# Evaluation of outbreak response immunization in the control of pertussis using agent-based modeling

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**Background.** Pertussis control remains a challenge due to recently observed effects of waning immunity to acellular vaccine and suboptimal vaccine coverage. Multiple outbreaks have been reported in different ages worldwide. For certain outbreaks, public health authorities can launch an outbreak response immunization campaign to control pertussis spread. We investigated effects of an outbreak response immunization targeting young adolescents in averting pertussis cases. Methods. We developed an agent-based model for pertussis transmission representing disease mechanism, waning immunity, vaccination schedule and pathogen transmission in a spatially-explicit 500,000-person contact network representing a typical Canadian Public Health district. Parameters were derived from literature and calibration. We used published cumulative incidence and dose-specific vaccine coverage to calibrate the model's epidemiological curves. We endogenized outbreak response by defining thresholds to trigger simulated immunization campaigns in the 10-14 age group offering 80% coverage. We ran paired simulations with and without outbreak response immunization and included those resulting in a single ORI within a 10year span. We calculated the number of cases averted attributable to outbreak immunization campaign in all ages, in the 10-14 age group and in infants. The count of cases averted were tested using Mann-Whitney U test to determine statistical significance. Numbers needed to vaccinate during immunization campaign to prevent a single case in respective age groups were derived from the model. We varied adult vaccine coverage, waning immunity parameters, immunization campaign eligibility and tested stronger vaccination boosting effect in sensitivity analyses. Results. 189 gualified paired-runs were analyzed. On average, ORI was triggered every 26 years. On a per-run basis, there were an average of 124, 243 and 429 pertussis cases averted across all age groups within 1, 3 and 10 years of a campaign, respectively. During the same time periods, 53, 96, and 163 cases were averted in the 10-14 age group, and 6, 11, 20 in infants under 1 (p<0.001, all groups). Numbers needed to vaccinate ranged from 49 to 221, from 130 to 519 and from



1031 to 4903 for all ages, the 10-14 age group and for infants, respectively. Most sensitivity analyses resulted in minimal impact on a number of cases averted. **Discussion.** Our model generated 30 years of longitudinal data to evaluate effects of outbreak response immunization in a controlled study. Immunization campaign implemented as an outbreak response measure among adolescents may confer benefits across all ages accruing over a 10-year period. Our inference is dependent on having an outbreak of significant magnitude affecting predominantly the selected age and achieving a comprehensive vaccine coverage during the campaign. Economic evaluations and comparisons with other control measures can add to conclusions generated by our work.



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#### 30 Abstract

**Background.** Pertussis control remains a challenge due to recently observed effects of waning 31 immunity to acellular vaccine and suboptimal vaccine coverage. Multiple outbreaks have been 32 reported in different ages worldwide. For certain outbreaks, public health authorities can launch 33 34 an outbreak response immunization campaign to control pertussis spread. We investigated effects of an outbreak response immunization targeting young adolescents in averting pertussis cases. 35 **Methods.** We developed an agent-based model for pertussis transmission representing disease 36 mechanism, waning immunity, vaccination schedule and pathogen transmission in a spatially-37 explicit 500,000-person contact network representing a typical Canadian Public Health district. 38 39 Parameters were derived from literature and calibration. We used published cumulative incidence and dose-specific vaccine coverage to calibrate the model's epidemiological curves. 40 41 We endogenized outbreak response by defining thresholds to trigger simulated immunization campaigns in the 10-14 age group offering 80% coverage. We ran paired simulations with and 42 43 without outbreak response immunization and included those resulting in a single ORI within a 10-year span. We calculated the number of cases averted attributable to outbreak immunization 44 45 campaign in all ages, in the 10-14 age group and in infants. The count of cases averted were tested using Mann-Whitney U test to determine statistical significance. Numbers needed to 46 47 vaccinate during immunization campaign to prevent a single case in respective age groups were derived from the model. We varied adult vaccine coverage, waning immunity parameters, 48 immunization campaign eligibility and tested stronger vaccination boosting effect in sensitivity 49 50 analyses.

51 **Results.** 189 qualified paired-runs were analyzed. On average, ORI was triggered every 26

52 years. On a per-run basis, there were an average of 124, 243 and 429 pertussis cases averted

across all age groups within 1, 3 and 10 years of a campaign, respectively. During the same time

periods, 53, 96, and 163 cases were averted in the 10-14 age group, and 6, 11, 20 in infants under

55 1 (p<0.001, all groups). Numbers needed to vaccinate ranged from 49 to 221, from 130 to 519

and from 1031 to 4903 for all ages, the 10-14 age group and for infants, respectively. Most

57 sensitivity analyses resulted in minimal impact on a number of cases averted.

58 **Discussion.** Our model generated 30 years of longitudinal data to evaluate effects of outbreak

59 response immunization in a controlled study. Immunization campaign implemented as an

outbreak response measure among adolescents may confer benefits across all ages accruing over

61	a 10-year period. Our inference is dependent on having an outbreak of significant magnitude
62	affecting predominantly the selected age and achieving a comprehensive vaccine coverage
63	during the campaign. Economic evaluations and comparisons with other control measures can
64	add to conclusions generated by our work.
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#### 85 1. Introduction

#### 86 1.1 Recent epidemiology of pertussis

87 In recent years, pertussis control has re-emerged as a prominent public health challenge, with multiple outbreaks observed worldwide<sup>1</sup>, and with some jurisdictions reporting the highest 88 numbers of cases seen in decades.<sup>2</sup> In Canada, the last peak in pertussis activity was seen in the 89 90 mid-1990s, after which incidence rates were gradually declining prior to a 2012 resurgence. This 91 recent increase was driven by outbreaks in several provinces/territories.<sup>3</sup> The national agespecific incidence rate remains highest among infants under 12 months of age, an age group also 92 suffering the most hospitalizations and deaths. However, recently school-age children and 93 younger adolescents have also borne a disproportionate burden, particularly during outbreaks. 94 95 During the 2012 New Brunswick outbreak, the highest age-specific incidence rate fell in the 10-14 age group, which was twice as high as the incidence rate among infants (1240 vs. 660 per 96 100,000, respectively).<sup>4</sup> Such increases in incidence rates among older children were reported 97 from several US states <sup>2,5</sup>, suggesting a bimodal age distribution of cases in some jurisdictions. 98 During three most recent Minnesota outbreaks, the proportion of pertussis cases among children 99 7 to 18 years old exceeded 60%.<sup>6</sup> 100

The recent increase in pertussis activity is thought to be due to a combination of waning 101 immunity from acellular pertussis vaccine and sub-optimal vaccine coverage. In the Ontario 102 outbreak, cases were reported among unvaccinated individuals from a religious community and 103 among vaccinated school-aged children.<sup>8</sup> In New Brunswick, 67% of cases in the 10-14 age 104 group were up-to-date with their immunization.<sup>4</sup> Several studies estimated the annual decline in 105 protection after pertussis vaccination as ranging from 21% to 62%.<sup>9,10,11</sup> Vaccine-derived 106 107 protection among individuals who were primed with the whole-cell pertussis vaccine is reported to be greater compared to individuals who received purely acellular formulations.<sup>12</sup> Furthermore, 108 natural disease confers even greater -- but not life-long -- protection.<sup>13</sup> Genetic mutations in the 109 110 Bordetella pertussis bacterium and better detection and diagnosis have been suggested as other explanations for this recent pertussis trend.<sup>14</sup> 111

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113 Vaccination remains a cornerstone of public health measures to control pertussis. Improving
114 immunization schedule adherence by raising awareness among public is the most commonly

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used intervention. The strategy of "cocooning" infants (vaccinating parents and other individuals in close contact with infants) has been advocated, with mixed reviews.<sup>15,16</sup> Immunizing pregnant women in the third trimester of pregnancy to prevent pertussis disease in infants too young to receive vaccination is recommended in the US.<sup>17</sup> Modifications of the immunization schedule (changing the age of vaccine administration or adding doses) have been discussed.<sup>18</sup> Developing new vaccines will offer the best long-term control strategy, however it is not likely to occur in the short term.<sup>19</sup>

The ongoing occurrence of pertussis outbreaks presents a challenge to public health authorities 122 which may necessitate supplementary control measures. In Canada, immunization of pregnant 123 women is recommended only in outbreak situations.<sup>20</sup> Early contact tracing and 124 chemoprophylaxis of contacts has been advanced as protective in control of school-based 125 126 outbreaks.<sup>21</sup> Outbreak response immunization (ORI) has been employed if a particular group is disproportionately affected and it is feasible to reach and vaccinate this group in a relatively 127 128 short period of time.<sup>4</sup> ORI is supplementary immunization given over and above the routine vaccination schedule, including to those who may be fully immunized or those who did not 129 receive their scheduled vaccines. Potential benefits of ORI could accrue both in the short-term 130 (terminating or limiting an ongoing outbreak) and long-term (preventing future outbreaks) and 131 132 may extend to age groups other than the age group for whom ORI was targeted. The relevance of this intervention to all population (all other age groups) reflects the fact that interrupting 133 transmission among mostly affected group may also decelerate transmission to other age groups 134 with whom these individuals come in contact. Furthermore, it is very important to see whether 135 stopping outbreak in the ORI target group can have a material effect on a particularly vulnerable 136 population – babies under 1 year of age. ORI may also blunt natural boosting from circulating 137 sub-clinical infections. The cost of such immunization campaigns, including emergency response 138 infrastructure, cost of vaccines and their delivery is high, and often not included in routine 139 immunization programs budgets. Evaluation of such immunization campaigns is limited and the 140 need for pertussis outbreak response research has been advocated.<sup>22</sup> The objective of our study 141 was to investigate the effect of outbreak response immunization (ORI) among adolescents as an 142 emergency public health intervention in light of a recent re-emergence of pertussis outbreaks. 143

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#### 145 **1.2 Modeling approaches for pertussis**

Previous studies have used aggregate deterministic and stochastic models to understand pertussis 146 epidemiology and transmission and effects of vaccinations. In Grenfell and Anderson's 147 deterministic model, reduction of pertussis cases attributed to vaccination was estimated by 148 comparing pre-vaccine and vaccine eras.<sup>23</sup> Hethcote's model, originally published in 1997, 149 introduced differential levels of immunity and infectiousness.<sup>24</sup> Hethcote subsequently 150 contributed multiple adaptations of this model.<sup>25,26</sup> Hethcote's models were adapted by other 151 authors to evaluate effects of delays in pertussis immunization, improving vaccine coverage<sup>27,28</sup> 152 and effectiveness of a routine adolescent booster.<sup>29</sup> Wearing et al. used modeling to estimate 153 duration of pertussis immunity.<sup>30</sup> Gabmhir et al. used US surveillance data to fit the model to 154 estimate epidemiological and vaccine-related parameters responsible for recent increases in 155 pertussis activity and demonstrated difference in duration of protection conferred by acellular 156 versus whole-cell vaccine.<sup>31</sup> Sanstead et al. developed an agent-based model to characterize 157 pertussis outbreaks in Minnesota.<sup>6</sup> 158

#### 159 1.3 Rationale for ABM

Impacts of interventions such as ORI cannot be summarized directly by collecting surveillance 160 data because of the lack of controls (absent ORI intervention for the same outbreak). By contrast, 161 such features and the complex interplay of waning immunity, network-mediated transmission, 162 falling vaccination coverage, immunity boosting effects of exposure, and ORI and routine 163 vaccination schedules make this investigation well-suited to agent-based simulation modeling.<sup>32</sup> 164 Such models can be used to systematically evaluate health outcomes during pertussis outbreaks 165 in an otherwise identical context in the presence and absence of ORI. An agent-based modeling 166 approach was selected here due to several characteristics of the system involved, including -- but 167 not limited to -- the important role of individuals' connections, the spatially clustered character 168 169 of outbreaks, the need for a finer-grained representation of both age and waning immunity, and 170 the need for a longitudinal lens to understand the impact of individual vaccination compliance on vulnerability and to calibrate vaccination coverage data. An agent-based approach was further 171 valuable for representing certain ORI intervention scenarios, particularly the restriction of 172 administration of ORI to those with particular classes of vaccination histories. 173

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#### 175 **2. Methods**

We developed an agent-based simulation model (ABM) and estimated the age-specific effects of
the pertussis ORI campaign in the 10-14 age group in simulated outbreaks in terms of the
number of cases averted over the short-, medium- and long-term (1, 3 and 10 years following
ORI implementation) among young adolescents (ORI target group), infants under 1 year and
individuals of all ages. This study was approved by the Health Research Ethics Board at the
University of Alberta, study ID Pro00050642.

#### 182 2.1 Model structure and agents characteristics

The essential structure of the agent-base model is shown in figure 1A. Agents representing individual persons were associated with both fixed attributes and evolving states. Fixed attributes included a location (detailed below) and vaccination attitude, while evolving aspects of agent state included (continuous) age, count of vaccinations received and count of pertussis infections contracted. Statecharts were used to represent the natural history of infection, demographics and vaccination schedule.

189 The natural history of infection statechart drew its structure from the characterization in Hethcote's widely published and adapted compartmental model.<sup>24</sup> As described in previous 190 contributions (albeit at a compartmental rather than individual level), this representation includes 191 3 levels of severity of infection (I-full, I-mild, I-weak), and four levels of vaccination- (V1-V4) 192 193 and naturally-induced (R1-R4) immunity and transitions between V, R and I states (with time and rate constants  $\tau$ ,  $\alpha$  and  $\gamma$ ). Transitions were expressed by time-based and exposure-based 194 formulations (e.g., 2 year increments to transition from higher to lower V states and 5 years to 195 transition from higher to lower R states). In order to more realistically model the shapes of 196 197 epidemiological curves over time to capture the outbreak dynamics that is critical to ORI triggering algorithms, we added incubation periods to the state charts, based on triangular 198 distribution. While earlier adaptions of the Hethcote formulation typically assumed random 199 mixing, in our model, individuals are importantly exposed to pathogens over a contact network 200 (see below). In both cases, infection transmission is only possible to individuals who are 201 202 susceptible (S state) or in the lower two levels of vaccine- and naturally- induced immunity. Vaccination and pathogen exposure boosts the level of both vaccine- and naturally induced 203 immunity; waning of immunity decreases such immunity over time. While in an infected state, 204

individuals in our model expose network connections, chosen with uniform probability, topathogen at an age-specific contact rate.

207 Demographic statecharts reflected a possible lifespan varying from 0 to 100 years and illustrated

208 individual mortality and (for female agents) fertility, with both being characterized using age-

specific hazard rates derived from Hethcote model. We used the 2004 Canadian population

210 pyramid to initialize the simulation (figure 1B).

211 The vaccination schedule statechart is modeled on North American vaccination regimes. It characterizes possible vaccination episodes at ages 2, 4, 6 and 18 months, and 4-6 and 11-14 212 years (dose 6 is given at 11-12 years of age in the US and in grades 7 to 9 in Canada), with one 213 adult (18 years or older) vaccination also depicted. The range of ages when an adult dose is 214 administered in our model is between 18 and 35. This reflects the fact that parents of young 215 children may receive such a dose as a part of "cocooning" strategy. Alternatively, individuals 216 presenting to emergency departments with tetanus-prone wounds may also receive a pertussis-217 containing vaccine. At each such age juncture, a person has a vaccine attitude- (acceptor, rejector 218 and hesitant) (supplementary tables 1A and 1B) and age- dictated probability of securing a 219 vaccination encounter; conditional on such an encounter, a vaccine is delivered. In our model, 220 we built a function to offer a catch-up vaccine if the previous dose is missed up to the minimal 221 age of the next dose (e.g., if 5<sup>th</sup> dose is missed, an individual can have a chance to receive a 222 catch-up dose up to the age of 11 years). The probability of offering catch-up immunization is 223 90%, but this is conditional on an individual having a further encounter with a vaccine provider, 224 which in turn is dependent upon dose-specific vaccine coverage as well as contingent on 225 personal vaccine attitude (e.g., a vaccine rejecter will not have a catch-up vaccine offered). Each 226 occurrence of vaccination is associated with a fixed chance of vaccine failure (figure 1C). 227

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#### 229 Figure 1: Model structure.

230 (A) Pertussis natural history statechart. (B) Demographic statechart. (C) Vaccination schedule

231 statechart.

#### 232 2.2 Network and spatial context

- 233 To capture the spatially clustered nature of outbreaks, agents were distributed throughout a
- stylized geographical area. The agent population was divided into a low density periphery
- 235 (constituting 29% of the population but 89% of the area), and a central region of 20-fold higher
- population density (holding the balance of the population and occupying the remaining area).

237 Based on their spatial location, agents were placed in a quasi-static assortive network in which a

- pair of agents was connected only if they lay within a specified distance threshold of each other.
- 239 The model used different distance thresholds governing whether a given pair of persons was
- 240 connected according to the age group of pair members. Specifically, while most pairs were
- connected only if they were within a certain range of each other, if both members of the pair
- were between 0 and 16 years old (inclusive), an 11-fold larger connection threshold was used
- 243 guided by calibration.

#### 244 2.3 Parameterization

245 We configured our model using key parameters given in table 1. Disease mechanism parameters

246 pertaining to transitions between various *V*, *R* and *I* states were as described in the Hethcote

247 model.<sup>24</sup> A primary vaccine failure probability described in the literature,<sup>9</sup> and incubation

248 periods' range reflecting literature values<sup>33</sup> were incorporated. Vaccine coverage was generated

by the model. To simulate the dynamics of vaccine coverage, we classified all individuals into

three groups: those who accept, reject and are hesitant to receive vaccination. For each of these

251 groups, we assigned vaccination probabilities. By adding network characteristic parameters and

an exogenous infection rate, we generated real-time epidemiological curves.

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#### 257 Table 1: Model's configuration and key parameters

Parameter Category	Parameter Name	Description	Value
Demographics	Population size, (Persons)	Population size at the model's' initialization	500000
	Incubation period, (Days)	Incubation period corresponding to different <i>I</i> states	Follows triangular distribution (min = $\{7,10,14\}$ , mode = $\{10,14,21\}$ , max = $\{14,21,42\}$ )
Disease mechanism	Mean waning time between R states, (Years)		5
	Mean waning time between V states (whole-cell vaccine), (Years)	Determine vaccine-derived and natural disease-derived waning immunity	2
	Mean waning time between V states (acellular vaccine), (Years)		2
Disease propagation	Exogenous infection Rate, (1/Day)	Represents imported infections	5
	Connection range, (Length)		{Preferential = 55, Normal = 5}
	Base contact rate, (1/Day)		{Preferential = 20, Ordinary =3}
Network characteristics	Preferential mixing age, (Years)	Control mixing patterns and cumulative incidence and shape of epidemiological curve over time generated by the model	$\{\text{from} = 0, \text{ to} = 16\}, \text{ years}$
	Base population density, (Persons/Length <sup>2</sup> )		0.002
	Central-outer density ratio, (Unit)		20

Vaccine coverage	Initial distribution of vaccination attitude in population, %	Determine vaccine coverage generated by the model	{Vaccine Acceptor (HA) = 50, Vaccine Hesitant (VH) = 40, Vaccine Rejector (VR) = 10}

#### 259 2.2.4 Outbreaks and ORI triggers

We developed an automated algorithm for triggering ORI (supplementary figures 1A-1C). The 260 incidence rate of each month for the each age group was assigned a trichotomous S [sub-261 outbreak] tag [S-, S, S+]. S and S+ states would require exceedance of the 60-month moving 262 average (excluding designated outbreaks) by 2 and 3 standard deviations, respectively and, 263 additionally, exceedance of a specified monthly age-specific incidence rates (40 and 60 per 264 100,000, respectively); the latter being derived by examining surveillance and outbreak reports 265 <sup>2,4,5,34</sup> and further by calibration. An outbreak was defined as occurring if there were at least two 266 consecutive months in the S state while ORI was triggered only in a setting of three consecutive 267 268 months in S states or two consecutive months in S+ states. We computed the rates of simulated outbreaks and ORI occurrence by dividing the number of outbreaks and ORI interventions within 269 a specified age group across all realizations by the product of a total number of realizations in a 270 given experiment and the 30 years in each run (i.e., model run-years). For this study, we only 271 272 triggered ORIs in the 10-14 age group. Reciprocals of the outbreak and ORI rates represent the mean period between outbreaks within a given age group and *time between ORIs*, respectively. 273 274 The latter was used to evaluate sensitivity of our model to triggering ORIs. ORI implementation was modeled as achieving 80% vaccination coverage for all individuals aged 10-14 at the time of 275 276 ORI administration.

#### 277 2.3 Calibration and validation

To better capture epidemiological trends of pertussis, we employed both quantitative and 278 phenomenological approaches to validate and calibrate outputs from our model. More 279 specifically, for the latter, we used the pattern-oriented modeling (POM) technique <sup>35,36,37</sup> to 280 281 optimize our model structure to ensure that generated epidemiological curves are realistic. We used this bottom-up strategy<sup>37</sup> to model the highly complex system to improve our model 282 283 robustness in a situation when interplay of multiple factors governing pertussis transmission, 284 outbreak propagation and vaccination dynamic are less predictable and the understanding of the characteristics of the causal pathways involved remains incomplete. We extensively varied most 285 of our network parameters (connection range, contact rate, exogenous infections rate) and 286 287 studied resultant patterns by visual inspection of baseline endemic activity, age-specific peaks of outbreaks and intervals between outbreaks using a graphical-user interface. We identified 288

obviously unrealistic outputs and gradually converged towards a well-fitting combination ofparameters.

Quantitatively, we adjusted model parameters to better match empirical cumulative incidence 291 and dose-specific vaccine coverage. We calibrated the model to bring the 30-year cumulative 292 293 incidence generated by the model in line with surveillance reports from two public health jurisdictions of similar population size in Alberta (figure 2A and supplementary figure 2). 294 Comparability was defined as no more than 10% deviation between model-generated average 295 cumulative incidence and that from two reference public health districts. Age-specific incidence 296 rates were checked during calibration as described above to ensure that age groups with the 297 298 highest burden of disease in our model were comparable to those of reference populations.

299 We validated waning immunity outputs with data derived from literature. We defined vaccine-

300 derived and natural infection-derived waning immunity in the context of ABM logic as transition

from the (protected) V3 (or R3) state to (unprotected) V2 (or R2) for each year. We generated a

model output for waning immunity and illustrated it for the 4-16 age group (figure 2B and

supplementary figures 3, 4A and 4B).

We calibrated vaccine coverage (as defined by receipt of all eligible doses) by varying proportions of individuals by their vaccination attitudes and vaccination probabilities assigned to their respective vaccination attitudes. The calibrated model was compared against vaccine coverage statistics for doses 1 to 4 at age 2 published by Alberta Health<sup>38</sup> in the same public health jurisdictions used for cumulative incidence. Reference values for doses 5, 6 and 7 vaccine coverage were obtained from other Canadian sources<sup>39, 40</sup> given the reduced certainty for these doses in Alberta (figure 2C).

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316 Figure 2: Model's output validation and calibration.

317 (A) 30-year model-generated cumulative incidence. (B) Vaccine- and natural disease-derived

318 waning immunity fractions. (C) Vaccine coverage by dose (doses 1 to 7). Model-generated

outputs depicted in (A), (B) and (C) are compared to 30-year cumulative incidence derived from

320 surveillance data from two Alberta jurisdictions, waning immunity values described in the

321 literature and dose-specific vaccine coverage derived from Canadian data sources respectively.

- 322 To further test robustness of our model, we examined distribution of model-generated annual
- 323 incidence rates versus annual incidence rates distribution derived from empirical surveillance
- data from two Alberta jurisdictions (figure 3). We tested differences between these two data
- distributions by Mann-Whitney U-test (p-value = 0.1068) and by Kolmogorov-Smirnov test (p-
- value = 0.1075) with results indicating reasonable representation of simulated data versus
- 327 empirical data without evidence of overfitting.



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329 Figure 3: Distribution of the model-generated annual incidence rates in relation to

**empirical data.** Bars represent frequencies corresponding to a particular annual incidence rate

331 for the model-generated data. Red circles represent reference populations' (Alberta Central and

- 332 South Zones) annual incidence rates. The total number of data points (annual incidence rates)
- based on which frequencies are computed for model-generated data is 10,200.

#### 334 2.4 Sensitivity Analyses

As vaccine coverage for adult dose 7 may have the greatest uncertainty due to the lack of a fixed

- delivery age and underreporting of vaccination implemented as part of a cocooning strategy, we
- ran a sensitivity analysis increasing vaccine coverage for dose 7 by 20% (sensitivity analysis A).

338 We further investigated the impact of waning immunity with a sensitivity analysis that reduced

annual waning immunity by increasing transition time between V states ( $\tau$ ) by 50% (from 2 to 3

340 years) among individuals born before 1997, representing the receipt of whole-cell vaccine

341 (sensitivity analysis B).

Additionally, we performed sensitivity analyses by reducing naturally-derived waning immunity by doubling transition time between R states ( $\alpha$ ) from 5 to 10 years (sensitivity analysis C) and by imposing eligibility restriction to receive ORI vaccination to only those who did not receive a regular vaccine within last 6 months (sensitivity analysis D).

346 We also performed sensitivity analysis by including a scenario positing a more rapid boosting

347 effect from administration of vaccination (sensitivity analysis E). In this scenario, booster

immunization for an individual in lower V states would lead immediately to a V4 state (full

protection), without the multi-dose transition through V2 and V3 states as in the main

350 experiment. Finally, we conducted a multi-way sensitivity analysis (sensitivity analysis F) where

351 we considered the effects of simultaneous changes in  $(\tau)$  and  $(\alpha)$ .

352 2.5 Simulation setup and statistical analysis

An open model population of initial size 500,000 was simulated in continuous time using AnyLogic 7 software. We run multiple paired simulations (using identical random seeds) with and without enabling the automated ORI module for 33 years. The first three years of simulation were designated as a "burn-in period" and discarded, resulting in a 30-year period of observations per simulation run. To yield meaningful results, statistical analysis was only

358 performed on "qualified" pairs of simulations, as judged by the following criteria:

- 359 i. At least one ORI was triggered within a simulation run;
- 360 ii. At least a 10-year post-ORI observation period was available;
- 361 iii. There was no second ORI triggered within a 10-year observation period;

362 Furthermore, qualified simulations meeting above criteria had to exhibit a cumulative incidence

rate comparable to two Alberta jurisdictions as described above.

364 We ran simulations on a high-power computer cluster at the University of Saskatchewan for 200

node-hours resulting in 334 pairs. Analyses were performed on data generated by the model. An

illustration of differences between with-ORI and no-ORI case counts in a single paired 366 simulation run for all ages before and after a triggered ORI is shown in supplementary figure 5. 367 For each qualified pair, we calculated a number of cases averted within 1, 3 and 10 years after 368 ORI for three age groups: all ages, 10-14 (the ORI target age group) and infants under 1 year of 369 age (the most vulnerable group). The differences in the count of cases between the ORI and no-370 ORI groups for a given qualified simulation pair were tested using the one-way Mann-Whitney 371 U test to determine statistical significance. We calculated a number needed to vaccinate during 372 ORI (NNV-ORI) to prevent a single case directly from the model by dividing a number of 373 vaccinations delivered during an ORI by a number of cases averted in a respective age-group. 374 This quantity will vary significantly in the context of different assumptions regarding the 375 population size and population immunity and therefore only applies to our model. Given multiple 376 simulations, we reported minimum and maximum NNV values. 377

#### 378 **3. Results**

189 qualified paired-runs met the inclusion criteria and were analyzed in the main experiment. 379 Characteristics and summary statistics of model-generated data are shown in table 2. In the main 380 experiment, the outbreak rate for all ages was 0.315, indicating that outbreaks in all-ages group 381 were occurring approximately every 3 years in the model. The respective frequencies of outbreak 382 occurrence among adolescents 10-14 years of age and infants under 1 year of age were 383 approximately once in 7 and 13 years. Peak annual and monthly incidence rates for all ages 384 385 recorded in the main experiment across all realizations were 170 and 26 per 100,000, respectively. Similarly, while the overall outbreak rates were lower in the 10-14 year category 386 and among infants when compared with those outbreak classifications considering all age 387 groups, peak annual and monthly incidence rates for children 10-14 years were 931 and 181 per 388 100,000, respectively, and for infants under 1 year of age, 725 and 207 per 100,000. On average, 389 an ORI campaign was triggered every 26 years. There were few variations in the rates of 390 outbreaks' occurrence and ORI triggering between the main experiment and all sensitivity 391 analysis scenarios other than sensitivity analysis involving more rapid boosting from vaccination 392 (sensitivity analysis E), which demonstrated significantly lower outbreak and ORI frequency. 393 394 The scenario in sensitivity analysis E was also the only situation where comparability criteria with empirical data were not met. In the course of pattern-oriented modeling (POM) validation, 395

- 396 we observed that reducing the exogenous infection rate resulted in a lower background incidence
- 397 rate, punctuated by more pronounced outbreaks for a given cumulative incidence.

#### 398 Table 2: Characteristics and summary statistics of the main experiment and sensitivity

399 analyses

	Description of	ORI rate in	Outbreak	Outbreak	Outbreak rate	Comparability
	parameter(s) alterations	10-14 age	rate in all	rate in	in 10-14 age	with
		group <sup>§</sup> per	ages¶ per	under 1¶	group <sup>¶</sup> per	benchmark
		model run-	model	per model	model run-	cumulative
		years	run-years	run-years	years	incidence#
Main experiment	Reference	0.038	0.315	0.075	0.129	Yes
Sensitivity analysis A	Increase vaccine coverage for dose 7 by 20%	0.037	0.315	0.080	0.127	Yes
Sensitivity analysis B	Increase value of $(\tau)$ to 3 among those born after 1997	0.039	0.323	0.075	0.127	Yes
Sensitivity analysis C	Increase value of $(\alpha)$ to 10	0.040	0.341	0.082	0.135	Yes
Sensitivity analysis D	Restrict ORI eligibility to those who did not receive vaccine within last 6 months	0.036	0.324	0.078	0.129	Yes
Sensitivity analysis E	Implement stronger vaccine boosting effect	0.005	0.047	0.013	0.021	No
Sensitivity analysis F	Multi-way sensitivity analysis B and C combined	0.025	0.325	0.083	0.129	Yes

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#### 401 Notes:

402 § ORI rate is computed by dividing the number of triggered ORIs by the product of a total

number of simulation runs in a given experiment and 30 years in each run. Reciprocal of the ORI

404 rate represents mean time between occurrences of triggering ORIs; for example, the rate of 0.038

- 405 per model run-years in the main experiment indicates that ORI in the 10-14 age group was
- 406 triggered every 26 years in the model (1/0.038=26.3).
- 407 ¶ Outbreak rate is computed by dividing the number of outbreaks within a specified age group
- 408 (or when judged with respect to all age groups) by the product of a total number of simulation
- 409 runs in a given experiment and 30 years in each run. Reciprocal of the outbreak rate represents

- 410 the mean period between outbreaks occurring within a given age group; for example, the rate of
- 411 0.315 per model run-years in the main experiment indicates that outbreaks in all age groups were 412 occurring every 3 years in the model (1/0.315=3.17).
- <sup>413</sup> <sup>#</sup> Comparability with benchmark cumulative incidence was defined as model-generated 30-years
- 414 cumulative incidence rate falling within 10% of the average empirical cumulative incidence rate
- 415 derived from 15 years of observations in two jurisdictions in Alberta (15 years of observations
- 416 were up-scaled to derive 30-year cumulative incidence).
- 417
- 418 Vaccine-induced and natural disease-derived waning immunity rates in our model were
- calculated to be 29% and 6.5% per year, respectively, in line with values reported from the
- 420 literature.<sup>9,13</sup> Our model generated the following vaccine coverage for doses 1 to 7: 89%, 87%,
- 421 82%, 68%, 67%, 67% and 7%, respectively (figure 2C and supplementary figures 3 and 4A-4B).
- In the main experiment, on a per-run basis, there were an average of 124, 243 and 429 pertussis 422 cases averted across all age groups within 1, 3 and 10 years of a campaign, respectively. During 423 the same time periods, 53, 96, and 163 cases were averted in the 10-14 age group, and 6, 11, 20 424 in infants under 1 (p<0.00001 for all groups of comparisons of counts of cases in ORI versus no-425 ORI simulations, one-way Mann Whitney U test). NNV-ORI ranged from 49 to 221, from 130 to 426 519 and from 1031 to 4903 for all ages, the 10-14 age group and for infants, respectively (table 427 3). Boxplots for the number of cases averted for durations following ORI are depicted in figure 428 429 4, with each data point being associated with a particular realization. Over a 10-year period, there was a gradual accrual of cases averted across all studied age groups; however, the accrual rate 430 exhibited diminishing gains in years 5 through 10. 431
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- 439 Table 3: Number of pertussis cases averted and numbers needed to vaccinate by time
- 440 periods after the outbreak-response immunization campaign and by age groups: modeling-

#### 441 generated results

Age groups	Post-outbreak- response immunization period, years	Average number of cases averted*	Minimum number needed to vaccinate <sup>§</sup>	Maximum number needed to vaccinate <sup>§</sup>
All ages	1	124	171	221
All ages	3	243	87	112
All ages	10	429	49	64
Under 1 year	1	6	3784	4903
Under 1 year	3	11	1834	2377
Under 1 year	10	20	1031	1336
10-14 years old	1	53	400	519
10-14 years old	3	96	220	285
10-14 years old	10	163	130	168

442

#### 443 Notes:

444 \* p<0.00001 for all groups of comparisons of counts of cases in outbreak-response immunization

445 (ORI) versus no-ORI simulations, one-way Mann Whitney U test.

446 § Number needed to vaccinate (NNV) was calculated directly from the model by dividing a

447 number of vaccinations delivered during the ORI by a number of cases averted in a respective

448 age group. NNV only applies to a current model and for a given population size.

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# 450 Figure 4: Number of pertussis cases averted over a 10-year period after implementation of 451 ORI campaign

452 (A) All ages group. (B) Infants under 1 year of age. (C) Adolescents 10-14 years of age

453 Results of sensitivity analyses are summarized in table 4.

Age	Post-	Number of cases averted <sup>§</sup> by experiment						
group	ORI	Main	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity	Sensitivity
	period,	experiment	analysis	analysis	analysis	analysis	analysis	analysis
	years	*†	A*†	B*†	C*†	D*†	E*	F*†
All ages	1	124	119	112	148	108	41	130
All ages	3	243	256	228	262	241	93	229
All ages	10	429	410	409	422	429	148	378
Under 1	1	6	5	5	7	4	1**	6
Under 1	3	11	12	10	13	10	4	10
Under 1	10	20	20	20	21	21	6	18
Age	1	53	51	48	61	47	19	54
10-14								
Age	3	96	102	92	104	96	40	90
10-14								
Age	10	163	156	156	161	162	60	143
10-14								

454 Table 4: Number of pertussis cases averted: summary of sensitivity analyses

455

#### 456 Notes:

457 § The number of cases averted was determined by subtracting count of pertussis cases in the

458 simulation ORI arm from the no-ORI arm within the same experiment for a given age group and

a given post-ORI period (count of cases expected to be lower in an ORI arm if cases are averted)

460 and expressed as an average on a per-run basis.

461 \*p<0.00001 for all groups of comparisons of counts of cases in outbreak-response immunization

462 (ORI) versus no-ORI simulations, one-way Mann Whitney U test (p-values apply to the entire463 column).

464 \*\*p=0.12

Prolonging the duration of vaccine-induced immunity among those who received whole-cell

vaccine had minimal impact on overall waning immunity and number of cases averted by ORI.

467 Prolonging the duration of natural disease-derived immunity resulted in such an annual waning

- 468 immunity decreasing to 2% but had minimal impact on the number of cases averted. Equally,
- 469 multi-way sensitivity analysis of combining both the effect of prolongation of whole-cell
- 470 vaccine-induced and natural disease-derived immunity had little impact on the number of cases
- 471 averted. Increasing vaccine coverage for dose 7 to 26% and restricting eligibility to receive

vaccination during the ORI campaign to those who did not receive pertussis vaccine within 6 472 months had also minimal impact on cases averted relative to the baseline. However positing a 473 significantly stronger boosting effect from vaccination (bypassing V2 and V3 states in the state 474 chart in figure 1A) resulted in significantly fewer cases averted by ORI (148 cases averted in 475 sensitivity analysis E versus 429 in the main experiment for all-ages group over 10 years). Also, 476 the difference between ORI and no-ORI arms was not statistically significant for infants under 1 477 years of age at 1 year post ORI campaign (p-value = 0.12) in sensitivity analysis E. Interested 478 readers can refer to the supplemental material for additional results of sensitivity analyses 479 (supplementary tables 2A-2F and supplementary figures 6A-6F). 480

#### 481 4. Discussion

Our ABM successfully generated 30 years of longitudinal data to evaluate the effects of supplemental ORI in a controlled study. For this purpose, we expanded mechanisms widely adopted from a previously published pertussis compartmental model by developing a spatiallylocalized 500,000-person contact network representing a typical small-to-moderate size Canadian public health district, and also supplemented such elements with novel mechanisms to dynamically recognize outbreaks suitable for ORI, and trigger resulting immunization campaigns.

Modeling is used to enhance fundamental understanding of pertussis characteristics and 489 transmission and to more pragmatically to evaluate impacts of interventions (e.g., adolescent or 490 adult routine vaccination or cocooning strategy). While latter is often a subject of recent 491 enquiries, our model, to our knowledge, is the first to represent and evaluate the effects of 492 pertussis ORI. Such an ORI-specific evaluation is an important contribution to our understanding 493 494 of outbreaks dynamics, as the force of infection of the sort of focused, large scale outbreak needed to motivate ORI may generate different transmission patterns which cannot be seen in the 495 496 non-outbreak settings, and because ORI can re-shape both short- and long-term transmission 497 dynamics either for the benefit or possibly to a detriment. The large scale outbreak itself may exhaust the pool of susceptibles and consequently yield a decrease in the number of cases in 498 post-outbreak years, and lower incidence can lead to diminished natural boosting. For example, 499 500 annual pertussis incidence rates were at historically low levels in 2 years following a large scale outbreak in New Brunswick in 2012 (187, 0.5 and 1.2 per 100,000 in 2012, 2013 and 2014, 501

respectively) with a smaller outbreak reported in the third year.<sup>41,42</sup> While this observation could
be due to the effect of the outbreak itself, the contribution of the ORI (which was implemented in
New Brunswick 2012 outbreak) is an important consideration.

We conclude that the effect of ORI is beneficial independently of the effect of the outbreak itself 505 506 and leads to a net number of cases averted in all age groups, particularly in the short and medium term. While the objective of this model project focused on evaluation of the effects of ORI, the 507 model also supported a set of interesting secondary observations. We found that reducing the 508 exogenous infection rate resulted in a lower background incidence rate punctuated by more 509 pronounced outbreaks. This may suggest that jurisdictions with lower migration may be more 510 511 prone to larger scale but less frequent outbreaks, while jurisdiction with higher migration may exhibit more frequent outbreaks with lower peak incidence. No significant changes to our 512 513 conclusions were observed from positing prolonged duration of natural disease-derived immunity, increasing adult vaccine-coverage or restricting vaccination eligibility during ORI. 514 515 We observed no effect of altering the assumptions concerning waning immunity for those who received whole-cell vaccine, which may be due to the fact that our model ran prospectively into 516 the future, with the number of individuals who had whole-cell vaccines progressively decreasing 517 over time. However, our findings in a sensitivity analysis that positing a stronger boosting effect 518 519 of vaccination implies a notably reduced burden of pertussis supports current thinking that insufficient duration of immunity contributes to the recent resurgence of pertussis outbreaks. 520

521 One of the considerations in modeling/reproducing outbreaks is that, while historical surveillance data plays an important role in defining whether an outbreak exist or not, the identification of an 522 outbreak is often judgement-based, with similar magnitude of pertussis incidence determined to 523 be an outbreak in a one jurisdiction, but not in others. We set outbreak and ORI thresholds in our 524 525 model high, effectively excluding instances of "borderline" outbreaks where ORI is unlikely to ever be a consideration. As a result, ORI in our simulations was triggered once every 26 years 526 on average. This reflects the reality that ORI is not a commonplace intervention, particularly if 527 disease is endemic. In our model, we implemented ORIs only to adolescents 10-14 years of age, 528 reflecting recent outbreaks affecting this age group, who are largely fully immunized (and for 529 530 whom immunization schedule adherence was not protective) and their accessibility to schoolmediated campaigns; however, our model has the capability to test outbreak response in any age 531

group. To ascertain whether ORI administered to young adolescents confer an indirect protection 532 to other age groups via interruption of transmission, we specifically examined the effects of ORI 533 administered to the adolescent age group on the number of cases averted among individuals of 534 all ages and among infants, as protecting infants is one the main priorities for public health 535 interventions. While we observed protective effect among adolescents and individuals of all 536 ages, our study revealed that a protective effect to infants is modest, as suggested by high NNV 537 generated by our model. These results are in the agreement with recent recommendations 538 concluding that a booster dose in adolescence or adulthood had minimal impact on infant 539 disease<sup>43</sup>; however, the latter recommendation was not specifically in the ORI context. 540

541 The main strength of our study is that we analysed longitudinal data generated by the model in a manner of a controlled study, thus allowing us to independently evaluate and quantify the effects 542 543 of the ORI. As propagation of outbreaks depends on both intrinsic characteristics of individuals as well as transmission-permitting connections, which exist between these agents, including both 544 545 characteristics in a single agent-based model allowed us to examine their interplay in outbreak occurrence. Our model included age-structure to model pertussis vaccination and incorporated 546 547 vaccination attitudes into determination of vaccine coverage. Our model quantified both vaccineinduced and natural disease-derived waning immunity. Furthermore, we calibrated and validated 548 549 the model by statistical comparison of the model-generated data and observed surveillance data as well as by utilizing pattern-oriented modeling. Our model could be adapted, with varying 550 levels of ease, for different contexts and to investigate different types of research questions. 551 Adaptation to investigate similar ORI phenomena in other jurisdictions would involve a 552 circumscribed set of changes, including primarily changes to the vaccination statechart and 553 associated probabilities (to represent local vaccination regimes), probabilities associated with 554 vaccine attitude (reflecting differences in local attitudes towards vaccination), population sizes 555 and population density, and potentially age-specific mixing assumptions. With a greater degree 556 of modifications, and contingent on retaining current disease transmission logic, our model 557 would also permit to investigate effects of other public health interventions ranging from altering 558 vaccination schedules, evaluating effects of passive messaging to adhere to immunization 559 schedules and adding vaccine doses in adults. 560

561

Our study has several limitations. We used disease mechanism parameters initially outlined in 562 the Hethcote model. While conducting several sensitivity analyses involving key parameters, our 563 experiments with different disease transmission logic were limited to enhancing boosting effect; 564 a broader set of altered assumptions in this area may or may not yield different results for our 565 research question. Recent study suggests that non-human primates vaccinated with acellular 566 pertussis vaccine were protected from severe symptoms, but not infection, and readily 567 transmitted Bordetella pertussis to contacts.<sup>44</sup> In recent review of pertussis models Campbell et 568 *al.* identified incomplete understanding relating infection and disease and lack of supporting data 569 to derive parameters as common limitations of proposed pertussis models.<sup>45</sup> While our 570 calibration process helped ensure that our model output is realistic, we did not test variations in 571 every single parameter given the multi-faceted nature of our model. Furthermore until further 572 knowledge emerges to narrow down or alter parameters value, using the classic model structures 573 on which our model is based would appear appropriate. We did not aim to examine and compare 574 public health strategies other than ORI, and the need to pursue such research is strong. Economic 575 evaluations can offer valuable additions to conclusions generated by our work. 576 577

#### 578 5. Conclusions

We developed an agent-based model to investigate effects of outbreak response immunization 579 campaigns targeting young adolescents in averting pertussis cases. We concluded that such an 580 581 immunization campaign confers benefits across all age groups accruing over a 10-year period. Our inference is dependent on having an outbreak of significant magnitude affecting 582 predominantly the selected age and achieving a comprehensive age-specific coverage rate during 583 the campaign. Our results demonstrated that while outbreak response may yield modest benefits 584 585 for protecting infants, additional strategies to protect this vulnerable group are needed. Our experience indicates that ABM offers a promising methodology to evaluate other public health 586 interventions used in pertussis control. We also identify the strong need for further research into 587 application of modeling to further our understanding of pertussis epidemiology. 588 589

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- 595

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