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Tetanus, diphtheria and acellular pertussis (Tdap) vaccine for prevention of pertussis among adults aged 19 years and older in the United States: A cost-effectiveness analysis

Bo-Hyun Cho[a,*], **Anna M. Acosta**[b], **Andrew J. Leidner**[c,1], **Amanda E. Faulkner**[b,2], **Fangjun Zhou**[a]

[a]National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE Mailstop H24-4, Atlanta, GA 30329, United States of America

[b]National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE Mailstop H24-6, Atlanta, GA 30329, United States of America

[c]Berry Technology Solutions, 525 Westpark Dr Suite 310, Peachtree City, GA 30269, United States of America

Abstract

Currently, the Advisory Committee on Immunization Practices recommends one-time tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination for all adults 19 years and older. This study is designed to evaluate the cost-effectiveness of Tdap vaccination for Tdap-eligible adults aged 19 through 85 in the United States. A cost-effectiveness model was developed to compute costs and health outcomes associated with pertussis among 100,000 Tdap-eligible persons of each age cohort. From the societal perspective, the cost per quality-adjusted life-year (QALY) saved was evaluated under the vaccination scenarios. Sensitivity analyses were also conducted to evaluate the impacts of changes in key variables. All costs were adjusted to 2018 US $ with an annual discount rate of 3% applied to costs and outcomes. The incremental cost-effectiveness ratios (ICERs) for vaccinating US adults aged 19 to 85 with Tdap ranged from $248,000/QALY to $900,000/QALY. The lowest cost per QALY was found to be $248,000 for the

[*]Corresponding author at: Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS H24-4, Atlanta, GA 30329, United States of America., bcho@cdc.gov (B.-H. Cho).

CRediT authorship contribution statement

Bo-Hyun Cho: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Anna M. Acosta:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing. **Andrew J. Leidner:** Validation, Data curation, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Amanda E. Faulkner:** Validation, Investigation, Data curation, Writing - review & editing. **Fangjun Zhou:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization, Supervision, Project administration.

[1]Present affiliations: National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, 1600 Clifton Rd. NE Mailstop H24-4, Atlanta, GA 30329, United States of America

[2]Present affiliations: Oregon Health Authority, Public Health Division Acute & Communicable Disease Prevention, 800 NE Oregon Street, Suite 772, Portland, OR 97232, United States of America

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age 65 cohort, followed by $332,000 for the cohort of age 19, and followed by $477,000 for the age 50 cohort. Sensitivity analysis showed the most dramatic changes in ICER occurred when changing the underreporting factor, vaccine effectiveness and vaccination costs. While Tdap vaccination may not be as cost effective as predicted earlier, it remains the best available preventive measure against pertussis. Further investigation of the true burden of pertussis disease among adults and the effectiveness of Tdap vaccination in this population is needed to better estimate the impact of Tdap vaccination.

Keywords

Tetanus toxoid; Reduced diphtheria toxoid; Acellular pertussis Vaccine; Tdap; Vaccination; Cost-effectiveness

1. Introduction

Pertussis is a vaccine-preventable disease caused by the bacterium *Bordetella pertussis* (Edwards and Decker, 2018). Several different vaccines are licensed for prevention of pertussis among children, adolescents, and adults in the United States (Liang et al., 2018). Introduction of vaccines against pertussis in the 1940s effectively reduced incidence (Liang et al., 2018; Centers for Disease Control and Prevention, 1997), but the disease has resurged in recent years (Skoff et al., 2018) and pertussis continues to infect persons of all ages (*Pertussis Cases by Year* (1922–2017), 2017).

In 2005, the Advisory Committee on Immunization Practices (ACIP) recommended a one-time tetanus toxoid, reduced diphtheria, and acellular pertussis (Tdap) vaccination for adolescents and adults < 65 years of age. In 2012, the ACIP expanded the recommendation to include all adults (Centers for Disease Control and Prevention, 2012). Despite the recommendations, Tdap vaccination coverage for adults age 19 and older is suboptimal: 33.4% for adults aged 19–64 years and 24.4% among those aged 65 years and older (Vaccination Coverage among Adults in the United States, National Health Interview Survey, 2017 [Internet], 2018). This is especially striking when compared to Tdap vaccination coverage (88.7%) among adolescents age 13–17 (Walker and Yankey, 2018).

Despite the demonstrated overall cost effectiveness of Tdap vaccination among adults ≥65 years of age and among adults 20–64 years of age (Acosta, 2012; Lee et al., 2005a; Lee et al., 2007; Lee et al., 2008; McGarry et al., 2013; McGarry et al., 2014), many adults continue to not receive vaccination. This presents an opportunity to improve Tdap vaccination coverage to prevent pertussis; however, stronger, updated evidence may be required to support the resource expenditure likely needed achieve success. To update stakeholders of the cost-effectiveness of Tdap vaccination, we assessed health and economic outcomes associated with Tdap vaccination in a population of adults aged 19 to 85 years who have never been vaccinated with Tdap, updating previous cost-effectiveness evaluations by utilizing current epidemiological data and recent evidence of Tdap vaccine effectiveness and vaccination costs. Specifically, the model assessed the cost-effectiveness of Tdap vaccination by incorporating varying epidemiologic and economic inputs for different age cohorts.

2. Methods

2.1. Model structure

We developed a cost-effectiveness model to estimate Tdap vaccination costs and the burden of disease associated with pertussis under two different scenarios: receipt of Tdap vaccination and no Tdap vaccination. The model is based on a static cohort simulation with a simple Markov model to follow a cohort of 100,000 adults of each year of age from 19 to 85 years in the United States and applied different sets of probabilities and inputs specific to their age and scenario (see Fig. 1 for a visual depiction).

We followed the adults until their age of life expectancy according to the United States life table (Arias et al., 2019); the analytic horizon was the lifespan of the individual. Disease outcomes included number of pertussis cases, outpatient cases with pertussis, hospitalizations with or without pneumonia due to pertussis, and deaths due to pertussis. In addition to disease outcomes, the following economic parameters were utilized: health-state utilities, direct costs, indirect costs, and vaccine program costs. Vaccination-related adverse events were also considered in the model. Future costs and outcomes were discounted to present value at an annual rate of 3% (Corso and Anne, 2003). Final model outcomes were presented as costs averted, vaccination program costs, quality-adjusted life years (QALYs) saved, and incremental cost-effectiveness ratios (ICERs). To calculate ICERs, net cost was divided by the number of QALYs saved. The net cost was the vaccination program costs minus the disease costs that were averted by Tdap vaccination. Health outcomes, costs, and ICERs were computed for age-specific cohorts. Hence, ICERs were estimated for each cohort from age 19 to 85 years. The detailed results of administration of one dose of Tdap at selected ages-19, 50, and 65 years-are presented in this article, as those ages represent current or potential age thresholds in the current adult immunization schedule. The base case input values and sources used in the model are shown in Table 1.

This study was reviewed by CDC Human Research Protection Office and determined to be exempt from requirement for institutional review board review, because all analyses used either surveillance data, secondary data, or de-identified records from Truven Health MarketScan© Research Databases (MarketScan).

2.2. Epidemiologic parameters

Incidence rates, i.e., the proportion of hospitalization due to pertussis and case fatality ratios (CFRs) for pertussis, were based on age-specific data from the National Notifiable Diseases Surveillance System (NNDSS) from 2008 through 2017 (Centers for Disease Control and Prevention, 2019). For incidence rates, pertussis case counts were divided by age-specific population estimates from the US Census (U.S. Census Bureau Population Division, 2015). Hospitalization rates were estimated using hospitalized case counts with and without pneumonia from NNDSS. These hospitalized cases were divided by the total number of reported cases for each age group: 19–49, 50–64, and ≥ 65 years of age (Centers for Disease Control and Prevention, 2019). All other nonhospitalized cases were assumed to be outpatient care cases. Similarly, pertussis CFRs were estimated from NNDSS-reported pertussis-related deaths divided by the total number of NNDSS-reported pertussis cases by age group. As NNDSS is a passive surveillance system, cases of pertussis may go unreported, especially among adults (McGuiness et al., 2013; Sutter and Cochi, 1992). To adjust for this potential bias, we incorporated an under-reporting factor for pertussis cases, which in the base case scenario assumed 100 additional cases of pertussis for every one case reported in NNDSS (Centers for Disease Control and Prevention, 2012). We believe that by their nature, unreported pertussis cases are likely to be less severe than cases that were reported to NNDSS. For this reason, both the CFR and the proportion of hospitalization were reduced by 50% when the under-reporting factor was applied. The duration of pertussis infection was assumed to be 93 days (Lee et al., 2004). Age-specific background mortality rates were used to represent natural death in the model (Arias et al., 2019).

2.3. Vaccine effectiveness

We adapted Tdap vaccine effectiveness (VE) and estimated trends of waning immunity against pertussis from a recent study of adolescents (Acosta et al., 2015). VE was estimated as 74% during the first year after vaccination. For every year thereafter, annual decline of immunity was estimated to be 22%.

2.4. Vaccine adverse events

Adverse reactions to Tdap vaccines are extremely rare but plausible. Rates of adverse events were obtained from studies published previously (Tseng et al., 2013; Jackson et al., 2009).

2.5. Costs

Pertussis-related costs included direct medical costs, direct non-medical costs (e.g., caregiver-associated costs during medical services), opportunity costs of time travelling to a provider office for outpatient visits or for vaccinations, and indirect costs related to pertussis infections.

For direct medical costs due to pertussis, we estimated medical expenditures associated with outpatient visits and hospitalizations (with and without pneumonia) for three age groups: 19–49, 50–64, and ≥65 years of age. The estimates were based on data extracted from the Commercial Claims and Encounters (2003–2012) and Medicare Supplemental (2003–2012) portions of the MarketScan databases from 2003 to 2012 (Truven Health Analytics, 2013). These datasets represent a large convenience sample of private-sector paid insurance claims and encounters from health insurance payers and have been used extensively to estimate health care costs associated with disease (Gastañaduy et al., 2013; Molinari et al., 2007). From MarketScan databases, we identified claims associated with hospitalized pertussis using five ICD-9-CM codes (033, 033.0, 033.8, 033.9, and 484.3). We tabulated the number of health care encounters following a pertussis hospitalization and the length of stay for a typical hospitalization with and without pneumonia. Pneumonia-related hospitalizations were identified using 22 ICD-9-CM codes (481, 003.22, 020.3, 020.4, 020.5, 055.1, 073.0, 112.4, 115.05, 115.15, 115.95, 130.4, 136.3, 487.0, 484.3, 011.6x, 482.x, 483.x, 484.x, 480.x, 486.x, and 485.x) (Grijalva et al., 2007).

For direct non-medical costs, we used an estimate of $26.10 per outpatient visit from the literature to represent patient travel cost to and from the provider office or hospital locations

(Avendano et al., 1993). For the cost of time lost incurred by the patient and, when relevant, by an informal caregiver for outpatient visits, we used 1.68 h per visit (Russell et al., 2008). For hospitalized cases, we assumed time loss of 4 h per day by caregivers and full days for patients. To evaluate the value of time, we used average hourly wage by age. The costs of informal family caregiving for infected individuals were compiled from several sources (Russell et al., 2008; Chari et al., 2015).

Vaccination program costs included the cost of Tdap vaccine, the administration fee for Tdap vaccine, vaccine wastage, and non-medical costs such as travel time for vaccination as well as direct and indirect costs related to any adverse events after vaccination (Table 1). The vaccine cost and vaccine administration costs used in the model came from two sources. For adults age 19 to 64, costs from the published literature were used (Tsai et al., 2019). For adults aged 65 and older, costs were obtained from the Medicare Part B Drug and Biological Average Sales Price Quarterly Payment files for calendar year 2018 (Centers for Medicare and Medicaid Services, 2019a; Centers for Medicare and Medicaid Services, 2019b) and from Physician Fee Schedule for 2018 (Centers for Medicare and Medicaid Services, 2019b), respectively. A 5% vaccine wastage rate was assumed (Setia et al., 2002). Transportation costs and time loss associated with visits to healthcare settings related to immunization were calculated using the same costs per outpatient or hospital visit as above for non-medical and indirect costs due to pertussis. Time spent at the provider's office when receiving the Tdap vaccine was assumed to be 2 h.

We assumed that Tdap vaccination could have been given during an immunization-only visit, a preventive health visit, or a sick visit. In addition, Tdap vaccine could have been given in conjunction with other vaccines during the visit. To take that into account, the transportation cost per encounter was adjusted (i.e., reduced) to reflect a potential plurality of reasons for the encounter. Age-specific adjustment factors (ranging from 0.2 to 0.6) were calculated from MarketScan databases on primary care visits tabulated by the number of vaccine doses received and whether the visit was categorized as a sick visit or preventive health visit. For costs associated with adverse reactions following the receipt of Tdap, we estimated the hospitalization costs of anaphylaxis and the outpatient clinic costs for allergic reactions from MarketScan databases for 2012 and 2013.

All costs were adjusted to 2018 US dollars using the medical Consumer Price Index (CPI) for medical expenditures and the all-item CPI for non-medical and indirect costs (*Consumer Price Index [Internet*], n.d.).

2.6. Quality-adjusted life years

Morbidity caused by pertussis was quantified using QALYs. Utility decrements for pertussis were categorized by severity of the disease following Lee et al. (2005b): mild, severe, or pneumonia. In our model, we considered outpatient pertussis cases as mild and hospitalization without pneumonia as severe. We assumed that all pertussis-associated pneumonia cases needed hospitalization. Therefore, we used a health utility of 0.85 for outpatient cases, 0.81 for those hospitalized due to pertussis without pneumonia, and 0.82 for those hospitalized due to pertussis with pneumonia (Lee et al., 2005b). QALYs saved were calculated by subtracting total QALYs under the no-vaccination scenario from total QALYs under the vaccination scenario.

2.7. Sensitivity analysis

We conducted univariate and deterministic sensitivity analyses on key variables to assess results under different values of inputs under uncertainty. For the under-reporting factor, we changed the base case value of 100 to lower bounds of 10 or 70 and a higher bound of 200. In addition, we assessed results when there was a 0% reduction in CFR and in-hospitalization rates when the under-reporting factor was applied.

To evaluate the influence of VE on model results, we varied VE as follows: 1) where initial VE was lower than base case at 63%, based on another VE study (Baxter et al., 2013) and 2) where vaccine-induced immunity against pertussis waned to zero after 10 years, but where initial VE was still 74%. In other scenarios, all medical costs were changed ± 20% from the base value in order to consider any uncertainty over the medical costs. To investigate informal caregiver time, we made two assumptions: 1) no informal caregiver costs for patients aged 65 and older and 2) the value of time lost changed to 2 h or to 8 h.

In addition, we made two additional changes to reflect any variaions or uncertainties in absence of any alternative sources of data: 1) ± 50% changes in transportation costs from the base value and 2) 150% of the transportation cost adjustment factor and no transportation cost adjustment (factor = 1). For vaccination program costs, we reduced vaccine price and vaccine administration costs by 50%.

Finally, we assessed the best-case and worst-case scenarios to provide the ICERs under the extreme scenarios with the most favorable and the least favorable values of the variables. For the best-case scenario, we applied the most favorable assumptions: 1) under reporting factor for pertussis is 200, 2) under-reported cases have 100% CFR and hospitalization rates among pertussis cases, 3) all medical costs are 20% lower than base case, 4) transportation costs is 50% lower than base case, 5) time lost is 50% lower than base case, 6) informal caregiver time is 2 h per hospitalization, 7) vaccine costs are 50% lower than base case and 8) vaccine administration costs are 50% lower than base case. For the worst-case scenario, we used the least favorite values: 1) under reporting factor for pertussis is 10, 2) all medical costs are 20% higher than base case, 3) transportation costs is 50% higher than base case, 4) time lost is 50% higher than base case, 5) Informal caregiver time is 8 h per hospitalization, 6) 150% of transportation cost adjustment factor, 7) no adjustment of transportation cost (that is, factor = 1) and 8) vaccine effectiveness at Year 0 is 64%.

3. Results

3.1. Base case

ICERs for vaccinating US adults aged 19 to 85 years with Tdap are presented in Fig. 2a: a range of values from $248,000 per QALY saved for the cohort aged 65 to $900,000 per QALY saved for the cohort aged 85 cohort. The curve shows fluctuation in ICERs among adults between ages 19 and 64, while ICERs for adults age 65 and older showed a steep increase. The lowest cost per QALY was found to be $248,000 for the age 65 cohort, followed by $332,000 for the cohort of age 19, and followed by $346,000 for the age 37 cohort.

The proportion of those three cost components were stable, while the value of time lost changed with cohort age (Fig. 2b). Net costs for the 19, 50, and 65-year-old cohorts were $9.4 million, $9.9 million, and $5.9 million, respectively. QALYs gained were greatest among the 19-year-old cohort, which gained 28 QALYs for every 100,000 people vaccinated, followed by the 64-year-old cohort and the 50-year-old cohort, each gaining 24 and 21 QALYs for every 100,000 people vaccinated, respectively. As results, ICERs for the cohorts aged 19 years, 50 years, and 65 years were calculated as $332,000, $477,000, and $248,000, respectively.

Focusing on three age cohorts (ages 19, 50, and 65 years) of 100,000 people each, the societal costs averted by the vaccine program were greatest for the 65-year-old cohort ($700,000), followed by the 50-year-old ($500,000) and 19-year-old ($300,000) cohorts. The lowest vaccination program cost among the three cohorts was $6.7 million for the 65 year-old cohort. Vaccination program costs were estimated to be $9.4 and $9.9 million for the 19-year-old and 50 year-old cohorts, respectively. Across all three cohorts, the largest component of program costs was the cost of vaccines, followed by vaccine administration costs and transportation costs (Table 2).

3.2. Sensitivity analyses

The results from several deterministic sensitivity scenarios stratified by three cohorts aged 19, 50, and 65 years are shown in Table 3. Changing under-reporting factor yielded a range of ICERs: from $109,000/QALY among 65-year-olds, assuming there were 200 under-reported cases for each case reported to NNDSS, to $5.5 million/QALY among 50-year-olds, assuming 10 under-reported cases for each case reported to NNDSS. Assuming a 50% reduction in time lost due to either infection or preventive health visits, ICERs declined overall, with ICERs of $325,000, $432,000, and $181,000 per QALY saved for the 19, 50, and 65-year-old cohorts, respectively (Table 3). We also varied informal caregiver cost parameters for caregiving that occurred on vaccination visits, as well as on outpatient visits and hospital stays. If no caregiver time was needed for patients receiving vaccinations or receiving outpatient or inpatient healthcare under 65 years, changing informal caregiver time from 4 h per hospitalization to 8 h or 2 h per hospitalization yielded changes in ICERs that were less than $1000/QALY. If immunity to pertussis fell to 0% by 10 years post-vaccination, ICERs were $278,000, $397,000, and $295,000 per QALY for the cohorts aged 19, 50, and 65 years, respectively. Lower first-year vaccine effectiveness assumption yielded higher ICERs than base case ICERs: $380,000, $548,000, and $287,000 for per QALY for the cohorts aged 19, 50, and 65 years, respectively. Also, the tornado diagrams present the percentage changes in ICERs of the selected variables whose variations resulted in the substantial changes from the base case estimates including the under-reporting factor of the pertussis incidence, vaccine cost, and initial vaccine-effectiveness (Fig. 3).

Under the most favorable (the best-case) scenario, ICERs could decrease to $8000/QALY for the cohort of age 65 followed by $67,000/QALY for age 50 and $76,000/QALY for age

19. For the worst-case scenario, ICERs resulted in $5,195,000/QALY for age 19, $7,760,000/QALY for age 50 and $4,950,000 for age 65 cohort.

4. Discussion

A single dose of Tdap vaccination is recommended for adults 19 years and older for prevention of pertussis, tetanus, and diphtheria (Liang et al., 2018). The recent pertussis resurgence in the United States has raised awareness of the disease and provided an opportunity to reiterate the importance of vaccination and support vaccine uptake, given low Tdap vaccination coverage rates among adults (Skoff et al., 2018). To further support Tdap vaccination among adults, our study evaluated the cost-effectiveness of Tdap vaccination among United States adults between 19 and 85 years old. At most ages, ICERs were estimated to be more than $300,000/QALY saved; ICER was lowest for the 65-year-old cohort and highest for the 50-year-old cohort. Sensitivity analysis shows the greatest changes in ICER occurred when the under-reporting factor, vaccine effectiveness, and vaccination costs varied.

Several recent studies have evaluated Tdap vaccination strategies in prevention of pertussis among targeted cohorts such as adolescents, young adults, or pregnant women (Lee et al., 2005a; Atkins et al., 2016; Terranella et al., 2013). With respect to adults, several studies focused on adults age ≥ 65, found the incremental benefit of additional pertussis protection to decennial Td was cost effective (Acosta, 2012; McGarry et al., 2013; McGarry et al., 2014). One-time use of Tdap against pertussis has been found to be cost effective among adults aged 20–64 years old in the United States (Lee et al., 2007) and in Germany (Lee et al., 2008). A systematic review reports almost all cost-effectiveness ratios of age-based Td/ Tdap vaccinations are lower than $300,000 per QALY saved (Leidner et al., 2019). Thus, considering that our lowest ICER is $290,000 per QALY saved for adults age 65, the incremental cost-effectiveness ratios from the previous literature are lower than our results.

However, previous studies required updates in epidemiological data, vaccine effectiveness, and vaccine costs. For example, previous studies applied incidence rates in their model based on older surveillance data (Acosta, 2012; Lee et al., 2007; McGarry et al., 2013) or on higher-than-expected incidence rates, such as those observed during an outbreak (McGarry et al., 2014). In contrast, our study reflects the most recent data including national pertussis surveillance data from 2008 to 2017.

Because incidence is one of most sensitive factors in determining cost effectiveness, studies are more likely to demonstrate that Tdap vaccination is cost effective when using higher pertussis incidences (Lee et al., 2005a; Lee et al., 2007). Incidence is also affected by the magnitude of the under-reporting factor incorporated into the cost-effectiveness model. There is presumed to be some level of under-reporting of disease among adolescents and adults for a variety of reasons, including presentation of non-classic disease symptoms, presentation later in the disease course when available tests may not be accurate, and lack of awareness of disease in adults on the part of healthcare providers (Nennig et al., 1996; Strebel et al., 2001; Ward et al., 2005; Cherry, 2005). There is little consensus regarding how best to address uncertainties regarding pertussis incidence or the magnitude of under-reporting among young adults or adolescents, and further investigation is needed to confirm the true burden of disease among these age groups. Like previous studies, we conducted sensitivity analyses to allow for a range of incidences by applying several under-reporting factors; however, we allowed for lower under-reporting factors, which likely resulted in higher ICERs compared to previous studies.

In addition, previous cost-effectiveness studies relied on higher VE estimates, but more recent studies have shown that Tdap provides a more modest immediate effectiveness followed by waning protection within 2 years of receipt (Acosta et al., 2015; Briere et al., 2018; Klein et al., 2016). Our analyses incorporated these more recent VE estimates and a waning data. The less effective protection against pertussis might have contributed to increased ICERs. Finally, some previously published models considered the effect of herd immunity induced by Tdap vaccination among adults by reducing the chances of pertussis transmission to infants or other age groups (Lee et al., 2007; McGarry et al., 2014). The inclusion of herd immunity results in increased avoided costs due to pertussis infection, subsequently leading to lower CE ratios (Lee et al., 2005a; Lee et al., 2007) or in some cases to cost savings (McGarry et al., 2014). However, more recent studies suggest that achieving herd immunity with Tdap is unlikely, and we did not include this factor in our model (Domenech de Celles et al., 2014; Warfel and Merkel, 2014; Warfel et al., 2014; Trainor et al., 2015).

For vaccination program costs, we used the cost of Tdap vaccine as well as the vaccine administration costs. In previous studies, only the incremental price of replacing Td vaccine with Tdap vaccine were considered in order to answer the question of the one-time replacement of Td with Tdap (Acosta, 2012; McGarry et al., 2013; McGarry et al., 2014) or assuming that Tdap vaccination is to offer the protection against pertussis in addition to the protection against two other components; diphtheria and tetanus (Lee et al., 2005a; Lee et al., 2007). Although the objective of our study was to assess the impact of immunization in prevention of pertussis, there is no stand-alone pertussis vaccine available in the current market. Hence, Tdap vaccination is the only vaccine recommended for the protection against pertussis for adults. Also, despite the chances that the patients are likely to receive their Tdap vaccine instead of their decennial Td booster, we did not know the proportion of patients receiving Tdap in replacement of decennial Td. Thus our vaccination costs are based on the most recent payments or allowable amount for Tdap vaccine paid by insurers (Tsai et al., 2019; Centers for Medicare and Medicaid Services, 2019a).

Our study is subject to several limitations. Our CEA model does not include a dynamic transmission model in the study population. Our model is designed to investigate the impact of Tdap vaccination by age cohort, however modelling the dynamics of transmission within and between other age cohort might be needed. Yet, given the lack of definitive evidence of herd immunity in addition to the data indicative of waning VE (Acosta et al., 2015; Baxter et al., 2013; Domenech de Celles et al., 2014; Warfel and Merkel, 2014; Warfel et al., 2014), we do not expect the results to change drastically. Also, we assumed declining vaccine-induced immunity based on recent Tdap VE studies among adolescents, due to the lack of information regarding Tdap VE for adults aged 19 and older (Klein et al., 2016; Koepke et al., 2014). While these data constitute the best available information on the topic, we acknowledge that adults may have different immune responses to vaccine, and therefore different VE than adolescents; further studies are needed in the adult population in order to understand how VE may differ in these populations.

For the cost of informal care of patients due to acute disease like pertussis, to our knowledge, there is little data readily available to use for the cost-effectiveness analysis. Thus, we had made our own assumptions to address the uncertainty over the cost of caring. In doing so, as our study considered cohorts of varying ages, the cost inputs such as medical costs or hourly wage of patients or caregivers also vary by age of the underlying cohort. Thus, in order to incorporate the variation in the cost inputs varying by the age of cohort, we applied the changes of baseline inputs by certain percentage points. However, as shown in the tornado diagrams, the impact of changes in the cost of informal care to the outcome measures is minimal compared to other critical factors such as under-reporting factors or vaccine cost.

In addition, this study does not consider any specific risk-based targeted adult groups for intervention, such as pregnant women or individuals in outbreak settings. Tdap vaccination for pregnant women during each pregnancy provides protection against pertussis not only for pregnant women but also newborn infants (Liang et al., 2018). Although it would not be easy to obtain data or inputs from such vulnerable groups as pregnant women and infants, given higher incidence and mortality among infants, the benefits of conferred immunity to newborn infants would have likely improved CFRs. In pertussis outbreak settings, vaccination with Tdap will provide individual protection but there is no available data indicating that re-vaccination or mass vaccination campaigns prevent further transmission; therefore, we did not include this scenario in our model.

Finally, our model did not include consideration of herd immunity, because there is not conclusive evidence that Tdap provides herd immunity (Domenech de Celles et al., 2014; Warfel and Merkel, 2014; Warfel et al., 2014). Given the limited evidence of herd immunity from the vaccination, more people need to be vaccinated with Tdap to protect themselves against pertussis. However, the most recent estimate of Tdap vaccination coverage is 27.6% among adults age 19 and older (Williams et al., 2017). Thus, the coverage could be increased with greater awareness of the health benefits from vaccination, especially now that ACIP recommendations support decennial dosing with Tdap or Td (Havers et al., 2020).

5. Conclusions

Our model predicts wide variability in the cost-effectiveness of Tdap vaccination among adults depending on many factors including assumptions about under-reporting and the age of target population. Tdap vaccination is the best available preventive intervention against pertussis. With the updated ACIP recommendations for decennial booster with Tdap or Td, more information regarding the health benefits and the cost of vaccination to reduce infections is warranted. Therefore, further investigation of the burden of pertussis disease among adults and the effectiveness of Tdap vaccination in this population would be greatly benefit more precise estimate the cost effectiveness of Tdap vaccination.

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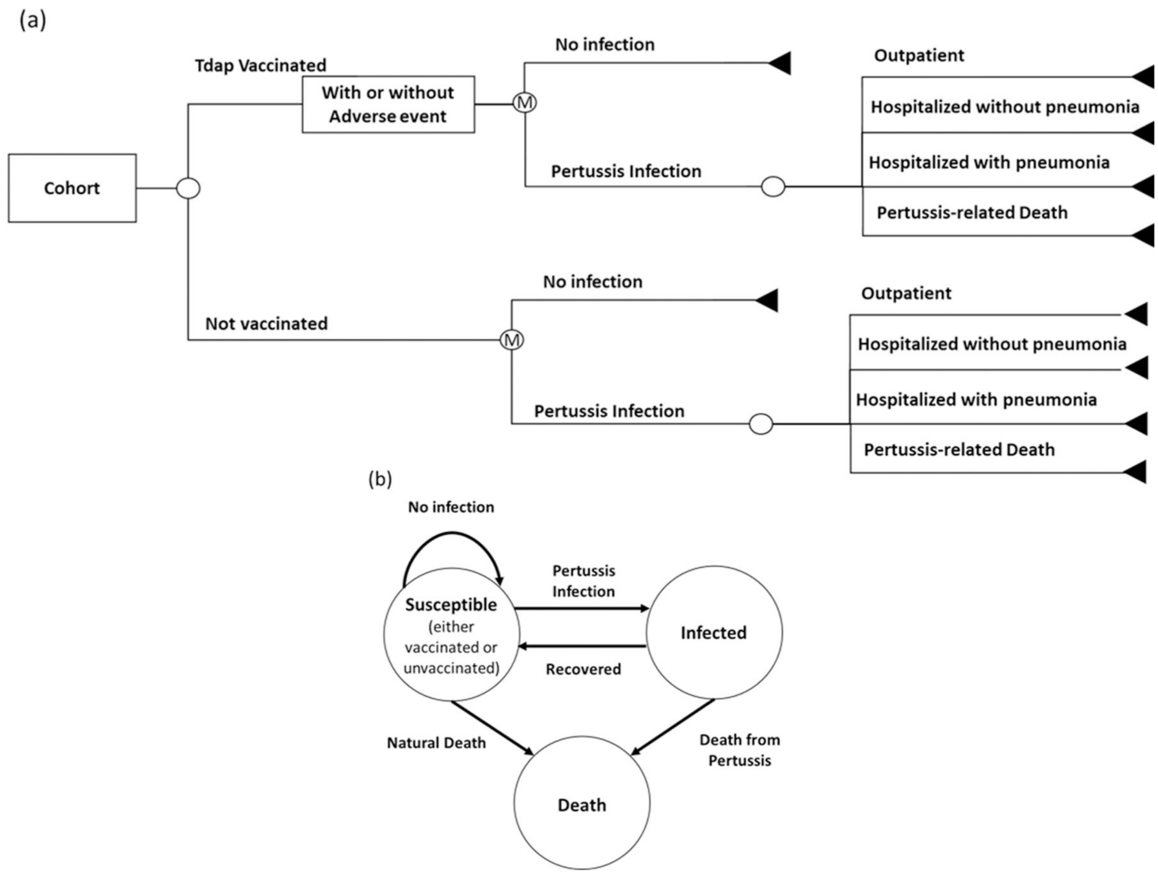

Fig. 1.

Disease progression diagram for pertussis with and without Tdap vaccination of US adults (a) and a diagram of a simple Markov model (b).

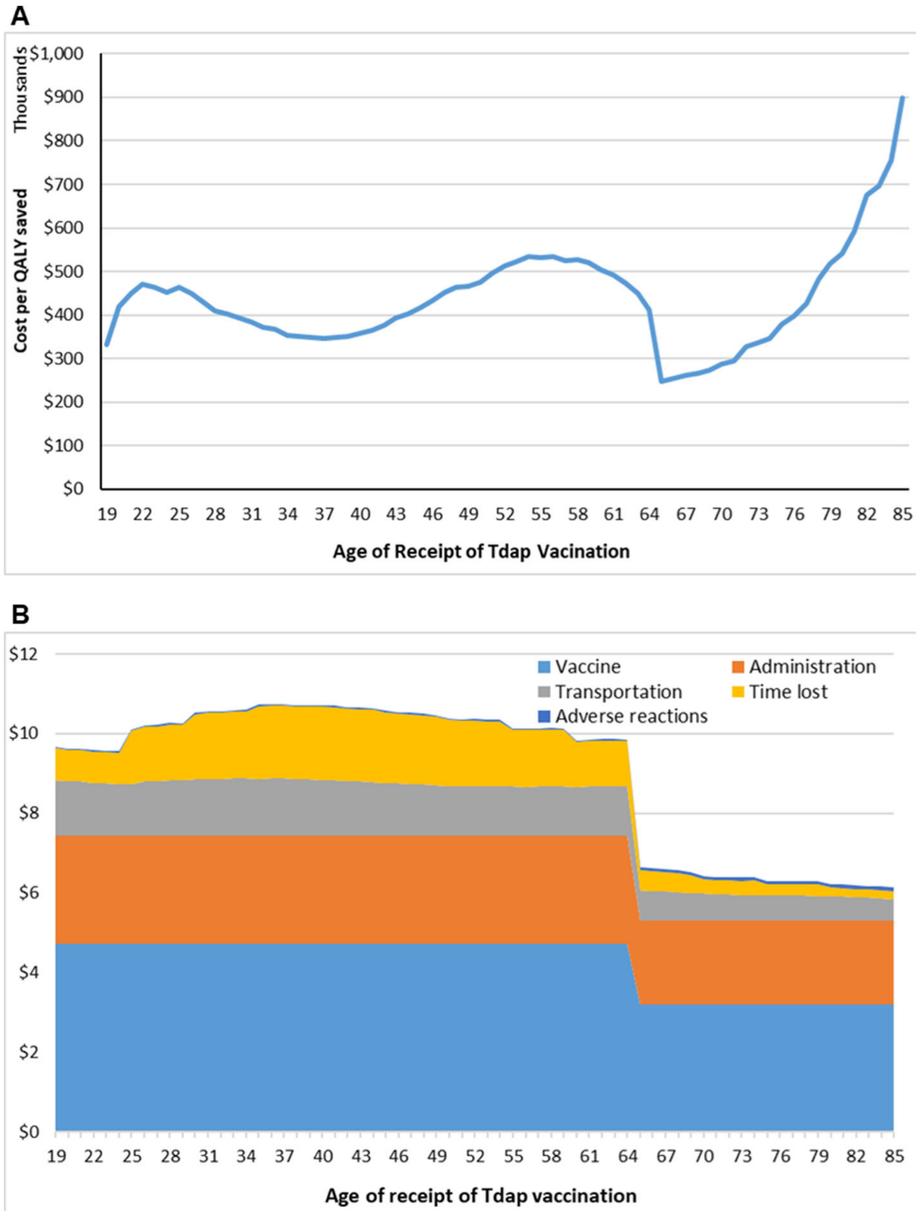

Fig. 2.

Model results for different ages of US adults receiving Tdap vaccine (a) Cost per QALY saved and (b) components of total program costs.

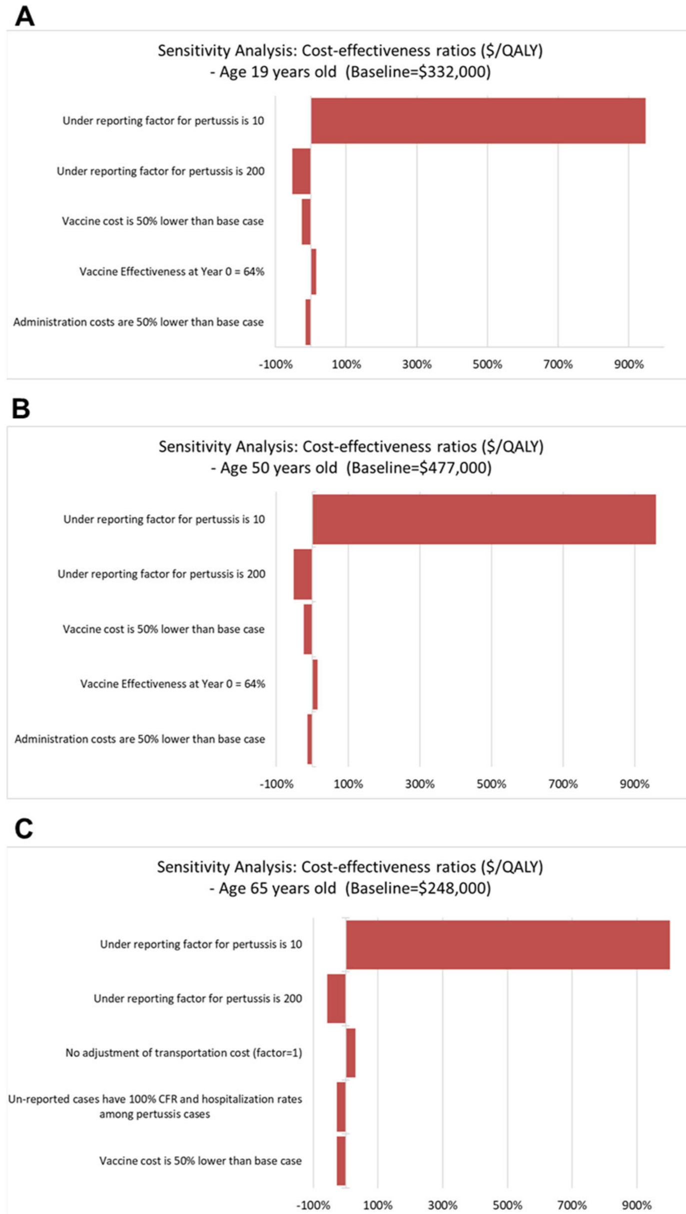

Fig. 3.

Tornado diagrams from the univariate and deterministic sensitivity analysis on selected variables for the cohort of age 19, 50 and 65.

Table 1

Base case parameter values and sources used in the model of Tdap vaccination of individuals aged ≥65 years - United States (2018$).

Input name	Base case value	Source
Epidemiology		
Pertussis incidence w/o vaccination	Age-specific	National Notifiable Diseases Surveillance System 2008–2017
Pertussis days per episode	93	Lee et al. 2004
Pertussis case-fatality rate (%)		
Age 19–49 years	0.000%	National Notifiable Diseases Surveillance System 2008–2017
Age 50–64 years	0.024%	National Notifiable Diseases Surveillance System 2008–2017
Age 65 years and older	0.178%	National Notifiable Diseases Surveillance System 2008–2017
Pertussis case under-reporting factor (age 19–100)	100	
Health outcomes		
Pertussis outpatient only (%)		
Age 19–49 years	97.2%	National Notifiable Diseases Surveillance System 2008–2017
Age 50–64 years	94.3%	National Notifiable Diseases Surveillance System 2008–2017
Age 65 years and older	88.4%	National Notifiable Diseases Surveillance System 2008–2017
Pertussis hospitalizations without pneumonia (%)		
Age 19–49 years	1.96%	National Notifiable Diseases Surveillance System 2008–2017
Age 50–64 years	3.47%	National Notifiable Diseases Surveillance System 2008–2017
Age 65 years and older	6.84%	National Notifiable Diseases Surveillance System 2008–2017
Pertussis hospitalizations with pneumonia (%)		
Age 19–49 years	0.86%	National Notifiable Diseases Surveillance System 2008–2017
Age 50–64 years	2.25%	National Notifiable Diseases Surveillance System 2008–2017
Age 65 years and older	4.78%	National Notifiable Diseases Surveillance System 2008–2017
Pertussis number outpatient visits (days)		
Age 19–49 years	1.09	Truven MarketScan databases 2003–2012
Age 50–64 years	1.10	Truven MarketScan databases 2003–2012
Age 65 years and older	1.87	Truven MarketScan databases 2003–2012
Pertussis length of stay, hospitalizations w/o pneumonia (days)		
Age 19–49 years	2.93	Truven MarketScan databases 2003–2012
Age 50–64 years	5.48	Truven MarketScan databases 2003–2012

Input name	Base case value	Source
Age 65 years and older	5.09	Truven MarketScan databases 2003–2012
Pertussis number additional visits, hospitalizations w/o pneumonia (times)		
Age 19–49 years	0.07	Truven MarketScan databases 2003–2012
Age 50–64 years	0.1	Truven MarketScan databases 2003–2012
Age 65 years and older	1.3	Truven MarketScan databases 2003–2012
Pertussis length of stay, hospitalizations w/ pneumonia (days)		
Age 19–49 years	4.81	Truven MarketScan databases 2003–2012
Age 50–64 years	5.89	Truven MarketScan databases 2003–2012
Age 65 years and older	6.59	Truven MarketScan databases 2003–2012
Pertussis number additional visits, hospitalizations w/ pneumonia (times)		
Age 19–49 years	0.24	Truven MarketScan databases 2003–2012
Age 50–64 years	0.33	Truven MarketScan databases 2003–2012
Age 65 years and older	0.88	Truven MarketScan databases 2003–2012
Quality of life per event (age 19–100)		
Pertussis outpatient only	0.85	Lee et al. 2005
Pertussis hospitalizations without pneumonia	0.81	Lee et al. 2005
Pertussis hospitalizations with pneumonia	0.82	Lee et al. 2005
Disease cost ($)		
Pertussis outpatient only		
Age 19–49 years	$165	Truven MarketScan databases 2003–2012
Age 50–64 years	$173	Truven MarketScan databases 2003–2012
Age 65 years and older	$205	Truven MarketScan databases 2003–2012
Pertussis hospitalization without pneumonia		
Age 19–49 years	$17,590	Truven MarketScan databases 2003–2012
Age 50–64 years	$23,551	Truven MarketScan databases 2003–2012
Age 65 years and older	$24,616	Truven MarketScan databases 2003–2012
Pertussis hospitalization with pneumonia		
Age 19–49 years	$11,266	Truven MarketScan databases 2003–2012
Age 50–64 years	$16,514	Truven MarketScan databases 2003–2012
Age 65 years and older	$16,216	Truven MarketScan databases 2003–2012
Indirect costs		

Input name	Base case value	Source
Informal caregiver time hours per outpatient visit (hr)	1.68	Russell et al. 2008
Informal caregiver time hours per hospitalization day (hr)	4	Assumption
Proportion of informal care given by person older than age 65 (%)	58%	Chari et al. 2014
Proportion of informal care given by person younger than age 65 (%)	42%	Chari et al. 2014
Informal caregiver value of time older than age 65 ($)	$22.66	Chari et al. 2014
Informal caregiver value of time younger than age 65 ($)	$15.03	Chari et al. 2014
Transportation cost adjustment factor	0.2–0.6	Truven MarketScan databases 2003–2012
Vaccination program		
Tdap vaccine effectiveness (%)	74%	Acosta et.al (2015)
Average vaccine cost per dose		
Age 19–64	$46.15	Tsai, Zhou, Lindley, 2019
Age 65 and older	$31.27	Payment Allowance Limits for Medicare Part B Drugs,2018
Vaccine administration cost per dose		
Age 19–64	$26.97	Tsai, Zhou, Lindley, 2019
Age 65 and older	$20.88	2018 physician fee schedule
Transportation costs per visit	$26.10	Avendano, et al. 1993
Vaccine wastage rate (%)	5%	Setia et al. 2002
Adverse reaction among vaccine recipients		
Medically attended inflammatory or allergic events		
Proportion (%)		
Age 19–64	0.03	Jackson, et al. 2009
Age 65 and older	0.19	Tseng et al. 2013
Cost		
Age 19–64	$227	Truven MarketScan databases 2012
Age 65 and older	$266	Truven MarketScan databases 2012
Anaphylaxis		
Proportion (%)		
Age 19–64	0.002%	Tseng et al. 2013
Age 65 and older	0.002%	Tseng et al. 2013
Length of stay (days)		
Age 19–64	2.3	Truven MarketScan databases 2012

Input name	Base case value	Source
Age 65 and older	3.5	Truven MarketScan databases 2012
Cost ($)		
Age 19–64	$13,413	Truven MarketScan databases 2012
Age 65 and older	$15,448	Truven MarketScan databases 2012
Natural death rate	Age-specific	US Life Table 2016
Annual discount rate (%)	3%	Gold et al. 1996

Table 2

Total costs and cost per QALY saved for Tdap vaccination of 100,000 US adults at three different ages.

Item	Age of cohort at the time of Tdap vaccination		
	19 years	**50 years**	**65 years**
Total societal costs for pertussis-related death and morbidity averted by program (A)	$300,000	$500,000	$700,000
Total Program costs (B)	$9,700,000	$9,700,000	$6,700,000
Vaccine	$4,700,000	$4,700,000	$3,200,000
Administration	$2,700,000	$2,700,000	$2,100,000
Transportation	$1,400,000	$1,300,000	$800,000
Time lost	$800,000	$1,700,000	$500,000
Adverse reactions	$0 *	$0 *	$100,000
Net costs (= B-A)	$9,400,000	$9,900,000	$5,900,000
QALYs saved	28	21	24
Cost per QALYs saved	$332,000	$477,000	$248,000

*Less than $50,000.

Table 3

Cost-effectiveness ratios ($/QALY) from the deterministic sensitivity analysis: univariate and best-case/worst-case scenarios.

Variables	Age of cohort at the time of Tdap vaccination		
	19 years	50 years	65 years
Base case	$332,000	$477,000	$248,000
Under reporting factor			
Under reporting factor for pertussis is 10	$3,476,000	$5,055,000	$2,834,000
Under reporting factor for pertussis is 70	$479,000	$691,000	$367,000
Under reporting factor for pertussis is 200	$160,000	$227,000	$109,000
Under-reported cases have 100% CFR and hospitalization rates among pertussis cases	$325,000	$432,000	$181,000
Direct and indirect costs			
All medical costs 20% higher than base case	$330,000	$473,000	$243,000
All medical costs 20% lower than base case	$333,000	$481,000	$253,000
Patients under 65 years old do not incur any caregiver costs	$332,000	$477,000	$248,000
Transportation costs is 50% lower than base case	$307,000	$447,000	$232,000
Time lost is 50% lower than base case	$317,000	$437,000	$238,000
Transportation costs is 50% higher than base case	$356,000	$506,000	$263,000
Time lost is 50% higher than base case	$346,000	$516,000	$257,000
Informal caregiver time is 2 h per hospitalization	$332,000	$477,000	$248,000
Informal caregiver time is 8 h per hospitalization	$331,000	$476,000	$247,000
Vaccine effectiveness			
Vaccine induced immunity for pertussis is 0.0 after 10 years	$350,000	$502,000	$255,000
Vaccine effectiveness at year 0 = 64%	$380,000	$548,000	$287,000
Program costs			
Vaccine costs are 50% lower than base case	$248,000	$363,000	$181,000
Administration costs are 50% lower than base case	$284,000	$412,000	$204,000
150% of transportation cost adjustment factor	$356,000	$507,000	$264,000
No adjustment of transportation cost (factor = 1)	$375,000	$542,000	$324,000
Best-case scenarios[1]	$67,000	$76,000	$8000
Worst-case scenarios[2]	$5,195,000	$7,760,000	$4,950,000

[1]Under the best-case scenario, the following assumptions were made: 1) under reporting factor for pertussis is 200, 2) under-reported cases have 100% CFR and hospitalization rates among pertussis cases, 3) all medical costs are 20% lower than base case, 4) transportation costs is 50% lower than base case, 5) time lost is 50% lower than base case, 6) informal caregiver time is 2 h per hospitalization, 7) vaccine costs are 50% lower than base case and 8) vaccine administration costs are 50% lower than base case.

[2]Under the worst-case scenario, the following assumptions were made: 1) under reporting factor for pertussis is 10, 2) all medical costs are 20% higher than base case, 3) transportation costs is 50% higher than base case, 4) time lost is 50% higher than base case, 5) informal caregiver time is 8 h per hospitalization, 6) 150% of transportation cost adjustment factor, 7) no adjustment of transportation cost (factor = 1) and 8) vaccine effectiveness at year 0 is 64%.