abstract

BACKGROUND: Infants <2 months of age are at highest risk of pertussis morbidity and mortality. Until recently, the US Advisory Committee on Immunization Practices (ACIP) recommended protecting young infants by “cocooning” or vaccination of postpartum mothers and other close contacts with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) booster vaccine. ACIP recommends pregnancy vaccination as a preferred and safe alternative to postpartum vaccination. The ACIP cocooning recommendation has not changed.

METHODS: We used a cohort model reflecting US 2009 births and the diphtheria-tetanus-acellular pertussis schedule to simulate a decision and cost-effectiveness analysis of Tdap vaccination during pregnancy compared with postpartum vaccination with or without vaccination of other close contacts (ie, cocooning). We analyzed infant pertussis cases, hospitalizations, and deaths, as well as direct disease, indirect, and public health costs for infants in the first year of life. All costs were updated to 2011 US dollars.

RESULTS: Pregnancy vaccination could reduce annual infant pertussis incidence by more than postpartum vaccination, reducing cases by 33% versus 20%, hospitalizations by 38% versus 19%, and deaths by 49% versus 16%. Additional cocooning doses in a father and 1 grandparent could avert an additional 16% of cases but at higher cost. The cost per quality-adjusted life-year saved for pregnancy vaccination was substantially less than postpartum vaccination ($414 523 vs $1 172 825).

CONCLUSIONS: Tdap vaccination during pregnancy could avert more infant cases and deaths at lower cost than postpartum vaccination, even when postpartum vaccination is combined with additional cocooning doses. Pregnancy dose vaccination is the preferred alternative to postpartum vaccination for preventing infant pertussis. Pediatrics 2013;131: e1748–e1756

AUTHORS: Andrew Terranella, MD, MPH,a,b Garrett R. Beeler Asay, PhD,c Mark L. Messonnier, PhD,c Thomas A. Clark, MD, MPH,a,b and Jennifer L. Liang, DVM, MPVMb

aEpidemic Intelligence Service, Scientific Education and Professional Development Office, bDivision of Bacterial Diseases, and cImmunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

KEY WORDS: pertussis, pregnancy, Tdap, vaccines

ABBREVIATIONS
ACIP—Advisory Committee on Immunization Practices
CDC—Centers for Disease Control and Prevention
DTaP—diphtheria-tetanus-acellular pertussis
NDSS—National Notifiable Diseases Surveillance System
QALY—quality-adjusted life-year
Tdap—tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed
VE—vaccine effectiveness

WHAT’S KNOWN ON THIS SUBJECT: Infants aged <2 months are at highest risk for pertussis morbidity and mortality but are too young to receive pertussis vaccines. To protect young infants, the Advisory Committee on Immunization Practices recommends mothers receive 1 dose of Tdap during pregnancy.

WHAT THIS STUDY ADDS: This article evaluates the effect of Tdap during pregnancy compared with postpartum Tdap and cocooning in preventing infant pertussis cases, hospitalizations, and deaths, as well as their relative cost-effectiveness.

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

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Address correspondence to Jennifer L. Liang, DVM, MPVM, 1600 Clifton Rd, Mail Stop C-25, Atlanta, GA 30333. E-mail: jliang@cdc.gov

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Prevention of pertussis morbidity and mortality in infants remains a challenge to public health practitioners. From 2001 to 2010, there were 27,995 cases and 189 deaths due to pertussis in infants aged <1 year reported in the United States (Centers for Disease Control and Prevention [CDC], unpublished data, 2011). Infants aged <2 months have an annual incidence of pertussis of 160 per 100,000 and account for 57% of all infant hospitalizations and 85% of all infant deaths (CDC, unpublished data, 2011). Pertussis is understood to be underreported, with true incidence among infants potentially twice the reported rate.1 Protecting the youngest infants is challenging because they are too young to be vaccinated with diphtheria-tetanus-acellular pertussis (DTaP) vaccines.

Of identified sources of pertussis transmission to infants, parents are the source in 50% to 55% of young infant cases, grandparents 6% to 8%, and siblings up to 20%.2,3 Strategies have been proposed to prevent infant pertussis infection, including vaccinating parents and close contacts with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) booster vaccine.4 In 2005, the US Advisory Committee on Immunization Practices (ACIP) recommended a “cocooning” strategy in which mothers are vaccinated with Tdap immediately postpartum and all other close contacts are ideally vaccinated before an infant’s birth.5 However, programmatic challenges and institutional hurdles have prevented widespread implementation of cocooning both in the United States and other countries.4,6

In 2011, the ACIP recommended vaccinating pregnant women during the second or third trimester as the preferred strategy to postpartum vaccination.7 Vaccination of mothers during pregnancy would allow maternal antibody production to reach protective levels by the time of delivery, providing protection directly to the mother and indirectly to the infant.8,9 A pregnancy dose of Tdap could also provide direct protection to the infant through transplacental transfer of maternal antibodies. These maternally derived antibodies persist in infants for 36 to 55 days at levels consistent with those that might confer protection.10–12

Before the current study, the potential benefits and cost-effectiveness of pregnancy vaccination and postpartum/cocooning had not been evaluated in the United States; however, one study in the Netherlands found that both interventions were cost-effective.13 The current study presents the results of a decision and cost-effectiveness model comparing a pregnancy vaccination strategy with postpartum vaccination with or without vaccination of other close contacts (ie, cocooning) for preventing infant pertussis in the United States.

METHODS

A Markov cohort model was used to calculate the health benefits, cost, and cost-effectiveness of pregnancy vaccination of mothers in the third trimester and of postpartum cocooning. The model used the 2009 US birth cohort of 4,131,019 infants followed for 1 year.14

Incidence and expected number of infant pertussis cases were calculated by using 2000–2007 National Notifiable Diseases Surveillance System (NNDSS) data. Although some studies have documented underreporting of pertussis in infants to be as high as 50%, we conservatively assumed a 15% underreporting rate for infant pertussis.1 Probability of hospitalization with respiratory disease and death were calculated according to month of age from 2000–2007 NNDSS data. Annual probability of encephalopathy and death were also calculated from NNDSS data. The average annual incidence of pertussis in infants aged <1 year was 62.6 cases per 100,000 infants. We assumed a duration of infant illness of 80 days.15 Age-specific incidence according to month of life is shown in Table 1.

Three strategies were analyzed: a pregnancy dose of Tdap, a postpartum dose of Tdap, and limited cocooning doses including the postpartum mother, the father, and one grandparent. The strategies were compared with the primary DTaP series with no pregnancy or cocooning doses (henceforth referred to as the base case). There were no data on Tdap vaccination...
coverage during pregnancy; therefore, vaccination coverage of 72% was used based on reported postpartum coverage under an existing postpartum cocooning program in the United States with ideal conditions. The same coverage was used for postpartum doses and cocooning doses. For all adults, vaccine effectiveness (VE) was 85%. Tdap VE between 65% and 72% has been documented, but these evaluations were conducted among adolescents 1 to 4 years after vaccination and therefore may include waning of immunity. The higher VE was chosen to reflect that effectiveness would not have significantly waned between vaccine administration and up to 6 months postpartum.

Under a pregnancy vaccination strategy, mothers were vaccinated during their third trimester of pregnancy and were considered to have full efficacy of the vaccine at the time of delivery; fathers were not vaccinated. Transfer of maternal antibodies was assumed to be 100%, with effectiveness in the infant of 60%. The duration of maternal antibody protection was assumed to last 2 months. To model potential interference of maternal antibodies on an infant’s immune response to the primary DTaP series, the risk for pertussis disease was increased by 10% during the third and fourth months of infant life.

For postpartum vaccination, mothers were assumed to be vaccinated immediately postpartum with a 2-week delay in protection, reflecting observed anti-pertussis antibody kinetics. For cocooning, parameters for postpartum vaccination of mothers remained the same; a father and grandparent were vaccinated before delivery and considered immune at the time of infant birth. Mothers and fathers were assumed to be the source of infection in 35% and 15% of infant cases, respectively. Grandparents were assumed to be the source in 6% of cases (Table 2).

We assumed a vaccine cost per dose of $37.60 and an administrative fee of $20. Costs of disease were obtained from the literature. Direct disease costs included laboratory tests, outpatient visits, hospitalizations, radiographs, and antibiotics (Table 2). Direct

<table>
<thead>
<tr>
<th>TABLE 2 Epidemiologic and Cost Variables Used in the Model</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
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<td>Vaccine efficacy</td>
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<td>Vaccine delivery</td>
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<td>Pregnancy</td>
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<td>Postpartum</td>
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<td>Paternal</td>
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<td>Maternal antibody efficacy</td>
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<td>Discount rate</td>
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<td>Infant disease duration</td>
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<td>Underreporting</td>
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<td>Disease costs, 2011 $US</td>
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<td>Outpatient respiratory illness</td>
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<td>Inpatient respiratory illness</td>
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<td>Neurologic illness</td>
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<td>Public health response</td>
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<td>Disease QALY</td>
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<td>Neurologic illness</td>
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<td>Vaccine costs, 2011 $US</td>
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<td>Vaccine price</td>
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<td>Vaccine administration</td>
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</tbody>
</table>

NIS, National Immunization Survey. a Distributions used in Monte Carlo simulations. b Medical costs included laboratory tests, outpatient/inpatient visits, radiography, and antibiotics. c Nonmedical costs included time missed from work, transportation, child care, and over-the-counter medications.
nonmedical costs included missed
time from work, child care, trans-
portation, and over-the-counter drugs.
We also included public health re-
spose costs.21 All costs were updated
to 2011 US dollars by using the Per-
sonal Consumption Expenditures Price
Index (Health Care).22
Outcomes analyzed include pertussis
cases, hospitalizations and deaths
prevented, and quality-adjusted life-
years (QALYs) saved. One QALY is de-
efined as 1 year of perfect health. In our
model, we valued perfect health as 1
and death as 0. To reflect the possibility
that infants are not all born healthy, we
valued perfect health at .93 in a sensi-
tivity analysis. We calculated total pro-
gram costs and cost-effectiveness
ratios in terms of cost in US dollars per
QALY’s saved and cases averted. All costs
and health benefits were discounted to
present value by using an annual dis-
count rate of 3%. Cost-effectiveness
ratios were estimated by using dis-
counted QALYs, cases, and hospital-
izations. We modeled each intervention
as a mutually exclusive strategy and
compared pregnancy, postpartum, and
cocooning with the base case by using
average cost-effectiveness ratios. We
measured direct medical and non-
medical costs for infant disease with an
analytic horizon of 1 year. The model
was built by using Excel 2007 (Microsoft
Corporation, Redmond, WA). One-way
and multiway sensitivity analyses were
performed to assess the impact of
varying vaccine coverage and effective-
ness, maternal antibody effectiveness,
level of underreporting, and the effects
of blunting.
We conducted a threshold analysis to
find the Tdap cost per dose (including
administration fee) that would result in
cost per QALY saved ratios of $50 000,
$100 000, and $150 000. We used a
Monte Carlo simulation with Latin hy-
percube sampling to estimate a range
of outcomes for all variables ( @Risk
5.7; Palisades, 2012).

RESULTS

Health Benefits
Under the base case, an estimated 3041
infant pertussis cases would occur
annually, resulting in 1463 hospital-
izations and 22 deaths (Table 3). Post-
partum vaccination could avert 596
infant cases annually, a 20% reduction
from the base case. Moving the post-
partum dose to late pregnancy could
avert 1012 infant cases annually, a 33%
reduction from the base case. As part
of the cocooning strategy, postpartum
vaccination plus father and a grand-
parent could avert 987 infant cases
annually (32% reduction from base
case). A majority of infant pertussis
cases averted in both strategies would
occur in the first 2 months of life
(Fig 1).
Pregnancy vaccination also prevented
a greater proportion of infant deaths
and hospitalizations; pregnancy vacci-
nation reduced infant hospitalizations
by 38% and deaths by 49% relative to
base case, compared with reductions of
32% and 29% for postpartum vaccina-
tion with cocooning. Overall, pregnancy
vaccination resulted in more QALYs
saved per year when compared with
postpartum vaccination and cocooning
(396 QALYs vs 253 QALYs saved).

TABLE 3  Health Benefits, Costs, and Cost-effectiveness Ratios

| Variable                        | Total Cases | % Reduction
|---------------------------------|-------------|-------------
|                                 | Base Case   | Pregnancy  | Postpartum | Cocooning b,c | Pregnancy | Postpartum | Cocooning b,c |
| Cases                           | 3041        | 2029       | 2445       | 2054         | 33        | 20         | 32          |
| Hospitalizations                | 1420        | 876        | 1152       | 970          | 38        | 19         | 32          |
| Neurologic disorder             | 43          | 28         | 34         | 29           | 33        | 20         | 32          |
| QALY’s lost (discounted)        | 1927        | 1006       | 1614       | 1437         | 48        | 16         | 25          |
| Without death                   | 186         | 120        | 150        | 127          | 35        | 19         | 32          |
| Death only                      | 670         | 341        | 564        | 502          | 49        | 16         | 25          |
| Total                           | 857         | 461        | 714        | 604          | 46        | 17         | 30          |
| QALY’s lost (undiscounted)      | 1927        | 1006       | 1614       | 1437         | 48        | 16         | 25          |
| Deaths                          | 22          | 11         | 19         | 16           | 49        | 16         | 29          |
| YLL (discounted)                | 670         | 341        | 564        | 422          | 49        | 16         | 29          |
| YLL                             | 1740        | 886        | 1463       | 1239         | 49        | 16         | 29          |
| Total disease costs             | $19 837 821 | $12 581 562 | $16 047 843 | $13 498 286 | 37        | 19         | 32          |
| Program cost                    | —           | $171 172 903 | $171 172 903 | $513 518 710 | —         | —          | —           |
| Net cost                        | —           | $163 916 644 | $167 382 925 | $507 179 174 | —         | —          | —           |
| Cost per case averted           | —           | $161 938 | $280 632 | $513 714 | —         | —          | —           |
| Cost per hospitalization averted | —           | $205 863 | $405 199 | $507 179 174 | —         | —          | —           |
| Cost per QALY saved             | —           | $414 523 | $1 172 825 | $2 005 940 | —         | —          | —           |
| Cost per life-year saved        | —           | $407 856 | $1 568 164 | $2 629 309 | —         | —          | —           |

Cost values are given in 2011 US dollars. YLL, years of life lost.

a Relative to base case.

b Cocooning consists of postpartum vaccination, plus father and 1 grandparent.

c We compare cocooning doses with the base case, providing average reductions for all doses combined.
Costs and Cost-Effectiveness

The total annual disease costs and program costs are presented in Table 3. The annual cost for pregnancy or postpartum vaccination programs, with an estimated 3 million vaccine doses annually, was $171.2 million. Expanding a postpartum strategy to include a father and 1 grandparent would add an additional $342 million annually (program cost for all 3 doses was $513 million). The cost per QALY saved under pregnancy vaccination ($414 523) was lower than both postpartum vaccination ($1.2 million) and cocooning ($2.0 million). Our model predicted that for the same program cost, pregnancy vaccination would save more QALYs than postpartum vaccination (396 vs 143 or 277% more QALYs). Additional cocooning doses could increase QALYs saved; however, cocooning did not save as many QALYs as pregnancy vaccination and had a higher program cost. Pregnancy vaccination was also superior in other effectiveness measures such as cost per case, hospitalization, and death averted.

Sensitivity Analysis

We performed 1-way sensitivity analyses to assess the impact of a range of values on the model (Table 4). Under nearly all scenarios, a pregnancy vaccination strategy would result in fewer overall cases and deaths at lower cost per case averted and per QALY saved. To account for possible disparate vaccination coverage among pregnant women versus postpartum women, we compared the reduction in cases and deaths between a pregnancy program with 40% vaccine coverage and a postpartum program with 72% coverage. Under this reduced coverage scenario, our model also showed that pregnancy vaccination would reduce all adverse health outcomes by more than postpartum vaccination. The greatest impact was on deaths; pregnancy vaccination was predicted to reduce deaths by 27% relative to base case; postpartum vaccination had an estimated reduction of 14%.

When analyzing the effect of vaccine dose cost on cost-effectiveness, our threshold analysis revealed that under base case values, vaccine cost per dose (vaccine plus administration cost) would need to be $9, $16, and $22.50 to achieve a cost per QALY ratio of $50 000, $100 000, and $150 000, respectively. However, if we increase underreporting to 50%, vaccine dose costs could be higher to achieve similar thresholds ($16, $27, and $38, respectively).
Under our assumptions, a Monte Carlo simulation showed large differences in health outcomes between the postpartum and pregnancy scenarios (Fig 2). The mean difference in cases, hospitalizations, and deaths (with inter-90th percentile range) between the 2 programs was 416 (23–804), 283 (72–495), and 5.4 (1.5–9.4), respectively. Pregnancy vaccination was favored for all 3 outcomes.

**DISCUSSION**

We present the results of the first decision and cost-effectiveness analysis in the United States comparing the use of pregnancy Tdap vaccination with postpartum and cocooning vaccination for preventing infant pertussis. Our analysis showed that a Tdap dose during pregnancy could avert more infant pertussis cases, hospitalizations, and deaths than postpartum or cocooning strategies. Reductions in morbidity and mortality could be achieved by shifting the timing of vaccination from postpartum to late second or third trimester of pregnancy and at no additional cost. The primary drivers of the reduction in infant illness were earlier indirect protection from vaccinating the mother before infant birth and the provision of direct immunity to the infant through transplacental transfer of antibodies. These benefits were concentrated early in infancy when morbidity and mortality are highest. Additional cocooning doses in the father and a grandparent could approach the number of cases averted by pregnancy vaccination; however, because these additional reductions are primarily in older infant age groups, the number of hospitalizations and deaths averted were not comparable.

In terms of cost-effectiveness, pregnancy vaccination was preferred to postpartum vaccination or cocooning under a robust set of situations. Changes in VE and coverage, maternal antibody effect, and potential blunting of efficacy of the primary DTaP vaccine series did not alter the relative benefits of a pregnancy vaccination. In our scenarios, because women vaccinated during pregnancy were protected at delivery, a 1-time pregnancy dose strategy was more effective than a postpartum strategy, even if the child received no maternal antibodies. Furthermore, even with a 50% increase in the risk of disease from interference with infant antibody responses to DTaP (blunting), pregnancy vaccination averted more cases and was more cost-effective than postpartum vaccination and cocooning. Altering other variables in the model changed cost-effectiveness values for

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**TABLE 4** One-Way and Multiway Sensitivity Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cases</th>
<th>Total Deaths</th>
<th>Cost ($US)/Case Averted</th>
<th>Cost ($US)/QALY Saved</th>
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<td>Postpartum</td>
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Cost values are given in 2011 US dollars.

* Vaccine coverage, 72%; VE, 85%; transmission rate, 35% (0–11 months); maternal antibody effectiveness, 72%; duration of protection, 2 months; blunting, 15%; underreporting, 15%; incidence at 2000–2007 average; hospitalization rate at 2000–2007 average.

* Best case pregnancy: blunting, 0%; maternal antibody effectiveness, 92%; and all other parameters at base case values.

* Worst case pregnancy: blunting, 50%; maternal antibody effectiveness, 20%; and all other parameters at base case values.
each of the strategies, but a pregnancy dose remained the most effective in preventing infant pertussis and was the most cost-effective. Concerns about vaccinating pregnant women with Tdap remain, including vaccine safety and the presence and magnitude of blunting of the infant immune response to DTaP. Regarding vaccine safety, data from vaccine manufacturer pregnancy registries and the national Vaccine Adverse Event Reporting System have identified no unusual patterns or occurrence of serious adverse events, and Td has been used safely worldwide in pregnant women to prevent neonatal tetanus.7,23 The clinical implications of potential blunting are unknown, and results from studies using DTaP have been mixed.12,24 The current study analyzed a range of blunting effects and found that even if pregnancy vaccination increased the risk of pertussis by 50% in 3- and 4-month-old infants, annual infant pertussis cases did not exceed the number of cases observed from postpartum vaccination or cocooning. Increased cases in the third and fourth months of life were unlikely to result in significant increases in hospitalizations and deaths because the risk of severe and fatal pertussis declined substantially after 2 months of age; in addition, even a single dose of DTaP protects against death and severe pertussis morbidity.25 Questions regarding the feasibility of pregnancy vaccination programs remain. This study used 72% coverage based on coverage of postpartum mothers achieved under a well-supported cocooning program, which provides vaccine at no charge.16 When reducing coverage of the pregnancy dose and maintaining coverage of the postpartum dose (40% vs 72%), a pregnancy vaccination program still achieved reductions comparable to postpartum vaccination and prevented twice as many deaths. Nevertheless, achieving high pregnancy coverage, while challenging, is feasible. The platform for a pregnancy Tdap dose already exists through routine prenatal care visits in which providers have numerous opportunities for education and vaccination. Many obstetrician/gynecologists now routinely offer human papillomavirus and influenza vaccines, and the American College of Obstetricians and Gynecologists supports Tdap vaccination for pregnant women.26–28 The obstetrician/gynecologist experience with influenza vaccine has demonstrated that routine vaccine coverage of ≥50% can be achieved in pregnant women. Higher coverage levels (70%–86%) are achievable when the influenza vaccines are routinely discussed with pregnant women and offered by their obstetricians.29–31 This existing platform could be expanded to include Tdap. Conversely, postpartum vaccination and cocooning programs do not have existing infrastructure and require development of new platforms for vaccine delivery through coordination of hospitals and multiple providers to reach postpartum mothers, fathers,
and other contacts. In our analysis, we used a best case scenario vaccinating close contacts before delivery. However, most family members are not vaccinated until after the infant is born, reducing cocooning effectiveness. We also used high vaccination coverage (72%) among close contacts, although Tdap coverage in all adults aged 19 to 64 years in 2010 was only 12.5%. Achieving higher postpartum maternal coverage is difficult and resource intense. However, with a shift in emphasis from postpartum to pregnancy, pregnant women are educated earlier and they, in turn, could educate and encourage family members as well as other contacts to get vaccinated before the infant is born.

Despite the strength of the findings, this study has several limitations. First, we excluded direct and indirect benefits to adults from vaccination with Tdap, which underestimates the cost-effectiveness of all strategies. Second, data were not available to further characterize infant health outcomes according to ICU admissions, pneumonias, or other pertussis-related complications, and therefore we might have underestimated pertussis costs. Third, effectiveness of maternal antibodies in preventing infant pertussis is unknown, as is the clinical effect of blunting, forcing us to rely largely on expert opinion of possible effects. Fourth, this analysis is based on simulation data only because no clinical trials have been published. Also, this study used a “static” model to estimate epidemiologic changes; use of a dynamic model would increase the strength of the results. Fifth, we analyzed a limited set of cocooning contacts: mothers, fathers, and 1 grandparent. The ACIP recommends cocooning all close contacts of an infant; however, our model showed that the benefits of a pregnancy dose outweighed the benefits of postpartum vaccination, and additional Tdap doses for other family members would have incrementally higher costs with decreasing relative benefit. Finally, we only included a slight inflation in cases to account for underreporting; cost-effectiveness of all strategies would improve markedly if incidence was higher at baseline.

In June 2011, the ACIP recommended Tdap for all previously unvaccinated pregnant women. Factors considered included absolute reduction in cases, morbidity and mortality, and the disproportionate impact of this intervention on young infants. Although cost per QALY was higher than other commonly used metrics, the pregnancy dose was more cost-effective than previously recommended Tdap strategies. By recommending Tdap during pregnancy, these vaccination guidelines now target the timing of vaccination to achieve maximum impact at the least cost. Although initial challenges remain in implementation, when compared with cocooning, pregnancy vaccination offers an economically efficient method to substantially reduce infant pertussis morbidity and mortality.

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Andrew Terranella, Garrett R. Beeler Asay, Mark L. Messonnier, Thomas A. Clark and Jennifer L. Liang

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