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Economic impact of implementing decennial tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccination in adults in the United States

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ABSTRACT

Background: In the United States, persons ≥11 years are recommended to receive one dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine, followed by decennial tetanus- and diphtheria-toxoid (Td) boosters. Many providers use Tdap instead of Td. We evaluated epidemiologic and economic impacts of replacing Td boosters with Tdap.

Methods: We used a static cohort model to examine replacing Td with Tdap over the lifetime of 4,386,854 adults ≥21 years. Because pertussis is underdiagnosed and true incidence is unknown, we varied incidence from 2.5 cases/100,000 person-years to 500 cases/100,000 person-years. We calculated vaccine and medical costs from claims data. We estimated cost per case prevented and per quality-adjusted life year (QALY) saved; sensitivity analyses were conducted on vaccine effectiveness (VE), protection duration, vaccine cost, disease duration, hospitalization rates, productivity loss and missed work. We did not include programmatic advantages resulting from use of a single tetanus-toxoid containing vaccine.

Results: At lowest incidence estimates, administering Tdap resulted in high costs per averted case ($111,540) and QALY saved ($8,972,848). As incidence increased, cases averted increased and cost per QALY saved decreased rapidly. With incidence estimates of 250 cases/100,000 person-years, cost per averted case and QALY saved were $984 and $81,678 respectively; at 500 cases/100,000 person-years, these values were $427 and $35,474. In multivariate sensitivity analyses, assuming 250 cases/100,000 person-years, estimated cost per QALY saved ranged from $971 (most favorable) to $217,370 (least favorable).

Conclusions: Our findings suggest that replacing Td with Tdap for the decennial booster would result in high cost per QALY saved based on reported cases. However, programmatic considerations were not accounted for, and if pertussis incidence, which is incompletely measured, is assumed to be higher than reported through national surveillance, substituting Tdap for Td may lead to moderate decreases in pertussis cases and cost per QALY.

1. Introduction

Since the 1980s, there has been an overall increase in reported pertussis cases, especially among adolescents and adults [1,2]. Improved diagnosis and reporting and waning of pertussis protection from acellular vaccines, introduced in the 1990s to replace whole cell vaccines, are among factors that contributed to the rise in reported pertussis cases.

Although fatalities resulting from pertussis are rare among adolescents and adults, high costs can result from medical visits and missed work. In addition, adolescents and adults serve as the source of transmission to infants too young to have received their full pertussis immunization series and in whom there is a higher risk of adverse outcomes from pertussis infection, including hospitalization and death [1].

In 2005, the Advisory Committee on Immunization Practices (ACIP) recommended a single dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine for all adolescents aged 11–18 (preferred at 11–12 years) and for adults aged 19–64 years who have not yet received a Tdap dose. This recommendation was expanded to adults ≥ 65 years of age in

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2012 [3]. After receipt of a single dose of Tdap, non-pregnant adults are recommended to receive a dose of tetanus toxoid and reduced diphtheria toxoid (Td) vaccine every 10 years to maintain protection against tetanus and diphtheria [1].

Clinical trial data of a second dose of Tdap administered at 5- or 10-year intervals suggest that the immune response generated is similar to that generated by the initial dose, and there were no unexpected safety concerns [4–10]. Current ACIP recommendations indicate there is no minimum interval required between the most recent Td vaccination and Tdap vaccination [1]. Since 2012, ACIP has recommended that pregnant women receive a Tdap dose during every pregnancy regardless of the interval since previous Td or Tdap vaccination; [1] no safety concerns have been reported with this off-label use. In addition, many healthcare facilities are no longer stocking Td vaccine, but instead are using Tdap; published data indicates that clinicians are giving repeat Tdap vaccinations more frequently than Td in some healthcare settings [11].

Assessing the impact of replacing the decennial Td booster with repeat Tdap in adults is challenging. High quality data on disease burden is necessary to evaluate the impact of any given vaccination strategy. However, pertussis is often unrecognized, misdiagnosed, or underreported, particularly in adults, and reliable data on the true burden of disease is lacking. Previous economic analyses have presented cost-effectiveness estimates of various Tdap vaccination strategies over a wide range of pertussis incidence [12,13], while other studies have estimated pertussis incidence to be approximately 100-fold higher than the reported incidence [14].

Given changing clinical practice patterns using repeat Tdap vaccination, as well as the increase in pertussis in the United States in recent decades, we evaluated the economic impact of replacing Td with Tdap for the decennial adult vaccine booster, and present cost-effectiveness data over a range of incidence estimates.

2. Methods

2.1. Model

We constructed a static cohort model to predict the epidemiologic and economic impact of replacing the decennial Td booster with a decennial Tdap vaccination in adults (Supplementary Figure). Children that are vaccinated with Tdap at 11–12 years, as recommended by ACIP, would be eligible to receive their first decennial Td booster at age 21. Given this, we examined a hypothetical cohort of persons aged 21 years. The number in the cohort was based on U.S. Census data indicating the number of 21 year-olds in the United States in 2016 and standard mortality tables (Supplementary Table 1) [15]. Based on current vaccination coverage estimates (see below), a certain proportion of this cohort would receive a vaccine dose at age 21 and every subsequent 10 years over the course of their lifespan. We compared two strategies: receipt of a Tdap booster every 10 years (Tdap booster) and the current decennial Td booster strategy. More details on model structure are provided in Supplementary materials. Values for model parameters are show in Table 1.

Table 1
Population, disease, and vaccine parameters used in the model.

Input	Baseline Value [Value for sensitivity analysis]	Source
Population parameters		
Cohort of 21-year-olds	4,386,854	NCHS bridged-race population estimates [15]
All-cause mortality rate	Age-specific	Arias 2017 [42]
Disease parameters		
Pertussis incidence	Varied from 2.5 to 500 per 100,000 person-years	NNDSS 2008-2016 [2]; Strebel 2001 [18]; Ward 2005 [17]; Nennig 1996 [16]
Disease duration	56 days [46-93 days]	Senzilet 2001 [19]; Birkebaek 1999 [21]; Lee 2004 [20]
Number of outpatient visits by hospitalized pertussis cases	Age 21-49: 1.26. Age 50-64: 1.30. Age 65-74: 1.39. Age 75-84: 1.43. Age 85+: 1.53	MarketScan (2007-2016) [36] CMS (2006-2015)[1] [24]
Number of outpatient visits by non-hospitalized pertussis cases	Age 21-64: 1.04, Age 65-74: 1.13, Age 75-84: 1.12, Age 85+: 1.13	MarketScan (2007-2016) [36] CMS (2006-2015)[1] [24]
Pertussis health utility	Outpatient: 0.85, Hospitalized: 0.73	Lee 2005 [40]; Melegaro 2004 [41]
Proportion of cases that were hospitalized	Incidence: 2.5 per 100,000: Age 21-49: 2.781%, Age 50-64: 5.6051%, Age 65+: 11.1709%. Higher incidence values: Proportion hospitalized divided by 3 for each 4x increase in pertussis incidence[2]	NNDSS 2008-2016 [2] Authors' Assumptions
Vaccine Parameters		
Initial Tdap effectiveness	73.1% [60.3%, 81.8%]	Acosta 2015 [33]
Tdap effectiveness waning rate	22% [10% to 30%] Relative annual reduction	Acosta 2015 [33]
Tdap coverage	Intervention group: Age 21-49: 62.1%, Age 50-64: 64.1%, Age 65+: 56.9%. Comparison group: 0%	Williams 2017 [31]

Abbreviations: NCHS: National Center for Health Statistics. NNDSS: Nationally Notifiable Disease Surveillance System. CMS: Centers for Medicaid and Medicare Services. Tdap: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine.

[1] Outliers, defined as the top and bottom 2.5 percentile, were excluded in the calculation of hospitalization costs.

[2] For Sensitivity analysis, two different scenarios considered: All additionally identified cases are outpatient cases and the same base age group specific hospitalization rates applied.

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2.2. Disease parameters

Pertussis is underdiagnosed and underreported. Thus, as has been presented in previous cost-effectiveness analyses, the incidence of reported medically attended adult pertussis was presented over a wide range, from 2.5 cases to 500 cases per 100,000 person-years [12]. The lower bound of 2.5 cases per 100,000 person-years was based on the number of cases in adults aged ≥ 21 years reported to the Nationally Notifiable Diseases Surveillance System (NNDSS) from 2008 to 2016, and divided by the age-stratified U.S. population for those same years [15]. Higher incidence estimates are in a range similar to those found in population-based U.S. studies [16–18]. Among cases reported to NNDSS, disease incidence does not vary widely by age in adults, so we used the same incidence for all age groups.

For the lowest incidence examined (2.5 cases/100,000 person-years), in order to estimate the proportion of cases who were hospitalized, we used NNDSS data on hospitalizations among reported cases. We assumed that more severe cases were more likely to be diagnosed and reported, so that as true incidence increased, the proportion of hospitalized cases decreased; for every four-fold increase in incidence, we assumed a three-fold decrease in the proportion of cases requiring hospitalization (Supplementary Table 1). Based on NNDSS data, we observed that the proportion of reported cases who are hospitalized varied by age. Thus for the range of incidence estimates, while the proportion of all cases who were hospitalized varied by incidence, among those hospitalized, the proportion that were <50, 50–64 and ≥65 years of age was kept the same as among hospitalized patients reported in the NNDSS data. Disease duration was estimated to be 56 days [19–21].

We used a static model structure that did not include indirect effects resulting from repeat Tdap vaccination. Evidence from animal models suggest that vaccination with acellular pertussis vaccines may reduce risk of infection but may not prevent transmission and therefore may not afford indirect protection against pertussis [22,23]. The effect of Tdap vaccination on disease transmission is poorly understood, and thus herd immunity was not included in this model.

2.3. Disease costs

For direct medical costs due to pertussis, we estimated medical expenditures associated with outpatient visits and hospitalizations by specific age groups (21 to 49, 50 to 64, 65 to 74, 75 to 84 years and ≥85 years old) (Table 2). For persons aged 21 to 64, these were calculated based on Truven Health MarketScan Research Commercial Claims Databases of paid private insurance claims data from 2007 to 2016 associated with a pertussis ICD-9-CM (033, 033.0, 033.8, 033.9, and 484.3) or ICD-10-CM (A37.00, A37.01, A37.80, A37.81, A37.90, A37.91) diagnostic code. For those 65 years and older, direct costs were calculated using Centers for Medicare and Medicaid Services (CMS) Medicare claims data from 2006 to 2015 [24]. Outpatient costs included the cost of office and emergency room visits, including any visits within 14 days of the initial clinic visit as well as prescription drug costs within the same time period [25]. Hospitalization costs included both costs associated

Table 2
Disease and vaccine costs used in the model.

Input	Baseline Value [Value for sensitivity analysis]	Source
Disease costs		
Outpatient visit duration	121 minutes	Russell 2008 [25]
Hospitalization duration	Age 21-49: 3.7 days, Age 50-64: 4.6 days, Age 65-74: 6.8 days, Age 75-84: 9.5 days, Age 85+: 12.2 days	MarketScan (2007-2016) [36] CMS (2006-2015) [2] [24]
Direct medical expenditures	Age 21-49: Outpatient: $148, Hospitalized: $13,955, Age 50-64: Outpatient: $143, Hospitalized: $13,918, Age 65-74: Outpatient: $110, Hospitalized: $9,141, Age 75-84: Outpatient: $113, Hospitalized: $8,025, Age 85+: Outpatient: $135, Hospitalized: $9,495	MarketScan (2007-2016) [36] CMS (2006-2015)[2] [24]
Transportation cost[1]	$25.36 per medical visit	Avendano 1993 [26]
Discount rate	3% annually	Corso 2003 [30]
Productivity reduction	Outpatient visits, hospitalization, and periods of missed work: 100%, Other time with pertussis disease: 10% (0% applied to sensitivity analysis)	Grosse 2018 [27] Authors' assumptions
Days of missed work	Incidence: 2.5 per 100,000, 9.8 days. Higher incidence values: Outpatient cases: days missed halved for each 10x increase in pertussis incidence, Hospitalized cases: 9.8 days[4]	Lee 2004 [20] Authors' Assumptions
Annual productivity[3]	Age-specific, adjusted for inflation to 2017 dollars	Grosse 2018 [27]
Vaccine costs		
Tdap cost (incremental over Td)	$15 [$10, $20]	MarketScan databases (2017) [36]

Abbreviations: CMS: Centers for Medicaid and Medicare Services. Tdap: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine.
[1] Costs are presented in 2017 dollars using the Personal Consumption Expenditure health component price index by function.
[2] Outliers, defined as the top and bottom 2.5 percentile, were excluded in the calculation of hospitalization costs.
[3] Presented in 2017 dollars, adjusted for inflation using the Consumer Price Index (Chained CPI).
[4] For sensitivity analyses: (1) no missed work days applied to additional cases and (2) same 9.8 days of missed work days applied to all cases.

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with an inpatient hospital stay as well as the cost of outpatient visits and prescription drugs in the 14 days before and after hospitalization. Outliers, defined as the top 2.5 percentile, were excluded in the calculation of hospitalization costs.

Direct non-medical costs included transportation costs [26] and productivity loss due to illness based on age-stratified daily production values [27] (Table 2). For outpatients, a 100% loss in daily production value was estimated for days of missed work, or, if not working outside the home, to have the equivalent loss of 100% productivity. Based on published data from a cohort of persons with confirmed pertussis, we assumed that the proportion of adults with pertussis illness who missed work was 61%, with a mean of 9.8 days of missed work in those individuals [20]. We assumed a 10% loss in daily production value assumed for the remaining duration of their illness; we assumed the other 39% of persons had a 10% loss in daily production value for the duration of their illness. As with hospitalizations, we assumed that more severe cases would be more likely to be diagnosed and reported; if incidence is significantly higher than NNDSS estimates, this likely represents a higher proportion of patients with milder disease. Thus, as incidence estimates increased above 2.5 cases/100,000 person-years, estimates for the number of days of missed work decreased; for every ten-fold increase in incidence, we assumed a two-fold decrease in the number of days of work missed (Supplementary Table 3).

Hospitalized patients and outpatients were assumed to have the same total duration of illness. Age-stratified length of stay for pertussis-associated hospitalizations was derived from MarketScan claims data for persons aged 21 to 64 years and from CMS data for those ≥65 years. For hospitalized patients, 100% loss in daily production values was assumed to be 9.8 days, with an additional 10% loss in daily production value for the remaining duration of their illness. While the mean hospitalization stay was shorter than 9.8 days, this value was comparable to the mean number of days of missed work for those adults who sought outpatient care and who were ill enough to miss work.

All costs are presented in 2017 dollars using the Personal Consumption Expenditures Price Index for medical costs and chained Consumer Price Index (all item) for non-medical costs [28,29] and discounted to present value at an annual rate of 3% [30]. We performed the model in Microsoft Excel.

2.4. Vaccination program parameters

Coverage for the decennial Tdap booster was assumed to be 62.1% based on 2015 vaccination coverage estimates in adults 19 to 49 years who reported receiving either a Td or Tdap vaccination in the preceding 10 years [31]. Estimates of vaccination coverage in this population have changed little since 2010 [31] and we assumed that vaccination coverage remained stable over the cohort's lifetime. However, under the current recommendations, persons who received the adolescent booster dose at age 11–12 years would not be recommended to receive any adult Tdap booster. This study assumes a state in which adults do not routinely receive Tdap vaccine.

Tdap vaccine effectiveness has been shown in multiple studies to initially be high, but with rapid waning in the years following vaccination [32–35]. Based on results of a case-control study, we assumed initial Tdap vaccine effectiveness to be 73%, and estimated a relative 22% decrease of VE for each year following vaccination [33] (Table 1, Supplementary Table 2).

2.5. Vaccine costs and outcomes

The cost of vaccination included the higher cost of a dose of Tdap vaccine compared with the Td vaccine. This was estimated to be an additional $15 based on the difference in mean values of payments for Tdap and Td vaccines from MarketScan claims data [36]. Because Tdap vaccination replaced decennial Td boosters and did not represent a new vaccination event, vaccine administration costs and the value of the time spent for vaccination were not included as costs in this model. Previous economic analyses have included costs associated with possible vaccine adverse reactions [12,37]. However, most adverse reactions to Tdap are attributable to the Td components and not the pertussis component of the vaccine, and there is no evidence that there is an increased risk of adverse events following Tdap vaccination compared with Td, including among older adults [11,38,39]. Thus we did not include any increased costs associated with adverse events in this model.

Outcomes were followed each year from age 21 over the lifespan of the cohort. Outcomes examined included the total number of pertussis cases, outpatient visits, and hospitalizations averted, and quality-adjusted life years (QALYs) saved. The values representing preferences for different health outcomes associated with pertussis were used to estimate QALYs. For outpatient outcomes, a health utility of 0.85 was derived from a published study on pertussis [40]. For pertussis-associated hospitalization, we used a health utility of 0.73, which was derived from a study on costs for those hospitalized with pneumococcal pneumonia [41]. Disutilities were calculated as 1 minus health utilities; QALY loss for an underlying pertussis outcome was calculated by multiplying the disutility for the outcome to the length of time experiencing that outcome.

From 2008 to 2016, 12 pertussis-related deaths in adults aged ≥21 years of age were reported to NNDSS (CDC unpublished data). We only included pertussis cases that resulted in either an outpatient medical visit or hospitalization; we did not include pertussis-related deaths in this model due to this small number.

2.6. Sensitivity analyses

Sensitivity analyses were performed to identify the influence on cost-effectiveness estimates of changes in key parameters, particularly those parameters based on author assumptions. We conducted univariate sensitivity analyses for the following parameters: initial vaccine effectiveness, duration of protection, vaccination coverage, proportion hospitalized, days of work missed, illness duration, and direct and indirect costs. We also performed deterministic multivariate sensitivity analyses in which we examined cost per case and cost per QALY saved based on sets of different parameters of inputs considered in univariate sensitivity analyses. Scenarios using the values that would optimize cost-effectiveness ("favorable assumptions"), as well as unfavorable assumptions for input parameters were compared to the scenario with the baseline parameters as described above.

This project was reviewed in accordance with CDC human research protection procedures and was determined to be non-research. Therefore CDC Institutional Review Board approval was not required.

3. Results

3.1. Health outcomes

Health outcomes were modeled over a hypothetical cohort of 4,386,854 persons aged 21 years throughout their lifetime [42]. At the lowest incidence estimates (2.5 cases/100,000 person-years), approximately 5,930 pertussis cases would occur in adults if decennial Tdap boosters were not implemented, including 5,614 outpatient and 316 hospitalized cases (Table 3). The decennial Tdap booster strategy would prevent 1,141 cases (19%),

Table 3
Estimated health outcomes from replacing decennial Td booster with Tdap revaccination every 10 years.

Incidence: pertussis cases per 100,000 person-years	Total number of cases		Hospitalized cases averted	Non-hospitalized cases averted	QALYs saved
	Decennial Td booster	Decennial Tdap booster			
2.5	5,930	4,790	58	1,083	14
10	23,722	19,160	77	4,485	56
50	118,609	95,800	107	22,702	275
100	237,218	191,600	124	45,495	550
150	355,827	287,399	135	68,293	825
200	474,436	383,199	143	91,094	1,099
250	593,046	478,999	150	113,896	1,374
300	711,655	574,799	156	136,700	1,649
350	830,264	670,599	161	159,504	1,923
400	948,873	766,399	165	182,309	2,198
450	1,067,482	862,198	169	205,114	2,472
500	1,186,091	957,998	173	227,920	2,747

All values rounded to the nearest whole case or QALY. Abbreviations: Td: Tetanus toxoid and reduced diphtheria toxoid vaccine. Tdap: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. QALY: Quality-adjusted life year.

including 58 hospitalized cases and 1083 outpatient cases; 14 net QALYs would be saved, 13 (93%) of which would result from averted non-hospitalized cases. At incidence estimates approximately 100-fold higher than the NNDSS estimates (250 cases per 100,000 person-years), 593,046 pertussis cases would occur without Tdap decennial boosters. If the Tdap booster strategy were implemented, 114,046 cases (19%) would be prevented, including 150 hospitalized and 113,896 outpatient cases; 1,374 net QALYs would be saved, 1,371 (99%) of which would result from averted non-hospitalized cases.

3.2. Program costs and cost effectiveness measures

Approximately 15,182,766 doses of Tdap vaccine would be administered over the lifetime of the cohort (Supplementary Table 1). Accounting only for the higher cost for Tdap, the cost for the Tdap booster strategy over the cohort's lifetime would be $127,670,798 compared with a Td booster strategy.

At the lowest incidence estimates (2.5 cases per 100,000 person-years), if Tdap replaced Td for the decennial Td booster, the cost per case averted would be $111,540, with a cost-effectiveness (CE) ratio of $8,970,848 per QALY saved (Table 4). As incidence increased, the cost per case averted and cost per QALY saved decreased (Table 4 and Fig. 1). When pertussis incidence was estimated at 250 cases per 100,000 person-years, cost per case averted was $984 with a cost-effectiveness ratio of $81,678 per QALY saved; these values dropped to $427 and $35,474, respectively, when an incidence of 500 cases per 100,000 person-years was assumed. The decennial Tdap vaccination strategies result in cost-effectiveness ratios of <$100,000 per QALY saved if disease incidence in adults were greater than 210 cases per 100,000 person-years; the cost per QALY saved was <$50,000 if disease incidence were greater than 380 cases per 100,000 person-years.

3.3. Sensitivity analyses

In univariate and multivariate sensitivity analyses, we varied initial Tdap vaccine effectiveness from 60.3% to 81.8%, the rate of waning of protection from 10% to 30% per year, the cost of Tdap compared with Td from $10 to $20, disease duration from 46 days to 93 days. We also examined the exclusion of productivity loss and the impact of varying days of missed work and hospitalization rates. The result of the univariate sensitivity analysis at different incidence estimates is shown in the Supplementary Tables 4 and 5.

Table 4
Cost-Effectiveness Results: Economic outcomes resulting from decennial Tdap boosters compared with no Tdap booster.

Incidence: pertussis cases per 100,000 person-years	Total costs		Medical costs		Non-medical costs		Costs averted	Cost per pertussis case averted[3]	Cost per QALY saved
	Decennial Td booster	Decennial Tdap booster	No Tdap booster	Decennial Tdap booster	No Tdap booster	Decennial Tdap booster			
2.5	$2,319,061	$1,855,769	$1,806,579	$1,444,864	$512,482	$410,905	$463,292	$111,540	$8,972,848
10	$4,974,180	$3,974,806	$3,540,156	$2,828,143	$1,434,024	$1,146,662	$999,374	$27,768	$2,281,893
50	$17,330,310	$13,831,077	$11,059,294	$8,823,232	$6,271,015	$5,007,845	$3,499,233	$5,444	$450,873
100	$32,231,474	$25,715,686	$19,942,864	$15,904,476	$12,288,610	$9,811,210	$6,515,788	$2,656	$220,242
150	$46,986,962	$37,483,608	$28,689,147	$22,875,802	$18,297,815	$14,607,805	$9,503,354	$1,727	$143,277
200	$61,676,513	$49,198,712	$37,373,417	$29,797,478	$24,303,096	$19,401,234	$12,477,800	$1,263	$104,780
250	$76,327,495	$60,882,923	$46,021,456	$36,690,146	$30,306,039	$24,192,777	$15,444,572	$984	$81,678
300	$90,952,855	$72,546,609	$54,645,445	$43,563,558	$36,307,410	$28,983,051	$18,406,246	$798	$66,277
350	$105,559,820	$84,195,560	$63,252,180	$50,423,155	$42,307,640	$33,772,405	$21,364,260	$666	$55,275
400	$120,152,869	$95,833,363	$71,845,867	$57,272,306	$48,307,002	$38,561,058	$24,319,505	$566	$47,024
450	$134,734,981	$107,462,406	$80,429,304	$64,113,250	$54,305,677	$43,349,156	$27,272,574	$489	$40,607
500	$149,308,246	$119,084,363	$89,004,453	$70,947,559	$60,303,794	$48,136,804	$30,223,883	$427	$35,474

Abbreviations: Td: Tetanus toxoid and reduced diphtheria toxoid vaccine. Tdap: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. QALY: Quality-adjusted life year.

[1] Medical costs include direct costs for outpatient visits and hospitalizations.

[2] Includes direct non-medical costs such transportation to medical visits and productivity loss during medical visits or hospitalizations, as well as indirect costs for patient and caregiver productivity loss during illness episode.

[3] Calculated by subtracting averted pertussis costs from the cost of the vaccination program over the lifetime of the cohort, $127,670,798. Medically attended cases only. All values rounded to the nearest whole dollar.

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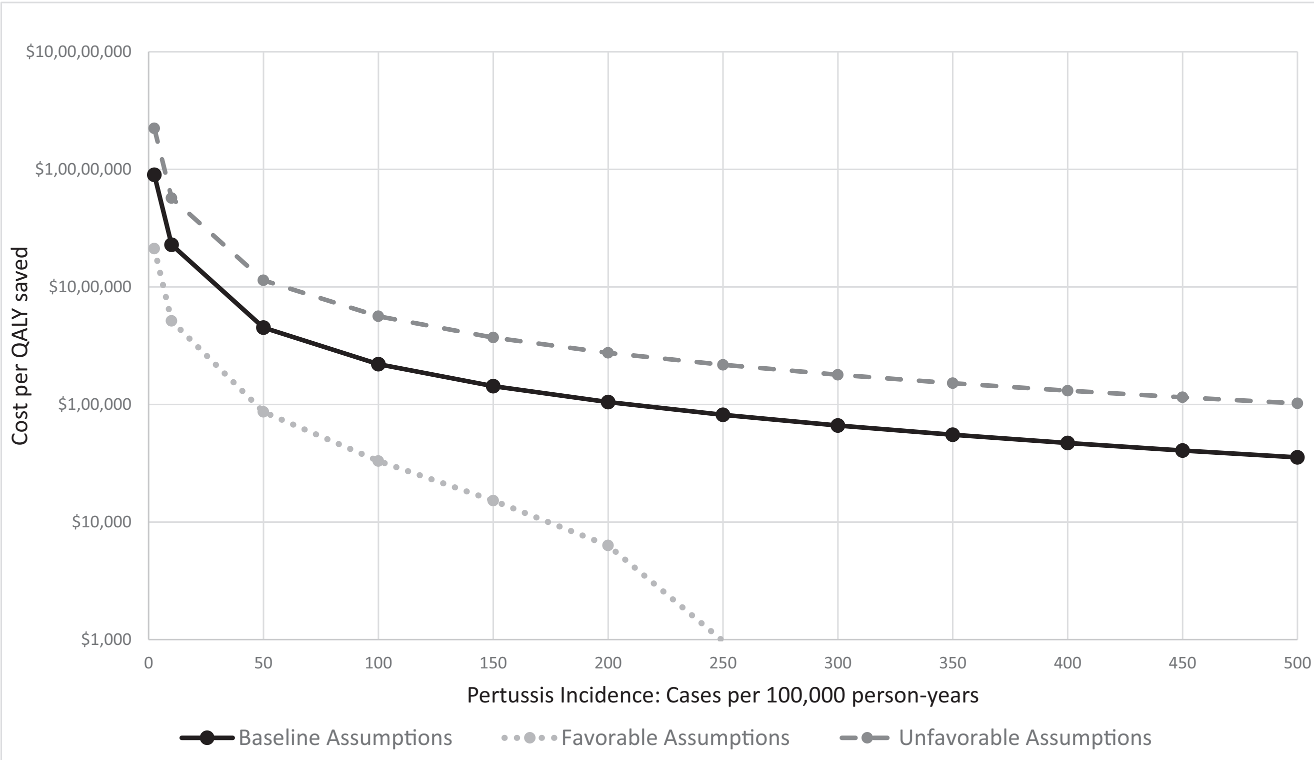

Fig. 1. Estimated cost per Quality-Adjusted Life Year (QALY) saved at varying estimates of pertussis incidence using baseline assumptions. Cost per QALY also shown for multivariate sensitivity analyses under favorable and unfavorable assumptions. Note: Favorable case assumes higher values for initial vaccine effectiveness (81.8%), longer duration of protection (protection wanes 10% per year), a smaller difference in cost between Tdap and Td ($10 higher than Td vaccine), longer duration of disease (93 days), higher hospitalization rate (observed hospitalization rates applied at higher incidence rates), 10% productivity loss, and 9.8 days of missed work days for all additional cases when incidence rate is greater than observed rate (2.5 per 100,000 person-years). Note that in this scenario, above incidence estimates of 250 cases/100,000 person years, Tdap is cost-saving. 2. Unfavorable case assumes lower values for initial VE (60.3%), shorter duration of protection (30% waning of protection per year), larger difference in cost between Tdap and Td ($20 higher than Td vaccine), shorter duration of disease (46 days), lower hospitalization rate (no hospitalization for additional cases at higher incidence rate than the observed pertussis incidence rate (2.5 per 100,000 person-years), no productivity loss, and base case assumption of missed days of work.

To evaluate the robustness of our findings to assumptions regarding the proportion of cases who were hospitalized, we compared cost-effectiveness under our base case to a scenario in which all additional cases beyond those reported to NNDSS (incidence of 2.5 cases per 100,000 person-year) are outpatients. In this alternative scenario, where the rate of hospitalization and therefore the potential benefits of vaccination is lower, the estimated cost per QALY saved was less than 1% higher than our base case at all incidence levels (Supplementary Table 5). Similarly, changing estimates of days of work missed and productivity loss had minimal effect on estimates of cost per QALY saved (Supplementary Table 5).

The most favorable combination of parameters assumes higher values for initial vaccine effectiveness (81.8%) with longer duration of protection (protection wanes 10% per year), a smaller incremental cost between Tdap and Td ($10 higher than Td vaccine), longer duration of disease (93 days), higher hospitalization rate (observed hospitalization rates applied at higher incidence rates), 10% productivity loss, and 9.8 days of missed work days for all additional cases when incidence rate is greater than observed rate of 2.5 per 100,000 person-year). Under the most favorable scenario, cost per QALY saved was estimated $2,116,393 at the observed incidence rate and $971 at 250 per 100,000 person-years. At higher incidence rates than 250 cases per 100,000 person-years, the intervention was cost-saving. The most unfavorable scenario assumes lower values for initial VE (60.3%), shorter duration of protection (30% waning of protection per year), larger difference in cost between Tdap and Td ($20 higher than Td vaccine), shorter duration of disease (46 days), no hospitalization for additional cases at higher incidence rate than the observed pertussis incidence rate (2.5 per 100,000 person-year), no productivity loss, and base case assumption of missed days of work. The most unfavorable scenario yielded the cost per QALY saved ranging from $102,201 to $22,307,832. Both the most favorable and unfavorable scenarios in deterministic multivariate sensitivity analyses are presented along with the baselines assumptions in Fig. 1 and Supplementary Table 6.

4. Discussion

This analysis evaluates the impact of replacing the recommended adult decennial Td booster with a Tdap booster over a range of possible incidence estimates, and demonstrates how the model results varied with disease burden and other key parameters. If pertussis incidence is assumed to be 100-fold higher than that reported through national surveillance, substituting Tdap for Td may lead to an approximately 19% decrease in adult pertussis cases and a cost per QALY saved of $81,678. However, evaluating the economic impact of this change is challenging given the uncertainty for certain key parameters.

The uncertainty surrounding baseline pertussis incidence has led to a wide range of cost-effectiveness estimates for different Tdap vaccination strategies [12–14,37,43]. Pertussis cases in the United States are reported to the National Notifiable Disease System (NNDSS) if they meet a specific case definition [2]. Confirmed cases must meet specific clinical criteria, and have either have laboratory confirmation of *B. pertussis* infection with PCR or culture or contact with a laboratory-confirmed case of pertussis; probable cases in adults must meet specific clinical criteria [2]. Incidence of reported pertussis in adults aged >20 years in recent years has ranged from 1.2 per 100,000 (2018) to 4.5 per 100,000 (2012). However, NNDSS likely does not capture a large proportion of medically-attended pertussis cases, as pertussis is underdiagnosed and underreported by healthcare providers, particularly in adults [44]. Prospective studies in which patients with qualifying symptoms are systematically tested for pertussis report much higher estimates of adult pertussis incidence in the United States, [16–18] ranging from 176 cases per 100,000 [16] to 368 cases per 100,000 [17,44] for pertussis diagnoses associated with a medical visit. Most of these studies were done prior to the increase in cases reported in recent decades. Evidence from population-based serosurveys suggests that the incidence of recent pertussis infection is far higher [45]. Incidence estimates from administrative databases that examined insurance claims for pertussis-related diagnostic codes, although highly variable, were all higher than the incidence estimated based on cases reported to NNDSS. Two studies using a database combining insurance claims and laboratory test results estimated an incidence in adults <50 years of 3 per 100,000, [46] and 2.1 and 4.6 per 100,000, people aged 50–64 and $\geq$65 years respectively [47]. Another study using insurance claims and electronic health record data estimated the incidence of cough illness attributed to pertussis at 202 and 257 per 100,000 people aged 50–64 and $\geq$65 years respectively [48]. We demonstrate that the cost per QALY saved markedly decreased as incidence estimates increased, but the extent to which under-reporting and underdiagnosis impacts incidence estimates in adults is unknown.

While this study and previous cost-effectiveness analyses assumed that current recommendations are being followed and that decennial boosters of Td are being given to nonpregnant adults who have already received a single dose of Tdap, recent data suggests that many clinicians are using Tdap for the recommended decennial tetanus and diphtheria booster. Public sector orders from providers for both Td and Tdap indicate that in 2017, the total number of Tdap doses ordered for adults was approximately 10-fold higher than the number for Td (Tdap: 441,075 doses; Td: 41,881 doses. CDC unpublished data). Data from commercially insured persons indicates a similar trend; one source of insurance claims in 2017 among persons 19 to 64 years included 716,638 claims for Tdap compared with 61,468 claims for Td [36]. A recent study indicated that among 68,915 adolescents and adults who were vaccinated with Tdap and then received a subsequent dose of a tetanus-containing vaccine, 89.1% received a second dose of Tdap; only 10.9% receiving Td as their next dose of tetanus-containing vaccine [11]. The impact of what is likely current use of repeat Tdap doses for the decennial Td booster was not accounted for in this study.

Our analysis differed from previous analyses that evaluated the cost-effectiveness of various Tdap vaccination strategies. Unlike several analyses which looked at a new vaccination event for specific age groups, including analyses that examined cost-effectiveness before the Tdap vaccine was approved and one analysis that looked at revaccinating an adolescent cohort at ages 16 and 21, [37] we assumed that the Tdap vaccine would replace the recommended Td booster. Thus, there would be no additional vaccination costs other than the higher price of the vaccine relative to Td. Also, multiple recent studies that have shown that adverse events for repeat Tdap vaccination are no more common than for Td vaccination [5,6,8–10]. Given this evidence and the fact that in our model, Tdap was replacing Td, unlike other analyses, we did not include costs for adverse events in our model. In addition, as noted above, given that we know that pertussis is underdiagnosed, we did not assume that the incidence reported to the NNDSS as the base case, but rather estimated the economic impact at varying levels of pertussis incidence.

As noted above, the major limitations of this analysis include uncertainty around values for important parameters, including pertussis incidence, illness severity, initial vaccine effectiveness, and duration of protection. In addition, our estimates of the economic and epidemiologic benefits of Tdap revaccination were conservative in a number of ways. We lacked data to estimate any cost savings that may result from stocking only Tdap vaccine compared with both Td and Tdap, as well as savings resulting from decreased need for public health investigations of pertussis cases. We also did not include costs from pertussis-associated deaths or from pertussis disease that did not result in medical care. We did not take into account the fact that the practice of using Tdap to replace the decennial Td booster, even in the setting of previous Tdap administration, is already widespread and may have already affected pertussis epidemiology. We also used the estimated cost differences between Td and Tdap vaccines estimated from private insurance claims data, but, as demonstrated in a sensitivity analysis, if CDC price data [49] are used and the price differential between the vaccines is smaller, the relative cost-effectiveness of repeat Tdap doses would be more favorable.

In addition, we did not factor decreased transmission that results from Tdap vaccination into any of our analyses. While the effect of acellular pertussis on transmission and herd immunity is not well understood, animal models suggest that acellular pertussis vaccines may prevent disease but not block transmission, and thus the impact on herd immunity may be limited [22,23]. However, persons fully vaccinated against pertussis vaccines are less likely to have severe disease compared with those who are not, [50] and it is likely that vaccinated persons with less severe disease would be less likely to transmit *Bordetella pertussis*. The fact that we did not include any herd immunity likely underestimates the benefits resulting from Tdap revaccination.

Multiple studies have indicated that Tdap vaccines have a high initial effectiveness, but that protection wanes rapidly within several years [32–35]. Based on our analysis, we would anticipate that replacing the decennial Td booster with Tdap would likely have a limited impact on overall disease burden, especially if true incidence of disease is close to the currently reported rates in adults. However, programmatic changes resulting from using a single tetanus toxoid-containing vaccine, such as increased simplicity of vaccine ordering and ease of implementing routine vaccination recommendations, could result in cost-savings; our model did not account for these considerations.

5. Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.104.

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