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

Alexander Doroshenko, Weicheng Qian, Nathaniel D Osgood

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 10-year 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 and immunization campaign eligibility in sensitivity analysis. **Results.** 193 qualified paired-runs were analyzed. On average, ORI was triggered every 19 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. Sensitivity analyses resulted in minimal impact on a number of cases averted. **Discussion.** Our model generated 30 years of longitudinal data to evaluate the effects of outbreak response immunization in a controlled study. Immunization

campaign implemented as an outbreak response measure among adolescents may confer benefits across all age groups 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 age-specific coverage rate during the campaign. Economic evaluations and comparisons with other control measures can add to the conclusions generated by our work.

1   **Evaluation of outbreak response immunization in the control of pertussis using agent-**
2   **based modeling**

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Abstract

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31 **Background.** Pertussis control remains a challenge due to recently observed effects of waning

32 immunity to acellular vaccine and suboptimal vaccine coverage. Multiple outbreaks have been

33 reported in different ages worldwide. For certain outbreaks, public health authorities can launch

34 an outbreak response immunization campaign to control pertussis spread. We investigated effects

35 of an outbreak response immunization targeting young adolescents in averting pertussis cases.

36 **Methods.** We developed an agent-based model for pertussis transmission representing disease

37 mechanism, waning immunity, vaccination schedule and pathogen transmission in a spatially-

38 explicit 500,000-person contact network representing a typical Canadian Public Health district.

39 Parameters were derived from literature and calibration. We used published cumulative

40 incidence and dose-specific vaccine coverage to calibrate the model's epidemiological curves.

41 We endogenized outbreak response by defining thresholds to trigger simulated immunization

42 campaigns in the 10-14 age group offering 80% coverage. We ran paired simulations with and

43 without outbreak response immunization and included those resulting in a single ORI within a

44 10-year span. We calculated the number of cases averted attributable to outbreak immunization

45 campaign in all ages, in the 10-14 age group and in infants. The count of cases averted were

46 tested using Mann-Whitney U test to determine statistical significance. Numbers needed to

47 vaccinate during immunization campaign to prevent a single case in respective age groups were

48 derived from the model. We varied adult vaccine coverage, waning immunity parameters and

49 immunization campaign eligibility in sensitivity analysis.

50 **Results.** 193 qualified paired-runs were analyzed. On average, ORI was triggered every 19

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

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

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

54 1 (p<0.001, all groups). Numbers needed to vaccinate ranged from 49 to 221, from 130 to 519

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

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

57 **Discussion.** Our model successfully generated 30 years of longitudinal data to evaluate the

58 effects of supplemental outbreak response immunization in a controlled study. Immunization

59 campaign implemented as an outbreak response measure among adolescents may confer benefits

60 across all age groups accruing over a 10 year period. Our inference is dependent on having an

61   outbreak of significant magnitude affecting predominantly the selected age and achieving a

62   comprehensive age-specific coverage rate during the campaign. Economic evaluations and

63   comparisons with other control measures can add to the conclusions generated by our work.

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1. Introduction

In recent years, pertussis control has re-emerged as a prominent public health challenge, with multiple outbreaks observed worldwide[1], and with some jurisdictions reporting the highest numbers of cases seen in decades.[2] In Canada, the last peak in pertussis activity was seen in the mid-1990s, after which incidence rates were gradually declining prior to a 2012 resurgence. This recent increase was driven by outbreaks in several provinces/territories. [3] The national age-specific incidence rate remains highest among infants under 12 months of age, an age group also suffering the most hospitalizations and deaths. However, recently school-age children and younger adolescents have also borne a disproportionate burden, particularly during outbreaks. 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 100,000, respectively).[4] Such increases in incidence rates among older children were reported from several US states [2,5], suggesting a bimodal age distribution of cases in some jurisdictions. During three most recent Minnesota outbreaks, the proportion of pertussis cases among children 7 to 18 years old exceeded 60%.[6]

The recent increase in pertussis activity is thought to be due to a combination of waning immunity from acellular pertussis vaccine and sub-optimal vaccine coverage. In the Ontario outbreak, cases were reported among unvaccinated individuals from a religious community and among vaccinated school-aged children.[8] In New Brunswick, 67% of cases in the 10-14 age group were up-to-date with their immunization.[4] Several studies estimated the annual decline in protection after pertussis vaccination as ranging from 21% to 62%.[9,10,11] Vaccine-derived 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.[12] Furthermore, natural disease confers even greater -- but not life-long -- protection.[13] Genetic mutations in the *Bordetella pertussis* bacterium and better detection and diagnosis have been suggested as other explanations for this recent pertussis trend.[14]

Vaccination remains a cornerstone of public health measures to control pertussis. Improving immunization schedule adherence by raising awareness among public is the most commonly used intervention. The strategy of "cocooning" infants (vaccinating parents and other individuals

114   in close contact with infants) has been advocated, with mixed reviews.[15,16] Immunizing pregnant

115   women in the third trimester of pregnancy to prevent pertussis disease in infants too young to

116   receive vaccination is recommended in the US.[17] Modifications of the immunization schedule

117   (changing the age of vaccine administration or adding doses) have been discussed.[18] Developing

118   new vaccines will offer the best long-term control strategy, however it is not likely to occur in

119   the short term.[19]

120   The ongoing occurrence of pertussis outbreaks presents a challenge to public health authorities

121   which may necessitate supplementary control measures. In Canada, immunization of pregnant

122   women is recommended only in outbreak situations.[20] Early contact tracing and

123   chemoprophylaxis of contacts has been advanced as protective in control of school-based

124   outbreaks.[21] Outbreak response immunization (ORI) has been employed if a particular group is

125   disproportionately affected and it is feasible to reach and vaccinate this group in a relatively

126   short period of time.[4] ORI is supplementary immunization given over and above the routine

127   vaccination schedule, including to those who may be fully immunized or those who did not

128   receive their scheduled vaccines. Potential benefits of ORI could accrue both in the short-term

129   (terminating or limiting an ongoing outbreak) and long-term (preventing future outbreaks).

130   However ORI may also blunt natural boosting from circulating sub-clinical infections. The cost

131   of such immunization campaigns, including emergency response infrastructure, cost of vaccines

132   and their delivery is high, and often not included in routine immunization programs budgets.

133   Evaluation of such immunization campaigns is limited and the need for pertussis outbreak

134   response research has been advocated.[22]

135   Impacts of interventions such as ORI cannot be summarized directly by collecting surveillance

136   data because of the lack of controls (absent ORI intervention for the same outbreak). By contrast,

137   such features and the complex interplay of waning immunity, network-mediated transmission,

138   falling vaccination coverage, immunity boosting effects of exposure, and ORI and routine

139   vaccination schedules make this investigation well-suited to simulation modeling.[23] Such models

140   can be used to systematically evaluate health outcomes during pertussis outbreaks in an

141   otherwise identical context in the presence and absence of ORI. In this study, we developed an

142   agent-based simulation model (ABM) to estimate the age-specific effects of the pertussis ORI

143   campaign in the 10-14 age group in simulated outbreaks in terms of the number of cases averted

144   over the short-, medium- and long-term (1, 3 and 10 years following ORI implementation).

145   **2. Methods**

146   **2.1 Rationale for ABM**

147   Previous studies have used aggregate and agent-based simulations to understand pertussis

148   dynamics. An agent-based modeling approach was selected here due to several characteristics of

149   the system involved, including -- but not limited to -- the important role of individuals'

150   connections, the spatially clustered character of outbreaks, the need for a finer-grained

151   representation of both age and waning immunity, and the need for a longitudinal lens to

152   understand the impact of individual vaccination compliance on vulnerability and to calibrate

153   vaccination coverage data. An agent-based approach was further important to represent ORI

154   intervention scenarios. This section discusses the essential structure of the model; interested

155   readers are referred to the supplemental material for additional information on model design and

156   implementation. This study was approved by the Health Research Ethics Board at the University

157   of Alberta, study ID Pro00050642.

158   **2.2 Model structure**

159   **2.2.1 Agent characteristics**

160   Agents representing individual persons were associated with both fixed attributes and evolving

161   states. Fixed attributes included a location (detailed below) and vaccination attitude, while

162   evolving aspects of agent state included (continuous) age, count of vaccinations received and

163   count of pertussis infections contracted. Statecharts were used to represent the natural history of

164   infection, demographics and vaccination schedule.

165   The natural history of infection statechart drew its structure from the characterization in

166   Hethcote's widely published and adapted compartmental model.[24] As described in previous

167   contributions (albeit at a compartmental rather than individual level), this representation includes

168   3 levels of severity of infection (full, mild, weak), and four levels of vaccination- (V1-V4) and

169   naturally-induced (R1-R4) immunity. While earlier adaptions of the Hethcote formulation

170   typically assumed random mixing, in our model, individuals are importantly exposed to

171 pathogens over a contact network (see below). In both cases, infection transmission is only

172 possible to individuals who are susceptible (S state) or in the lower two levels of vaccine- and

173 naturally- induced immunity. Vaccination and pathogen exposure boosts the level of both

174 vaccine- and naturally induced immunity; waning of immunity decreases such immunity over

175 time. While in an infected state, individuals in our model expose network connections, chosen

176 with uniform probability, to pathogen at an age-specific contact rate.

177 The vaccination schedule statechart is modeled on the North American vaccination regimes. It

178 characterizes possible vaccination episodes at ages 2, 4, 6 and 18 months, and 4-6 and 11-14

179 years (dose 6 is given at 11-12 years of age in the US and in grades 7 to 9 in Canada), with one

180 adult (18 years or older) vaccination also depicted. At each such juncture, a person has a vaccine

181 attitude- and age- dictated probability of securing a vaccination encounter; conditional on such

182 an encounter, a vaccine is delivered, and a catch-up for all missing doses may be delivered with a

183 specified probability. Each occurrence of vaccination is associated with a fixed chance of

184 vaccine failure.

185 Demographic statecharts characterize individual mortality and (for female agents) fertility, with

186 both being characterized using age-specific hazard rates.

187

188 **2.2.2 Network and spatial context**

189 To capture the spatially clustered nature of outbreaks, agents were distributed throughout a

190 stylized geographical area. The agent population was divided into a low density periphery

191 (constituting 29% of the population but 89% of the area), and a central region of 20 fold higher

192 population density (holding the balance of the population and occupying the remaining area).

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

194 pair of agents was connected only if they lay within a specified distance threshold of each other.

195 The model used different distance thresholds governing whether a given pair of persons was

196 connected according to the age group of pair members. Specifically, while most pairs were

197 connected only if they were within a certain range of each other, if both members of the pair

198 were between 0 and 16 years old (inclusive), an 11-fold larger connection threshold was used

199 guided by calibration.

200   **2.2.3 Parameterization**

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

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

203   model.[24] A primary vaccine failure probability described in the literature,[9] and incubation

204   periods' range following a triangular distribution reflecting literature values[25] were incorporated.

205   Vaccine coverage was generated by the model. To simulate the dynamics of vaccine coverage,

206   we classified all individuals into three groups: those who accept, reject and are hesitant to receive

207   vaccination. For each of these groups, we assigned vaccination probabilities. By adding network

208   characteristic parameters and an exogenous infection rate, we generated real-time

209   epidemiological curves.

210   **2.2.4 Outbreaks and ORI triggers**

211   We developed an automated algorithm for triggering ORI. The incidence rate of each month for

212   the each age group was assigned a trichotomous S [sub-outbreak] tag [S-, S, S+]. S and S+ states

213   would require exceedance of the 60-month moving average (excluding designated outbreaks) by

214   2 and 3 standard deviations, respectively and, additionally, exceedance of a specified monthly

215   age-specific incidence rates (40 and 60 per 100,000, respectively); the latter being derived by

216   examining surveillance and outbreak reports [2,4,5,26] and further by calibration. An outbreak was

217   defined as occurring if there were at least two consecutive months in the S state while ORI was

218   triggered only in a setting of three consecutive months in S states or two consecutive months in

219   S+ states. For this study, we only triggered ORIs in the 10-14 age group and used *"time to*

220   *generate ORI"* to evaluate sensitivity of our model to triggering ORIs. ORI implementation was

221   modeled as achieving 80% vaccination coverage for all individuals aged 10-14 at the time of

222   ORI administration.

223

224   **2.3 Calibration and validation**

225   To better capture epidemiological trends, we adjusted model parameters to better match

226   empirical cumulative incidence and dose-specific vaccine coverage. We calibrated the model to

227   bring the 30-year cumulative incidence generated by the model in line with surveillance reports

228   from two public health jurisdictions of similar population size in Alberta (figure 1).

229   Comparability was defined as no more than 10% deviation between model-generated average

230   cumulative incidence and that from two reference public health districts. Age-specific incidence

231   rates were checked during calibration to ensure that age groups with the highest burden of

232   disease in our model were comparable to those of reference populations. We observed that

233   reducing the exogenous infection rate resulted in a lower background incidence rate punctuated

234   by more pronounced outbreaks for a given cumulative incidence.

235   We calibrated vaccine coverage (as defined by receipt of all eligible doses) by varying

236   proportions of individuals by their vaccination attitudes and vaccination probabilities assigned to

237   their respective vaccination attitudes. The calibrated model was compared against vaccine

238   coverage statistics for doses 1 to 4 at age 2 published by Alberta Health[27] in the same public

239   health jurisdictions used for cumulative incidence. Reference values for doses 5, 6 and 7 vaccine

240   coverage were obtained from other Canadian sources[28, 29] given the reduced certainty for

241   these doses in Alberta.

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

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

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

245   model output for waning immunity and illustrated it for the 4-16 age group (figure1).

246   **2.4 Sensitivity Analyses**

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

248   delivery age and underreporting of vaccination implemented as part of a cocooning strategy, we

249   ran a sensitivity analysis increasing vaccine coverage for dose 7 by 20%. We further investigated

250   the impact of waning immunity with a sensitivity analysis that reduced annual waning immunity

251   by increasing transition time between V states by 50% (from 2 to 3 years) among individuals

252   born before 1997 (representing the receipt of whole-cell vaccine).

253   Additionally, we performed sensitivity analyses by reducing naturally-derived waning immunity

254   by doubling transition time between R states from 5 to 10 years and by imposing eligibility

255   restriction to receive ORI vaccination to only those who did not receive a regular vaccine within

256   last 6 months.

257

258 **2.5 Simulation setup and statistical analysis**

259 An open model population of initial size 500,000 was simulated in continuous time using

260 AnyLogic 7 software. We run multiple paired simulations (using identical random seeds) with

261 and without enabling the automated ORI module for 33 years. The first three years of simulation

262 were designated as a "burn-in period" and discarded. To yield meaningful results, statistical

263 analysis was only performed on "qualified" pairs of simulations, as judged by the following

264 criteria:

265 i.   At least one ORI was triggered within a simulation run;

266 ii.   At least a 10-year post-ORI observation period was available;

267 iii.   There was no second ORI triggered within a 10-year observation period;

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

269 rate comparable to two Alberta jurisdictions as described above.

270 We ran simulations on a high-power computer cluster for 200 node-hours resulting in 334 pairs.

271 For each qualified pair, we calculated a number of cases averted within 1, 3 and 10 years after

272 ORI for three age groups: all ages, 10-14 (the ORI target age group) and infants under 1 year of

273 age (the most vulnerable group). The differences in the count of cases between the ORI and no-

274 ORI groups for a given qualified simulation pair were tested using the one-way Mann-Whitney

275 U test to determine statistical significance. We calculated a number needed to vaccinate during

276 ORI (NNV-ORI) to prevent a single case directly from the model by dividing a number of

277 vaccinations delivered during an ORI by a number of cases averted in a respective age-group.

278 This quantity will vary significantly in the context of different assumptions regarding the

279 population size and population immunity and therefore only applies to our model. Given multiple

280 simulations, we reported minimum and maximum NNV values.

281 **3. Results**

282 Vaccine–induced and natural disease-derived waning immunity rates in our model were

283 calculated to be 29% and 6.5% per year, respectively, in line with values reported from the

284 literature.[9,13] Our model generated the following vaccine coverage for doses 1 to 7: 89%, 87%,

285 82%, 68%, 67%, 67% and 7%, respectively.

286   193 qualified paired-runs met the inclusion criteria and were analyzed. On average, ORI was

287   triggered every 19 years. On a per-run basis, there were an average of 124, 243 and 429 pertussis

288   cases averted across all age groups within 1, 3 and 10 years of a campaign, respectively. During

289   the same time periods, 53, 96, and 163 cases were averted in the 10-14 age group, and 6, 11, 20

290   in infants under 1. NNV-ORI ranged from 49 to 221, from 130 to 519 and from 1031 to 4903 for

291   all ages, the 10-14 age group and for infants, respectively (table 2). Boxplots for the number of

292   cases averted for durations following ORI are depicted in figure 2, with each data point being

293   associated with a particular realization.

294   In sensitivity analysis, prolonging the duration of vaccine-induced immunity among those who

295   received whole-cell vaccine had minimal impact on overall waning immunity and number of

296   cases averted. Prolonging the duration of natural disease-derived immunity resulted in such a

297   waning immunity decreasing to 2% but had minimal impact on the number of cases averted.

298   Increasing vaccine coverage for dose 7 to 26% and restricting eligibility to receive vaccination

299   during the ORI campaign to those who did not receive pertussis vaccine within 6 months had

300   equally minimal impact on cases averted relative to the baseline. Interested readers can refer to

301   the supplemental material for detailed results of sensitivity analyses.

302   **4. Discussion**

303   Our ABM successfully generated 30 years of longitudinal data to evaluate the effects of

304   supplemental ORI in a controlled study. We expanded mechanisms widely adopted from a

305   previously published structured pertussis compartmental model by developing a distance-

306   thresholded 500,000-person contact network representing a typical small-to-moderate size

307   Canadian public health district. Propagation of outbreaks depends on both intrinsic

308   characteristics of individuals -- who may be either susceptible, partly protected or fully protected

309   -- as well as transmission-permitting connections, which exist between these agents. Including

310   both characteristics in a single model allowed us to examine their interplay in outbreak

311   occurrence. While modeling has previously been used to evaluate effects of delays in pertussis

312   immunization, improving vaccine coverage,[30,31] the effectiveness of a routine adolescent

313   booster[32] and for understanding age-related trends and reasons for the recent surge in pertussis

314   incidence[7,33], our model, to our knowledge, is the first to represent and evaluate the effects of

315   pertussis ORI. Such an evaluation is important contribution to our understanding of outbreaks

316   dynamics as the force of infection of a large scale outbreak may generate different transmission

317   patterns which cannot be seen in the non-outbreak settings, and because ORI can re-shape both

318   short- and long-term transmission dynamics.

319   We adjusted network-related parameters to ensure that our model generated realistic

320   epidemiological curves. We found that reducing exogenous infection rate resulted in a lower

321   background incidence rate punctuated by more pronounced outbreaks. This may suggest that

322   jurisdictions with lower migration may be more prone to larger scale but less frequent outbreaks,

323   while jurisdiction with higher migration may exhibit more frequent outbreaks with lower peak

324   incidence.

325   Outbreak and ORI thresholds used in our model were set high, resulting in ORI being triggered

326   once every 19 years. This reflects the fact that the ORI is not a frequent intervention, particularly

327   if disease is endemic. In our model, we implemented ORIs only to adolescents 10-14 years of

328   age, reflecting recent outbreaks affecting this age group who are largely fully immunized (and

329   for whom immunization schedule adherence was not protective) and their accessibility to school-

330   mediated campaigns; however, our model has the capability to test outbreak response in any age

331   group. The large scale outbreak itself may exhaust the pool of susceptibles and consequently

332   yields a decrease in the number of cases in post-outbreak years. Our study, however, was

333   controlled and demonstrated that the effect of ORI leads to a net number of cases averted in all

334   age groups, particularly in the short and medium term. We specifically examined the effects of

335   ORI in the adolescent age group on a number of cases averted among infants, as protecting

336   infants is one the main priorities for public health interventions. Our study revealed that a

337   protective effect to infants is modest, as suggested by high NNV generated by our model. These

338   results are in the agreement with recent recommendations concluding that a booster dose in

339   adolescence or adulthood had minimal impact on infant disease[34]; however, the latter

340   recommendation was not specifically in the ORI context.

341   No significant changes to our conclusions were observed from positing prolonged duration of

342   natural disease-derived immunity, increasing adult vaccine-coverage and restricting vaccination

343   eligibility during ORI assumptions. We observed no effect of altering waning immunity for

344   those who received whole-cell vaccine, which may be due to the fact that our model ran

345 prospectively into the future with a number of individuals who had whole-cell vaccines

346 progressively decreasing over time.

347 Our study has several limitations. We used disease mechanism parameters initially outlined in

348 the Hethcote model. While conducting several sensitivity analyses involving key parameters, we

349 did not experiment with different disease transmission logic, which may or may not yield

350 different results for our research question. Recent study suggests that non-human primates

351 vaccinated with acellular pertussis vaccine were protected from severe symptoms, but not

352 infection, and readily transmitted *Bordetella pertussis* to contacts.[35] Representing such a lack of

353 protection by acellular vaccine associated with transmissible but not symptomatic states will

354 require restructuring the disease mechanism logic. As there is no universally-accepted definition

355 of outbreaks based on predetermined incidence rates to set ORI trigger thresholds we relied on

356 calibration by examining the resultant numbers of ORIs to ensure that our model did not generate

357 excessive ORIs. We did not aim to examine and compare public health strategies other than ORI,

358 and the need to pursue such research is strong. Economic evaluations can offer valuable

359 additions to conclusions generated by our work.

360

361 **5. Conclusions**

362 We developed an agent-based model to investigate effects of outbreak response immunization

363 campaigns targeting young adolescents in averting pertussis cases. We concluded that such an

364 immunization campaign confers benefits across all age groups accruing over a 10-year period.

365 Our inference is dependent on having an outbreak of significant magnitude affecting

366 predominantly the selected age and achieving a comprehensive age-specific coverage rate during

367 the campaign. Our results demonstrated that while outbreak response may yield modest benefits

368 for protecting infants, additional strategies to protect this vulnerable group are needed. Our

369 experience indicates that ABM offers a promising methodology to evaluate other public health

370 interventions used in pertussis control.

371

372 **6. Acknowledgements**

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374 in obtaining surveillance data.

375   **7. References**

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TABLE 1 - Model's configuration and key parameters

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

FIGURE 1 – Model's output calibration and validation: (A) – 30-years cumulative incidence, (B) – vaccine- and natural disease- derived waning immunity fractions, (C) – vaccine coverage by dose.

A

B

C
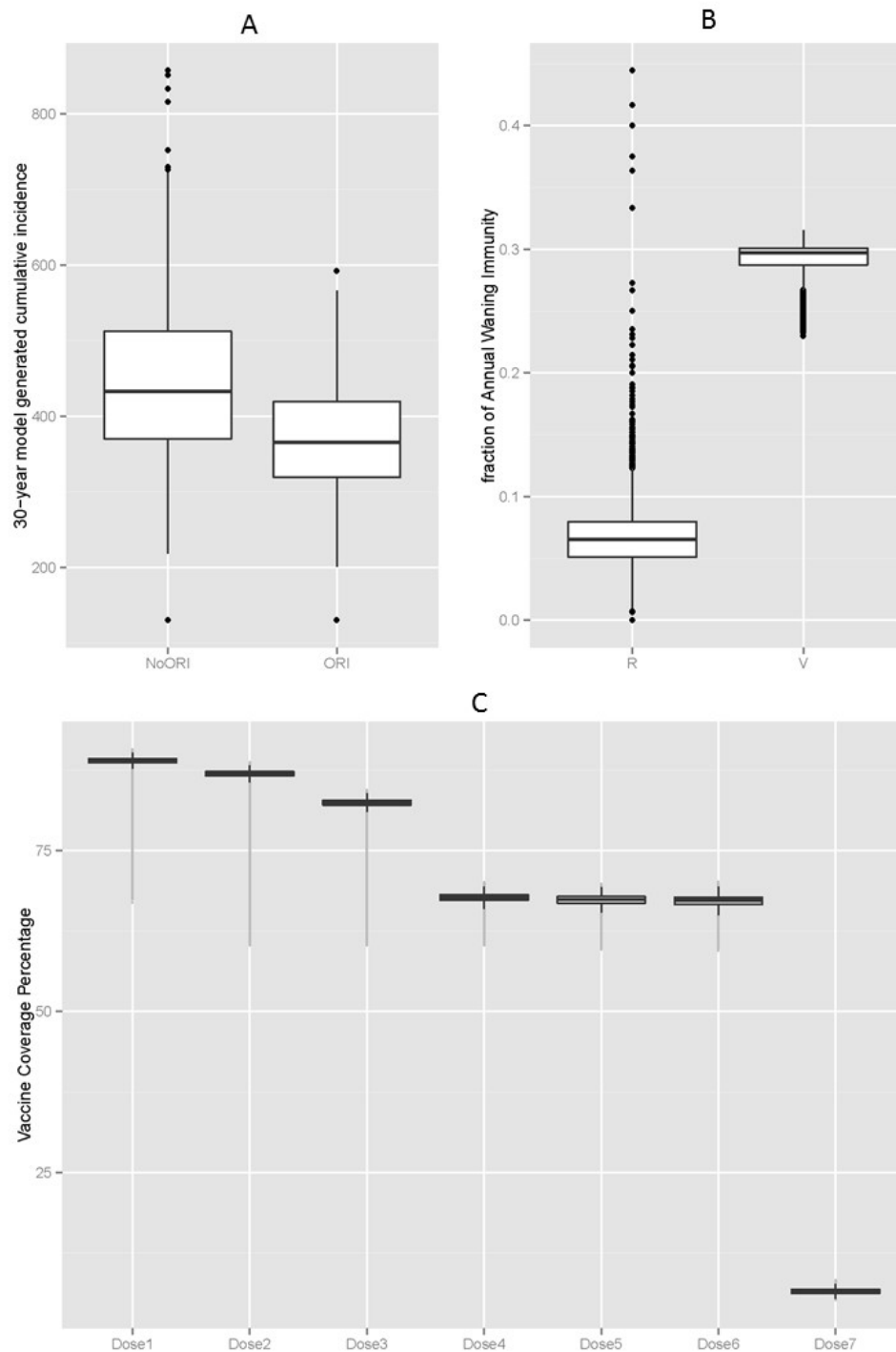
FIGURE 2 – Boxplot of pertussis cases averted over time, up
to 10 years after outbreak response immunization campaign:
All ages (A), infants under 1 year of age (B) and adolescents
10-14 years of age (C)
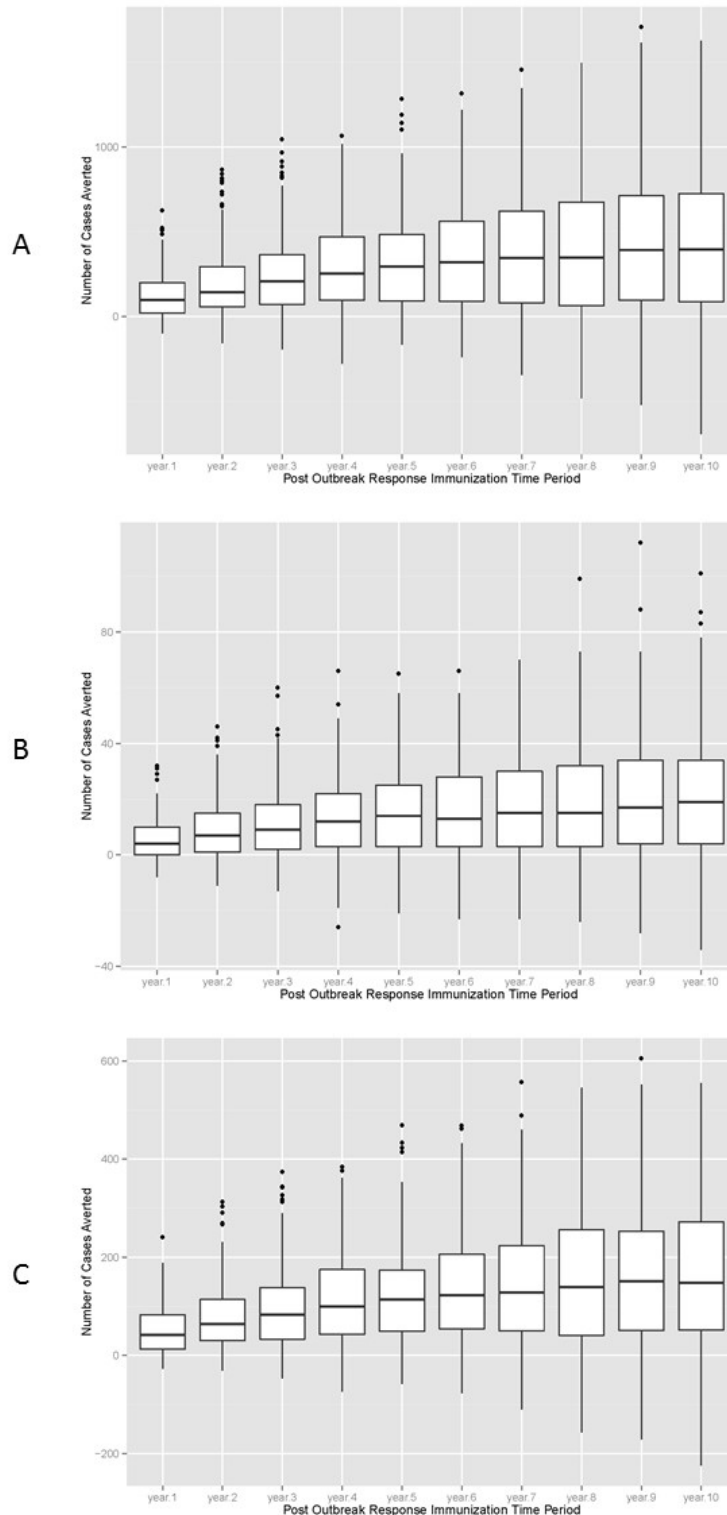
TABLE 2 - Number of pertussis cases averted and numbers needed to vaccinate by time periods after the outbreak-response immunization campaign and by age groups: modeling-generated results

Age groups	Post-outbreak-response immunization period, years	Average number of cases averted*	Minimum number needed to vaccinate§	Maximum number needed to vaccinate§
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

* $p < 0.00001$ for all groups of comparisons of counts of cases in outbreak-response immunization (ORI) versus no-ORI simulations, one-way Mann Whitney U test

§ Number needed to vaccinate (NNV) was calculated directly from the model by dividing a number of vaccinations delivered during the ORI by a number of cases averted in a respective age group. NNV only applies to a current model and for a given population size.