Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Model Description

We formulate an age-structured Susceptible, Infected, Removed (SIR) model for the transmission of *B. pertussis*. In the model, susceptibles are born at rate μ, where 90% are vaccinated with either aP or wP, depending on the the strategy being tested (see main text for description of strategies). To allow for age-specific contact rates, individuals mix according to a contact matrix, C [1]. Unvaccinated individuals are infected at rate β and become symptomatic with probability σ. Symptomatically infected individuals are hospitalized at rate δ, and recover at rate δr, which depends on age (0-5 years, 5-18 years, more than 18 years). Hospitalized infants die at rate ρ. Both asymptomatically and symptomatically infected individuals recover at rate γ. Individuals vaccinated with either aP or wP incur a benefit from vaccination in the form of a reduced β, which is determined by dividing β by the vaccine efficacy values (ve1 − 9). Those vaccinated solely with aP enter a class where they can become asymptomatically infected at rate β, the same rate at which susceptibles become symptomatically infected. On the other hand, individuals vaccinated with the combined strategy can only become asymptomatically infected at rate β/(ve1−9). In the removed class, individuals with natural immunity are subject to waning immunity at rate ωa for adolescents and ωb for adults. Finally, adults age out of the model at rate ν, which is equal to μ.

In the model, the only difference between aP and wP vaccines is that aP allows for asymptomatic infection and wP reduces it. Both vaccines have the same coverage rates, both have the same efficacy and the same rate of waning vaccine induced immunity.

Model Parameterization

We used a mixture of literature values and model fitting to estimate the parameters. Pertussis case counts were obtained from the Centers for Disease Control and Prevention *B. pertussis* surveillance reports for 2012 [2]. All parameters and references are listed in eTable 1. Individuals infected with *B. pertussis* are typically contagious for the first 2 weeks of infection followed by 4-6 weeks of characteristic paroxysmal cough [3, 4], thus we set the duration of infectiousness, γ, to two weeks. The hospitalization rate for infants and children 0-5 years old (δ1) is 60%; for adolescents, 5-18 years old (δ2) is 0.8%; and for adults (δ3) is 3% [5, 6]. The length of hospital stay, δr1, for infants and children is one week, for adolescents, δr2, four days, and for adults, δr3, two days [5, 6]. Finally, the infant death rate, ρ, is 16/100,000. The contact matrix, C, by which individuals in our model interact is based on published mixing patterns of several European countries [1]. The force of infection, β, and the probability of symptomatic infection, σ, are unknown but essential model parameters; thus we conducted a thorough sensitivity analysis for β and σ. In the base case β is set to 6.5×10^{-6} and σ is set to 50%, indicating that half of infected individuals will become symptomatically infected, and the other half will become asymptomatically infected. The birth rate, μ, death rate, ν are set equal to 1/75 years to keep population sizes constant. The total population size, NN, was varied to account for transient, or chaotic effects from 525,350 to 648,775.

There is evidence that immunity to pertussis from vaccination and natural infection wanes over time [7, 8]. However, since the rates at which these types of immunity wane are difficult to determine from epidemiological data [5], our model's estimates for waning natural immunity, ωa for adults and ωb for adolescents, were chosen by hand to fit the data [7]. Interestingly, the values fit were near 0, indicating that the duration of immunity is quite long: for adolescents, ωa is 1/5 years, and for adults, ωb is 1/50 years. In this model, we manifest these waning rates in the form of a weakening vaccine efficacy. The first vaccine, for both the aP and wP strategies, gives a vaccine efficacy of β/ve1 where ve1 equals 1.5. For each vaccine after the first, in both the aP and the wP strategies, vaccine efficacy increases by a factor of ten. For example, after the second vaccine, vaccine efficacy is β/ve2 where ve2 equals 15. After the last vaccine, ve7, which equals 15,000, vaccine efficacy begins to wane. This is accomplished by decreasing ve8 and ve9 by a factor of ten for the adolescent age group and again for the adult age group. These values were chosen to match the proportion infected in the four age classes reported by the CDC [2] (Figure 1).

Sensitivity Analysis: Potential vaccine scare

The potential for a drop in wP vaccine coverage due to an increase in wP-related side-effects is not negligible. Thus, we ran the model with varying levels of wP coverage after the switch. We find reductions in symptomatic cases in all groups besides children 1-6 years old (Figure 3). This is due to a large decrease in the numbers of asymptomatically infected individuals.

Sensitivity Analysis: Changing the Probability of Symptomatic Infection, σ

Since the Probability of Symptomatic Infection, σ, is unknown, in the base case, we set σ to the most agnostic value possible, 0.5. In the sensitivity analysis, though, we verified that the model's conclusions were consistent with other values of σ. We tested σ at vales of 0.25 and 0.75, the results are displayed in Figures 6-7. In both cases each of the other parameters were held constant, and the model was run with a single value of σ over a range of population values. The data was analyzed in the same manner as the base case. For both values of σ the conclusions held. Namely, there were significant decreases in pertussis incidence, hospitalizations, and infant deaths due to pertussis.

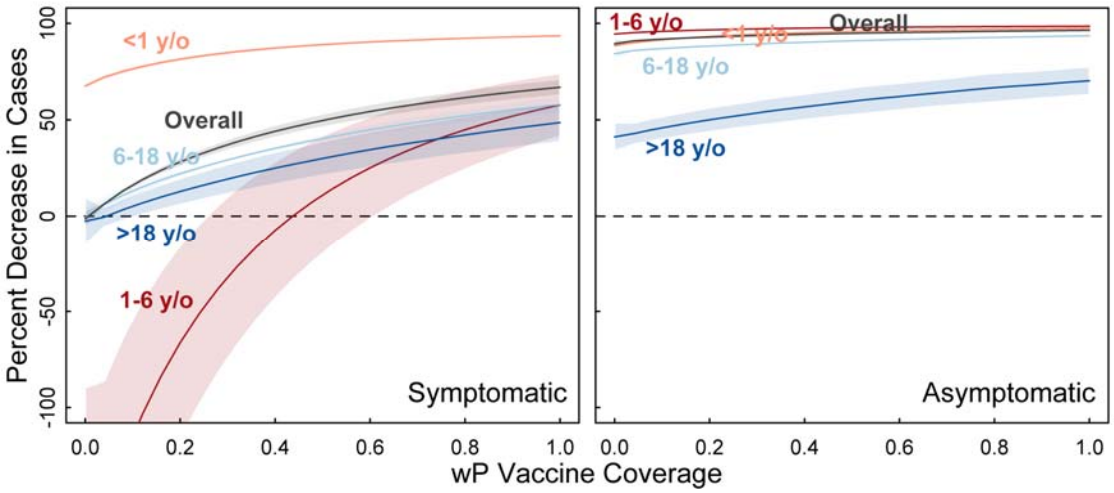
Sensitivity Analysis: Changing the Force of Transmission, β

Next, we tested the model's sensitivity to the force of transmission, β. To do this we picked a single base case with initial population 580,650 and varied β by 0.1×10^{-6} from $\beta = 5.1 \times 10^{-6}$ to 2.0×10^{-5}. We calculated the average rate of infection per 100,000 for each value of β. The results are displayed in Figure 8. For each value of β, there were significant decreases in rates of pertussis incidence.

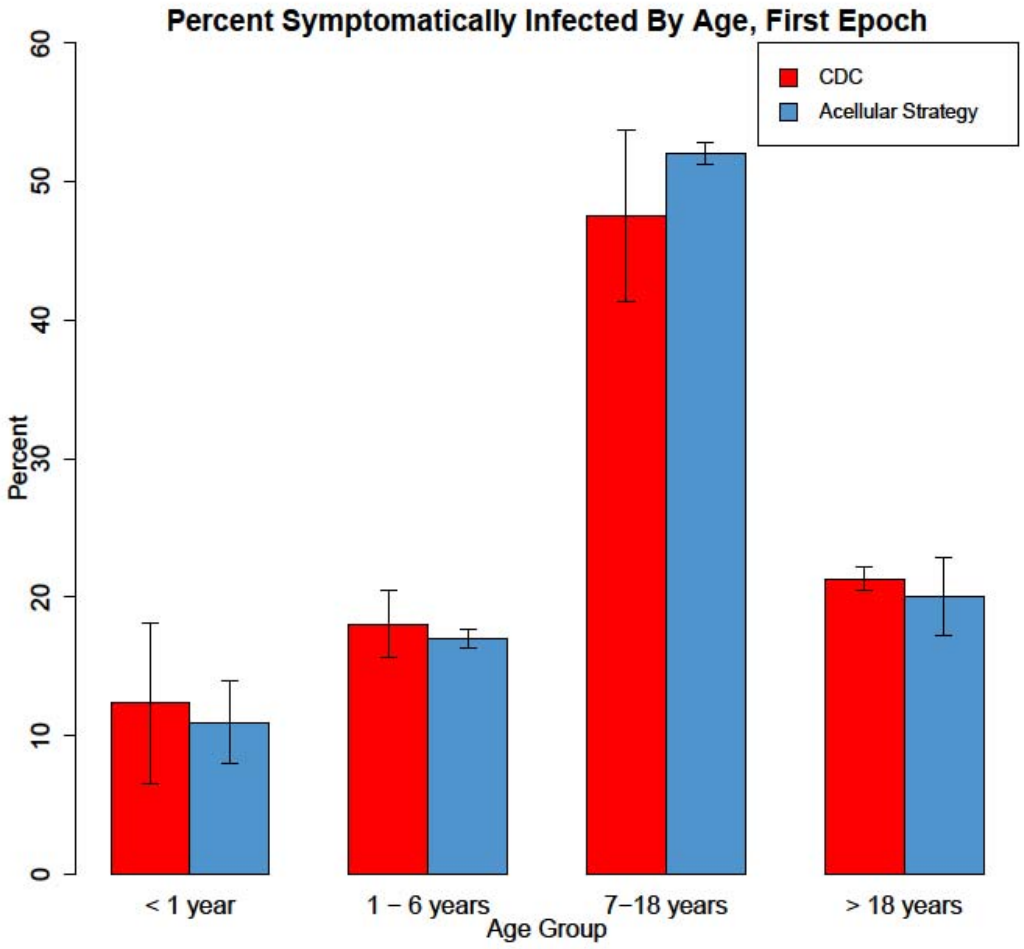
Sensitivity Analysis: No Catch Up Campaign

We considered a combined strategy with no catch up wP vaccine for 5 year old children and the results held. With out the catch up campaign, the combined strategy has fewer vaccine related adverse events but allowed for more asymptomatic and symptomatic infections. In this case, the model predicted an infant rate of symptomatic *B. pertussis* infection of 0.1745 per 100,000 (95% CI: 0.1228, 0.2557), which is a decrease of 91.6% (95% CI: 87.7, 94.0) compared to the acellular strategy. It predicted an average rate of symptomatic infection for all age groups of 3.265 (95% CI: 2.565, 4.139), which is a percent decrease of 82.7% (95% CI:78.3, 86.5) compared to the acellular strategy. The combined strategy without the catch up campaign would cost $4,442 per 100,000 (95% CI: 3,025, 5,859) and would loose 0.12 QALYs per 100,000. This is an 84.6% reduction in QALYs lost and an 90.8% (95% CI: 87.8, 93.7) reduction in costs. As with the base case, the combined strategy without the catch-up campaign provides significant health benefits as well as economic savings.

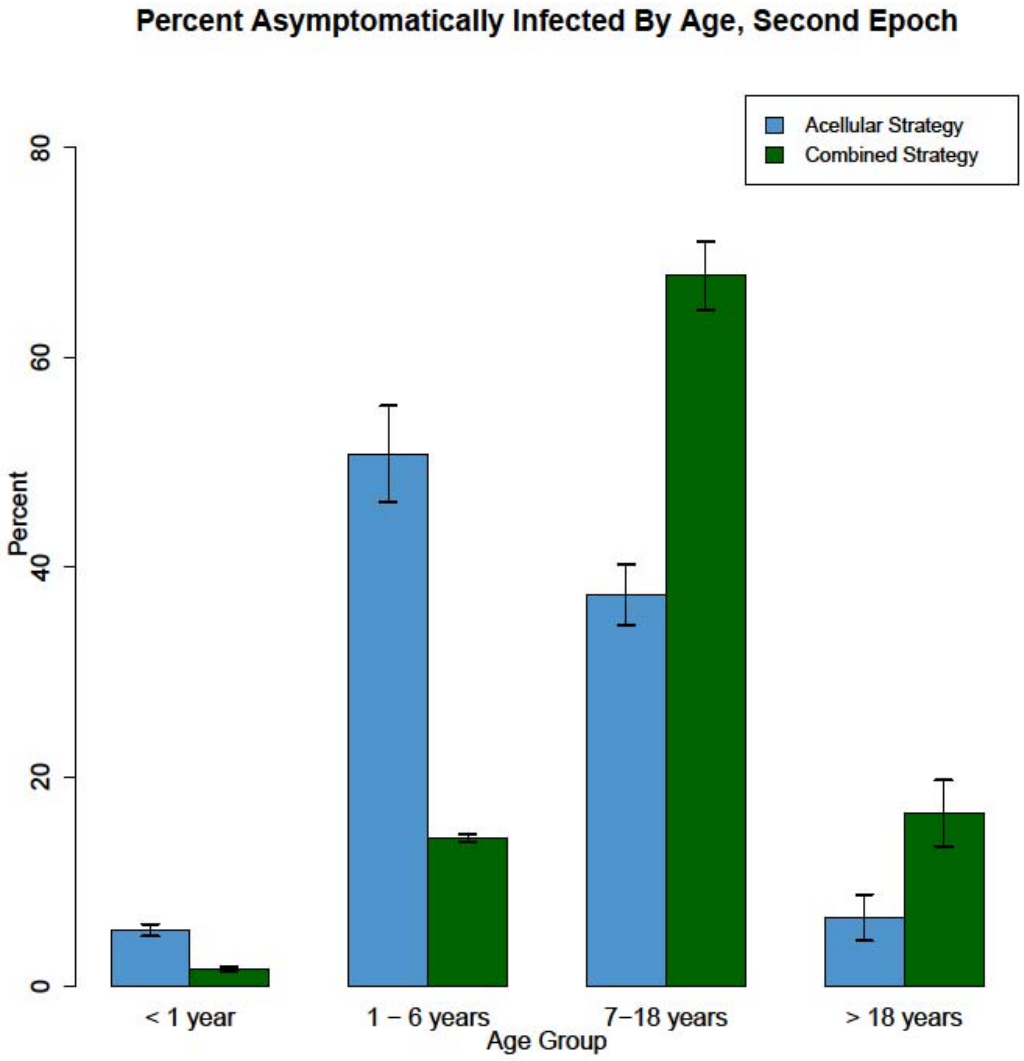
Sensitivity Analyses



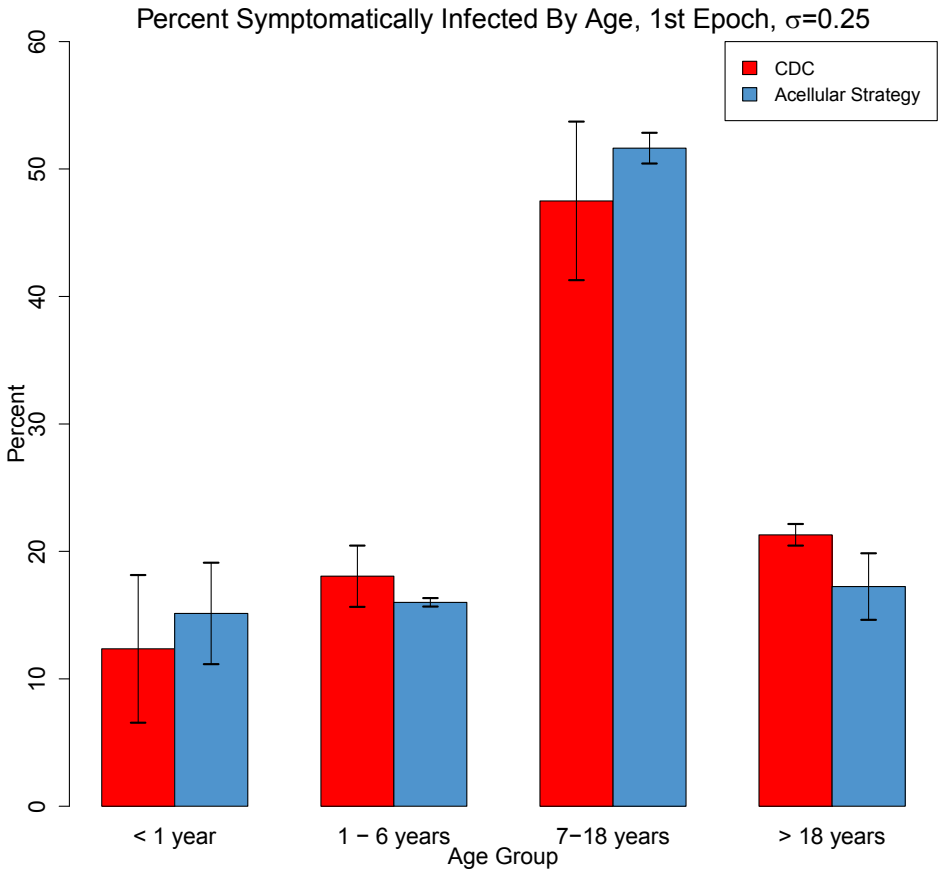
eFigure 1. Potential Vaccine Scare. Figure shows the expected decrease in symptomatic cases by age for varying levels of wP coverage after the switch to the combined campaign. Large decreases in asymptomatic individuals lowers the overall force of infection in the population.



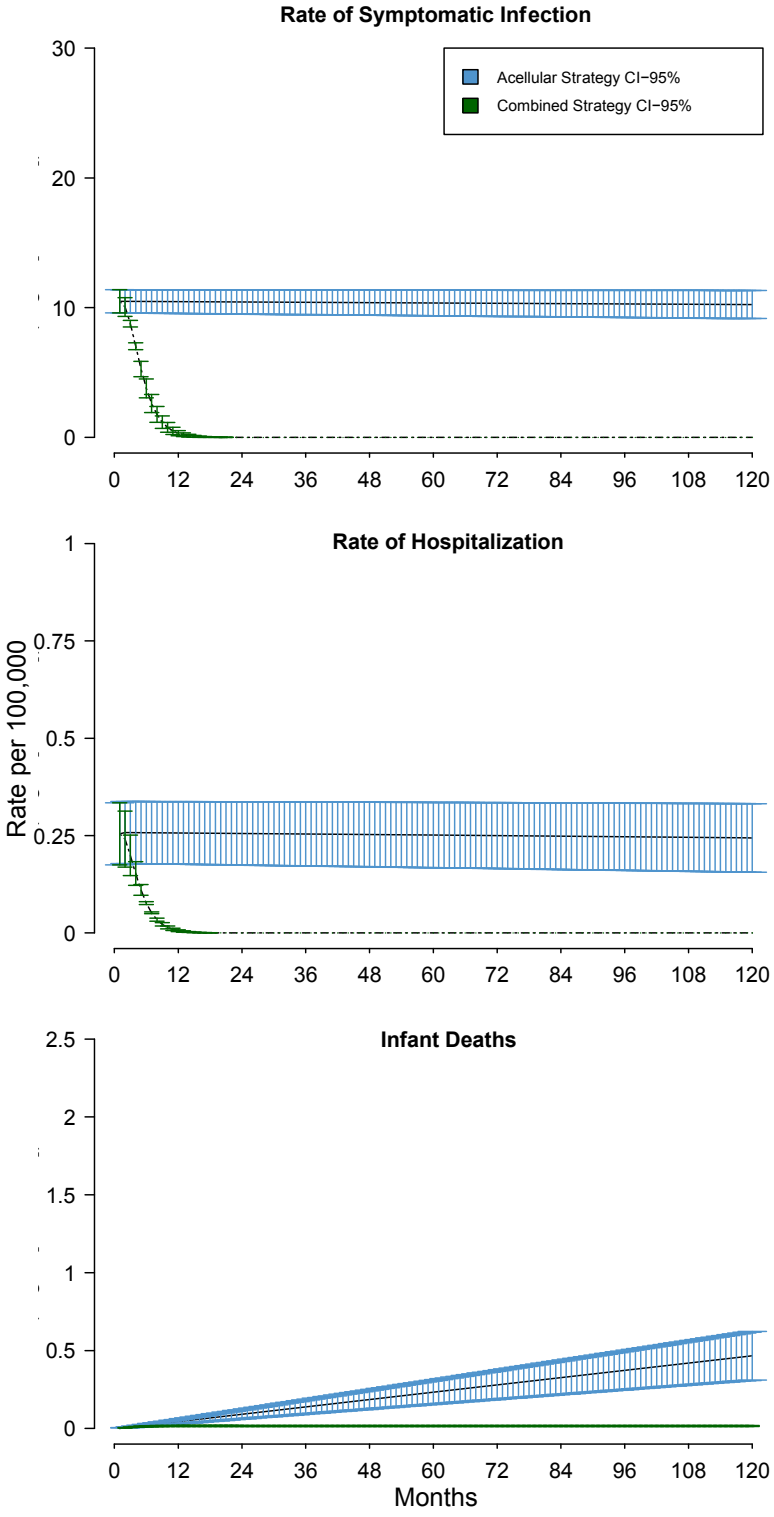
eFigure 2. Breakdown of Symptomatically Infected Individuals According to CDC Data Compared With the σ = 0.5 Model Output After 50 Years in the First Epoch. Data are displayed with 95% confidence intervals.



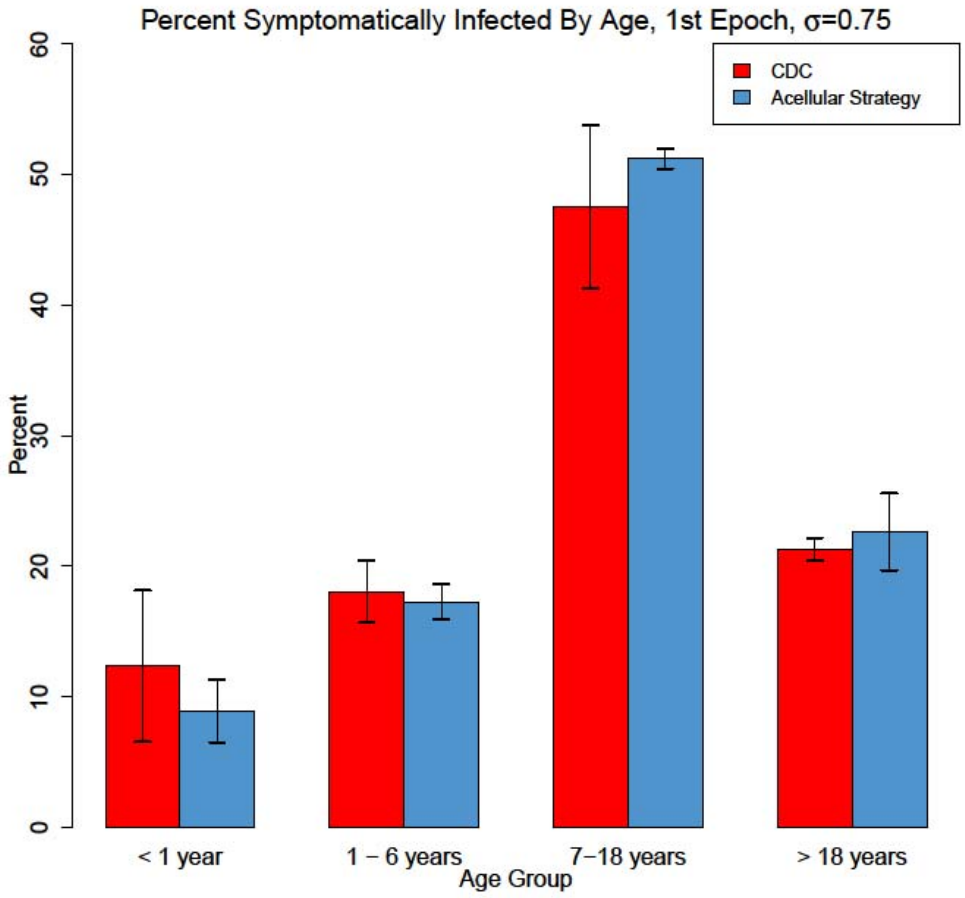
eFigure 3. Breakdown of Asymptomatically Infected Individuals According to Model Output Where σ = 0.50 After 50 Years in the Second Epoch. Data are displayed with 95% confidence intervals



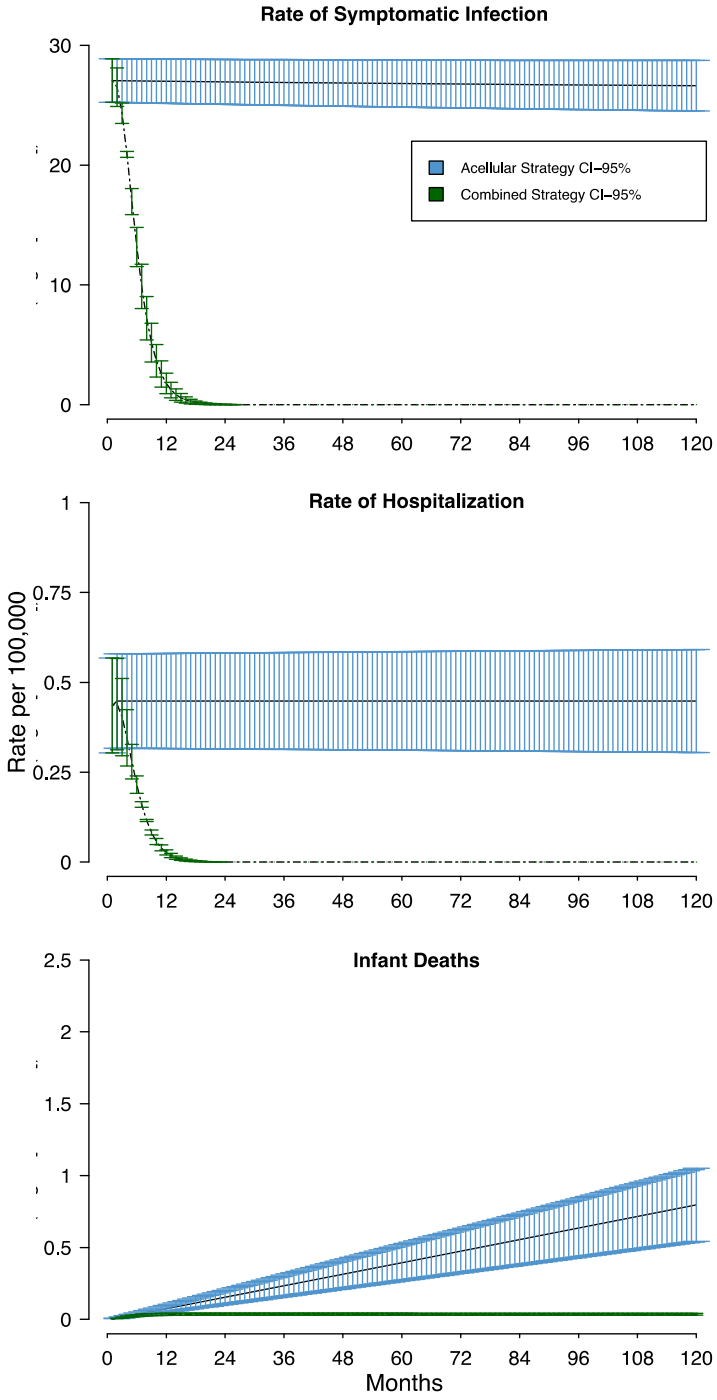
eFigure 4. Breakdown of Symptomatically Infected Individuals According to CDC Data Compared With the σ = 0.25 Model Output After 50 Years in the First Epoch.



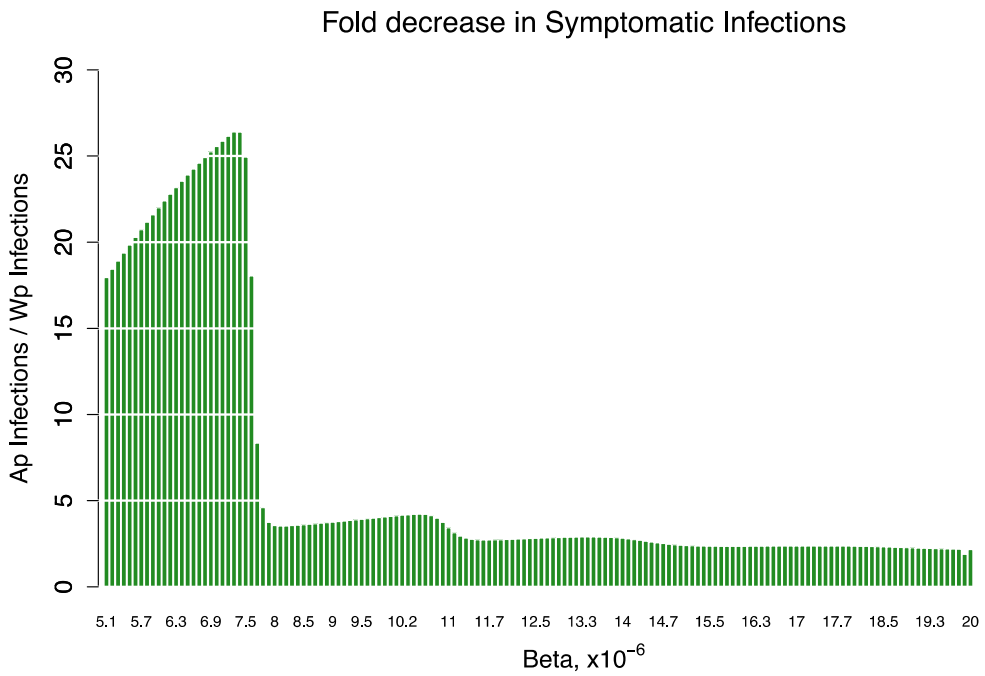
eFigure 5. Estimates for the Rates of Symptomatic Infection, Hospitalizations, and Infant Deaths per 100,000 Total Population During the First 10 Years in the Second Epoch When σ = 0.25.



eFigure 6. Breakdown of Symptomatically Infected Individuals According to CDC Data Compared With the σ = 0.75 Model Output After 50 Years in the First Epoch.



eFigure 7. Estimates for the Rates of Symptomatic Infection, Hospitalizations, and Infant Deaths per 100,000 Total Population During the First 10 Years in the Second Epoch When σ = 0.75.



eFigure 8. Average Rate of Symptomatic Infection Over 10 Years in the Second Epoch When σ = 0.5.

Parameters			
			Source
β	Force of infection	$6.5*10^{-6}$	--
σ	Probability of symptomatic infection	0.5	--
γ	Rate of recovery	2 weeks	[3]
ωa	Rate of waning natural immunity	1/600	--
ωb	Rate of waning natural immunity adults	1/6000	--
μ	Birth rate	1 in 75 yrs	--
ν	Death rate	μ	--
δ1	Rate of hospitalization 0-5 yrs	60%	[6]
δ2	Rate of hospitalization 5-18 yrs	0.8%	[5]
δ3	Rate of hospitalization >18 years	3%	[5]
rδ1	Length of hospitalization 0-5 yrs	7 days	[6]
rδ3	Length of hospitalization 5-18 yrs	4 days	[9]
rδ3	Length of hospitalization >18 years	2 days	[9]
ρ	Infant death rate	16/1000†	[5]
C	Contact matrix	--	[1]
ve1	Vaccine efficacy in 2-4 mo	1.5	--
ve2	Vaccine efficacy in 4-6 mo	15	--
ve3	Vaccine efficacy in 6-8 mo	150	--
ve4	Vaccine efficacy in 8-18mo	150	--
ve5	Vaccine efficacy in 18-24 mo	1,500	--
ve6	Vaccine efficacy in 2-4yrs	1,500	--
ve7	Vaccine efficacy in 4-5yrs	15,000	--
ve8	Vaccine efficacy in 5-18yrs	1,500	--
ve9	Vaccine efficacy in >18 yrs	150	--
NN	Initial population	525,350 - 648,775	--
η	Demographic Adjustment	4	--

eTable 1. Parameters Used in the Base Case. † of hospitalized infants.

eTable 2. Rates of Adverse Events to *B pertussis.* All rates per hospitalized individuals.

	Infants and Children 0-6yrs	Adolescents and Adults	Source
Pneumonia	0.23	0.02	[5]
Seizures	$1.6*10^{-2}$	--	[5]
Encephalopathy	$4.0*10^{-3}$	--	[5]

eTable 3. Rates of Adverse Events to *B pertussis* Vaccines

All rates per vaccinated Individuals

	Rate	Source
Fever		
aP	1/16,000	[10]
wP	1/330	[11]
Persistent, inconsolable crying		
aP	1/1,000	[10]
wP	1/100	[11]
Seizures		
aP	0.5/100,000	[12]
wP	1.7/100,000	[12]
Encephalopathy		
aP	--	--
wP	1/170,000	[13]

eTable 4. Base Case Cost Estimates for Pertussis and Vaccine-Related Side Effects. All costs are adjusted to 2012 U.S. Dollars.

	Age Group				
Cost, $	**Infants <1yr**	**Children 1-6yrs**	**7-18yrs**	**Adults >18**	**Source**
Pertussis Complications					
Hospitalization	4,269	2,085	4,876	7,966	[16]
In addition:					
Pneumonia	2,300	2,300	1,500	1,200	[14]
Seizures	4,700	4,700	3,500	2,400	[14]
Encephalopathy	7,000	7,000	5,800	4,700	[14]
Death	18,200	--	--	--	[15]
Societal cost:	8.3 million	--	--	--	[17]
Vaccine Side Effects					
Fever					
Persistent, inconsolable crying	2,200	2,200	--	--	[13,14]
Seizures	9,100	9,100	--	--	[13,14]
Encephalopathy	16,000	16,000			[13,14]
Societal cost:	24,000	24,000	--	--	[14]

Cost estimates for *B. pertussis* complications and vaccine related adverse events were taken from previously published *B. pertussis* cost-effectiveness analyses [13, 14, 15]. The value of societal cost of death was taken from US Environmental Protection Agency 2014 estimates. . All costs were adjusted to 2012 US dollars.

eTable 5. QALY Disutility Estimates. Disutility= 1–Utility.

	Age Group				
	Infants <1yr	**Children 1-6yrs**	**7-18yrs**	**Adults > 18**	**Source**
Pertussis Complications					
Pertussis infection	0.15	0.26	0.21	0.15	[18]
Hospitalization	0.42	0.37	0.3	0.19	[18]
Pneumonia	0.42	0.37	.33	0.18	[9,19]
Seizures	0.49	0.49	--	--	[9]
Encephalopathy	0.49	0.49	--	--	[9]
Death	1	--	--	--	[20]
Vaccine Side Effects					
Seizures	0.49	0.49	--	--	[9]
Encephalopathy	49	0.49	--	--	[9]

eTable 6. Transmission Model Estimates of Incidence of *B pertussis* in 10 years in the Second Epoch. *All rates are per 100,000 and are listed with 95% confidence intervals.

Incidence Rates					
	Age Group				
	Infants <1yr	**Children 1-6yrs**	**7-18yrs**	**Adults >18**	**Total**
Rate of Infection					
aP strat.	2.074	3.235	9.854	3.758	18.92
95% CI	[2.071, 2.077]	[3.233, 3.237]	[9.845, 9.862]	[3.753, 3.763]	[18.90, 18.94]
comb. strat.	0.087	0.149	0.471	0.178	0.885
95% CI	[.041, .176]	[.073, .292]	[.226, .899]	[.083, .344]	[.428, 1.701]
Percent Decrease	96	95	95	95	95
95% CI	[92, 98]	[91, 98]	[91, 98]	[91, 98]	[91, 98]
Rate of Hospitalization					
aP strat.	0.3449	$2.70 *10^{-3}$	0.0104	0.0075	0.3645
95% CI	[.3434, .3444]	[2.70, $2.70 *10^{-3}$]	[.0104, .0105]	[.0071, .0075]	[.3641, .3651]
comb. strat.	0.0155	$1.286 *10^{-4}$	$5.127 *10^{-4}$	$2.966*10^{-4}$	0.0164
95% CI	[.0071, .0299]	[1.0, $2.0*10^{-4}$]	[.2, $1.0*10^{-3}$]	[1.0, $6.0*10^{-4}$]	[.0076, .0311]
Percent Decrease	96	95	95	96	96
95% CI	[91, 97]	[93, 96]	[90, 98]	[92, 99]	[95, 99]
Infant Death Rate					
aP strat.	$5.554*10^{-3}$	--	--	--	--
95% CI	[1.106, $1.107*10^{-2}$]	--	--	--	--
comb. strat.	$2.230*10^{-4}$	--	--	--	--
95% CI	[1.00, $5.00*10^{-4}$]	--	--	--	--
Percent Decrease	96	--	--	--	--
95% CI	[92, 98]	--	--	--	--

eTable 7. Transmission Model Estimates Incidence of *B pertussis* Complications in 10 Years in the Second Epoch. *All rates are per 100,000, are listed with 95% confidence intervals, and are based on estimates from eTable 6.

Pertussis Complications					
	Age Group				
	Infants <1yr	**Children 1-6yrs**	**7-18yrs**	**Adults >18**	**Total**
Rate of Pneumonia					
aP strat.	0.0791	$6.235*10^{-4}$	$2.097*10^{-4}$	$1.491*10^{-4}$	0.0801
95% CI	[.0790, .0792]	[6.233, $6.238*10^{-4}$]	[2.095, $2.099*10^{-4}$]	[1.466, $1.516*10^{-4}$]	[.07996, .0802]
comb. strat.	$3.555*10^{-3}$	$2.958*10^{-5}$	$1.025*10^{-5}$	$5.933*10^{-6}$	$3.601*10^{-3}$
95% CI	[1.057, 6.052 $*10^{-3}$]	[.9300, $4.987*10^{-5}$]	[.3339, $1.717*10^{-5}$]	[.1610, $1.026*10^{-5}$]	[1.102, 6.099 $*10^{-3}$]
Percent Decrease	95	95	95	96	96
95% CI	[92, 99]	[92, 99]	[92, 98]	[93, 99]	[92, 99]
Rate of Seizures					
aP strat.	$5.502*10^{-3}$	$4.338*10^{-5}$	--	--	$5.5545*10^{-3}$
95% CI	[5.494, 5.551 $*10^{-3}$]	[4.336, 4.339 $*10^{-5}$]	--	--	[5.534, $5.5553*10^{-3}$]
comb. strat.	$2.473*10^{-4}$	$2.058*10^{-6}$	--	--	$2.493*10^{-4}$
95% CI	[.7355, $4.211*10^{-4}$]	[.6469, $3.469*10^{-6}$]	--	--	[.7560, $4.231*10^{-4}$]
Percent Decrease	95	95	--	--	96
95% CI	[92, 99]	[91, 99]	--	--	[92, 99]
Rate of Encephalopathy					
aP strat.	$1.376 * 10^{-3}$	--	--	--	--
95% CI	[1.373, $1.378* 10^{-3}$]	--	--	--	--
comb. strat.	$6.182 * 10^{-5}$	--	--	--	--
95% CI	[.1838, $1.053* 10^{-4}$]	--	--	--	--
Percent Decrease	96	--	--	--	--
95% CI	[92, 99]	--	--	--	--

eTable 8. Transmission Model Estimates Incidence of Pertussis Vaccine Side Effects in 10 Years in the Second Epoch. *All rates are per 100,000 and are listed with 95% confidence intervals.

Vaccine Side-Effects					
	Age Group				
	Infants <1yr	**Children 1-6yrs**	**7-18yrs**	**Adults >18**	**Total**
Persistent, inconsolable Crying					
aP strat.	0.583	5.051	--	--	5.635
95% CI	[.583, .584]	[5.047, 5.056]	--	--	[5.630, 5.640]
comb. strat.	1.602	39.68	--	--	41.28
95% CI	[1.562, 1.640]	[35.97, 43.39]	--	--	[37.58, 44.99]
Percent Increase	175	686	--	--	632
95% CI	[161, 188]	[539, 833]	--	--	[370, 894]
Rate of Fever					
aP strat.	0.036	0.316	--	--	0.352
95% CI	[.036, .036]	[.315, .316]	--	--	[.352, .352]
comb. strat.	0.337	10.28	--	--	10.62
95% CI	[.329, .344]	[9.158, 11.41]	--	--	[9.498, 11.74]
Percent Increase	811	3150	--	--	2917
95% CI	[794, 851]	[2453, 3865]	--	--	[1642, 4180]
Rate of Seizures					
aP strat.	$2.92*10^{-3}$	$2.53*10^{-2}$	--	--	$2.82*10^{-2}$
95% CI	[2.91, $2.92*10^{-3}$]	[2.52, $2.53*10^{-2}$]	--	--	[2.81, $2.82*10^{-2}$]
comb. strat.	$4.76*10^{-3}$	$9.13*10^{-2}$	--	--	$9.61*10^{-2}$
95% CI	[4.605, $4.92*10^{-3}$]	[8.18, $9.76*10^{-2}$]	--	--	[8.98, $10.2*10^{-2}$]
Percent Increase	63	261	--	--	240
95% CI	[53, 74]	[212, 311]	--	--	[152, 333]
Rate of Encephalopathy					
aP strat.	--	--	--	--	--
comb. strat.	$5.78*10^{-4}$	--	--	--	--
95% CI	[5.59, $5.87*10^{-4}$]	--	--	--	--

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