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SHORT REPORT

Undervaccination with diphtheria, tetanus, and pertussis vaccine: National trends and association with pertussis risk in young children

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ABSTRACT

Background: The high coverage for ≥3 pertussis vaccine doses among Taiwanese children might not imply timely vaccination. Recently, resurgence of pertussis and challenges with availability of DTaP-IPV-Hib prompted this study. **Methods**: In the 1996–2012 national birth cohort, we calculated the prevalence and days of undervaccination against pertussis by age 36 months. We also compared the odds of undervaccination in each laboratory-confirmed pertussis patient at ages 3–35 months with sex-, residence-, and age-matched controls from the general population, using conditional logistic regression. **Results**: The prevalence of undervaccination was 60.6% (median 16 days) and decreasing ($p < 0.0001$). Among 145 cases and 2,900 controls, 58 (40.0%) and 721 (24.9%) were undervaccinated (OR 2.28, 95% CI 1.57–3.31). The attributable risk percent was 22.5% (95% CI 14.5–27.9). **Conclusions**: Undervaccination was decreasing. Approximately up to one-fifth pertussis cases in children aged 3–35 months could have been prevented with on-time vaccination.

Introduction

Age-appropriate vaccination reduces a child's risk of pertussis and prevents disease outbreaks.[1-3] In Taiwan, control of pertussis was achieved through widespread use of whole-cell pertussis vaccine, combined with diphtheria and tetanus toxoids (as DTwP) since 1954.[4,5] In 1996, the country started the transition from DTwP to acellular pertussis vaccines (DTaP) and by March 2010, a pentavalent vaccine (combined DTaP, inactivated polio [IPV], and *Haemophilus influenzae* type b [Hib] vaccine) (DTaP-IPV-Hib) was being used for all 4 doses at ages 2, 4, 6, and 18 months.[5] Vaccination coverage among children aged 12–23 months was 97.4% for at least 3 doses.[6]

This high vaccination coverage, however, did not necessarily imply timely vaccination.[7,8] In January 2014, Taiwan Centers for Disease Control issued a recommendation to defer the fourth dose of DTaP-IPV-Hib from age 18 months to 27 months because of a global shortage.[9] The challenges with availability of DTaP-IPV-Hib and recent resurgence of pertussis in infants and young children[10] prompted us to (1) describe national prevalence and trends of undervaccination with pertussis vaccines during the first 36 months of life; and (2) examine the association between undervaccination and risk of pertussis among children 3–35 months of age.

Materials and methods

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board at Taiwan Centers for Disease Control (#105203).

Study population

The study was conducted within a cohort of Taiwanese children registered in the National Immunization Information System (NIIS), a central database that periodically consolidates distributed immunization records from clinics, hospitals, and local health authorities.[11] For each child born since 1995, details of vaccines administered mainly at preschool ages are recorded in an NIIS account under his/her unique personal identification number, and compiled through secure data exchange between local and central databases. This mechanism allows children to be vaccinated anywhere in the country without being missed or repeated, and ensures overall high (>98%) data completeness.[11]

The study observation period was January 1, 1996 through December 31, 2015. We used the NIIS database to create a retrospective cohort of children born between 1996 and 2012 and their vaccination records; each child was followed up until the age of 36 months or death, whichever earlier.

Children undervaccinated

For each child, date(s) of DTwP or DTaP vaccination and date of birth were used to determine age at vaccination. Days undervaccinated for specific doses were calculated based on a modified metric[7,12,13] that measures the difference between when the vaccine dose was administered and when the vaccine dose should have been administered (Table S1). The magnitude of undervaccination accumulated until the child was vaccinated or at age 36 months.
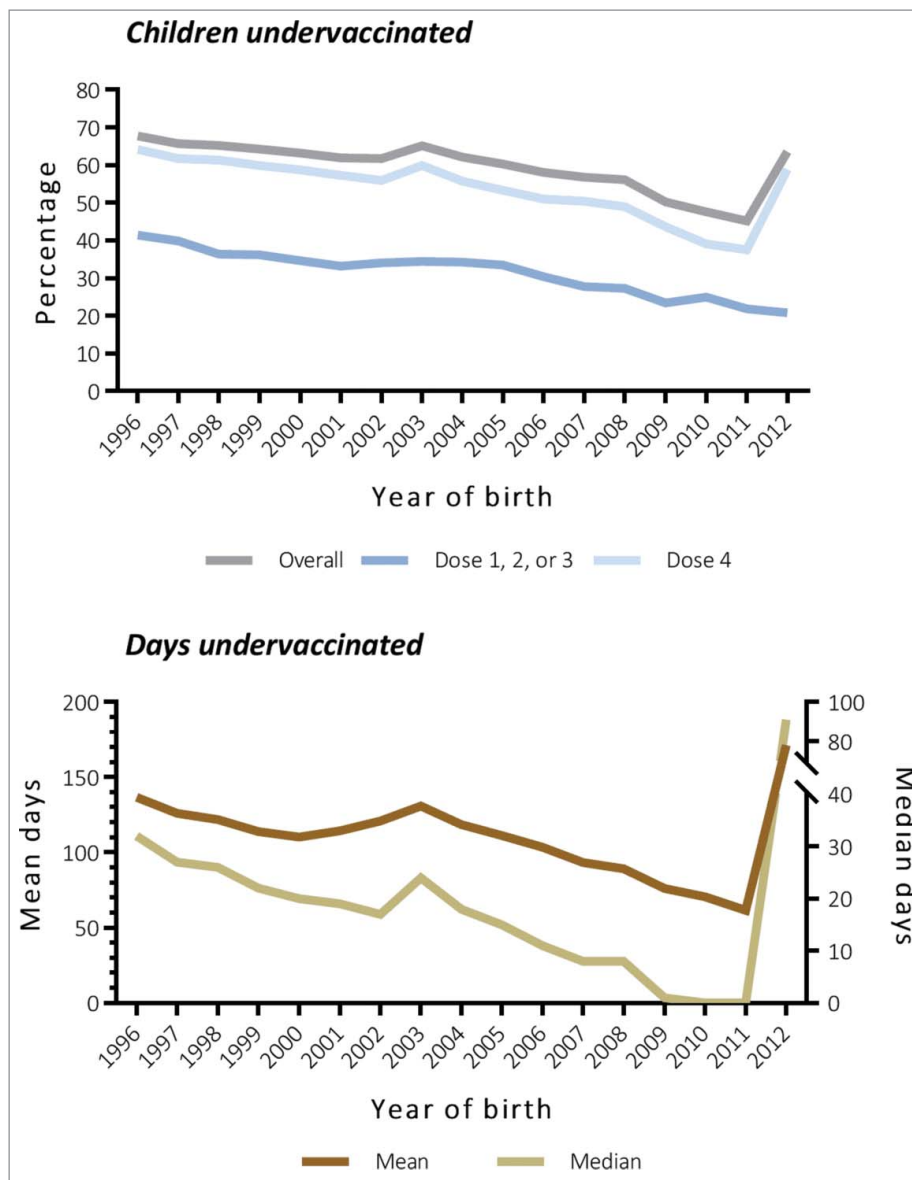
Figure 1. Trends in prevalence (top) and mean and median days (bottom) of undervaccination with DTwP or DTaP by birth cohort. All trends were significant using the Cochran-Armitage trend test ($p < 0.0001$) and linear regression ($p < 0.0001$). Numbers were listed in Table S2. DTwP, diphtheria, tetanus and whole-cell pertussis vaccine; DTaP, diphtheria, tetanus, and acellular pertussis vaccine.

Cases and controls

Pertussis is a notifiable disease in Taiwan.[4] Physicians are required to report suspect cases to corresponding local health authorities within 7 days and submit nasopharyngeal and/or serum specimens for culture, polymerase chain reaction (PCR), and/or serologic tests for *Bordetella pertussis*. By linking NIIS to the National Notifiable Disease Surveillance System, we defined case patients as children who had onset of illness during January 1, 1996–December 31, 2015, and were positive for *B. pertussis* on culture or PCR tests at ages 3–35 months. Each case patient was matched to 20 controls by sex (male or female), age at the illness onset date (the index date) (±7 days), and county of residence. The control group consisted of the 1996–2012 nationwide birth cohort; children were excluded as controls if they had a record of pertussis prior to the index date.

Analysis

The data were processed and analyzed using SAS® 9.4 (SAS Institute Inc., Cary, North Carolina).

Timeliness of vaccination

We calculated the prevalence of DTwP or DTaP undervaccinated children, and mean and median days undervaccinated within each birth cohort from 1996 through 2012.[13] Time trends were analyzed with linear regression and Cochran-Armitage trend tests. Trends in undervaccination of dose 1, 2, or 3 were compared with dose 4 across the birth cohorts.

Risk of pertussis

Case patients and controls were linked to the NIIS database using their personal identification number, and classified as either age-appropriately vaccinated (0 doses/days missing or

Table 1. Characteristics of *Bordetella pertussis* positive children (cases) and matched controls.

	Cases (n = 145)	Controls (n = 2,900)	p-value
Sex			1.0000
Male	81 (55.9)	1,620 (55.9)	
Female	64 (44.1)	1,280 (44.1)	
Age at index date, mean (SD), months	9.77 (8.57)	9.77 (8.55)	1.0000
Age group, months			0.9775
<12	106 (73.1)	2,116 (73.0)	
12–23	26 (17.9)	529 (18.2)	
24–35	13 (9.0)	255 (8.8)	
Region of residence[a]			1.0000
Northern	62 (42.8)	1,240 (42.8)	
Central	15 (10.3)	300 (10.3)	
Southern	13 (9.0)	260 (9.0)	
Others	55 (37.9)	1,100 (37.9)	
Year of index date			1.0000
1996–2007	100 (69.0)	2,000 (69.0)	
2008–2011	29 (20.0)	580 (20.0)	
2012–2015	16 (11.0)	320 (11.0)	

SD, standard deviation.
[a]Northern (from Keelung to Miaoli), Central (Taichung, Changhua, and Nantou), and Southern (from Yunlin to Pingtung) Taiwan are broad geographic regions along the west coast. Other regions included Eastern Taiwan (Hualien and Taitung) and offshore islands (Penghu, Kinmen, and Lienchiang).

delayed) or undervaccinated (by 1, 2, 3, or 4 doses; or for 1–30, 31–90, or 91–1,003 days) of DTwP or DTaP at the index date. We conditioned the logistic regression model on all matching variables to compare the odds of undervaccination in the cases with the control group. Age-appropriately vaccinated children represented the referent group.

Results

Among 4,104,526 children born between 1996 and 2012, 2,487,831 (60.6%) were undervaccinated with DTwP or DTaP (median 16 days, interquartile range 0–109 days). Of those with any delay, 755,306 (30.4%) were undervaccinated for more than 6 months while other children had shorter periods of delay (28.5% for 1–30 days, 25.6% for 1–3 months, and 15.6% for 4–6 months). The prevalence of undervaccinated children and mean and median days undervaccinated decreased significantly ($p < 0.0001$), but rebounded for those born in 2012 (Fig. 1). This rebound effect was only observed for the fourth dose.

Of 145 case patients (mean age 9.77 months), 73 (50.3%) were hospitalized. Characteristics of cases and controls (n = 2,900) were similar (Table 1). At the index date, 58 (40.0%) of the cases and 721 (24.9%) of the controls were undervaccinated of DTwP or DTaP (odds ratio [OR] 2.28, 95% confidence interval [CI] 1.57–3.31). A dose-response relationship was observed between risk of pertussis and the magnitude of undervaccination, but only with delays in the first 3 vaccination doses (Table 2). Overall, 22.5% (95% CI 14.5–27.9) of all *B. pertussis* patients were attributed to undervaccination.

Discussion

Our analysis found that more than half of the children were delayed for at least one DTwP or DTaP vaccine doses before age 36 months; among them, approximately one-third were undervaccinated for more than 6 months. Contrary to the rising trend in the US,[13,14] this analysis also suggested that undervaccination in Taiwan decreased over time. The decreasing prevalence and magnitude of undervaccination against pertussis highlighted public health successes in improving access to healthcare, vaccine delivery, and systems to identify and catch up children behind on immunizations over the past decade. Although timeliness of vaccination for children born in 2012 was hindered by the limited supply of DTaP-IPV-Hib,[9] 54.8% of those born in the previous year (2011) received all 4 doses of DTaP-IPV-Hib at age-appropriate times, a rate that was comparable to US estimates of 52.1% and 55.9% for DTaP from the National Immunization Survey.[7,15]

In the case-control analysis we found significant associations between undervaccination and laboratory-confirmed pertussis in children aged 3–35 months. Had these children received vaccination with DTwP or DTaP on time, approximately up to 1 in 5 *B. pertussis* infections in this age group could have been

Table 2. Matched OR and 95% CI for *Bordetella pertussis* infection, under- versus age-appropriately vaccinated of DTwP or DTaP[a].

	Cases (n = 145)	Controls (n = 2,900)	Matched OR[b]	(95% CI)[b]	p-value[b]
Number of doses undervaccinated					
0	87 (60.0)	2,179 (75.1)	1.0		
1, 2, 3, or 4	58 (40.0)	721 (24.9)	2.28	(1.57–3.31)	<0.0001
1	29 (20.0)	439 (15.1)	1.84	(1.17–2.89)	0.0080
2	12 (8.3)	129 (4.4)	2.80	(1.44–5.44)	0.0023
3	13 (9.0)	113 (3.9)	3.85	(1.93–7.67)	0.0001
4	4 (2.8)	40 (1.4)	3.79	(1.19–12.07)	0.0243
Days undervaccinated					
0	87 (60.0)	2,179 (75.1)	1.0		
1–30	26 (17.9)	370 (12.8)	1.93	(1.21–3.06)	0.0057
31–90	13 (9.0)	193 (6.7)	2.06	(1.09–3.88)	0.0255
91–1,003	19 (13.1)	158 (5.4)	4.16	(2.26–7.67)	<0.0001
Dose number undervaccinated					
None	87 (60.0)	2,179 (75.1)	1.0		
Dose 1, 2, or 3 only	47 (32.4)	500 (17.2)	2.52	(1.71–3.71)	<0.0001
Dose 4 only	5 (3.4)	115 (4.0)	1.02	(0.33–3.15)	0.9784
Dose 1, 2, or 3; plus dose 4	6 (4.1)	106 (3.7)	1.35	(0.49–3.72)	0.5657

OR, odds ratio; CI, confidence interval; DTwP, diphtheria, tetanus and whole-cell pertussis vaccine; DTaP, diphtheria, tetanus, and acellular pertussis vaccine.
[a]Children undervaccinated by 0 doses or 0 days, or none of the dose number of DTwP or DTaP were considered as age-appropriately vaccinated.
[b]The ORs and 95% CIs were estimated by conditioning on sex, county of residence, and age at index date.

prevented, as the vaccines could fail to prevent infection, but still protect children against severe disease. We also observed a dose-effect relationship that had been reported for US children of the same ages by Glanz et al.[1] Within cohorts of children born during 2004–2008, Glanz argued that children who missed 3 or 4 doses of DTaP vaccine were nearly 19 and 28 times more likely to develop pertussis than children who were age-appropriately vaccinated.[1] Our data, however, showed that this increased risk of acquiring pertussis was only associated with delays in the 3-dose primary series, and comparing risk between children undervaccinated by 3 and 4 doses of DTwP- or DTaP-containing vaccine showed very similar results (OR 3.85 and 3.79, respectively). Given the lack of association of pertussis with delaying receipt of the fourth vaccination by age 36 months, our findings provide additional support for the government's policy that has been deferring this routine booster dose of DTaP-IPV-Hib to age 27 months since 2014, particularly when this vaccine is still in short supply.

This study has limitations. First, the validity of NIIS data compared with actual vaccine receipt is unknown. Misclassification of vaccination status can occur if the vaccines are not administered in Taiwan. Second, prior studies estimate that overall 10%–25% of children were undervaccinated because of vaccine-hesitant parents.[13,16,17] Our study, however, was unable to provide reasons for undervaccination as this information was not captured in the NIIS or assessed through reviews of medical records. Third, pertussis is highly underreported. While we applied a matched analysis, controls from the general population might have contracted pertussis, but not been tested and notified. Also, physicians' awareness differed and could be higher among under- compared with age-appropriately vaccinated children. This misclassification of disease status and diagnostic bias could have resulted in an overestimate of the true association between undervaccination and pertussis. Finally, use of laboratory tests and availability of whole-cell or acellular pertussis vaccines changed over the study period. Also, the variable patterns of undervaccination contributed to exposure heterogeneity in vaccination histories.[12] We were unable to perform stratified analyses for a subset of these variants due to low numbers of exposed cases in each stratum.

Despite these limitations, linking national immunization with notifiable disease datasets had allowed us to efficiently ascertain vaccination status among pertussis patients. Our study indicated that in Taiwan, undervaccination was decreasing but had placed young children at risk for pertussis. By pooling additional data from multiple sources (e.g., hospital/laboratory, cancer, and mortality registries), this model can be further used to study other rare outcomes following the childhood immunization schedules.

Abbreviations

CI	confidence interval
DTaP	diphtheria, tetanus, and acellular pertussis vaccine
DTaP-IPV-Hib	diphtheria, tetanus, and acellular pertussis, inactivated polio, and *Haemophilus influenzae* type b vaccine
DTwP	diphtheria, tetanus, and whole-cell pertussis vaccine
NIIS	National Immunization Information System
OR	odds ratio
PCR	polymerase chain reaction

Author contributions

Conceived and design the experiments: WTH. Performed the experiment: WTH. Analyzed the data: WTH. Contributed reagents/materials/analysis tools: WTH CHY. Wrote the first draft of the manuscript: WTH. Contributed to the writing of the manuscript: WTH HCL CHY. Agree with manuscript results and conclusions: WTH HCL CHY.

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