

Preplanned Studies

Effectiveness of DTaP Against Pertussis in ≤ 2 -Year-Old Children — Linyi Prefecture, Shandong Province, China, 2017–2019

Pinpin Zhu¹; Dan Wu¹; Yan Wang²; Xiaoxue Liu³; Lance E. Rodewald¹; Yixing Li¹; Hui Zheng¹; Lei Cao¹; Yifan Song¹; Li Song²; Xiaodong Zhao³; Jianyi Yao⁴; Fuzhen Wang¹; Mingshuang Li¹; Qian Zhang¹; Tingting Yan¹; Zundong Yin^{1,†}

Summary

What is already known about this topic?

Vaccine effectiveness (VE) is positively correlated with the number of administered co-purified diphtheria, tetanus, and acellular pertussis vaccine (DTaP) doses. A matched case-control study conducted in Zhongshan City revealed that the co-purified DTaP VE against pertussis-related illnesses in children aged 4–11 months was 42% for one dose, 88% for two doses, and 95% for three doses, respectively.

What is added by this report?

The results of this study contribute to the current body of research. We found that the VE of co-purified DTaP against pertussis-related illness and hospitalization increased substantially, ranging from 24%–26% after one dose to 86%–87% after four doses.

What are the implications for public health practice?

The results of this study underscore the significance of prompt and comprehensive immunization using co-purified DTaP to decrease the incidence of pertussis. Additionally, these findings offer evidence supporting the modification of China's pertussis vaccination approach.

Pertussis, a highly contagious acute respiratory disease caused by *Bordetella pertussis* bacteria, has been a significant contributor to morbidity and mortality in infants and young children (1). The average incubation period spans 7 to 10 days, with a range of 2 to 21 days (2). Since the initiation of China's national immunization program in 1978, pertussis has been effectively controlled through the widespread use of the diphtheria, tetanus, and whole-cell pertussis vaccine (DTwP). From 2007 to 2013, DTwP was gradually replaced by the co-purified diphtheria, tetanus, and acellular pertussis vaccine (DTaP).

There are three primary types of pertussis vaccines utilized worldwide: whole-cell, component purified acellular, and co-purified acellular vaccines (Supplementary Materials, available in <https://weekly.chinacdc.cn/>). In countries with high DTaP vaccination rates, such as the United States and Australia, the incidence of pertussis has increased following years of low incidence — a phenomenon referred to as the “pertussis resurgence” (1). In China, the reported coverage for three doses of the pertussis vaccine has been maintained at over 99% in recent years (3), yet the incidence of pertussis has also risen, with the majority of cases occurring among infants (4). This increase followed the transition from DTwP to co-purified DTaP, and since few countries employ the co-purified DTaP, it is of critical importance to evaluate the vaccine effectiveness (VE) of co-purified DTaP on a dose-by-dose basis. Since 2016, Linyi Prefecture in Shandong Province has conducted enhanced pertussis surveillance, revealing that the number of reported cases rose from 96 in 2016 to 688 in 2018.

In this study, a retrospective cohort design was employed to assess the absolute VEs of each of the four recommended doses of co-purified DTaP in preventing pertussis-related illnesses and hospitalizations. The aim was to provide empirical support for optimizing pertussis immunization strategies.

The study was conducted in Linyi Prefecture, the largest city in Shandong Province, China, encompassing a population of 10 million residents spread over 17,000 square kilometers. The pertussis vaccination schedule in Linyi aligns with that of Chinese mainland, consisting of four 0.5 mL doses of co-purified DTaP administered at 3 months, 4 months, 5 months, and 18 months of age.

The study population consisted of children born between January 1, 2017, and December 31, 2017,

who were permanent residents in Linyi Prefecture and had records in Shandong's Immunization Information System. Exclusion criteria included children who received vaccinations outside of Linyi Prefecture, those vaccinated with co-purified DTaP-Hib or component purified DTaP-IPV/Hib, individuals missing gender information, those with a history of pertussis vaccination prior to 3 months of age, or those diagnosed with pertussis before 3.5 months of age.

Data on vaccination and key demographic information were obtained from the China Immunization Information System. Pertussis diagnoses were gathered from the National Notifiable Diseases Reporting System (NNDRS), the Hospital Management Information System (HIS), and telephone surveys. Pertussis cases were either clinically diagnosed or laboratory-confirmed.

The definitions, such as cases, cumulative vaccination rates, timely vaccination rates, n-group, and VE, can be found in the Supplementary Materials. The cohort was divided into 0-, 1-, 2-, 3-, and 4-dose groups based on the number of doses received and infection status by 24 months of age (Supplementary Figure S1, available in <https://weekly.chinacdc.cn/>). VE was estimated using the hazard ratio (HR).

Descriptive statistics were utilized to summarize cumulative vaccination rates, and timely vaccination rates. HRs and their 95% confidence intervals (CIs) for doses 1, 2, 3, and 4 were obtained using multivariate Cox regression models. HRs were employed to calculate VE and its associated 95% CIs. Data analyses were conducted using Excel software (version Home

and Student 2019, Microsoft Office, USA) and SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

The cohort included 194,981 individuals (Supplementary Figure S2, available in <https://weekly.chinacdc.cn/>). 104,210 (53.45%) were male and 90,771 (46.55%) were female; 77,112 (39.55%) lived in urban areas and 117,869 (60.45%) lived in rural areas (Table 1). Figure 1 displays the cumulative vaccination rate for each dose of co-purified DTaP by age in days. The cumulative vaccination rates for 1–4 doses of co-purified DTaP by age 2 years were 92.30%, 90.73%, 88.89%, and 73.34%, respectively, while timely vaccination rates with a one-month grace period were 69.77%, 52.36%, 39.27%, and 27.30%. Details on vaccination ages and intervals for 1–4 doses of co-purified DTaP can be found in Supplementary Table S1 and Supplementary Figure S3 (available in <https://weekly.chinacdc.cn/>).

Participants were categorized into non-mutually exclusive 0-, 1-, 2-, 3-, and 4-dose groups as follows: 194,981 individuals (100%) were in the 0-dose group, 179,856 (92.24%) in the 1-dose group, 176,658 (90.60%) in the 2-dose group, 172,895 (88.67%) in the 3-dose group, and 139,252 (71.42%) in the 4-dose group.

In the study cohort, 266 individuals (0.14%) were diagnosed with pertussis between the ages of 3.5 months and 2 years, including 135 clinically diagnosed cases and 131 laboratory-confirmed cases. Among the pertussis cases, 180 were hospitalized (comprising 113 clinically diagnosed cases and 67 confirmed cases).

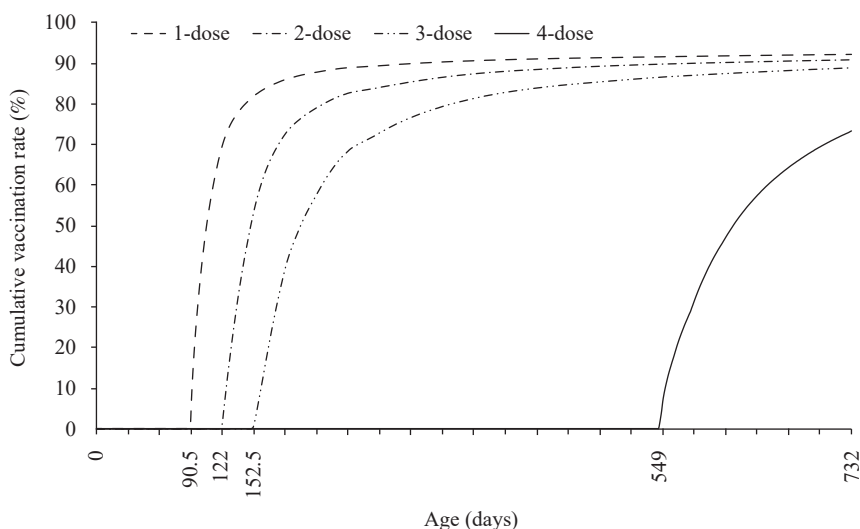


FIGURE 1. Cumulative vaccination rates for each dose of the co-purified diphtheria, tetanus, and acellular pertussis vaccine (DTaP) by age in days.

Three of the hospitalized individuals were admitted to an intensive care unit (ICU), including one clinically diagnosed case and two confirmed cases (Table 1).

After adjusting for gender and urban/rural residency, the adjusted VEs of 1–4 doses in the prevention of pertussis-related diseases were as follows: 24.1% (95% CI: -18.3, 51.3), 45.5% (95% CI: 14.4, 65.3), 57.9% (95% CI: 41.4, 69.7), and 87.1% (95% CI: 75.0, 93.4). Additionally, the adjusted VEs against pertussis-related hospitalization were 25.6% (95% CI: -27.2, 56.5), 63.2% (95% CI: 31.5, 80.2), 60.3% (95% CI: 41.7, 73.0), and 86.6% (95% CI: 69.7, 94.1). Due to the limited number of patients admitted to an ICU (3 cases), a reliable estimate of VE against ICU admission could not be calculated (Table 2).

DISCUSSION

Our study revealed that the co-purified DTaP manufactured in China demonstrated considerable effectiveness against pertussis disease and associated hospitalizations in children aged 2 years and below. Furthermore, the effectiveness increased progressively with each subsequent dose. When adjusted for gender and urban/rural status, the absolute VEs for the prevention of pertussis-related disease were found to be 24.1%, 45.5%, 57.9%, and 87.1% for the first through the fourth doses, respectively. Corresponding effectiveness levels against pertussis-related hospitalization were 25.6%, 63.2%, 60.3%, and 86.6%, respectively.

Our VE findings align with those reported in previous DTaP VE investigations. Two case-control studies, matching participants based on residence and sex, were conducted in Guangdong Province. One study in Zhongshan City demonstrated VE against pertussis in children aged 4–11 months to be 42%, 88%, and 95% for one, two, and three doses of co-purified DTaP, respectively (5). Another study in Shenzhen found VE against pertussis-related illness among children aged 4 months to 6 years to be 82% for one or two doses, 87% for three doses, and 91% for four doses of DTaP, analyzing co-purified DTaP, co-purified DTaP-Hib, and component purified DTaP-IPV/Hib together (6). Both studies classified infants vaccinated within 21 days of illness onset as unvaccinated, potentially leading to an overestimation of VE.

A systematic review estimated acellular pertussis VEs for pertussis diagnosis and hospitalization to be 82% and 91%, respectively (7). A retrospective case series in

Singapore reported the VE of acellular pertussis vaccines (component purified DTaP-IPV/Hib and DTaP-HBV-IPV/Hib) against intensive care unit or high-dependency admission to be 87% among children with a median age of 2.75 months (8). A case-cohort study in Switzerland indicated that, among children under 2 years old, VE of one to four doses of component purified DTaP against pertussis hospitalization was 42%, 84%, 98%, and 100% (9).

In the present study, VE against pertussis incidence and hospitalization revealed a significantly higher VE following a booster dose when compared to the outcome after the primary three-dose series. VE estimates may vary due to factors such as the definition of pertussis infection timing, study design, vaccine type, and immunization schedule. Although direct comparison of study results is not feasible, VE investigations generally indicate enhanced protection after the fourth dose of DTaP, suggesting that timely and complete vaccination with DTaP can effectively minimize the risk of pertussis-related illness and hospitalization.

A strength of our study design lies in the ability to estimate dose-by-dose VE through the calculation of HRs using Cox regression model, even in the context of high vaccine coverage. Cohort members were categorized into five non-mutually exclusive groups (0–4 dose groups) based on the time each dose was deemed effective and the time of pertussis infection, and then we obtained VE for doses 1, 2, 3, and 4. A similar method was utilized in a study conducted in Switzerland using a case-cohort design, yielding positive results (9). We believe our approach allows immunization programs to accurately evaluate dose-by-dose VE in the context of high vaccination coverage.

Additionally, the large cohort size of nearly 200,000 young children provided sufficient power to construct a robust Cox regression model for estimating VE against two outcomes: pertussis disease and pertussis hospitalization.

The study design facilitated the determination of cumulative vaccination rates, revealing that the coverage levels for 1–4 doses among children aged ≤ 2 years in Linyi Prefecture were 92.30%, 90.73%, 88.89%, and 73.34%, respectively. The cumulative 3-dose coverage rate was marginally higher than the global rate estimated by WHO (86%) but marginally lower than the 90% target value proposed in 2015 (10). Cumulative 4-dose coverage, however, remained relatively low. This discrepancy could be attributed to the inclusion of doses administered only before the

TABLE 1. Demographic characteristics of the study cohort.

Characteristics	All participants N (%)	Pertussis cases N (%)	Pertussis hospitalization N (%)	0-dose group N (%)	1-dose group N (%)	2-dose group N (%)	3-dose group N (%)	4-dose group N (%)
Gender								
Male	104,210 (53.45)	134 (0.13)	91 (0.09)	104,210 (100)	95,854 (91.98)	94,018 (90.22)	91,846 (88.14)	73,368 (70.40)
Female	90,771 (46.55)	132 (0.15)	89 (0.10)	90,771 (100)	84,002 (92.54)	82,640 (91.04)	81,049 (89.29)	65,884 (72.58)
Living place								
Urban	77,112 (39.55)	88 (0.11)	59 (0.08)	77,112 (100)	69,584 (90.24)	67,994 (88.18)	66,238 (85.90)	51,304 (66.53)
Rural	117,869 (60.45)	178 (0.15)	121 (0.10)	117,869 (100)	110,272 (93.55)	108,664 (92.19)	106,657 (90.49)	87,948 (74.62)
Total	194,981 (100)	266 (0.14)	180 (0.09)	194,981 (100)	179,856 (92.24)	176,658 (90.60)	172,895 (88.67)	139,252 (71.42)

TABLE 2. VE of 1–4 doses of co-purified DTaP.

Immunization group	Total		Pertussis onset			Pertussis-related hospitalization				
	Median observation time, person-days	observation time, person-days	Case number	Incidence density, 100,000 person- days	Unadjusted VE, % (95% CI)	Adjusted VE, % (95% CI)*	Case number	Incidence density, 100,000 person- days	Unadjusted VE, % (95% CI)	Adjusted VE, % (95% CI)*
0	15.5	15,138,796.5	56	0.370	ref.	ref.	42	0.277	ref.	ref.
1	36	10,463,060.0	38	0.363	23.4 (-19.4, 50.8)	24.1 (-18.3, 51.3)	25	0.239	24.4 (-29.3, 55.8)	25.6 (-27.2, 56.5)
2	38	11,462,479.0	33	0.288	44.8 (13.3, 64.9)	45.5 (14.4, 65.3)	15	0.131	62.7 (30.7, 79.9)	63.2 (31.5, 80.2)
3	399	68,429,951.0	127	0.186	55.4 (38.1, 67.9)	57.9 (41.4, 69.7)	90	0.132	58.3 (38.8, 71.5)	60.3 (41.7, 73.0)
4	131	16,553,757.0	12	0.072	86.4 (73.7, 93.0)	87.1 (75.0, 93.4)	8	0.006	85.7 (67.7, 93.6)	86.6 (69.7, 94.1)

Abbreviation: VE=vaccine effectiveness; DTaP=diphtheria, tetanus, and acellular pertussis vaccine; CI=confidence interval; ref.=reference.

* Adjusted for sex, urban/rural status.

second birthday, excluding those given to older children. Timely vaccination rates (allowing for a one-month grace period) for all four doses were low, with respective values of 69.77%, 52.36%, 39.27%, and 27.30%. It is crucial to emphasize the role and importance of DTaP, regularly review missed vaccinations, and implement catch-up vaccinations to enhance timely and comprehensive vaccination coverage among age-eligible children.

In China, the existing co-purified DTaP vaccination schedule commences at three months of age. However, the current WHO position paper suggests that the initial dose could be administered as early as six weeks and should be administered no later than eight weeks of age (11). Consequently, it is important to investigate the potential benefits of introducing pertussis vaccination at an earlier age in China.

Our study presents several limitations. While we took into account the effects of gender and urban/rural status on VE, other confounding variables, such as pre-existing medical conditions, might also impact VE. Moreover, due to the heightened sensitivity of pertussis surveillance in China for children under 2 years of age, our VE assessments were confined to this particular age group.

In children under 2 years of age, the overall VE against pertussis disease or hospitalization demonstrated an increase with a higher number of administered co-purified DTaP doses; four doses providing substantial protection. We recommend reinforcing the importance of timely and complete DTaP vaccination for age-appropriate children and investigating the possibility of administering the first dose at 2 months of age to minimize the risk of pertussis disease and hospitalization in infants.

Conflicts of interest: No conflicts of interest.

Acknowledgments: Linyi Center for Disease Control and Prevention and Jinan Center for Disease Control and Prevention.

Funding: Supported by the Joint Foundation of Beijing Natural Science Foundation and Haidian Original Innovation (L202037), as well as the Chinese Center for Disease Control and Prevention's Operation of Public Health Emergency Response Mechanism (131031001000200001).

doi: 10.46234/ccdcw2023.071

Corresponding author: Zundong Yin, yinzd@chinacdc.cn.

¹ National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China; ² Linyi Center for Disease Control and Prevention, Linyi City, Shandong Province, China; ³ Jinan Center for Disease Control and Prevention, Jinan City, Shandong Province, China; ⁴ Health Communication Center, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: March 24, 2023; Accepted: April 18, 2023

REFERENCES

1. Chinese Preventive Medicine Association, Vaccine and Immunology Branch of the Chinese Preventive Medicine Association. Expert consensus on the China pertussis initiative. *Chin J Public Health* 2021;42(6):955 – 65. <http://dx.doi.org/10.3760/cma.j.cn112338-20210308-00186>. (In Chinese).
2. Chinese Center for Disease Control and Prevention. Pertussis. <https://www.chinacdc.cn/nip/kpyd/xjxcrb/brkpsf/>. [2022-12-6]. (In Chinese).
3. World Health Organization. Diphtheria tetanus toxoid and pertussis (DTP) vaccination coverage. <https://immunizationdata.who.int/pages/coverage/dtp.html?CODE=CHN&ANTIGEN=&YEAR=>. [2022-12-6].
4. Ning GJ, Gao Y, Wu D, Li JH, Li YX, Shao ZJ, et al. Epidemiology of pertussis in China, 2011-2017. *Chin J Vaccines Immun* 2018;24(3):264-7,273. <https://d.wanfangdata.com.cn/periodical/zgjhmy201803004>. (In Chinese).
5. Wang CL, Lü HY, Wang M. Effectiveness of diphtheria, tetanus and acellular pertussis combined vaccine against pertussis in <5-year-old children: a case-control study. *Chin J Vaccines Immun* 2019;25(5):528-31. <http://qikan.cqvip.com/Qikan/Article/Detail?id=7100439971>. (In Chinese).
6. Li WH, Qiu CH, Peng YZ, Xie X, Cheng JQ, Huang F, et al. Effectiveness of pertussis vaccine among children 4 months to 6 years of age in Shenzhen City: a matched case-control study. *Chin J Vaccines Immun* 2022;28(5):525 – 8. <http://dx.doi.org/10.19914/j.CJVI.2022100>. (In Chinese).
7. Wilkinson K, Righolt CH, Elliott LJ, Fanella S, Mahmud SM. Pertussis vaccine effectiveness and duration of protection - a systematic review and meta-analysis. *Vaccine* 2021;39(23):3120 – 30. <http://dx.doi.org/10.1016/j.vaccine.2021.04.032>.
8. Chong CY, Yung CF, Tan NWH, Acharyya S, Thoon KC. Risk factors of ICU or high dependency requirements amongst hospitalized pediatric pertussis cases: a 10 year retrospective series, Singapore. *Vaccine* 2017;35(47):6422 – 8. <http://dx.doi.org/10.1016/j.vaccine.2017.09.085>.
9. Mack I, Erlanger TE, Lang P, Sinniger P, Perisa D, Heining U. Dose-dependent effectiveness of acellular pertussis vaccine in infants: a population-based case-control study. *Vaccine* 2020;38(6):1444 – 9. <http://dx.doi.org/10.1016/j.vaccine.2019.11.069>.
10. World Health Organization. The global vaccine action plan 2011-2020: review and lessons learned: strategic advisory group of experts on immunization. <https://apps.who.int/iris/handle/10665/329097>. [2022-12-8].
11. World Health Organization. Pertussis vaccines: WHO position paper, August 2015—recommendations. *Vaccine* 2016;34(12):1423 – 5. <http://dx.doi.org/10.1016/j.vaccine.2015.10.136>.

SUPPLEMENTARY MATERIALS

Pertussis Vaccines

Three primary types of pertussis vaccines are utilized worldwide: whole-cell, component purified acellular, and co-purified acellular vaccines. Whole-cell pertussis (wP) vaccines involve standardized cultures of selected *Bordetella pertussis* strains, which are subsequently inactivated, typically through heating and formalin treatment. These wP vaccines have been employed for many years, significantly reducing pertussis morbidity and mortality. Acellular pertussis (aP) vaccines were developed to decrease reactogenicity, with the first aP vaccine originating in Japan in 1981 (1). Component purified aP vaccines comprise one or more separately and highly purified antigens, including pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM) types 2 and 3.

Co-purified aP vaccines contain antigen components from *Bordetella pertussis*, primarily PT and FHA, but are produced without determining the exact antigen composition. Nearly all developed countries exclusively utilize component purified aP combination vaccines, while co-purified aP vaccines are used in China and other Asian countries. In contrast, wP combination vaccines are employed in most low- and middle-income countries (2–3).

Case Definitions

A suspected case of pertussis was defined by the presence of paroxysmal spasmodic cough or apnea, asphyxia, cyanosis, and bradycardia following coughing in infants, or a persistent cough lasting ≥ 2 weeks in children, adolescents, or adults. A clinically diagnosed case referred to a patient with pertussis as determined by clinicians, a suspected case with markedly elevated leukocyte or lymphocyte counts in peripheral blood, or a patient with a cough persisting for ≥ 2 weeks accompanied by at least one of the following symptoms: 1) paroxysmal spasmodic cough, 2) inspiratory whoop after coughing, 3) vomiting with no other cause following coughing.

A confirmed case was identified as a suspected or clinically diagnosed case with one or more positive laboratory test results, including: 1) isolation of *Bordetella pertussis* from sputum or nasopharyngeal secretions, 2) a four-fold or greater increase in serum specific antibody titers between acute and convalescent sera, 3) a positive *Bordetella pertussis* PCR test, 4) positive PT-IgG serology in children over 4 months old who had received the pertussis vaccine more than one year prior (some hospitals reference this item in laboratory diagnosis reports) (4).

Cumulative Vaccination Rates and Timely Vaccination Rates

Cumulative vaccination rates were determined by dividing the cumulative number of vaccinated individuals by the total number of individuals and multiplying by 100%. Timely vaccination was defined as administering a dose within the recommended month according to the China national immunization schedule during the study period. Timely vaccination rates for 1-, 2-, 3-, and 4-dose groups were calculated by dividing the number of people who received the 1st, 2nd, 3rd, and 4th doses by the number of people in the cohort at 3 months, 4 months, 5 months, and 18–19 months of age, respectively, and then multiplying by 100%.

N-dose Group

The date of infection was defined as ten days prior to illness onset for a diagnosed case of pertussis, representing the longest average incubation period before symptom onset. One month was standardized to 30.5 days. It was assumed that a co-purified DTaP dose would elicit an immune response by the 14th day post-administration. For example, a dose given at 3 months of age was considered to induce a response by 3.5 months (105.5 days). Observation time referred to the interval between a dose's immune response time (assumed effectiveness) and an endpoint event, such as the subsequent dose's effect, the end of the observation period, or the age of infection.

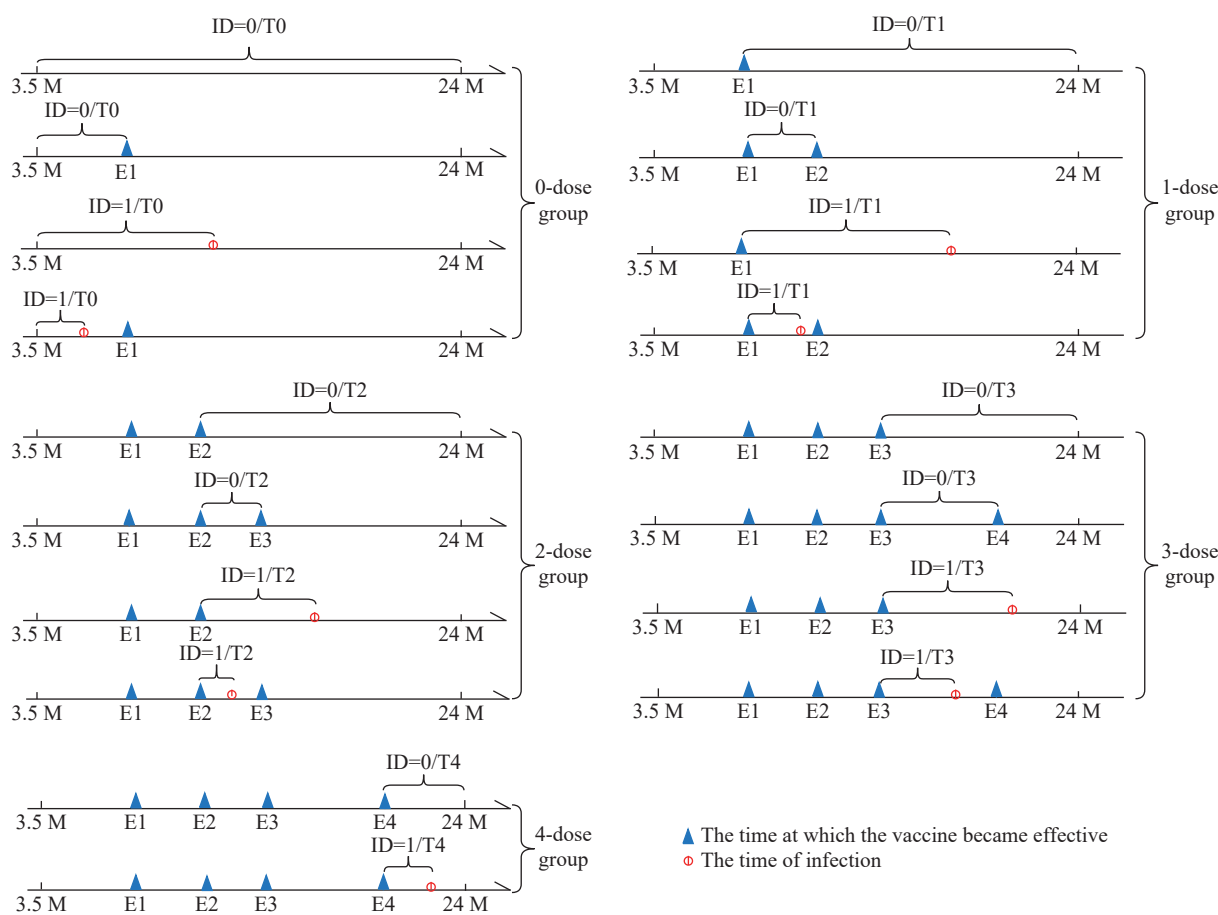
The maximum observation time for a non-pertussis case was 20.5 months, calculated from 14 days following the earliest date for administering the first co-purified DTaP dose (3.5 months) until the child's second birthday (i.e., 24 months – 3.5 months = 20.5 months observation time). The maximum observation time for a pertussis case ranged from 3.5 months of age to the child's age at infection (10 days before illness onset).

The 0-dose group comprised individuals who received at least one dose by 24 months of age, regardless of infection status, indicating that all participants belonged to the 0-dose group. The 1-dose group included uninfected individuals who received at least one effective dose before 24 months of age, as well as infected individuals who

contracted the infection between the first dose taking effect and either the second dose taking effect or the age of 24 months, whichever occurred first. Similar categorizations were applied to the 2- and 3-dose groups. Given that a fifth dose is not advised, the 4-dose group consisted of uninfected individuals who received four effective doses prior to 24 months of age, and infected participants who became infected between the fourth dose taking effect and the age of 24 months.

Supplementary Figure S1: Illustration of determination of observational times for subjects. Observational time refers to the time at risk for contracting pertussis due to under-vaccination. For the 0-dose group, observational time was calculated as the time accrued during the delayed first dose [i.e., each day between 3.5 months and the point when the first dose became effective (14 days after the actual dose-1 vaccination date) or until reaching 24 months of age, whichever came first]. If a subject was diagnosed with pertussis before 24 months, the observational time was truncated on the day of infection. The total observational time for the 0-dose group (T_0) is the sum of all individual observational times. Incidence density for the 0-dose group (ID_0) is calculated as the number of cases (S_0) divided by the total observational time: $ID_0 = S_0 / \sum \text{member observational time}$.

The participants in the 1-dose group received one or more co-purified DTaP doses. They accumulated observational (risk) time for each day that their second dose was delayed, in a manner similar to the 0-dose group members, who accumulated observational time for each day their first dose was delayed. Likewise, the individuals in the 2- and 3-dose groups accrued observational (risk) time for each day that their third or fourth dose was delayed. The accrual period for the 4-dose group began at the fourth dose taking effect and ended at 24 months of age or upon infection, whichever occurred first.



SUPPLEMENTARY FIGURE S1. Potential scenarios for calculating incidence density among groups receiving 0–4 doses. Note: M represents months of age; E1–4 denotes the assumed time at which 1–4 doses of co-purified diphtheria, tetanus, and acellular pertussis vaccine (DTaP) take effect; ID represents incidence density; T0–4 represents the members observational time in the 0–4 dose group. Groups with 0–4 doses are allocated based on the assumed time of the vaccine taking effect and the time of infection.

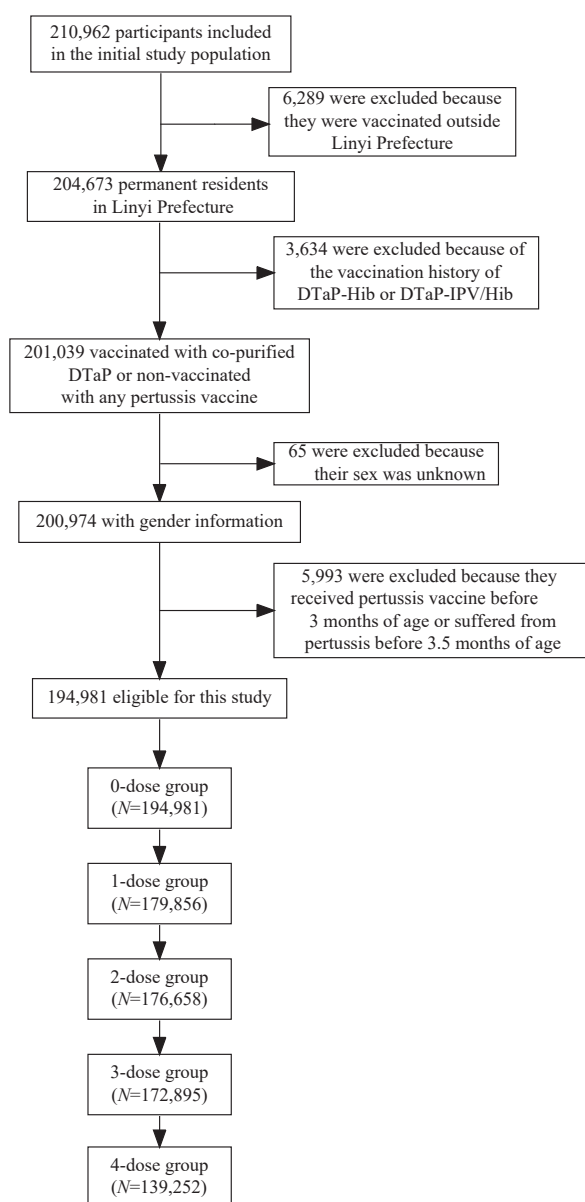
The incidence density for each n-dose group, represented as ID_n , is determined by dividing the number of cases within the n-dose group (S_n) by the total observational time for the n-dose group (T_n):

$$ID_n = S_n / \sum (n - \text{dose group member observational time}).$$

VE

VE was determined by calculating the percentage reduction in disease incidence rate or density among vaccinated individuals compared to unvaccinated individuals. In our study, VE was computed for each dose by employing the rate ratio (RR) for each respective dose group. The formula used was $VE = (1 - RR) \times 100\%$. Alternatively, VE can also be calculated using the hazard ratio (HR), which is considered to be roughly equivalent to RR when accounting for time (5): $VE \approx (1 - HR) \times 100\%$.

The Study Enrollment Flow Diagram



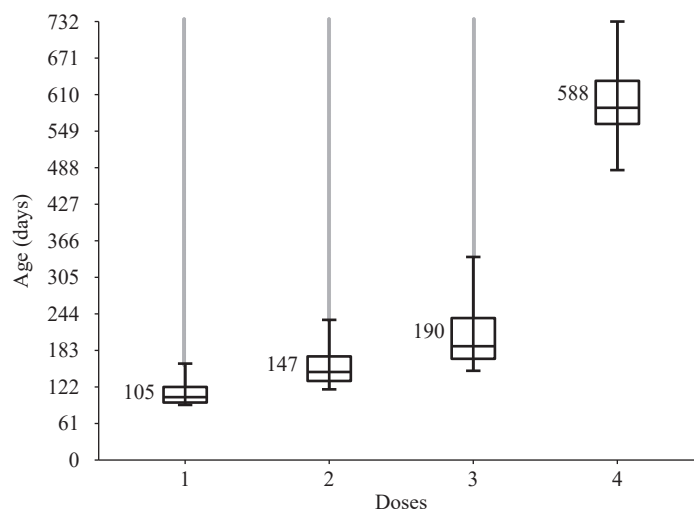
SUPPLEMENTARY FIGURE S2. Study participants and cohort eligibility.

Vaccination Ages and Intervals

The distribution of vaccination ages and intervals for the 1st, 2nd, 3rd, and 4th doses of co-purified DTaP was found to be non-normal ($P < 0.01$). The age ranges for the 1st, 2nd, 3rd, and 4th doses were 92–732 days, 118–732 days, 149–732 days, and 484–732 days, respectively. The median vaccination ages for these doses were as follows: 105 days [Interquartile range (IQR): 96–122] for the 1st dose, 147 days (IQR: 132–173) for the 2nd dose, 190 days (IQR: 169–237) for the 3rd dose, and 588 days (IQR: 561–633) for the 4th dose. The median intervals between the doses were 36 days (IQR: 31–50) between the 1st and 2nd doses, 38 days (IQR: 32–60) between the 2nd and 3rd doses, and 395 days (IQR: 362–434) between the 3rd and 4th doses. Further details can be found in Supplementary Table S1 and Supplementary Figure S3.

SUPPLEMENTARY TABLE S1. Age (in days) and interval of administered co-purified DTaP before the second birthday.

Actual doses	All participants	Age (days)	Interval of vaccination
		Median (IQR)	Median (IQR)
1	179,969	105 (96–122)	–
2	176,898	147 (132–173)	36 (31–50)
3	173,317	190 (169–237)	38 (32–60)
4	142,991	588 (561–633)	395 (362–434)



SUPPLEMENTARY FIGURE S3. Age (in days) of participants receiving each dose of co-purified diphtheria, tetanus, and acellular pertussis vaccine (DTaP) before their second birthday.

REFERENCES

- World Health Organization. Pertussis vaccines: WHO position paper. *Wkly Epidemiol Rec* 2010;85(40):385–400. <https://apps.who.int/iris/handle/10665/241645>.
- Xu YH, Tan YJ, Asokanathan C, Zhang SM, Xing D, Wang JZ. Characterization of co-purified acellular pertussis vaccines. *Hum Vaccin Immunother* 2015;11(2):421–7. <http://dx.doi.org/10.4161/21645515>.
- World Health Organization. Vaccination schedule for pertussis. <https://immunizationdata.who.int/pages/schedule-by-disease/pertussis.html>. [2022-12-8].
- Cherry JD, Tan TN, Wirsing von König CH, Forsyth KD, Thisyakorn U, Greenberg D, et al. Clinical definitions of pertussis: summary of a global pertussis initiative roundtable meeting, February 2011. *Clin Infect Dis* 2012;54(12):1756–64. <http://dx.doi.org/10.1093/cid/cis302>.
- Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010;21(1):13–5. <http://dx.doi.org/10.1097/EDE.0b013e3181c1ea43>.