition of culture confirmation considerably increased VE. This was likely due to higher case definition specificity as non-pertussis cases were eliminated. Optimal specificity (and higher VE estimates) was reached when symptoms of typical pertussis such as paroxysmal cough were included in the case definition along with laboratory confirmation. We treated studies measuring VE against severe disease as a distinct outcome in this review; VE estimates against severity were higher than estimates against disease, likely due to the even greater specificity of the severe disease case definition.

No included studies measured VE against asymptomatic infection. Individuals vaccinated with aP vaccine may still be infected with pertussis, but have either mild or asymptomatic disease [7, 135] and there is considerable underdiagnosis and underreporting of cases [136, 137]. Older individuals with mild disease, who may still be a source of transmission, are also less likely to appear in studies restricted to medically-attended pertussis due to diagnostic awareness and testing practices of physicians [138]. This under-ascertainment of cases may result in differential misclassification if older, vaccinated individuals are less likely to be tested.

Household contact studies can help understand the role of asymptomatic pertussis transmission. A recent systematic review of household contact studies demonstrated a high prevalence of subclinical pertussis infections and evidence consistent with asymptomatic transmission [139]. Individuals residing in a household with a known case may be at an elevated risk of infection compared to participants included in population-based analyses; non-cases in a population-based analysis may be a result of non-exposure rather than a result of vaccine protection.

In our review, the source of pertussis infection status was highly variable and largely dependent on study design. Estimates using laboratory records alone had lower VE estimates than estimates

from disease surveillance systems, consistent with the lower VE estimates observed from test-negative study designs. A capture-recapture study from Ontario showed wide variability in sensitivity of different data sources used to identify pertussis cases; laboratory sources alone had the lowest sensitivity [137].

Exposures

The source of pertussis vaccination status was inconsistent in the included studies; although confidence intervals were wide and overlapped, aP studies using vaccine registries had comparable VE estimates to clinical trials and were higher than estimates from administrative databases.

In the literature we reviewed, absolute VE estimates (comparing vaccinated individuals against vaccine-naïve individuals) were higher than relative VE estimates (comparing vaccinated individuals to a population that had received some previous doses of vaccine). This was also observed in a modeling study measuring duration of aP vaccine protection that showed the absolute VE in the boosted adolescent population was higher than estimates from the relative VE studies previously reported [68].

Confounding

To accurately assess VE, confounding must be addressed in either the design or analysis stage. Most included observational studies were adjusted for at least one confounder from among the four main identified categories: host (e.g., sex, age/birth year), behavioral (e.g., health-seeking behavior), epidemiological (e.g., vaccine schedules, vaccine coverage rates), and environmental (e.g., geography, physician testing patterns). Directed acyclic graphs should be considered to visualize causal assumptions by making underlying relations between variables explicit [140].

Knowledge gaps

We identified considerable knowledge gaps in the field; one of the most urgent to understand is the role of asymptomatic transmission on pertussis VE estimates. Future studies should consider

pertussis VE against infection, especially with evidence accumulating around asymptomatic and mild disease in previously vaccinated individuals.

The VE studies in this review all measured the direct effectiveness of vaccination, i.e., the risk of pertussis in vaccinated versus unvaccinated individuals. Less is known about the indirect population-level effectiveness of pertussis vaccinations, such as the proportion of pertussis cases averted by vaccination. Both direct and indirect effects of pertussis vaccination are important in understanding the overall effectiveness of vaccine programs.

Strengths and Limitations

A strength of this systematic review was the comprehensive search with no restrictions on study design or vaccine product. Previous SRMAs have relied on strict inclusion criteria [66, 68] or required homogeneity of participants, vaccines, and outcomes [65] to reduce heterogeneity in meta-analyses. Although limitations such as variability of study design (e.g. inclusion of observational studies), dosage schedules, and differences in case ascertainment have been noted as possible contributors to heterogeneity [10, 66], this is the first SRMA to explore the impact of multiple sources of heterogeneity on pertussis VE estimates through extensive subgroup analyses. Even with this high heterogeneity, the findings from our analyses were consistent with those from previous SRMAs showing high protection following any pertussis vaccine with declining aP VE over time.

Subgroup analysis of methodological and biological considerations failed to explain the heterogeneity in our estimates, likely because our analysis was limited to single subgroups; each study had multiple characteristics which might influence each other or bias VE estimates in different directions. We were unable to assess the net direction of competing biases on the pooled estimates. Although we considered meta-regression as an extension of our subgroup analyses [69], it was not possible due to the low number of studies in each stratum.

We assessed funnel plot asymmetry to examine the role of heterogeneity and reporting bias on the results of our meta-analysis and observed horizontal scattering indicative of high between-study heterogeneity [141]. There may be missing studies in the plot area containing regions of

lower VE, making reporting bias possible and we only included English publications which may also have introduced bias.

Conclusions

Evidence continues to suggest that receipt of any pertussis vaccine confers protection against disease although this protection wanes rapidly for aP vaccine. In this SRMA, we observed a high degree of heterogeneity that was only partially explained by subgroup analyses, highlighting the numerous challenges in establishing the effectiveness of pertussis vaccines.

Broad generalizability of VE estimates may be less than expected; in addition to differences between timing, magnitude, and trend in pertussis activity, vaccine schedules and products also vary widely across jurisdictions. Any decisions made around vaccine policy based on these studies should be done carefully, with a thorough consideration of sources of heterogeneity.

Our review of heterogeneity may help interpretation of other VE studies and aid design decisions in future pertussis VE research.

Chapter 4. A nested case-control study measuring pertussis vaccine effectiveness and duration of protection in Manitoba, Canada, 1992-2017

Preface

In chapter 2, we explored the impact of major changes in Manitoba's pertussis vaccine schedule on pertussis incidence at the population level; findings suggested that the low vaccine effectiveness of the adsorbed whole-cell vaccine and waning immunity of the acellular pertussis vaccine contributed to increases in disease incidence. In chapter 3, we summarized the evidence from available literature and identified substantial sources of heterogeneity that impacted estimates of pertussis vaccine effectiveness. Considering the sources of heterogeneity identified in our systematic review and meta-analysis as potential sources of bias in this next study, we measured pertussis VE in Manitoba over a 25-year period, spanning both the whole-cell and acellular pertussis vaccine eras.

This chapter was previously published covering the period from 1992-2015 and has been updated in this dissertation to include two additional years of data.

Manuscript

Wilkinson K, Righolt CH, Kwong JC, Schwartz KL, Russell ML, Crowcroft NS, Mahmud SM. (2019). A nested case-control study measuring pertussis vaccine effectiveness and duration of protection in Manitoba, Canada, 1992-2015: A Canadian Immunization Research Network Study, *Vaccine*, 37:7132-7137.

Abstract

Background: Pertussis persists in Manitoba despite the universal availability of pertussis vaccines. Recent cases have included previously vaccinated individuals, raising concerns about declining vaccine effectiveness (VE). We measured pertussis VE and duration of protection using Manitoba's provincial immunization and communicable disease registries.

Methods: Using a nested case-control design, individuals with laboratory-confirmed pertussis in Manitoba diagnosed between April 1, 1992, and March 31, 2017, were matched to up to five population-based controls on age, gender, geography, and case physician or number of physician visits. Conditional logistic regression was used to estimate VE against pertussis for both the whole-cell (wP) and acellular (aP) pertussis vaccines. Duration of protection was assessed using time since last dose.

Results: Data on 1424 eligible cases and 6,707 controls were available for analysis. The adjusted VE estimate for aP-containing vaccines was 90% (95% CI: 86-93%); VE was 96% (91-98%) one to three years after the last vaccination. The adjusted VE of wP-containing vaccines was 25% (-0-44%) during a large outbreak in 1994 and 1995 compared to 46% (20-63%) during non-outbreak years.

Conclusions: Our estimates suggest that the aP vaccine was effective in preventing pertussis since its introduction in Manitoba. VE was lower during a large outbreak, highlighting the importance of separately analyzing outbreak periods when estimating pertussis VE over time.

Introduction

Pertussis (whooping cough) is a highly contagious respiratory disease that remains one of the most common vaccine-preventable diseases reported in Canada [36]. Whole-cell pertussis vaccination was first introduced in Canada in 1943 and the annual incidence dropped from 160 cases per 100,000 people in the pre-vaccine era to less than 20 cases per 100,000 people by the 1980s [3]. This pattern changed, however, in the 1990s, with a rise in incidence largely attributed to the low efficacy of the whole-cell vaccine in use in Canada during that time [18, 48]. Due to concerns about the safety and low efficacy of the whole-cell pertussis vaccine, Canada switched to a combination vaccine that included an acellular pertussis component in 1997, which led to a long period of good pertussis control. Then, in 2012, incidence of the disease increased in several parts of Canada [3].

Manitoba, a Canadian province with a population of almost 1.3 million, had a large pertussis outbreak in the mid-1990s, which was followed by an extended period of low pertussis activity [3]. Disease incidence rose from 1.2 cases per 100,000 people in 2008 to 9.4 cases per 100,000 people in 2012 [26]. Pertussis incidence increased elsewhere around the same time and patients were older and more likely to be fully-vaccinated against pertussis compared to earlier outbreaks [10, 142, 143] raising concerns that the immunity conferred by the acellular pertussis (aP) vaccine may wane over time [10, 49, 63, 64].

To better understand the limitations of current and past pertussis vaccine programs, we measured the vaccine effectiveness (VE) and duration of protection of both the wP and aP vaccines in Manitoba. We estimated wP VE separately for cases diagnosed during the large disease outbreak of 1994/1995 to assess for effect modification by this outbreak.

Methods

We conducted a population-based nested case-control study linking the Manitoba Immunization Monitoring System (MIMS) with public health surveillance, hospital, physician, and prescription

claims databases housed at the Manitoba Centre for Health Policy [30, 31, 144]. Manitoba Health (MH) is a government agency that provides universal publicly funded health care to the province's residents; insured services include hospital, physician, and preventive services such as vaccinations. The electronic databases used to record provided services are linkable using a unique lifetime personal health identification number (PHIN). We deterministically linked (using the PHIN) six MH administrative and public health databases to establish the study cohort, identify individuals diagnosed with pertussis, and match population-based controls. This study was approved by the University of Manitoba Research Ethics Board and by MH's Health Information Privacy Committee.

Data sources

The Manitoba Health Insurance Registry (MHR) tracks addresses and dates of birth, insurance coverage, and death for all insured persons in the province. Postal codes are updated semi-annually, making it possible to track residents' locations over time. MIMS is the population-based province-wide registry that contains records of all childhood vaccinations administered in Manitoba since 1988 and all adult vaccinations since 2000. Information, including vaccine type and administration date, is captured either through direct data entry (for vaccines administered by public health staff) or through physician billing claims. Estimates of the completeness and accuracy of vaccination information are high, with 2% or fewer immunizations coded incorrectly [145]. Vaccine coverage in our study was consistent with estimates from both Manitoba Health and the National Childhood Immunization Survey [13, 146].

The Communicable Disease Surveillance Database (CDS) records all cases of notifiable diseases reported by clinicians and laboratories to MH since 1992. Under *The Manitoba Public Health Act*, clinicians must report all cases and deaths due to pertussis and laboratories must report any positive pertussis tests. The CDS database stores information on laboratory specimen type, collection date, and test results. The Hospital Abstracts Database (HAD) records virtually all services provided since 1971 by hospitals in the province (including admissions and day surgeries) using the International Classification of Diseases, Tenth Revision, Canadian Edition

(ICD-10-CA) since 2004 and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) prior to that. The Medical Services Database (MSD), also in operation since 1971, collects similar information on services provided by physicians and other clinicians in offices, hospitals, and outpatient departments across the province. The Drug Program Information Network (DPIN) captures data from pharmacy claims since 1995 for formulary drugs dispensed to all Manitobans including those without prescription drug insurance.

Study cohort

We defined an eligible participant as any individual who was born after 1988 and was continuously registered in the MHR within two months of birth at any time between April 1, 1992, and March 31, 2017 (the study period). Participants entered the study cohort at the start of the study period (if born between 1988 and March 31, 1992) or at birth (if born after April 1, 1992) and exited the study cohort on earliest of the date they lost MH coverage for any reason, the end of the study period, or the date of pertussis diagnosis (see below).

Definition of cases and controls

We defined a pertussis case as any member of the study cohort who tested positive for pertussis by any microbial testing method, as recorded in the CDS database, during the study period. Using risk-set (incidence density) sampling, we matched each case to up to 5 members of the study cohort who (1) had not been diagnosed with pertussis by the case's date of diagnosis (the index date) and (2) who had the same age (+/- 365 days), gender, and place of residence as the case (Table D.1). To account for possible bias due to systematic between-physician differences in testing and vaccine administration practices, we also matched on the principal physician (most frequently visited physician in the year prior to index date). We filled incomplete sets (i.e., sets where cases had no principal physician or had less than five physician-matched controls) by matching on the number of physician visits to any physician in the year prior to index date. Cohort members diagnosed with non-laboratory confirmed pertussis ("clinical case") in the CDS

database, or a healthcare encounter coded as ICD-9 code=033* or ICD-10 code=A37* in the MSD or HAD exited the cohort at the date of diagnosis.

Vaccination history and covariates

We obtained pertussis vaccination histories for both cases and controls using pertussis-specific tariff codes in MIMS (Table A.2) [147, 148]. Manitoba used adsorbed wP vaccine from the early 1980s until the province moved to the aP vaccine in 1997 [75].

Pertussis vaccine schedules change over time. We used the vaccine schedules in place between an individual's birth and index dates to determine the recommended number of pertussis vaccine doses they should have received by their index date (Table B.1). An *up-to-date* person had received the recommended number of pertussis vaccine doses, a *partially vaccinated* person had received at least one pertussis vaccine dose but had not received the recommended number of doses, an *unvaccinated* person had not received any pertussis vaccine doses. The product used (wP only, aP only, mixed/both wP and aP) was based on all vaccines received between birth and the index date. Cases and controls with pertussis vaccine received ≤14 days before their index date were excluded.

We obtained household income level from the 2006 Canadian census using neighbourhood-level income quintiles. Information on health services utilization and comorbidities prior to the index date was obtained from the HAD, MSD, and DPIN using previously validated algorithms. A complete list of study variables and definitions is available in the supplementary material (Table D.1).

Statistical Analysis

We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95% CI) of the association between overall and type-specific vaccination and pertussis while adjusting for number of physician visits and hospitalizations in the previous year (as a proxy for healthcare-seeking behaviour) and having a pre-existing chronic or

immunocompromising condition. VE was calculated as (1-OR) x 100. We also estimated duration of VE using time since last dose as the exposure variable in conditional logistic regression models; up-to-date vaccine status was determined *a priori* as the exposure variable for estimates of VE duration. Estimates of pertussis VE tend to be lower in epidemic periods and Manitoba experienced a large outbreak in 1994 and 1995 [3, 103, 149]. To assess for effect modification by this outbreak, we estimated VE separately for cases diagnosed during the outbreak years [150]. To assess the robustness of matching (principal physician vs. number of physician visits), we repeated the analysis after restricting to controls selected by each method.

Results

We identified 1591 pertussis cases diagnosed among the study population during the study period. We excluded 98 (6%) cases with non-continuous MH coverage, 59 (4 %) cases with a pertussis vaccine 14 days before the index date, and 10 (1%) cases without a suitable match (Table D.2). The final study population included 1424 cases (of which 545 [38%] were diagnosed during the 1994-95 outbreak) and 6,707 matched controls (Table 9).

Table 9. Socioeconomic and clinical characteristics of pertussis cases and population-based controls by outbreak status

	Non-outbreak years		Outbreak years*	
	Case (N=879)	**Control (N=4,170)**	**Case (N=545)**	**Control (N=2,537)**
Male	440 (50.1%)	2,112 (50.6%)	252 (46.2%)	1,173 (46.2%)
Age group (years)				
<1	303 (34.5%)	1,250 (30.0%)	93 (17.1%)	363 (14.3%)
1-2	116 (13.2%)	647 (15.5%)	111 (20.4%)	557 (22.0%)
3-5	159 (18.1%)	798 (19.1%)	250 (45.9%)	1,205 (47.5%)
6-8	133 (15.1%)	667 (16.0%)	91 (16.7%)	412 (16.2%)
9-13	136 (15.5%)	663 (15.9%)	0 (0.0%)	0 (0.0%)
14+	32 (3.6%)	145 (3.5%)	0 (0.0%)	0 (0.0%)
Rural residence	450 (51.2%)	2,115 (50.7%)	172 (31.6%)	764 (30.1%)
Income in lower 40%	418 (47.6%)	1,927 (46.2%)	204 (37.4%)	935 (36.9%)
Has chronic condition	98 (11.1%)	424 (10.2%)	32 (5.9%)	129 (5.1%)
Immunocompromised	75 (8.5%)	> 282 (> 6.8%)	< 6 (< 1.1%)	17 (0.7%)
Four or more physician visits†	457 (52.0%)	2,110 (50.6%)	294 (53.9%)	1,281 (50.5%)
One or more hospitalizations	69 (7.8%)	162 (3.9%)	10 (1.8%)	20 (0.8%)
Two or more prescriptions	272 (30.9%)	1,272 (30.5%)	38 (7.0%)	136 (5.4%)
Year of index date				
1992-1996	107 (12.2%)	567 (13.6%)	545 (100.0%)	2,537 (100.0%)
1997-2001	284 (32.3%)	1,366 (32.8%)	0 (0.0%)	0 (0.0%)
2002-2006	138 (15.7%)	621 (14.9%)	0 (0.0%)	0 (0.0%)
2007-2011	102 (11.6%)	457 (11.0%)	0 (0.0%)	0 (0.0%)
2012-2017	248 (28.2%)	1,159 (27.8%)	0 (0.0%)	0 (0.0%)
Vaccine status‡				
Unvaccinated	362 (41.2%)	777 (18.6%)	75 (13.8%)	310 (12.2%)
Partial	180 (20.5%)	1,030 (24.7%)	168 (30.8%)	661 (26.1%)
Up-to-date	337 (38.3%)	2,363 (56.7%)	302 (55.4%)	1,566 (61.7%)
Product used in vaccination series				
Unvaccinated	362 (41.2%)	777 (18.6%)	75 (13.8%)	310 (12.2%)

Acellular	178 (20.3%)	> 1,563 (> 37.5%)	0 (0.0%)	< 6 (< 0.2%)
Mixed	38 (4.3%)	275 (6.6%)	0 (0.0%)	0 (0.0%)
Whole-cell	301 (34.2%)	> 1,543 (> 37.0%)	470 (86.2%)	> 2,218 (> 87.4%)
Time since most recent vaccination				
Unvaccinated	362 (41.2%)	777 (18.6%)	75 (13.8%)	310 (12.2%)
15-364 days	144 (16.4%)	1,341 (32.2%)	168 (30.8%)	911 (35.9%)
1-3 years	202 (23.0%)	1,249 (30.0%)	265 (48.6%)	1,227 (48.4%)
4-7 years	122 (13.9%)	624 (15.0%)	37 (6.8%)	89 (3.5%)
8+ years	49 (5.6%)	179 (4.3%)	0 (0.0%)	0 (0.0%)

* 1994 and 1995
† In the 365 days prior to index date
‡ According to the recommended number of vaccine doses for their age and birth cohort

Over the study period, most laboratory-confirmed pertussis cases in Manitoba were younger than 14 years old (Table 9). Of the 879 cases diagnosed in non-outbreak years, 38% were up-to-date on their pertussis vaccination compared to 57% of controls. During outbreak years, 55% of cases were up-to-date compared to 62% of controls. Only 14% of cases diagnosed during outbreak years were never vaccinated compared to about 41% of cases in non-outbreak years (Table 9). Cases in the acellular vaccine cohort were more likely to have up-to-date or partial vaccine status compared to cases in the whole-cell vaccine cohort (Table D.3).

During non-outbreak years, the adjusted VE estimates of any pertussis vaccine against laboratory-confirmed pertussis were 80% (95% CI 75-84%) for up-to-date vaccination and 75% (67-81%) for partial vaccination (Table 10). The corresponding estimates for those who only received a wP vaccine, 46% (20-63%) and 35% (–61-58%), were both lower and less precise than those for persons who received the aP vaccine only: 90% (86-93%) and 86% (79-90%) respectively. During the outbreak years, only the wP vaccine was used in Manitoba and the VE estimates during that period were imprecise, but consistent with lower effectiveness (Table 11).

Table 10. Pertussis vaccine effectiveness (%) during non-outbreak years in Manitoba by vaccine type and certain vaccination characteristics

	Whole cell vaccine		Acellular vaccine		Any vaccine	
	Model A* (95% CI)	Model B† (95% CI)	Model A* (95% CI)	Model B† (95% CI)	Model A* (95% CI)	Model B† (95% CI)
Vaccine status§						
Unvaccinated	ref	ref	ref	ref	ref	ref
Partial	31 (-6-56)	35 (-1-58)	86 (79-90)	86 (79-90)	75 (67-81)	75 (67-81)
Up-to-date	43 (17-61)	46 (20-63)	90 (86-93)	90 (86-93)	80 (75-84)	80 (75-84)
Elapsed time since most recent vaccination‡						
Unvaccinated	ref	ref	ref	ref	ref	ref
15-364 days	65 (38-80)	65 (37-80)	86 (79-90)	85 (78-90)	82 (75-86)	81 (74-86)
1-3 years	21 (-39-55)	22 (-38-56)	96 (90-98)	96 (91-98)	78 (68-85)	78 (68-85)
4-7 years	-51 (-258-36)	-34 (-219-43)	84 (54-95)	86 (58-95)	45 (1-70)	48 (5-71)
≥ 8 years	26 (-228-83)	37 (-187-86)	71 (-137-97)	74 (-118-97)	57 (-31-86)	60 (-23-87)

* Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits).
† Model B is adjusted for the matching variables, >=4 physician visits in the previous year, hospitalized in the previous year, has a chronic disease, and immunocompromised status; ref = reference group.
‡ Elapsed time estimates use up-to-date vaccine status.
§ According to the recommended number of pertussis disease doses for their age and birth cohort

Table 11. Whole-cell pertussis vaccine effectiveness (%) during outbreak years 1994 and 1995 in Manitoba by certain vaccination characteristics

	Model A* (95% CI)	Model B† (95% CI)
Vaccine status§		
Unvaccinated	ref	ref
Partial	-10 (-52-21)	-8 (-50-22)
Up-to-date	25 (0-44)	25 (-0-44)
Elapsed time since most recent vaccination‡		
Unvaccinated	ref	ref
15-364 days	40 (15-57)	40 (15-58)
1-3 years	19 (-20-45)	19 (-20-45)
4-7 years	N/A	N/A
≥ 8 years	N/A	N/A

* Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits).
† Model B is adjusted for the matching variables, >=4 physician visits in the previous year, hospitalized in the previous year, has a chronic disease, and immunocompromised status; ref = reference group.
‡ Elapsed time estimates use up-to-date vaccine status.
§ According to the recommended number of pertussis disease doses for their age and birth cohort.
N/A = not applicable

During non-outbreak years (Table 10), the overall adjusted VE against laboratory-confirmed pertussis for individuals with up-to-date vaccine status was 78% (68-85%) in the 1-3 years following vaccination and 60% (–23-87%) more than eight years post-vaccination. For the wP vaccine, the adjusted VE was 22% (–38-56%) in the 1-3 years following vaccination and 37% (-187-86%) more than 8 years post-vaccination. For the aP vaccine, VE was 96% (91-98%) at 1-3 years post-vaccination and 74% (–118-97%) more than 8 years post-vaccination (Table 10).

Adjusted VE estimates for individuals partially vaccinated with aP vaccine were 93% (84-97%) at 1-3 years post vaccination and, although imprecise, were consistent with declining

effectiveness by eight years post-vaccination at 62% (-68-91%) (Table D.4). Considering all vaccinated persons together did not change our interpretation of the results.

A total of 457 (32%) and 31 (2%) cases were excluded due to the inability to identify a suitable match when restricting analysis to physician seen most frequently or to number of physician visits in the year prior to index date respectively (Table D.2). In a sensitivity analysis, VE estimates were similar in both control groups (Table D.5).

Discussion

We estimated that the overall VE was higher for the aP vaccine at 90% (86-93%) compared to 46% (20-63%) for the wP vaccine during non-outbreak years. The data were also consistent with declining VE over time.

Although imprecise, our estimate of wP VE during non-outbreak years (46%; 20-63%) is consistent with the range of estimates (20-60%) reported in Canada for wP vaccine used between 1984 and 1998 [151]. Due to this low VE and concerns around its safety, the wP vaccine was replaced by aP vaccines throughout Canada by 1998 [24]. Estimates for the whole-cell products currently in use in other countries are higher at 94% (88-97%) [66]. Similarly, our aP VE estimates against laboratory-confirmed pertussis (90%; 86-93%) are slightly higher, but consistent with those seen in a recent test-negative case-control study carried out in the Canadian province of Ontario, which demonstrated VE for the acellular vaccine of 84% (77-89%) for up-to-date vaccination in the first three years following vaccination [49]. Our estimates are also comparable to VE estimates from the 2016 systematic review and meta-analysis done by Fulton *et al.*, which showed a pooled short-term protective effect of 84% (81-87%) for the aP vaccine [66].

The Ontario study further suggested that the protective effect of the aP vaccine declines over time and observed that the odds of pertussis increased by 27% per year since last vaccination [49]. A systematic review and meta-analysis that pooled 11 long-term studies from multiple

countries had similar results, with the odds of pertussis increasing by 33% per year since last vaccination [10]. The meta-analysis and Ontario study both concluded that protection against pertussis would not be expected to extend longer than 7-8.5 years for most individuals after the last acellular pertussis dose. Although imprecise, our estimates are consistent with those reported in these other studies.

We saw lower wP VE during a large outbreak in 1994 and 1995, consistent with a contemporaneous outbreak of pertussis in the Canadian province of Nova Scotia that reported wP VE estimates against laboratory-confirmed pertussis for up-to-date vaccination among children of 14% (–158-71%) [75]. Previous pertussis VE studies have also demonstrated lower estimates of effectiveness in outbreak periods as compared to non-outbreak periods [103, 149]. The differences in VE estimates may be attributed to testing bias; since VE estimates are higher for typical/severe cases, heightened physician awareness and enhanced testing and reporting of cases with atypical/milder disease during outbreaks could result in lower VE estimates [149]. It is also possible that the pertussis vaccine offers less protection during periods of intense exposure which may contribute to the lower VE seen in outbreak periods [103, 149].

Strengths and limitations

A major strength of our study was the population-based design; the availability of accurate, high-quality health administrative databases in Manitoba makes our VE estimates less susceptible to misclassification of vaccine status and to the selection and recall biases that often affect observational studies.

Pertussis remains a relatively uncommon occurrence in Manitoba and a limitation of our study was the low number of pertussis cases available for analysis. The need to present separate analyses for the outbreak and non-outbreak periods due to effect modification further limited the precision of our estimates. Although our point estimates suggested declining protection over time, the confidence intervals were wide and often overlapped. Our point estimates were consistent with previous studies; they could, however, also be interpreted as showing no VE,

especially for the whole-cell pertussis vaccine. We did not exclude off-schedule doses or doses administered too close together (which may result in a suboptimal immune response). Each time period since the most recent vaccination included different mixes of ages and number of doses; due to the low number of cases, we were unable to stratify by both elapsed time and age together. We also lacked the power to analyze the VE of Tdap separately, because our study consisted mostly of children younger than the recommended Tdap booster age (96% of our population). There is emerging evidence that individuals primed with acellular pertussis vaccine have increased odds of disease compared to individuals primed with whole-cell vaccine [49]. We were unable to assess the role of the priming dose as only 38 of our cases received both vaccines.

Since cases were restricted to individuals with diagnosed pertussis-related episodes, our estimates reflect VE against medically attended pertussis and are not necessarily generalizable to all cases of pertussis infection. Although classic whooping cough illness is described by paroxysmal cough, post-tussive vomiting, and inspiratory whoop lasting over a prolonged period of time, evidence has shown that previously vaccinated individuals may still be infected, but experience reduced disease severity and duration [135]. Individuals with mild disease of a shorter duration may be less inclined to seek medical attention and thus would not be included in these analyses.

A national survey in the US exploring physician practices for managing pertussis in adolescents suggested that a substantial number of primary care physicians may not be able to recognize the clinical symptoms of pertussis in adolescents and that nearly one out of six physicians do not test adolescents for pertussis as part of their clinical practice [58]. This could confound VE estimation if these physicians are also less (or more) likely to administer pertussis vaccines. To minimize confounding, we matched cases and controls on physician seen most frequently in the year prior to the index date. However, not all cases had documented physician visits in the year before the index date, and for these cases we instead matched on frequency of physician visits before the index date. In sensitivity analyses, estimates from the physician-matched controls were similar to the visit frequency-matched controls, suggesting that either approach is a

reasonable choice, especially given that our results were similar to those obtained from test-negative study designs where all participants were tested for pertussis [116, 128].

In conclusion, our estimates suggest that the aP vaccine was effective in preventing pertussis since its introduction in Manitoba, albeit with a possible decline in effectiveness by eight years post-vaccination. VE was lower during a large outbreak, highlighting the importance of separately analyzing outbreak periods when estimating pertussis VE over time.

Additional analyses:

Vaccine effectiveness against hospitalization

Methods

We defined a hospitalized case as any individual with a separation diagnosis of pertussis, as recorded in the HAD (Table A.1), between April 1, 1992, and March 30, 2017 and used the methods outlined earlier in this chapter to measure pertussis VE against hospitalization.

Results

We identified 482 hospitalized cases (Table 3). Hospitalized cases were younger, more likely to live in a rural area, and more likely to live in a neighborhood in the lower 40% income quintile compared to laboratory-confirmed cases.

During non-outbreak years, the adjusted VE estimates of any pertussis vaccine against pertussis hospitalization were 79% (95% CI 68-86%) for up-to-date vaccination and 83% (69-90%) for partial vaccination (Table 12). The corresponding estimates for those who only received a wP vaccine, 74% (47-87%) and 68% (18-88%), were both lower and less precise than those for persons who received the aP vaccine only: 80% (67-88%) and 89% (75-95%).

As 77% of the hospitalized cases were under 1 year old (Table 3), duration of protection against hospitalization estimates longer than one year were not presented due to low case counts.

Table 12. Pertussis vaccine effectiveness (%) against hospitalization during non-outbreak years in Manitoba by vaccine type and certain vaccination characteristics

	Whole cell vaccine		Acellular vaccine		Any vaccine	
	Model A[1] (95% CI)	Model B[2] (95% CI)	Model A[1] (95% CI)	Model B[2] (95% CI)	Model A[1] (95% CI)	Model B[2] (95% CI)
Vaccine status						
Unvaccinated	ref	ref	Ref	ref	ref	ref
Partial	58 (4-81)	68 (18-88)	85 (72-92)	89 (75-95)	79 (66-87)	83 (69-90)
Up-to-date	77 (56-88)	74 (47-87)	85 (76-90)	80 (67-88)	83 (76-88)	79 (68-86)
Elapsed time since most recent vaccination						
Unvaccinated	ref	ref	Ref	ref	ref	ref
≤ 14 days	51 (-31-82)	60 (-16-86)	55 (21-74)	45 (-12-73)	53 (25-71)	49 (10-72)
15-364 days	84 (64-93)	79 (49-92)	90 (82-94)	86 (74-93)	87 (80-92)	83 (72-90)

* Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits).
† Model B is adjusted for the matching variables , >=4 physician visits in the previous year, hospitalized in the previous year, has a chronic disease, and immunocompromised status; ref = reference group.
‡ Elapsed time estimates use up-to-date vaccine status.
§ According to the recommended number of pertussis disease doses for their age and birth cohort

Conclusions

In Manitoba, most pertussis hospitalizations occurred in children less than one year old. Both the whole-cell and acellular pertussis vaccines conferred high protection against hospitalization in the year following the last vaccine dose. We couldn't extend our estimates past one year due to the low number of hospitalizations in older individuals. These findings highlight that the

prevention of illness in infants should be an important focus of the provincial pertussis vaccine program.

Chapter 5. Discussion

Summary of key findings

Pertussis persists in Manitoba, despite a long-standing universal vaccine program. The objectives of this dissertation were to examine pertussis disease incidence in Manitoba over a 25-year period and to estimate the effectiveness of the pertussis vaccines used in the province. Periodic increases of disease in Manitoba were attributable to both a vaccine birth cohort effect resulting from the low VE of the adsorbed wP vaccine as well as the waning immunity of the acellular pertussis vaccine. Children under one year old had the highest incidence of both laboratory-confirmed cases and pertussis-related hospitalizations over the study period.

Interpretation

Evidence from our SRMA (Chapter 3) suggested that receipt of any pertussis vaccine conferred short-term protection against disease although this protection appeared to wane rapidly for aP vaccines. However, this analysis also demonstrated that broad generalizability of VE estimates may be less than expected given the substantial heterogeneity observed, highlighting the challenges in making direct comparisons between results from different studies. One of the strategies for reducing heterogeneity in meta-analysis is by excluding studies; this is also one of the reasons previous pertussis SRMAs were largely limited to clinical trials. Differences in study methods also led NACI to caution in 1997 that each efficacy trial (in the eight studies done between 1990 and 1993) should be interpreted independently [24]. Basing vaccine policies solely on research from other jurisdictions should be done carefully, with a thorough consideration of sources of heterogeneity including an assessment of study validity. Manitoba's unique characteristics with respect to timing, magnitude, and trends in pertussis activity along with its vaccine program history and vaccine uptake underscores the need for provincial analysis for jurisdictional awareness and decision-making.

One of the key findings from our VE analysis (Chapter 4) was that the wP and aP vaccines used in Manitoba had markedly different estimates of VE; the adjusted VE estimate for aP-containing vaccines was 90% (95% CI: 86-93%) and the adjusted VE of wP-containing vaccines was 46% (20-63%). As introduced in Chapter 3, some of the differences in effectiveness between wP and aP vaccines may be attributed to differing mechanisms of action involving both humoral and cellular adaptive immunity [132].

Vaccine-specific antigens determine the antibodies produced via the humoral immune response; wP vaccines are made of a suspension of the whole-cells of one or more strains of killed *Bordetella pertussis* while aP vaccines consist of selected antigens [152]. Studies have shown that high levels of antibodies to the pertussis toxin, pertactin, and fimbrial agglutinogens antigens protect both singly and synergistically, i.e. having antibodies to one antigen provides some protection, but having antibodies to all three confers even greater protection [153]. Upon exposure to *B. pertussis*, vaccine recipients respond more strongly to the antigens in the vaccines with which they were immunized [154]. Whole-cell vaccines naturally contain multiple antigens while aP vaccines contain only select antigens; since antibodies to multiple antigens confer greater protection, this helps explain in general why aP vaccines may have a less robust immune response [154].

Although both wP and aP vaccines elicit pertussis-specific antibodies after vaccination, innate immunologic mechanisms may be different depending on the vaccine type [73]. The innate response is not antigen specific and can occur quickly, even in the absence of a previous exposure to the pathogen [155]. The innate response is also required to initiate the antigen-specific adaptive response [155]; after immunization with a wP vaccine, the innate immune response is different than that following an aP vaccine, allowing for a more rapid recall of antibody when the individual is subsequently exposed to *B. pertussis* [156]; baboon models have demonstrated that wP vaccines induce a more rapid Th1 and Th17 response compared to the Th1/Th2 response that follows an aP vaccine [157].

Although immunologic mechanisms suggest that wP vaccines may induce a more rapid and robust immune response upon subsequent exposure to *B. Pertussis* – and, by extension, a higher VE - the opposite was observed in Manitoba. Our APC analysis (Chapter 2) suggested the largest outbreak of the disease in the 25-year study period was attributed to a birth cohort effect for individuals born between 1980 and 1995 who were recipients of the adsorbed wP vaccine. A study that looked at trends of pertussis incidence in the Canadian province of Quebec identified a similar cohort effect around the same time, although that study did not include an APC analysis [48]. Our VE estimates for the outbreak years 1994/1995 provided further support for a cohort effect and were consistent with little vaccine protection offered by the wP vaccine (25% [-0-44%]).

Although imprecise, our estimate of wP VE during non-outbreak years (46%; 20-63%) was consistent with the range of estimates (20-60%) reported in Canada for wP vaccine used between 1984 and 1998 [151]; during this period Canada exclusively used an adsorbed wP vaccine manufactured by Connaught Laboratories. The United States experienced a contemporaneous outbreak in 1993 in a population that was also highly vaccinated with wP vaccine; receipt of the Connaught vaccine was documented in 72% of those cases, although no specific vaccine was ever implicated [158]. The Connaught vaccine met potency regulations; however, it also induced a poor antibody response to pertussis antigens, with no antibodies detected in most children by 15 months post-vaccination [159].

As discussed in detail in Chapter 3, the bulk of the evidence from previous research shows that substantial heterogeneity creates challenges in predicting effectiveness of wP vaccines. Estimates of wP VE in our SRMA ranged from a minimum of 28% to a maximum of 95% and varied widely by country. Estimates from a recent SRMA estimating short-term VE for the whole-cell products currently in use in other countries were considerably higher at 94% (88-97%) [66].

The low efficacy of the adsorbed wP used in Canada and promising vaccine efficacy estimates from the initial aP clinical trials along with fewer local and systemic adverse events following aP vaccination all contributed to NACI's 1997 endorsement of aP over wP vaccines [24]. After the

introduction of aP vaccines in Manitoba in 1997, the annual incidence of pertussis declined and remained low for a long period of time. However, we observed an increase in pertussis incidence in 2012 occurring mostly in individuals born after 1997 who would have received the aP vaccine and approximately 40% of those cases occurred in individuals over 7 years old, consistent with waning vaccine protection (Chapter 2). This was supported by our VE estimates (Chapter 4) which suggested that the aP vaccine was effective in preventing pertussis since its introduction in Manitoba, albeit with a possible decline in effectiveness by eight years post-vaccination. Our adjusted VE estimate of aP vaccine against laboratory-confirmed pertussis was 96% (91-98%) at 1-3 years post-vaccination and had declined to 74% (–118-97%) at more than 8 years post-vaccination.

A 2015 SRMA measuring duration of immunity for the aP vaccine following the childhood priming series estimated that for every year after the last dose, the odds of pertussis increased by 1.33 times (95% CI 1.23-1.43) [10]. A more recent SRMA from 2019 focused on adolescent and adult aP boosters but was restricted to clinical trials, of which only one included a VE estimate of 89% after 2.5 years of follow-up [67]. A meta-regression modeling study using discrete time points since vaccination to estimate the duration of protection of the aP vaccine estimated that VE for the childhood and adolescent series declined 10% and 12% annually [68]. Our SRMA included more recent studies and looked at reported VE estimates at discrete time-points for both the primary series and booster dose cohorts; vaccine effectiveness for the 0-10 year-old cohort declined from 98% (90-100; I^2=94%) in the first year to 81% (69-89; I^2=0%) by five years post-vaccination. In the 11-20 year-old cohort, VE declined from 72% (66-76; I^2=0%) in the first year to 42% (16-60; I^2=2%) at four years post-vaccination.

Since the completion of our SRMA, a CIRN meta-analysis of four population-based pertussis VE studies from three Canadian provinces has been published [160]. Although this analysis also highlighted the heterogeneity that can occur between studies, all results were suggestive of declining aP VE over time. In the pooled analysis, estimates of pertussis VE declined from 86% (79-90; I^2=81.5%) in the first year following vaccination to 51% (11-74; I^2=80.9%) by more than

eight years following vaccination. Other studies have estimated that protection against pertussis would not be expected to extend longer than 7-8.5 years for most individuals after the last acellular pertussis dose [10, 49]. Although imprecise, Manitoba-specific VE estimates were also consistent with declining protection for the aP vaccine (Chapter 4).

Our findings were consistent with cohort effects resulting from the low VE of the wP vaccine as well as from the waning protection of the aP vaccine. Although these cohort effects may explain Manitoba's large disease outbreaks, the highest risk across the study period was consistently in young children regardless of birth cohort. In addition to laboratory-confirmed incidence, we also observed that most pertussis hospitalizations occurred in children less than one year old.

A study done by the IMPACT pediatric tertiary-care hospital surveillance network explored the effects of changing from wP to aP vaccines on pertussis-related hospitalizations in Canada [161]. They observed that there was an overall decrease in the incidence of hospitalized pertussis following the introduction of aP vaccines in Canada with the highest proportion of hospitalizations occurring in children too young to be vaccinated. We saw a similar decline in the incidence of pertussis hospitalizations in our APC analyses and observed that hospitalization rates were lower for the under one-year old age group in the aP vaccine cohort as compared to the wP vaccine cohort.

Although the IMPACT study results were consistent with improved effectiveness of aP vaccines compared to wP vaccines, the analysis was not designed to provide direct estimates of VE against hospitalization. As seen in our SRMA, the pooled estimate for the five included studies that measured VE against hospitalization was 91% (87-94; I^2=67%). Our Manitoba-specific VE analysis further suggested that both the whole-cell and acellular pertussis vaccines conferred high protection against hospitalization in the year following the last vaccine dose (79% [49-92%] and 86% [74-93%] respectively), however as 77% of all hospitalizations occurred in children under one year old, we couldn't extend our estimates to measure duration of protection past one-year post-vaccination.

Factors other than waning protection of the aP vaccine have been proposed to explain the recent resurgence of pertussis. These factors include i) the expected long-term impacts of a vaccination program with incomplete coverage and a sub-optimal vaccine, ii) subclinical infections increasing transmission to vulnerable populations, iii) pathogenic evolution, and iv) the impact of surveillance/awareness.

Using a pertussis transmission dynamics model, Riolo et al showed that the resurgence of pertussis in Britain among adults and adolescents may have been the result of historically inadequate coverage of an imperfect vaccine [57]. They proposed that the impacts of infection and vaccination can be seen in a population's immunity profile for several decades; during the early years when the pertussis vaccine was first introduced there was a combined effect of herd-immunity from natural infection as well as increased short-term protection from vaccination. As infection-derived herd immunity decreased due to the shrinking size of the pre-vaccine cohort and as the impacts of waning vaccine immunity due to an imperfect vaccine were being realized, the incidence of pertussis rose. In Manitoba, pertussis coverage rates have consistently been well below the national target of 95%, and our findings also indicate waning of protection for the aP vaccine; given these factors, it should be expected that Manitoba will continue to experience periodic outbreaks of pertussis.

Another important contributor is subclinical infection; it has been hypothesized that individuals immunized with aP vaccine can still be infected with pertussis, but have either mild or asymptomatic disease (i.e., pertussis vaccination prevents classical pertussis clinical illness, but does not prevent infection or transmission) [7, 135]. Thus, infected, asymptomatic individuals may act as a source of transmission to vulnerable non-vaccinated populations. As most pertussis surveillance is based on medically-attended disease, the impact of subclinical infections on pertussis incidence is not well understood. We were unable to determine what role subclinical infection played in Manitoba.

It has been suggested that pathogenic evolution due to genetic changes in *B. pertussis* may render the aP vaccine less effective [162, 163] and there have been reports of strains having

modification or absence of the antigens included in aP vaccines [164]. However, there is not yet consensus as to the role these genetic changes have had on the effectiveness of the aP vaccine.

Finally, it has been proposed that there hasn't been an actual increase in pertussis incidence, but rather an increase in awareness and an improvement in surveillance and laboratory-testing [156]. It was suggested that as laboratory tests such as PCR replaced culture and as surveillance methods improved, the inevitable impact was more reporting of disease. We demonstrated in Chapter 2 that period effects (such as those due to changes in laboratory testing) were less important than age and cohort effects in Manitoba. Our exploration of laboratory-confirmed and outpatient diagnosis patterns further supported that the resurgence of pertussis disease in the province in the 2010s was not the result of incomplete identification of pertussis prior to the implementation of PCR but was more consistent with waning immunity. However, we also observed a shift towards greater proportions of older outpatient cases in later years; in 2011/12 approximately 40% of cases were more than 12 years old as compared to approximately 15% in 1992/93 and the mean age of outpatient cases increased from 7 years old in 1992 to 19 years old in 2017 (data not shown). The outpatient group represents individuals who were diagnosed with pertussis during a physician visit and the shift to the older age group may suggest a change in diagnostic awareness. This change in testing behavior may also partially explain the slight period effects in the lab-confirmed and outpatient APC models that were not seen for the younger, hospitalized cases.

Study limitations

A major strength of this study was the availability of high quality, population-based health administrative databases in Manitoba. However, a cautious approach is still necessary when using routine health databases for evaluation of vaccine effectiveness [165]; it is important to be clear on definitions, limitations, and methods of measurement as there may be issues with the data available, especially with respect to study outcome and exposure variables [166]. Consistent case finding and accurate vaccine status ascertainment remain key considerations for valid VE estimates, even when using large, administrative datasets [165].

Misclassification of case status

A core decision when using administrative data is how to ascertain cases; a strength of our approach was in the use of case definitions derived from three separate administrative datasets (lab-confirmed cases, outpatient cases, hospitalized cases) with different diagnostic thresholds. We observed differences in demographics and incidence based on case definition, especially for the hospitalized cases, highlighting the importance of not collapsing pertussis case counts from different sources in a single analysis. Including multiple case definitions allowed for a more complete understanding of the burden of disease.

A study in Ontario evaluated the completeness of pertussis data sources using capture-recapture data analysis and determined that none of the sources of information on pertussis was complete and that the burden was likely higher than their routine data indicated [137]. Although we did not do a capture-recapture analysis, we did look at the overlap in cases between the different datasets used to identify cases in our analyses. Although an individual could potentially appear in all three datasets (e.g., an outpatient visit and subsequent hospitalization along with a lab-confirmed pertussis result), that was an uncommon scenario that occurred only about 1% of the time. The highest proportion of episodes were outpatient visits with no corresponding laboratory confirmation (76%); however, we were unable to determine if that was due to clinical diagnoses with no confirmatory laboratory testing sought or due to negative results to which we did not have access. We also observed that approximately 7% of all pertussis episodes were restricted to laboratory-confirmed pertussis alone, with no corresponding outpatient visit or hospitalization; these episodes may represent positive pertussis laboratory results for a medical visit that was not recorded with a pertussis tariff code in the outpatient dataset or from testing occurring in settings not captured in the hospital or outpatient datasets.

Although under-ascertainment of laboratory-confirmed pertussis (our primary case definition) was possible, any under-ascertainment of case status was likely non-differential with respect to vaccine status. In addition, the sensitivity and specificity of laboratory testing was likely non-differential with respect to vaccination status. There is a “rule of thumb” that non-differential

misclassification of binary disease status and independence of other errors tends to bias VE estimates towards the null and results in an observed reduction in the strength of the vaccine-disease association [167]. However, non-differential disease misclassification alone is not sufficient to ensure that bias is towards the null and this "rule of thumb" only works when other conditions are met (e.g., pertussis disease misclassification error doesn't depend on errors in other variables, including measures of vaccine status). In our analyses, the use of different, unrelated, databases to identify cases and define pertussis vaccine status makes it unlikely that non-differential errors in the measurement of disease and vaccine status were correlated. It has also been further demonstrated in a study looking at the single impact of either disease or exposure misclassification on estimates of pertussis VE, that exposure misclassification had a larger impact compared to disease misclassification [168].

Misclassification of vaccination status

Our exposure of interest in the VE analysis was pertussis vaccination. MIMS has been validated for the pediatric population and is used by clinicians as the patient's official immunization record [145]. As such, our study was less susceptible to vaccine status misclassification and recall bias than studies relying on parental-report or medical records. Further, we expect that any residual error in recording vaccine status in MIMS was non-differential with respect to case status. Even if all rules are met for non-differentiality (misclassification probabilities are exactly non-differential; exposure misclassification errors are independent of errors in other variables; conditions are in place to guarantee bias toward the null when the exposure has more than two levels; and absence of interaction with other sources of systematic error), bias towards the null doesn't always result in an underestimate of VE [167]. Misclassification may be non-differential on average across a number of hypothetical study repetitions, but with random variation in a single study the classification may be differential [167].

Although the data in MIMS itself have been validated, the definition of vaccination status can be complicated in settings where the exposure varies with time or when recentness of exposure is of interest [169]. Categorizing vaccination status as a dichotomous variable (i.e., vaccinated versus

not-vaccinated) is not recommended when defining pertussis vaccine status; given that the recommended series consists of multiple doses, individuals can be classified as non-vaccinated, fully vaccinated for age, or partially vaccinated for age. When collapsing as a dichotomous variable, including partially vaccinated individuals in the vaccinated group can underestimate VE. However, including partially vaccinated individuals in the unvaccinated group may also lower estimates of VE if partial protection is conferred (the Will Rogers Phenomenon) [170]. We countered this by retaining partially vaccinated as a discrete category in the analysis.

Another concern in assessing vaccination status is that of timeliness (i.e., adherence to vaccination schedule). Definitions of timeliness can be strict (e.g., allowing only a week after the scheduled dose to be considered "up-to-date") or lenient (e.g., allowing eight weeks after scheduled dose to be considered "up-to-date") and the choice of definition can impact estimates. We followed a strict definition with respect to timing that did not allow for off-schedule dosing and some individuals may have been misclassified as partially vaccinated or non-vaccinated as a result. For example, children aged 7-17 with no history of previous pertussis vaccination are recommended to have a three-dose Tdap-IPV priming series with a Tdap booster either in the Grade 8/9 school program or ten years after the third priming dose [45]. In our analyses, these individuals would be classified as partially vaccinated as they didn't have the recommended number of doses as per the routine schedule. However, as we retained partially-vaccinated as a distinct category and used the unvaccinated as the reference category throughout, this will not have affected our estimates of pertussis VE under the routine schedule.

Vaccination status for this study was derived completely from MIMS, and decisions on how to handle missing or incomplete vaccine histories can impact estimates of VE. Our cohort was registry-based and thus participants may not have been registered with MH at the time of immunizations. To avoid differential ascertainment of exposure status, the same inclusion and exclusion criteria were applied equally to both cases and controls.

Whole-cell vaccine priming

Despite the periodic increases of pertussis observed in Manitoba, it remains a disease of rare occurrence provincially, thus limiting some of our intended analyses. In particular, we were interested in the role of wP vaccine priming as emerging evidence suggests that VE might be impacted by the vaccine type used in the priming series [49, 171, 172]. There have been no meta-analyses looking at the role of whole cell priming, however a mathematic model of pertussis transmission estimated that an alternative priming schedule that included one dose of whole-cell pertussis vaccine could reduce incidence by up to 95% (91-98%) [171]. Preliminary evidence from observational studies indicates that having at least one wP vaccine during the primary childhood series confers better protection against pertussis than being primed with all aP vaccine [172]. Schwartz et al reported that individuals primed with only aP vaccine had 2.2 times higher odds of pertussis than those primed with the previously used wP vaccine [49]. In a large study done in California, teenagers who had received four doses of aP vaccine were much more likely to have pertussis disease as compared to those who had received four doses of wP vaccine (OR 5.63, 95% CI 2.55-12.46); in addition a decreasing number of whole-cell doses was significantly associated with an increased risk of pertussis [173]. Although our study included both the wP and aP vaccine periods, there were only 38 cases in our cohort who had received a mixed priming series and we were unable to assess VE for this group.

Implications for policy and practice

There is a conceptual hierarchy of public health objectives when it comes to infectious diseases: control, elimination of disease, elimination of infections, eradication, and extinction [174]. Pertussis is not a likely candidate for elimination or eradication due to the lack of lifelong immunity following vaccination or natural infection along with the role of asymptomatic or mild disease as a source of ongoing transmission [175]. Following this conceptual hierarchy, public health interventions should be focused on the control of pertussis with the objectives of reducing the overall incidence of disease, preventing pertussis-associated hospitalizations, and ultimately saving lives.

Our analyses demonstrated that the greatest burden of pertussis in Manitoba has consistently been in children less than one year old, highlighting the need to target interventions at preventing illness in this age group. Strategies used to decrease pertussis transmission to infants include cocooning (indirect protection by vaccinating close contacts of infants) and vaccinating pregnant women (indirect protection through passive transfer of maternal antibodies). Vaccination during pregnancy has emerged as the recommended primary strategy and has been adopted by the national health organizations in multiple countries, including Canada [25, 176]. MH adopted a partial cocoon strategy with the addition of primary caregivers of newborns to the provincially funded program in 2012; pregnant women with no history of adult pertussis vaccinations were added to the provincial program in 2015; and a maternal booster during every pregnancy was added in 2019. Given the relatively recent addition of maternal boosters to the recommended provincial vaccine schedule, we were unable to assess the impact of this vaccine program change on infant pertussis incidence or hospitalizations in this study.

The use of age-period-cohort analyses can also help identify targets for public health interventions and responses would conceivably be very different where period effects were seen as opposed to cohort effects. In Manitoba, we identified two at-risk cohorts that were potentially available for intervention – the wP vaccine cohort who had almost no protection as a result of a vaccine with low efficacy and aP vaccine recipients with waning vaccine protection. Although no attempt was made to catch-up the vulnerable adsorbed wP cohort with a more effective vaccine, additional aP doses were added in adolescence and in adulthood to boost protection for recipients primed with the aP vaccine based largely on evidence from other jurisdictions.

Directions for future research

The studies presented in this dissertation begin to address the knowledge gap around the burden of pertussis in Manitoba, and the effectiveness and duration of protection of pertussis vaccines in the province; however, further research is required to address remaining questions.

An outstanding question that could not be addressed in our analyses was the impact of the maternal pertussis booster vaccine program on pertussis incidence and hospitalizations in infants, which should be prioritized for future research. Our analyses included only medically-attended pertussis, and studies exploring the role of asymptomatic or mild disease are also needed.

Outside the scope of this dissertation was an exploration of the predictors of low pertussis vaccine uptake in Manitoba. This is important to understand as the under-vaccinated population remains at high risk for resurgence of pertussis disease.

In the absence of a novel pertussis vaccine that offers high VE with long-term protection, questions remain about the optimal timing and number of aP doses required to ensure maximum individual protection and reduction of transmission risk. There are still unanswered questions about the role of wP vaccine priming and whether wP dose(s) should be considered for inclusion in the childhood priming series.

Last thoughts

Through this series of studies, we demonstrated that changes in the provincial vaccine program had impacts on the incidence of pertussis disease that were often not realized until years later. Limited protection in the cohort who received the low VE adsorbed whole-cell pertussis vaccine may have resulted in the largest pertussis outbreak in the 25-year study period. The shift to the acellular pertussis vaccine reduced the incidence of pertussis disease immediately following its introduction due to its high short-term effectiveness; however, evidence suggests that this protection waned rapidly and contributed to disease resurgence. In Manitoba, most pertussis hospitalizations occurred in children less than one-year old across the study period, highlighting that the focus of pertussis vaccine programs should be on preventing illness in this vulnerable group.

Appendices

Appendix A. Supplemental Material for Chapter 1

Table A.1 ICD9 and ICD10 codes used to identify pertussis cases from the Manitoba Hospital Abstracts database

Source	Code	Description
ICD-9th Revision	033.0	Whooping cough due to Bordetella pertussis
	033.1	Whopping cough due to Bordetella parapertussis
	033.8	Whooping cough due to other specified organism
	033.9	Whooping cough, unspecified organism
ICD-10th Revision	A37.0	Whooping cough due to Bordetalla pertussis
	A37.1	Whopping cough due to Bordetella parapertussis
	A37.8	Whooping cough due to other Bordetella species
	A37.9	Whooping cough, unspecified

Table A.2 Current and cancelled pertussis-related tariff codes used in the Manitoba Immunization Monitoring System[177]

Name	Current codes	Cancelled codes
DTAP-P-HIB	8802	8804, 8806, 8807
TDAP	8907	
TDAP-IPV	8964	
AP	8720	
DPT	8601	8602, 8603, 8609
DPT-HIB	8781	8782, 8783, 8789
DTAPPHIBHB	8680	8676, 8677, 8678, 8679
DTAP-IPV	8924	
DPTP		8921, 8922, 8923, 8929
DPTP-HIB		8801
P		8721, 8722, 8723, 8729

Appendix B. Supplemental Material for Chapter 2

Table B.1 Changes in the recommended pertussis vaccine schedule in Manitoba, 1988-2017

	Recommended vaccine schedule			
Year schedule active	2,4,6, 18 months	4-6 years	14-16 years	>18 years
1988-1997	DPT-HIB	DPT-HIB		
1997-2003	DTaP-IPV-HIB	DTaP-IPV-HIB		
2003-2012	DTaP-IPV-HIB	DTaP-IPV-HIB	Tdap	
2012-2017	DTaP-IPV-HIB	Tdap-IPV	Tdap	Tdap

DPT-HIB = Diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b

DTaP-IPV-HIB = Diphtheria, tetanus, acellular pertussis, polio, *Haemophilus influenzae* type b

Tdap-IPV = Tetanus, diphtheria, acellular pertussis, polio

Table B.2 Crude and age-standardized rates (95% confidence interval) of pertussis cases per 100,000 person-years in Manitoba by index year

Index year	Crude (95%CI)	Age-standardized (95%CI)
1992	4 (2-4)	3 (2-4)
1993	5 (3-5)	4 (3-5)
1994	72 (52-59)	55 (52-59)
1995	33 (23-28)	25 (23-28)
1996	9 (5-8)	7 (5-8)
1997	7 (4-7)	5 (4-7)
1998	18 (12-16)	14 (12-16)
1999	8 (6-8)	7 (6-8)
2000	3 (2-4)	3 (2-4)
2001	1 (1-2)	1 (1-2)
2002	5 (3-5)	4 (3-5)
2003	4 (2-4)	3 (2-4)
2004	5 (3-6)	5 (3-6)
2005	2 (1-3)	2 (1-3)
2006	1 (0-1)	1 (0-1)
2007	1 (0-1)	1 (0-1)
2008	1 (0-2)	1 (0-2)
2009	2 (1-3)	2 (1-3)
2010	4 (3-5)	4 (3-5)
2011	2 (1-3)	2 (1-3)
2012	9 (6-9)	8 (6-9)
2013	0 (0-1)	0 (0-1)
2014	1 (0-2)	1 (0-2)
2015	4 (3-5)	4 (3-5)
2016	9 (6-9)	8 (6-9)
2017	2 (1-3)	2 (1-3)

Figure B.1 Age-period-cohort model with 95% confidence intervals of pertussis incidence in Manitoba, 1992-2017, with average cohort effect constrained to be zero.

A) Estimated age effect.

B) Cohort effect (dashed) and period effect (dashed-dot) rate ratios. The reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of the cases (1989).

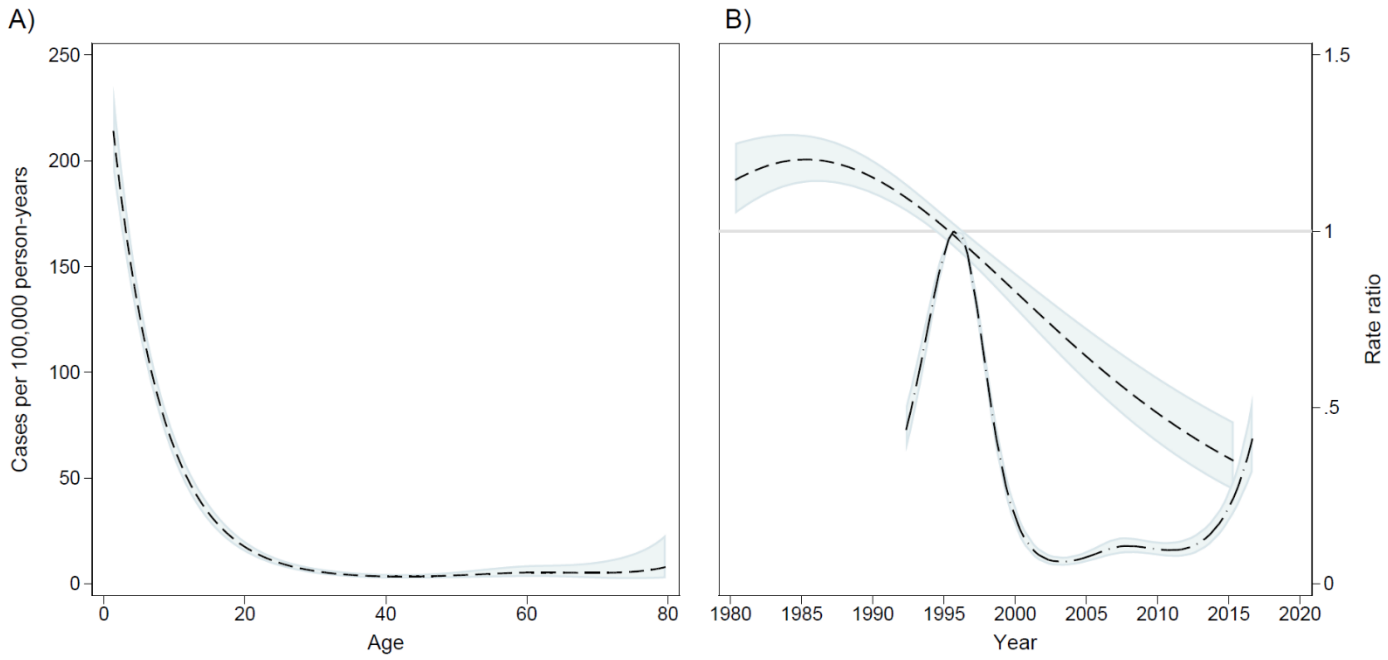


Figure B.2 Age-period-cohort model with 95% confidence intervals of pertussis hospitalizations in Manitoba, 1992-2017, with average cohort effect constrained to be zero.

A) Estimated age effect.

B) Cohort effect (dashed) and period effect (dashed-dot) rate ratios. The reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of the cases (1989).

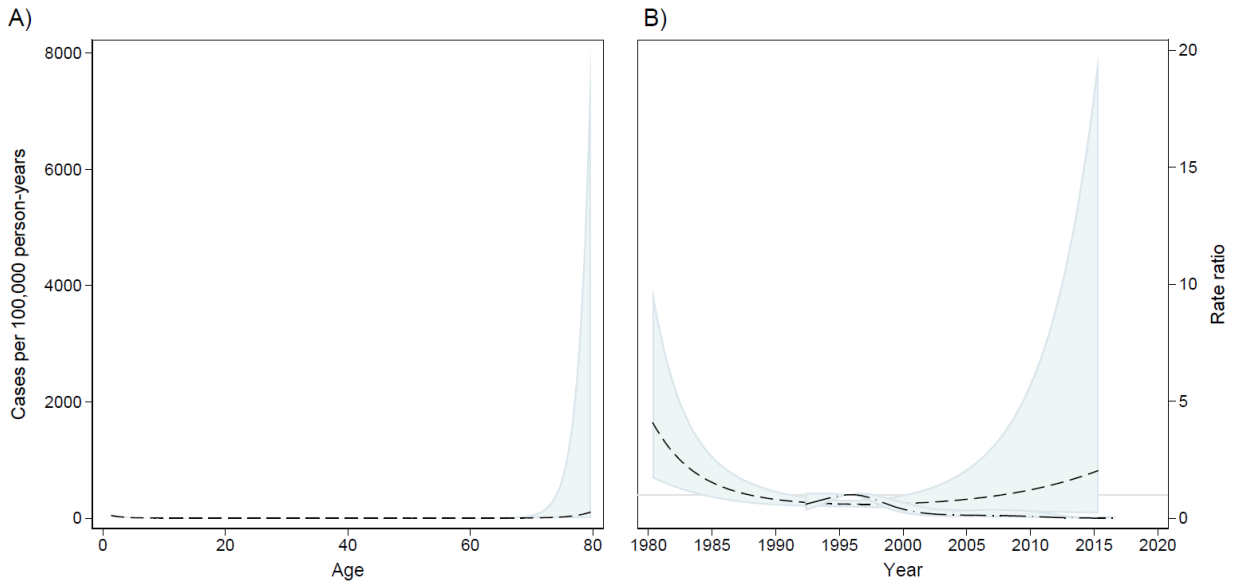


Figure B.3 Age-period-cohort model with 95% confidence intervals of pertussis outpatient incidence in Manitoba, 1992-2017, with average cohort effect constrained to be zero.

A) Estimated age effect.

B) Cohort effect (dashed) and period effect (dashed-dot) rate ratios. The reference year for the period effect was the median episode year of the cases (1996) and the reference year for the cohort effect was the median birth year of the cases (1989).

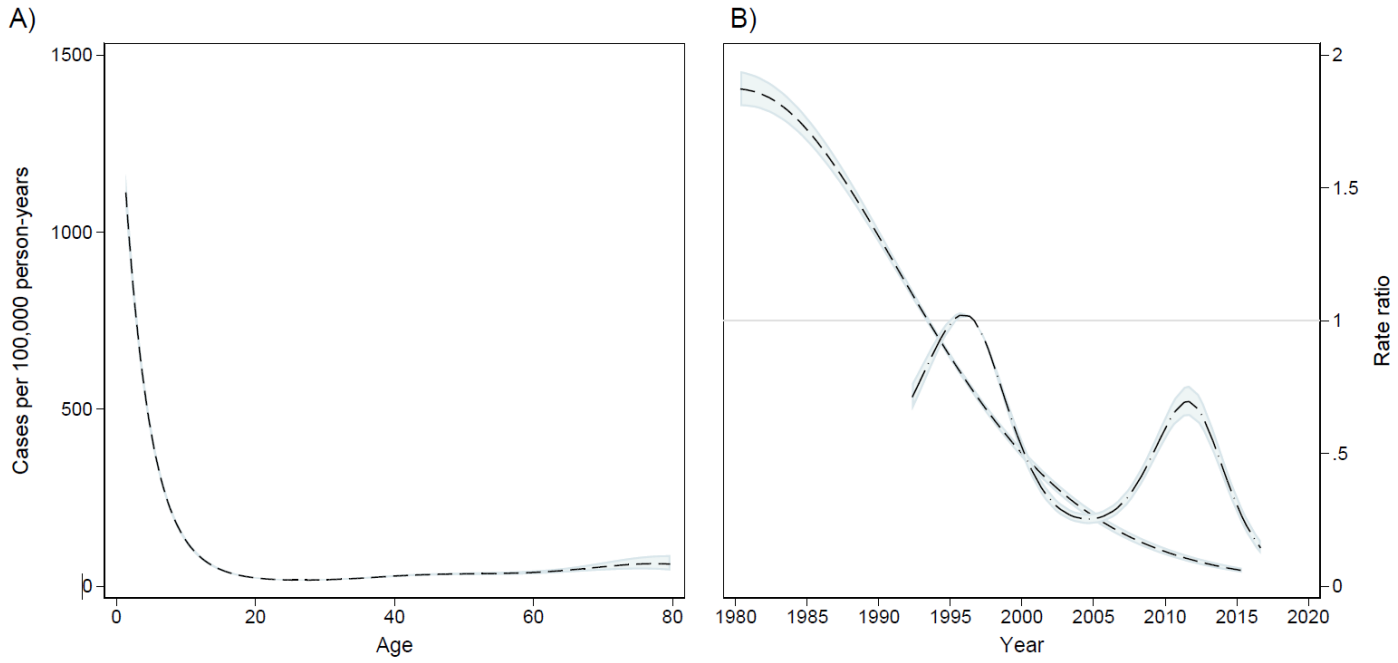


Table B.3 Laboratory-confirmed cases of pertussis in Manitoba by index year and diagnostic test

	Missing	Culture	DFA	PCR	Serology
Index year					
1992	28	15	0	0	s
1993	34	21	0	0	s
1994	s	540	9	0	269
1995	59	221	10	0	85
1996	0	94	s	S	s
1997	0	68	s	S	0
1998	0	186	0	17	s
1999	0	90	0	7	0
2000	0	30	0	S	0
2001	0	15	0	S	0
2002	0	50	0	S	s
2003	s	39	0	0	0
2004	s	55	s	S	0
2005	0	28	0	0	0
2006	0	7	0	0	0
2007	0	10	0	0	0
2008	0	13	0	0	0
2009	0	29	0	0	0
2010	0	51	0	0	0
2011	0	23	s	S	0
2012	s	58	0	52	0
2013	0	s	0	S	0
2014	s	0	0	11	0
2015	0	s	0	52	0
2016	s	34	0	83	0
2017	s	15	0	16	0

s=suppressed; DFA=Direct fluorescent antibody test; PCR=Polymerase chain reaction test

Appendix C. Supplemental Material for Chapter 3

Table C.1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or	

Section and Topic	Item #	Checklist item	Location where item is reported
		synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table C.2 Medline search strategy

Database: Embase <1974 to 2019 November 26>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

1. exp Pertussis Vaccine/
2. diphtheria pertussis tetanus vaccine.ti,ab,kw.
3. diphtheria tetanus pertussis vaccine.ti,ab,kw.
4. diphtheria-pertussis-tetanus vaccine.ti,ab,kw.
5. diphtheria-tetanus-pertussis vaccine.ti,ab,kw.
6. vaccine, diptheria-pertussis-tetanus.ti,ab,kw.
7. vaccine, diphtheria-tetanus-pertussis.ti,ab,kw.
8. acellular pertussis vaccines.mp.
9. whole cell pertussis vaccines.mp.
10. acel imune.ti,ab,kw.
11. acel-imune.ti,ab,kw.
12. acelimune.ti,ab,kw.
13. dtap vaccine.ti,ab,kw.
14. diphtheria tetanus acellular pertussis vaccines.ti,kw,ab.
15. diphtheria-tetanus-acellular pertussis vaccine.ti,ab,kw.
16. infanrix.ti,ab,kw.
17. pertussis vaccine, diphtheria-tetanus-acellular.ti,ab,kw.
18. tripedia.ti,ab,kw.
19. vaccine, dtap.ti,ab,kw.
20. vaccines, dtap.ti,ab,kw.
21. vaccine, dpt.ti,ab,kw.
22. vaccine, dtp.ti,ab,kw.
23. vaccine, dtwp.ti,ab,kw.
24. vaccine, di-te-per.ti,ab,kw.
25. vaccines, diphtheria-tetanus-acellular pertussis.ti,ab,kw.
26. dtp vaccine.ti,ab,kw.
27. dpt vaccine.ti,ab,kw.
28. di te per vaccine.ti,ab,kw.
29. di-te-per vaccine.ti,ab,kw.
30. Vaccination/
31. active immuniz*.ti,ab,kw.
32. immunization*, active.ti,ab,kw.
33. (immuniz* or immunis*).ti,ab,kw.
34. effectiveness.mp,ti,ab,kw.
35. efficacy.mp,ti,ab,kw.
36. compar*.ti,ab,kw.
37. exp Bordetella infections/
38. bordetella pertussis infection, respiratory.ti,ab,kw.
39. cough, whooping.ti,ab,kw.
40. pertusses.ti,ab,kw.
41. pertussis.ti,ab,kw.
42. pertussis infection.ti,ab,kw.
43. bordetella pertussis.mp. or Bordetella pertussis/
44. or/1-33 [all Vaccine]
45. or/34-36 [all VE]
46. or/37-43 [all Bacteria]
47. and/44-46 [all concept combination]

Table C.3 List of derived variables and definitions

Variable	Definition
Vaccine type	Based on the vaccine type as reported in included study methodology: • Acellular pertussis – any acellular pertussis vaccine • Whole-cell pertussis – any wP pertussis vaccine • Mixed vaccines – Unspecified vaccines, both vaccines, any pertussis vaccine
Maximum elapsed time since last pertussis vaccine dose	Based on maximum number of years since last pertussis dose according to study; e.g. if a study reported vaccine effectiveness at 1-3 years since last dose, it was coded as a maximum of 3 years since last dose in the meta-analysis
Age group	Based on the age range of study participants; • Child – 0-10 years old • Adolescent – 11-19 years old • Adult – 20 years or older • Other - other ranges not fitting into the above category (e.g. a study that placed no restriction on age and contained individuals from 0 to 65 years old)
Case definition categories	Any combination of the definitions below as per the study criteria: • Lab - Confirmed case requires positive pertussis laboratory result by any testing method as defined in the study methodology

	• Clinical – Confirmed case requires clinical symptoms as defined in study methodology • Epi-link – Case is epi-linked to a confirmed case as defined in study methodology
Epidemic status	Based on whether the study reported that their analysis occurred during an epidemic period (e.g. outbreak), an endemic period, both an epidemic and endemic period (e.g. study spanning multiple years that contain at least one epidemic period), or was unspecified by the authors.

Figure C.1 Acellular pertussis vaccine effectiveness against disease

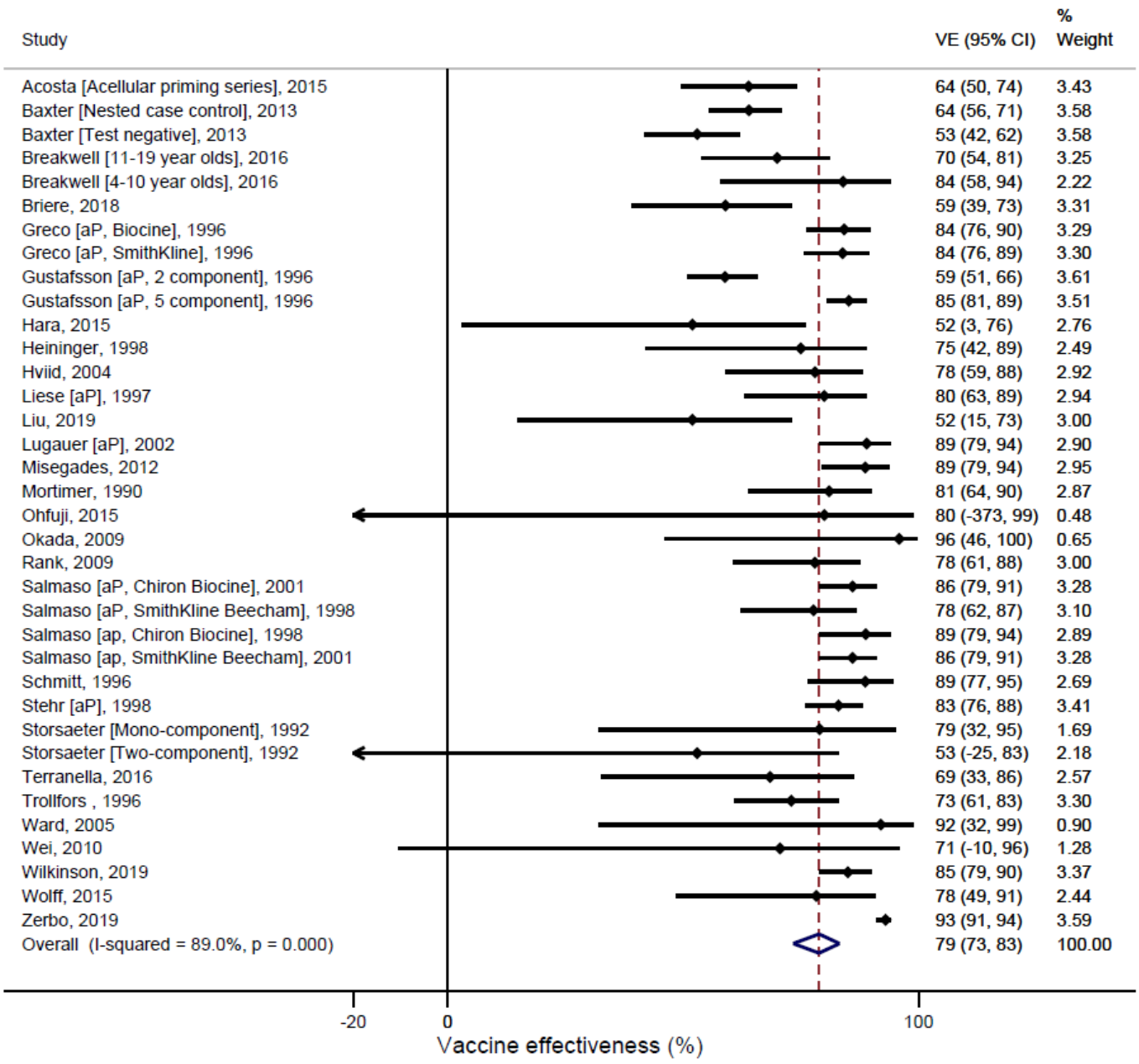


Figure C.2 Whole-cell pertussis vaccine effectiveness against disease

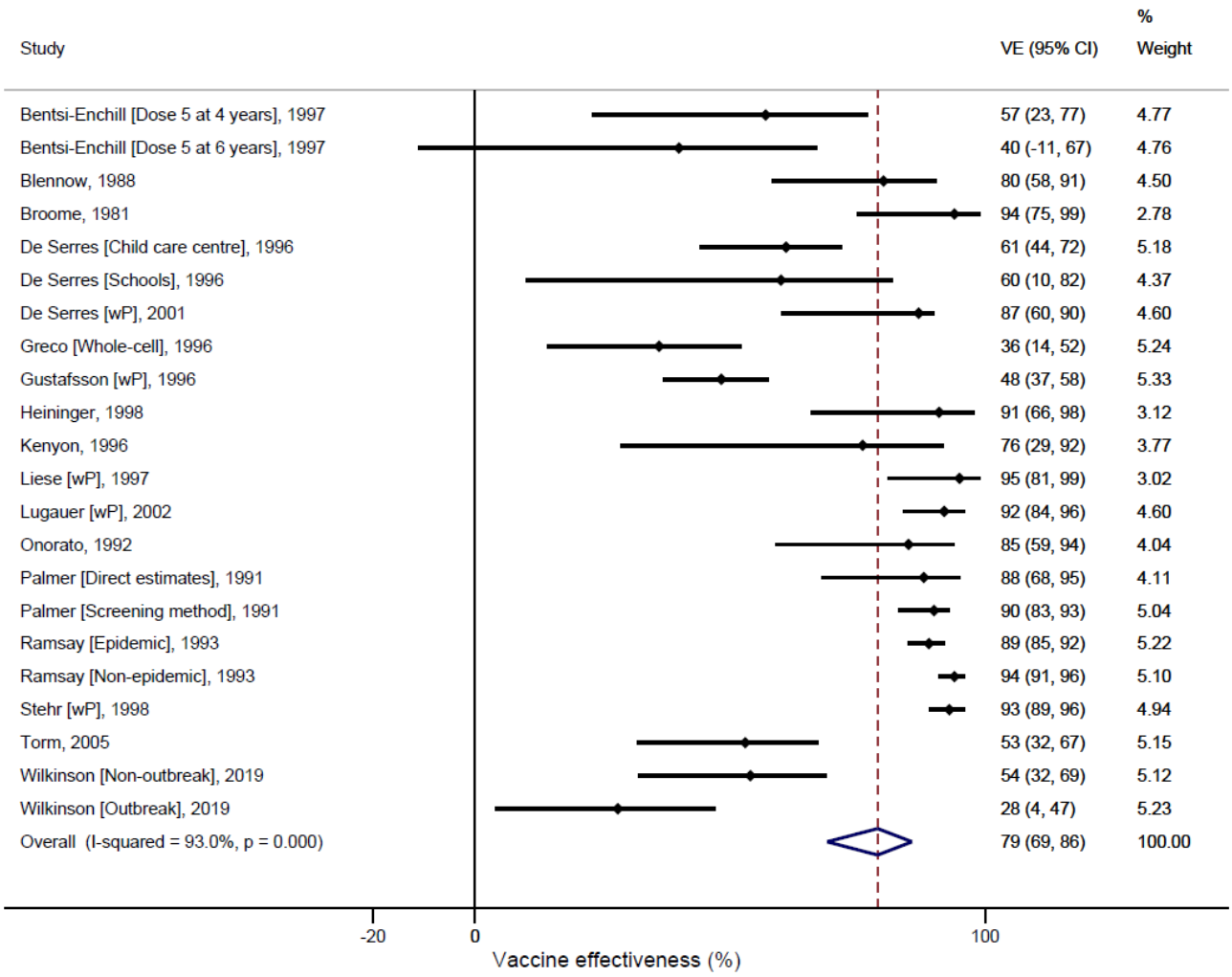


Figure C.3 Pertussis vaccine effectiveness for unspecified or mixed vaccine type against disease

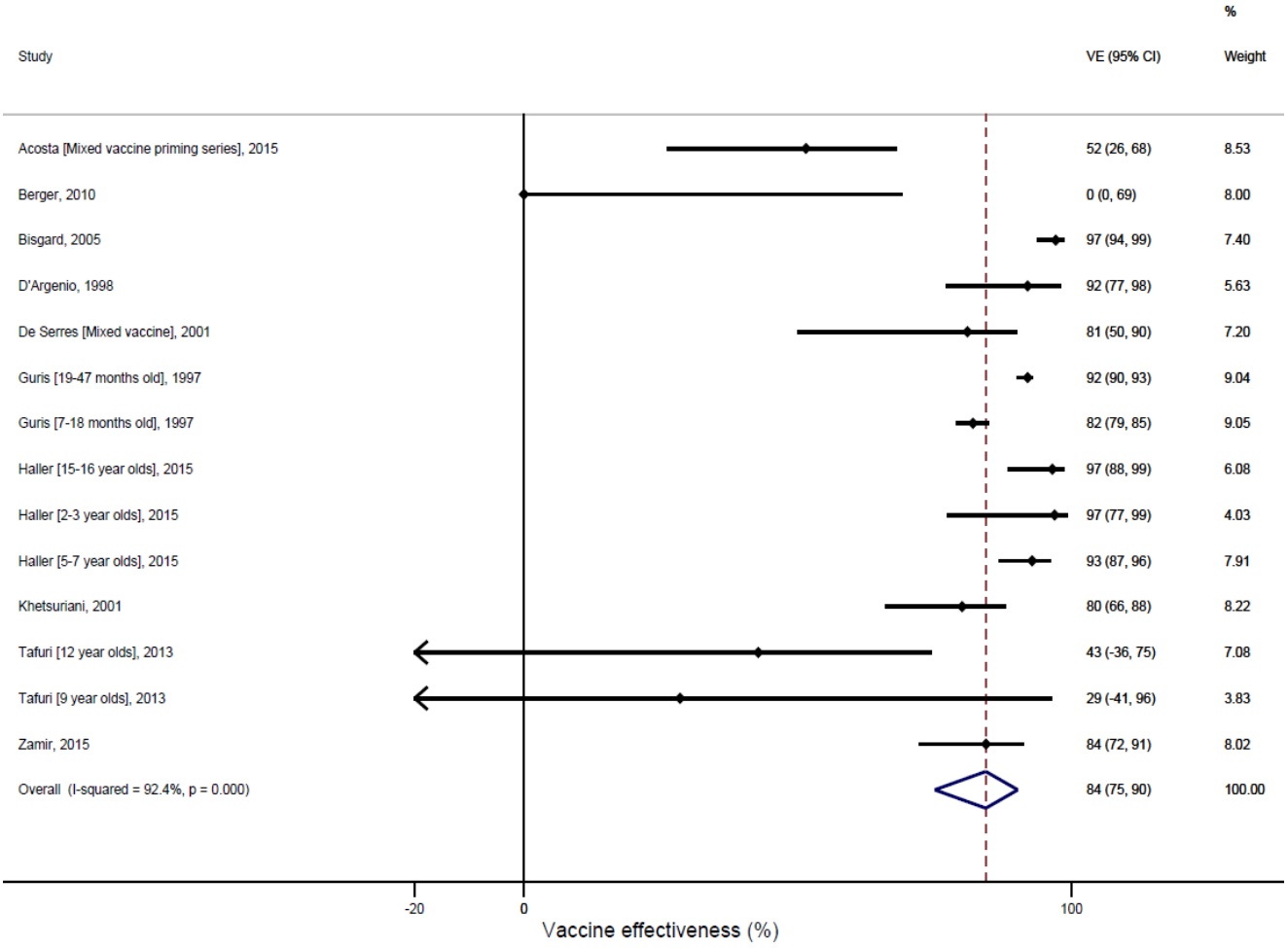
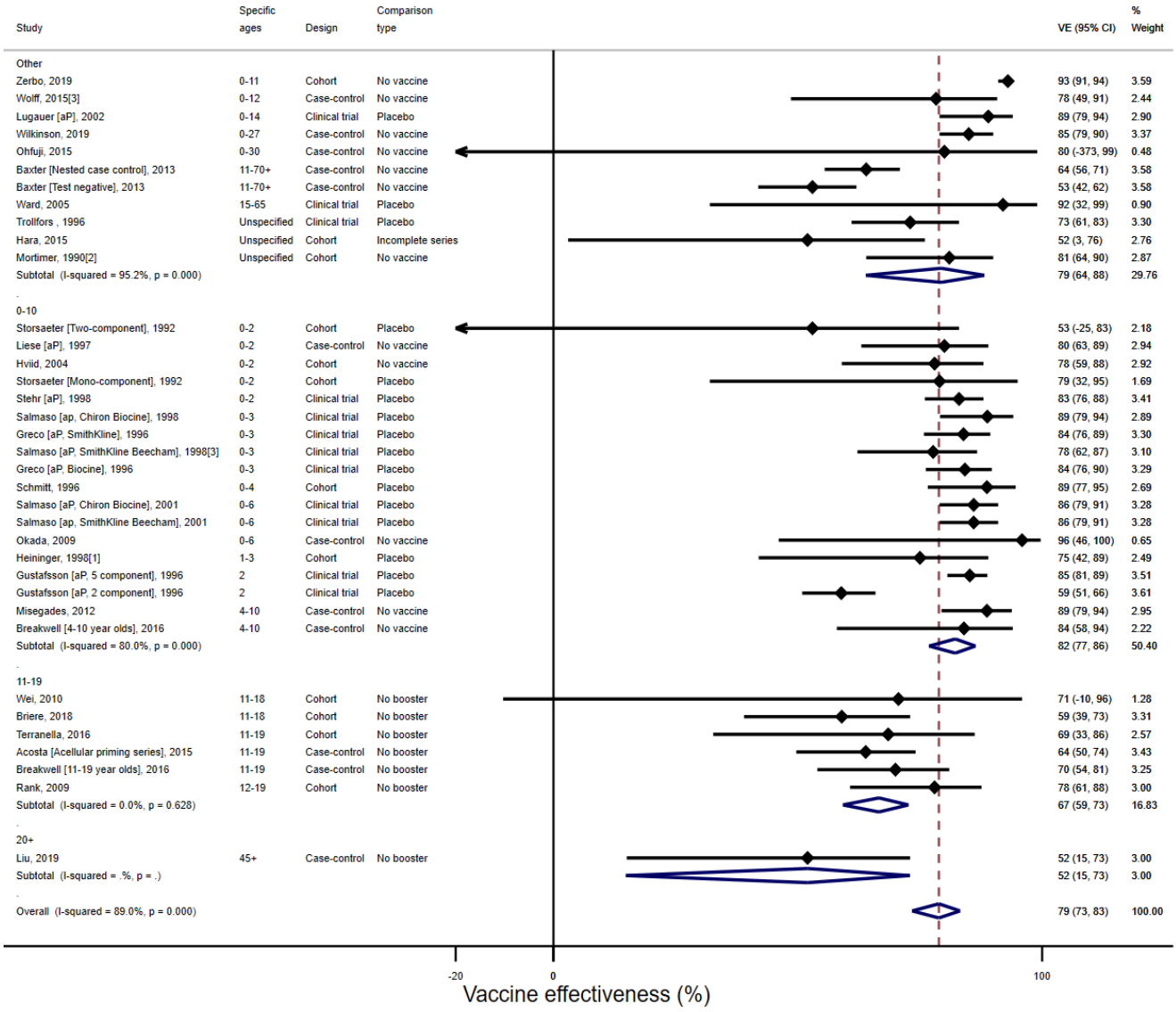


Figure C.4 Acellular pertussis vaccine effectiveness against disease by age group



Appendix D. Supplemental Material for Chapter 4

Table D.1 List of variables and definitions

Variable	Definition
Vaccination history	
Vaccine status	According to the recommended schedule for their age and birth cohort: An *Up-to-date* person had received the recommended number of pertussis vaccine doses at the index date. A *partially vaccinated* person had received at least one pertussis vaccine dose but had not received the recommended number of doses at the index date. An *unvaccinated* person had not received any pertussis vaccinations at the index date
Elapsed time since most recent vaccination	Unvaccinated, 15-354 days, 1-3 years, 4-7 years, >=8 years; based on days since last pertussis vaccine dose (N.B. Persons with pertussis vaccine received less than 14 days before their index date were excluded)
Total number of pertussis vaccine doses	Total number of doses received by index date
Matching variables	
Age (years)	Age at index date
Gender	Male or female
Geography	Community area in Winnipeg, health district outside Winnipeg or public trustee (for person in PT/CFS care)

Physician match	Matched on specific physician visited most frequently in the 365 days prior to index date; ties are broken by more recent physician
Number of visits match	Matched on number of outpatient physician visits in the 365 days prior to index date
Physician and visit match	Up to five physician-matched controls with incomplete sets filled with different visit-matched controls
Outbreak years	1994 and 1995
Sociodemographic variables	
Income in lower 40%	Based on 2006 census data; the two lowest income quintiles (Q1 and Q2)
Healthcare utilization	365 days prior to index date
Hospitalizations	One or more hospitalizations or zero hospitalizations
Physician visits	Four or more outpatient physician visits or less than four outpatient physician visits (median of study cohort)
Prescriptions	Two or more prescriptions for any drug or less than two prescriptions
Medical characteristics	
Chronic disease	The presence of at least one of: chronic cardiovascular disease (excluding hypertension), diabetes, chronic liver disease, chronic renal failure, or chronic respiratory disease (excluding asthma)
Immunocompromised	The presence of at least one of: cancer (excluding non-melanoma skin cancer), HIV/AIDS, other immune deficiency, or blood transfusion

Table D.2 Number (%) of case exclusions by match type for non-outbreak years

	Most frequent physician	**Number of physician visits**	**Physician and number of visits**
Starting cases	1,591	1,591	1,591
Non-continuous coverage since first scheduled vaccine	98 (6)	98 (6)	98 (6)
Vaccine given within 14 days of index date	59 (4)	59 (4)	59 (4)
Unable to identify suitable match	457 (32)	31 (2)	10 (1)
Included cases	977 (61)	1,403 (88)	1,424 (90)
Outbreak years	405 (42)	540 (39)	545 (38)
Non-outbreak years	572 (36)	863 (54)	879 (55)

Table D.3 Socioeconomic and clinical characteristic of pertussis cases and population-matched controls by vaccine type

	Acellular		Whole-cell	
	Case (N=493)	**Control (N=2,231)**	**Case (N=931)**	**Control (N=4,476)**
Male	244 (49.5%)	1,126 (50.5%)	448 (48.1%)	2,159 (48.2%)
Age group (years)				
<1	274 (55.6%)	1,112 (49.8%)	122 (13.1%)	501 (11.2%)
1-2	81 (16.4%)	457 (20.5%)	146 (15.7%)	747 (16.7%)
3-5	62 (12.6%)	309 (13.9%)	347 (37.3%)	1,694 (37.8%)
6-8	25 (5.1%)	116 (5.2%)	199 (21.4%)	963 (21.5%)
9-13	41 (8.3%)	189 (8.5%)	95 (10.2%)	474 (10.6%)
14+	10 (2.0%)	48 (2.2%)	22 (2.4%)	97 (2.2%)
Rural residence	306 (62.1%)	1,391 (62.3%)	316 (33.9%)	1,488 (33.2%)
Income in lower 40%	266 (54.0%)	1,125 (50.4%)	356 (38.2%)	1,737 (38.8%)
Has chronic condition	24 (4.9%)	107 (4.8%)	106 (11.4%)	446 (10.0%)
Immunocompromised	30 (6.1%)	135 (6.1%)	49 (5.3%)	170 (3.8%)
Four or more physician visits*	278 (56.4%)	1,263 (56.6%)	473 (50.8%)	2,128 (47.5%)
One or more hospitalizations*	56 (11.4%)	107 (4.8%)	23 (2.5%)	75 (1.7%)
Two or more prescriptions*	119 (24.1%)	549 (24.6%)	191 (20.5%)	859 (19.2%)
Year of index date				
1992-1996	0 (0.0%)	0 (0.0%)	> 646 (> 69.4%)	> 3,098 (> 69.2%)
1997-2001	83 (16.8%)	> 350 (> 15.7%)	201 (21.6%)	> 1,004 (> 22.4%)
2002-2006	75 (15.2%)	325 (14.6%)	63 (6.8%)	296 (6.6%)
2007-2011	> 91 (> 18.5%)	> 430 (> 19.3%)	< 6 (< 0.6%)	21 (0.5%)
2012-2017	> 232 (> 47.1%)	> 1,108 (> 49.7%)	10 (1.1%)	45 (1.0%)
Vaccine status†				
Unvaccinated	312 (63.3%)	611 (27.4%)	125 (13.4%)	476 (10.6%)
Partial	69 (14.0%)	522 (23.4%)	279 (30.0%)	1,169 (26.1%)
Up-to-date	112 (22.7%)	1,098 (49.2%)	527 (56.6%)	2,831 (63.2%)
Product used in vaccination series				

Unvaccinated	> 306 (> 62.1%)	> 605 (> 27.1%)	> 119 (> 12.8%)	476 (10.6%)
Acellular	178 (36.1%)	> 1,561 (> 70.0%)	0 (0.0%)	< 6 (< 0.1%)
Mixed	< 6 (< 1.2%)	36 (1.6%)	35 (3.8%)	> 233 (> 5.2%)
Whole-cell	0 (0.0%)	17 (0.8%)	> 765 (> 82.2%)	> 3,750 (> 83.8%)
Time since most recent vaccination				
Unvaccinated	312 (63.3%)	611 (27.4%)	125 (13.4%)	476 (10.6%)
15-364 days	101 (20.5%)	997 (44.7%)	211 (22.7%)	1,255 (28.0%)
1-3 years	41 (8.3%)	401 (18.0%)	426 (45.8%)	2,075 (46.4%)
4-7 years	24 (4.9%)	170 (7.6%)	135 (14.5%)	543 (12.1%)
8+ years	15 (3.0%)	52 (2.3%)	34 (3.7%)	127 (2.8%)

*In the 365 days prior to index date; †According to the recommended number of pertussis vaccine doses for their age and birth cohort

Table D.4 Estimates of pertussis vaccine effectiveness by vaccine status and elapsed time since most recent pertussis vaccination by vaccine type during non-outbreak years (physician and visit matched controls)

	Whole cell vaccine		Acellular vaccine		Any vaccine	
	Model A* (95% CI)	**Model B†** (95% CI)	**Model A*** (95% CI)	**Model B†** (95% CI)	**Model A*** (95% CI)	**Model B†** (95% CI)
Up-to-date‡						
15-364 days	65 (38-80)	65 (37-80)	86 (79-90)	85 (78-90)	82 (75-86)	81 (74-86)
1-3 years	21 (-39-55)	22 (-38-56)	96 (90-98)	96 (91-98)	78 (68-85)	78 (68-85)
4-7 years	-51 (-258-36)	-34 (-219-43)	84 (54-95)	86 (58-95)	45 (1-70)	48 (5-71)
≥ 8 years	26 (-228-83)	37 (-187-86)	71 (-137-97)	74 (-118-97)	57 (-31-86)	60 (-23-87)
Partially-vaccinated‡						
15-364 days	76 (11-93)	83 (34-96)	89 (78-94)	89 (78-94)	87 (76-92)	87 (77-93)
1-3 years	41 (-19-71)	42 (-18-72)	93 (84-97)	93 (84-97)	80 (68-87)	81(69-88)
4-7 years	-18 (-191-52)	-13 (-187-56)	91 (67-98)	91 (64-98)	65 (32-82)	66 (34-83)
≥ 8 years	-65 (-498-54)	-68 (-538-56)	62 (-65-91)	62 (-68-91)	28 (-68-69)	31 (-65-71)
Ever vaccinated						
15-364 days	68 (45-81)	69 (47-81)	88 (83-91)	87 (82-91)	84 (79-88)	84 (79-88)
1-3 years	27 (-16-54)	31 (-10-57)	92 (86-95)	92 (86-95)	76 (67-82)	76 (68-82)
4-7 years	-47 (-163-17)	-44 (-158-20)	90 (77-95)	89 (77-95)	55 (34-70)	55 (33-70)
≥ 8 years	-58 (-271-33)	-56 (-266-34)	55 (-24-84)	52 (-32-83)	35 (-15-63)	32 (-19-61)

*Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits);
†Model B is adjusted for the matching variables, ≤ 4 physician visits (median for study cohort), hospitalized in previous year, chronic disease and immunocompromised status;
‡According to the recommended number of pertussis vaccine doses for their age and birth cohort;
N/A=not applicable;
The reference category is the unvaccinated population

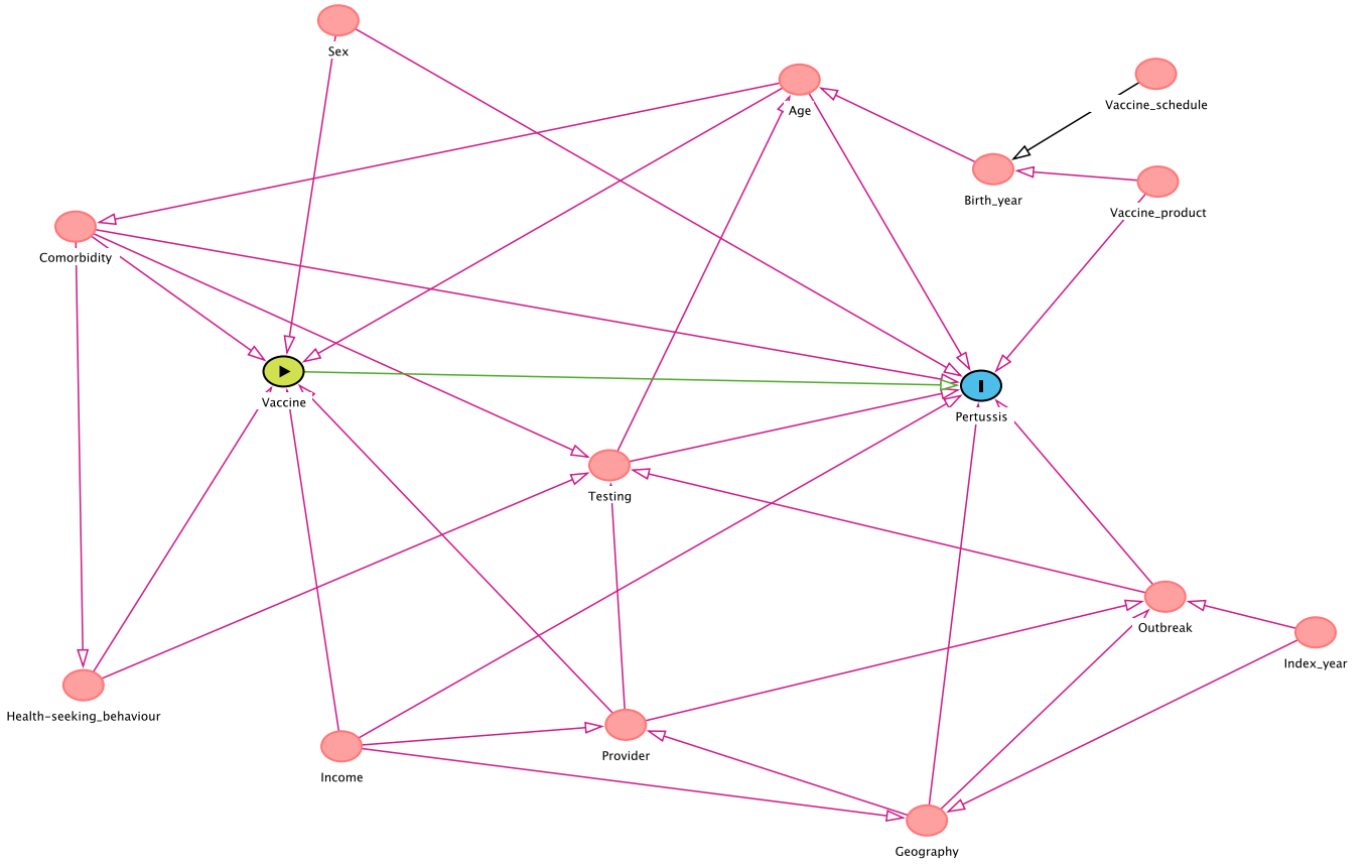
Table D.5 Pertussis vaccine effectiveness (%) during non-outbreak years in Manitoba by vaccine type, certain vaccination characteristics, and control group

	Whole cell vaccine		Acellular vaccine		Any vaccine	
	Model A* (95% CI)	**Model B† (95% CI)**	**Model A* (95% CI)**	**Model B† (95% CI)**	**Model A* (95% CI)**	**Model B† (95% CI)**
Most frequent physician control group						
Vaccine status§						
Partial	34 (-0-56)	35 (2-57)	85 (78-89)	86 (80-90)	75 (68-81)	76 (69-81)
Up-to-date	45 (20-62)	46 (21-63)	90 (86-92)	90 (87-93)	81 (76-84)	81 (77-85)
Elapsed time since most recent vaccination‡						
15-364 days	63 (34-79)	63 (35-79)	87 (81-91)	88 (83-92)	83 (77-87)	83 (78-88)
1-3 years	25 (-32-57)	24 (-33-57)	95 (90-98)	96 (90-98)	78 (68-85)	79 (69-85)
4-7 years	-5 (-127-51)	0 (-116-54)	88 (65-96)	89 (67-96)	62 (35-78)	64 (37-79)
≥ 8 years	2 (-267-74)	12 (-231-77)	82 (-15-97)	83 (-12-98)	56 (-25-84)	58 (-19-85)
Number of physician visits control group						
Vaccine status§						
Partial	35 (-18-64)	36 (-17-65)	79 (68-86)	81 (71-88)	73 (63-81)	75 (65-82)
Up-to-date	43 (1-67)	43 (2-67)	88 (82-91)	89 (84-92)	80 (74-85)	82 (76-86)
Elapsed time since most recent vaccination‡						
15-364 days	67 (19-86)	68 (22-87)	84 (77-90)	86 (79-91)	82 (74-87)	83 (76-88)
1-3 years	20 (-74-63)	21 (-75-64)	96 (86-99)	96 (86-99)	75 (59-85)	77 (61-86)
4-7 years	-5 (-184-61)	-7 (-196-61)	97 (68-100)	97 (68-100)	68 (31-85)	69 (32-86)
≥ 8 years	-17 (-496-77)	-9 (-463-79)	97 (13-100)	97 (14-100)	61 (-48-90)	64 (-41-91)
Physician and number of visits control group						
Vaccine status§						
Partial	31 (-6-56)	35 (-1-58)	86 (79-90)	86 (79-90)	75 (67-81)	75 (67-81)
Up-to-date	43 (17-61)	46 (20-63)	90 (86-93)	90 (86-93)	80 (75-84)	80 (75-84)
Elapsed time since most recent vaccination‡						
15-364 days	65 (38-80)	65 (37-80)	86 (79-90)	85 (78-90)	82 (75-86)	82 (74-86)
1-3 years	21 (-39-55)	22 (-38-56)	96 (90-98)	96 (91-98)	78 (68-85)	78 (68-85)
4-7 years	-51 (-258-36)	-34 (-219-43)	84 (54-95)	86 (58-95)	45 (1-70)	48 (5-71)
≥ 8 years	26 (-228-83)	37 (-187-86)	71 (-137-97)	74 (-118-97)	57 (-31-86)	60 (-23-87)

*Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits);
†Model B is adjusted for the matching variables, ≤ 4 physician visits (median for study cohort), hospitalized in previous year, chronic disease and immunocompromised status;
‡Elapsed time estimates use up-to-date vaccine status;
§According to the recommended number of pertussis vaccine doses for their age and birth cohort; The reference group is the unvaccinated population;
N/A= not applicable

Appendix E. Supplemental material for Chapter 5

Figure E.1 Directed acyclic graph (DAG) for the relationship between pertussis vaccination (exposure in green circle) and pertussis diagnosis (outcome in blue circle); the green line represents the causal path. Pink circles represent ancestors of both exposure and outcome; pink lines represent biasing paths. An arrow from a factor to another means a possible association.



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