EVALUATING THE EFFICACY OF AN ACCELERATED DIPHTHERIA, TETANUS, AND PERTUSSIS (DTAP) RECOMMENDATION IN SOUTHWESTERN OREGON COUNTIES DURING A PERTUSSIS OUTBREAK IN 2003

by
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A THESIS

Presented to the Department of Public Health and Preventive Medicine at Oregon Health and Science University School of Medicine in partial fulfillment of the requirements for the degree of Masters of Public Health

MAY 2006

School of Medicine
Oregon Health and Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

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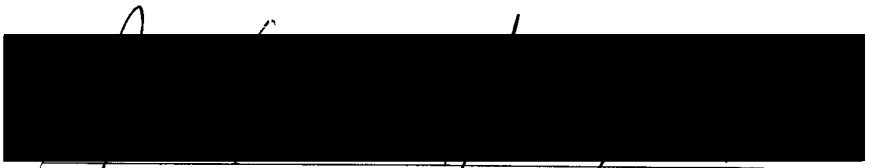

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TABLE OF CONTENTS

List of Tables and Figures

Figures

ACKNOWLEDGEMENTS

I would like to thank my thesis committee for their dedication, encouragement, and support throughout this project. My chair, Jim Gaudino, MD, MS, MPH has been a patient teacher and mentor throughout an interesting project that turned out to be much more complicated than originally thought. Nichole Carlson, PhD was instrumental in helping guide the SAS code and statistical challenges posed by this project. And Katrina Hedberg, MD, MPH brought refreshing clarity into waters that sometimes got quite muddy!

Many individuals at the State of Oregon Immunization Program made this project possible, through their assistance with data management and program design. They include Barbara Canavan, Don Dumont, PhD, Mary Beth Kurilo, MPH, MSW, Juventila Liko, MD, MPH, Steve Robison, Deborah Rochat, and Martha Skiles, MPH.

I would also like to thank members of the Department of Public Health and Preventive Medicine at OHSU for their continued presence throughout my medical school career, and more importantly, throughout my public health year and thesis. They include Donald Austin, MD, MPH, Thomas Becker, MD, MPH, Dongseok Choi, PhD, Jay Kravitz, MD, MPH, Yvonne Michael, ScD, Dawn Peters, PhD, Katherine Riley, EdD, and Gail Yamashita. A special thanks goes to John Stull, MD, MPH, for his strong commitment to the success of the MD/MPH program and its students.

Finally, my MD/MPH student colleagues, family and Doran all made the completion of this thesis possible, with their encouragement, reassurance, patience, and HUMOR!

ABSTRACT

Introduction

In the 20th century, pertussis was one of the most common childhood diseases and a major cause of childhood mortality in the U.S. Incidence decreased significantly since the introduction of (1949) and routine administration of the pertussis vaccine, as recommended by the Advisory Committee on Immunization Practices. However, pertussis outbreaks continue to occur, and infants, many of whom are not age-eligible to be fully immunized, are the most susceptible to the disease's severe complications. During these outbreaks, a question remains whether an accelerated Diphtheria, Tetanus, and Pertussis (DTaP) immunization schedule is an effective outbreak control method. Despite its regular use during outbreaks, the true efficacy of such a recommendation has not yet been evaluated. In 2003, Oregon experienced a pertussis outbreak with 422 cases, the majority of which occurred in Lane, Jackson, and Klamath counties. In July 2003, public health officials recommended an accelerated DTaP vaccination schedule to immunization providers in these three counties. Neighboring Douglas County did not recommend the accelerated schedule, despite experiencing an elevated number of cases. We conducted a retrospective cohort study to determine if mean DTaP interval spacing: a) differed between recommendation and non-recommendation counties after the recommendation was made; b) differed within recommendation counties before and after the recommendation was made; and c) differed by clinic specialty and other child characteristics.

Methods

Oregon's ALERT immunization registry was used to identify 5,036 children in two birth cohorts surrounding the timing of the recommendation. We used Chi-square statistics to identify differences in demographic distributions between the two birth cohorts. We used generalized linear models to summarize baseline intervals and compare differences in mean intervals between clinics in recommendation and non-recommendation counties. GLM also compared mean intervals in the pre- and post-recommendation periods only among children who received shots from clinics in recommendation counties, and investigated whether these differences depended on clinic specialty. Multivariate models were created to adjust for potential confounders of delayed immunization.

Results

Effectiveness of the recommendation was assessed by detecting a reduction in mean interval spacing between DTaP doses following the recommendation of an accelerated DTaP schedule. Post-recommendation mean intervals were significantly shorter in the recommendation counties ($p<0.0001$), whereas no post-recommendation intervals were significantly shorter in the non-recommendation county. Among immunization providers in the recommendation counties, all three unadjusted mean intervals were significantly shorter after the recommendation ($p<0.0001$) compared to before the recommendation. Once adjusted for potential confounders, a significant reduction in post-recommendation mean interval spacing among Pediatric, Family Medicine, and County Health

Departments, despite the difference not depending on clinic specialty of the immunization provider ($p>0.05$).

Conclusions

These results suggest that DTaP dosing significantly changed after a recommendation was made to accelerate the DTaP schedule in the midst of a pertussis outbreak. This study provides needed evidence that some clinics are able to adopt and implement a new public health recommendation for an accelerated immunization schedule, supporting the use of an accelerated DTaP schedule as a feasible and perhaps effective pertussis outbreak control measure.

INTRODUCTION

In the 20th century, pertussis, or "whooping cough," was one of the most common childhood diseases and a major cause of childhood mortality in the U.S., with an average incidence of 150/100,000 [1, 2]. The highly contagious respiratory infection can result in a wide range of outcomes, from a persistent cough, to pneumonia, or rarely, to more severe neurological complications, including death [3]. Existing unified recommendations for routine childhood immunizations put forth by the Advisory Committee on Immunization Practices (ACIP) are effective in reducing endemic disease [4], yet sporadic outbreaks persist. During these outbreak situations, a scientific question remains whether the introduction of an accelerated DTaP immunization schedule is an effective method for controlling a pertussis outbreak. Despite its regular use during pertussis outbreaks, the true efficacy of such a recommendation has not yet been evaluated. While the ultimate public health goal is full vaccination and complete eradication of pertussis, this study addresses a more immediate step in achieving this goal. By gaining a better understanding of how best to control an outbreak, public health can more effectively minimize the significant, and entirely preventable, personal, societal, and financial costs of pertussis outbreaks.

BACKGROUND AND SIGNFICANCE

Disease Background and Epidemiology

Following the introduction of the whole cell pertussis vaccine in 1949, the incidence of pertussis declined from its peak of 260,000 U.S. cases in 1938 [1, 2] by more than 99% to a nadir of 1,010 national cases in 1976 [5, 6] and an average incidence of 1/100,000 by 1980 [7]. However, since the early 1980s, a significant increase in disease incidence has been documented with 11,647 U.S. cases reported in 2003 and outbreaks occurring every three to five years [8, 9]. These numbers are thought to significantly underestimate the true incidence of disease, as diagnostic and reporting deficiencies make the prevalence of pertussis difficult to document [8]. Although it has been speculated that this increased incidence merely represents increased surveillance among clinicians, a review of recent pertussis trends by Tanaka *et al* found unchanged laboratory diagnosis rates, unchanged ages of infected individuals, and unchanged disease severity, all evidence suggesting that this increased incidence it not simply a result of increased reporting [10].

Pertussis transmissibility approaches 100% following close contact with an infected person. After an incubation period that can range from 5-21 days, pertussis typically presents with mild upper respiratory symptoms and a progressive cough, which develops into a paroxysmal cough with an inspiratory "whoop," after which the disease is named [11]. While symptoms usually begin to resolve after 4-6 weeks, some patients acquire a bacterial pneumonia or suffer post-tussive complications, which can include hypoxemia, apnea, neurological disorders, seizures, encephalopathy, and death [11]. The

diagnosis of pertussis is generally based on clinical history alone, but relatively non-specific laboratory data such as bacteriologic cultures, direct fluorescent antibody tests, or serologies can be used as supportive evidence for suspected infections.

According to Oregon State Public Health, a *confirmed case* of pertussis is defined as "a positive nasopharyngeal culture of positive PCR with at least one of the following: paroxysmal cough, cough with inspiratory 'whoop,' any cough lasting two weeks, or post-tussive vomiting" [12]. *Presumptive case-definitions* are "persons who are epidemiologically-linked to a confirmed case and have: an acute onset of cough within 7-14 days of exposure and *either* a paroxysmal cough lasting more than 14 days, *or* a paroxysmal cough and white blood cell count in excess of 25,000/ml with 70% or more lymphocytes" [12]. In 1996, the CDC and Council of State and Territorial Epidemiologists (CSTE) changed the case definition in the midst of an outbreak to read "a cough illness lasting 2 weeks or longer without other criteria" [13].

Although pertussis can occur at any age, children, especially those less than one year of age, experience the greatest morbidity and mortality. As of 2000, approximately 40% of reported cases in the U.S. were among children less than 5 years of age [14]. Infants less than 12 months are more likely than older children or adults to experience severe disease, suffer complications, require hospitalization, or die [5]. Whereas only 20% of reported child and adult cases during 1997-2000 were hospitalized, 63% of all infants < 6 months of age required specialized hospital care [6]. Finally, 50% of all pertussis-related deaths in that same time period occurred in infants under 12 months [6].

Apart from the clinical implications of a pertussis outbreak, patient families and the health care system also bear a large financial burden due to medical costs and lost

days of work. In a retrospective analysis of the economic consequences of pertussis in a New York county over a 6-year period, Pichichero and Treanor [15] determined the total indirect and direct costs for 107 cases of pertussis to be $381,052, or an average of $3561.23/case. Of these costs, 51% was associated with hospitalized care, and 32% was associated with lost work days. The estimated costs and frequencies of events (in parentheses) per individual case were: $95 for antibiotic charges (91%), $48 for symptomatic treatment (100%), $202 for the average emergency room visit (28%), and $13,425 for the average hospital admission cost (14%). In addition, 50% of families had at least one adult who missed on average 8.3 days of work to provide childcare, and additional childcare costs were as high as $2688/family [15].

Vaccine Information

Routine childhood immunization with the DTaP vaccine remains the primary disease and outbreak prevention strategy. The Advisory Committee on Immunization Practices (ACIP), together with the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP), comprise the primary body in the United States that discusses and makes nationwide recommendations for vaccine usage and schedules. The ACIP recommends that the first three doses of DTaP vaccine be given at 2, 4, and 6 months. The first booster dose should be given at least 12 months after the third dose, and is routinely given at 15-18 months. A second booster dose should be given at 4-6 years [4] (see Appendix 1). The 2003 National Immunization Survey estimated that, among 13-month-olds, 91.2 +/- 0.7% and 88.3 +/- 4.5% of children were up-to-date on 3 DTaP doses in the U.S. and Oregon, respectively [16]. However, rates in

Oregon are lower for the most vulnerable children who are less than 12 months old; only 84.6 +/- 5.2% of 3- month-olds and 71.7 +/- 6.2% of 5-month-olds were up-to-date on pertussis vaccinations [16].

The increased susceptibility in infants and children mentioned above is directly related to the immunity granted by routine vaccination and the course of pertussis infection in different age groups. Immunity after natural infection is presumed to be complete and lifelong [16], whereas immunity secondary to vaccination is somewhat decreased. Therefore, even a child who is appropriately immunized for their age may still become infected, although having been vaccinated generally shortens and minimizes the severity of the illness [17]. Vaccine efficacy data vary widely due to different study designs, however estimates have ranged from 79-90% after receiving three doses of whole cell vaccine to 71-89% after three doses of acellular pertussis vaccine, which is the currently licensed form of the pertussis vaccine [18]. With both vaccines, the protection against disease declines steadily after 2-3 years following immunization, such that virtually no immunity exists against pertussis a decade after the last vaccination [17]. This leaves virtually all adolescents and adults susceptible to infection. Because their disease is often milder and goes undiagnosed, adolescents and adults are capable of unknowingly transmitting pertussis to younger infants and children. Therefore, although adolescents and adults may experience higher rates of infection due to their decreased immunity, younger children are the most susceptible to the worst complications of pertussis.

Opponents of routine immunization may cite the cost of vaccination as one of several barriers to their administration. Indeed, costs of childhood vaccine purchases

over the last 25 years have grown at an inflation-adjusted mean rate of 19% per year [19]. The Oregon Immunization Program and CDC, in their 2003-2004 lists of vaccine pricing data, reported the direct vaccine costs for DTAP doses 1- 4 ranging from $51-$80.96, in the public and private sectors, respectively [20]. Costs increase to $63.75 - $101.20 when including the second booster dose. Clearly, these costs pale in comparison to the financial implications of pertussis cases, as described above [20, 21]. The elevated risk of transmissibility and long-lasting complications, as well as the high societal costs of an outbreak, all underscore the need for prevention of transmission to vulnerable populations and treatment of infected cases.

Pertussis Outbreak Control Measures and Accelerated DTaP Schedule

The overall increase in incidence of pertussis has been complicated by outbreaks that occur every 3-5 years and last for several months. A pertussis outbreak has been defined as "two or more non-household cases clustered in time or space" [13]. Once an outbreak has been identified, several routine strategies exist for outbreak management and containment. These include case reporting to public health authorities, early recognition, and antibiotic prophylaxis/treatment of infected persons, suspected cases, and close contacts [14]. Accelerated DTaP vaccination has also been considered an acceptable outbreak control measure, based on the fact that children are most susceptible to pertussis when they have not yet been vaccinated, especially during their first two months of life. However, the actual efficacy of the accelerated DTaP immunization schedule during an outbreak has yet to be fully evaluated.

Under the accelerated DTaP schedule which uses minimum dose spacing (Appendix 1), the first DTaP dose is given at six weeks of age, with subsequent doses given in 4-week intervals at 10 and 14 weeks [22]. According to this schedule, infants are capable of completing their first three DTaP doses by 14 weeks (3.5 months), compared to 24 weeks (6 months) under the routine schedule. Refer to Table 1 below for a comparison of the standard and accelerated vaccination schedules.

***Table 1**- Routine and accelerated minimum dose spacing recommendations for DTaP vaccines [4]*

DTaP Dose	Customary Age for Routine Administration	Minimum age and dosing intervals
Primary 1	6 weeks – 2 months	*6 weeks of age*
Primary 2	4 months	*4 weeks after first dose*
Primary 3	6 months	*4 weeks after second dose*
First Booster	15 – 18 months	*6 months after third dose but not before 12 months of age*
Second Booster	4-6 years	Same as customary

Although limited, immunologic studies have found evidence in support of the accelerated DTaP schedule beginning at 4-6 weeks [23]. While maternal antibodies have been shown to block an infant's antibody response to a vaccination during the first few weeks of life [24], vaccination at 4 or 6 weeks results in a nearly identical antibody response as vaccination at 8 weeks [25]. Furthermore, dosing the pertussis vaccine at one-month intervals for the first three doses results in a high degree of clinical protection even when begun at an early age [26]. A 1992 British study was conducted to compare the immunogenicity of the standard and accelerated schedules [27]. In that study, Booy *et al* found that both schedules resulted in satisfactory antibody responses to three pertussis antigens, and that the serum tetanus and diphtheria antibody levels exceeded the minimum protective levels in both schedules [27]. While most of these previous studies

have been conducted using whole-cell pertussis vaccines, there is evidence that some acellular vaccine preparations may mount an even earlier and stronger antibody response than the whole cell vaccine [28]. Therefore, because of the comparable immunoprotection granted by both schedules, the youngest, most vulnerable children are theoretically protected better and sooner because of the earlier antibody response granted under the accelerated schedule.

Although an accelerated schedule is likely to have both scientific and cost-saving justifications as an acceptable outbreak measure, limited epidemiologic data exist regarding how often accelerated schedules are used or what impacts such a recommendation may have during an outbreak. Several efforts have been made to both utilize the accelerated strategy and document its efficacy, however none have generated evidence to answer the question of whether an accelerated schedule altered DTaP dosing practices with the potential for slowing the rate of a pertussis outbreak. The recommendation to accelerate DTaP immunizations was made during a large pertussis outbreak in 1993 in Cincinatti, Ohio [29] and during a school-based outbreak in Yavapai County, Arizona in late-2002 [30]. However, these studies were descriptive case reports that did not facilitate the direct evaluation of the recommendation itself.

A separate study in the United Kingdom was conducted out of a concern about the accelerated schedule's efficacy, because a series of fully immunized infants were thought to have contracted pertussis during an outbreak when the accelerated schedule was implemented [31]. In this study, White *et al* monitored the duration of protection under the accelerated schedule to evaluate its continuing impact on the risk of pertussis infection. The authors found a 94% whole-cell vaccine efficacy in children aged 6

months to 5 years, and 89% efficacy in children aged 5-15 years, both results being similar to the expected values for the routine vaccine schedule. Not only did this study demonstrate that an accelerated schedule did not increase the incidence of pertussis, but it also provided support that children who are eligible to be vaccinated under the accelerated schedule were granted adequate immunoprotection. However, this study did not compare vaccine coverage or morbidity data before and after the implementation of the accelerated schedule, and therefore was unable to assess the true impact of the recommendation of an accelerated schedule on DTaP dosing

With any new clinical recommendation, a cost-effectiveness analysis is warranted to justify its use. Because of the limited evaluation of accelerated schedules, little cost-analysis information is available. However, based on the fact that the highest rates of hospitalization and death occur before the first vaccination at 2 months, Scuffham [32] used Markov modeling to estimate the costs and health consequences of different strategies used to reduce infantile pertussis in the first six months of life. Disability-adjusted life-years (DALYs) were used to compare earlier vaccination (at birth *or* 1 month, as well as standard immunization practices) with the current practice of vaccination at 2, 4 and 6 months. Originally calculated in Australian dollars, the averted costs per disability-adjusted life-years (DALY), converted into U.S. dollars, were US$259,319 and $578,059 for vaccination at birth and one month respectively. Although these interventions have not been discussed in the U.S. as potential prevention strategies, this study demonstrates that earlier vaccination can significantly reduce pertussis-related costs and morbidity.

Correlates of Immunization Practice

Other factors are known to be correlated with delayed immunization and must be considered when studying interventions to change immunization practices such as the recommendation to accelerate DTaP doses. Among the more frequently explored areas are immunization provider characteristics and parent/child characteristics such as race and socioeconomic status. Zimmerman et al showed that providers were more likely to refer a hypothetical child without insurance to the health department for immunizations (66%) than they were for a child who had vaccination benefits included in his insurance (8%). Furthermore, physicians who did *not* receive free vaccines from state or federal source such as Vaccines for Children (VFC) were significantly more likely to refer a child to the health department (90%) than were providers who *did* receive free vaccine (44%) [36]. Each of these patterns creates the potential for loss to follow-up of children who were referred to another clinic, a loss of a sense of a "medical home" at a single clinic since their care is fragmented between two clinics, and the potential for more delayed immunization rates at health departments.

Clinical specialty of the immunization provider has also been show to impact early immunization rates. Through the use of immunization behavior surveys of Pediatric, Family Medicine, and general immunization providers, Koepke demonstrated that Pediatricians had higher rates of up-to-date immunization coverage at 12 months than Family Medicine or General Practitioners (78% vs 58%), and identified provider specialty as the strongest predictor of immunization coverage in multivariable analysis [37]. Huetson et al demonstrated in their birth certificate survey that, while patients at

both private and public clinics experienced immunization delays, patients at public clinics were more likely to experience delays due to missed opportunities [38].

Finally, Gaudino et al reviewed the evidence from 1980-1995 of risk and protective factors of incomplete pre-school vaccination. They identified a wide variation among studies suggesting weak and/or inconsistent associations between race/ethnicity and vaccine status, and suggested that any effect of race on vaccine status must be adequately adjusted for potential confounders such as socioeconomic status [39].

The results from these and other studies suggest that, while delayed immunization is a persistent problem in the overall population, certain characteristics of sub-populations impact immunization delivery and receipt and must be considered, not only for analytic purposes, but also for public health education and outreach.

Oregon's Pertussis Experience in 2003

Oregon is unique in that it not only reports frequent pertussis outbreaks, but also that it has implemented a comprehensive computerized statewide immunization registry (Immunization ALERT) that collects data from participating public and private providers. In 2003, Oregon experienced a 30-year high in pertussis cases, with at least 422 reported cases, which equated to the 4th highest incidence rate in the U.S. that year [33]. Lane, Jackson, and Klamath counties, in the southwestern portion of the state reported the most cases in the state, at a rate of 11 times the average national pertussis incidence [34]. The demographics of this 2003 Oregon outbreak were as follows: 39% of cases were in adults, the median age of cases was 13 years, 7% of all cases were hospitalized, and 79% of those hospitalized were less than 4 months of age. Of the 245 cases reported in 2002-

2003 who were less than 10 years of age, 51% were not up-to-date on their immunizations per routine ACIP recommendations and 52% had never received any pertussis vaccine [33].

In July 2003, public health officials from Lane, Jackson, and Klamath counties recommended the implementation of the accelerated DTaP schedule as an outbreak control measure. Although neighboring Douglas County also experienced an elevated incidence of disease, the decision was made not to accelerate the DTaP schedule, as it was felt that there were not enough cases to anticipate an impact of the intervention. County Health Departments utilized a variety of methods to notify immunization providers of the accelerated DTaP schedule [35]. In Lane County, officials mailed a letter to immunization providers and clinics, along with a copy of the recommended accelerated DTaP schedule. Additionally, community media interviews about the outbreak were broadcast, but no specific information was given publicly regarding the accelerated schedule, and no additional immunization clinics were held. Klamath's implementation strategies included a fax disseminated to all practitioners, articles in the local newspaper, and radio interviews. Jackson County e-mailed their message to providers, and created a short educational video about pertussis for training purposes for day care providers, teachers, and adult foster home care providers. Again, no special advertising of shot clinics was done at the public level. In lieu of recommending the accelerated DTaP schedule, Douglas County conducted a pertussis recall, as part of a special state-funded grant opportunity to increase childhood immunization coverage, in which they recalled all children who needed DTaP and other doses in the primary series.

PURPOSE, OBJECTIVES, AND HYPOTHESES

The existence of the ALERT registry and a multi-county recommendation to accelerate the DTaP immunization schedule provided a unique opportunity to evaluate the efficacy of the recommendation. The purpose of the study was to determine if a public health recommendation to clinicians to use an accelerated diphtheria, tetanus, and pertussis (DTaP) immunization schedule during a pertussis outbreak significantly changed the mean interval spacing between DTaP doses 1-3.

Specifically, the objectives of this study were to determine if:

- mean DTaP dose spacing differed between recommendation and non-recommendation counties after the recommendation was made.
- mean DTaP dose spacing differed within recommendation counties before and after the recommendation was made.
- differences in mean DTaP dose spacing between pre- and post-recommendation periods depended on clinic specialty of the immunization provider, child's sex, mother's race, and maternal WIC enrollment at birth.

We hypothesized that:

- post-recommendation mean interval spacing between DTaP doses would be shorter in counties where the recommendation was made, compared to those counties where the recommendation was not made.

- mean interval spacing between DTaP doses would be shorter after the recommendation was made compared to before the recommendation was made, among those counties where the recommendation was implemented.
- mean interval spacing between DTaP doses would be different between Pediatric, Family Medicine, and County Health Department practices at baseline and following the recommendation.

METHODS

Overview

We conducted a retrospective cohort study of birth cohorts using two sources of data: 1) vaccine service data from Oregon's computerized statewide tracking and recall immunization registry (ALERT), linked to 2) Oregon Birth Certificate Data. We compared these data before and after recommendations were made to accelerate the DTaP schedule during a pertussis outbreak, to determine if providers adopted the recommendation and significantly changed DTaP dose spacing.

Approval to conduct this secondary data analysis was granted by both the Internal Review Board of the State of Oregon Department of Health Services, and Oregon Health and Science University.

Description of Outbreak and Implementation of Recommendation

Four counties in Southwestern Oregon were identified as having elevated rates of pertussis in the summer of 2003. Three of these counties (Lane, Jackson, and Klamath) were formally considered "outbreak" counties, whereas one (Douglas) was not. The three outbreak counties (Lane, Jackson, and Klamath) recommended the accelerated schedule, whereas the non-outbreak county (Douglas) did not recommend the accelerated DTaP schedule, due to a perceived insufficiency of cases to anticipate an impact of the intervention. Prior to the analysis, we called the immunization coordinators from each county health department to confirm the dates of when accelerated DTaP dose recommendations were implemented and rescinded in each county [35]. Lane County Health Department was first to recommend the accelerated schedule on July 12, 2003.

Klamath County was next to recommend the schedule, starting on July 18, 2003. Jackson County was last to implement the schedule starting on July 31, 2003. The end dates of the recommendation varied slightly as well. Klamath County was first to rescind the recommendation on November 7, 2003. Lane County withdrew the recommendation on December 16, 2003. While Jackson County never officially notified providers to terminate the schedule, they did not aggressively pursue the accelerated DTaP schedule.

Data Sources and Data Quality

a. Oregon Immunization ALERT

ALERT is a statewide immunization information system developed to facilitate complete and timely immunization of all children in Oregon, particularly those who are under age 2, and are at the highest risk of complications if not immunized properly. ALERT collects immunization service data from public and private health care providers, as well a large number of secondary data sources, and creates individual child vaccine records using complex linkage and de-linkage algorithms (including some hand review) that keep the records accurate and up-to-date. The ALERT registry was implemented beginning in 1996 with the voluntary enrollment of public and private immunization providers throughout the state, as well as children receiving immunizations from these providers. As of November 2004, 100% of public and 87% of private providers in Oregon were enrolled to submit data, and over 27 million vaccinations were recorded for 1.8 million children [40].

Once a child is identified and registered in the system, the child receives a de-identified code number, and the child's identifying information is stored separately.

Health care providers use multiple methods to report immunization data to the ALERT data system following the administration of any vaccination. Private providers primarily send service data through the electronic transfer of records or through submission of bar-coded hard copy reports [40] (see Appendix 2). County health departments, health plans, and larger insurance companies electronically submit their data, including their electronic billing data. In the event that a child receives immunizations at multiple sites, the data from the various sites are reported, stored, and then carefully linked into a dynamically updated comprehensive individual immunization record for each child. The quality of the data is maintained through regular checks by ALERT staff following each submission, and follow-up is done with the immunization provider for any questions regarding the validity of the data.

b. Oregon Birth Certificate Data

Oregon birth certificate data, available through the Oregon Department of Human Services, provided further demographic variables of interest in this investigation. As a component of its routine operations, the Oregon State ALERT system and Oregon State Immunization program links data from the birth certificate (i.e., race, parental education, WIC eligibility) to the ALERT system. This linkage is done early on by the ALERT system to assist in validating child identifiers. Additional linkages of birth certificates are done later for routine surveillance and public health evaluation purposes by the Oregon Immunization Program. Birth certificate variables that were used in this study will be discussed in the Data Analysis section of this Methods Section.

Data Collection and Management

a. Creation of Initial Dataset

Prior to the release of the ALERT data to the investigators, all data for this project was de-identified with unique codes for child records. This unique coding allowed the investigators to make additional data queries of ALERT staff, as needed. A smaller dataset, based on the inclusion and exclusion criteria listed below, was extracted from the statewide database by ALERT staff for the purposes of this investigation.

Inclusion Criteria for Initial Data Extract:

All child subjects must have been born on or after April 1, 1996, had at least one DTP or DTaP immunization reported to ALERT, and had at least one address reported in one of the four study counties (Lane, Jackson, Klamath, Douglas). This dataset included 35,274 child records, with data reported from April 1, 1996 through the extraction of data for analysis in May 2005.

Exclusion Criteria for Initial Data Extract:

Apart from not meeting the inclusion criteria, no additional exclusion criteria existed for this initial dataset, as we intentionally kept the initial dataset large in order to increase the potential for exposure to the recommendation.

b. Shot Selection

Like most immunization registries, ALERT was originally designed as an immunization data repository for use by ALERT clinical clients and partners, rather than

a research database. Therefore, significant data cleaning was required prior to beginning the analysis. Upon receipt of the original data, up to 10 different date variables were available for DTaP vaccinations for one child, if multiple dates were reported. A complex shot selection algorithm was created in SAS that used the timing of vaccinations and characteristics of each report to select 5 final DTaP dates from multiple reports that likely represented the same shot. This algorithm eliminated any shot date reported within 14 days (2 weeks) of the child's birth, as this was thought to be misreporting of the first Hepatitis B shot as the first DTaP dose, since the minimum age for the first DTaP dose under either the routine or accelerated schedule is 6 weeks, and the first Hepatitis B vaccination can be given as early as a child's first day of life for certain clinical indications.

Furthermore, in previous analyses of ALERT data quality, at least 80% of shots reported within 10 days of each other were determined to be the same shot. Therefore, a series of shot characteristics was used to select among multiple reported shots within a 10 day window of each other. DTaP shots were preferentially selected if the shot date was: 1) reported from a primary reporting source (clinic) rather than a secondary or an unidentified reporting source (health plan, insurance company); 2) associated with a vaccine manufacturer lot number, and 3) the first of multiple reports that included absent or identical dates, reporting sources, and/or vaccine manufacturer information. In addition to selecting the date of the final selected shot, the algorithm captured these corresponding shot variables: 1) a de-identified clinic site code for each shot's reporting source, and 2) Vaccines for Children (VFC) eligibility at the administration of each shot.

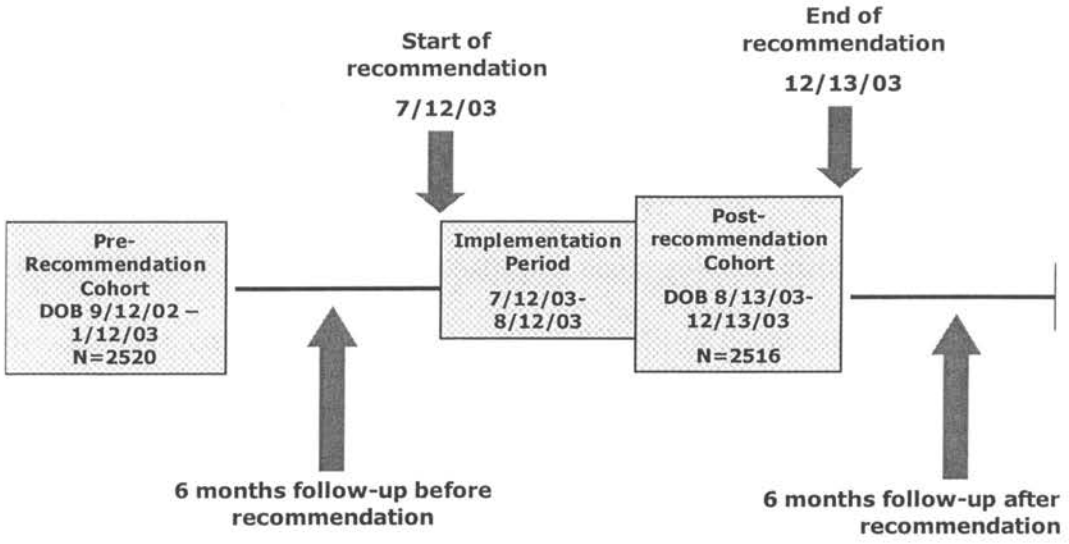
c. Child Cohort Selection

Child cohorts for analysis were selected from the following periods. Because the recommendation started at different times in the three intervention counties, July 12, 2003 (the first implementation date of the recommendation) was selected as the start of the study's recommendation period to minimize this variability. A month-long "implementation period" was defined from 7/12/03-8/12/03. We assumed this allowed adequate time for message dissemination, provider education, and incorporation into clinical practice, and gave each intervention county at least two weeks of potential exposure to the recommendation before starting analysis on shots given in the "post-recommendation" period. No analysis was performed on children who were born during the implementation period. The post-recommendation period was defined as the four month period from the end of the implementation period to the time at which the recommendation was rescinded. This period included dates from 8/13/03-12/13/03, and corresponded to the period when the accelerated schedule would most likely have been used. A six-month period of follow-up was available following the end of the post-recommendation eligibility period, which extended until 6/13/03. To facilitate a balanced design, a pre-recommendation period of four months was also selected, the dates of which were 9/12/02-1/12/03. Although the same length of time, the pre-recommendation period was selected to start one month earlier than the post-recommendation period to allow an equivalent six months of follow-up before the implementation of the recommendation. During this period, we could also evaluate mean DTaP intervals at baseline.

In order to obtain the most accurate comparisons using independent samples, two cohorts were selected of all children *born* during the two periods defined above. This selection of children born during the pre-recommendation period identified children who would have a significant period of follow-up during the pre-recommendation period, such that baseline intershot intervals could be established and summarized. Optimally, this six-month period of follow-up allowed the calculation of at least two mean intervals during the routine and/or accelerated schedule. By separating the birth cohorts by many months, this study design minimized the possibility that any of the first three DTaP shots received by children born during the pre-recommendation cohort would be influenced by the accelerated schedule recommendations. Therefore, the children born in the pre-recommendation cohort served as an internal baseline control for the analysis.

Thus, 2520 children were selected in the pre-recommendation and 2516 children were selected in the post-recommendation period, for a total sample size of 5036. See Figure 1 below for a schematic of the cohort selection.

Figure 1: Summary of Study Design



Study Design and Variable Definitions

a. Study Design

This was a retrospective cohort secondary data analysis of two birth cohorts before and after recommendations were made to accelerate the DTaP immunization schedule. Two birth cohorts were defined in each of the four study counties, and three mean intervals between the dates of birth and DTaP1, DTaP1 and DTaP2, and DTaP2 and DTaP3 were compared between the pre- and post-recommendation periods, both between the recommendation and non-recommendation counties, and within the recommendation counties (see Figure 2).

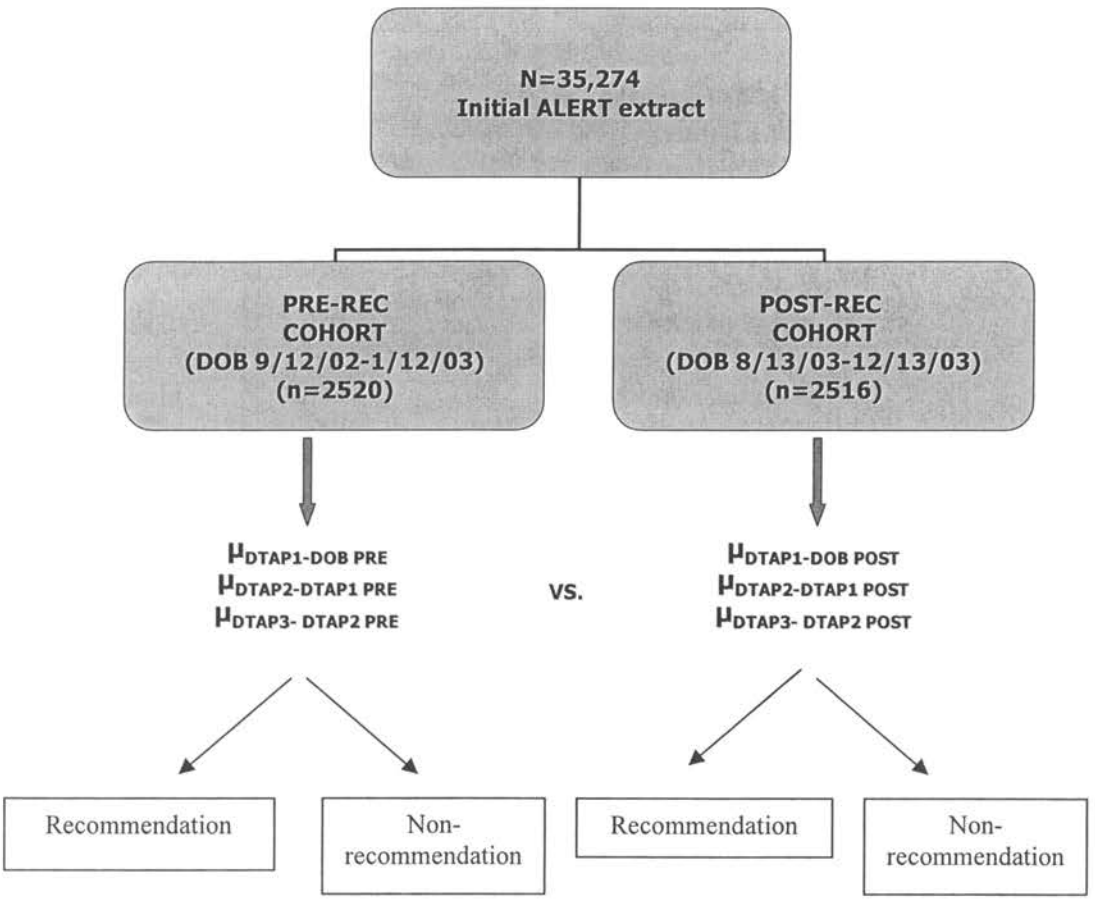


Figure 2: Overview of cohort selection and comparative analyses

b. Study Variables

Table 2 summarizes the independent and dependent variables used in this analysis, including the original sources of data from which covariates were derived.

Table 2: Summary of original and final analysis variables from ALERT and Oregon Birth Certificate Data

Original ALERT Variables	Oregon Birth Certificate Variables	Independent Variables*	Dependent Variables*
• Unique child identification number • Date of birth • Final selected dates of DTaP1-DTaP5 • Child's sex • Vaccines for Children status at each shot • Provider site code • Primary language in household • Child's county of residence	• Mother's race • # of months mother enrolled in WIC during pregnancy	Categorical • Birth cohort (pre-recommendation, post-recommendation) • Child's sex • Primary language in household • Mother's race (individual and grouped) • Clinic specialty • County of clinic • Clinic location in recommendation, non-recommendation, or other county • Vaccine funding source for each shot • Maternal WIC enrollment at birth • Child's county of residence • Child's residence in recommendation or non-recommendation county	• Intervals (in weeks) between dates of : - Birth- DTaP 1 - DTaP 1- DTaP 2 - DTaP 2- DTaP 3

* Includes new variables that were recoded from ALERT and Birth Certificate Data for use in the analysis

1. Outcome of Interest

Intervals between DTaP doses

An accelerated DTaP schedule recommendation could potentially have an impact on a pertussis outbreak by altering immunization dosing practices, reducing the number of "at-risk" unvaccinated children, and therefore reducing disease. Because the number of confirmed and presumed cases of pertussis in children less than two years is small, directly detecting any significant difference in disease morbidity is likely to be difficult. In fact, case ascertainment is likely to be incomplete, as all but the more severe cases often go undetected. In lieu of this direct measurement, an intermediate outcome was used instead that measures DTaP dose timing and indicates how soon children might be immunologically protected. The outcomes of interest were the mean intervals between DTaP doses in the pre- and post-recommendation periods.

Intervals between the each of the first three DTaP doses were calculated in the following manner. For each child born during the pre-recommendation period, the difference in days between two consecutive DTaP doses (i.e. Date of Dose 2 – Date of Dose 1) was calculated, and converted into units of weeks. Any child who never received a subsequent shot was ineligible for calculation of that interval, and the value was coded as a missing value. For example, if a child only had DTaP 1 and DTaP 2 reported, the interval between DTaP2-DTaP3 was considered "missing." Therefore, values for pre-recommendation intervals were determined for the following doses: Birth to Dose 1, Dose 1 to Dose 2, and Dose 2 to Dose 3. Likewise, intervals were calculated for children born during the post-recommendation period. Even though the accelerated schedule applies to all five shots, only the first three doses were considered in this study,

as coverage rates for the 4th dose are lower and may be influenced by other clinic and parent factors [41].

The intervals calculated for each child were averaged across all children born in each birth cohort who obtained the same two consecutive vaccinations. Three mean intervals were thereby determined for each group of two subsequent shots in each period. The differences in mean DTaP dose intervals between the pre- and post-recommendation periods were calculated by regression models, and served as the primary statistical comparisons of the study.

Follow-Up Periods

Depending when a child was born, entered the dataset, and received his immunizations, they could have different periods of follow-up and person-year contribution compared to other subjects. An effort was made to standardize the cohort eligibility and follow-up periods (and any biases that might result from this imbalance) by truncating the intervals between two shots to a maximum of six months (26 weeks). Any child whose interval between doses was greater than six months received an assignment of 26.01 weeks (greater than 6 months) for that particular interval. To evaluate the differences between the untruncated and truncated outcome intervals, preliminary analyses, including a comparison of means, ranges, and graphical depictions of distributions were done using both types of intervals. See Appendix 3 for a summary of these comparative analyses.

2. Covariates

All independent variables for this analysis were categorical, and were recoded from raw data in Immunization ALERT and Oregon birth certificates, when necessary.

Correlates of the Outcome of Interest

- *Pre- and post-recommendation birth cohort* was derived from the date of birth listed in ALERT and represented a child's membership in either the pre-recommendation (born 9/12/02-1/12/03) or post-recommendation (born 8/13/03-12/13/03) cohort for the study.
- *Clinic specialty* was derived from the de-identified ALERT clinic site code that corresponded to the last shot in an interval that was captured by the shot selection algorithm. For example, clinic specialty for DTaP1 was used in the analysis of the interval between birth and DTaP1. This code was available for each vaccine administration, and represented the code for the vaccination provider or a secondary reporting source (insurance/billing agency) that reported the administered vaccination.

  Clinic site characteristics such as city, county, zip code, clinic specialty (Pediatrics, Family Practice, Other, Unknown), reporting source type (primary, secondary), and specific clinic details (school-based health center, federally qualified health center, delegate health agency) were linked to each site code. Pre-assigned designations from ALERT of primary reporting source clinics as "Family Medicine," "Pediatric," or "County Health Department" clinics were maintained as the three primary categories for analysis. All clinics identified as

the main or satellite county health departments were included in the "county health department" category. "Other" clinic sites included hospitals, general medicine clinics, federally-qualified health centers, school-based health centers, delegate agencies, and other unspecified clinics. Delegate agencies included private, independent clinics that operate under the umbrella and authority of the county health department, but are not formally considered county health departments. Only a few clinic site codes were labeled as "unknown" and remained as such in the coding. "Unknown-missing" incorporated all other unidentified clinic specialties. Secondary reporting sources such as billing or insurance agencies did not have associated clinic specialties and were eligible to be included in the other, unknown, or missing categories, depending on which data fields for the above characteristics were available.

- *Clinic location in recommendation, non-recommendation, or other county* was also based on the ALERT clinic site code that was assigned to each final shot in the selection algorithm. The three categories for this variable included "recommendation", "non-recommendation," and "other counties outside the study area." This served as one of the primary variables for evaluating the effectiveness of the recommendation, as the primary hypothesis sought to investigate whether a recommendation assumed to be delivered to *providers*, rather than a child's family, was adopted.
- *Child's county of residence* was derived from one of the ALERT-defined counties of residence, and captured a child's residence at one point in time. County of residence was reported to ALERT over time by sources that updated demographic

information for children. However, for this analysis, we chose the county of residence designated by ALERT, which was the county of residence at first entry into ALERT. The counties of residence included Lane, Jackson, Klamath, and Douglas. The current analysis did not account for children who moved between counties or outside of the study counties altogether.

- A child's *residence in a recommendation/non-recommendation county* was similarly derived from the ALERT-defined county of residence at first entry into ALERT, and was condensed into two categories: "child lived in a recommendation county (Lane, Jackson, Klamath)" or "child lived in a non-recommendation county (Douglas)."

Potential Confounding Variables

- *Child's sex* was obtained from ALERT and remained categorized as male, female, or missing. Despite limited research showing any difference in immunization practices by child's sex, sex was maintained as a potential confounder out of a standard of practice.
- *Primary language spoken in household* was the only available variable that approximated sociocultural demographics in the ALERT database. Therefore, it was deemed potentially useful for detecting any cultural barriers in vaccination delivery. Nineteen categories were originally reported within this variable, and included Arabic, Chinese, German, Dutch, English, Spanish, Freesian, Italian, Japanese, Korean, Lao, Marshall, Mayan, Russian, Telugu, Thai, Vietnamese, Other, and Missing. It was recoded into four categories: English, Spanish, other,

and missing due to the overwhelming minority of non-English speakers (<5%). 47.2% of children were missing data on primary language, therefore excluding this variable from further analyses.

- *Mother's race* was recoded from the original values on the birth certificate variable into seven categories, which included: White, African-American, Other Non-White/Hispanic, American Indian/Indian, Asian-Pacific Islander (including Chinese, Japanese, Hawaiian, Filipino, Other API), Unknown Race, and Missing (no race reported). These were subsequently condensed into White, Non-White, and Missing, again due to the minority of non-white subjects in this study. Unfortunately, "maternal hispanicity" was not available at the time of these analyses.
- *"Vaccine funding source"* was recoded from ALERT data on a child's Vaccines for Children eligibility reported at each shot, which was also captured by the shot selection algorithm. In the absence of direct markers of socioeconomic status, such as household income, VFC status was used to approximate socioeconomic status, which has been repeatedly shown to affect the receipt of immunization services. Vaccines for Children is a federal program created in the 1990s to provide publicly purchased vaccine to enrolled public and private health care providers who care for eligible children. These children include those who are 18 years of age and under who are Medicaid eligible, uninsured, American Indian or Alaska Native, or underinsured.

  Any child coded as "OHP/Medicaid," "American Indian/Alaska Native," "no insurance," "underinsured," "insured, copay or deductible not affordable," and

"other-eligible for state funding" was grouped into the "Public Vaccine" category. Children coded as "billable" and "ineligible" were grouped into the "Private Vaccine" category. Children coded as "locally owned," "special projects," or "history" were grouped in the "other" category. Finally, children that lacked this information altogether or were labeled as "unknown" were grouped into the "unknown/missing" category.

ALERT enrolled clinics (primary reporting sources) may, but are not required, to report VFC status for each shot. These data would most likely be missing for shots reported to ALERT by secondary sources. In the event that vaccine funding information was included for a secondary source, it was included in the unknown/missing category. 55-60% of children were missing data on vaccine funding source, and this variable was excluded from further analysis.

- *"Maternal WIC enrollment at birth"* was transformed into a categorical variable from an ordinal birth certificate variable that tabulated the number of prenatal months (0-9) a child's mother was enrolled in the WIC program. The Special Supplemental Nutrition Program for Women, Infants, and Children, or WIC (Women Infants and Children) is a federal program that provides nutritional assistance to low-income pregnant, breastfeeding, and postpartum women, as well as infants and children up to five years of age. The recoded categories were "mother on WIC (1-9 months)," "mother not on WIC (0 months)," and "missing (no report)." This served as our primary variable representing socioeconomic status, given the high proportion of missing data for vaccine funding source.

Statistical Analysis

SAS 9.1 [42] was used for the data analysis, using child records with ALERT and birth certificate variables as described above that were imported into SAS.

a. Descriptive Statistics

Baseline demographic and subject characteristics were compared between the pre-recommendation and post-recommendation cohorts in the total population and in the recommendation counties using Chi-Square tests and Fisher's Exact tests, when expected cell sizes were less than five (mother's race, primary language in household). These comparisons were made for sex, clinic specialty, primary language spoken, vaccine funding source, maternal WIC enrollment at birth, clinic site location class, child's county of residence, and child's exposure to the recommendation. A separate missing category was maintained for variables that contained > 10% missing data in at least one of the birth cohorts (mother's race, primary language in household, vaccine funding source, and maternal WIC enrollment). Any significant differences ($p<0.05$) between birth cohorts across a specific characteristic were considered potential confounders, and were controlled for in the final analysis.

b. Analysis of Outcome

After graphing the distributions of the six intershot mean intervals (3 overall pre- and post, 3 pre, 3 post) using both the untruncated and truncated intervals, no gross departures from normality were detected. Untruncated and truncated mean intervals were compared using standard deviations, and ranges. (Refer to Appendix 3 for a complete

discussion of this analysis.) Despite being influenced by outliers, means were selected over medians in this analysis, primarily for their ease of use in parametric analyses under the assumption of a normally distributed outcome variable. (See Appendix 3 for a comparison of mean and median values.)

General linear models were used to summarize baseline immunization patterns for all children born in the pre-recommendation period, regardless of where the child lived or clinic was located. GLM was then used to compare mean intervals in the pre-recommendation and post-recommendation period among all children in the two birth cohorts to identify clinic and child factors that were potentially associated with a change in interval spacing. General linear models were also used to assess whether the difference between pre- and post-recommendation periods depended on whether a clinic was located in a recommendation, non-recommendation, or other county. Two sample t-tests were used to assess whether the mean shot intervals were different before and after the recommendation within the recommendation counties only. Finally, prior to construction of multivariate regression models, simple linear regression using general linear modeling was performed to estimate the crude independent associations between different covariates (clinic specialty, maternal WIC enrollment at birth, mother's race, and sex) and the differences in mean intervals between the two periods, among shots given by clinics located in recommendation counties. Interactions were also tested to evaluate whether the difference in mean intervals between the pre- and post-recommendation period depended on the clinic specialty of the immunization provider, maternal WIC enrollment at birth, mother's race, or sex of child.

Three multivariate models were then built to estimate the difference between pre- and post-recommendation mean intervals between DTaP doses, among children vaccinated in clinics in recommendation counties. These models included a child's birth cohort, the clinic specialty, an interaction between birth cohort and clinic specialty, mother's race, and maternal WIC enrollment at birth. These latter two factors are known to be associated with differences in immunization practices, different between clinic types, and associated with the outcome on univariate analysis, and therefore warranted adjustment as potential confounders. This model allowed for an assessment of the differences in groups by clinic specialty when adjusting for potential confounders of the difference.

Tukey tests for pairwise comparisons were performed to compare mean differences between groups. Overall F tests of significance were used to determine if at least one covariate in the model was significantly associated with the outcome, adjusting for the other covariates in the model. P-values for the Type III Sum of Squares were used to test the contribution of each covariate in a multivariable model, given that all other covariates were included in that model, and p-values of <0.05 were considered statistically significant.

Because of the study's relatively large child cohorts ($n_{pre} = 2520$, $n_{post}=2516$), the study had adequate power to detect relatively small differences between groups. Rather, the more pertinent issue was the clinical significance of any detected differences, which will be addressed in the discussion.

RESULTS

Characteristics of Study Population

Of the 5,036 children originally selected by date of birth, 99.98% children received DTaP1, 4,751 (94.3%) received DTaP2, and 4,296 (85.3%) received DTaP3. These same numbers corresponded to the numbers of children who had a shot interval calculated between date of birth-DTaP1, DTaP1-DTaP2, and DTaP2-DTaP3, respectively. One child was excluded from the analysis, as his only recorded DTaP occurred on his date of birth, and was not captured by the shot selection algorithm. 50.05% (n=2,520) of the remaining 5,035 children in the birth cohorts were born during the pre-recommendation period, and 49.95% (n=2,515) were born during the post-recommendation period.

Table 3 contains characteristics of all 5,036 child subjects in the pre-recommendation and post-recommendation birth cohorts. The study population was overwhelmingly white and English-speaking; however 9% of children lacked information on mother's race, and 48% lacked information on the primary language spoken in their home. "Primary language in household" was therefore excluded from further analysis despite its potential for insight into cultural barriers to immunization access. Eighty-six percent of children in the birth cohorts resided in the three counties that recommended the accelerated DTaP schedule, with Lane County being the most populous. Nearly two-thirds of children in the two birth cohorts received DTaP1 and DTaP2 from clinics in the recommendation counties, whereas only 59% received DTaP3 in the recommendation counties. Approximately 10-13% of children received shots from clinics in the non-

recommendation county. Eighteen to 25% of shots were given by practices in counties other than the four study counties.

Although public funding for vaccine was the most frequently reported type of funding (22-24%), this information was missing in 57-60% of subjects, precluding its usefulness in further analysis. Maternal WIC enrollment at birth was distributed equally between mothers who were enrolled and not enrolled in WIC during their pregnancy, with slightly less than 10% children missing data overall. Finally, Pediatric clinics practices were the most commonly utilized immunization practices among children in the birth cohorts surrounding the time of the outbreak, with about 40-50% of shots given by these practices. Less than 10% of children had missing data reported for sex, clinic site location, and clinic specialty.

Table 3: *Characteristics of Study Population*

	Overall for both birth cohorts (n=5036)	Children born in pre-recommendation period (n=2520)	Children born in post-recommendation period (n=2516)	X^2 p-value pre vs. post
Sex[1]				0.99
Male	2519 (50.52%)	1258 (50.50%)	1261 (50.54%)	
Female	2467 (49.48%)	1233 (49.50%)	1234 (49.46%)	
Mother's Race				0.012 [2]
White	4293 (85.25%)	2143 (85.04%)	2150 (85.45%)	
Non-White Hispanic	6 (0.12%)	1 (0.04%)	5 (0.20%)	
Black	33 (0.66%)	15 (0.60%)	18 (0.72%)	
Asian/Pacific Islander	129 (2.56%)	58 (2.30%)	71 (2.82%)	
American Indian/Indian	99 (1.97%)	43 (1.71%)	56 (2.23%)	
Unknown	14 (0.28%)	3 (0.12%)	11 (0.44%)	
Missing	462 (9.17%)	257 (10.20%)	205 (8.15%)	
Mother's Race (grouped)				0.0027
White	4293 (85.25%)	2143 (85.04%)	2150 (85.45%)	
Other	281 (5.58%)	120 (4.76%)	161 (6.40%)	
Missing	462 (9.17%)	257 (10.20%)	205 (8.15%)	
Primary Language in Household				<0.0001 [2]
English	2437 (48.39%)	1394 (55.32%)	1043 (41.45%)	
Spanish	189 (3.75%)	107 (4.25%)	82 (3.26%)	
Other	10 (0.20%)	7 (0.28%)	3 (0.12%)	
Missing	2400 (47.66%)	1012 (40.16%)	1388 (55.17%)	
County of Child Residence, per ALERT				0.0036
Lane	2377 (47.20%)	1169 (46.39%)	1208 (48.01%)	
Jackson	1391(27.62%)	744 (29.52%)	647 (25.72%)	
Klamath	548 (10.88%)	245 (9.72%)	303 (12.04%)	
Douglas	720 (14.30%)	362 (14.37%)	358 (14.23%)	
Child Residence in recommendation or non-recommendation county				0.89
Recommendation	4316 (85.7%)	2158 (85.63%)	2158 (85.77%)	
No recommendation	720 (14.3%)	362 (14.37%)	358 (14.23%)	

[1] Less than 10% of the data was missing for this characteristic

[2] Performed using Fisher's Exact Test for small cell sizes

Clinic Location for DTaP1, by receipt of recommendation [1]				0.26
Recommendation	3388 (67.29%)	1672 (66.35%)	1716 (68.23%)	
No recommendation	641 (12.73%)	322 (12.78%)	319 (12.68%)	
Other	1006 (19.98%)	526 (20.87%)	480 (19.09%)	
Clinic Location for DTaP 2, by receipt of recommendation [1]				0.083
Recommendation	3244 (68.25%)	1619 (67.29%)	1625 (69.24%)	
No recommendation	616 (12.96%)	305 (12.68%)	311 (13.25%)	
Other	893 (19.79%)	482 (20.03%)	411 (17.51%)	
Clinic Location for DTaP3, by receipt of recommendation [1]				0.41
Recommendation	2960 (62.28%)	1517 (63.05%)	1443 (61.48%)	
No recommendation	537 (11.30%)	259 (10.76%)	278 (11.84%)	
Other	1256 (26.43%)	630 (26.18%)	626 (26.67%)	
Funding Source for DTaP1				<0.0001
Public	1209 (24.01%)	531 (21.07%)	678 (26.95%)	
Private	815 (16.18%)	397 (15.75%)	418 (16.61%)	
Other [3]	234 (4.65%)	95 (3.77%)	139 (5.52%)	
Unknown/Missing [4]	2778 (55.16%)	1497 (59.40%)	1281 (50.91%)	
Funding Source for DTaP2				<0.0001
Public	1155 (22.93%)	530 (21.03%)	625 (24.84%)	
Private	800 (15.89%)	394 (15.63%)	406 (16.14%)	
Other [3]	204 (4.05%)	80 (3.17%)	124 (4.93%)	
Unknown/Missing [4]	2877 (57.13%)	1516 (60.16%)	1361 (54.09%)	
Funding Source for DTaP3				0.003
Public	1116 (22.16%)	546 (21.67%)	570 (22.66%)	
Private	711 (14.12%)	382 (15.16%)	329 (13.08%)	
Other [3]	188 (3.73%)	73 (2.90%)	115 (4.57%)	
Unknown/Missing [4]	3021 (59.99%)	1519 (60.28%)	1502 (59.7%)	

[1] Less than 10% of the data was missing for this characteristic.

[3] Nearly 100% of shots in the "other" category were reported from primary clinic sites.

[4] Approximately 12-16% of shots in the "unknown/missing" category were reported from secondary sources, such as insurance agencies.

Maternal WIC Enrollment at birth				0.0044
Not on WIC	2262 (44.92%)	1155 (45.83%)	1107 (44.00%)	
On WIC	2312 (45.91%)	1108 (43.97%)	1204 (47.85%)	
Missing	462 (9.17%)	257 (10.20%)	205 (8.15%)	
Clinic Specialty for DTaP1 [1]				<0.0001
Pediatrics	2373 (47.13%)	1234 (48.97%)	1139 (45.29%)	
Family Medicine	1028 (20.42%)	452 (17.94%)	576 (22.90%)	
County Health Dept.	388 (7.71%)	210 (8.33%)	178 (7.08%)	
Other[5]	852 (16.92%)	380 (15.08%)	472 (18.77%)	
Unknown[6]	394 (7.83%)	244 (9.68%)	150 (5.96%)	
Clinic Specialty for DTaP2 [1]				<0.0001
Pediatrics	2232 (46.962%)	1172 (48.71%)	1060 (45.16%)	
Family Medicine	979 (20.60%)	431 (17.91%)	548 (23.35%)	
County Health Dept.	353 (7.43%)	196 (8.15%)	157 (6.69%)	
Other[5]	827 (17.40%)	397 (16.50%)	430 (18.32%)	
Unknown[6]	362 (7.62%)	210 (8.73%)	152 (6.48%)	
Clinic Specialty for DTaP3 [1]				<0.0001
Pediatrics	2035 (42.82%)	1059 (44.01%)	976 (41.59%)	
Family Medicine	912 (19.19%)	429 (17.83%)	483 (20.58%)	
County Health Dept.	303 (6.37%)	171 (7.11%)	132 (5.62%)	
Other[5]	724 (15.23%)	407 (16.92%)	317 (13.51%)	
Unknown[6]	779 (16.39%)	340 (14.13%)	439 (18.70%)	

[1] Less than 10% of the data was missing for this characteristic.

[5] Approximately 74% of shots in the "other" category were reported from secondary sources, such as insurance agencies.

[6] 100% of shots in the "unknown" category were reported from primary clinic sites with an unidentified clinic specialty.

Mean Intervals at Baseline

As just discussed, the baseline characteristics for the pre-recommendation birth cohort (n=2520) are summarized in the second column of Table 3. Table 4 summarizes the overall and stratified baseline mean intervals during the pre-recommendation period in the four study counties. The pre-recommendation mean intervals were higher than the ACIP recommended intervals of 8 weeks between each of the first three doses, and appeared progressively longer throughout the course of the first three doses (DOB-DTaP1: 10.76 weeks (95% CI: 10.59-10.93); DTaP1-DTaP2: 10.59 weeks (95% CI: 10.41-10.77); DTaP2-DTaP3: 11.12 weeks (95% CI: 10.91-11.34).

Among all children born during the pre-recommendation period, a child's sex was not significantly associated with baseline DTaP spacing for any of the three doses (p=0.50, 0.24, 0.44, respectively). Mother's race demonstrated borderline significance for the interval between birth and DTaP1 (p=0.061), but lost significance for the second and third intervals (p=0.81, p=0.15, respectively). Although not statistically different, children of white mothers had shorter intervals than children of non-white mothers for all three intervals.

Maternal WIC enrollment at birth demonstrated a borderline or statistically significant association with baseline intervals between date of birth and DTaP1 (0.042), and became more significantly associated for the second and third intervals (p=0.008, 0.003, respectively). Children whose mothers were *not* enrolled on WIC during their pregnancy had mean intervals between birth and DTaP1 that were 0.33 weeks shorter (95% CI: 0.01-0.64, p=0.042) than children whose mothers *were* on WIC during their pregnancy. Children whose mothers were *not* enrolled on WIC during their pregnancy

had intervals between DTaP1-DTaP2 that were 0.51 (95% CI: 0.13-0.88; p=0.0008) weeks shorter than childen whose mothers *were* on WIC during their pregnancy. Finally, children whose mothers were *not* enrolled on WIC during their pregnancy had intervals between DTaP2-DTaP3 that were 0.68 (95% CI: 0.24-1.11; p=0.0003) weeks shorter than childen whose mothers *were* on WIC during their pregnancy. Thus, trends suggested that, unadjusted for other covariates, children whose mothers were white and whose mothers were not on WIC during the child's pregnancy had shorter intervals for all three doses at baseline than their counterparts.

Overall, clinic specialty was significantly associated with baseline mean intervals for all three DTaP doses (p<0.0001). Children vaccinated at Pediatric and Family Medicine clinics did *not* have significantly different mean intervals between date of birth and DTaP1 in the pre-recommendation period (p=0.61). However, children vaccinated at county health departments did have significantly longer intervals between date of birth and DTaP1 compared to Pediatric (p<0.0001) and Family Medicine (p<0.0001) practices. Pre-recommendation mean intervals between date of birth and DTaP1 among children vaccinated at "other" clinics were not significantly different from county health department intervals (p=0.72).

Children vaccinated at Pediatric and Family Medicine clinics *did* have significantly different mean intervals between DTaP1 and DTaP2, with Pediatric clinics, on average, administering DTaP2 0.81 (95% CI: 0.14-1.50, p<0.01) weeks earlier than Family Medicine clinics. Children vaccinated at county health departments had approximately two week longer intervals between DTaP1 and DTaP2 compared to Pediatric (p<0.0001) and Family Medicine (p=0.003) practices. Pre-recommendation

mean intervals in "other" clinics were not significantly different from county health department intervals (p=0.12).

Finally, children vaccinated at Pediatric clinics had significantly shorter mean intervals between DTaP2 and DTaP3 than did children vaccinated at Family Medicine clinics (Difference=0.90 weeks; 95% CI: 0.09 - 1.70, p=0.02). Again, mean intervals for children vaccinated at county health departments were significantly longer than Pediatric (Difference= 1.87 weeks; 95% CI: 0.72-3.03, p<0.0001) practices, but not Family Medicine (Difference=0.98 weeks; 95% CI: -0.29-2.25, p=0.22) practices, as the average shot interval for Family Medicine clinics fell between Pediatric and County Health Department values. Pre-recommendation mean intervals in "other" clinics were not significantly different from county health department intervals (p=0.74).

Table 4--Baseline mean intervals (in weeks) among children born during pre-recommendation, overall and by covariates

		n	Mean (95% CI)	p-value
DOB-DTaP1 (n)				
Overall (2520)		2520	10.76 (10.59, 10.93)	
*By Sex (2491)**				0.50
	Male	1258	10.79 (10.56, 11.03)	
	Female	1233	10.68 (10.44, 10.91)	
*By Mother's Race (2263)**				0.061
	White	2143	10.40 (10.24,10.56)	
	Other	120	11.07 (10.38, 11.75)	
*By Maternal WIC Enrollment at birth (2263)**				0.042
	Not On WIC	1155	10.27 (10.05, 10.49)	
	On WIC	1108	10.60 (10.38, 10.83)	
by Clinic specialty of DTaP1 (2520)				<0.0001
	Pediatrics	1234	10.14 (9.91, 10.37)	
	Family Medicine	452	10.47 (10.08, 10.86)	
	Health Dept.	210	12.61 (12.05, 13.18)	
	Other	380	12.16 (11.74, 12.58)	
	Unknown	244	10.65 (10.12, 11.17)	
DTaP1-DTaP2				
Overall		2404	10.59 (10.41, 10.77)	
*By Sex (2491)**				0.24
	Male	1258	10.71 (10.45, 10.96)	
	Female	1233	10.49 (10.24, 10.75)	
*By Mother's Race (2263)**				0.81
	White	2143	10.56 (10.36, 10.75)	
	Other	120	10.66 (9.84, 11.48)	
*By Maternal WIC Enrollment at birth (2263)**				
	Not On WIC	1155	10.31 (10.05, 10.57)	0.008
	On WIC	1108	10.82 (10.55, 11.09)	
by Clinic specialty of DTaP2 (2404)				<0.0001
	Pediatrics	1172	10.06 (9.80, 10.31)	
	Family Medicine	431	10.87 (10.46, 11.29)	
	Health Dept.	196	12.23 (11.61, 12.85)	
	Other	397	11.31 (10.88, 11.75)	
	Unknown	208	10.12 (9.51, 10.72)	

Table 4 (continued)

DTaP2-DTaP3				
Overall		2249	11.12 (10.91, 11.34)	
*By Sex (2491)**				0.44
	Male	1258	11.05 (10.74, 11.35)	
	Female	1233	11.22 (10.91, 11.53)	
*By Mother's Race (2263)**				0.15
	White	2143	11.01 (10.78, 11.23)	
	Other	120	11.74 (10.77, 12.71)	
*By Maternal WIC Enrollment at birth (2263)**				
	Not On WIC	1155	10.71 (10.41, 11.02)	0.003
	On WIC	1108	11.39 (11.08, 11.70)	
by Clinic specialty of DTaP3 (2249)				<0.0001
	Pediatrics	1059	10.58 (10.27, 10.89)	
	Family Medicine	429	11.47 (10.99, 11.96)	
	Health Dept.	171	12.45 (11.68, 13.22)	
	Other	407	11.88 (11.38, 12.38)	
	Unknown	183	10.53 (9.78, 11.27)	

** Table 4 only presents the baseline mean intervals for each level of the covariate. Differences between levels are discussed in the text.*

Comparisons of mean intervals between periods among all children in birth cohorts

Table 5 highlights the results from an analysis of all children in the two birth cohorts (n=5036) that assessed the effect of child and clinic factors on the overall difference between pre- and post-recommendation periods, without separating recommendation and non-recommendation counties. Post-recommendation mean intervals were significantly shorter than pre-recommendation intervals for all three intervals, among all children in the two cohorts, regardless of child residence or clinic location. However, the difference in mean intervals between periods decreased for each successive dose. Overall, the interval between date of birth and DTaP1 was 1.43 weeks (95% CI: 1.20-1.66) shorter following the administration of the recommendation. The interval between DTaP1-DTaP2 was 1.28 weeks (95% CI: 1.02-1.54) shorter following the recommendation, and the interval between DTaP2-DTaP3 was 1.17 weeks (95% CI: 0.87- 1.47) shorter following the recommendation.

Without adjusting for other factors, differences between intervals depended on a child's residence in a recommendation county for the first and second intervals (p=0.018, p=0.0001), but not for the third interval (p=0.436). On average, children living in recommendation counties received their first shot 1.54 (95% CI: 1.21-1.86) weeks earlier in the post-recommendation period than they did in the pre-recommendation period. The interval between DTaP1-DTaP2 was 1.46 (95% CI: 1.10-1.82) weeks shorter in the post-recommendation period compared to the pre-recommendation period.

For the interval between DTaP2-DTaP3, the difference between the two time periods did not depend on a child's residence within or out of a recommendation county (p=0.436). However, among children living in recommendation counties, the interval

was 1.22 (95% CI: 0.80-1.64) weeks shorter following the recommendation ($p<0.0001$). Adjusted for child residence, the overall difference in mean intervals for DTaP2-DTaP3 was 1.17 weeks (95% CI: 0.88-1.47) between the two cohorts ($p<0.0001$). Of note, children living in the non-recommendation county demonstrated a marginally significant difference in mean DTaP intervals for the first interval (mean difference 0.75, 95% CI: 0.04-1.54, $p=0.072$), despite not living in counties where the recommendation was formally implemented.

The unadjusted difference between groups was only dependent on maternal WIC enrollment at birth for the interval between DTaP1-DTaP2 ($p=0.033$). The differences between periods were 1.67 (95% CI: 1.18-2.16) and 1.10 (95%: 0.62-1.58) weeks among those children enrolled and not enrolled in WIC, respectively. For the first interval between birth and DTaP1, the overall difference between groups, adjusted for WIC enrollment, was 1.36 weeks (95% CI: 1.14-1.58, $p<0.0001$). For the third interval, the difference between DTaP2-DTaP3, adjusted for WIC enrollment, was 1.19 weeks (95% CI: 0.89-1.50, $p<0.0001$).

The unadjusted difference between mean intervals between the pre- and post-recommendation periods was dependent on mother's race for the first and third interval ($p=0.021$, $p=0.022$, respectively). Children with mothers of "other" races received DTaP1 2.37 weeks (95% CI: 1.20-3.54, $p<0.0001$) earlier in the post-recommendation period compared to the pre-recommendation period, whereas the difference in children with white mothers was 1.28 weeks (95% CI: 0.99-1.58, $p<0.0001$). Similarly children of mothers of "other" races received DTaP3 2.97 weeks (95% CI: 0.94-4.21, $p<0.0001$) earlier in the post-recommendation period compared to the pre-recommendation period,

whereas the difference in children with white mothers was 1.09 weeks (95% CI: 0.53-1.64, p<0.0001). For the second interval between DTaP1 and DTaP2, however, the interaction was not significant (p=0.955). However, the overall difference between the pre- and post-recommendation periods for DTaP1-DTaP2, adjusted for mother's race, was 1.36 (95% CI: 1.09-1.62) weeks.

Finally, the difference between groups was modified by a child's sex for the interval between DTaP1-DTaP2 (p=0.05). The difference between periods was larger for males than for females (1.53 vs. 1.01 weeks). However, the difference in mean intervals between birth cohorts was not dependent on sex for the first and third intervals (p= 0.845, p=0.512, respectively). Adjusted for sex, the mean intervals between date of birth and DTaP1 were 1.42 weeks (95% CI: 1.19-1.65, p<0.0001) shorter after the recommendation was made. Likewise, mean intervals between DTaP2-DTaP3 were 1.19 (95% CI: 0.89-1.49, p<0.0001) weeks shorter following the recommendation, when adjusted for a child's sex.

Table 5-- Comparison of unadjusted mean intervals (in weeks) between pre- and post-recommendation periods, among all children born in two birth cohorts, overall and stratified by covariates

DOB-DTaP 1 (n)	Pre-recommendation Cohort	Post-recommendation cohort	μ_{pre}- μ_{post} (95% CI)	p-value
Overall (n=5035)	10.76 +/- 4.29	9.33 +/- 4.06	1.43 (1.20, 1.66)	<0.0001
By Child Residence (n=5035)				Interaction 0.018
Recommendation	10.62 +/- 0.09	9.09 +/- 0.09	1.54 (1.21, 1.86)	<0.0001
Non-recommendation	11.57 +/- 0.22	10.82 +/- 0.22	0.75 (0.04, 1.54)	0.072
By Maternal WIC Enrollment at birth (n=4573)				Interaction 0.60
On WIC	10.6 +/- 0.11	9.30 +/- 0.11	1.30 (0.90, 1.71)	<0.0001
Not on WIC	10.27 +/- 0.11	8.85 +/- 0.11	1.43 (1.01, 1.83)	<0.0001
By Mother's Race (n=4573)				Interaction 0.021
White	10.40 +/- 0.81	9.11 +/- 0.81	1.28 (0.99, 1.58)	<0.0001
Other	11.08 +/- 0.34	8.70 +/- 0.30	2.37 (1.20, 3.54)	<0.0001
By Sex of Child (n=4985)				Interaction 0.85
Male	10.79 +/- 0.12	9.35 +/- 0.12	1.40 (0.97, 1.83)	<0.0001
Female	10.68 +/- 0.12	9.28 +/- 0.12	1.45 (1.02, 1.87)	<0.0001
DTaP1-DTaP2 (n)	**Pre-recommendation Cohort**	**Post-recommendation cohort**	**μ_{pre} - μ_{post} (95% CI)**	**p-value**
Overall (n=4751)	10.59 +/- 4.47	9.31 +/- 4.52	1.28 (1.02, 1.54)	<0.0001
By Child Residence (n=4751)				Interaction 0.001
Recommendation	10.53 +/- 0.10	9.07 +/- 0.10	1.46 (1.10, 1.82)	<0.0001
Non-recommendation	11.01 +/- 0.24	10.74 +/- 0.24	0.26 (0.62, 1.14)	0.87
By Maternal WIC Enrollment at birth (n=4370)				Interaction 0.033
On WIC	10.82 +/- 0.14	9.72 +/- 0.13	1.67 (1.18, 2.16)	<0.0001
Not on WIC	10.31 +/- 0.13	8.64 +/- 0.14	1.10 (0.62, 1.58)	<0.0001
By Mother's Race (n=4370)				Interaction 0.96
White	10.56 +/- 0.10	9.20 +/- 0.10	1.35 (1.00, 1.71)	<0.0001
Other	10.66 +/- 0.42	9.28 +/- 0.36	1.39 (0.03, 2.81)	0.059
By Sex of Child (n=4706)				Interaction 0.050
Male	10.71 +/- 0.13	9.18 +/- 0.13	1.53 (1.05, 2.00)	<0.0001
Female	10.50 +/- 0.13	9.48 +/- 0.13	1.01 (0.53, 1.49)	<0.0001

Table 5 (continued)

DTaP2-DTaP3	Pre-recommendation Cohort	Post-recommendation cohort	$\mu_{pre} - \mu_{post}$ (95% CI)	p-value
Overall (n=4296)	11.12 +/- 5.18	9.95 +/- 4.72	1.17 (0.87, 1.47)	<0.0001
By Child Residence (n=4296)				Interaction 0.44
Recommendation	11.09 +/- 0.11	9.87 +/- 0.12	1.22 (0.80, 1.64)	<0.0001
Non-recommendation	11.29 +/- 0.28	10.40 +/- 0.28	0.89 (0.14, 1.91)	0.12
By Maternal WIC Enrollment at birth (n=3974)				Interaction 0.62
On WIC	11.39 +/- 0.15	10.12 +/- 0.15	1.27 (0.71, 1.83)	<0.0001
Not on WIC	10.72 +/- 0.15	9.60 +/- 0.16	1.11 (0.54, 1.68)	<0.0001
By Mother's Race (n=3974)				Interaction 0.022
White	11.01+/- 0.11	9.93 +/- 0.12	1.08 (0.66, 1.49)	<0.0001
Other	11.74 +/- 0.48	9.16 +/- 0.42	2.97 (0.94, 4.21)	0.0003
By Sex of Child (n=4262)				Interaction 0.51
Male	11.05 +/-0.15	9.76 +/- 0.15	1.09 (0.53, 1.64)	<0.0001
Female	11.22 +/- 0.15	10.13 +/- 0.16	1.29 (0.74, 1.84)	<0.0001

***For non-significant interaction terms, a model was repeated with only main effects, and the difference between birth pre- and post-recommendation periods, adjusted for the other covariate, is presented in the text*

Comparison of mean intervals by location of clinic in recommendation, non-recommendation, or other county

Table 6 compares the characteristics of children who received shots at clinics in the three recommendation counties and in the non-recommendation county. The two groups were similarly matched on sex. Children who received DTaP in a non-recommendation were slightly more White. Douglas County (non-recommendation county) appeared to provide more shots for children whose mother's were enrolled in WIC prenatally. More children in the non-recommendation county received shots at the county health department, whereas a smaller proportion of children in the non-recommendation county received shots at Pediatric clinics.

Table 6--Comparison of overall characteristics of subjects who received shots by clinics in recommendation and non-recommendation counties

	Overall % in recommendation counties	Overall % in non-recommendation counties
Sex[1]		
Male	1680 (50.21%)	323 (50.39%)
Female	1666 (49.79%)	318 (49.61%)
Mother's Race[1]		
White	2916 (93.49%)	567 (95.78%)
Other	203 (6.51%)	25 (4.22%)
Maternal WIC Enrollment at birth[1]		
Not on WIC	1635 (52.42%)	242 (40.88%)
On WIC	694 (45.45%)	350 (59.12%)
Clinic Specialty for DTaP1 [1]		
Pediatrics	2067 (21.01%)	231 (36.04%)
Family Medicine	862 (25.44%)	114 (17.78%)
County Health Dept.	100 (2.95%)	288 (44.93%)
Other	359 (10.60%)	8 (1.25%)
Clinic Specialty for DTaP2 [1]		
Pediatrics	1936 (59.68%)	228 (37.1%)
Family Medicine	818 (25.22%)	111 (18.02%)
County Health Dept.	90 (2.77%)	263 (42.69%)
Other	400 (12.33%)	14 (2.27%)
Clinic Specialty for DTaP3 [1]		
Pediatrics	1785 (60.30%)	192 (35.75%)
Family Medicine	749 (25.30%)	113 (21.04%)
County Health Dept.	87 (2.94%)	216 (40.22%)
Other	339 (11.45%)	16 (2.98%)

[1] Less than 10% of the data was missing for this characteristic.

The next analysis evaluated whether the difference in mean intervals between pre- and post-recommendation periods depended on the clinic location where the shot was administered. Table 7 presents the unadjusted differences in mean intervals between providers among clinics in the three recommendation counties (Lane, Jackson, Klamath), one non-recommendation county (Douglas), and other counties outside the four study counties.

The difference in mean intervals depended on the location of the clinic for the interval between date of birth and DTaP1 ($p<0.016$) and DTaP1 and DTaP2 ($p<0.0003$). Among clinics in the recommendation counties, mean intervals were significantly shorter in the post-recommendation period for the first interval (mean difference: 1.54 weeks; 95% CI: 1.14-1.95, $p<0.00001$) and second interval (mean difference: 1.58 weeks; 95% CI: 1.13-2.02, $p<0.0001$). There were no significant differences between time periods among providers in the non-recommendation period for either of the first two intervals ($p=0.59$, $p>0.99$, respectively). Significant differences in mean intervals between the pre-recommendation and post-recommendation period were observed for the first two intervals among providers in counties other than the four study counties. 37.3% of DTaP1, 34.6% of DTaP2, and 22.9% of DTaP3 shots administered by clinics in "other" counties were reported by secondary sources.

However, the difference in mean intervals did not depend on the general location of the clinic for the third interval between DTaP2-DTaP3 ($p=0.54$). Nevertheless, a trend toward a reduced interval following the recommendation was observed in recommendation counties, whereas no such trend was observed in the non-recommendation county. Adjusted for clinic location, post-recommendation mean

intervals between DTaP2 and DTaP3 were 1.16 weeks shorter than pre-recommendation intervals (95% CI: 0.86-1.45, p<0.0001).

Table 7 -- Mean intervals (in weeks) and differences between mean intervals, by location of clinic in recommendation, non-recommendation, or other county

	Pre-recommendation cohort	Post-recommendation cohort	$\mu_{pre} - \mu_{post}$ (95%CI)	p-value
DOB-DTaP1 (n=5035)				Interaction 0.016
Recommendation (3388)	10.35 +/- 0.10	8.80 +/- 0.10	1.54 (1.14, 1.95)	<0.0001
Non-recommendation (641)	11.28 +/- 0.23	10.75 +/- 0.23	0.53 (-0.40, 1.45)	0.59
Other (1006)	11.76 +/- 0.18	10.28 +/- 0.19	1.48 (0.74, 2.22)	<0.0001
DTaP1-DTaP2 (n=4751)				Interaction 0.0003
Recommendation (3244)	10.41 +/- 0.11	8.84 +/- 0.11	1.58 (1.13, 2.02)	<0.0001
Non-recommendation (616)	10.89 +/- 0.26	10.84 +/- 0.25	0.05 (-0.97, 1.08)	>0.99
Other (893)	11.01 +/- 0.20	10.05 +/- 0.22	0.97 (0.11, 1.82)	0.016
DTaP2- DTaP3 (n=4296)				Interaction 0.54
Recommendation (2960)	10.96 +/- 0.13	9.82 +/- 0.13	1.15 (0.63, 1.67)	<0.0001
Non-recommendation (537)	11.27 +/- 0.31	10.46 +/- 0.30	0.81 (-0.41, 2.03)	0.41
Other (1256)	11.55 +/- 0.23	10.11 +/- 0.27	1.43 (0.41, 2.45)	0.001

Comparison of mean intervals before and after the recommendation, among shots given by clinics in recommendation counties

The next set of analyses uses data from children who received immunizations at clinics in the recommendation counties (n=3388) and compared mean intervals before and after the recommendation. Table 8 below compares the characteristics of all children who received shots by immunization providers in the three recommendation counties (n=3388). Compared grossly to Table 3 that highlighted similar characteristics among the entire study population, children given shots by providers in the recommendation counties were predominantly white, distributed similarly across sex and maternal WIC

enrollment at birth, and received the majority of shots in Pediatric clinics. Of note, fewer children received shots in Pediatric clinics in the post-recommendation period compared to the pre-recommendation period, whereas more children received shots at Family Medicine clinics in the post-recommendation period compared to the pre-recommendation period.

Table 8-- Characteristics of subjects who only received shots at clinics in three recommendation counties (n=3388)

	Overall for both birth cohorts	Pre-recommendation cohort	Post-recommendation cohort	X^2 p-value pre vs. post
Sex[1] (3346)				0.47
Male	1680 (50.21%)	818 (50.42%)	862 (49.17%)	
Female	1666 (49.79%)	832 (49.58%)	834 (50.83%)	
Mother's Race[1] (3119)				0.008
White	2916 (93.49%)	1446 (94.70%)	1470 (92.34%)	
Other	203 (6.51%)	81 (5.30%)	122 (7.66%)	
Maternal WIC Enrollment at birth[1] (3119)				0.02
Not on WIC	1635 (52.42%)	833 (54.55%)	802 (50.38%)	
On WIC	1484 (47.58%)	694 (45.45%)	790 (49.62%)	
Clinic Specialty for DTaP1 [1] (3388)				<0.0001
Pediatrics	2067 (61.01%)	1076 (64.35%)	991 (57.75%)	
Family Medicine	862 (25.44%)	369 (22.07%)	493 (28.73%)	
County Health Dept.	100 (2.95%)	55 (3.29%)	45 (2.62%)	
Other	359 (10.60%)	172 (10.29%)	187 (10.90%)	
Clinic Specialty for DTaP2 [1] (3244)				0.0001
Pediatrics	1936 (59.68%)	1015 (62.69%)	921 (56.68%)	
Family Medicine	818 (25.22%)	356 (21.99%)	462 (28.43%)	
County Health Dept.	90 (2.77%)	52 (3.21%)	38 (2.34%)	
Other	400 (12.33%)	196 (12.11%)	204 (12.55%)	
Clinic Specialty for DTaP3 [1] (2960)				0.044
Pediatrics	1785 (60.30%)	945 (62.29%)	840 (58.21%)	
Family Medicine	749 (25.30%)	351 (23.14%)	398 (27.58%)	
County Health Dept.	87 (2.94%)	47 (3.10%)	40 (2.77%)	
Other	339 (11.45%)	174 (11.47%)	165 (11.43%)	

[1] Less than 10% of the data was missing for this characteristic.

Table 9 displays the unadjusted mean intervals and their differences among only children receiving shots from clinics in the three recommendation counties, overall and by covariates that were associated with mean intervals at baseline. Overall, all three mean intervals were significantly shorter in the post-recommendation period compared to the pre-recommendation period ($p<0.0001$). Mean differences in weeks ranged from 1.15 (95% CI: 0.79-1.51) for the interval between DTaP2-DTaP3, to 1.54 (95% CI: 1.29-1.80) for date of birth-DTaP1 and 1.58 (95% CI: 1.28-1.88) for DTaP2-DTaP3.

The difference in intervals for the interval between date of birth and DTaP1 was *not* statistically dependent on clinic specialty ($p=0.117$). However, trends of significant differences were observed between the pre- and post- periods among Pediatric and Family Medicine practices, with the largest difference exhibited among Pediatric practices (mean difference 1.80 weeks, 95% CI: 1.30-2.30, $p<0.0001$). No significant difference was observed between pre- and post-recommendation periods among County Health Department providers (mean difference 0.55 weeks, 95% CI: -1.7-2.8, $p>0.99$) or "Other" providers (mean difference 1.10 weeks; 95% CI: 0.10-2.30, $p=0.10$). When the interaction term between birth cohort and clinic specialty was removed from the model, post-recommendation intervals (9.40 weeks) between date of birth and DTaP1 were 1.58 (95%CI: 1.32-1.83, $p<0.0001$) weeks shorter than pre-recommendation intervals (10.97 weeks), when adjusting for the clinic specialty for DTaP1.

The same trend was evident for the interval between DTaP1 and DTaP2, where the difference between groups among children given shots by providers who received the recommendation, did *not* depend on clinic specialty ($p=0.27$). Trends toward significant differences were again observed between the pre- and post-recommendation periods for

Pediatric and Family Medicine Practices ($p<0.0001$), with the largest difference occurring among Pediatric practices (mean difference 1.82 weeks, 95% CI: 1.22-1.41). Again, no significant differences in mean intervals were observed between pre- and post-recommendation periods among County Health Department (mean difference=0.40; 95% CI: -2.40-3.19, $p>0.99$) or "Other" providers (mean difference=1.20 weeks; 95% CI: 0.11-2.51, $p=0.101$). When the interaction term between birth cohort and clinic specialty was removed from the model, post-recommendation intervals between DTaP1 and DTaP2 (9.69 weeks) were 1.62 (95% CI: 1.32-1.92; $p<0.0001$) weeks shorter than pre-recommendation intervals (11.31 weeks), adjusting for the type of immunization provider that administered DTaP2.

Finally, the significant difference between birth cohorts in the interval between DTaP2-DTaP3 did not depend on clinic specialty ($p=0.44$). Mean intervals between DTaP2-DTaP3 were significantly different for children vaccinated at Pediatric clinics (mean difference= 1.37 weeks, 95% CI: 0.66-2.09, $p<0.0001$), but the difference between periods was markedly reduced to 0.66 weeks (95% CI: 0.4-1.8, $p=0.60$) among Family Practice clinics. Although not statistically significant, third DTaP shots given by county health department clinics were given 1.39 weeks (95% CI: -1.9- 4.6) earlier in post-recommendation periods compared to pre-recommendation periods. When the interaction term between birth cohort and clinic specialty was removed from the model, post-recommendation intervals between DTaP2 and DTaP3 (10.76 weeks) were 1.18 weeks (95% CI: 0.82, 1.54; $p<0.0001$) shorter than pre-recommendation intervals (11.94 weeks), after adjusting for clinic specialty.

Table 9 --Comparison of unadjusted mean intervals (in weeks) and differences in mean intervals for children who were vaccinated by clinics located in three recommendation counties, overall and by covariates

DOB-DTaP 1	**Pre-rec cohort**	**Post-rec cohort**	**$\mu_{pre} - \mu_{post}$ (95% CI)**	**p-value**
Overall (n=3388)				
	10.35 +/- 0.09	8.80 +/- 0.09	1.54 (1.29, 1.80)	<0.0001
By Maternal WIC Enrollment				Interaction 0.69
Not on WIC	9.94 +/- 0.12	8.38 +/- 0.12	1.56 (1.13, 1.99)	<0.0001
On WIC	10.21 +/- 0.13	8.74 +/- 0.12	1.46 (1.01, 1.91)	<0.0001
By Mother's Race				Interaction 0.063
White	10.04 +/- 0.09	8.61 +/- 0.09	1.44 (1.12, 1.76)	<0.0001
Other	10.36 +/- 0.37	8.00 +/- 0.30	2.36 (1.12, 3.60)	<0.0001
By Clinic specialty				Interaction 0.12
Pediatrics (2067)	10.15 +/- 0.11	8.35 +/- 0.12	1.80 (1.30, 2.30)	<0.0001
Family Medicine (862)	10.55 +/- 0.19	9.20 +/- 0.17	1.36 (0.57, 2.14)	<0.0001
County Health Department (100)	11.78 +/- 0.50	11.23 +/- 0.56	0.55 (-1.74,2.83)	>0.99
Other (359)	10.69 +/- 0.29	9.59 +/- 0.27	1.10 (0.10, 2.30)	0.10
DTaP1-DTaP2	**Pre-rec cohort**	**Post-rec cohort**	**$\mu_{pre} - \mu_{post}$ (95% CI)**	**p-value**
Overall (n=3244)				
	10.41 +/- 0.11	8.84 +/- 0.11	1.58 (1.28, 1.88)	<0.0001
Maternal WIC Enrollment				Interaction 0.049
Not on WIC	10.14 +/- 0.15	8.17 +/- 0.16	1.97 (1.41, 2.53)	<0.0001
On WIC	10.62 +/- 0.16	9.27 +/- 0.15	1.35 (0.77, 1.93)	<0.0001
Mother's Race				Interaction 0.72
White	10.37 +/- 0.12	8.73 +/- 0.11	1.65 (1.23, 2.06)	<0.0001
Other	10.17 +/- 0.48	8.75 +/- 0.41	1.41 (0.22, 3.04)	0.12
By Clinic specialty (n=3244)				Interaction 0.27
Pediatrics (1936)	10.06 +/- 0.14	8.24 +/- 0.14	1.82 (1.22, 2.41)	<0.0001
Family Medicine (818)	10.96 +/- 0.23	9.47 +/- 0.20	1.49 (0.56, 2.41)	<0.0001
County Health Department (90)	12.89 +/- 0.60	12.49 +/- 0.70	0.40 (-2.40,3.19)	>0.99
Other (400)	10.61 +/- 0.31	9.41 +/- 0.30	1.20 (0.11, 2.51)	0.10

DTaP2-DTaP3	Pre-rec cohort	Post-rec cohort	$\mu_{pre} - \mu_{post}$ (95% CI)	p-value
Overall (n=2960)				
	10.96 +/- 0.13	9.82 +/- 0.13	1.15 (0.79, 1.51)	<.0001
Maternal WIC Enrollment				Interaction 0.93
Not on WIC	10.53 +/- 0.18	9.34 +/- 0.19	1.19 (0.52, 1.86)	<0.0001
On WIC	11.33 +/- 0.20	10.11 +/- 0.19	1.23 (0.53, 1.92)	<0.0001
Mother's Race				Interaction 0.18
White	10.87 +/- 0.14	9.78 +/- 0.14	1.09 (0.59, 1.59)	<0.0001
Other	11.31 +/- 0.59	9.16 +/- 0.49	2.14 (0.17, 4.12)	0.027
By Clinic specialty (n=2960)				Interaction 0.44
Pediatrics (1785)	10.60 +/- 0.16	9.23 +/- 0.17	1.37 (0.66, 2.09)	<0.0001
Family Medicine (749)	11.28 +/- 0.27	10.61 +/- 0.25	0.66 (0.44, 1.77)	0.60
County Health Department (87)	14.49 +/- 0.72	13.11 +/- 0.79	1.39 (-1.85,4.63)	0.90
Other (339)	11.33 +/- 0.38	10.07 +/- 0.39	1.26 (0.38, 2.89)	0.28

**All DTaPs had a clinic specialty assigned to them in the recommendation counties. The only unknowns were outside of the study area.

Maternal WIC enrollment at birth did not consistently interact with a change in mean intervals between birth cohorts (p=0.69, 0.05, 0.93). For the intervals between DTaP1-DTaP2 only, the difference in mean intervals between periods marginally depended on maternal WIC enrollment (p=0.05). Post-recommendation intervals were 1.97 weeks shorter (95% CI: 1.41- 2.53; p<0.0001) than pre-recommendation intervals among children whose mothers were *not* enrolled on WIC, whereas children whose mothers *were* on WIC reported a 1.35 week reduction (95% CI: 0.77-1.93; p<0.0001) in post-recommendation intervals compared to pre-recommendation intervals. When the non-significant interaction terms between birth cohort and maternal WIC enrollment were removed from the model, post-recommendation mean intervals between date of birth and DTaP1 (8.56 weeks) were 1.51 weeks (95% CI: 1.28-1.75; p<0.0001) shorter than pre-recommendation intervals (10.07 weeks), adjusted for maternal WIC enrollment at birth.

Similarly, post-recommendation intervals between DTaP2 and DTaP3 (9.73 weeks) were 1.21 weeks (95% CI: 0.84-1.58, p<0.0001) shorter than pre-recommendation intervals, adjusted for maternal WIC enrollment.

The difference between pre- and post-recommendation mean intervals was marginally dependent on mother's race for DOB-DTaP1 only (p=0.06). Post-recommendation mean intervals were 2.36 weeks (95% CI: 1.12 - 3.60; p<0.0001) shorter than pre-recommendation mean intervals for children whose mothers were of an "other" race, whereas post-recommendation intervals in children whose mothers were white were 1.44 weeks (95% CI: 1.12-1.76; p<0.0001) shorter than pre-recommendation intervals. When the non-significant interaction term between birth cohort and mother's race was removed from the model for the second and third intervals, post-recommendation mean intervals (8.70 weeks) between DTaP1 and DTaP2 were 1.63 weeks shorter (95% CI: 1.32-1.94, p<0.0001) than pre-recommendation intervals (10.33 weeks), adjusted for mother's race. Post-recommendation mean intervals (9.66 weeks) between DTaP2 and DTaP3 were 1.15 weeks shorter (95% CI: 0.78-1.52, p<0.0001) than pre-recommendation intervals (10.81 weeks), adjusted for mother's race.

Multivariate models of differences in mean intervals before and after the recommendation, among shots given by clinics in recommendation counties

In order to further evaluate the difference in mean intervals before and after the recommendation among children given shots by clinics in the three recommendation counties, multivariate models were constructed using data from these children (n=3388) to adjust for potential modifiers of this difference. First, Table 10 demonstrates the distribution of demographic characteristics in the populations served by Pediatric, Family

Medicine, and County Health Department clinics in the three recommendation counties, as these three clinic types generally serve different populations. A higher proportion of missing data existed for mother's race, vaccine funding source, and maternal WIC enrollment among data reported by county health departments compared to Pediatric or Family Medicine clinics, which makes it difficult to know the true distribution of these characteristics across the clinic populations.

Table 10--Demographics of children who received DTaP1 at a Pediatric, Family Medicine, or County Health Department clinic in a recommendation county

	Pediatrics (n=2067)	Family Medicine (n=862)	County Health Department (n=100)
Sex			
Male	1034 (50.0%)	404 (46.9%)	55 (55.0%)
Female	1005 (48.6%)	448 (52.0%)	45 (45.0%)
Missing	28 (1.4%)	10 (1.1%)	0 (0%)
Mother's Race			
White	1804 (87.3%)	750 (87.0%)	61 (61.0%)
Other	121 (5.8%)	43 (5.0%)	6 (6.0%)
Missing	142 (6.9%)	69 (8.0%)	33 (33.0%)
Vaccine Funding Source for DTaP1			
Public	355 (17.2%)	269 (31.2%)	26 (26.0%)
Private	587 (28.4%)	161 (18.7%)	2 (2.0%)
Other	35 (1.7%)	16 (1.9%)	0 (0%)
Unknown/Missing	1090 (52.7%)	416 (48.3%)	72 (72.0%)
Maternal WIC Enrollment at birth			
Not on WIC	775 (37.5%)	384 (44.6%)	33 (33.0%)
On WIC	1150 (55.6%)	409 (47.4%)	34 (34.0%)
Missing	142 (6.9%)	69 (8.0%)	33 (33.0%)

Table 11 summarizes results from multivariate models of the differences in mean intervals by clinic specialty among children who were vaccinated at clinics in recommendation counties, adjusted for maternal WIC enrollment at birth and mother's race. Although the interaction terms between birth cohort and clinic specialty were not statistically significant, they were kept in the model to demonstrate that the differences in

mean intervals observed between clinic specialties on univariate analyses, particularly those patterns observed for county health departments, were minimized once adjusted for factors known to be associated with delayed immunization, such that the differences in county health departments ultimately approximated or exceeded those of other clinic specialties. In contrast to the crude univariate results that showed a reduction of only 0.40-1.39 weeks in the post-recommendation period for all three intervals among county health departments, adjusted differences ranged from 1.65 weeks (95% CI: -1.75-5.05, p=0.82) for DTaP1-DTaP2 to 1.98 weeks (95% CI: -1.72-5.68, p=0.74) for DTaP2-DTaP3.

On average, however, mean interval estimates, even during the post-recommendation period, were still substantially higher in the county health departments compared to Pediatric or Family Medicine clinics. For the interval between birth and DTaP1, post-recommendation intervals were significantly higher in County Health Department clinics than in Pediatric clinics (p= 0.03), but not significantly higher than Family Medicine clinics (p=0.62). Likewise, for the interval between DTaP1 and DTaP2, County Health Departments reported significantly higher post-recommendation intervals than Pediatric clinics (p= 0.002) but not Family Medicine clinics (p=0.21). Finally, post-recommendation intervals between DTaP2 and DTaP3 were significantly higher in County Health Departments compared to both Pediatric (p=0.0002) and Family Medicine clinics (p=0.05).

Table 11-- Multivariate analyses of mean intervals (in weeks) and differences in mean intervals for children vaccinated at clinics in recommendation counties, overall and by clinic specialty, adjusted for maternal WIC enrollment at birth and mother's race

	Pre-recommendation cohort	Post-recommendation cohort	$\mu_{pre} - \mu_{post}$ (95% CI)	p-value
DOB-DTaP1				
Overall	10.54 +/- 0.19	9.04 +/- 0.20	1.50 (1.04, 1.97)	<0.0001
By Clinic Specialty				Interaction 0.23
Pediatrics	9.74 +/- 0.15	8.04 +/- 0.15	1.70 (1.24, 2.17)	<0.0001
Family Medicine	10.18 +/- 0.21	8.89 +/- 0.19	1.28 (0.56, 2.01)	<0.0001
Health Department	12.03 +/- 0.54	10.07 +/- 0.64	1.97 (-0.54, 4.47)	0.25
Other	10.21 +/- 0.29	9.15 +/- 0.27	1.06 (-0.05, 2.17)	0.08
DTaP1-DTaP2				
Overall	11.08 +/- 0.25	9.55 +/- 0.27	1.53 (0.91, 2.15)	<0.0001
By Clinic Specialty				Interaction 0.22
Pediatrics	10.06 +/- 0.20	8.12 +/- 0.20	1.94 (1.33, 2.55)	<0.0001
Family Medicine	10.96 +/- 0.27	9.40 +/- 0.25	1.56 (0.62, 2.51)	<0.0001
Health Department	13.21 +/- 0.74	11.56 +/- 0.86	1.65 (-1.75, 5.05)	0.82
Other	10.11 +/- 0.35	9.14 +/- 0.34	0.97 (-0.37, 2.31)	0.36
DTaP2-DTaP3				
Overall	11.90 +/- 0.29	10.58 +/- 0.31	1.32 (0.63, 2.01)	0.0002
By Clinic Specialty				Interaction 0.48
Pediatrics	10.48 +/- 0.24	9.48 +/- 0.24	1.39 (0.66, 2.12)	<0.0001
Family Medicine	11.12 +/- 0.32	10.36 +/- 0.30	0.76 (-0.37, 1.88)	0.45
Health Department	15.17 +/- 0.84	13.19 +/- 0.91	1.98 (-1.72, 5.68)	0.74
Other	10.83 +/- 0.43	9.66 +/- 0.43	1.16 (-0.51, 2.84)	0.41

DISCUSSION

The results of this study suggest that DTaP dosing significantly changed after a recommendation was made to accelerate the DTaP schedule in the midst of a pertussis outbreak. A significant reduction in post-recommendation mean intervals occurred for all three dose intervals among clinics located in recommendation counties, whereas no significant reduction was observed in the sole non-recommendation county. The significant difference between pre- and post-recommendation mean intervals depended on whether the immunization provider was in a recommendation county or not for the first two intervals, but not the third.

When investigating just those clinics located in counties that received the recommendation, all three intervals were significantly shorter after the recommendation compared to before the recommendation. However, this difference did not depend on clinic specialty for any of the intervals. Despite the lack of a significant interaction, mean intervals were consistently shorter in the post-recommendation period compared to the pre-recommendation period in Pediatric practices. While Family Medicine clinics showed comparable differences between groups for the first two intervals, the difference between groups waned for the third interval. This trend may parallel those observed by Koepke et al [37], in which pediatricians had higher coverage rates than family practitioners, despite both types of practices demonstrating delayed up-to-date rates among children 12 months of age.

Without adjusting for other covariates, univariate analyses of the difference in mean intervals by clinic specialty showed that DTaP dosing changed more substantially among Pediatric and Family Medicine clinics, compared to County Health Departments,

for which we did not find a significant change in DTaP dosing. However, after adjusting for mother's race and maternal WIC enrollment at birth, both factors that have been associated with delayed immunization practices, the differences between clinic specialties observed on univariate analysis were no longer so prominent. Most notably, the minimal change observed in county health departments on univariate analysis became more substantial in an adjusted model, suggesting that other factors among county health department clients, rather than the providers or system itself, may influence immunization dosing and any delay in immunization delivery and/or receipt.

These findings support previous research that providers are able to incorporate a new public health recommendation into practice [43, 44], although no studies have investigated this capability in the setting of a pertussis outbreak. Clark *et al* conducted a telephone survey of U.S. hospitals to investigate nursery vaccination practices before and after a recommendation was made in July 1999 to discontinue vaccination of low-risk infants with a thimerosal-containing vaccine. Prior to the recommendation, 78% of hospital nurseries reported vaccinating in accordance with the recommended schedule, whereas almost all hospitals stated they discontinued vaccination of low-risk infants after the recommendation. Later, only 39% of hospitals reported vaccinating all low-risk infants once the thimerosal-free vaccine was reinstated [43]. Similarly, Oram et al found a significant reduction in routine HBV vaccination following the initial recommendation, but a failure to resume the original high rates of adherence to a recommended schedule once the alternative vaccine was reinstated [44]. While these studies suggest that providers are initially able to adopt a new recommendation, the possibility of longer term

decreased provider adherence exists in the face of multiple recommendations of new vaccination schedules.

The differences in mean interval spacing by clinic specialty observed at baseline parallel previous research demonstrating better rates of adherence to recommended immunization schedules among Pediatric compared to Family Medicine clinics [37]. Additionally, our results from univariate analyses demonstrated small differences, and higher overall mean intervals, in county health departments, which correspond to results from other studies that demonstrate children who receive shots in public health settings and/or have public or no health insurance typically receive shots in a less timely manner than children in private settings [38, 45].

Before adjusting for potential confounders, we speculated as to why intervals were higher and the differences between periods less significant in county health departments, since one might have expected higher adherence from within the same system that delivered the recommendation. Several explanations may help account for these findings. First, the site codes identified as "county health department" were only four, whereas other sites may have functioned under the umbrella of county health department without being labeled as such. For example, a "delegate" agency is an offsite clinic that operates under the same technical standards as a county health department and receives funding from similar sources, but functions under a different administration. A future comparison of results from an analysis with all county health departments and delegate clinics included in one category may shed light on any differences for all children served by a county-related clinic as opposed to those going to county health department locations only.

Secondly, the sample size in the "county health department" category was significantly smaller than other categories, thereby increasing the relative contribution of data from less adherent children in that subset. The observed univariate results may indeed have been a true representation of actual behavior. It is also possible that more attention was paid to delivering the recommendation to the private clinics in the community, or that administrative or logistical challenges inherent in the county health department system may have made it difficult for the public clinics to change practice. Furthermore, many clients at county health departments may have already visited a primary care provider, but were referred to a county clinic for vaccination due to their lack of insurance/ability to pay for vaccines. This would necessarily be associated with delayed intervals. Moreover, county health departments may not have functioned in these counties as a "medical home" for these children, as a private clinic might have. Children and families, therefore, may not have had future appointments scheduled for them in advance, and would have been left to schedule and receive subsequent vaccinations based on their own volition. Previous literature suggests that clients at county health systems are likely to be poorer, be of minority race, and be less educated, and all of these have been associated with delayed immunization in at least some studies [39].

The fact that the differences in mean intervals between clinic specialties, particularly county health departments, became more uniform following multivariate adjustment for socioeconomic status and race echoes studies that identify these factors as important predictors and confounders of immunization practice [39], and that after adjusting for these differences, county health departments behave more similarly to other

clinics where immunizations are provided. Still, however, it is important to note that county health departments continued to have the longest overall intervals after adjusting for demographic confounders, suggesting that there is something inherently unique about the county health department populations or immunization practices that could not be fully explained by the socioeconomic and race variables we controlled for in our analysis.

In general, Pediatric practices demonstrated more significant changes in post-recommendation mean intervals than did Family Medicine clinics, which might be expected given the different types of training, practice settings, number of children served, and continuing medical education opportunities between the two specialties [46]. Despite this difference, it is important to recognize that both Pediatric and Family Medicine clinics lag behind ACIP recommended intervals for both the routine or accelerated DTaP dosing [37], results that were confirmed by our study as well.

Our results also paralleled another general trend demonstrated in previous immunization research that has shown DTaP immunizations being administered progressively later with each successive DTaP dose [45]. Although some immunity is conferred by two on-time DTaP shots, the third dose is necessary to ensure more optimal immunity. This was true for children regardless of where they received their shot. Insurance status has also been shown to modify this effect, where, on average, the third DTaP was given 2.9-3.8 months later among Medicaid and uninsured children compared to children with insurance [45]. Our study showed that even after adjusting for potential confounders, children at county health departments (more likely to be Medicaid and uninsured, despite us not having this actual variable) received shots later than children in private Pediatric or Family Medicine clinics.

In addition to the results of this study that showed that most providers were able to significantly reduce mean DTaP intervals following the recommendation to accelerate DTaP dosing, this study has other strengths as well. The existence of the ALERT registry allowed a unique opportunity to study immunization practices before and after recommendations were made to temporarily accelerate the DTaP immunization schedule during a pertussis outbreak. While other studies have attempted to analyze the efficacy of the accelerated DTaP schedule, most entailed retrospective analyses of a pertussis outbreak and its resolution without a comparison to clinical practice before the outbreak [29, 30]. To our knowledge, this is the first large population-based study designed to test this research question. Our detection of significant differences in mean intervals in the recommendation counties compared to the non-recommendation county suggests that immunization providers may have integrated a local public health recommendation into their clinical practice enough to achieve a noticeable difference in immunization patterns.

The population sampled by our study was representative of the overall population in southwestern Oregon, namely White, English-speaking, a balanced distribution of socioeconomic status, and the largest percentage of immunizations being delivered by Pediatric clinics, thereby making these results likely to be generalizable to similar communities. Although this analysis did not investigate age appropriate up-to-date rates of child subjects, the trends observed in this analysis, where 99.98% children received DTaP1, 94.3% received DTaP2, and 85.3% received DTaP3, parallel national and statewide patterns of decreasing adherence with the higher numbered doses [18], suggesting that immunization patterns observed in our study may be similar to those in other communities.

The use of ALERT data itself is an inherent strength of this study. First, ALERT boasts high participation and is likely to represent actual immunization practice in Oregon. Secondly, its availability as an existing public health surveillance registry significantly reduced the costs of this study. Third, its use facilitated objective, rather than subjective, measurements of likely changes in immunization patterns, which has been a common limitation of other studies that have investigated such changes. Fourth, ALERT's capability to collect immunization data from secondary sources such as insurance companies or billing agencies likely improved vaccine reporting and captured shots that would otherwise have been missing. Finally, this is one of the first studies to successfully use an immunization registry system for research purposes. Our creation of algorithms to characterize immunization practice will be beneficial to future studies using ALERT and other registries similar to ALERT.

Several aspects of the study design lend credence to the observed results as well. Without the use of survival analysis to adjust for discrepancies in lengths of follow-up for each child, the results may have been subject to bias by outliers. Although the final criteria for inclusion into the two birth cohorts reduced the sample size, our standardization of rolling entry and exit criteria by selecting two equivalent four-month cohorts and using truncated follow-up periods significantly reduced the potential biases that may have resulted from imbalanced cohort eligibility and follow-up periods. Such biases that might result from assigning a "non-adherent" child a fixed, but lesser, value of a six-month interval are discussed in more detail in the limitations section. Nevertheless, less than 0.05% of children in the two birth cohorts had shots that were subject to truncation of shot intervals, making the possibility of significant bias much less likely.

The selection of balanced cohorts contributed to the ability to test our hypotheses in other areas as well. By choosing data that immediately preceded and followed the intervention, any significant differences in reporting to ALERT were minimized. Furthermore, limiting the cohort eligibility periods to four-month periods that matched the length of the recommendation itself maximized any true impact of the intervention by minimizing any dilution of the recommendation's effect by data collected in more remote months when the accelerated DTaP schedule was not formally in place. Finally, the existence of a built-in control of baseline data in the recommendation counties strengthens the internal validity of the results, as there were not likely to have been significant shifts in practice composition or immunization patterns during such a short period of time that could have modified the effect of the recommendation on the outcome interval. Unfortunately, this analysis did not take into account any differences that may have occurred from data reported by immunization providers who were newly enrolled in ALERT. Although the number of newly enrolled providers was not available at this writing, the number was likely to be small and would likely have biased any results toward the null.

The existence of Douglas County as a comparison county offered an additional opportunity to test whether providers and clinics responded to the public health recommendation to accelerate the DTaP schedule in the face of a pertussis outbreak. Even with an increased number of cases in Douglas County during this time (and an ongoing pertussis recall) the lack of a significant difference in mean intervals between the pre- and post-recommendation periods is consistent with the fact that no recommendation was made to providers to change their minimum interval spacing in Douglas County. In

contrast, the significant differences observed in the intervention counties appear to have occurred in response to the public health recommendations of an accelerated DTaP schedule.

Limitations

Despite its many strengths, several limitations of this study warrant discussion. As with any public health surveillance project, the possibility of underreporting of immunization data must be considered, both underreporting of clinics to ALERT, and underreporting of individual shots that could not be captured in the dataset. Although 100% of public and 87% of private clinics in Oregon are enrolled in ALERT, sheer enrollment does not guarantee consistent and/or reliable reporting to the registry. Additionally, ALERT is not capable of consistently tracking shots from children who move out of the ALERT capture area, even if that child was later "re-captured" by ALERT, unless clinic staff are able to collect historical immunization data once a child presents to the clinic. This is particularly a potential issue in Southern Oregon, where mobility between Oregon and California is a real possibility. In fact, results in Table 10 suggested that Southern Oregon clinics, particularly county health departments, may have served more children who were born outside of Oregon and subsequently moved into the state. 33% of children served by the county health department were missing birth certificate data on mother's race and maternal WIC enrollment, whereas only 6.9-8.0% of children served by Pediatric and Family Medicine clinics, respectively, were missing that same information. It is possible that these children may not have brought all their immunization records with them to Oregon, leading to an underestimate of vaccine

coverage. Additionally, children who moved across state borders during their early months of life are likely to have delayed immunizations. Both of these reasons may offer a partial explanation for the higher intervals observed in county health departments compared to private clinics.

The current analysis did not adjust for children who moved or received shots from different providers in the ALERT capture area. Evidence that children may indeed move between providers and/or counties for immunizations was offered in Table 3, which showed that 67-68% of children received DTaP1 or DTaP2 at a clinic in a recommendation county, whereas only 63% of children received DTaP3 at a clinic in a recommendation county. A slightly higher proportion of children received DTaP3 in an "other" county, one third of which were reported from secondary sources. It is unclear why this may have occurred. Future analyses could be repeated using only data from children who received shots in the recommendation or non-recommendation counties, rather than had a reported residence in one of these counties, as this would have forced the investigation to a more specific analysis of children whose immunization providers were located in counties that received and did not receive the recommendation.

Secondly, the ALERT database was initially created for clinical rather than analytic purposes. Its primary goal has been to collect *all* available immunization data on a child from the provider or previous immunization record. Data from outside immunization records, practice-specific immunization databases, and billing sources are all entered into ALERT, using standardized barcode scanning, electronic transfer, or manual data entry. The completeness of a child's immunization record depends on several factors, including regular reports from the participating ALERT provider, a child

who continuously sees an ALERT participating and reporting provider, and accurate "linkage" of multi-source child records. ALERT uses "deterministic linkage" methods to maximize completeness of child records and minimize data duplication by merging records using combinations of child identifiers (i.e. child name, parent name, date of birth). It is possible that if a parent's last name is misspelled, and other linkage criteria are not met, that a record that should be linked to its counterpart may be maintained as a separate record, thereby underestimating the vaccine coverage of that particular child. However, the quality of data entry and reporting has improved markedly since 2000, after which time the children eligible for this study were born. Furthermore, the second stage linkage of ALERT data with Oregon Birth Certificate data provided an additional opportunity for data de-duplication and merging, which contributed to the validity of the data among children born in Oregon. In general, with more sources to link (as is the case with ALERT and birth certificate data), there is a greater likelihood that child identifiers from the same child will overlap and be linkable.

Once child records are combined, ALERT records may contain multiple reports from different reporters. The database obtained at the beginning of the study required some arbitrary decision-making about what was considered a "unique" shot. The selection criteria (i.e., skipping any shot reported during the first 14 days of life, and choosing a single shot from amongst multiple shots within 10 days of each other) were based upon expected values under the routine schedule and experience of ALERT data managers. It is possible that this strategy may have introduced some erroneous selection of shots. However, because the selection criteria were applied uniformly across all child

records, regardless of their timing in the dataset, one would expect a non-differential selection bias, which if anything, would bias any results toward the null.

A second source of bias pertains to the decision to truncate intervals between shots to a maximum of six months (see Appendix 3). A six month window was selected based on the period of time from after the recommendation was rescinded and before the date on which the data was pulled for the study. Six months also allowed the potential for two to three shot interval calculations in the most "compliant" children. By truncating all intervals at six months, the contribution of outliers after six months of children who had intervals longer than six months (only 0.03-0.05%) was minimized; in doing so, the estimates became less influenced by variability. Truncated intervals may have underestimated the "true" intervals, and therefore generated a more conservative comparison of mean intervals. Since the observed differences in mean intervals between the two time periods were still significant, however, we can assume that the difference between groups is at least as large as was observed in the current analysis.

This study did not fully investigate factors other than basic clinic characteristics that may have been associated with a significant change in mean intervals. We had no direct measure of provider practice changes, and no way to identify which providers made changes. While increased provider adherence is a logical assumption when immunization patterns change in accordance with a new recommendation, we may not have fully accounted for other factors that may have affected the outcome. Without a more direct assessment of provider adherence, such as a survey of providers' knowledge of the recommendation and practice changes made, or a review of each clinic's use of the revised schedule and/or provider recalls, we have no assurance that the public health

recommendation itself necessarily caused significant practice changes. However, we have good evidence that immunization practice changes may have occurred in response to the public health recommendation, because the changes that we observed in the recommendation counties were not observed in the non-recommendation county.

This study only measured providers and subjects enrolled in ALERT, clinical practices that likely already possess higher awareness of immunization practices than non-registry practitioners. It is likely that mean intervals at baseline and after the recommendation may more closely approximate the recommended guidelines in this study population than in a population that does not participate in an immunization registry. This may lessen the generalizability of results to communities with providers with less awareness or involvement with local health department recommendations, or to communities (urban, rural, or underserved) that may face logistical challenges when disseminating community-wide public health announcements. This issue of generalizability may be especially true with results from our final analyses that evaluated shots given only by clinics in recommendation counties that were reporting to ALERT.

Unfortunately, two important variables (primary language spoken in the child's household and vaccine funding source) were not reliably reported to the ALERT registry, precluding any analyses about how language, family culture, and financial barriers to vaccination may have affected a child's ability to access immunization services, and whether these may have affected shot spacing. Future studies may investigate alternate strategies for assessing how language and socioeconomic status impact a child's or provider's level of adherence to the new schedule. Furthermore, the current analysis did not do multivariable modeling to adjust for potential confounders in the non-

recommendation counties. It is possible that after adjusting for mother's race, maternal WIC enrollment, and clinic specialty that the significant difference observed between recommendation and non-recommendation counties might have been less so. Additionally, our analysis did not examine change within a particular child or immunization provider, but rather examined trends among groups of practitioners or children with similar demographic characteristics.

A final limitation of this study was its inability to directly examine the effect of the recommendation on pertussis morbidity. With only 422 cases reported in the entire 2003 outbreak, it would have been difficult to measure the number of cases prevented by the intervention in children less than two years of age. Therefore, incidence may not have served as an accurate marker, particularly for a disease such as pertussis, where less severe cases are frequently undiagnosed and are not factored into the overall measure of disease burden in a population. If incidence were to be used to measure an impact of the recommendation, multiple sites with large numbers of reported cases would have been required, thereby significantly increasing the cost of the investigation. However, our study was designed to specifically examine a different intermediate outcome that was just as likely to be impacted by the recommendation to accelerate the DTaP immunization schedule.

Despite these limitations, our results strongly suggest that immunization practice changes occurred in response to a new public health recommendation, as mean intervals significantly changed among those providers in the recommendation counties, whereas they did not among providers who were *not* in the recommendation counties.

Public Health Implications

Although significant differences were observed following the recommendation, it is important to consider the public health significance of such a change. First, statistical significance must be considered. With the large sample size, the study is more likely to be overpowered than underpowered, meaning that a smaller difference in mean intervals is more likely to be statistically significant. Even at higher cutoff levels of statistical significance, such as $p<0.01$, the results of the primary analyses would have still been highly significant. Therefore, clinical and public health significance of the results becomes important to consider as well.

In the most focused of analyses, which examined dose spacing among clinics located in recommendation counties (Tables 9 and 11), mean intervals were 1.15-1.58 weeks shorter in the post-recommendation period compared to the pre-recommendation period. Because immunization receipt may be delayed for children, any improvement in how soon children are vaccinated would be beneficial in the face of an outbreak, especially in this case when baseline intervals between shots already deviate from the recommended intervals (eight weeks) by approximately two weeks, as they did in our study. Immunologic evidence has shown that administration of immunizations two weeks earlier than typically recommended confers equivalent antibody levels to the routine schedule [24, 25, 26, 27]. This posits that a difference of even one week following the recommendation, as was observed in this study, has the potential of being significant, both clinically and public health-wise. Therefore, even though the intervals in the recommendation period using the accelerated schedule are not close to minimum spacing, and, at best, approximate the intervals under the routine schedule, any

improvement assures earlier and higher immunoprotection against pertussis during an outbreak, which ultimately bears implications for public health significance.

It is also important to recognize that this intervention is likely to have its greatest impact on the most severe forms of the disease. Because pertussis is frequently limited to milder symptoms in adolescents and adults, the published incidence rates are more likely a representation of the numbers of more severe cases in infants and younger children who suffer the worst complications of the disease. Because an accelerated DTaP schedule focuses on the earliest doses of the DTaP series, these youngest children are most likely to be affected, thereby reducing the burden of severe morbidity from the disease. While complete eradication of pertussis is the ultimate goal, this intervention has perhaps more immediate public health significance by reducing the greatest clinical, financial, and societal costs of the disease.

Future Research

While the results of this study strongly suggest that providers were able to incorporate the accelerated schedule into their practice, further investigations are needed. More complex multivariate modeling might assist in future targeting of public health messages around an accelerated schedule, by identifying more specific clinic and child characteristics that are associated with changes in dose spacing. For example, inclusion of the length of a child's previous interval between shots would serve as an indicator of a child's previous level of schedule adherence, and a likely predictor of subsequent shot behavior. Examining other practice characteristics such as geographic location (rural vs. urban) using GIS techniques, as well as practice size (number of providers, number of

pediatric patients seen) would also be helpful in sorting out which additional factors are associated with changes in practice. Understanding more about which provider or child groups were less affected by the recommendation would help determine appropriate outreach and educational strategies when disseminating a similar recommendation in the future.

A third time period of analysis could be added to confirm that the mean intervals returned to or trended toward their previous baseline after the recommendation was rescinded in December 2003. As demonstrated in previous studies [43, 44], providers successfully adopted a recommendation initially, but were less successful at returning to standard practice once the recommendation was rescinded. Observation of such a return to baseline would offer further support that the changes observed in this study corresponded closely to practice recommendations and were likely due to provider practice changes at clinics.

These results were observed in the absence of a direct measure of provider adherence, thereby allowing only hypotheses that the differences observed were a result of providers making conscious changes to their individual and clinics' practices. It would have been insightful to have conducted a survey of providers at the time of (or soon thereafter) the outbreak, to record how providers received and perceived the recommendation, but this was not possible in our study given the resources available at the time. Key knowledge, attitudes, and barriers to implementation of the recommendation may have been identified, which would be very beneficial for future outreach planning. Additionally, such a survey could identify providers' preferred

methods of receiving public health messages, so that future messages may be more effectively and efficiently delivered to busy providers and clinics.

Another important step in determining the efficacy of an accelerated DTaP recommendation would be to evaluate its impact on up-to-date rates of other vaccinations that do not fall under the recommendation of the accelerated DTaP schedule, but that can also be given at minimum spacing intervals under the routine schedule. Given the fact that intershot intervals at baseline exceeded the recommended routine intervals, and that intervals were significantly reduced under the accelerated schedule, one might question why an accelerated schedule is not recommended all the time, particularly in areas that are prone to recurrent pertussis outbreaks. Examination of the childhood immunization schedule reveals a complex mixture of shots given at different times and in different combinations, with most of the earlier shots given at 2, 4, and 6 months. Because a public health recommendation of an accelerated DTaP schedule does not pertain to other vaccines, such as polio or Hepatitis B, one would assume that vaccines would remain on the routine schedule used by providers, whereas DTaP dosing would be shifted to an alternate schedule during an outbreak. Although early immunization against other diseases may be warranted in specific situations, those recommendations are not typically made, and their minimum intervals differ from those of the accelerated DTaP schedule.

Consequently, unless all vaccinations are given according to their minimum spacing along with the accelerated DTaP schedule, or unless insurance/billing policies reimburse for additional "off-schedule" well-child clinic visits for vaccination, the implementation of an accelerated DTaP schedule might have the potential for altering immunization spacing and coverage rates for other vaccines. If other vaccines are

missed, then a child's protection against other vaccine-preventable diseases may be compromised. While our results suggest an adoption of the new schedule by some clinics, we do not know if children received other vaccinations at the same time as the accelerated DTaP doses, or missed their other vaccinations that were scheduled for traditional well-child checks at 2, 4, and 6 months because of an inability to pay for the additional visit. Future investigation into rates of uptake of other vaccines during accelerated DTaP dosing, as well as policy and clinic barriers to any new schedule changes, would offer important insight into the larger utility of an accelerated DTaP schedule during a pertussis outbreak.

Finally, different statistical approaches could be used to address our research questions. First, to address the issue of varying contributions of person-years of follow-up, a sensitivity analysis using truncated and untruncated intervals could be performed to evaluate the impact of truncation on our study findings. Survival analysis techniques could be applied to the same data to generate a better appreciation of how children with different times to vaccination (i.e.,"compliant vs. noncompliant") were influenced by the recommendation, while accounting for different lengths of follow-up. A repeated measures design would lend insight into the effect of the recommendation on changes in mean interval spacing with individual children, which could be used in conjunction with other covariates to determine how different demographic variables modify the effect of the recommendation within a single child. Although no significant departures from a normal distribution were observed in this analysis, log transformed outcome variables could be incorporated into future analyses. Finally, our results could be confirmed

through the use of non-parametric methods using medians rather than means, as means (even truncated means) have the potential for being more influenced by outliers.

Conclusions

The results of this study suggest that DTaP dosing significantly changed after a recommendation to accelerate the DTaP schedule in the midst of a pertussis outbreak, suggesting that some providers adopted the accelerated DTaP schedule. In contrast to the sole comparison county which did not demonstrate a change in immunization practice, all 3 mean DTaP intervals in the three recommendation counties were significantly shorter following the recommendation in the recommendation counties, suggesting an impact of the intervention. After adjusting for potential confounders (mother's race, maternal WIC enrollment), minimal differences existed between clinic specialties for mean DTaP dose spacing, suggesting that future outreach efforts should be directed toward populations that are more typically affected by these child characteristics, namely the populations served by county health departments.

Unfortunately, mean intervals did not closely approximate the ACIP recommended routine or accelerated minimum spacing intervals for DTaP vaccination. Since on-time DTaP vaccination remains the primary outbreak prevention strategy, these results suggest the continued need for dedicated efforts to reinforce these recommended schedules and to understand the factors associated with delayed immunization. The results also highlight the possibility that providers from different specialties may require different amounts of education and outreach to facilitate increased adherence to a new immunization schedule.

This study provides needed evidence that clinics are able to adopt and implement a new public health recommendation for an accelerated DTaP immunization schedule. Even with the recent addition of the adolescent and adult TdaP vaccine that holds promise for reducing transmission to vulnerable infants and children, these results offer early evidence that the accelerated DTaP schedule is a feasible and perhaps effective pertussis prevention strategy during a pertussis outbreak. With this added information, public health officials may gain greater insight into community strategies that may ultimately lead to the complete suppression of pertussis altogether.

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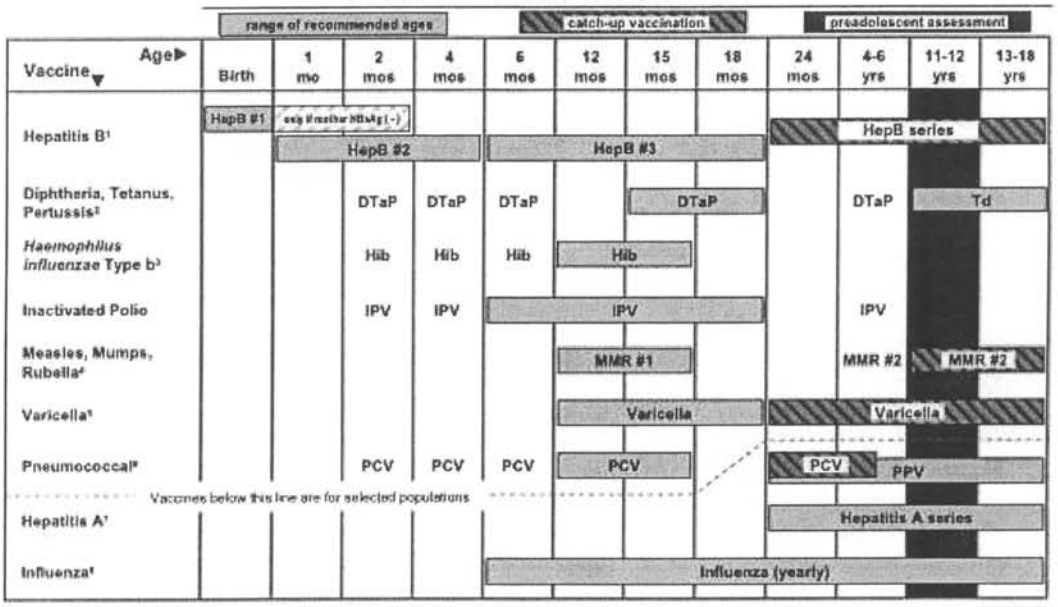
Appendix 1 Routine Childhood Immunization Schedule (2003) and Accelerated DTaP Schedule (2006) (CDC NIP)

Recommended Childhood and Adolescent Immunization Schedule -- United States, 2003



Recommended Immunization Schedule for Children and Adolescents Who Start Late or Who Are More Than 1 Month Behind

UNITED STATES • 2006

The tables below give catch-up schedules and minimum intervals between doses for children who have delayed immunizations. There is no need to restart a vaccine series regardless of the time that has elapsed between doses. Use the chart appropriate for the child's age.

CATCH-UP SCHEDULE FOR CHILDREN AGED 4 MONTHS THROUGH 6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Diphtheria, Tetanus, Pertussis	6 wks	4 weeks	4 weeks	6 months	6 months[1]

**Note: DTaP minimum spacing recommendations were identical to those listed above during the time of this study (2003).

Oregon Immunization ALERT
New Enrollee Form

↓ Clinic or Attending Provider Stamp ↓

Provider's office staff:
Place *Name* bar code label here and complete information:

Place this label on patient's ID form

Name_First_____Middle_____Last_____

Birthdate MM/DD/YY

MOTHER'S HBsAg []Pos []Neg []Unk

OR-000-000-007

Parents: Please **PRINT** the following information concerning your **CHILD**:

REQUIRED INFORMATION

Date of birth: ____/____/____
MM DD YYYY

☐ Male ☐ Female

OR - _____-_____-_____
Previous bar code number
(only if known)

First name(s) Middle name(s) Last name(s)

Last name at birth

Mother's maiden name
(mother's last name before she was married)

Place of birth
(state or country)

Parent/guardian name: _____
First name(s) Last name(s)

Home address: _____
Street Apt. # City State Zip code

Mailing address: (if different) _____
Street Apt. # City State Zip code

Phone number

Work or message phone (if any) x_____

Child's Social Security Number
(**not** parents')

Medicaid ID # or insurance #
(if applicable)

Primary language

Comments:

To contact ALERT:

phone: **1-800-980-9431**
(503) 731-3348
fax: **(503) 731-3042**
email: **OHD.ALERT@state.or.us**

Oregon Immunization ALERT Records and Reminders

DHS 8000C 12/99

Optional for clinics: Attach a copy of the child's immunization record and ALERT will enter the full immunization history.

PLEASE PRINT IN BLACK INK

Oregon Immunization ALERT – Update/Addition Form

Use to update original blue New Enrollee Form information
or to add or correct patient information

CLINIC INFORMATION (required):

↓ Clinic or Attending Provider Stamp ↓

Date of Update: _____

Staff Providing Update: _____

Staff Phone Number: _____

PATIENT INFORMATION (required):

Child's Name: _____ Date of Birth: ____/____/____

Current ALERT Barcode Number: OR-_____-_____-_____ (assigned by **your** clinic) ***OR***

Current Electronic Transfer ID Number: _____ (assigned by **your** clinic for e-transfer records)

DEMOGRAPHIC CHANGES, ADDITIONS, AND/OR CORRECTIONS (e.g., address, phone number):

IMMUNIZATION CHANGES, ADDITIONS AND/OR CORRECTIONS (Use only for missing or incorrect immunizations; for new immunizations, use pink form or e-transfer):

Note: You cannot change or correct information submitted by a clinic/source other than your own.

To contact ALERT:

Phone: (800) 980-9431 (Statewide)
(503) 731-3348 (Portland Metro)
FAX: (503) 731-3042
Email: OHD.ALERT@state.or.us

Oregon Immunization ALERT
Records and Reminders

PLEASE PRINT IN BLACK INK

Appendix 3 Results and discussion of truncation method used to calculate mean intervals

Only a small percentage was subject to truncation of shot intervals. Of the 5,035 children who had a calculable interval between birth and DTaP1, 156 (0.03%) children had shot intervals longer than six months. Of the 4,751 children who had a calculable interval between DTaP1 and DTaP2, 142 (0.03%) children had shot intervals longer than six months. And finally, of the 4,296 children who had a calculable interval between DTaP2 and DTaP3, 207 (0.05%) children had shot intervals longer than six months

Two sets of histograms were generated for the three overall outcome variables to evaluate for departures from a normal distribution. Standard curves for a normal distribution were superimposed on the histogram for comparison. Samples are demonstrated below for the interval between DTaP1 - DTaP2. The first set (Figure 3a) depicted the three intervals in the pre- and post-recommendation periods combined with an unlimited follow-up period, whereas the second set depicted the three intervals with the follow-up period until subsequent shot truncated at 26 weeks for all children in the pre- and post-recommendation birth cohorts who exceeded 6 months between two shots in series (Figure 3b). Of note, graphs for the truncated and untruncated measures use different scales. Each histogram demonstrated a relatively normal distribution with a slight shift to the right due to the delayed receipt of shots in a small (<0.05%) proportion of the population. A spike was appreciated at 26 weeks (6 months) on the histograms using the truncated interval values.

A third set of histograms was generated to compare separate distributions of the three outcome intervals in the pre- and post-recommendation periods, using untruncated and truncated intervals (see samples for DTaP1-DTaP2 below). Figures 4a and 4b depict

the distribution of mean intervals between DTaP1-DTaP2 in the two periods, using untruncated values, and Figures 5a and 5b depict results from a similar analysis using truncated values. Again, the scales differ between each graph. Even with this difference in scales, a clear shift to the left in the mean is appreciated in the post-recommendation distribution compared to the pre-recommendation distribution using both untruncated and truncated intervals, implying that DTaP doses were given earlier following the recommendation.

Table 12 below highlights the mean intervals, standard deviation, and ranges for shot intervals in the baseline pre-recommendation period using untruncated (unlimited follow-up to the next shot in series) and truncated (a maximum of six months follow-up to the next shot in series) follow-up periods. Truncated intervals were shorter, particularly in the pre-recommendation period, with smaller standard deviations and ranges compared to the raw, untruncated intervals. In the pre-recommendation period, mean intervals between all three shots were 0.69-1.15 weeks shorter using the truncated follow-up period, with narrower ranges and standard deviations, than the untruncated period. In the post-recommendation period, the truncated intervals were 0.16-0.31 weeks shorter than untruncated intervals, with smaller standard deviations and ranges that reached a maximum of 26.01 weeks (where 26.01 represented all children whose follow-up period extended beyond 6 months, or 26 weeks). Less influenced by outliers, the median interval was somewhat lower than the mean interval and remained constant in the analyses using untruncated and truncated intervals.

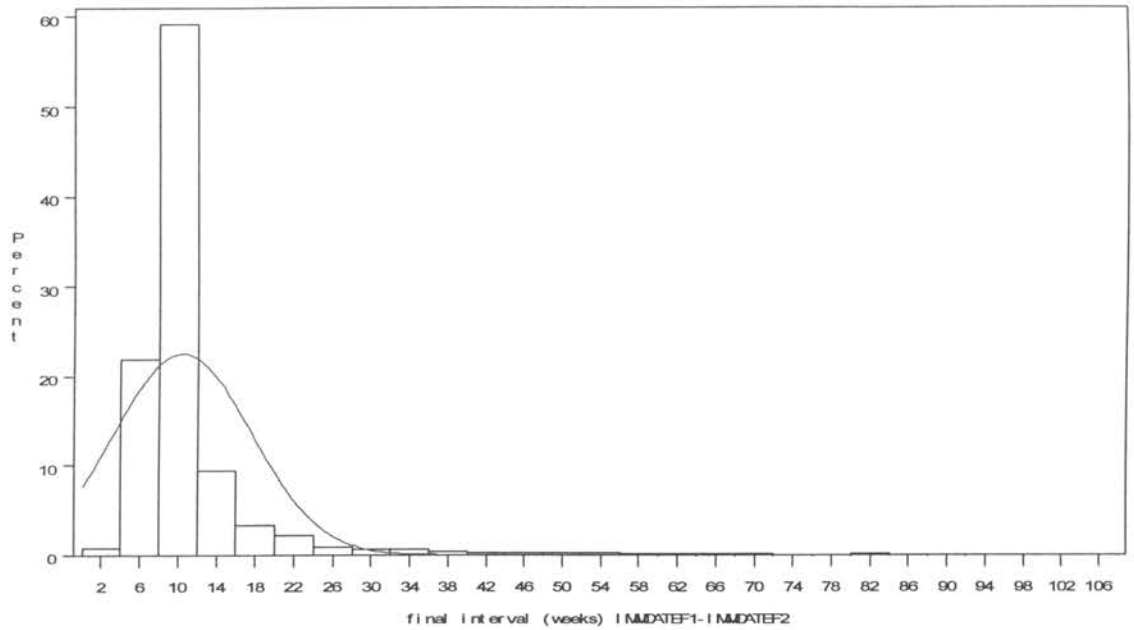
Table 12- Comparison of untruncated and truncated mean intervals, and medians, among all child subjects in birth cohorts (n=5,036)

	n (# missing)	Mean +/- SD	Range	Mean +/- SD	Range	Median
Pre-Recommendation		Untruncated		Truncated		
DOB-DTaP1	2520 (0)	11.74 +/- 9.24	2.43-109.71	10.76 +/- 4.29	2.43-26.01	9.14
DTaP1-DTaP2	2404 (116)	11.28 +/- 7.98	1.71-106.86	10.59 +/- 4.47	1.71-26.01	9.00
DTaP2-DTaP3	2249 (271)	12.27 +/- 9.60	3.00-81.14	11.12 +/- 5.18	3.00-26.01	9.14
Post-Recommendation		Untruncated		Truncated		
DOB-DTaP1	2515 (1)	9.49 +/- 4.95	2.00-72.29	9.33 +/- 4.06	2.00-26.01	8.71
DTaP1-DTaP2	2347 (169)	9.59 +/- 5.93	2.00-68.00	9.31 +/- 4.52	2.00-26.01	9.00
DTaP2-DTaP3	2047 (469)	10.26 +/- 6.11	2.00-61.43	9.95 +/- 4.72	2.00-26.01	9.00

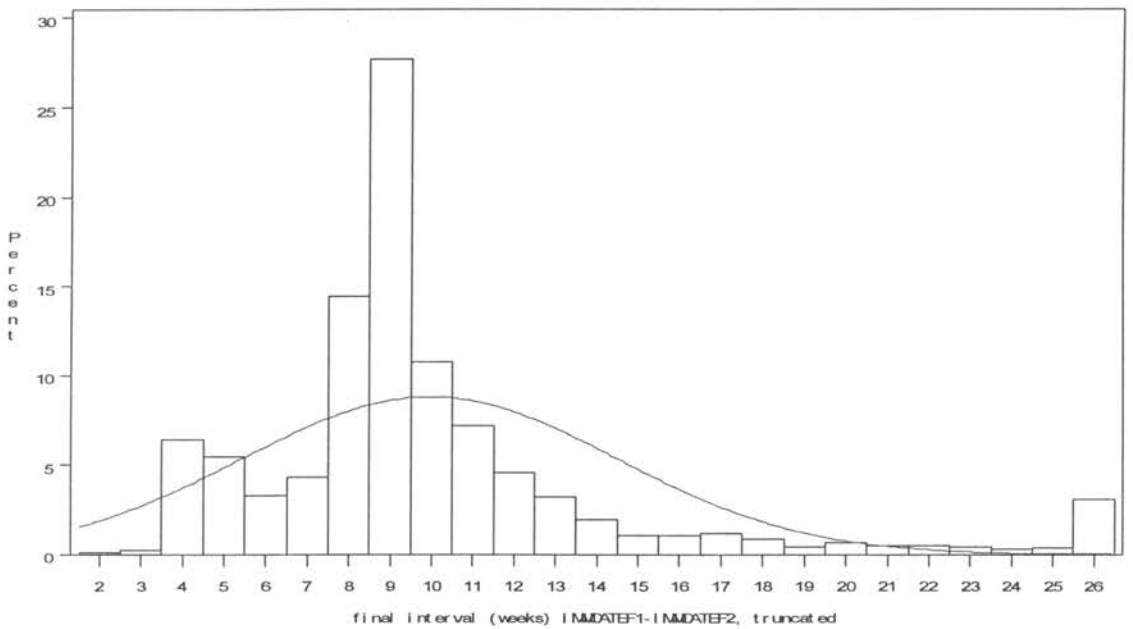
Although not shown here, log transformation demonstrated a slight improvement in the fit of a normal distribution. However, non-transformed data was analyzed in this study to facilitate interpretation with more readily accessible public health implications of a change in weeks as opposed to a percent change.

Figure 3: Overall Intervals between DTaP1-DTaP2, using untruncated and truncated periods of follow-up to subsequent shot

3a: Untruncated



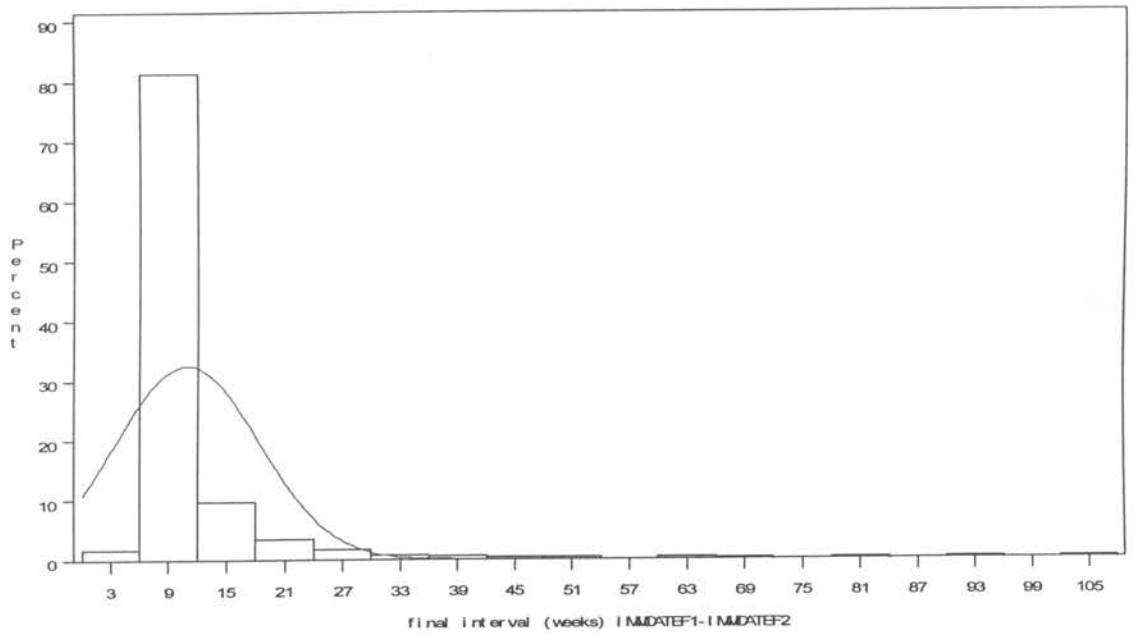
3b:Truncated



***note: scales are different for untruncated and truncated figures.**

Figure 4: Distribution of mean intervals between DTaP1 and DTaP2 in pre- and post-recommendation periods, using untruncated intervals

4a: Pre-recommendation period



4b: Post-recommendation period

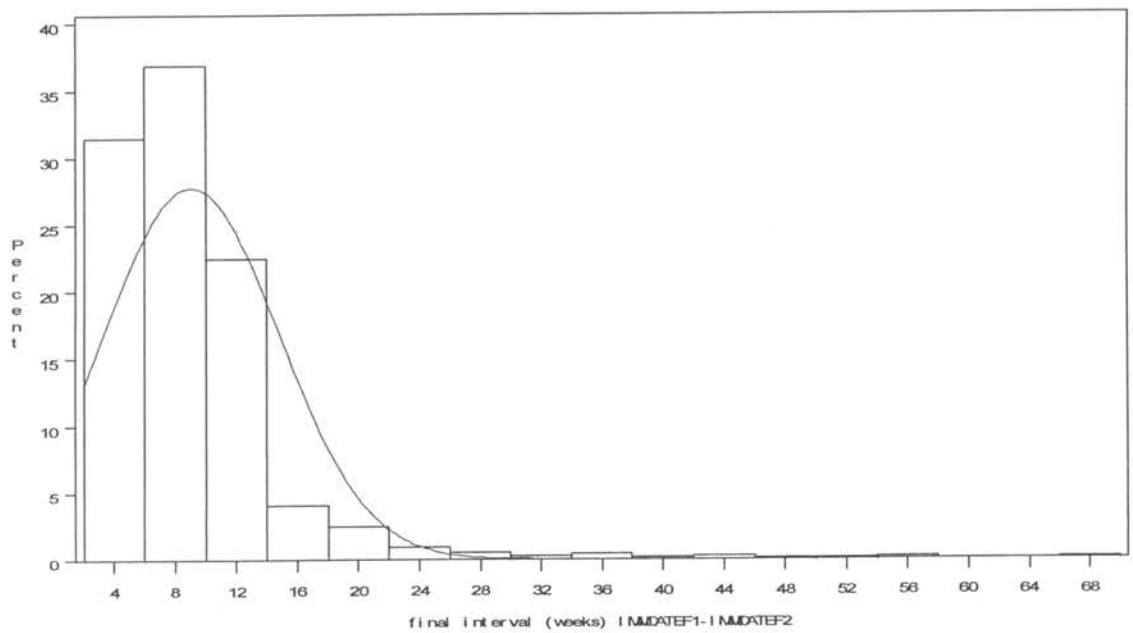
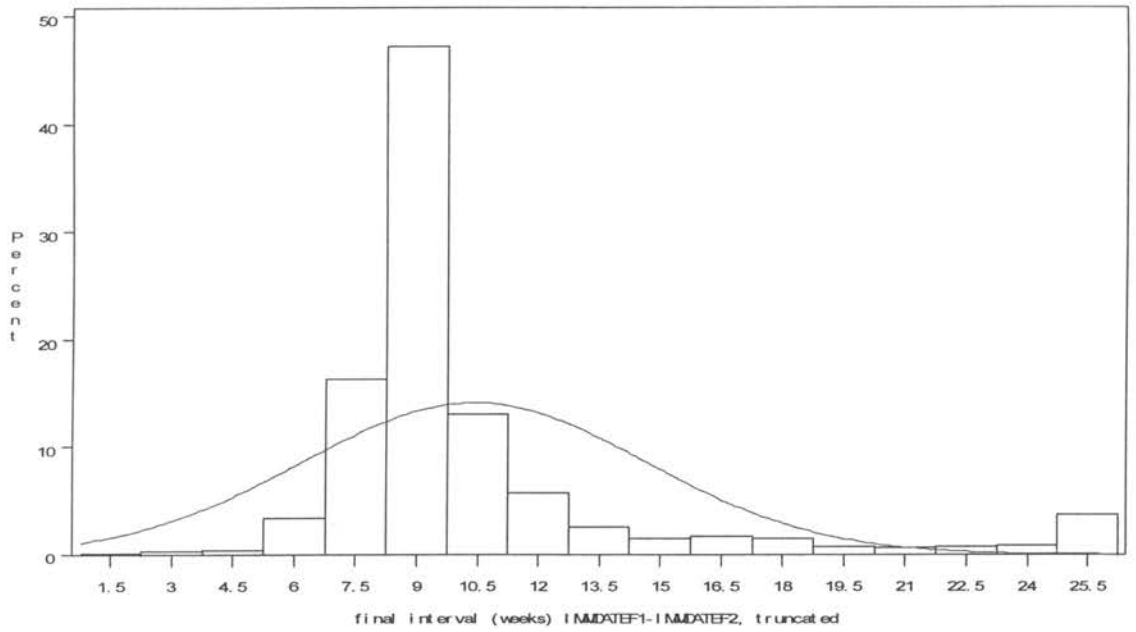


Figure 5: Distribution of mean intervals between DTaP1 and DTaP2 in pre- and post-recommendation periods, using truncated intervals

5a: Pre-recommendation period



5b: Post-recommendation period