ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 5 No. 17 Apr. 28, 2023

中国疾病预防控制中心周报

WORLD IMMUNIZATION WEEK ISSUE

Preplanned Studies

Healthy China

ISSN 2096-7071

China CDC Weekly

Cover Image: adapted from the World Health Organization, https://www.who.int/campaigns/world-immunization-week/2023.

This week's issue was organized by Guest Editor Zundong Yin.

Preplanned Studies

Effectiveness of COVID-19 Vaccination Against SARS-CoV-2 Omicron Variant Infection and Symptoms — China, December 2022–February 2023

Di Fu[1,&]; Guanhao He[2,3,&]; Huanlong Li[4]; Haomin Tan[1,3]; Xiaohui Ji[1,3]; Ziqiang Lin[1,3]; Jianxiong Hu[1,3]; Tao Liu[1,3]; Jianpeng Xiao[5]; Xiaofeng Liang[2,3,#]; Wenjun Ma[1,3,#]

Summary

What is already known about this topic?

A considerable percentage of the population has received both primary and booster vaccinations, which could potentially provide protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron infections and related symptoms.

What is added by this report?

The self-reported infection rate, as determined from an online survey, reached its peak (15.5%) between December 19 and 21, 2022, with an estimated 82.4% of individuals in China being infected as of February 7, 2023. During the epidemic, the effectiveness of booster vaccinations against SARS-CoV-2 Omicron infection was found to be 49.0% within three months of vaccination and 37.9% between 3 and 6 months following vaccination. Furthermore, the vaccine effectiveness of the booster vaccination in relation to symptom prevention varied from 48.7% to 83.2% within three months and from 25.9% to 69.0% between 3 and 6 months post-booster vaccination.

What are the implications for public health practice?

The development and production of efficacious vaccines, together with prompt vaccinations or emergency vaccinations, have the potential to mitigate the epidemic's impact and safeguard public health.

Since December 2022, a significant coronavirus disease 2019 (COVID-19) epidemic has emerged in China following the easing of prevention and control measures. The objective of the current study was to characterize the epidemic curve and investigate the vaccine effectiveness (VE) against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant infection and associated symptoms during this epidemic in China. A total of 4 online surveys were conducted across 31 provincial-level administrative divisions (PLADs) in China to collect data on vaccination and infection status and to delineate the epidemic curve. Furthermore, a test-negative case-control study was carried out to examine the effectiveness of COVID-19 vaccines. The findings of our study revealed that the self-reported infection rate reached its peak between December 19 and 21, 2022, with 82.4% of the Chinese population being infected as of February 7, 2023. The booster vaccination demonstrated effectiveness against infection and symptoms within six months, albeit VE declined over time. These results underscore the importance of developing and producing efficacious vaccines and promoting timely or emergency vaccinations among eligible populations.

In the context of high vaccination coverage in China (91.5% and 89.3% of people received partial and full vaccination, respectively), along with the relatively weak virulence of the SARS-CoV-2 Omicron variant (comprising 99.8%, 99.7%, and 99.3% of analyzed sequences in China, the United States, and the United Kingdom, respectively; sourced from: https://ourworldindata.org/coronavirus), the Chinese government relaxed COVID-19 prevention and control measures in December 2022 (*1*). However, a significant surge in cases occurred between December 2022 and January 2023, as reported by the China CDC (*2*). Due to the relaxation of control measures, many infected individuals may not have undergone nucleic acid or antigen testing, potentially resulting in an imprecise representation of the epidemic's magnitude in the China CDC data. In this situation, online surveys may serve as a rapid surveillance tool for assessing the epidemic status. Moreover, this sizable epidemic presented an opportunity to evaluate the real-world effectiveness of domestic vaccines in China (*3*).

Although previous research has demonstrated the effectiveness of vaccines against overall symptoms (the occurrence of any COVID-19-related symptoms)

rather than specific COVID-19 symptoms (e.g., sore throat, cough, fever, etc.), more detailed symptomatology information could prove valuable for future vaccine research (*3*–*4*). To address these knowledge gaps, the present study conducted multiple online surveys from December 2022 to February 2023, aiming to describe the large-scale epidemic and explore VE in relation to the SARS-CoV-2 Omicron variant's infection and associated symptoms.

From December 2022 to February 2023, a four-wave online survey was conducted across 31 PLADs in China. Using an anonymous questionnaire provided by "Wen Juan Xing (www.wjx.cn)", data was collected on participants' gender, age, address, occupation, vaccination status, vaccine type, time since last vaccination, infection status (symptoms, diagnosis date, and diagnosis method), and the number of infected cohabitants. The characteristics of participants are presented in Supplementary Table S1 (available in https://weekly.chinacdc.cn/).

In this study, the data from the fourth wave online survey of individuals with confirmed infection dates were utilized to estimate the epidemic curve and cumulative infection rate. A test-negative case-control study was employed to investigate the efficacy of COVID-19 vaccines in preventing SARS-CoV-2 Omicron variant infections and associated symptoms. A total of 4,688 individuals with confirmed infections were included, with an equal number of uninfected participants selected as controls from the four-wave online surveys (Supplementary Figure S1, available in https://weekly.chinacdc.cn/).

In this study, vaccine effectiveness against COVID-19 infection was evaluated, considering that some participants exhibited COVID-19 related symptoms but did not undergo nucleic acid or antigen tests. We categorized cases into three types: 1) those identified by positive nucleic acid tests; 2) those identified by positive antigen tests; and 3) those identified by self-reported COVID-19 related symptoms. To control for confounding factors, such as sex and age, these cases were matched 1∶1 using a propensity score approach (*5*).

A caliper of 0.2 standard deviation (SD, with a specific value of 0.002) was implemented for the distance of all participants to prevent far matching. Cases without controls within the 0.2 SD distance were discarded. To estimate vaccine effectiveness against COVID-19 related symptoms, individuals reporting specific symptoms were defined as cases, and they were also matched 1∶1 using the propensity score approach.

Vaccination status was categorized based on the number of vaccination doses received (unvaccinated, partially vaccinated, fully vaccinated, or boosted), booster vaccination status, the time elapsed since the last vaccination and subsequent infection (<3 months, 3–6 months, >6 months), and the type of booster vaccine administered (inactivated, adenovirus vector, or recombinant protein vaccine). Unvaccinated individuals were those who had not received any COVID-19 vaccinations; partially vaccinated individuals had received only the first dose of an inactivated vaccine; fully vaccinated individuals had received two doses of an inactivated vaccine; and those with a booster vaccination had received two doses of inactivated vaccine plus one booster dose of either an inactivated, adenovirus vector, or recombinant protein vaccine.

The daily self-reported infection rate, derived from the online survey, was calculated by dividing the number of new cases by the total number of survey participants. Similarly, the cumulative self-reported infection rate was determined by dividing the number of cumulative cases by the total number of survey participants. A conditional logistic regression was employed to assess the odds ratio of vaccination between cases and controls. Subsequently, the vaccine effectiveness and corresponding 95% confidence interval (*CI*) were estimated utilizing the given formula:

$$\mathrm{VE} = (1 - \text{odds ratio of vaccination in cases compared to controls}) \times 100\%. \quad (1)$$

The primary focus of this study was to investigate the effectiveness of the booster vaccination. Subgroup analyses were conducted based on age (≤18, 19–59, and ≥60 years) and sex to provide additional insights into specific population groups.

All *P*-values were evaluated using a two-sided test, with a significance level of $\alpha = 0.05$ to indicate the presence of a Type I error. Statistical analyses were conducted using R software (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria).

The epidemic curve was constructed using data from 2,391 participants in the fourth online survey, in which 82.4% reported being infected as of February 7, 2023. The self-reported infection rate began to rise in early December 2022, reaching a peak between December 19 and 21, 2022 (15.5%), before declining to 0.1% during February 2 to 4, 2023 (Figure 1). The

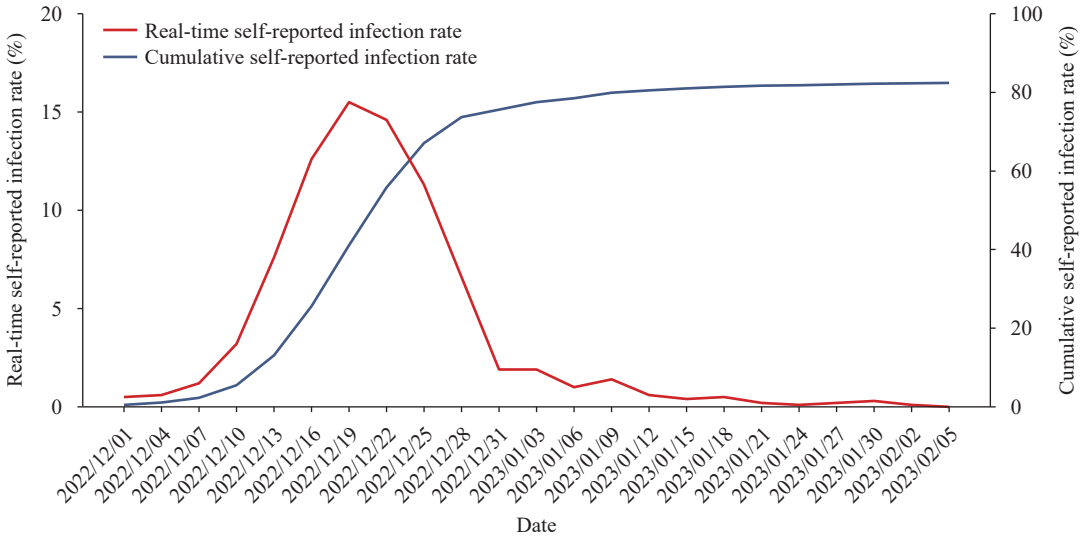


FIGURE 1. Real-time and cumulative self-reported infection rates of COVID-19 in China based on an online survey conducted between December 1, 2022 and February 7, 2023.
Abbreviation: COVID-19=coronavirus disease 2019.

epidemic curves by gender and age were generally consistent with the pattern observed in the total population (Supplementary Figure S2, available in https://weekly.chinacdc.cn/).

A total of 4,688 participants were infected with SARS-CoV-2. Among them, 3.5% were unvaccinated, while 1.7%, 14.9%, and 79.9% had received partial, full, and booster vaccinations, respectively (Supplementary Table S2, available in https://weekly.chinacdc.cn/). In the matched control group of 4,688 uninfected participants, the proportions of unvaccinated, partially vaccinated, fully vaccinated, and booster-vaccinated individuals were 3.1%, 1.3%, 12.8%, and 82.8%, respectively. No significant VE against infection was observed for full or booster vaccinations beyond 6 months post-vaccination. However, within 3 months of receiving a booster vaccination, significant protection against infection was observed (VE: 49.0%; 95% *CI*: 27.1%–64.3%), as well as between 3–6 months (VE: 37.9%; 95% *CI*: 13.7%–55.4%). Similar results were observed for various case definitions and different vaccines (Figure 2, Supplementary Figure S3, available in https://weekly.chinacdc.cn/). Notably, the VE of the booster vaccination was lower among individuals aged >60 years (Supplementary Table S3, available in

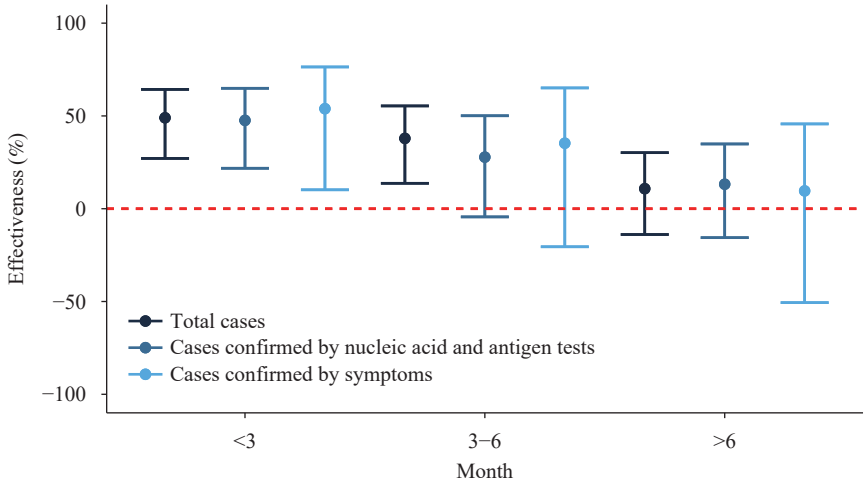


FIGURE 2. Effectiveness of booster vaccination against SARS-CoV-2 infection, categorized by time period following vaccination.
Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

https://weekly.chinacdc.cn/).

The booster vaccination demonstrated effectiveness against various COVID-19 symptoms, including fever, nasal obstruction, rhinorrhea, sore throat, cough, expectoration, headache, muscle soreness, anorexia, fatigue, and hypogeusia within six months after administration. However, VEs were not statistically significant beyond six months post-booster vaccination. Within three and six months following the booster vaccination, VEs ranged from 48.7% to 83.2% and 25.9% to 69.0%, respectively (Figure 3)

DISCUSSION

In December 2022, a significant COVID-19 outbreak occurred in China, with over 82% of the population being infected within a two-month period. Accurately monitoring the daily number of infections during such a large-scale outbreak within a short timeframe has proven to be challenging for health departments because mass nucleic acid testing was discontinued in China after December 2022. Health authorities consequently relied on the positive rate of nucleic acid and antigen tests from fever clinics to dynamically monitor the epidemic (*2*).

Nonetheless, since most infected individuals did not undergo nucleic acid and antigen testing after December 2022, and only a select few symptomatic or suspected individuals visiting fever clinics received these tests, the positive rate from fever clinics could overestimate the epidemic's scale. Consequently, online surveys have emerged as a rapid approach to monitoring the epidemic. A study utilizing an online survey of teachers and students in public health schools across China found that the epidemic peaked between December 17 and 22, 2022, in most PLADs (*6*). Our findings align with those of national community-based surveillance, which also indicated a peak between December 20 and 22 (*7*).

A series of studies have documented the efficacy of inactivated vaccines used in China (*3*,*8*). However, these investigations were conducted within clinical trials or limited regional outbreaks during the "dynamic zero" policy, thus not providing real-world evidence. According to our findings, booster vaccinations demonstrated effectiveness against infection within a six-month period, and the VE diminished over time. These results align with previous studies conducted in China and Brazil (*3*,*9*). Furthermore, a recent meta-analysis that reviewed 27 randomized controlled trials confirmed significant effectiveness against symptomatic infection and the waning of VE over time (*10*). Nevertheless, few studies have investigated VE against specific symptoms within a real-world context in China. Our study reveals that booster vaccinations can effectively protect against COVID-19 symptoms such as fever, nasal congestion, and runny nose.

This study had several limitations. First, the online survey utilized a convenience sample conducted through WeChat. Second, the epidemic curve was constructed using data from only 2,316 participants with a specific infection date. Third, study participants were not evenly distributed throughout China. Finally, the infection history of participants was not collected, which may introduce bias. Fourth, when exploring the VE against specific symptoms, the limited sample size may lead to relatively large confidence intervals, and further study with larger sample is necessary in the future.

In conclusion, China faced a significant COVID-19 epidemic, resulting in over 82% of individuals becoming infected between December 2022 and February 2023. Throughout this epidemic, booster

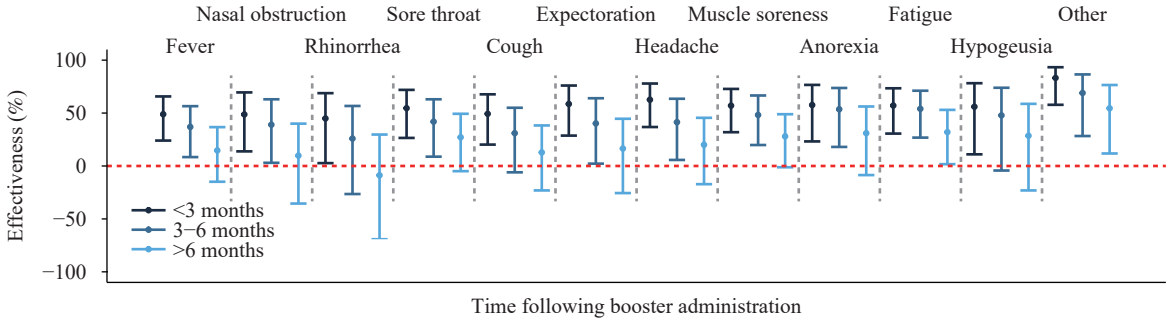


FIGURE 3. Effectiveness of COVID-19 vaccination in reducing related symptoms over time (months) following booster administration.
Abbreviation: COVID-19=coronavirus disease 2019.

vaccinations administered within a six-month period demonstrated effectiveness in preventing infection and mitigating COVID-19 symptoms. The findings of this study may contribute valuable insights to inform the development of future COVID-19 vaccination strategies.

Funding: This study was supported by the National Key Research and Development Program of China (2021YFC2301604), the Young Elite Scientists Sponsorship Program by CAST (2022QNRC001), Emergency Grants for Prevention and Control of SARS-CoV-2 in Guangdong Province (2022A1111090004), and the Science and Technology Program of Guangzhou (202102021285).

doi: 10.46234/ccdcw2023.070

[#] Corresponding authors: Xiaofeng Liang, liangxf@jnu.edu.cn; Wenjun Ma, mawj@gdiph.org.cn.

[1] Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou City, Guangdong Province, China; [2] Disease Control and Prevention Institute, Jinan University, Guangzhou City, Guangdong Province, China; [3] Key Laboratory of Ministry of Education for Viral Pathogenesis & Infection Prevention and Control, Jinan University, Guangzhou City, Guangdong Province, China; [4] Fuyang District Center for Disease Control and Prevention, Hangzhou City, Zhejiang Province; [5] Guangdong Provincial Institute of Public Health, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou City, Guangdong Province, China.
[&] Joint first authors.

Submitted: April 17, 2023; Accepted: April 24, 2023

REFERENCES

1. Joint Prevention and Control Mechanism of State Council. Notice on further optimizing epidemic prevention and control measures of COVID-19. 2022. http://www.gov.cn/xinwen/2022-12/07/content_5730475.htm. [2023-3-10]. (In Chinese).
2. Chinese Center for Disease Control and Prevention. Epidemic situation of COVID-19 infection in China. 2023. https://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_13141/202303/t20230304_264035.html. [2023-3-10]. (In Chinese).
3. Huang ZY, Xu SF, Liu JC, Wu LL, Qiu J, Wang N, et al. Effectiveness of inactivated and Ad5-nCoV COVID-19 vaccines against SARS-CoV-2 Omicron BA. 2 variant infection, severe illness, and death. BMC Med 2022;20(1):400. http://dx.doi.org/10.1186/s12916-022-02606-8.
4. Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med 2021;385(10):875 – 884. http://dx.doi.org/10.1056/NEJMoa2107715.
5. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70(1):41 – 55. http://dx.doi.org/10.1093/biomet/70.1.41.
6. Wei YY, Gao WJ, Zhang LY, Wang SG, Zhan SY, Ren T, et al. Epidemiological survey of 2019-nCoV infection in staff and students in some public health schools in China. Chin J Epidemiol 2023;44(2):175 – 183. http://dx.doi.org/10.3760/cma.j.cn112338-20221231-01092. (In Chinese).
7. Liu J, Ding F, Wu Y, Jing WZ, Yan WX, Qin CY, et al. Trends of SARS-CoV-2 infection in sentinel community-based surveillance after the optimization of prevention and control measures — China, December 2022–January 2023. China CDC Wkly 2023;5(7):159 – 164. http://dx.doi.org/10.46234/ccdcw2023.028.
8. Kang M, Yi Y, Li Y, Sun LM, Deng AP, Hu T, et al. Effectiveness of inactivated COVID-19 vaccines against illness caused by the B.1.617.2 (Delta) variant during an outbreak in Guangdong, China: a cohort study. Ann Intern Med 2022;175(4):533 – 540. http://dx.doi.org/10.7326/m21-3509.
9. Cerqueira-Silva T, Katikireddi SV, De Araujo Oliveira V, Flores-Ortiz R, Júnior JB, Paixão ES, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. Nat Med 2022;28(4):838 – 843. http://dx.doi.org/10.1038/s41591-022-01701-w.
10. Yang ZR, Jiang YW, Li FX, Liu D, Lin TF, Zhao ZY, et al. Efficacy of SARS-CoV-2 vaccines and the dose-response relationship with three major antibodies: a systematic review and meta-analysis of randomised controlled trials. Lancet Microbe 2023;4(4):E236 – E246. http://dx.doi.org/10.1016/s2666-5247(22)00390-1.

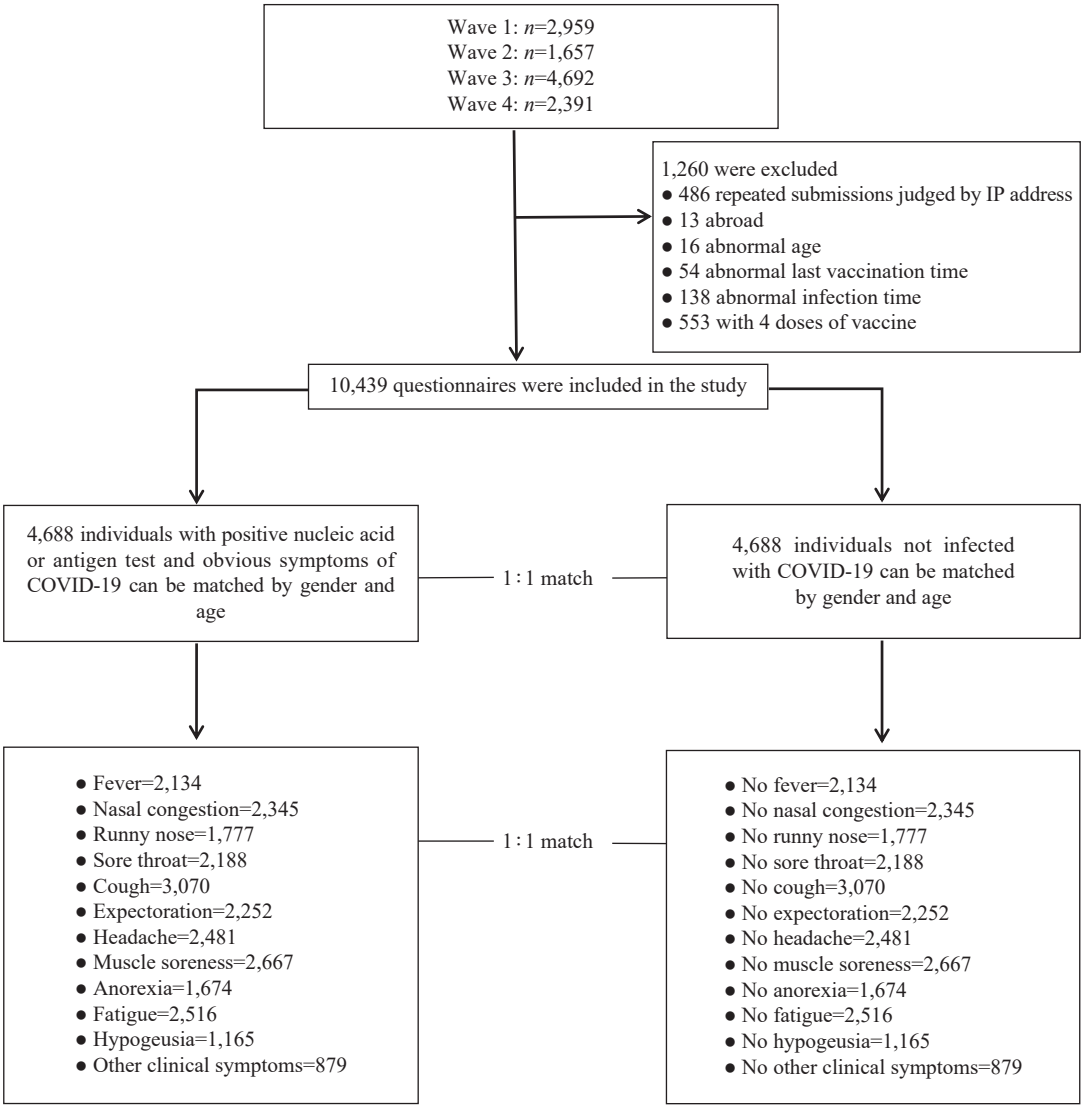
SUPPLEMENTARY MATERIALS

The COVID-19-related Symptoms Involved in Case Definition

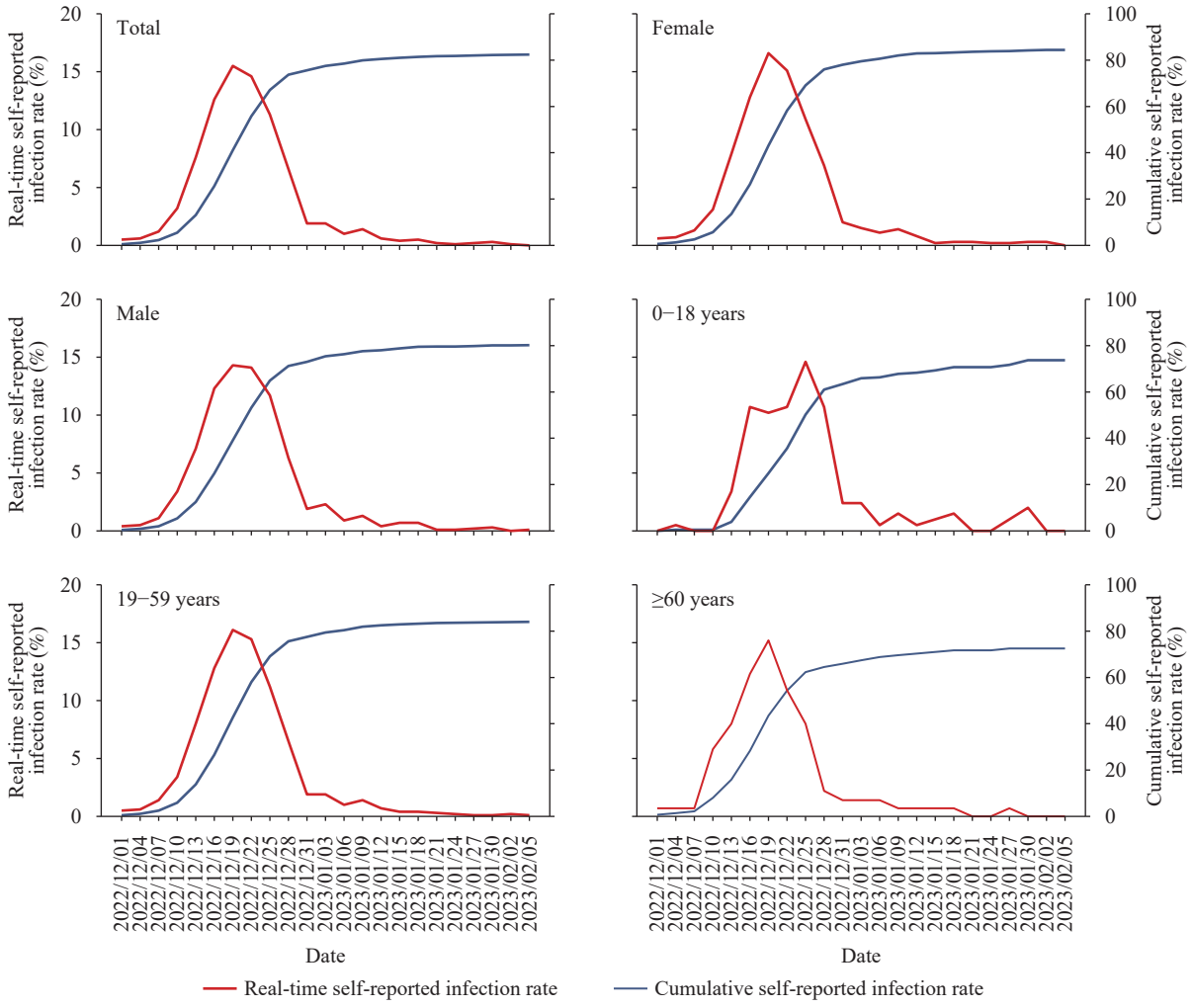
In accordance with the treatment protocol, symptoms related to coronavirus disease 2019 (COVID-19) assessed in this study included fever, nasal obstruction, rhinorrhea, sore throat, cough, expectoration, headache, muscle soreness, anorexia, fatigue, hypogeusia, and other related symptoms.

The Details of Vaccines

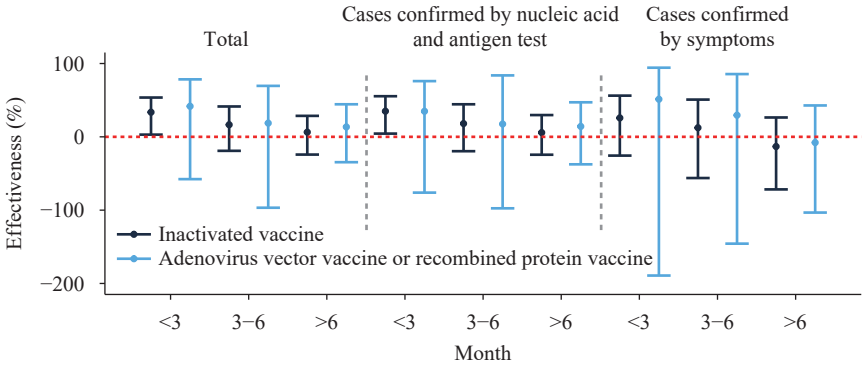
In this study, the inactivated vaccines examined included Sinovac-CoronaVac, KCONVAC, Sinopharm/BIBP COVID-19 vaccine, and Sinopharm/WIBP COVID-19 vaccine. The Ad5-vectored vaccine referred to the Cansino Ad5-nCoV-S COVID-19 vaccine, while the recombinant protein vaccine pertained to the recombinant SARS-CoV-2 vaccine (CHO cell) developed by Anhui Zhifei Longcom Biopharmaceutical, the Institute of Microbiology, and the Institute of Biophysics at the Chinese Academy of Sciences.



SUPPLEMENTARY FIGURE S1. Flowchart depicting participant enrollment and the process for obtaining case and control groups.
Abbreviation: IP=internet protocol; COVID-19=coronavirus disease 2019.



SUPPLEMENTARY FIGURE S2. Real-time and cumulative self-reported infection rates among various gender and age groups as collected from an online COVID-19 survey conducted between December 1, 2022 and February 7, 2023. Abbreviation: COVID-19=coronavirus disease 2019.



SUPPLEMENTARY FIGURE S3. Effectiveness of various booster vaccines in preventing SARS-CoV-2 infection as confirmed by nucleic acid and antigen testing, stratified by months post-booster vaccination and vaccine type.

The Process of Choosing Cases and Controls

In the current study, a total of 10,439 participants were initially included, of which 4,688 were identified as cases. Subsequently, these cases were matched on a 1∶1 basis using a propensity score method, resulting in a final sample

SUPPLEMENTARY TABLE S1. Descriptive characteristics of subjects and cases by gender, age group and region.

Variable	Total	Control	Cases confirmed by nucleic acid and antigen tests	Cases confirmed by symptoms
Sex				
Female	5,850	3,178	1,957	715
Male	4,589	2,573	1,552	464
Age (years)				
0–18	732	400	195	137
19–59	9,194	5,089	3,160	945
≥60	513	262	154	97
Region				
Anhui	253	118	101	34
Beijing	779	261	448	70
Fujian	118	87	30	1
Gansu	56	24	23	9
Guangdong	3,645	2,294	1,022	329
Guangxi	193	91	53	49
Guizhou	170	53	83	34
Hainan	83	63	15	5
Hebei	259	130	111	18
Henan	231	100	82	49
Heilongjiang	57	29	20	8
Hubei	216	74	90	52
Hunan	410	183	152	75
Jilin	87	20	44	23
Jiangsu	240	167	59	14
Jiangxi	259	110	93	56
Liaoning	137	46	69	22
Inner Mongolia	121	49	44	28
Ningxia	8	8	0	0
Qinghai	10	5	4	1
Shandong	235	112	86	37
Shanxi	234	99	95	40
Shaanxi	132	78	39	15
Shanghai	253	169	71	13
Sichuan	161	53	64	44
Tianjin	89	38	38	13
Xizang	11	5	4	2
Xinjiang	52	24	20	8
Yunnan	122	41	53	28
Zhejiang	1,749	1,194	461	94
Chongqing	69	26	35	8

size of 9,376 individuals for the case-control study. Therefore, 1,063 participants were not included in the analysis. The investigation of vaccine effectiveness (VE) against infection was conducted with the 9,376 participants in the case-control study.

SUPPLEMENTARY TABLE S2. Effectiveness of the vaccine against SARS-CoV-2 infection in matched case-control analysis, categorized by sex, age, vaccination course, and time post-vaccination.

Group	Total			Cases confirmed by nucleic acid and antigen tests			Cases confirmed by symptoms		
	No. of cases (%) (*n*=4,688)	No. of controls (%) (*n*=4,688)	VE (95% *CI*) (%)	No. of cases (%) (*n*=3,509)	No. of controls (%) (*n*=3,509)	VE (95% *CI*) (%)	No. of cases (%) (*n*=1,179)	No. of controls (%) (*n*=1,179)	VE (95% *CI*) (%)
Total									
Unvaccinated	165 (3.5)	146 (3.1)	Reference	128 (3.6)	99 (2.8)	Reference	37 (3.1)	46 (3.9)	Reference
With any vaccine	4,523 (96.5)	4,542 (96.9)	7.4 (−15.6, 25.9)	3,381 (96.5)	3,410 (37.2)	16.2 (−7.0, 36.5)	1,142 (96.9)	1,133 (96.1)	2.1 (−44.7, 46.6)
Sex									
Female	2,672 (57.0)	2,672 (57.0)	5.8 (−24.3, 28.6)	1,957 (55.8)	1,957 (55.8)	32.4 (3.3, 52.8)	715 (60.6)	715 (60.6)	−6.2 (−110.3, 46.3)
Male	2,016 (43.0)	2,016 (43.0)	11.7 (−27.8, 39)	1,552 (44.2)	1,552 (44.2)	−4.0 (−53.1, 29.4)	464 (39.4)	464 (39.4)	37.5 (−37.7, 71.6)
Age (years)									
0–18	332 (7.1)	332 (7.1)	−18.8 (−90.0, 25.8)	195 (5.6)	195 (5.6)	−40.0 (−171.6, 27.8)	137 (11.6)	137 (11.6)	−9.1 (−147.2, 51.9)
19–59	4,105 (87.6)	4,105 (87.6)	24.3 (−1.0, 43.3)	3,160 (90.1)	3,160 (90.1)	32.5 (5.3, 51.9)	945 (80.2)	945 (80.2)	40.0 (−37.1, 73.7)
≥60	251 (5.4)	251 (5.4)	−9.1 (−94.6, 38.8)	154 (4.4)	154 (4.4)	−22.2 (−194.9, 49.4)	97 (8.2)	97 (8.2)	28.6 (−125.1, 77.3)
Vaccination course									
Unvaccinated	165 (3.5)	146 (3.1)	Reference	128 (3.6)	99 (2.8)	Reference	37 (3.1)	46 (3.9)	Reference
Partial vaccination			−11.8 (−70.8, 26.8)			3.5 (−56.5, 40.4)			−14.2 (−155.2, 48.9)
Full vaccination	697 (14.9)	601 (12.8)	−3.2 (−34.6, 20.7)	509 (14.5)	445 (12.7)	11.6 (−20.3, 35.0)	188 (15.9)	174 (14.8)	−7.4 (−84.2, 37.4)
Booster vaccination	3,747 (79.9)	3,881 (82.8)	17.0 (−8.1, 33.6)	2,815 (80.2)	2,922 (83.3)	16.5 (−9.8, 37.9)	932 (79.1)	492 (79.9)	17.2 (−37.2, 50.0)
Period after vaccination									
Unvaccinated	165 (3.5)	146 (3.1)	Reference	128 (3.6)	99 (2.8)	Reference	37 (3.1)	46 (3.9)	Reference
Full vaccination (months)	79 (1.7)	60 (1.3)		57 (1.6)	43 (1.2)		22 (1.9)	17 (1.4)	
≤3	24 (0.5)	38 (0.8)	38.2 (−16.6, 68.4)	15 (0.4)	34 (1.0)	50.4 (−0.4, 75.5)	9 (0.8)	17 (1.4)	32.3 (−76.2, 72.4)
3–6	53 (1.1)	56 (1.2)	20.7 (−24.9, 49.6)	37 (1.1)	48 (1.4)	36.2 (−7.7, 62.2)	16 (1.4)	26 (2.2)	19.0 (−83.7, 64.3)
≥6	620 (13.2)	507 (10.8)	−5.4 (−39.7, 20.8)	457 (13.0)	363 (10.3)	3.4 (−32.4, 29.5)	163 (13.8)	131 (11.1)	−10.4 (−87.2, 34.4)
Booster vaccination (months)									
≤3	105 (2.2)	173 (3.7)	49.0 (27.1, 64.3)	79 (2.3)	129 (3.7)	47.6 (21.8, 64.9)	26 (2.2)	49 (4.2)	53.9 (10.2, 76.4)
3-6	175 (3.7)	200 (4.3)	37.9 (13.7, 55.4)	130 (3.7)	142 (4.0)	27.8 (−4.4, 50.1)	45 (3.8)	57 (4.8)	35.3 (−20.5, 65.1)
≥6	3,467 (74.0)	3,508 (74.8)	10.8 (−13.9, 30.2)	2,606 (74.3)	2,651 (75.5)	13.2 (−15.6, 34.9)	861 (73.0)	836 (70.9)	9.6 (−50.6, 45.7)

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; *CI*=confidence interval; VE=vaccine effectiveness.

SUPPLEMENTARY TABLE S3. The effectiveness of vaccination against SARS-CoV-2 infection, by period (months) after booster vaccination, age group, and sex.

Group	Sex		Age (years)	
	Female	Male	0–59	≥60
Vaccination course				
Unvaccinated	Reference	Reference	Reference	Reference
Booster vaccination	7.8 (−27.3, 33.3)	−6.0 (−58.5, 29.2)	12.3 (−14.2, 32.6)	−7.4 (−101.4, 42.1)
Time after vaccination (months)				
Unvaccinated	Reference	Reference	Reference	Reference
Booster vaccination				
≤3	41.5 (5.2, 63.9)	39.7 (−11.4, 62.9)	44.2 (18.7, 61.7)	32.6 (−102.6, 77.5)
3–6	19.6 (−22.2, 47.1)	20.3 (−33.8, 52.5)	32.8 (5.1, 52.4)	17.2 (−102.5, 66.1)
≥6	4.9 (−31.5, 31.3)	−13.9 (−70.9, 24.1)	8.0 (−19.9, 29.4)	−21.6 (−124.2, 33.9)

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

When estimating the VE against specific symptoms, individuals with SARS-CoV-2 Omicron infection who exhibited one of the particular symptoms were categorized as the case group. In contrast, uninfected individuals served as the control group.

Preplanned Studies

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

Pinpin Zhu[1]; Dan Wu[1]; Yan Wang[2]; Xiaoxue Liu[3]; Lance E. Rodewald[1]; Yixing Li[1]; Hui Zheng[1]; Lei Cao[1]; Yifan Song[1]; Li Song[2]; Xiaodong Zhao[3]; Jianyi Yao[4]; Fuzhen Wang[1]; Mingshuang Li[1]; Qian Zhang[1]; Tingting Yan[1]; 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 (*CI*s) for doses 1, 2, 3, and 4 were obtained using multivariate Cox regression models. HRs were employed to calculate VE and its associated 95% *CI*s. 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).

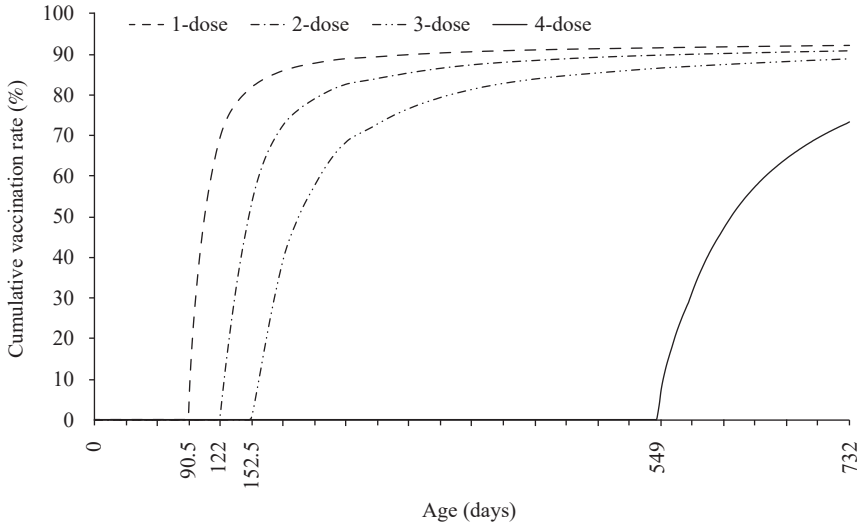


FIGURE 1. Cumulative vaccination rates for each dose of the co-purified diphtheria, tetanus, and acellular pertussis vaccine (DTaP) by age in days.

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	Median observation time, person-days	Total observation time, person-days	Pertussis onset				Pertussis-related hospitalization			
			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, Heininger 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, d) 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.

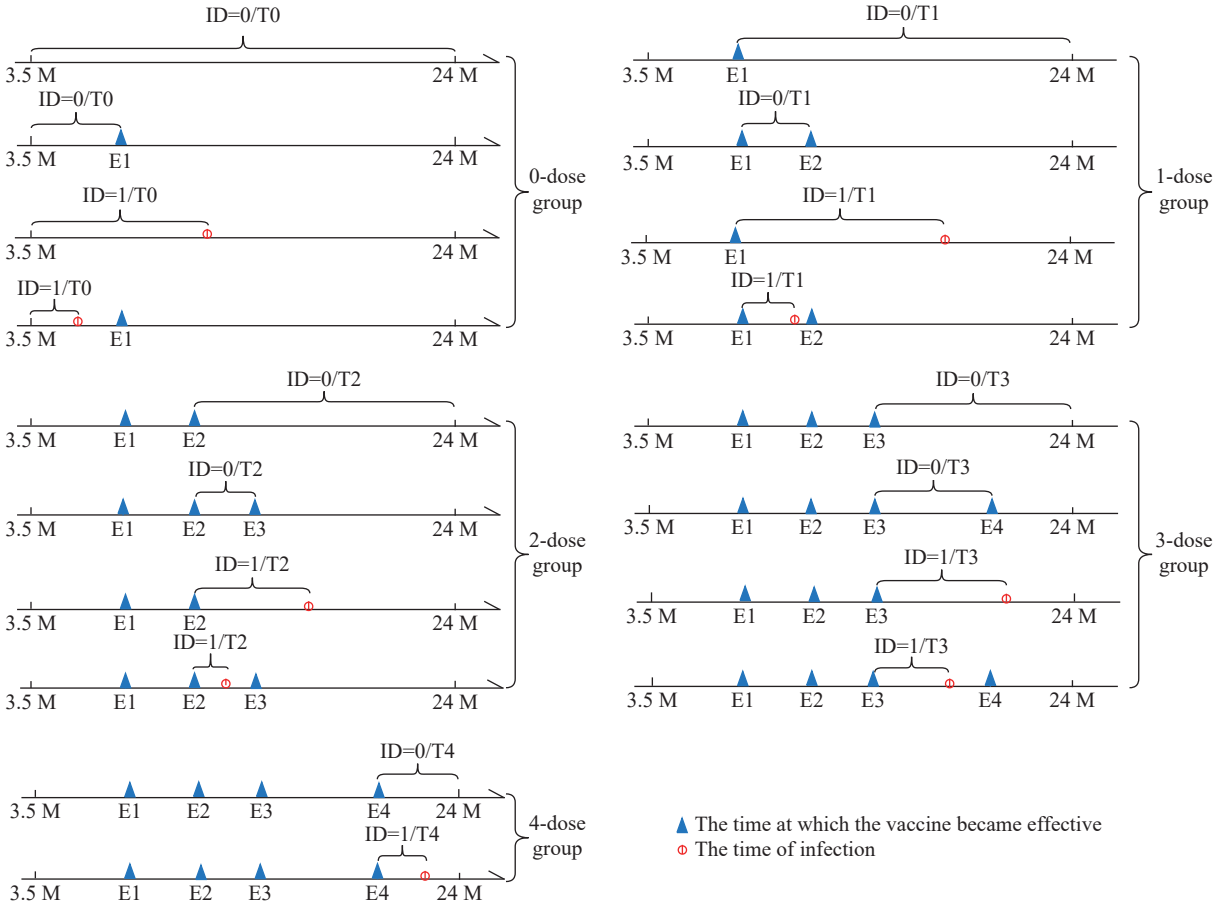
The maximum observation time for a non-pertussis case was 20.5 months, calculated from 14 days following the earliest date for administering the first co-purified DTaP dose (3.5 months) until the child's second birthday (i.e., 24 months – 3.5 months = 20.5 months observation time). The maximum observation 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 (T0) is the sum of all individual observational times. Incidence density for the 0-dose group (ID0) is calculated as the number of cases (S0) divided by the total observational time: $ID0 = S0/\sum member\ observational\ time$.

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.

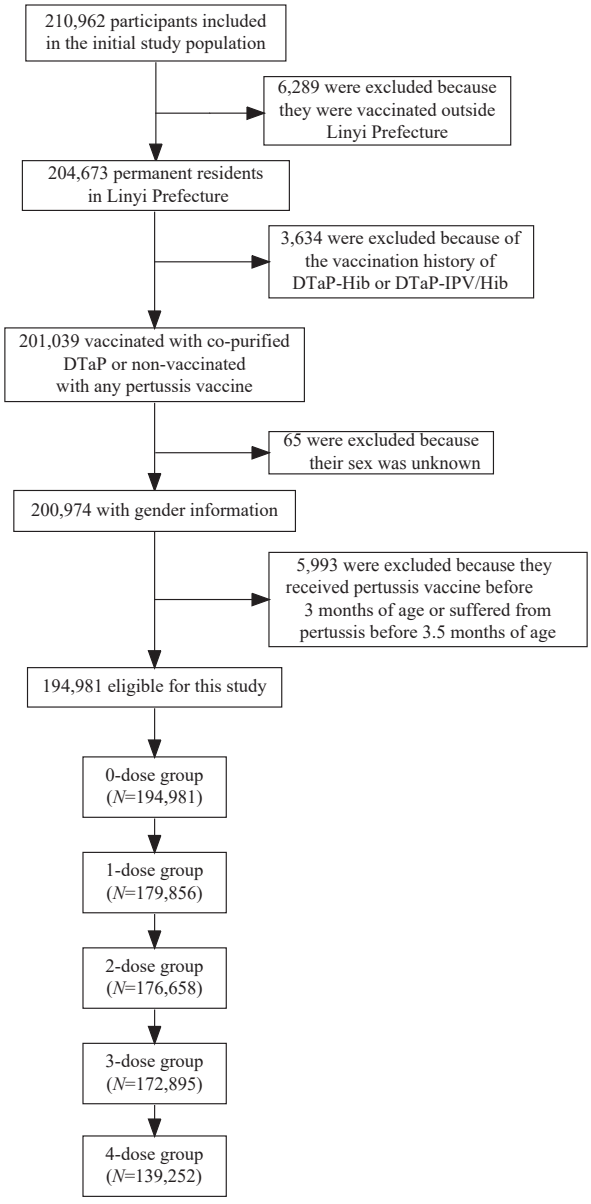
The incidence density for each n-dose group, represented as IDn, is determined by dividing the number of cases within the n-dose group (Sn) by the total observational time for the n-dose group (Tn):

$$IDn = Sn/\sum(n - dose\ group\ member\ observational\ time).$$

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) × 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 ≈ (1–HR) × 100%.

The Study Enrollment Flow Diagram



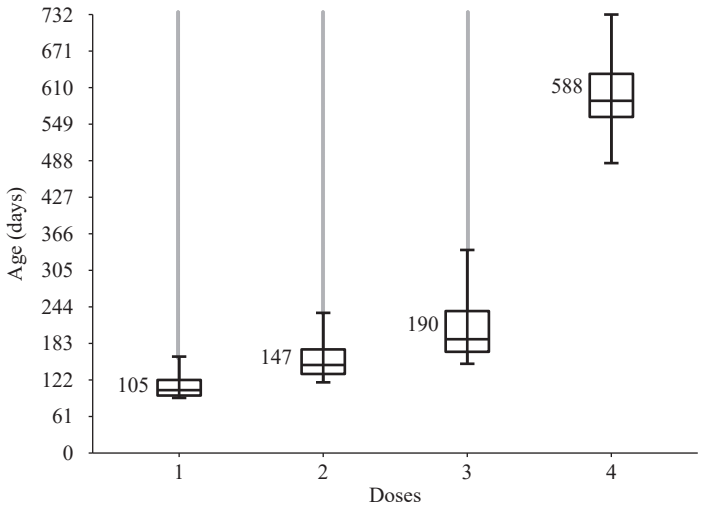
SUPPLEMENTARY FIGURE S2. Study participants and cohort eligibility.

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

1. World Health Organization. Pertussis vaccines: WHO position paper. Wkly Epidemiol Rec 2010;85(40):385-400. https://apps.who.int/iris/handle/10665/241645.
2. 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.
3. World Health Organization. Vaccination schedule for pertussis. https://immunizationdata.who.int/pages/schedule-by-disease/pertussis.html. [2022-12-8].
4. 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.
5. Hernán MA. The hazards of hazard ratios. Epidemiology 2010;21(1):13 – 5. http://dx.doi.org/10.1097/EDE.0b013e3181c1ea43.

Preplanned Studies

Coverage of 13-Valent Pneumococcal Conjugate Vaccine Among Children 0–15 Months of Age — 9 Provinces, China, 2019–2021

Lijun Liu[1]; Zhaonan Zhang[2]; Xixi Zhang[2]; Changsha Xu[3]; Yifan Song[2]; Li Li[2]; Jiakai Ye[2]; Zhiguo Wang[4]; Hui Liang[5]; Weiyan Zhang[6]; Ling Lin[7]; Ning Li[8]; Shujun Zhang[9]; Qianli Ma[1]; Wen Du[10]; Yongzhuo Jiao[11]; Lingsheng Cao[2]; Qi Qi[1]; Lei Cao[2]; Wenzhou Yu[2,#]

Summary

What is already known on this topic?

Limited data exist regarding the coverage of the 13-valent pneumococcal conjugate vaccine (PCV13) in China. A lack of official statistics, coupled with an insufficient body of published literature, hinders the accurate depiction of the current situation.

What is added by this report?

This study investigated the utilization of PCV13 and estimated its coverage in nine provinces across eastern, central, and western China between 2019 and 2021. Despite an annual increase in PCV13 usage during this period, the overall coverage remained suboptimal.

What are the implications for public health practice?

Consideration should be given to incorporating vaccines into the Expanded Program of Immunization, reducing vaccine prices, and addressing the vaccination coverage gap between eastern and western regions when there is an adequate supply of PCV13, particularly with domestic vaccines.

Streptococcus pneumoniae (Spn) infection can lead to invasive pneumococcal diseases (IPD), such as meningitis, bacteremia, and pneumonia, predominantly affecting children. The disease burden and economic impact on families and society are substantial. Among individuals without underlying health conditions, children under 2 years of age demonstrate the highest susceptibility to IPD (*1*). In China in 2017, an estimated 218,200 severe IPD cases and 8,000 IPD deaths occurred in children <5 years old (*2*). In 2019, the World Health Organization (WHO) classified pneumococcal conjugate vaccine (PCV) as a "very high priority" vaccine and advised its integration into national immunization programs worldwide (*3*). An estimated 400,000 child deaths and 54.6 million *Streptococcus pneumoniae*-associated illnesses could be averted annually if 13-valent pneumococcal conjugate vaccine (PCV13) was implemented in all countries (*4*). As of now, 160 countries have incorporated PCV into their national immunization programs (NIP) (*5*).

Evaluating current PCV13 vaccination coverage is crucial to inform decisions regarding the vaccine's introduction in China. However, there is a lack of data on the coverage of non-immunization program vaccines within the country. Official statistics are unavailable, and the limited published literature fails to accurately represent the existing situation. To analyze the utilization, coverage, and trends associated with PCV13, this study examined PCV13 usage data and estimated PCV13 coverage across nine provinces in eastern, central, and western China from 2019 to 2021.

In this study, nine provinces in the eastern, central, and western regions of China were selected for analysis. These provinces, as categorized in the China Health Statistical Yearbook, include Jiangsu, Zhejiang, and Shandong in the east; Anhui, Hubei, and Hunan in the central region; and Sichuan, Guizhou, and Gansu in the west. In China, the PCV13 vaccine is not part of the national immunization program and is administered voluntarily with informed consent. Three versions of the PCV13 vaccine are currently available in China: PCV13-CRM197, which is conjugated to the non-toxic diphtheria toxin mutant (CRM197); PCV13-TT, conjugated to tetanus toxoid (TT); and PCV13-TT/DT, conjugated to both TT and diphtheria toxoid (DT). Table 1 provides detailed information regarding the available PCV13 vaccines and their approved and recommended primary series and booster dose schedules.

Data from the provincial Immunization Information System (IIS) were utilized to ascertain the number of children born in 2019, 2020, and 2021 within the study setting. By examining IIS vaccination records, we determined the number of children in each of these three years who received at least one dose of PCV13

TABLE 1. Pneumococcal conjugate vaccines currently available in China.

Item	PCV13- CRM197	PCV13-TT	PCV13-TT/DT
Manufacturer	Pfizer Ireland Pharma	Yuxi Walvax Bio-Tech Co.	Beijing Minhai Bio-Tech Co.
Approved age range	6 weeks to 15 months*	6 weeks to 5 years	
Number of doses in recommended schedules	4 doses	1 to 4 doses (depend on the age of the first dose)	
Recommended schedules	Three-dose primary series (2, 4, and 6 months of age), 4–8 week intervals, the first dose can be given at 6 weeks One booster dose at 12 to 15 months In principle, the first dose should be given before 5 months of age, the three primary series doses should be completed before 6 months of age.	Infants from 6 weeks to 6 months of age: 3-dose primary series, 1- or 2-month intervals, and 1 booster dose at 12 to 15 months Infants 7 to 11 months of age: 2 doses of primary series at least 2 months apart and 1 booster dose after 12 months Children 12–23 months of age: 2 doses at least 2 months apart Children 2 to 5 years old: 1 dose	

Abbreviation: PVC=pneumococcal conjugate vaccine; CRM=cross reacting material; TT=tetanus toxoid; DT=diphtheria toxoid.
* PCV13-CRM197 was suitable for children aged 6 weeks to 15 months in 2016–2022, the age range for vaccination has been extended to 6 weeks – 5 years in April 2023.

during their first 12 months of life. Additionally, we assessed the number of children who completed the primary series of PCV13 vaccinations within the same age range and the number of children who were administered a booster dose of PCV13 between 12–15 months of age. Adherence to primary series and booster dose schedules was assessed in accordance with the recommendations outlined in Table 1.

For each study year, 3 immunization coverage rates were computed: 1) the proportion of children who received at least one dose during their first year of life in the study year, calculated by dividing the number of children receiving ≥1 dose by the number of children born within the study year; 2) the proportion of children who completed a full primary series during their first year of life in the study year, calculated by dividing the number of children receiving the full primary series by the total number of children born within the same year; and 3) the proportion of children who received a booster dose between 12 and 15 months of age within the study year, calculated by dividing the number of children administered the booster dose by the total number of children born within that study year.

Data were compiled and analyzed using Microsoft Excel 2021 (Microsoft Corporation, Redmond, WA, USA) to determine the three vaccination rates. These rates were examined based on province, region, and urban/rural settings. The number of PCV13 doses administered annually was compared in a year-to-year manner within the study timeframe.

Over the course of three years, a total of 22,560,400 children were born within the study setting, subsequently enrolled in the IISs, and included in this research. Table 2 provides a breakdown of the administered doses by both study province and year. A consistent increase in PCV13 utilization was observed across all provinces annually. Specifically, from 2019 to 2020, there was a 43.54% increase in PCV13 use, with the highest increase observed in Shandong Province (92.63%) and the lowest in Zhejiang Province (20.21%). Furthermore, between 2020 and 2021, a 44.24% increase in PCV13 use was reported, in which Shandong Province exhibited the highest increase (80.20%) and Jiangsu Province, the lowest (19.78%).

Table 3 shows coverage by outcome, province, and year. Coverage of ≥1-dose, primary series, and booster doses consistently increased on an annual basis across all provinces and regions, showing significant differences by province. The coverage for ≥1-dose was 12.05% in 2019, 21.99% in 2020, and 35.44% in 2021; primary series coverage levels reached 5.99%, 12.30%, and 16.13%; and booster dose coverage levels attained 3.25%, 9.15%, and 14.52%. In 2021, the highest ≥1-dose coverage was in the eastern region (Zhejiang) at 59.57%, while the lowest was in the western region (Gansu) at 6.03%. The rate of ≥1-dose coverage was 2.09 times higher in the east (17.17%) than in the west (8.21%) in 2019, 2.63 times higher in the east (34.56%) than in the west (13.12%) in 2020, and 2.46 times higher in the eastern region (51.19%) than in the western region (20.79%) in 2021.

Table 4 shows coverage by province, region, year, and urban/rural status. Coverage demonstrated an annual increase and was consistently higher in urban areas compared to rural areas, though with a decreasing disparity. In 2019, coverage of ≥1-dose was 3.16 times higher in urban areas (16.61%) than rural areas

TABLE 2. PCV13 use in 9 provinces in China, 2019–2021 (million doses).

Province	2019	2020	2021	The year-on-year growth rate in 2020 (%)	The year-on-year growth rate in 2021 (%)
Jiangsu	33.48	44.49	53.29	32.91	19.78
Zhejiang	53.95	64.86	78.61	20.21	21.19
Anhui	12.51	20.53	30.68	64.16	49.44
Shandong	18.12	34.90	62.89	92.63	80.20
Hubei	10.56	15.83	20.36	49.92	28.64
Hunan	12.99	23.29	37.68	79.30	61.82
Sichuan	22.41	30.15	51.58	34.51	71.10
Guizhou	4.46	7.25	12.80	62.39	76.63
Gansu	1.67	2.93	4.38	75.53	49.30
Total	170.15	244.23	352.27	43.54	44.24

Abbreviation: PCV13=13-valent pneumococcal conjugate vaccine.

TABLE 3. PCV13 vaccination coverage among children aged 0–15 months in 9 provinces of China, 2019–2021.

Province	2019			2020			2021		
	At least 1 dose	Full vaccination of primary series	Booster	At least 1 dose	Full vaccination of primary series	Booster	At least 1 dose	Full vaccination of primary series	Booster
Eastern Region	17.17	8.46	4.54	34.56	20.30	13.84	51.19	23.26	17.06
Jiangsu	10.43	6.20	1.51	31.78	31.25	12.88	43.95	33.00	15.41
Zhejiang	27.49	16.55	10.81	41.01	22.80	21.42	59.57	25.80	25.52
Shandong	14.40	4.03	2.07	31.45	9.50	8.34	50.15	13.31	11.45
Central Region	8.71	3.82	2.21	15.24	6.92	5.93	30.04	13.15	10.98
Anhui	13.60	3.68	1.76	22.11	6.57	5.10	46.96	13.65	12.70
Hubei	4.61	3.77	2.87	9.90	8.10	7.15	20.00	16.37	13.23
Hunan	6.69	3.99	2.21	11.56	6.50	5.98	21.70	10.42	7.82
Western Region	8.21	4.90	2.53	13.12	8.03	6.04	20.78	10.04	8.10
Sichuan	13.40	7.58	4.16	22.26	12.79	10.21	33.21	16.45	14.13
Guizhou	2.66	2.02	0.96	4.14	3.42	2.30	10.75	4.13	3.13
Gansu	2.06	1.78	0.23	2.83	2.52	0.52	6.03	4.28	1.17
Total	12.05	5.99	3.25	21.99	12.30	8.96	35.44	16.13	12.47

Abbreviation: PCV13=13-valent pneumococcal conjugate vaccine.

(5.25%), in 2020, it was 2.73 times higher in urban areas (29.01%) than in rural areas (10.59%), and in 2021, it was 2.20 times higher in urban areas (44.50%) than in rural areas (20.17%).

DISCUSSION

In October 2016, Pfizer's PCV13 was licensed in China, followed by the domestic PCV13 in December 2019 and June 2021. A supply shortage occurred during this period, indicating that accelerating the continued production and supply of PCV13 could help improve vaccination coverage (*6*). The present study demonstrated that the number of PCV13 doses administered and the resulting coverage increased annually from 2019 to 2021 in nine Chinese provinces. Furthermore, the coverage was higher in urban settings compared to rural areas. In 2021, 35.44% of infants received at least one PCV13 dose, 16.13% completed a full primary series, and 12.47% obtained a booster dose. The highest coverage was observed in eastern China and the lowest in the western region. In addition to regional disparities in coverage, significant province-level differences were also identified.

Prior researches on PCV13 coverage in China

TABLE 4. Urban and rural vaccination coverage of PCV13 among children aged 0–15 months in 9 provinces of China, 2019–2021.

Region	2019				2020				2021			
	Urban		Rural		Urban		Rural		Urban		Rural	
	Number of vaccinations (×10,000)	Coverage rate (%)	Number of vaccinations (×10,000)	Coverage rate (%)	Number of vaccinations (×10,000)	Coverage rate (%)	Number of vaccinations (×10,000)	Coverage rate (%)	Number of vaccinations (×10,000)	Coverage rate (%)	Number of vaccinations (×10,000)	Coverage rate (%)
Eastern region	38.91	21.03	8.65	9.40	62.40	41.89	12.13	18.20	75.90	59.68	17.46	31.63
Jiangsu	6.65	11.36	2.00	8.21	16.29	33.88	4.51	25.96	19.42	46.88	5.21	35.67
Zhejiang	16.98	28.99	6.02	23.98	22.06	44.94	5.83	30.81	25.33	61.17	8.62	55.31
Shandong	15.28	22.49	0.63	1.48	24.05	46.43	1.79	5.89	31.15	70.24	3.63	14.52
Central region	17.56	13.27	2.42	2.50	25.25	21.45	4.84	6.08	35.27	39.22	9.18	15.81
Anhui	9.98	20.98	1.61	4.28	13.66	30.57	3.28	10.27	17.91	58.55	6.28	30.03
Hubei	2.73	7.42	0.05	0.21	4.80	15.56	0.05	0.30	7.89	30.92	0.08	0.53
Hunan	4.85	10.11	0.76	2.12	6.79	16.09	1.51	5.11	9.47	28.01	2.82	12.36
Western region	10.79	12.31	3.20	3.86	14.42	16.94	5.96	8.49	20.58	26.07	8.80	14.10
Sichuan	8.90	18.51	3.08	7.45	11.76	26.37	5.75	16.89	14.22	36.40	8.22	28.84
Guizhou	1.39	5.10	0.09	0.31	2.03	7.17	0.18	0.71	5.16	18.00	0.51	2.12
Gansu	0.50	4.04	0.03	0.19	0.63	5.14	0.03	0.29	1.20	10.69	0.07	0.70
Total	67.26	16.61	14.26	5.25	102.07	29.01	22.93	10.59	131.75	44.50	35.44	20.17

Abbreviation: PCV=pneumococcal conjugate vaccine.

primarily relied on estimates derived from modeling. In 2017, the estimated primary series coverage for children under five years old in China was a mere 1.3% (*4*). Based on the latest PCV coverage rates reported by the World Health Organization/United Nations Children's Fund Joint Reporting Form on Immunization (JRF), the European Region demonstrated the highest final-dose coverage (82%) in 2021. In contrast, the Americas, Africa, Eastern Mediterranean, Southeast Asia, and Western Pacific regions reported final-dose coverage levels of 74%, 66%, 54%, 29%, and 19%, respectively (*7*). Within the JRF, Australia reported a final-dose coverage of 96.27%, while the United States, France, and India indicated coverage rates of 92.0%, 91.8%, and 69.3%, respectively (*7*).

Despite observing annual increases, our study found that coverage levels for both primary series and booster doses remained below 20% by the end of the study period. In China, the "3+1" immunization schedule, consisting of a 3-dose primary series and one booster dose, is recommended for PCV13. Schedules involving multiple doses can negatively impact vaccination timeliness, decrease the willingness to vaccinate, and make completing all recommended doses a challenge. WHO and several developed countries suggest reducing the PCV13 schedules to "3+0" or "2+1" to enhance coverage and achieve greater population immunity through improved compliance with a simplified schedule (*8*).

In the United Kingdom, the implementation of a "2+1" immunization program resulted in 92.0% [95% confidence interval (*CI*): 81.7%–96.7%] IPD protection against PCV7 serotypes and 72.7% (95% *CI*: 31.1%–89.9%) protection against the six additional serotypes in PCV13 (*9*). Furthermore, meningitis caused by vaccine serotypes nearly disappeared in children fully immunized with PCV13 after nine years of employing a "3+0" schedule in Australia (*10*).

We discovered that PCV13 coverage rates were highest in the eastern regions and lowest in the western regions. This finding contrasts with the regional distribution of IPD burden, in which incidence, morbidity, and mortality rates are highest in the less economically developed western regions due to the natural environment and relatively weaker healthcare conditions (*2*). Vaccination rates in both urban and rural areas have increased annually; however, coverage among urban children remains significantly higher compared to rural children, with the disparity gradually decreasing.

In China, PCV13 is not included in the immunization program, and its cost poses a significant barrier to utilization. Completing a four-dose series in China requires an out-of-pocket expenditure of 1,900–2,800 Chinese Yuan (CNY). The high price may contribute to the low affordability in central and western provinces as well as rural areas of China, leading to a prominent issue of vaccine inequity (*10*–*11*). The WHO recommends that all countries introduce PCV into their national childhood immunization programs, particularly in developing countries where safe and effective PCV vaccination has demonstrated significant progress in reducing IPD-related morbidity and mortality (*5*). A study conducted in China estimated that incorporating PCV13 into the National Immunization Program (NIP) could result in a birth cohort gaining 3.58 million quality-adjusted life years (QALYs) and averting 147,500 associated deaths, with a net benefit of 13.5 billion CNY (*12*).

Our study presents several limitations. First, despite utilizing official vaccination records, the data were sourced from provincial IISs, encompassing only those children with enrollment in the IIS and possessing vaccination histories. Consequently, we could not acquire data for children lacking IIS enrollment, which may result in an overestimation of PCV13 vaccination rates. Additionally, data constraints hindered our ability to determine the birth cohort immunization rate, allowing us to solely provide an approximation of PCV13 coverage.

In conclusion, the utilization and coverage of PCV13 among children aged 0–15 months in China have demonstrated a consistent upward trend. However, significant issues persist, including regional coverage disparities and vaccination rates substantially below the global average. Several challenges hinder the improvement of PCV13 coverage in China, such as high vaccine costs for non-program vaccines, complex vaccination schedules, limited vaccine supply, and the recent licensing of domestic vaccines.

We recommend incorporating PCV13 into the National Immunization Program to reduce its price, enhance coverage, mitigate regional disparities, and promote equitable access to the vaccine.

Acknowledgements: We'd like to show our sincere gratitude to Lance Everett Rodewald for polishing the article in English and giving us advice on modifications.

doi: 10.46234/ccdcw2023.072

[#] Corresponding author: Yu Wenzhou, yuwz@chinacdc.cn.

[1] Sichuan Center for Disease Control and Prevention, Chengdu City, Sichuan Province, China; [2] National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China; [3] Suqian Center for Disease Control and Prevention, Suqian City, Jiangsu Province, China; [4] Jiangsu Center for Disease Control and Prevention, Nanjing City, Jiangsu Province, China; [5] Zhejiang Center for Disease Control and Prevention, Hangzhou City, Zhejiang Province, China; [6] Shandong Center for Disease Control and Prevention, Jinan City, Shandong Province, China; [7] Anhui Center for Disease Control and Prevention, Hefei City, Anhui Province, China; [8] Hubei Center for Disease Control and Prevention, Wuhan City, Hubei Province, China; [9] Hunan Center for Disease Control and Prevention, Changsha City, Hunan Province, China; [10] Guizhou Center for Disease Control and Prevention, Guiyang City, Guizhou Province, China; [11] Gansu Center for Disease Control and Prevention, Lanzhou City, Gansu Province, China.

Submitted: April 08, 2023; Accepted: April 24, 2023

REFERENCES

1. Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000;49(RR – 9):1 – 35.
2. Lai XZ, Wahl B, Yu WZ, Xu TT, Zhang HJ, Garcia C, et al. National, regional, and provincial disease burden attributed to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children in China: Modelled estimates for 2010-17. Lancet Reg Health West Pac 2022;22:100430. http://dx.doi.org/10.1016/j.lanwpc.2022.100430.
3. World Health Organization. Pneumococcal conjugate vaccines: WHO position paper. 2019. https://www.who.int/publications-detail-redirect/10665-310968. [2023-3-6].
4. Chen C, Liceras FC, Flasche S, Sidharta S, Yoong J, Sundaram N, et al. Effect and cost-effectiveness of pneumococcal conjugate vaccination: a global modelling analysis. Lancet Glob Health 2019;7(1):e58 – 67. http://dx.doi.org/10.1016/S2214-109X(18)30422-4.
5. World Health Organization. Introduction of PCV (Pneumococcal conjugate vaccine). 2022. https://immunizationdata.who.int/pages/vaccine-intro-by-antigen/pneumo_conj.html?ISO_3_CODE=CHN+BRA&YEAR=. [2023-3-6].
6. Wang J, Wu QS, Lu J, Ni YH, Zhou F. Low vaccination coverage of pneumococcal conjugate vaccines (PCVs) in Shanghai, China: a database analysis based on birth cohorts from 2012 to 2020. Vaccine 2021;39(42):6189 – 94. http://dx.doi.org/10.1016/j.vaccine.2021.09.011.
7. World Health Organization. Pneumococcal vaccination coverage. 2022. https://immunizationdata.who.int/pages/coverage/pcv.html?GROUP=WHO_REGIONS&ANTIGEN=PCV3&YEAR=&CODE=. [2023-3-6].
8. GOV.UK. The complete routine immunisation schedule from February 2022. 2022. https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule/the-complete-routine-immunisation-schedule-from-february-2022. [2023-3-6].
9. Andrews N, Kent A, Amin-Chowdhury Z, Sheppard C, Fry N, Ramsay M, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: the indirect cohort design, 2006-2018. Vaccine 2019;37(32):4491 – 8. http://dx.doi.org/10.1016/j.vaccine.2019.06.071.
10. Jayasinghe S, Menzies R, Chiu C, Toms C, Blyth CC, Krause V, et al. Long-term impact of a "3 + 0" schedule for 7- and 13-valent pneumococcal conjugate Vaccines on invasive pneumococcal disease in Australia, 2002-2014. Clin Infect Dis 2017;64(2):175 – 83. http://dx.doi.org/10.1093/cid/ciw720.
11. Du YZ, Wang Y, Zhang T, Ma LB, Xie SY, Wang Y, et al. Factors associated with PCV13 vaccine hesitancy in parents under an innovative immunization strategy: a cross-sectional study — Weifang city, Shandong province, China, 2021. China CDC Wkly 2023;5(12):271 – 7. http://dx.doi.org/10.46234/ccdcw2023.049.
12. Shen KL, Wasserman M, Liu DD, Yang YH, Yang JF, Guzauskas GF, et al. Estimating the cost-effectiveness of an infant 13-valent pneumococcal conjugate vaccine national immunization program in China. PLoS One 2018;13(7):e0201245. http://dx.doi.org/10.1371/journal.pone.0201245.

Healthy China

Effects of Three Major Immunization Interventions on Measles Control — China, 1952–2021

Quanwei Song[1]; Chao Ma[1]; Lixin Hao[1]; Fuzhen Wang[1]; Zhijie An[1]; Zundong Yin[1]; Huaqing Wang[1,#]

Measles, an acute respiratory infectious disease caused by the measles virus, was responsible for millions of deaths annually before the introduction of the measles vaccine (MV) (*1*). Widespread availability of measles vaccines and the initiation of the Expanded Program on Immunization, approved at the 27th World Health Assembly in 1974 (*2*), have significantly improved global measles control. In China, measles has been a statutorily notifiable disease since the establishment of the National Notifiable Diseases Reporting System (NNDRS) in 1950 (*3*). From 1950 to 1986, data were collected by subnational institutions of disease control and aggregated by the national institution using paper documentation. In 1987, an electronic documentation system replaced the paper-based system (*3*). In 2004, China upgraded the NNDRS to enable direct reporting via the Internet (*4*).

The measles vaccine was first introduced in China as a liquid formulation in 1965. In 1978, the National Expanded Program on Immunization (EPI) was launched, initiating a one-dose routine measles vaccination schedule (*5*). Between 2003 and 2009, 27 out of 31 provincial-level administrative divisions (PLADs) in China carried out unsynchronized provincewide supplementary immunization activities to combat measles, targeting approximately 185.7 million children (*6*). In 2010, China executed synchronized nationwide supplementary immunization activities against measles.

The epidemiology of measles has been described at subnational levels across four stages; however, a quantitative evaluation of the effects of major interventions at the national level has not yet been conducted. Interrupted time series (ITS) analyses are commonly employed to assess the impact of public health interventions, as they offer quantitative comparisons before and after interventions and evaluate both short-term changes and long-term trends. In this study, we utilized ITS analyses to examine the influence of three significant MV interventions at both the national and regional levels in China. These findings will enhance our understanding of the effects of previous immunization strategies and provide valuable evidence for the future development of immunization policies and strategies.

We obtained measles incidence data from the Public Health Science Data Center, along with provincial population data and per capita gross domestic product (GDP) data from the National Bureau of Statistics. We divided the study period from 1952 to 2021 into four stages based on the history of measles control in China:

Stage 1: Pre-vaccine (1952–1964) — Prior to the introduction of the MV, measles was a nearly ubiquitous childhood illness.

Stage 2: Pre-EPI (1965–1977) — Following MV introduction but before the EPI, MV availability was limited, and coverage rates remained low in China.

Stage 3: EPI (1978–2008) — During the EPI period, a standard routine immunization schedule was implemented to vaccinate a defined target population, resulting in gradually increased coverage.

Stage 4: Post-SIAs (2009–2021) — After the implementation of national and subnational Supplementary Immunization Activities (SIAs), MV coverage in children remained high.

The study period involved four stages that included three interventions as the focus of our research: 1) vaccine introduction in 1965, 2) the implementation of the EPI in 1978, and 3) the initiation of SIAs in 2009. The year 2009 was presumed to be when SIAs were conducted nationwide, taking into account the timeline of subnational and national SIAs.

Based on the economic status in China, four economic regions by PLADs were identified: western China (Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang); central China (Shanxi, Anhui, Jiangxi, Henan, Hubei, Hunan); eastern China (Beijing, Tianjin, Hebei, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, Hainan); and northeastern China (Liaoning, Jilin, Heilongjiang). Eastern China exhibits the highest GDP level, followed sequentially by central China, western China, and northeastern China (*7*).

A single-group ITS analysis was conducted on annual measles incidence data to assess the impact of three interventions on measles control in China from 1952 to 2021. In the ITS model, the outcome variable Y represents the annual incidence of measles, with X_1 representing the year (0, 1, 2, ..., n by year). X_2 signifies the first intervention (0 before 1965 and 1 after 1965), while X_3 denotes a trend variable following the first intervention (0 before 1965, with the value of 0, 1, 2, …, n by year after 1965). The second intervention is illustrated by X_4 (0 before 1978 and 1 after 1978), and X_5 corresponds to a trend variable following the second intervention (0 before 1978, with values of 0, 1, 2, …, n by year after 1978). X_6 represents the third intervention (0 before 2009 and 1 after 2009), and X_7 is a trend variable after the third intervention (0 before 2009, with values of 0, 1, 2, …, n by year after 2009). Lastly, X_8 denotes per capita GDP. The ITS model equation was as follows:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6 + \beta_7 X_7 + \beta_8 X_8 + \varepsilon$$

In the given model, β_0 represents the intercept term, signifying the average measles incidence at the beginning of the study. Meanwhile, β_1 indicates the slope or trend of the incidence before the introduction of the measles vaccine, reflecting the average direction of measles incidence over time. β_2 denotes the change in incidence after the measles vaccine was introduced in 1965, and β_3 signifies the slope change following the vaccine's introduction. Additionally, β_4 represents the change subsequent to the EPI implementation, and β_5 corresponds to the trend after the second intervention, illustrating the long-term impact of EPI implementation. Furthermore, β_6 demonstrates the short-term change resulting from SIAs; while β_7 indicates long-term trends after SIAs. Lastly, β_8 represents the association between per capita GDP and incidence.

The current study employed ITS analyses to assess the impact of three primary interventions on measles incidence in China. Segmented regression within a quasi-Poisson model was utilized, with annual measles cases as the dependent variable. In this model, annual measles incidence functioned as the response variable, accompanied by an offset component representing the total population for the given year. Additionally, GDP per capita was incorporated into the model to estimate its association with alterations in the level of measles incidence.

In this study, Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA) was employed to construct the measles incidence database. Statistical analyses were performed using the Statistical Analysis System (SAS, version 9.4; SAS Institute Inc, Cary, NC, USA).

Figure 1 shows the temporal patterns of measles incidence in China from 1952 to 2021. The annual reported measles incidence significantly decreased from

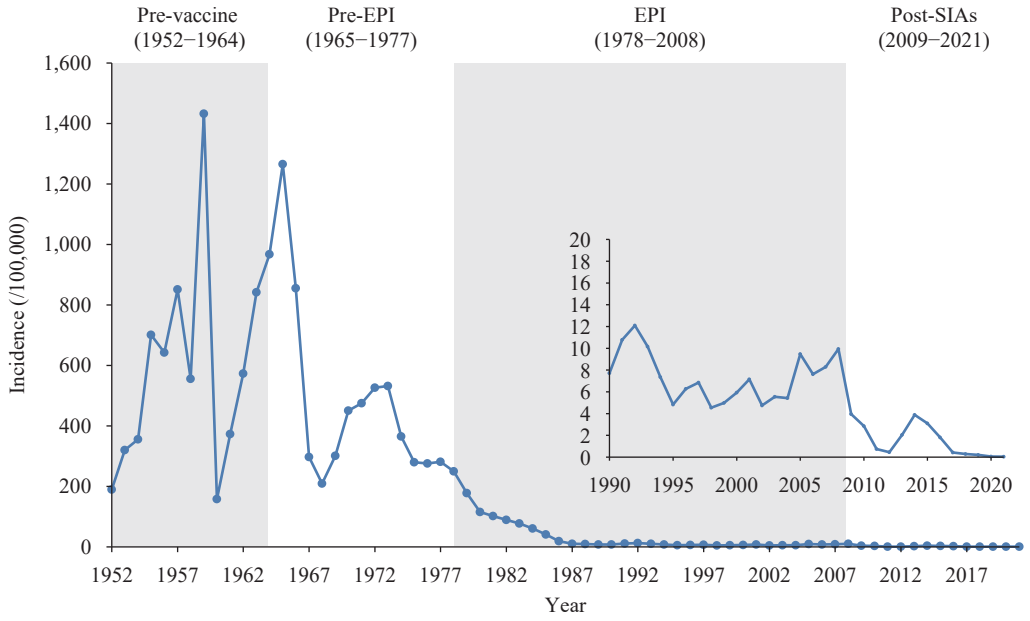


FIGURE 1. Annual reported measles incidence in China, 1952 to 2021.
Abbreviation: EPI=expanded program on immunization; SIAs=supplementary immunization activities.

189.44 cases per 100,000 individuals in 1952, with a maximum of 1,432.41 cases per 100,000 in 1959, to 0.04 cases per 100,000 in 2021. From 1952 to 1978, incidence remained high, ranging from 157.51 to 1,432.41 cases per 100,000, and exhibited periodic peaks every 3–5 years. A decline in incidence became evident after 1978, accompanied by the disappearance of periodic peaks. Incidence consistently remained low after 1987, falling below 10 cases per 100,000 in most years, and reached a nadir in 2012 (0.45 cases per 100,000). In 2015, incidence increased to 3.09 cases per 100,000, but subsequently declined to a historical low in 2021 (0.04 cases per 100,000). The annual measles incidence in China decreased by more than 99.99% from its peak in 1959 to 2021.

Between 1952 and 2021, a total of 111,925,154 measles cases were reported, averaging 1,599,316 cases annually and a cumulative average incidence of 153.45 per 100,000 population. Approximately 90% of these cases occurred during the pre-vaccine and pre-EPI stages. The average incidence rates for the pre-vaccine, pre-EPI, EPI, and post-SIAs stages were 615.06, 450.91, 31.15, and 1.62 per 100,000, respectively. This data demonstrate a declining trend in measles incidence from the pre-vaccine stage to the post-SIAs stage (Table 1).

According to analyses examining the spatial distribution of measles incidence across different stages and throughout the entire study period (1952–2021), high incidences were observed in eastern, central, and western China. The incidence was highest in western China (252.58/100,000) and lowest in eastern China (4.61/100,000). In the pre-vaccine era, eastern China displayed high incidence rates, peaking at 1,599.07/100,000. During the pre-EPI stage, most high-incidence PLADs were located in central China, but the highest incidence (848.96/100,000) was observed in western China. High incidence rates were reported in both western and central China during the EPI stage, with the highest rate of 200.74/100,000 occurring in western China. Finally, in the post-SIAs stage, most high incidences were observed in western China, peaking at 9.17/100,000.

In the pre-vaccine stage, measles incidence increased by 5.9% per year [incidence rate ratio (IRR)=1.059, P=0.016], as demonstrated in our Poisson model (Table 2). Following the introduction of the measles vaccine during the pre-EPI stage, incidence decreased by 13.9% (IRR=0.861, P<0.001) each year compared to the pre-vaccine stage. This resulted in a short-term decrease in measles incidence by 16.1% (IRR=0.839, P=0.432).

The introduction of measles vaccine led to significant declines in incidence over time. In the EPI stage, compared to the pre-EPI stage, incidences further decreased by 16.1% (IRR=0.839, P=0.002) each year. Additionally, a short-term level decrease of 4.1% in 1978 (IRR=0.959, P=0.901) was observed.

After the implementation of national and subnational SIAs in China (beginning in 2009), the post-SIAs stage (2009–2021) saw an average annual decrease in the incidence of 54.6% (IRR=0.454, P=0.132), and the short-term level of incidence decreased by 87.9% (IRR=0.121, P=0.355) compared to the EPI stage (1978–2008). Our model indicated an IRR of 1.0002 (P=0.007) with GDP, suggesting a slight increase in incidence associated with GDP.

The results of the ITS Poisson model for the four economic regions were consistent with those observed in China. In the pre-vaccine era, the annual incidence trend increased by 6.7% (IRR=1.067, P=0.005) in eastern China, 6.7% (IRR=1.067, P=0.015) in northeastern China, 5.5% (IRR=1.055, P=0.050) in central China, and 5.6% (IRR=1.056, P=0.044) in western China.

Following the introduction of the measles vaccine in 1965, incidence rates decreased in the short term by 29.5% (IRR=0.705, P=0.124) and 62.00% (IRR=0.380, P=0.002) in eastern and northeastern China. In contrast, incidence rates increased by 6.6% (IRR=1.066, P=0.795) and 3.5% (IRR=1.035, P=0.889) in central and western China. When

TABLE 1. National incidence of measles in different stages from 1952 to 2021.

Stage	Duration	No. of cases (%)	Average No. of cases/year	Average incidence rate (/100,000)
Pre-vaccine	1952–1964	51,189,211 (45.72)	3,937,632	615.06
Pre-EPI	1966–1977	49,324,478 (44.06)	3,794,191	450.91
EPI	1978–2008	11,147,975 (9.96)	359,612	31.15
Post-SIAs	2009–2021	290,490 (0.26)	22,345	1.62
Total	1952–2021	111,952,154 (100)	1,599,316	153.45

Abbreviation: EPI=expanded program on immunization; SIAs=supplementary immunization activities.

TABLE 2. Interrupted time series results for measles incidence in China.

Region	Variable	β (95% *CI*)	IRR (95% *CI*)	*P*
China	Trend before the first intervention (1952–1964)	0.057 (0.011, 0.104)	1.059 (1.011, 1.110)	0.016
	Level change with the first intervention (1965)	−0.176 (−0.613, 0.262)	0.839 (0.542, 1.300)	0.432
	Trend change with the first intervention (1966–1977)	−0.150 (−0.216, −0.084)	0.861 (0.806, 0.920)	<0.001
	Level change with the second intervention (1978)	−0.042 (−0.699, 0.615)	0.959 (0.497, 1.851)	0.901
	Trend change with the second intervention (1978–2008)	−0.175 (−0.286, −0.063)	0.840 (0.751, 0.938)	0.002
	Level change with the third intervention (2009)	−2.110 (−6.580, 2.361)	0.121 (0.001, 10.603)	0.355
	Trend change with the third intervention (2009–2021)	−0.790 (−1.818, 0.238)	0.454 (0.162, 1.269)	0.132
	GDP	2.300×10^{-4} (6.422×10^{-5}, 3.960×10^{-4})	1.000 (1.000, 1.000)	0.007
Eastern China	Trend before the first intervention (1952–1964)	0.065 (0.019, 0.110)	1.067 (1.019, 1.117)	0.005
	Level change with the first intervention (1965)	−0.350 (−0.795, 0.096)	0.705 (0.452, 1.100)	0.124
	Trend change with the first intervention (1966–1977)	−0.180 (−0.251, −0.110)	0.835 (0.778, 0.896)	<0.001
	Level change with the second intervention (1978)	0.112 (−0.669, 0.892)	1.118 (0.512, 2.440)	0.779
	Trend change with the second intervention (1978–2008)	−0.182 (−0.320, −0.044)	0.833 (0.726, 0.957)	0.010
	Level change with the third intervention (2009)	−1.945 (−6.195, 2.304)	0.143 (0.002, 10.013)	0.370
	Trend change with the third intervention (2009–2021)	−0.752 (−1.698, 0.194)	0.471 (0.183, 1.214)	0.119
	GDP	1.870×10^{-4} (5.768×10^{-5}, 3.157×10^{-4})	1.000 (1.000, 1.000)	0.005
Northeastern China	Trend before the first intervention (1952–1964)	0.065 (0.013, 0.117)	1.067 (1.013, 1.124)	0.015
	Level change with the first intervention (1965)	−0.967 (−1.564, −0.371)	0.380 (0.209, 0.690)	0.002
	Trend change with the first intervention (1966–1977)	−0.264 (−0.372, −0.155)	0.768 (0.689, 0.856)	<0.001
	Level change with the second intervention (1978)	1.206 (−0.054, 2.466)	3.340 (0.947, 11.777)	0.061
	Trend change with the second intervention (1978–2008)	−0.175 (−0.418, 0.068)	0.840 (0.658, 1.071)	0.159
	Level change with the third intervention (2009)	−1.372 (−7.526, 4.783)	0.254 (0.001, 119.420)	0.662
	Trend change with the third intervention (2009–2021)	−0.964 (−2.599, 0.671)	0.381 (0.074, 1.956)	0.248
	GDP	4.050×10^{-4} (3.951×10^{-5}, 7.715×10^{-4})	1.000 (1.000, 1.001)	0.030
Central China	Trend before the first intervention (1952–1964)	0.054 (0.000, 0.107)	1.055 (1.000, 1.113)	0.050
	Level change with the first intervention (1965)	0.064 (−0.420, 0.548)	1.066 (0.657, 1.730)	0.795
	Trend change with the first intervention (1966–1977)	−0.124 (−0.194, −0.054)	0.883 (0.823, 0.948)	0.001
	Level change with the second intervention (1978)	−0.282 (−0.938, 0.374)	0.754 (0.391, 1.453)	0.399
	Trend change with the second intervention (1978–2008)	−0.219 (−0.340, −0.098)	0.803 (0.712, 0.906)	<0.001
	Level change with the third intervention (2009)	−2.180 (−7.601, 3.242)	0.113 (0.000, 25.578)	0.431
	Trend change with the third intervention (2009–2021)	−1.124 (−2.563, 0.315)	0.325 (0.077, 1.370)	0.126
	GDP	3.320×10^{-4} (8.195×10^{-5}, 5.811×10^{-4})	1.000 (1.000, 1.001)	0.009
Western China	Trend before the first intervention (1952–1964)	0.055 (0.002, 0.108)	1.056 (1.002, 1.114)	0.044
	Level change with the first intervention (1965)	0.034 (−0.446, 0.515)	1.035 (0.640, 1.673)	0.889
	Trend change with the first intervention (1966–1977)	−0.140 (−0.211, −0.068)	0.870 (0.810, 0.934)	<0.001
	Level change with the second intervention (1978)	−0.035 (−0.662, 0.592)	0.966 (0.516, 1.807)	0.913
	Trend change with the second intervention (1978–2008)	−0.134 (−0.230, −0.038)	0.875 (0.795, 0.962)	0.006
	Level change with the third intervention (2009)	−2.819 (−8.163, 2.524)	0.060 (0.000, 12.479)	0.301
	Trend change with the third intervention (2009–2021)	−0.652 (−1.776, 0.473)	0.521 (0.169, 1.604)	0.256
	GDP	2.580×10^{-4} (3.717×10^{-5}, 4.796×10^{-4})	1.000 (1.000, 1.000)	0.022

Abbreviation: GDP=gross domestic product; IRR=incidence rate ratio.

compared to the pre-vaccine era (1952–1964), incidence rates during the pre-EPI stage (1965–1977) decreased by 16.5% (IRR=0.835, *P*<0.001), 23.2% (IRR=0.768, *P*<0.001), 11.7% (IRR=0.883, *P*=0.001), and 13.0% (IRR=0.870, *P*<0.001) in eastern, northeastern, central, and western China, respectively.

Following the implementation of EPI in 1978, incidence rates during the EPI stage (1978–2008) showed annual decreases of 16.7% (IRR=0.833, *P*=0.010), 16.0% (IRR=0.840, *P*=0.159), 19.7% (IRR=0.803, *P*<0.001), and 12.5% (IRR=0.875, *P*=0.006) in eastern, northeastern, central, and western China, respectively. Short-term level reductions were observed in central (IRR=0.754, *P*=0.399) and western China (IRR=0.966, *P*=0.913), whereas increases were found in eastern (IRR=1.118, *P*=0.779) and northeastern China (IRR=3.340, *P*=0.061).

Following the SIAs, the incidence of the disease decreased by 85.7% (IRR=0.143, *P*=0.370), 74.6% (IRR=0.254, *P*=0.662), 88.7% (IRR=0.113, *P*=0.431), and 94.0% (IRR=0.060, *P*=0.301) in the eastern, northeastern, central, and western regions of China, respectively. In the post-SIAs phase, the annual incidence reduction was 52.9% (IRR=0.471, *P*=0.119), 61.9% (IRR=0.381, *P*=0.248), 67.5% (IRR=0.325, *P*=0.126), and 47.9% (IRR=0.521, *P*=0.256) in the eastern, northeastern, central, and western regions of China.

DISCUSSION

Our analysis revealed a significant increase in measles incidence prior to the introduction of the MV. Following MV implementation, we observed substantial reductions in both short-term and longer-term incidence rates resulting from EPI implementation and the conduct of measles SIAs. The average annual incidence decreased from 615 cases per 100,000 individuals in the pre-vaccine stage to 1.62 cases per 100,000 individuals in the post-SIAs stage. Consequently, the past 70 years have seen remarkable progress in measles control and prevention efforts across China.

Consistent with previous research (*3*,*8*), our study demonstrated epidemic peaks occurring every 3 to 5 years during the pre-vaccine and early pre-EPI stages when measles was a prevalent childhood disease. Following the introduction of the vaccine and increased coverage, these peaks were no longer evident, suggesting that vaccination altered the temporal dynamics of measles.

The spatial distribution of measles incidence exhibited variation across different stages. In the pre-vaccine stage, the highest incidence PLADs were predominantly located in the northeastern and southern regions of China. This shifted to southern China in the pre-EPI stage, to southwestern China during the EPI stage, and finally to southeastern China in the post-SIAs stage. These fluctuations may be attributed to unequal increases in vaccine coverage rates across various PLADs at distinct stages (*9*). Additionally, differences in the sensitivity of measles surveillance could have contributed to the observed variation in the spatial distribution of incidence (*10*).

Through separate ITS analyses in China and its four economic regions, we demonstrated the significant impact of three primary interventions on measles control and prevention at both national and subnational levels. In China, the most substantial change in trend (54.6% per year, *P*=0.132) occurred following the implementation of SIAs, followed by annual declines of 16.0% (*P*=0.002) after EPI introduction in 1978, and 13.9% (*P*<0.001) after vaccine introduction in 1965. The SIAs contributed more to the changes in measles incidence trends compared to vaccine introduction and EPI implementation. This finding may be attributed to the higher baseline MV coverage before the SIAs relative to MV coverage before the other two interventions, as the SIAs were the final set of measures among the three interventions studied (*11*).

Measles incidence declines following vaccine introduction varied by region in China. The largest decrease was observed in northeastern China (23.2%, *P*<0.0001), followed by eastern (16.5%, *P*<0.0001), western (13.0%, *P*<0.001), and central China (11.7%, *P*=0.001). It is worth noting that northeastern China served as the heavy industrial base of China in the last century (*12*) and received substantial support for health services during this period (*13*). Consequently, the availability and affordability of the measles vaccine were higher in this region when vaccinations required out-of-pocket payments.

Following the implementation of the EPI in 1978, declines in annual measles incidence became more comparable across regions, as program vaccines were offered nationwide at no charge to families (*14*). However, the impact of SIAs on long-term trends was not significant in our study. This finding may be attributed to the already low measles incidence during the post-SIAs stage; the slope could not decrease further when the incidence was near zero (*15*).

We did not observe any significant changes in the level for all three interventions in both China and the four economic regions (with the exception of northeastern China in 1965), indicating a suboptimal short-term decline. Measles control is dependent on high coverage; therefore, the introduction of vaccines and the implementation of EPI would not achieve high coverage within a single year. The SIAs were conducted over several years to reach the entire country. Consequently, a short-term decline was not anticipated in 2009.

We also investigated the associations between per capita GDP and measles incidence. Our findings revealed a weak, positive correlation between China and its four economic regions, which contrasts with another study (*12*). A high GDP might be linked to increased interactions and population mixing, potentially facilitating measles transmission. Nevertheless, these findings should be interpreted cautiously. A more comprehensive evaluation, incorporating various potential influencing factors such as ecological environment, socioeconomic status, advancements in medical technology, population mobility, and meteorological factors, is warranted.

Our quasi-experimental study has several limitations. Although ITS analysis for public health intervention evaluation is a robust technique, we were only able to analyze the annual incidence of reported measles. The results of our ITS analysis rely on the quality and completeness of reporting. Given that all data originated from a passive surveillance system and the data collection transitioned from paper to digital reports during the study period, the sensitivity of the data, as well as the case definition, diagnostic, and reporting standards, varied across the four stages. Due to the inherent properties of ITS analysis, it was challenging to evaluate trend changes when the incidence reached very low levels, such as during the post-SIAs stage. Lastly, the incidence of respiratory disease may be influenced by numerous factors. We only included GDP per capita as a covariate, owing to data availability limitations.

Conflicts of interest: The authors declare no competing interests.

doi: 10.46234/ccdcw2023.073

[#] Corresponding author: Huaqing Wang, wanghg@chinacdc.cn.

[1] National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: April 03, 2023; Accepted: April 25, 2023

REFERENCES

1. Moss WJ. Measles. Lancet 2017;390(10111):2490 – 502. http://dx.doi.org/10.1016/S0140-6736(17)31463-0.
2. Keja K, Chan C, Hayden G, Henderson RH. Expanded programme on immunization. World Health Stat Q 1988;41(2):59-63. https://pubmed.ncbi.nlm.nih.gov/3176515/.
3. Li J, Lu L, Pang XH, Sun MP, Ma R, Liu DL, et al. A 60-year review on the changing epidemiology of measles in capital Beijing, China, 1951-2011. BMC Public Health 2013;13:986. http://dx.doi.org/10.1186/1471-2458-13-986.
4. Wang ZF, Chen YP, Pan JR. Trends of acute hepatitis B notification rates in eastern China from 2005 to 2013. PLoS One 2014;9(12):e114645. http://dx.doi.org/10.1371/journal.pone.0114645.
5. Lei M, Wang K, Li J, Zhang Y, Wei XM, Qi LF, et al. Phylogenetic and epidemiological analysis of measles viruses in Shenzhen, China from January 2015 to July 2019. Med Sci Monit 2019;25:9245 – 54. http://dx.doi.org/10.12659/MSM.920614.
6. Ma C, Hao LX, Zhang Y, Su QR, Rodewald L, An ZJ, et al. Monitoring progress towards the elimination of measles in China: an analysis of measles surveillance data. Bull World Health Organ 2014;92(5):340 – 7. http://dx.doi.org/10.2471/BLT.13.130195.
7. Shen T, Hu RP, Hu PL, Tao Z. Decoupling between economic growth and carbon emissions: based on four major regions in China. Int J Environ Res Public Health 2023;20(2):1496. http://dx.doi.org/10.3390/IJERPH20021496.
8. Li X, Kang D, Zhang Y, Wei G, Liu W, Fang L, et al. Epidemic trend of measles in Shandong Province, China, 1963-2005. Public Health 2012;126(12):1017 – 23. http://dx.doi.org/10.1016/j.puhe.2012.07.011.
9. Pan JH, Wang YS, Cao LS, Wang Y, Zhao Q, Tang SL, et al. Impact of immunization programs on 11 childhood vaccine-preventable diseases in China: 1950-2018. Innovation 2021;2(2):100113. http://dx.doi.org/10.1016/J.XINN.2021.100113.
10. Du M, Wang RT, Yuan J, Lv X, Yan WX, Liu Q, et al. Trends and disparities in 44 national notifiable infectious diseases in China: an analysis of national surveillance data from 2010 to 2019. J Med Virol 2023;95(1):e28353. http://dx.doi.org/10.1002/JMV.28353.
11. Yu WZ, Lee LA, Liu YM, Scherpbier RW, Wen N, Zhang GM, et al. Vaccine-preventable disease control in the People's Republic of China: 1949-2016. Vaccine 2018;36(52):8131 – 7. http://dx.doi.org/10.1016/j.vaccine.2018.10.005.
12. Shi TS, Meng L, Li DH, Jin N, Zhao XK, Zhang XS, et al. Effect of different vaccine strategies for the control of Japanese encephalitis in mainland China from 1961 to 2020: a quantitative analysis. Vaccine 2022;40(43):6243 – 54. http://dx.doi.org/10.1016/j.vaccine.2022.09.030.
13. Chen WW, Zhang SC, Tong QS, Zhang XL, Zhao HM, Ma SQ, et al. Regional characteristics and causes of haze events in northeast China. Chin Geogr Sci 2018;28(5):836 – 50. http://dx.doi.org/10.1007/s11769-018-0965-3.
14. Centers for Disease Control and Prevention. National poliomyelitis immunization days--People's Republic of China, 1993. MMWR Morb Mortal Wkly Rep 1993;42(43):837-9. https://pubmed.ncbi.nlm.nih.gov/8413173/.
15. Bernal JL, Cummins S, Gasparrini A. Corrigendum to: interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol 2020;49(4):1414. http://dx.doi.org/10.1093/ije/dyaa118.

Indexed by Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), PubMed Central (PMC), Scopus, Chinese Scientific and Technical Papers and Citations, and Chinese Science Citation Database (CSCD)

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 5 No. 17 Apr. 28, 2023

Responsible Authority
National Health Commission of the People's Republic of China

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071
CN 10-1629/R1