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The health and economic burden of pertussis in Canada: A microsimulation study

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ABSTRACT

Background: Despite excellent vaccine coverage, pertussis persists in Canada, with high incidence during recent outbreaks and non-negligible incidence in non-outbreak years. While Canadian pertussis incidence is well-characterized, the full health and economic impact of pertussis have not been examined in Canada. We estimated age-specific life years (LYs) and quality-adjusted life years (QALYs) lost, and costs due to pertussis in Ontario, Canada, using a model-based approach.
Methods: We developed a microsimulation model to simulate pertussis natural history. Daily probabilities of pertussis complications, hospitalizations, and disease sequelae as well as utilities and costs for health states were literature-derived. A healthcare payer perspective was used with a lifetime time horizon. Model outcomes were compared to those from a model with no pertussis health states. Probabilistic sensitivity analyses were used to generate distributions for estimates. Economic burden was estimated by multiplying case cost estimates by annual age-specific incidence.
Results: Overall, LYs lost per pertussis case was low, with negligible LYs lost in those aged >4 years. Infants (<6 months) had the greatest mean QALY loss per case (0.58), while adults lost only 0.05 QALYs per case. Infants experienced the greatest mean cost per case of $22,768 (95% CI: 21,144–23,406). Case costs generally declined with age, but increased in seniors (aged 65+) with mean cost of $1920 (95% CI: 1800–2033). Based on historic age-specific incidence, pertussis costs the Ontario healthcare system approximately $7.6–$21.5 M annually. In total economic cost estimates with QALYs valued at 1xGDP (3xGDP) per capita, the net impact of pertussis in Ontario was estimated at $21.7–$66.5 M annually ($50.0–$156.3 M). For all of Canada, total economic costs were estimated at $79.6–$241.3 M ($187.5–$580.5 M) annually.
Conclusion: The health and economic consequences of pertussis persistence are substantial and highlight the need for improved control strategies.

1. Introduction

Despite robust immunization programs, pertussis, or whooping cough, persists in Canada. Periodic outbreaks occur and in non-outbreak years incidence remains non-negligible. In 2012, an outbreak year, national pertussis incidence reached 13.08 cases per 100,000 population [1]. By contrast, in the following year, despite the absence of outbreak activity, incidence was 3.63 cases per 100,000 [1].

Although the burden of reported pertussis is well characterized, the full health and economic costs of infection and downstream sequelae have not been examined in the Canadian context. Understanding the health and economic burden of pertussis can help inform decisions around prioritization and resource allocation relating to interventions and strategies for improved pertussis control.

As adolescents and adults have less severe and non-specific symptoms of pertussis [2,3], infections may be undetected or under-diagnosed in these age groups [4]. Compounding this issue is the fact that disease sequelae for infants and young children differ from those experienced by adults and adolescents. Infants and young children are more likely to be hospitalized with pertussis [5,6], have more severe complications [6,7], and have a far higher mortality rate than adolescents and adults [7,8]. To accurately describe the health impact and costs associated with pertussis, it is important to consider the age distribution of cases.

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Previous cost-effectiveness studies of different pertussis immunization programs or outbreak response programs in Canada [9–13] have not estimated the total costs of pertussis infection. These studies have focussed on direct short-term hospitalization and ambulatory care costs [14], and have not accounted for costs associated with physician visits or long-term sequelae. Outside the Canadian context, studies estimating pertussis costs have also focussed on short term clinical case costs, or costs of hospitalization, without incorporating the full range of disease outcomes and sequelae [15–17].

Prospective, comprehensive, empirical evaluation of health and economic impacts of pertussis across the lifespan in Canada would present a formidable challenge to researchers. In order to address the informational gaps described above, we used a model-based approach to estimate age-specific life years lost (LYs), quality-adjusted life years (QALYs) lost, and costs associated with pertussis cases in Ontario, Canada. We also estimated the economic impact of pertussis on Ontario's healthcare system.

2. Methods

2.1. Model overview

We developed a microsimulation model that describes the natural history of pertussis and its sequelae. The disease model is comprised of pertussis infection health states (never-infected, prodromal, catarrhal, paroxysmal, convalescent, and recovered) with additional states for pertussis-related complications, hospitalizations, and death (Fig. 1). Age-specific inpatient and outpatient complications were derived from observational studies of pertussis patients in Canada [6,7]. These complications included pulmonary complications (pneumonia, atelectasis, and pneumothorax), neurological complications (seizures, encephalopathy, and long-term sequelae), hernias, sinusitis, otitis media, rib fracture, fainting, urinary incontinence, and weight loss. Because of the age-specific distribution of pertussis manifestations and complications, we examined 5 distinct age groups: infants (<6 months of age), children (6 months to 4 years of age), youth (5–17 years of age), adults (18–64 years of age), and seniors (65+ years of age).

We used a lifetime time horizon with a time step of one day to account for the relatively short duration of pertussis illness and the relatively long duration of pertussis complications. Cumulative incidence estimates were converted to daily probabilities based on the assumption that event times were Poisson-distributed. Outcomes of interest included age-specific per patient LYs lost, QALYs lost, and costs. All health outcomes and costs were discounted at 3% per annum in the base cases, with rates of 0% and 5% applied in sensitivity analysis. Model outcomes were compared to a counterfactual model where no individual contracted pertussis. The counterfactual model included the never-infected and dead states only.

The microsimulation model is probabilistic and incorporated both stochastic uncertainty and parameter uncertainty. To characterize uncertainty, the model was run 100,000 times per age group, with model parameters drawn from distributions as described in Table 1. This allowed us to generate distributions of outcomes as well as summary measures. The microsimulation model was built using TreeAge Pro [18] and analyses of model outputs were conducted in R [19].

2.2. Health state transitions

Transitions between health states were based upon both length of stay "rules" and daily probabilities (Table 1). For pertussis

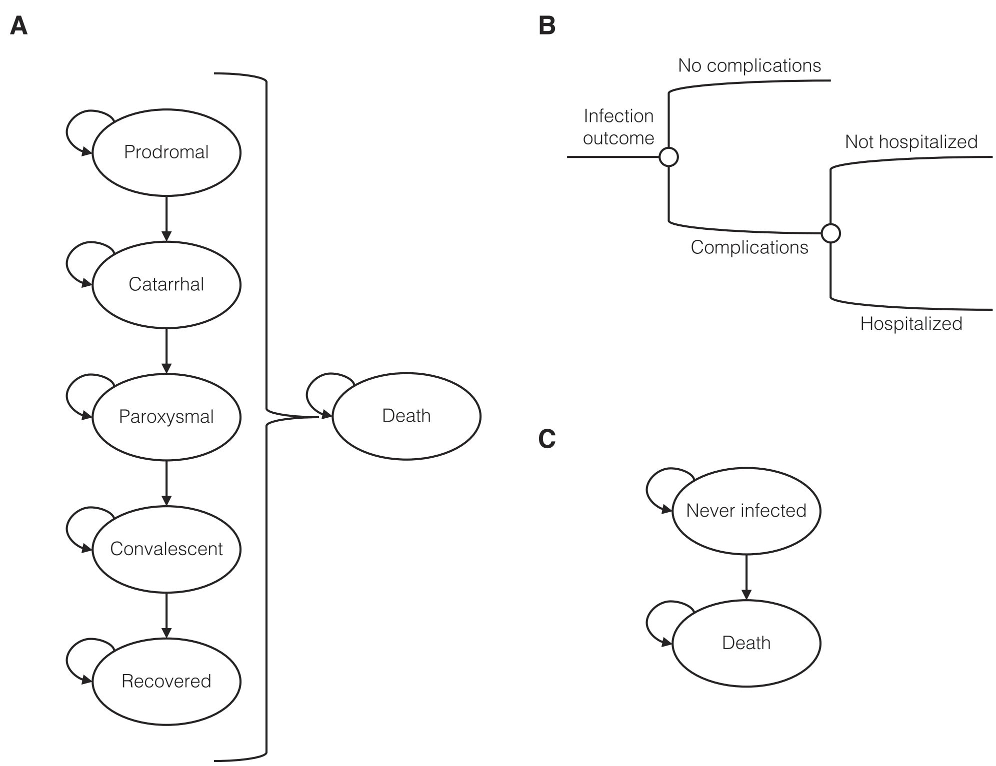

Fig. 1. Pertussis microsimulation model overview. (A) For the infection model, all individuals begin in the prodromal state and progress through the disease states. Individuals may transition to the death state from any model state, due to underlying mortality. Disutilities are associated with the catarrhal, paroxysmal, and convalescent states and costs are associated with the paroxysmal state. (B) Additional costs, disutilities, and mortality risk are associated with infection complications, which are allocated as individuals exit the paroxysmal state. (C) The counterfactual model assumes no pertussis infection, with individuals exiting the model due to underlying mortality only. Movement through the model health states depends on transition probabilities, as described in Table 1. The model was run separately for five age groups (<6 months, 6 months to 4 years, 5–17 years, 18–64 years, and 65+ years).

Table 1
Microsimulation model inputs and sources.

Health state or complication	Population group	Probability[a]	Duration[b], mean (SD)	Utility[c], mean (SD)	Cost ($)[d], mean (SD)	Source
HEALTH STATE						
Never infected						[24]
	Infant	–	–	0.94 (0.074)	–	
	Child	–	–	0.94 (0.074)	–	
	Youth	–	–	0.94 (0.074)	–	
	Adult	–	–	0.93 (0.08)	–	
	Senior	–	–	0.91 (0.09)	–	
Prodromal	All	–	7 days	Same as never infected		[3]
Catarrhal			7 days			[20,21,23]
	Infant	–	–	0.40 (0.30)	–	
	Child	–	–	0.45 (0.34)	–	
	Youth	–	–	0.51 (0.39)	–	
	Adult	–	–	0.67 (0.38)	–	
	Senior	–	–	0.67 (0.38)	–	
Paroxysmal			21 days		80.88	[20,21,23]
	Infant	–	–	0.27 (0.36)	–	
	Child	–	–	0.30 (0.37)	–	
	Youth	–	–	0.35 (0.38)	–	
	Adult	–	–	0.58 (0.42)	–	
	Senior	–	–	0.58 (0.42)	–	
Convalescent	All	–	14 days	Same as catarrhal	–	[20,21,23]
Recovered	All	–	Remaining lifetime in model	Same as never infected[i]	–	Assumption
COMPLICATION						
Pulmonary[e]						[7,14,23]
	Infant	0.136	3.9 (4.8)	0.27 (0.36)	1950	
	Child	0.083	3.9 (4.8)	0.27 (0.36)	1950	
Hernia[f]						[7,14]
	Infant	0.01	1.9 (2.2)	0.27 (0.30)	2725	
	Child	0.005	1.9 (2.2)	0.27 (0.30)	2725	
Neurological[g]						[7,14,23]
	Infant	0.21 (0.33)	5.2 (16.9)	0.042	2724	
	Child	0.21 (0.33)	5.2 (16.9)	0.033	2,724	
Long-term neurological	Infant	0.33, of those experiencing neurological complication	Lifetime	0.21 (0.33)	18,136 (5343–50,954), median (IQR) per year	[9,23,30,49]
Weight loss > 5%						[6,7,14,28]
	Infant	0.014	4.6 (4.4)	0.70 (0.30)[h]	1062	
	Child	0.01	4.6 (4.4)	0.70 (0.30)[h]	1062	
	Youth	0.03	4.6 (4.4)[h]	0.85 (0.30)[h]	33.70	
	Adult	0.03	4.6 (4.4)[h]	0.85 (0.30)[h]	33.70	
	Senior	0.03	4.6 (4.4)[h]	0.85 (0.30)[h]	33.70	
Sinusitis						[6,28,29,50–52]
	Youth	0.11	7 (3 [h])	0.56 (0.30 [h])	33.70	
	Adult	0.148	7 (3 [h])	0.56 (0.30 [h])	33.70	
	Senior	0.17	7 (3 [h])	0.56 (0.30 [h])	49.72	
Pneumonia						[6,23,28,29,53]
	Youth	0.02	7 (3)[h]	0.35 (0.37)	43.81	
	Adult	0.047	7 (3)[h]	0.62 (0.40)	43.81	
	Senior	0.09	7 (3)[h]	0.62 (0.40)	50.35	
Otitis media						[6,28,29,54]
	Youth	0.04	7 (3)[h]	0.79 (0.04)	33.70	
	Adult	0.04	7 (3)[h]	0.79 (0.04)	33.70	
	Senior	0.04	7 (3)[h]	0.79 (0.04)	54.20	
Rib fracture						[6,28,55]
	Youth	0.01	14 (5)[h]	0.69 (0.3)	59.50	
	Adult	0.04	14 (5)[h]	0.69 (0.3)	59.50	
	Senior	0.04	14 (5)[h]	0.69 (0.3)	59.50	
Fainting						[6,28]
	Adult	0.02	1 [h]	0.90 (0.29)[h]	33.70	
	Senior	0.02	1 [h]	0.90 (0.29)[h]	33.70	
Urinary incontinence (females only)			While paroxysmal			[6,28,56]
	Adult	0.093		0.8 (0.3 [h])	33.70	
	Senior	0.34		0.8 (0.3 [h])	33.70	
Hospitalization					1799 (2662), per day	[6,7,14,23,57]
	Infant	0.631 (0.006)	9.3	0.27 (0.36)		
	Child	0.148 (0.005)	4.9	0.30 (0.37)		
	Youth	0.01 (0.006)	3	0.35 (0.38)		

Table 1 (*continued*)

Health state or complication	Population group	Probability[a]	Duration[b], mean (SD)	Utility[c], mean (SD)	Cost ($)[d], mean (SD)	Source
	Adult	0.02 (0.008)	3	0.58 (0.42)		
	Senior	0.06 (0.033)	17	0.58 (0.42)		
Death, pertussis-attributable, conditional on hospitalization						[7,57]
	Infant	0.01 0.004)	–	–	–	
	Child	0.005 (0.005)	–	–	–	
	Youth	0.0003 (0.0003)	–	–	–	
	Adult	0.0003 (0.0003)	–	–	–	
	Senior	0.0003 (0.0003)	–	–	–	

Abbreviations: SD: Standard deviation.
[a] Converted to daily probabilities, beta distribution, unless otherwise specified.
[b] Exponential distribution, unless otherwise specified.
[c] Beta distribution, unless otherwise specified.
[d] Gamma distribution, unless otherwise specified.
[e] Includes pneumonia, atelectasis, and pneumothorax.
[f] Includes both inguinal and umbilical hernias.
[g] Includes seizures, encephalopathy, and other neurological complications.
[h] Assumption/Expert opinion.
[i] Unless case experiences long-term neurological complications. Refer to long-term neurological for lifetime utility associated with this complication.

natural history health states, the duration of each state reflected routinely described length of pertussis illness phases [3,20,21] and fixed durations for each of the states were applied to the entire population. In addition, a daily probability of death was applied.

For outpatient pertussis-related complications, the length of each complication was based on the literature and expert opinion. The Ontario Case Costing Initiative was used to estimate the duration of hospitalization for inpatient complications and duration of hospitalization from uncomplicated pertussis was obtained from two observational studies [6,7,14].

2.3. Complication probabilities

We estimated the age-specific probabilities for pertussis-related complications primarily from two observational studies. The first study examined the epidemiology of hospitalized children in pediatric tertiary care centers from across Canada [7] and the second study examined the morbidity of adolescents and adults during a pertussis outbreak in Quebec [6]. Complication probabilities were assumed to be independent; that is, experiencing one or more complications did not alter the probability of experiencing other pertussis-related complications. Two exceptions were: the probability of experiencing long-term neurological sequela, which was conditional on experiencing neurological complications, and the probability of pertussis-attributable mortality, which was conditional on hospitalization (based on available data). The model also incorporated competing mortality from Canadian life tables [22].

2.4. Utilities

The utility weights used to calculate QALYs were obtained from the only study examining the quality of life associated with the different health states of pertussis [23]. The study used a short-term time trade-off method to estimate utilities to better differentiate the severity of these short-term health states. Although children were not explicitly examined in this study, we interpolated utilities by assuming intermediate disease severity between that experienced by infants and adolescents. Utility values for "never infected" and "prodromal" phases of illness were obtained from a study which used responses from the National Population Health Survey (NPHS) [24]. We used age-specific utility scores from individuals with no chronic conditions to represent the underlying health of the population. As infants and children are not included in the NPHS, we assumed the same underlying health distribution as youths. Utility values for pertussis-related sequelae were also derived from the published literature (see Table 1).

2.5. Costs

Costs were assessed from the perspective of the healthcare payer and were inflated to year 2016 Canadian dollars using the health and personal care component of the Canadian consumer price index, published by Statistics Canada [25].

Hospitalization costs were extracted from the Ontario Case Costing Initiative (OCCI), an online database of person-level costs from ambulatory and acute inpatient care [14]. The OCCI data includes direct and indirect costs associated with provision of patient care and running the hospital. We included a 5% premium to represent physician costs not included in the OCCI [26,27]. The mean cost per hospitalized day was estimated for each pertussis-related complication, while length of stay was drawn from a probability distribution, allowing the hospitalization cost to vary for each patient.

Costs associated with outpatient physician visits were obtained from the Schedule of Benefits for Physician Services under the Health Insurance Act [28]. The average number of physician visits for each pertussis-related complication was estimated from the literature and expert opinion to create a distribution of physician costs. Outpatient prescription drugs were generally paid for by healthcare consumers in Ontario at the time of the analysis and were not included, with the exception of drug costs for seniors, which were covered by the Ontario Drug Benefit Program and were included as healthcare system costs. Antibiotic choice and dosages were obtained from the literature and costs were retrieved from the Ontario Drug Benefit Formulary [29].

We estimated the long-term costs of neurologic sequelae of pertussis-related encephalitis from a study of the costs of complex medical care for children in Ontario [30]. The median direct cost of caring for a child with neurological impairment was estimated at $36,272 (2016 $CAD) for the two years after the initial hospitalization, not including the costs of this first hospitalization [30]. We assumed the costs were distributed equally over the two years and would remain approximately the same each year over the child's lifetime.

2.6. Estimation of case-level health and economic burden

We used the outputs of 100,000 simulations per age group to compare life years lost, quality-adjusted life years lost, and costs associated with pertussis infection relative to the counterfactual scenario with no pertussis infection. This generated a distribution of age-specific estimates of per-infection outcomes which were used for subsequent analyses. We calculated mean values for each outcome, as well as bootstrap confidence intervals with 1000 replications.

2.7. Total healthcare and economic costs

We used the age-specific per-case estimates generated by the model to calculate the total healthcare costs and total economic costs of pertussis in the province of Ontario in a year with: (i) typical (non-outbreak year) or (ii) unusually high pertussis incidence (outbreak year). We scaled these estimates up to get Canadian national-level estimates by inflating incidence based on national to provincial population ratios. We used age-specific reported pertussis cases counts for two years: 2012 and 2013 (Table 2) [31,32]. Case counts were based on both confirmed and probable cases; Ontario case definitions are available from Public Health Ontario [33].

While there is a year-to-year variability in pertussis in Ontario and Canada, baseline incidence of the disease ranged from ≤ 2 per 100,000 population in non-outbreak years, to >6 per 100,000 in outbreak years, during the interval from 2005 to 2014 [34]; 4 of 10 years during that time interval would be considered "outbreak" years according to this schema. The incidence of pertussis in Canada as a whole mirrors incidence in Ontario, given the large share of the Canadian population (approximately 40%) residing in the province [34]. We used 2012 (incidence 7.8 per 100,000 population) and 2013 (incidence 2 per 100,000 population) as exemplars of outbreak and non-outbreak years, respectively, for the purposes of estimating health and economic burden. Cases counts were inflated by a factor of 5.6 to account for under-detection of pertussis and improved sensitivity of diagnostic testing over time (such that more current burden estimates would be influenced by increased likelihood of case ascertainment) [35,36].

Total healthcare costs were estimated by multiplying age-specific case cost estimates by annual case numbers. To calculate total economic costs, which allows for costs and QALY loss to be combined into a single cost metric, we used Canadian gross domestic product (GDP) per capita ($55,560 in 2015 [37]), and three times GDP per capita, as a range of plausible willingness-to-pay thresholds for a single QALY based on the WHO-CHOICE framework [38]. We drew 10,000 samples from the model outcome distributions for age-specific QALY losses and costs to derive estimates of total healthcare and economic costs.

Table 2
Estimated age-specific number of pertussis cases in Ontario and Canada during 2012–2013. Data obtained from Public Health Ontario and Canadian National Notifiable Disease Database and adjusted for under-detection [1,32,44].

	Ontario		Canada	
Age Group	2012	2013	2012	2013
<6 mo	799	293	2528	951
6 mo to 4 y	997	282	3693	1013
5 to 17 y	2342	529	12,504	2967
18 to 64 y	1605	372	5782	1909
65+ y	113	45	1025	332
Total	5855	1520	25,532	7173

3. Results

3.1. Case-level health and economic burden

Infants were projected to experience the greatest burden of pertussis, as measured by life years lost, QALYs lost, and costs following infection (Fig. 2 and Table 3). On average, pertussis infections in infants were associated with 0.19 years of life lost and 0.58 lost QALYs. Infections in infants were associated with a high amount of variability in terms of costs and health outcomes, with a subset of infections having relatively large costs and QALY losses.

Children also experienced a loss of life years associated with infection, while on average, there was negligible LY loss in youth, adults, and seniors (Table 3). QALY loss per case was smallest in adults (0.051 QALYs or 18.4 quality-adjusted life days (QALDs)) and seniors (0.053 QALYs or 19.2 QALDs. Children and youth had similar QALY loss per case (0.086 and 0.074 QALYs, or 31.5 and 27.0 QALDs respectively) (Fig. 2).

There was a U-shaped relation between age and average cost of infection, with the highest costs experienced in infants, children, and seniors (Fig. 2). Youth and adults were less likely to experience complications requiring hospitalization and had lower average infection costs (Table 3). Costs of pertussis in infants were markedly different depending on whether or not infection resulted in chronic neurological sequelae: in infants who suffered pertussis without chronic neurological sequelae, median case cost was $1765 (interquartile range $58,802); for infants with chronic neurological sequelae median case cost was $720,890 (interquartile range $447,267).

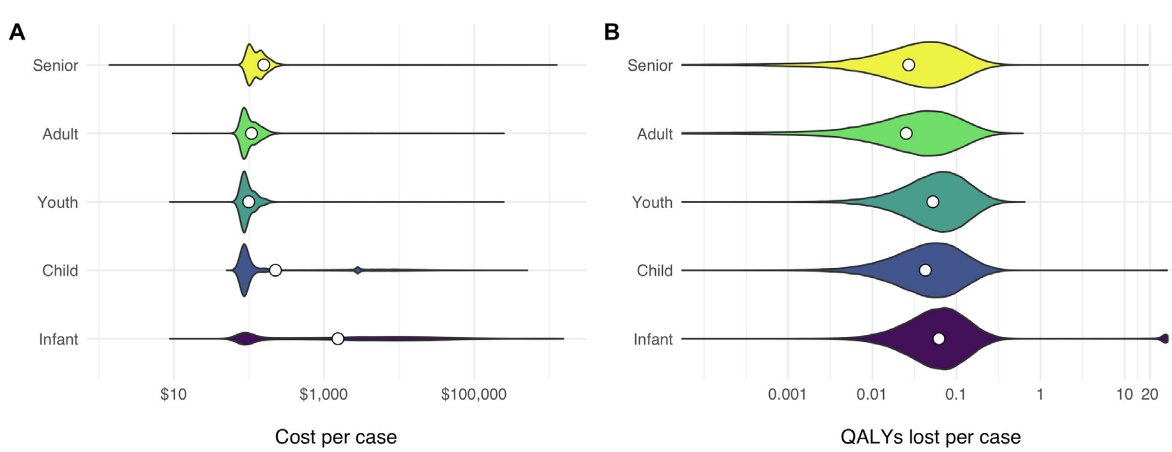

Fig. 2. (A) Costs and (B) quality-adjusted life years (QALYs) lost associated with pertussis infection, by age at infection. Results are based on 100,000 simulations per age group and mean values are indicated by white circles. The colored area represents a "violin plot", which is a kernel density plot reflected symmetrically around its long axis for ease of interpretation. A 3% per annum discount rate was applied. Note that costs and QALYs are presented on a logarithmic scale.

Table 3
Age-specific life-years lost, quality-adjusted life years lost, and costs associated with a pertussis infection assuming discount rates of 0, 3, and 5% per annum. Mean values and 95% confidence intervals are presented, based on 100,000 simulations per age group.

Age group	Life Years Lost			Quality-Adjusted Life Years Lost			Cost ($)		
	0%	3%	5%	0%	3%	5%	0%	3%	5%
Infant	0.501 (0.460, 0.540)	0.191 (0.176, 0.206)	0.126 (0.116, 0.136)	1.405 (1.339, 1.464)	0.579 (0.554, 0.603)	0.405 (0.389, 0.421)	39 452 (37 900, 41 009)	22 768 (22 144, 23 406)	19 265 (18 844, 19 690)
Child	0.059 (0.045, 0.072)	0.023 (0.018, 0.029)	0.015 (0.012, 0.019)	0.122 (0.109, 0.135)	0.086 (0.081, 0.091)	0.078 (0.075, 0.082)	2379 (2317, 2437)	2372 (2312, 2422)	2367 (2305, 2426)
Youth	0	0	0	0.074 (0.074, 0.075)	0.074 (0.074, 0.074)	0.074 (0.073, 0.074)	157 (147, 166)	157 (147, 165)	156 (147, 164)
Adult	0	0	0	0.051 (0.050, 0.051)	0.051 (0.050, 0.051)	0.050 (0.050, 0.051)	237 (223, 250)	237 (223, 250)	236 (223, 249)
Senior	0	0	0	0.053 (0.052, 0.054)	0.053 (0.052, 0.053)	0.053 (0.052, 0.053)	1926 (1813, 2029)	1920 (1800, 2033)	1916 (1797, 2026)

Results assuming no discounting or a 5% discount rate are included in Table 3 and were qualitatively similar to the base case analysis assuming a 3% discount rate.

3.2. Health and economic burden of pertussis in Ontario and Canada

Assuming the age-specific case numbers during a representative non-outbreak and outbreak year (Table 2), total QALY loss in Ontario was estimated to be 254 annually during a non-outbreak year and 809 in an outbreak year. For all of Canada, the total QALY loss was estimated at 971 annually in a typical year and 3053 in an outbreak year.

Pertussis was estimated to cost the Ontario healthcare system approximately $7.6 M annually in a non-outbreak year and $21.5 M in an outbreak year (Fig. 3). The total economic cost of pertussis during a non-outbreak year in Ontario was estimated to be between $21.7 M and $50.0 M when QALYs were valued at 1 and 3 times GDP per capita, respectively. During an outbreak year, costs were estimated at $66.5 M to $156.3 M, when QALYs were valued at 1 or 3 times GDP per capita, respectively. At the national level, total healthcare costs of pertussis were approximately $25.6 M annually and $71.6 M in an outbreak year. The total economic cost of pertussis during a non-outbreak year in Canada were between $79.6 M and $187.5 M when QALYs were valued at 1 and 3 times GDP per capita. During an outbreak year, these estimates increased to $241.3 M and $580.5 M.

4. Discussion

We calculated age-specific health and economic consequences associated with pertussis infection in Ontario and Canada, in order to estimate the burden of this disease at a provincial and national

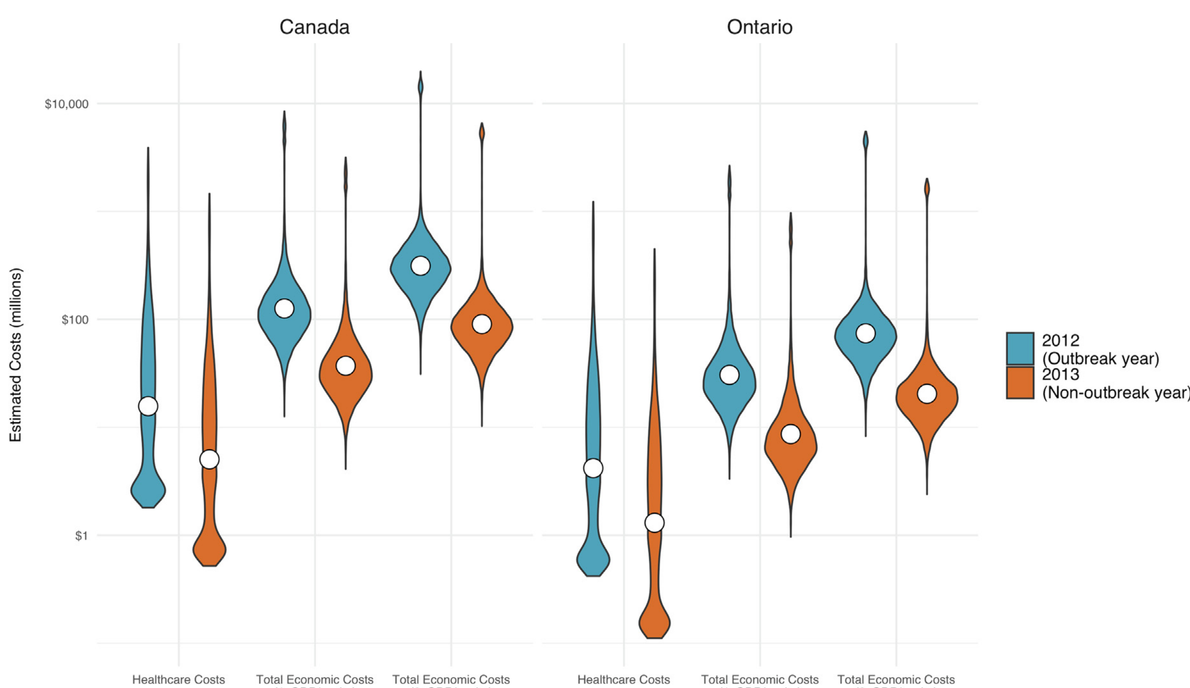

Fig. 3. Estimated annual total healthcare and economic costs for pertussis in Ontario and Canada during an outbreak and non-outbreak year. Results are based on 10,000 samples from the distributions for age-specific QALY losses and costs. A 3% per annum discount rate was applied. Mean values are indicated by white circles. The colored area represents a "violin plot", which is a kernel density plot reflected symmetrically around its long axis for ease of interpretation. Note that costs are plotted on a logarithmic scale.

level. Although pertussis incidence is far lower in Ontario and Canada now than was the case prior to the introduction of effective vaccines [4], we find that ongoing pertussis infections are a source of substantial costs and loss of health, even in non-outbreak years. Cases in infants and children were found to have the greatest impact on health and were also most costly. This is unsurprising given that pertussis cases in younger individuals are associated with the greatest risk of morbidity and mortality [3].

While there have been other studies examining the costs of pertussis [15–17,39], our study is the first to evaluate the age-specific costs of both pertussis and pertussis-related complications. In contrast to previous studies, which provide a snapshot of acute illness due to pertussis in the inpatient or outpatient setting, we provide per-case estimates that incorporate both inpatient and outpatient care, as well as long-term sequelae of infection; our model-based approach also permits incorporation of costs due to uncommon but costly sequelae of infection. As such, our per-case cost estimates for pertussis in infants are notably higher than those described above. We are also able to generate estimates for pertussis cost of illness in older adults, which are projected to be substantially higher than those in younger adults and adolescents.

It is important to note that while our model estimates average life years lost due to pertussis in infants and children, there were actually no reported pertussis deaths in Ontario in 2012 and 2013 [40,41]. Our projections are based on *average* annual risk of mortality, and pertussis deaths do continue to occur in Ontario and from 1991 to 2012 Canada has continued to identify between 0 and 4 infant deaths per year due to pertussis; this may represent an under-estimate, as pertussis in infants generally presents as apnea and encephalopathy rather than with cough [42].

Our estimates of disease burden, though derived using different metrics and methodologies, are consistent with health-adjusted life year estimates attributed to pertussis in the Ontario Burden of Infectious Diseases Study (ONBoIDS) [35], which suggested that pertussis results in a loss of 220 (undiscounted) health-adjusted life years (HALYs) in Ontario annually; ONBoIDS used pre-existing weights from the Global Burden of Disease study which assume that the only long-term impacts of pertussis are derived from downstream consequences of neurological injury if the disease is treated [43], which likely explains our assignment of a larger health burden to this disease than was the case in ONBoIDS.

Our microsimulation study has several limitations. Healthcare and total economic costs of pertussis in Ontario and Canada were estimated using reportable disease data from the provincial and national levels [1,32,44]. This surveillance data relies on physician index-of-suspicion, and laboratory testing of cases. We used an inflation factor of 5.6 to account for the under-detection of pertussis, based on the work of Deeks and colleagues [35,36]. However, such adjustment may not fully account for under-ascertainment of cases, particularly in older individuals. In previous published work we estimated that the overwhelming majority of pertussis cases in adults in Southern Ontario are unreported, with ratios of unreported to reported cases estimated in the hundreds or thousands [4]; similar estimates have been generated by other investigators in Poland, who estimated an under-reporting ratio of approximately 170-fold in 65–69 year old outpatients with prolonged cough [45]. More recent work from Ontario using the "capture-recapture" method supports the idea that under-reporting increases with age, but also suggests that pertussis under-reporting generally is declining over time, such that the relationship between pertussis reporting, age, and time period represents something of a moving target [46]. Marked under-reporting at older ages would result in conservative estimates of burden of disease, though it is likely that under-recognized and under-reported cases are milder, and impose a lower per-case health and economic burden than cases that are reported and recognized.

Other limitations are common to all models, including simplifying assumptions and data input quality (though we have sampled from broad prior distributions when substantial uncertainty exists). While the Ontario Case Costing Initiative served as a source of real-world costs of medical complications, only mean costs were available to us, meaning that the contribution of costs to parameter uncertainty in our model is fairly limited. One important simplifying assumption we have made relates to the independence of health consequences experienced by individuals with pertussis. While studies have shown that multiple complications of pertussis in an individual are possible[6,7] we assumed that the probability of any complication occurring was independent of any other complication.

Despite these limitations, our study is the first of its kind to address the health and economic impact of pertussis in Ontario and Canada. While our estimates of burden are higher than those reported in existing studies, this likely reflects our use of models to synthesize costs and health outcomes across the full spectrum of pertussis related illness, and through the lifespan. Our estimates suggest that the health and economic burden imposed by this disease are substantial and highlight the need for improved strategies for the use of existing vaccines. Our per-case cost and QALY-loss estimates provide "off the shelf" inputs for future models that aim to evaluate the effectiveness and cost-effectiveness of emerging pertussis immunization strategies, including immunization during pregnancy, "cocoon" immunization of all contacts of newborns, earlier boosters for adolescents, and decennial adult boosters [47,48] Such analyses will help policy makers and public health officials make informed decisions about optimal immunization programs to maximize health benefits, at a reasonable cost.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Neither Dr. Fisman nor Dr. Tuite has a conflict of interest.

Dr. McGirr was a doctoral student at the University of Toronto at the time she contributed to this work. She is currently an employee of, and holds shares in, the GlaxoSmithKline (GSK) group of companies, which manufactures vaccines, including vaccines that protect against pertussis. The opinions presented in this paper are those of the authors and do not reflect GSK's position, no funding was provided by GSK for this manuscript.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.070.

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