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Epidemiological and Economic Effects of Priming With the Whole-Cell *Bordetella pertussis* Vaccine

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Abstract

IMPORTANCE—Current acellular pertussis vaccines may not protect against transmission of *Bordetella pertussis*.

OBJECTIVE—To assess whether a priming dose of whole-cell pertussis (wP) vaccine is cost-effective at reducing pertussis infection in infants.

DESIGN, SETTING, AND PARTICIPANTS—Mathematical model of pertussis transmission fit to US incidence data in a simulation of the US population. In this simulation study conducted from June 2014 to May 2015, the population was divided into 9 age groups corresponding to the current pertussis vaccination schedule and fit to 2012 pertussis incidence.

INTERVENTIONS—Inclusion of a priming dose of wP vaccine into the current acellular pertussis vaccination schedule.

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MAIN OUTCOMES AND MEASURES—Reductions in symptomatic pertussis incidence by age group, increases in wP vaccine–related adverse effects, and quality-adjusted life-years owing to changing vaccine schedule.

RESULTS—Switching to a wP-priming vaccination strategy could reduce whooping cough incidence by up to 95% (95% CI, 91–98), including 96% (95% CI, 92–98) fewer infections in neonates. Although there may be an increase in the number of vaccine adverse effects, we nonetheless estimate a 95% reduction in quality-adjusted life-years lost with a switch to the combined strategy and a cost reduction of 94% (95% CI, 91–97), saving more than $142 million annually.

CONCLUSIONS AND RELEVANCE—Our results suggest that an alternative vaccination schedule including 1 dose of wP vaccine may be highly cost-effective and ethically preferred until next-generation pertussis vaccines become available.

Since the 1990s, the incidence of *Bordetella pertussis* infection, the primary causative agent of whooping cough, has continued to rise in many industrialized countries,[1,2] despite at least 90% vaccination coverage rates in many countries.[3,4] In 2012, the United States saw 48 277 reported pertussis cases, the highest number since 1955, which included 16 infant deaths.[2] This rise has been widely attributed to the switch from whole-cell pertussis(wP)–derived vaccines to acellular pertussis (aP) vaccines in the mid-1990s. A potential explanatory mechanism that has recently been posited is that aP vaccines protect against whooping cough symptoms, but not against colonization and secondary transmission of the *B pertussis* bacterium.[5,6] This hypothesis implies the existence of a large group of asymptomatically infected transmitters,[7] which would account for the documented failure of cocooning, the vaccination of the close contacts of neonatal infants who are too young to be vaccinated.[8,9] Despite calls for a more efficacious next-generation *B pertussis* vaccine,[10,11] new vaccines are not likely to be licensed in the near future.[12] Here, we consider whether a new interim strategy could minimize *B pertussis* transmission, lower incidence, and avert infant mortality.

Epidemiological studies have followed pertussis infection in cohorts of children born in the mid-1990s, at the time of the switch from the wP to the aP vaccines, who received their first dose of the *B pertussis* vaccine schedule as wP and the remainder of their vaccines as aP.[13–15] These studies found that those individuals who had been primed with wP vaccine had less than half the incidence of whooping cough than those who received the aP vaccines alone.[13–15] Here, we evaluate the effectiveness and cost-effectiveness of priming infants with the wP vaccine, then completing the vaccine series with aP. We developed a dynamic model of *B pertussis* transmission fit to incidence data on whooping cough to determine the expected number of whooping cough cases and vaccine-related adverse events, comparing the status quo of a vaccination series based entirely on the aP vaccine vs a schedule that combines wP and aP vaccines. Using the results from the dynamic model, in conjunction with literature-derived estimates of the health care costs associated with infant mortality, whooping cough complications, and vaccine-associated adverse events, we conducted a cost-effectiveness analysis for the wP-primed strategy as compared with the current aP strategy. We found that priming with a single dose of the wP vaccine, followed by the current aP schedule, would be associated with a reduction in asymptomatic transmission, thereby

averting substantial pertussis-related morbidity and mortality, as well as generating cost-savings sufficient to more than offset a potential increase in adverse vaccine-related events.

Methods

The Model

We assessed 2 vaccination strategies using an age-structured susceptible, infected, removed model for the transmission of *B pertussis*.[7,16] The first strategy is the current US vaccination policy of 5 doses of aP vaccine, given at ages 2 to 4 months, 4 to 6 months, 6 to 8 months, 18 to 24 months, and 4 to 5 years (henceforth referred to as the *aP strategy*).[17] The second strategy consisted of 1 initial priming dose of wP vaccine followed by 4 dosesof aP vaccine at thesamevaccination schedule, combined with a catch-up campaign over 5 years, in which children ages 4 to 5 years are vaccinated with wP vaccine (henceforth referred to as the *combined strategy*). We also explored scenarios without this catch-up campaign, as are reported in eFigure 1 in the Supplement.

Because this was a simulation study fit to publicly available data, no institutional review board approval was necessary. This study was conducted from June 2014 to May 2015.

The model was run for 600 months using the aP strategy to allow the system to reach dynamical equilibrium. At this point, the model matches the breakdown of symptomatic infections among age groups currently seen in the United States (eFigure 2 in the Supplement).[2] These equilibrium values were then used as initial values in the second epoch, in which the 2 vaccine strategies were compared.

Full model description and details on parameterization are given in the eAppendix and eTable 1, eTable 2, eTable 3, eTable 4, and eTable 5 in the Supplement.

Health Outcomes

We considered 2 types of age-stratified health outcomes: disease from *B pertussis* infection and adverse events in response to wP and aP vaccination. Disease outcomes included moderate infection (including those with paroxysmal episodes, vomiting, exhaustion, and low-grade fever from pertussis who reported their illness to a clinician[18]) and severe infection (those hospitalized for their infection, experiencing pneumonia, seizures, encephalopathy, or death). We did not account for underreporting or misclassification bias; however, we examined reductions in symptomatic incidence, which, even if misdiagnosed as pertussis, would still be treated and incur societal cost. Adverse events in response to wP and aP vaccination included fever, inconsolable crying, seizures, and encephalopathy. Local reactions and rashes have also been documented but were not included because they are both minor and difficult to quantify. We also excluded events too rare to have reliable incidence rates (ie, permanent brain damage owing to a lack of causal association with wP vaccination[17,19,20]). Adverse events following aP vaccination are based on data for the diphtheria, tetanus, and acellular pertussis vaccine, which is currently in use in the United States, whereas adverse events following the wP vaccine are based on data for the diphtheria, tetanus, and whole-cell pertussis vaccine, which was replaced by the diphtheria, tetanus, and acellular pertussis vaccine in the 1990s (eTable 3 in the Supplement).

Economic Inputs

Direct and indirect costs for *B pertussis* infection, complications, and vaccine-related adverse events were parameterized from published and publicly available sources and adjusted to 2012 US dollars (detailed in the eAppendix and eTable 4 in the Supplement). Hospital cost data were obtained from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project's Nationwide Inpatient Sample database[21] and the US Census Bureau. The Nationwide Inpatient Sample is a nationally representative hospital-stratified sample of hospital discharges per year. Patients diagnosed as having pertussis were identified in the Nationwide Inpatient Sample as having *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 033.0, 033.8, 033.9, or 484.3 as one of the first 15 diagnoses recorded (ie, principal diagnosis and as many as 14 secondary diagnoses). We calculated population-adjusted costs of pertussis hospitalization as the median hospital charge per pertussis hospitalization divided by the cost-to-charge ratio for that hospital obtained from the Healthcare Cost and Utilization Project. Hospitalization costs were adjusted to 2012 US dollars. We did not account for the dollar costs associated with ambulatory visits, which may be substantial, thus our estimates are conservative. We did account for reductions in quality-adjusted life-years (QALYs) lost.

Costs were applied to the corresponding outcomes projected for the different vaccination strategies. For example, the aP rate of hospitalized infants per 100 000 population was multiplied by the cost of hospitalizing an infant owing to *B pertussis*. This gives the cost of hospitalizing infants per 100 000 population for the aP strategy. This value can then be compared with the cost of hospitalizing infants per 100 000 population for the combined strategy. Costs from all outcomes are summed to give the total cost per 100 000 for each strategy, allowing direct cost comparison of strategies.

Quality-Adjusted Life-Years

To evaluate the health effect of pertussis disease and adverse vaccine-related events, we used QALYs. Disutility values— preference-based weights that measure from 0 to 1 the relative disutility of specific outcomes—were based on published literature (eTable 5 in the Supplement).[18,22–24] Individuals with moderate *B pertussis* symptoms experience disutility for 8 weeks. Individuals with severe *B pertussis* infection incur severe, hospitalizable symptoms for their duration of hospital stay followed by 6 weeks of moderate pertussis symptoms. This model does not consider mild *B pertussis* cases because mild cases tend to be unreported. The duration of other *B pertussis* complications, pneumonia, and seizures correspond to the duration of hospitalization. Because encephalopathy has residual effects, disutility incurs at time of infection and is discounted for the rest of the individual's lifespan. Because we only considered infant death, we assumed 77 years were lost.[25] Vaccine-related seizures and encephalopathy were assumed to have the same disutility and duration as pertussis-induced seizures and encephalopathy.

Results

Base Case

The combined strategy is predicted to be associated with a reduction in the rate of symptomatic pertussis infections, hospitalizations, and infant deaths (Figure 1, Table 1, and eTable 6, eTable 7, and eTable 8 in the Supplement). Compared with the aP strategy, the combined strategy would be predicted to achieve a 95% reduction (95% CI, 91–98) in symptomatic infections, and, importantly, a 96% reduction (95% CI, 92–98) in symptomatic infections in infants (Table 1).

The combined strategy was also predicted to generate a shift in the age distribution of asymptomatic infection, with a 69% decrease (95% CI, 69–70) in asymptomatic infections in infants aged 0 to 1 year, a 72% decrease (95% CI, 70–74) in children aged 1 to 6 years, and a 81% increase (95% CI, 76–87) in adolescents (eFigure 3 in the Supplement). Thus, the combined strategy is effective in preventing both symptomatic and asymptomatic infections in children and infants—the groups with the highest contact rates and at greatest risk for severe disease outcomes. Consequently, the combined strategy leads to substantial reductions in serious complications arising from *B pertussis* infection. Particularly important is the 96% decrease (95% CI, 91–97) in the rates of hospitalization and the 96% decrease (95% CI, 92–98) in deaths among infants younger than 1 year. These rates also saw a reduction in children, adolescents, and adults (Table 1).

Regarding adverse events related to vaccination, the combined strategy's rates of fever showed a 2917% increase (95% CI, 1642–4180) over the aP strategy and wP rates of seizures showed a 240% increase (95% CI, 152–333) over the aP rates, although the absolute increases were low (10.3 per 100 000 for fever and 0.07 per 100 000 for seizures). Additionally, the combined strategy is predicted to cause a rate of encephalopathy of 5.78×10^{-4} (95% CI, 5.59×10^{-4} to 5.87×10^{-4}) per 100 000 total population (Table 1). Despite the higher rates of adverse events, the combined strategy revealed a 96% decrease (95% CI, 95–99) in overall hospitalizations due to either *B pertussis* infection or vaccine-related adverse events, including pneumonia, seizures, and encephalopathy (Figure 2).

Economic Effect

The combined strategy would reduce disease-related hospitalization costs by 96% (95% CI, 93–98) compared with the aP strategy (Table 2). The economic costs associated with pertussis death would be reduced by 96% (95% CI, 93–99). However, hospital costs for treating vaccine adverse events would more than double (244% increase; 95% CI, 223–264). Considering all 3 components, the aP strategy would overall cost $48 310 per 100 000 population (95% CI, 48 290–48 330), while the combined strategy would overall cost only $2822 per 100 000 population (95% CI, 1395–4248). Consequently, the combined strategy could achieve a 94% cost-savings (95% CI, 91–97) compared with the current strategy. This translates to roughly $142 million per year in the United States.

Quality-Adjusted Life-Years

Quality-adjusted life-year loss from pertussis disease would be 0.58 QALYsper 100 000 individuals for the aP strategy and 0.02 QALYs per 100 000 individuals for the combined strategy (Table 3). Quality-adjusted life-year loss due to vaccine-related adverse events is predicted to be 2.6×10^{-4} per 100 000 for the acellular strategy and 9.4×10^{-3} per 100 000 for the combined strategy. On balance, the current acellular strategy incurs a total loss of 0.80 QALYs per 100 000 people, where the combined strategy predicts a total loss of only 0.04 QALYs per 100 000 people. This is a 95% decrease in total loss of QALYs with the combined strategy.

Sensitivity Analyses

As the probability of symptomatic infection (σ) is unknown, we set the base case to $\sigma = 0.5$ and tested the model at $\sigma = 0.25$ and $\sigma = 0.75$. Our finding that the combined strategy exhibited fewer infections, hospitalizations, adverse events, and deaths due to *B pertussis* is robust to this variation in the probability of symptomatic infection (eFigure 4, eFigure 5, eFigure 6, and eFigure 7 in the Supplement). We also conducted a sensitivity analysis for the force of infection (β). The model was run for 150 different β values (eFigure 8 in the Supplement). Throughout this variation, the combined strategy was predicted to cause fewer infections, hospitalizations, adverse events, and deaths. We conducted analyses without the catch-up campaign, which averted fewer pertussis incidences, QALYs, and costs than when the combined strategy is supplemented with a catch-up campaign. Finally, we explored a scenario where the rise in wP vaccine adverse events caused the wP vaccination rate to drop (eFigure 1 in the Supplement). This shows a decrease in both asymptomatic and symptomatic infections for all age classes when rates are greater than 50%.

Discussion

We evaluated the cost-effectiveness of an alternative pertussis vaccination schedule that incorporates 1 dose of wP vaccine, a strategy that increases vaccine effectiveness but also increases the risk for vaccine-related adverse events. Our dynamic transmission model was parameterized with empirical data from the United States. Despite the increase in vaccine-related adverse effects, we found a substantial net benefit to wP vaccination through reduced transmission of *B pertussis*. Specifically, the model predicted that the combined strategy would reduce QALY loss by 95% and reduce costs by 94%. These results suggest that the combined strategy is both an epidemiologically favorable and an economically viable alternative to aP vaccination.

The World Health Organization reports that adverse reactions to wP vaccination increase with age and the number of injections,[26] but it has not been determined which of these 2 confounded factors plays the more significant causative role. Because the combined strategy involves the administration of only 1 wP vaccine, the rates of wP adverse events that we assumed are likely overestimates, as our model was parameterized from the empirical estimates for adverse events related to vaccination based on regimens that involved multiple doses of wP vaccine. Consequently, our results with regard to the risk for increased adverse events are conservative. Furthermore, we highlight that despite the increased reactogenicity,

the World Health Organization recommends wP vaccines for infant pertussis immunization worldwide.[27]

There were some limitations to this study. As with any analysis, we made some simplifying assumptions in the absence of empirical data. We assumed that the transmissibility of asymptomatic infection was the same as that for symptomatic infection. Although asymptomatic individuals may shed less bacteria, they would be more likely to be active and expose more people to potential transmission. Additionally, we assumed that the rates of waning natural immunity in adolescents and adults were the same for symptomatic and asymptomatic infections. Both of these assumptions underestimate pertussis disease burden and are, therefore, conservative with regard to our findings. Owing to the nature of asymptomatic infection, studying and determining rates of asymptomatic pertussis infections is challenging without detailed serosurveys and/or immunological studies of household transmission.

We found that the rates of waning immunity, albeit low, are crucial to accurate fitting of the model to epidemiological data on age-specific incidence. Specifically, when waning is not considered, the model predicts almost no cases of pertussis in adolescents and adults. The necessity of incorporating waning immunity to generate an accurate fit to the incidence data underscores its importance to the epidemiological dynamics of pertussis.[28,29] Further research on waning immunity is needed to formulate more accurate models.

This study did not consider adolescent and adult boosting doses, as currently recommended by the Advisory Committee on Immunization Practices. Previous work has indicated that children initially vaccinated with aP do not have elevated T-cell responses after aP vaccination or natural boosting. On the other hand, those primed with wP vaccine do.[30] This would indicate that the combined wP-aP strategy explored here might be even more effective when considering adolescent and adult boosting, although more study of the Th17 response induced by wP and boosted by aP vaccination is needed.[31] We found an 81% increase in adolescent infections under the combined strategy, but inclusion of a booster may lessen this increase.

Finally, this model did not consider the current recommendation of vaccinating pregnant women with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.[32] The practice gives newborns transient passive protection against *B pertussis* infection for up to 8 weeks.[33] Several studies have verified the safety and effectiveness of maternal vaccination.[33–35] As maternal vaccination rates increase and cases in infants drop, the absolute number of pertussis cases averted by a switch from aP to the combined strategy would also be lower. However, as the benefits of maternal vaccination with aP do not have a large population level effect beyond the mother and infant,[36] our qualitative insight that a switch from aP to the combined strategy is likely to produce both health and economic benefits would not change.

The ethical implications of our results demand careful consideration. By switching to the combined strategy, the US population could avert 10.5 per 100 000 QALY loss over 10 years and reduce infant mortality from pertussis by 96%. On these grounds alone—and without

considering cost-savings—the combined strategy proves to be a much safer alternative than the current vaccine. Of course, rigorous clinical trials for safety and efficacy would be needed before recommendations could be made to support a change in the vaccine schedule. Conducting these studies (or studies for any new pertussis vaccines, for that matter) may be difficult to conduct in the United States where aP vaccines are already recommended for all children. Novel designs or surrogate end points for vaccine efficacy (protection in nonhuman animals, such as baboons; serologic data showing higher and more persistent antibody titers; or human challenge in adults with circulating strains of *B pertussis*) will likely have to be used to achieve regulatory approval.[37] Safety will be the most important consideration, with large enough study sample sizes necessary to observe adverse events. Fortunately, previously licensed wP vaccines with well-known safety profiles could be used in determining study design and in power calculations. Finally, in light of the public concerns regarding vaccine safety, care must be taken when introducing a vaccine schedule that may have increased risks for adverse events. Clear and transparent articulation of the risks and benefits of all recommended vaccine schedules to parents of newborns is essential. In this case, while the individual risk for adverse events may be higher, there are even greater individual- and population-level benefits to be realized by a switch from aP to a combined strategy, in terms of improved herd immunity and a direct immunological benefit.[13–15] A drop in coverage may still be expected, despite public education and outreach. We have shown that the combined strategy remains an effective alternative to aP even if vaccination coverage drops to 50%.

Conclusions

Although new pertussis vaccines combining the safety of aP and the efficacy of wP are in early development, such a novel vaccine is still a number of years away from regulatory approval and implementation.[12] In the interim, switching to the combined strategy is an effective option for reducing the disease and mortality burdens of *B pertussis*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Can a priming dose of the adverse effect–prone whole-cell pertussis (wP) vaccine in the current vaccination schedule cost-effectively reduce pertussis incidence?

Findings

This simulation study uses a mathematical model fit to observed pertussis incidence in the United States and found that switching to a wP vaccination strategy could reduce whooping cough incidence by up to 95%, including 96% fewer infections in neonates. While this will be associated with an increase in vaccine-related adverse effects, the model estimates a 95% reduction in quality-adjusted life-years lost with a switch to the combined strategy.

Meaning

Inclusion of a priming dose of wP could substantially reduce pertussis incidence and save more than $142 million annually.

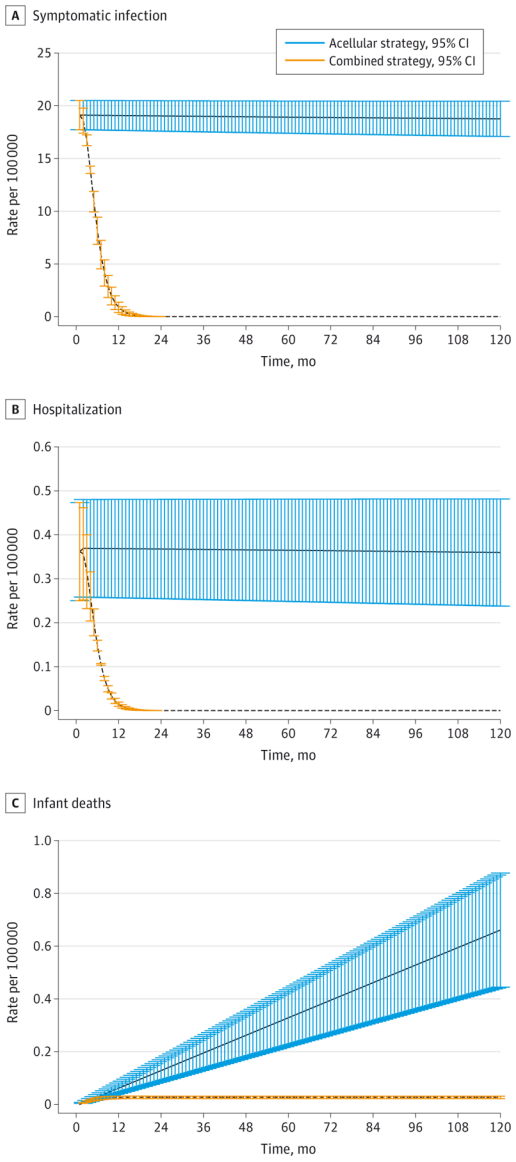

Figure 1. Base Case Results

Base case estimates for the rates of symptomatic infection (A), hospitalizations (B), and infant deaths (C) per 100 000 total population during the first 10 years in the second epoch. Parameters are given in the Supplement.

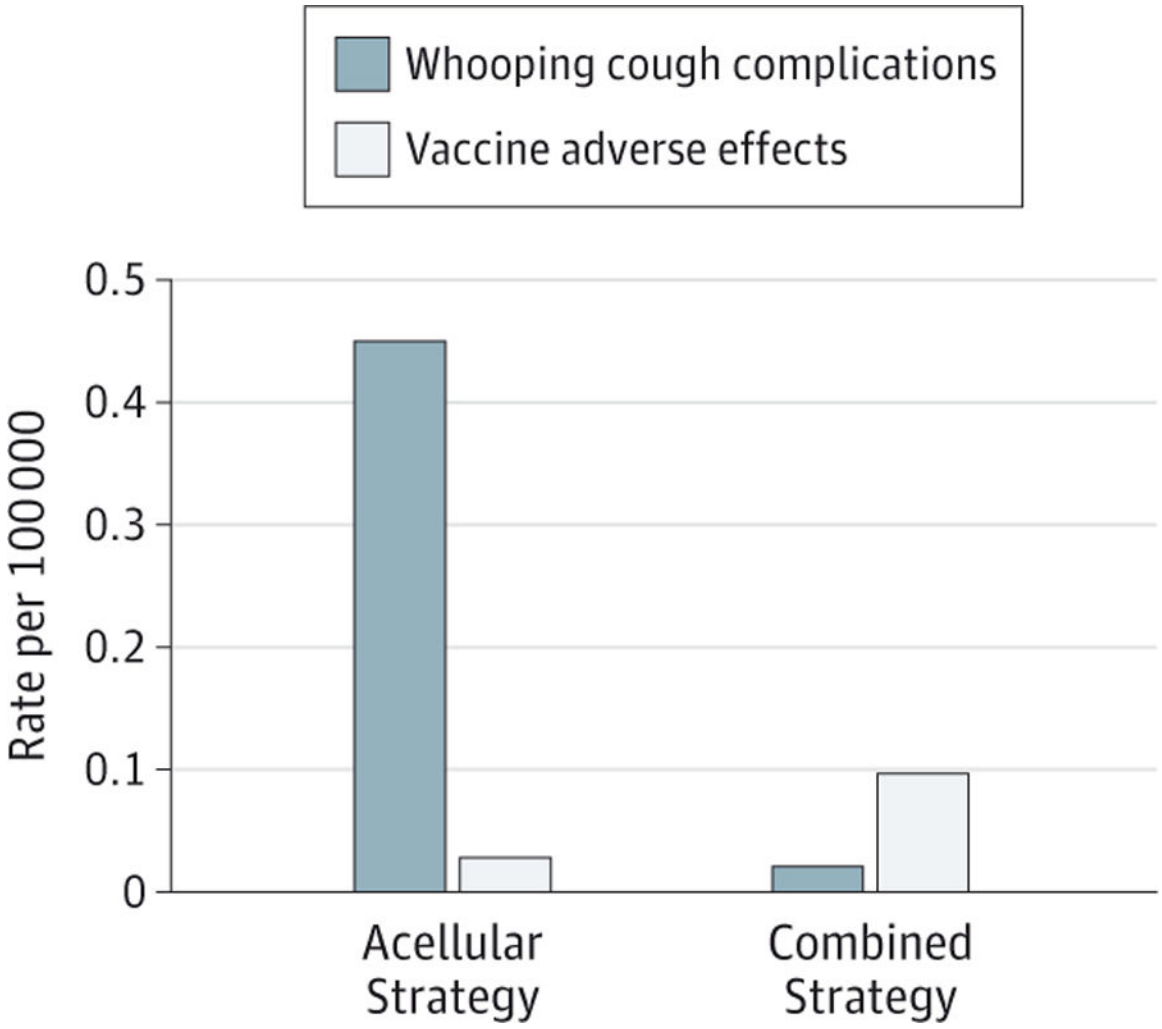

Figure 2. Total Hospitalizable *Bordetella pertussis*–Related Adverse Events

Whooping cough complications include hospitalizations, pneumonia, seizures, and encephalopathy; vaccine adverse effects include seizures and encephalopathy. Parameters are given in the Supplement.

Table 1.

Transmission Model Estimates of Pertussis Incidence, Complications, and Vaccine-Related Adverse Effects 10 Years Into the Second Epoch

	Age Group, y				
Characteristic	**<1**	**1–6**	**7–18**	**>18**	**Total**
B pertussis incidence, % decrease (95% CI)					
Infection	96 (92–98)	95 (91–98)	95 (91–98)	95 (91–98)	95 (91–98)
Rate of hospitalization	96 (91–97)	95 (93–96)	95 (90–98)	96 (92–99)	96 (95–99)
Infant death rate	96 (92–98)	NA	NA	NA	NA
B pertussis complications, % decrease (95% CI)					
Rate of pneumonia	95 (92–99)	95 (92–99)	95 (92–98)	96 (93–99)	96 (92–99)
Rate of seizures	95 (92–99)	95 (91–99)	NA	NA	96 (92–99)
Rate of encephalopathy	96 (92–99)	NA	NA	NA	NA
Vaccine-associated adverse effects, % increase (95% CI)					
Persistent, inconsolable crying	175 (161–188)	686 (539–833)	NA	NA	632 (370–894)
Rate of fever	811 (794–851)	3150 (2453–3865)	NA	NA	2917 (1642–4180)
Rate of seizures	63 (53–74)	261 (212–311)	NA	NA	240 (152–333)
Rate of encephalopathy	5.78×10^{-4} ($5.59–5.87 \times 10^{-4}$)	NA	NA	NA	NA

Abbreviations: aP, acelullar pertussis; *B pertussis*, *Bordetella pertussis*; NA, not applicable.

Table 2.

Cost of *Bordetella pertussis* Infection Complications and Pertussis Vaccine Adverse Effects

	Cost per 100 000 (95% CI), $[a]		
Variable	**Acellular Strategy**	**Combined Strategy**	**Change, %**
Pertussis complications			
Hospitalization	1584 (1582–1587)	71.12 (24.69–117.5)	96 (93–98)[b]
Pneumonia	194.4 (194.1–194.7)	8.74 (2.667–14.82)	94 (92–99)[b]
Seizures	26.98 (26.94–27.02)	1.213 (0.3678–2.059)	96 (92–99)[b]
Encephalopathy	9.629 (9.615–9.643)	0.4328 (0.1287–0.7369)	96 (92–99)[b]
Death	135.2 (135.1–135.2)	5.427 (1.251–9.603)	96 (93–99)[b]
Societal cost	46 100 (46 080–46 120)	1850 (426.6–3275)	96 (93–99)[b]
Total	48 050 (48 030–48 070)	1938 (512.7–3363)	96 (93–99)[b]
Vaccine adverse effects			
Seizures	256.3 (256.1–256.6)	874.5 (817.0–932.0)	241 (218–331)[c]
Encephalopathy	NA	9.25 (9.02–9.49)	NA
Total	256.3 (256.1–256.6)	883.8 (826.3–941.3)	244 (223–264)[c]
Total costs	48 310 (48 290–48 330)	2822 (1395–4248)	94 (91–97)[b]

Abbreviation: NA, not applicable.

[a] All costs are adjusted to 2012 US dollars.

[b] Indicates a decrease.

[c] Indicates an increase.

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Table 3.

QALYs Lost to Pertussis Infections, Complications, and Vaccine Adverse Effects per 100 000 Total Population

Variable	Acellular Strategy	Combined Strategy	Change, %
Pertussis infections	0.58	0.02	96[a]
Hospitalization	9.2×10^{-3}	4.2×10^{-4}	95[a]
Pertussis complications	2.1×10^{-2}	9.4×10^{-4}	96[a]
Death	0.33	0.01	96[a]
Vaccine adverse effects	2.6×10^{-4}	9.4×10^{-3}	3500[b]
Total	0.80	0.04	95[a]

Abbreviation: QALY, quality-adjusted life-year.

[a]Indicates a decrease.

[b]Indicates an increase.