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Cover Photo: Staff from the Base of Plague and Brucellosis Control and Prevention, China CDC, carrying out surveillance in a plague focus in Songliao Plain, May 2021.

Preplanned Studies

Plague Risk Assessment — China, 2022

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Summary

What is already known about this topic?

China has the largest and most complex natural reservoir of plague in the world. Since the 1980s, our country standardized animal plague surveillance and accumulated a substantial amount of useful epidemiological data. In accordance with the "Criteria for Determining Plague Natural Foci and Plague Epizootics (GB 16883–1997)," Ya Dong, Xizang (Tibet) was identified as a new plague focus in 2021 (*Marmota himalayana* plague).

What is added by this report?

Based on plague epidemiology in the past 20 years, we identify high-risk areas in 2022 to provide scientific evidence supporting plague prevention and control policy in China.

What are the implications for public health practice?

To avoid the spread of plague to humans, we recommend strengthening animal plague monitoring in high-risk and adjacent areas and timely investigation and response to animal plague epidemics. Early detection, early reporting, early diagnosis, early isolation, and early treatment of human plague helps prevent spread and long-distance transmission of plague.

Plague is an acute and severe infectious disease that is usually found in rodents but can spread to humans and seriously impact health and socio-economic development (*1*). By the end of 2021, there were 12 types of natural plague foci in the mainland of China, located in 322 county-level divisions of 19 provincial-level administrative divisions (PLADs), covering a total of 1,587,666.67 square kilometers. In 2021, one non-fatal case of human plague occurred in China.

Primary level prevention measures, including active surveillance and periodic epizootic plague risk assessments, are known effective methods to prevent the spread of plague from animals to humans. Based on the epidemiological situation of plague in the past 20 years in China, we identify high-risk areas in 2022 to provide support for domestic plague prevention and control policy.

We used risk matrix and Borda count methods to conduct a risk assessment of plague foci in China based on the frequency of human plague epidemics and plague epizootics and other relevant factors — plague foci, etiology, transmission characteristics, and hygiene practices (*2–3*). The data used in our analyses are from the "Information System for Plague Prevention and Control" and annual surveillance reports from PLADs.

Plague epizootics or positive indications were found for 5 types of natural plague foci (*Marmota himalayana* in Qinghai-Tibet Plateau, *Meriones unguiculatus* in Inner Mongolia Plateau, *Marmota baibacina-Spermophilus undulatus* in Tianshan Mountains, *Microtus fuscus* in Qinghai-Tibet Plateau, *Rhombomys opimus* in Junggar Basin), located in 33 county-level divisions of 7 PLADs and 1 regiment farm of Xinjiang Production and Construction Corps. Xinjiang Uygur Autonomous Region had 9 country-level foci: Xizang (Tibet) Autonomous Region had 8; Inner Mongolia Autonomous Region had 7; Gansu Province had 5; Sichuan Province had 2; and Qinghai Province and Ningxia Hui Autonomous Region each had 1.

From 2002 to 2021, plague epizootics or positive indications were found for 12 types of natural plague foci in 196 county-level divisions of 16 PLADs. In terms of plague foci, there were 458 occurrences of *Marmota himalayana* plague in 85 counties, 60 occurrences of *Rattus flavipectus* plague in 29 counties, 134 occurrences of *Meriones unguiculatus* plague in 23 counties, 104 occurrences of *Rhombomys opimus* plague in 16 counties, 109 occurrences of *Marmota baibacina-Spermophilus undulatus* plague in 12 counties, 30 occurrences of *Spermophilus dauricus* plague in 12 counties, 20 occurrences of *Apodemus chevrieri-Eothenomys milrtus* plague in 6 counties, 14 occurrences of *Microtus brandti* plague in 4 counties, 15 occurrences of *Marmota sibirica* plague in 3 counties, 7 occurrences of *Marmota caudata* plague in 3 counties, 3 occurrences of *Spermophilus alaschanicus* plague in 2 counties, and 20 occurrences of *Microtus fuscus* in 1 county.

There were 244 occurrences in 49 counties of Xizang (Tibet) Autonomous Region; 234 occurrences in 35 counties of Xinjiang Uygur Autonomous Region; 177 occurrences in 34 counties of Inner Mongolia Autonomous Region; 59 occurrences in 26 counties of Yunnan Province; 80 occurrences in 19 counties of Qinghai Province; 56 occurrences in 10 counties of Sichuan Province; 88 occurrences in 6 counties of Gansu Province; 10 occurrences in 6 counties of Ningxia Hui Autonomous Region; 8 occurrences in 3 counties of Zhejiang Province; 4 occurrences in 2 counties of Guangxi Zhuang Autonomous; 5 occurrences in 1 county of Hebei Province; 4 occurrences in 1 county of Guizhou Province; 1 occurrence in 1 county of Shaanxi Province; and 1 occurrence in 1 county each in Jilin, Liaoning, and Hunan provinces.

In terms of frequency of plague epizootics, 5 counties (2 in Gansu, 2 in Xinjiang, and 1 in Sichuan) experienced plague epizootics every year, 23 counties [7 in Xinjiang, 6 in Xizang (Tibet), 5 in Inner Mongolia, 3 in Gansu, and 2 in Qinghai] experienced plague epizootics between 10 and 19 times during the past 20 years; 55 counties [18 in Xizang (Tibet); 13 in Inner Mongolia; 11 in Xinjiang; 4 in each of Sichuan, Yunnan, and Qinghai; and 1 in Hebei] experienced plague epizootics between 5 and 9 times during the past 20 years; 113 counties experienced plague epizootics in fewer than 5 times during the past 20 years.

Based on the occurrence of human plague and plague epizootics in recent years and a comprehensive analysis of plague foci, etiology, transmission characteristics and other factors, the possibility of human plague in 2022 cannot be ruled out. The high-risk months for 2022 will be July to October, the medium-risk months are May, June and November, and other months are low-risk months.

The relative weights of significant risk factors of plague outbreaks (e.g. frequency, quiescent years of plague epizootics) were scored in consultation with experts (*4*). Risk probability ranking and risk impact ranking of 196 counties that had plague foci in the past 20 years were calculated and their Borda points were tallied [Borda=(196−Risk probability ranking)+(196−risk impact ranking)]. Overall, 30 county-level divisions with the highest risk were identified according to Borda point tallies and in consultation with experts (Table 1).

DISCUSSION

An occurrence of human plague has significant negative impact on an affected population and causes serious damage to normal life in the area (*5*). Strong emergency control measures requiring large amounts of resources are then needed to mitigate negative impact and damage.

Human plague risk assessment is based on several factors, such as plague epizootics characteristics, ground time of host animals, contact between host animals and human beings, and the virulence of *Yersinia pestis*. Risk assessments are sensitive to several related factors. For example, environmental factors of precipitation, temperature, vegetation, and land use indirectly affect the occurrence of human plague by influencing the survival and reproduction of animals and insects (*6*). Social factors, including healthcare and sanitary conditions, living standards, educational level, and religious beliefs and customs contribute to the occurrence and spread of human plague by increasing exposure to infected animals. When there is an outbreak of human plague abroad, the risk in China increases. Illegal hunting of infected animals in plague foci and long-distance transportation of prey increases the risk of human plague in other areas. Patients seeking medical treatment in other cities increases the risk of bringing plague into large and medium-sized cities. There is a risk of transmission from secondary hosts, that is, infection transmitted by contact with an infected host animal during its hibernation period in a plague foci. Natural disasters and large-scale engineering projects can lead to abnormal gathering of host animals, thus increasing the risk of human infection (*7*).

We identified 30 county-level divisions at high risk of human plague. However, unlisted divisions in our analyses are not risk-free but rather have a relatively lower risk. PLADs should take plague prevention and control measures in high-risk counties, cities, districts, and adjacent areas to prevent the spread of plague from animals to humans (*8*). At the beginning of each year, or during plague-prone seasons, PLADs should routinely conduct plague risk assessments and take timely and effective interventions in the plague foci areas based on risk assessment results.

TABLE 1. High-risk counties of human plague in China, 2022.

PLADs	County	Epidemic frequency	Number of quiescent years	Risk probability	Risk impact	Borda points	Rank
Inner Mongolia	Siziwang	15	20	8	8	348	1
Inner Mongolia	Erlianho	16	20	10	36	346	2
Inner Mongolia	Huade	12	20	13	36	343	3
Inner Mongolia	OtogBanner	10	20	15	36	341	4
Yunnan	Menghai	5	19	54	1	337	5
Gansu	Subei	20	20	1	59	332	6
Inner Mongolia	Otog Front Banner	9	20	24	36	332	6
Gansu	Aksay	20	20	2	59	331	8
Gansu	Yumen	19	20	5	59	328	9
Yunnan	Yulong	9	17	35	30	327	10
Gansu	Sunan	18	20	7	59	326	11
Xizang (Tibet)	Linzhou	17	20	9	59	324	12
Qinghai	Wulan	18	19	12	59	321	13
Xizang (Tibet)	Dangxiong	15	20	15	59	318	14
Xizang (Tibet)	Gar	14	19	17	59	316	15
Yunnan	Gucheng	5	19	48	30	314	16
Inner Mongolia	Wuchuan	3	20	43	36	313	17
Xizang (Tibet)	Jiangzi	8	20	22	59	311	18
Sichuan	Batang	9	19	25	59	308	19
Sichuan	Yajiang	5	20	33	59	300	20
Qinghai	Tianjun	6	19	35	59	298	21
Sichuan	Litang	6	19	35	59	298	21
Hebei	Kangbao	5	17	69	36	287	23
Qinghai	Dulan	2	20	61	59	272	24
Qinghai	Qilian	5	16	61	59	272	24
Xizang (Tibet)	Yadong	1	20	61	59	272	24
Yunnan	Jianchuan	1	16	96	30	266	27
Xinjiang	Midong	12	20	14	156	222	28
Xinjiang	Wusu	20	20	3	177	212	29
Xinjiang	Jinghe	20	20	5	177	210	30

Abbreviations: PLADs=provincial-level administrative divisions.

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Preplanned Studies

Willingness of Caregivers to Have Their Children Vaccinated with Pneumococcal Vaccines in the Context of an Innovative Immunization Strategy — Weifang City, Shandong Province, 2021

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Summary

What is already known about this topic?

Pneumococcal diseases (PDs) pose a serious health threat to children. Vaccination is the most cost-effective intervention to prevent PDs, but pneumococcal vaccines coverage among children is low in China.

What is added by this report?

This study investigated the willingness of children's caregivers to have their children vaccinated with pneumococcal vaccines under an innovative policy to offer 1-dose of the 13-valent pneumococcal conjugate vaccines at no charge to families. The research found that 70.51% of caregivers were willing to have their infants receive pneumococcal vaccines and that reducing the cost of vaccines may increase caregivers' willingness.

What are the implications for public health practice?

This is the first evaluation in China of acceptance of pneumococcal vaccines among children under a 1-dose, cost-free policy. The results provide scientific evidence for updating local and national pneumococcal immunization strategies to promote the use of the pneumococcal vaccine.

Pneumococcal diseases (PDs) pose a serious health threat to children (*1*). Vaccination is the most cost-effective intervention to prevent PDs (*2*). However, vaccination coverage of pneumococcal vaccines, which has not been introduced into the National Immunization Program (NIP) in China, is rather low among Chinese children (*3*). The cost of vaccines and the opinions of caregivers toward non-NIP vaccines are important factors that influence vaccination coverage (*4*). Exploring efficient strategies for increasing coverage of non-NIP vaccines are crucial initiative for public health.

To improve pneumococcal vaccination coverage and reduce the burden of PDs, starting in June 2021, the government of Weifang City (directly under the jurisdiction of Shandong province) implemented a policy of providing 1-dose of 13-valent pneumococcal conjugate vaccines (PCV13) at no charge to families for children aged 6 months to 2 years in registered households. Although the free dose does not necessarily have to be the first dose of PCV13, due to the limited financial capacity of the government, the cost of the remaining doses in the series must be borne by caregivers as voluntary vaccination. The Weifang program is the first in the mainland of China for PCV13. Our study investigated caregivers' willingness to vaccinate their children with pneumococcal vaccines under this one-free-dose policy and explored factors associated with acceptance.

There are 3 PCV13 manufacturers with market authorization in China, 2 of which are domestic. PCV13 is normally given in a multi-dose series in a schedule that varies by the child's age at the first dose. For example, 4 doses of PCV13 are recommended for full protection when starting at 3 months of age or younger, but only 1 dose is recommended when starting at 2 years of age or older. To avoid the influence of different immunization schedules for PCV13, we restricted the study population to children eligible for the full four-dose series of PCV13. Because our target population was infants younger than 3 months of age, we recruited caregivers as respondents, excluding those who were unable to determine the child's vaccinations.

The target sample size was determined by the formula, $N = \frac{Z_{1-\alpha/2}^{2}p(1-p)}{d^{2}}$. A previous study showed that the caregivers' willingness to vaccinate children with pneumococcal vaccines was between 37.9% and 89.1% in China (*5*), which is a large range. We conservatively assumed P=50%, the allowable error at 3%, and α =0.05. To allow for attrition, we increased the sample size by 10%, yielding a target sample size of 1,174.

The research team designed the questionnaires after discussing with project members and experts in related fields, and revised them after the pilot investigation. We obtained data on demographics, perceptions of the safety and effectiveness of vaccines, perceptions of the risk and seriousness of pneumonia, whether health workers (HWs) recommended pneumococcal vaccines, and whether caregivers trusted HWs. The questionnaires were administered by trained interviewers using portable Android devices to reduce input errors and missing values. We selected at random 30% of completed questionnaires for review each survey day.

Face-to-face and telephone interviews were conducted. During one working day in a clinic, caregivers who met the inclusion criteria were invited to participate in the interview. If the day's sample size target was not finished, we conducted a telephone survey of the children's parents with consent. Due to the impact of COVID-19, some vaccination clinics were unable to enroll the target sample size. To reach the overall target sample size, we increased survey sites based on the geographical location of each vaccination clinic and the number of children it served.

The study analyzed all data using SAS software (version 9.4, SAS Institute, Inc. Cary, NC, USA). Counts were expressed as n (%), and Chi-square tests and the Wilcoxon rank-sum test were used for comparisons. A multivariable logistic regression model was used to identify factors related to the caregivers' willingness. We chose independent variables using stepwise regression. Statistical tests were two-tailed; P<0.05 was considered significant.

Between July 17 and August 3, 2021, we conducted a survey in 57 vaccination clinics across 12 counties/districts. During this time, 1,195 caregivers were surveyed; 90.79% (1,085/1,195) of the questionnaires were completed and considered valid. Among the valid questionnaires, 72.35% (785/1,085) were face-to-face and the rest were via telephone. We conducted Chi-square analyses comparing caregivers' willingness and demographics by whether the survey was face-to-face or over telephone, and found no statistically significant differences (Supplementary Materials, available in https://weekly.chinacdc.cn/).

Mothers, fathers, and grandparents were 62.58% (679/1,085), 36.31% (394/1,085), and 1.11% (12/1,085) of the participants. The average age of the parents was 31.26±4.88 years old. Among all participants, 70.51% (765/1,085) were willing to have their infants receive pneumococcal vaccines. Factors associated with greater willingness included perception of the importance of vaccination, having an HWs recommendation for vaccination, trust in the vaccine information provided by HWs, awareness of the PCV13 policy in Weifang, and other significant factors (Table 1).

According to Table 2, caregivers who believed that vaccination was important (OR=3.96, 95% CI: 1.92–8.20), who received vaccination recommendations from HWs (OR=2.09, 95% CI: 1.11–3.93), and who trusted vaccine information provided by HWs (OR=1.92, 95% CI: 1.08–3.41) were more likely to have their infants vaccinated.

Table 3 shows factors related to hesitancy or refusal to accept pneumococcal vaccines. The top three factors were being unfamiliar with pneumococcal vaccines, lacking confidence in the effectiveness of pneumococcal vaccines, and worrying about adverse reactions.

DISCUSSION

This study found that 70.51% of caregivers were willing for their children to get pneumococcal vaccines under the one-free-dose policy in Weifang. The acceptance rate for pneumococcal vaccines in our study was lower than the acceptance found in an online survey conducted in 2020 and was higher than the acceptance found in field surveys in Shanghai and Guangzhou (*5*).

We speculated that the relatively higher willingness in Weifang may be related to the fact that caregivers have gained much in-depth health knowledge through various media during the COVID-19 pandemic. Additionally, immunization strategies may change vaccination willingness. Vaccine support from Gavi and other nonprofit organizations has significantly increased the coverage of pneumococcal vaccines in recipient countries (*6*). We also found that the willingness to accept pneumococcal vaccines was associated with the awareness of the one-free-dose policy in Weifang. The pneumococcal vaccination willingness among caregivers who knew about the one-free-dose immunization policy was 1.70 times higher than those who did not know.

Caregivers' perceptions of the risk of pneumonia and the safety and effectiveness of vaccines are important

TABLE 1. Characteristics and pneumococcal vaccination willingness among caregivers in Weifang, Shandong Province, China (n=1,085).

Characteristics	Category	Total (%)	Willing (%)	Unwilling (%)	*P*
Child gender	Male	569 (52.44)	400 (70.30)	169 (29.70)	0.88
	Female	516 (47.56)	365 (70.74)	151 (29.26)	
Family type	Single child family	455 (41.94)	341 (74.95)	114 (25.05)	<0.01
	Multiple child family	630 (58.06)	424 (67.30)	206 (32.70)	
Average annual household income (CNY)	<50,000	194 (17.88)	121 (62.37)	73 (37.63)	<0.01
	50,000–150,000	660 (60.83)	466 (70.61)	194 (29.39)	
	≥150,000	231 (21.29)	178 (77.06)	53 (22.94)	
Relationship between participant and child	Mother	679 (62.58)	480 (70.69)	199 (29.31)	0.95
	Father	394 (36.31)	277 (70.30)	117 (29.70)	
	Grandparent	12 (1.11)	8 (66.67)	4 (33.33)	
Education level	Elementary school or below	15 (1.38)	8 (53.33)	7 (46.67)	<0.01
	Junior high school	242 (22.30)	155 (64.05)	87 (35.95)	
	High school/technical school/vocational school	269 (24.79)	181 (67.29)	88 (32.71)	
	Junior college/bachelor degree	528 (48.66)	396 (75.00)	132 (25.00)	
	Graduate degree	31 (2.87)	25 (80.65)	6 (19.35)	
Participants' medical education background*	Yes	139 (12.81)	103 (74.10)	36 (25.90)	0.32
	No	946 (87.19)	662 (69.98)	284 (30.02)	
Whether the pneumococcal vaccine is the COVID-19 vaccine	Yes or unknown	333 (30.69)	202 (60.66)	131 (39.34)	<0.01
	No	752 (69.31)	563 (74.87)	189 (25.13)	
Perceived importance of vaccination	Yes	1046 (96.41)	751 (71.80)	295 (28.20)	<0.01
	No	39 (3.59)	14 (35.90)	25 (64.10)	
Perceived safety of vaccination	Yes	990 (91.24)	700 (70.71)	290 (29.29)	0.64
	No	95 (8.76)	65 (68.42)	30 (31.58)	
Perceived effectiveness of vaccination	Yes	984 (90.69)	703 (71.44)	281 (28.56)	<0.05
	No	101 (9.31)	62 (61.39)	39 (38.61)	
Perception that pneumonia is serious in children	Serious	1032 (95.12)	740 (71.71)	292 (28.29)	<0.01
	General	42 (3.87)	17 (40.48)	25 (59.52)	
	Light	11 (1.01)	8 (72.73)	3 (27.27)	
Perception that children can suffer from pneumonia	High	597 (55.02)	459 (76.88)	138 (23.12)	<0.01
	General	330 (30.41)	215 (65.15)	115 (34.85)	
	Low	158 (14.57)	91 (57.59)	67 (42.41)	
Awareness of Weifang's one-free-dose policy for PCV13	Yes	203 (18.71)	174 (85.71)	29 (14.29)	<0.01
	No	882 (81.29)	591 (67.01)	291 (32.99)	
HWs recommended pneumococcal vaccines for children	Yes	153 (14.10)	136 (88.89)	17 (11.11)	<0.01
	No	932 (85.90)	629 (67.49)	303 (32.51)	
Trust in the vaccine information provided by HWs	Yes	1024 (94.38)	733 (71.58)	291 (28.42)	<0.01
	No	61 (5.62)	32 (52.46)	29 (47.54)	
Child's siblings received pneumococcal vaccine	Yes	128 (20.32)	121 (94.53)	7 (5.47)	<0.01
	No	502 (79.68)	303 (60.36)	199 (39.64)	

* Medical education background refers to people with medicine-related training, such as medical workers, medical students, and teachers in medical schools.

Abbreviations: PCV13=13-valent pneumococcal conjugate vaccine; HWs=Health workers.

TABLE 2. Logistic regression analyses of caregivers' willingness to accept pneumococcal vaccines for their children, Weifang, Shandong Province, China.

Independent variables	Category	*P*	OR (95% CI)
Perceived importance of vaccination	No	–	Ref
	Yes	<0.01	3.96 (1.92–8.20)
HWs recommended pneumococcal vaccines for children	No	–	Ref
	Yes	<0.05	2.09 (1.11–3.93)
Trust in the vaccine information provided by HWs	No	–	Ref
	Yes	<0.05	1.92 (1.08–3.41)
Awareness of Weifang's one-free-dose policy for PCV13	No	–	Ref
	Yes	<0.05	1.70 (1.01–2.87)
Whether the pneumococcal vaccine is the COVID-19 vaccine	Yes or unknown	–	Ref
	No	<0.01	1.67 (1.23–2.25)
Average annual household income (CNY)	<50,000	–	Ref
	50,000–150,000	0.14	1.31 (0.92–1.87)
	≥150,000	<0.01	1.85 (1.18–2.90)
Perception that children can suffer from pneumonia	High	–	Ref
	General	<0.01	0.60 (0.44–0.83)
	Low	<0.01	0.43 (0.29–0.63)
Perception that pneumonia is serious in children	Serious	–	Ref
	General	<0.01	0.38 (0.19–0.77)
	Light	0.96	1.04 (0.25–4.27)

Note: Thirteen variables were included in the logistic model: type of family, average household income per year, education level of participants, participants' medical education background, whether the pneumococcal vaccine is the COVID-19 vaccine, perceived importance of vaccination, perception that pneumonia is serious in children, perception that children can suffer from pneumonia, awareness of Weifang's one-free-dose policy for PCV13, HWs recommended pneumococcal vaccines for children, trust in the vaccine information provided by HWs, perceived safety of vaccination, and perceived effectiveness of vaccination. Eight variables were statistically significant.
Abbreviations: PCV13=13-valent pneumococcal conjugate vaccine; HWs=Health workers.

TABLE 3. Reasons for hesitation or refusal to accept pneumococcal vaccines (n=320).

Reasons	Total	Proportion (%)
Unfamiliar with pneumococcal vaccines	244	76.25
Lack of confidence in the effectiveness of the PCV13	91	28.44
Worried about adverse reactions from vaccines	85	26.56
My child is healthy, and he/she does not need the vaccines	44	13.75
Pneumococcal vaccines are expensive	32	10.00
Too busy to go to the clinic or live too far from the clinic	13	4.06
Children have allergies or contraindications to vaccines	7	2.19
Do not know where to get the PCV13	1	0.31
Other reasons (participants may give detailed reasons)	12	3.75

Note: Reasons are not mutually exclusive. Each participant can select up to three answers.
Abbreviations: PCV13=13-valent pneumococcal conjugate vaccine; HWs=Health workers.

factors related to pneumococcal vaccination willingness (*7*). Hon et al. surveyed 3,485 parents in Hong Kong, China and found that pneumococcal vaccination of children was related to the awareness of parents regarding the seriousness of PDs and the belief that PCV can effectively prevent PDs (*8*). In our study, 95.12% of the participants perceived pneumonia as a serious threat to children's health, and most of the participants trusted in the safety and effectiveness of vaccines. Notably, many participants lacked knowledge about pneumococcal vaccines. For example, 30.69% of the participants misidentified the pneumococcal vaccine as the COVID-19 vaccine. In addition, the primary reason for hesitancy or refusal to vaccinate against PDs was being unfamiliar with pneumococcal vaccines. Health education for caregivers is extremely important for the public health sector.

Vaccine recommendations from HWs significantly increase acceptance of vaccines and improve vaccination willingness among the public (*9*). The opinions and attitudes of HWs toward vaccines are likely to influence their vaccine recommendation behavior (*10*). In our survey, 94.38% of the participants reported that they trusted the vaccine information provided by HWs, and the willingness of these participants was significantly higher than those who did not trust the vaccine information provided by HWs. Unfortunately, a minority of the participants had received a pneumococcal recommendation from HWs to vaccinate against PDs. To minimize the incidence of PDs in high-risk groups (such as infants and the elderly), HWs should be encouraged to take positive action to improve pneumococcal vaccination coverage.

In summary, reducing the burden of out-of-pocket costs for PCV may increase the willingness of caregivers to have their children vaccinated. Education of caregivers about vaccination should be reinforced, and the importance of HWs promotion of vaccination should be emphasized.

To our knowledge, this is the first study in China to investigate caregivers' willingness to vaccinate their children in the context of an immunization policy that provides one-free-dose of PCV13 per child. The results provide scientific evidence for updating local and national pneumococcal immunization strategies. Our study has limitations. We did not ask participants whether they were willing to have their infants complete the vaccination series if they must bear the cost of the remaining doses, and we did not explore measures to promote completion of the full-course, four-dose PCV13 series. These limitations will be addressed in future research.

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SUPPLEMENTARY MATERIAL

Sampling Method

Weifang City, located on the east coast of China, has a total of 12 counties with 195 vaccination clinics. We ranked the vaccination clinics in each county according to the number of births in the clinic service area in 2020. Through systematic sampling, each county selected three vaccination clinics. The sample size of each vaccination clinic is distributed proportionally, according to the number of births (Supplementary Table S1).

SUPPLEMENTARY TABLE S1. The Estimation of sample size in vaccination clinics.

County	Vaccination clinics	The number of births in 2020	Proportion (%)	Sample size
Fangzi	Clinic 1	1,140	71.65	37
	Clinic 2	265	16.66	9
	Clinic 3	186	11.69	6
	Subtotal	1,591		52
Gaomi	Clinic 1	512	55.05	69
	Clinic 2	278	29.89	37
	Clinic 3	140	15.06	19
	Subtotal	930		125
Hanting	Clinic 1	452	61.92	41
	Clinic 2	168	23.01	15
	Clinic 3	110	15.07	10
	Subtotal	730		66
Kuiwen	Clinic 1	1,425	43.67	70
	Clinic 2	1,088	33.34	54
	Clinic 3	750	22.99	37
	Subtotal	3,263		161
Linqu	Clinic 1	471	47.62	47
	Clinic 2	307	31.04	30
	Clinic 3	211	21.34	21
	Subtotal	989		98
Qingzhou	Clinic 1	346	49.08	52
	Clinic 2	216	30.64	32
	Clinic 3	143	20.28	21
	Subtotal	705		105
Shouguang	Clinic 1	1,299	67.41	107
	Clinic 2	391	20.29	32
	Clinic 3	237	12.30	19
	Subtotal	1,927		158
Weicheng	Clinic 1	607	60.58	57
	Clinic 2	339	33.83	32
	Clinic 3	56	5.59	5
	Subtotal	1,002		94

Continued

County	Vaccination clinics	The number of births in 2020	Proportion (%)	Sample size
Zhucheng	Clinic 1	1,067	81.64	89
	Clinic 2	178	13.62	15
	Clinic 3	62	4.74	5
	Subtotal	1,307		109
Anqiu	Clinic 1	1,957	87.60	84
	Clinic 2	191	8.55	8
	Clinic 3	86	3.85	4
	Subtotal	2,234		96
Changle	Clinic 1	257	58.01	38
	Clinic 2	124	27.99	18
	Clinic 3	62	14.00	9
	Subtotal	443		65
Changyi	Clinic 1	972	76.12	34
	Clinic 2	201	15.74	7
	Clinic 3	104	8.14	4
	Subtotal	1,277		45
Total		16,398		1,174

Survey Method

Face-to-face and telephone interviews were conducted. Face-to-face interviews used two recruitment methods. First, we have surveyed caregivers who brought infants younger than three months of age to the clinics for vaccination. Caregivers could participate in the survey whether they came to the vaccination clinic to receive PCV or another vaccine. These caregivers did not know our survey before they came to the vaccination clinics. The duration of this method in each vaccination clinic was one working day. We define this as the first means in the face-to-face survey (Mean 1).

When the first means was unable to reach the target sample size, we called caregivers who belonged to the vaccination clinic service area and had not accepted the survey. We invited them to come to the vaccination clinic to join in our survey. This is the second means used in the face-to-face survey (Mean 2).

If the called party refused our invitation, investigators would ask them whether they were willing to accept the telephone survey (Mean 3).

To explore whether data from the different survey means could be mixed, we selected two counties with more than 100 questionnaires; the number of different means questionnaires were relatively evenly distributed for analysis (Supplementary Table S2). We chose two districts, namely Shouguang and Linqu (Supplementary Table S3). We conducted a Chi-square analysis on the vaccination willingness and the participants' demographic characteristics (Supplementary Table S4).

SUPPLEMENTARY TABLE S2. Sample size of different survey means in each county of Weifang (n=1,085).

County	Face-to-face		Telephone	Total
	Mean 1	Mean 2	Mean 3	
Fangzi	6	39	4	49
Gaomi	31	46	17	94
Hanting	18	45	2	65
Kuiwen	68	31	85	184
Linqu	46	37	43	126
Qingzhou	6	69	26	101
Shouguang	70	90	65	225
Weicheng	6	7	10	23
Zhucheng	32	20	32	84
Anqiu	47	8	4	59
Changle	15	20	12	47
Changyi	1	27	0	28
Total	346	439	300	1,085

SUPPLEMENTARY TABLE S3. Pneumococcal vaccination willingness among caregivers with different survey means in Shouguang and Linqu (n=351).

Survey methods		Total (%)	Willing (%)	Unwilling (%)	*P*
Face-to-face	Mean 1	116 (33.05)	69 (59.48)	47 (40.52)	0.493
	Mean 2	127 (36.18)	84 (66.14)	43 (33.86)	
Telephone	Mean 3	108 (30.77)	71 (65.74)	37 (34.26)	

SUPPLEMENTARY TABLE S4. Characteristics of participants in different survey means (n=351).

Characteristic	Face-to-face		Telephone	*P*
	Mean 1	Mean 2	Mean 3	
Child gender				
Male	58	70	56	0.720
Female	58	57	52	
Family type				
Single child family	41	51	57	0.025
Multiple child family	75	76	51	
Education level				
Elementary school or below	0	3	0	0.143
Junior high school	31	24	22	
High school/technical school/vocational school	32	33	23	
Junior college/bachelor degree	52	66	59	
Graduate degree	1	1	4	
Average annual household income (CNY)				
<50,000	22	27	19	0.667
50,000–150,000	68	77	67	
≥150,000	26	23	22	

Preplanned Studies

The Health Demands of Designated Drivers — Four Cities, China, 2019

Meng Zhang[1]; Qiqi Wang[1]; Hongyan Yao[1]; Xiao Qi[1]; Shicheng Yu[1]; Jianjun Liu[2,#]

Summary

What is already known about this topic?

The health status of designated drivers is largely associated with road safety, which is a major public health issue. However, few studies have focused on the health demands of designated drivers.

What is added by this report?

This study investigated the health consciousness, first aid knowledge learning, acceptable ways to acquire health knowledge, and willingness to have physical examinations for designated drivers to provide suggestions for improving their health status.

What are the implications for public health practice?

The industry and platform should provide scientific and reasonable guidance on healthy lifestyles for designated drivers and implement physical examinations to monitor their health status.

As an emerging profession, the number of hired designated drivers is growing quickly in China. Designated driver services play an important role in reducing driving under the influence and road traffic fatalities (*1*). This kind of job is characterized by mobility, long hours, and high pressure, and therefore, designated drivers face a great deal of occupational health risks. This study aimed to investigate the health demands of designated drivers and provided targeted suggestions for improving their health. The survey was conducted from July to August 2019 in Beijing and Tianjin municipalities as well as Hangzhou and Zunyi cities, in which an electronic questionnaire was administrated to hired designated drivers who participated in physical examinations. A total of 327 designated drivers completed the questionnaire. The results showed that the percentage of drivers who had ever received a physical examination was low. The willingness of participants to have a medical examination decreased with an increase in the proportion of their own expenditure. Mobile phones, doctors/nurses, and TV/radio were the top three sources of health information for designated drivers. This study suggested that the platforms serving designated drivers should provide scientific and reasonable guidance on healthy lifestyles through the app and organize physical examinations for designated drivers to monitor their health status.

This survey was carried out using an electronic questionnaire from July to August 2019. Participants were recruited from designated drivers who participated in physical examinations organized by a designated driver service platform in Beijing, Tianjin, Hangzhou, and Zunyi. A total of 390 designated drivers participated in the questionnaire survey, and a total of 327 questionnaires were collected with a response rate of 83.85%. Of those, 98 subjects were from Beijing, 71 from Tianjin, 87 from Hangzhou, and 71 from Zunyi. An online survey tool of “Wenjuanxing” was employed to make the questionnaires, collect data, and store data. The contents of the questionnaire included general information (age, gender, income, insurance, education level, and daily working time), health status (sleep time, sleep problems, chronic disease, and driving fatigue), health-related behaviors (smoking, drinking, exercise, and fruit/pork/vegetable intake), and health demands (willingness to learn about the health knowledge and to get physical examinations). All the participants provided informed consent.

SAS (version 9.4, SAS Institute, North Carolina, the United States) was used to conduct all analyses. Data of working years, daily working time, and self-pay ratio were not normally distributed; therefore, these variables were presented by median and interquartile range, and the statistical inference was calculated using the Wilcoxon rank-sum test. The categorical data were described by constituent ratio, and chi-squared tests or Fisher’s exact probability test were employed to examine the difference between the two groups. A *P*-value of <0.05 was considered to be statistically significant.

Among the 327 designated drivers, 268 participants were full-time and 59 participants were part-time. A total of 82.87% of participants were under 45 years old, and 98.47% of them were male. The educational levels of designated drivers were ranged from less than or equal to junior high school to college, with a significant difference between full- and part-time drivers (*P*<0.05). Overall, 32.72% of participants did not have any type of medical insurance. The median of working years was 2 years, with no difference between the two working types (*P*>0.05). The median daily working time was 9 hours for full-time drivers and 7 hours for part-time drivers, with significant differences between the two (*P*<0.05). Results are shown in Table 1.

Overall, 93.27% of participants actively learned about health information, with no difference between the 2 working types (*P*>0.05); 66.67% of the participants had received physical examinations previously, 33.33% never received a physical examination, and the difference between the two working types was statistically significant (*P*<0.05). Under the following payment conditions for physical examinations, including free of charge, partially funded, and fully self-pay, 99.39%, 79.51%, and 41.90% of designated drivers, respectively, were willing to have physical examinations. The median proportion of willingness to pay was 45.5% for full-time drivers and 50% for part-time drivers, with no difference between the two (*P*>0.05).

The percentage of learning first aid knowledge among the respondents was low, 40.98% of the drivers had not learned about it. As for the view of carrying simple emergency medical supplies when working, 74.62% of the participants thought that they should carry, 7.64% of them did not think so, and 17.74% of them did not care about it. There was no significant difference between full-time and part-time drivers in terms of having first aid knowledge and willingness on carrying emergency medical supplies (*P*>0.05). The results are presented in Table 2.

Overall, 63.00%, 51.68%, and 47.09% of designated drivers obtained relevant health knowledge through mobile phones, doctors/nurses, and TV/radio, respectively. The other ways of accessing information were through newspapers/books, family, colleagues/friends, computers, etc. A total of 72.17% of participants agreed that mobile apps were the most acceptable way for participants to acquire health knowledge. With respect to health knowledge manuals and health knowledge lectures, the proportions of agreement were 13.15% and 13.15%. These numbers are illustrated in Figure 1 and Figure 2.

TABLE 1. Demographic and occupational characteristics of designated drivers by working types in China, 2019 [n (%)].

Variables	Full-time	Part-time	Total	*P*-value
Total	268	59	327	–
Age (years)				
<35	105 (39.18)	25 (42.37)	130 (39.75)	
35–45	112 (41.79)	29 (49.15)	141 (43.12)	0.144*
>45	51 (19.03)	5 (8.47)	56 (17.13)	
Gender				
Male	264 (98.51)	58 (98.31)	322 (98.47)	0.901†
Female	4 (1.49)	1 (1.69)	5 (1.53)	
Educational level				
Junior high school graduate	106 (39.55)	15 (25.42)	121 (37.00)	
Senior high school graduate	138 (51.49)	33 (55.93)	171 (52.30)	0.030*
College graduate	24 (8.96)	11 (18.64)	35 (10.70)	
Medical insurance				
Yes	177 (66.04)	43 (72.88)	220 (67.28)	0.311
No	91 (33.96)	16 (27.12)	107 (32.72)	
Working years	2.00 (1.00, 3.00)§	2.00 (1.00, 3.00)§	2.00 (1.00, 3.00)§	0.991
Daily working time (hours)	9.00 (8.00, 10.00)§	7.00 (5.00, 8.00)§	9.00 (8.00, 10.00)§	<0.001

* χ^2 test;
† Fisher's exact probability test;
§ Median and inter quartile range.

TABLE 2. Health demand of designated drivers in China, 2019 [n (%)].

Variables	Full-time	Part-time	Total	*P*-value
Total	268	59	327	–
Do you learn about health information actively?				
Yes	251 (93.66)	54 (91.53)	305 (93.27)	0.567*
No	17 (6.34)	5 (8.47)	22 (6.73)	
Have you ever had a physical examination?				
Yes	172 (64.18)	46 (77.97)	218 (66.67)	0.042*
No	96 (35.82)	13 (22.03)	109 (33.33)	
Do you want to have a physical examination?				
Free, yes	267 (99.63)	58 (98.31)	325 (99.39)	0.358†
Free, no	1 (0.37)	1 (1.69)	2 (0.61)	
Partially self-pay, yes	214 (79.85)	46 (77.97)	260 (79.51)	0.884*
Partially self-pay, no	54 (20.15)	13 (22.03)	67 (20.49)	
Fully self-pay, yes	113 (42.16)	24 (40.68)	137 (41.90)	0.949*
Fully self-pay, no	155 (57.84)	35 (59.32)	190 (58.10)	
If you accept partially self-pay, what proportion are you willing to pay?	45.50 (20.00, 80.25)§	50.00 (20.00, 64.50)§	46.00 (20.00, 80.00)§	0.753
Have you ever learned first aid knowledge?				
Yes	159 (59.33)	34 (57.63)	193 (59.02)	0.810*
No	109 (40.67)	25 (42.37)	134 (40.98)	
Do you want to carry simple emergency medical supplies when working?				
Yes	203 (75.75)	41 (69.49)	244 (74.62)	0.586*
No	20 (7.46)	5 (8.47)	25 (7.64)	
I don't care	45 (16.79)	13 (22.03)	58 (17.74)	

* χ^2 test;
† Fisher's exact probability test;
§ Median and inter quartile range.

DISCUSSION

The results of this study showed that designated drivers had some health consciousness, while they had insufficient knowledge regarding first aid. Designated drivers work in a complex environment during nights, in which they face threats such as road traffic accidents and sudden illnesses. Learning first aid knowledge could help them to avoid risk factors in a reasonable and timely way, which may save their lives and others when necessary (*2*). The study found that designated drivers obtained health knowledge from a variety of sources, but could not identify the authority of the information due to the lack of professional health knowledge. Therefore, it is necessary to provide specific health knowledge for designated drivers in appropriate ways. The survey found that 72.17% of participants hope to receive relevant health knowledge through mobile apps. As designated drivers take orders through the mobile app platforms and their working time and place are unfixed, designated driver service platforms could provide scientific guidance on healthy lifestyles through the mobile apps to enhance the health awareness of designated drivers.

The results indicated that the physical examination percentage of designated drivers was low and with the increase in the proportion of their own expenses, the willingness of the participants to have a medical examination decreased. The results were similar to the survey of the willingness of rural residents to have physical examinations (*3*). The possible reasons include not realizing the importance of regular physical examinations and worrying about the high cost of physical examinations. Given this, the designated driver platform can organize physical examinations for designated drivers to monitor their health status. Medical insurance plays an important role in reducing the economic burden of diseases. In this survey, 32.72% of respondents did not have medical insurance, implying that designated drivers face a

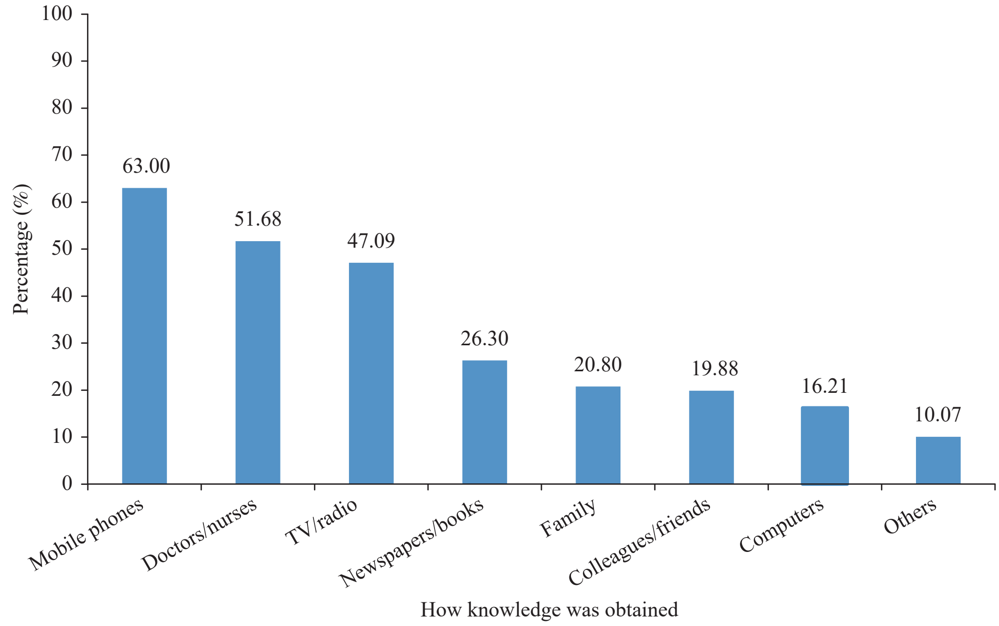

FIGURE 1. Ways for designated drivers to obtain health knowledge in China, 2019.
Note: Participants could select multiple answers.

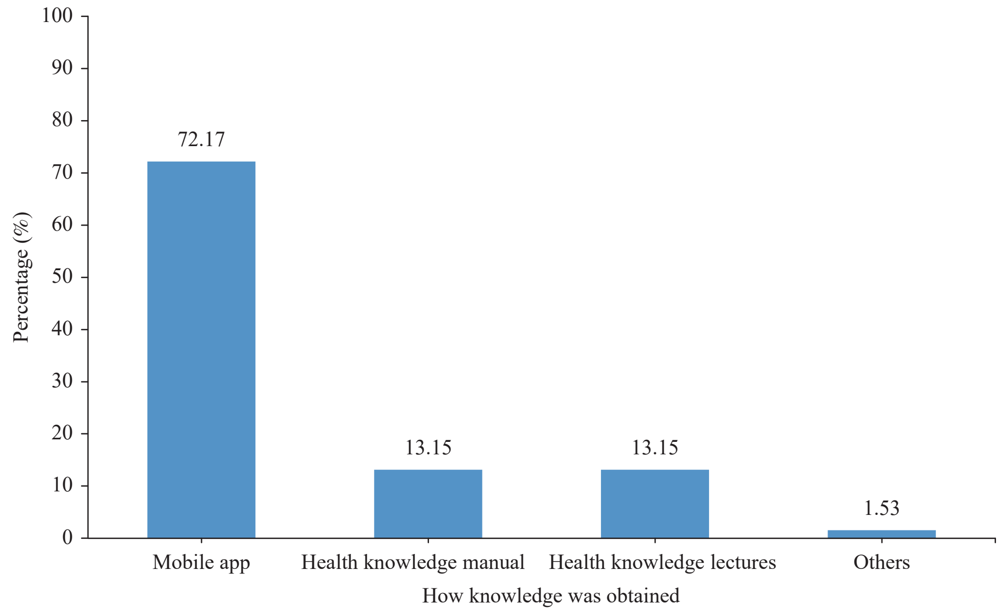

FIGURE 2. Acceptable ways for designated drivers to acquire health knowledge in China, 2019.
Note: Participants could only select single answers.

higher burden of disease. The government and industry should pay more attention to the medical insurance participation of designated drivers, and the platform could provide economic support for designated drivers to buy medical insurance (*4*).

Previous studies on designated drivers mainly focused on the legal disputes and the role they played in reducing driving under the influence (*5–8*), and few studies focused on the health status and health demands of designated drivers. This study investigated the health demand of the designated drivers to provide suggestions for improving their health status.

The study was subject to some limitations. Only the primary health needs of designated drivers were investigated and the sample size was relatively small due to limited funding and time. A purposive sampling method was used in the survey, which may have some bias on the outcome. In the following research, the sample size and survey sites should be further expanded and other health demand of designated drivers should be taken into consideration as well.

In conclusion, the health awareness of designated drivers was insufficient. Moreover, the health status of designated drivers could aggravate the safety of driver, customer, and other passengers, and their safety and health demand should be highlighted. The industry and platform should plan health education programs for designated drivers to improve their health and road safety.

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Preplanned Studies

Trends in Mortality of Low Birth Weight Infants — China, 2004–2019

Li Ma[1]; Xudong Li[1,#]; Miaomiao Wang[1]; Dongru Cao[2,#]; Qi Yan[3,#]

Summary

What is already known about this topic?

Low birth weight (LBW) significantly affects the health of children during the perinatal period, neonatal period, and infancy, and is an important risk factor for neonatal death.

What is added by this report?

The mortality rate of low birth weight infants(LBWI) decreased from 2004 to 2019 in China, while the proportion of overall infant deaths due to LBW increased.

What are the implications for public health practices?

A key way to reduce child mortality and improve children's health is to reduce the occurrence of LBW and associated mortality.

Low-birth-weight infants (LBWI) are newborns weighing less than 2,500 grams at birth (*1*). Low birth weight (LBW) significantly affects perinatal, neonatal, and infantile health (*2*) and is an important risk factor for neonatal death. LBW is associated with intellectual disability, obesity, diabetes, other metabolic diseases (*3*), and an increased risk of chronic diseases in the elderly (*4*).

This research used publicly available national mortality surveillance data to analyze the epidemiological characteristics of LBWI deaths in China from 2004 to 2019. We used joinpoint regression to estimate trends in death by gender, urban or rural residency, and region.

The study found that while the mortality rate of LBWI decreased between 2004 to 2019, the proportion of overall infant deaths due to LBW increased. LBW therefore continues to threaten the life and health of Chinese infants.

Systematic prevention of LBW during the pre-marital period, pre-pregnancy period, and pregnancy should be improved. It is necessary to strengthen professional neonatal healthcare specialties and improve the treatment of LBWI.

Data for this study came from the "Data set of national mortality surveillance 2004–2019". This monitoring system uses a multistage stratified cluster sampling technique. From 2004 to 2012, the monitoring system covered 161 monitoring points in 31 provincial-level administrative divisions (PLADs); the population monitored exceeded 77 million, accounting for 6% of the population of China. From 2013 to 2019, the number of monitoring points reporting deaths increased to 605, with a monitored population of more than 300 million, accounting for 24% of the national population.

We used Excel 2019 (Microsoft Office 2019, Microsoft Corporation, Redmond, USA) to input and sort data, calculate mortality rates, and determine the proportion of infant deaths due to LBW. The Joinpoint Regression Program (version 4.9.0.0; Information Management Services, Inc; Calverton, MD, USA) was used for statistical analysis. Joinpoint regression models were fit using a weighted least squares method and were used to estimate trends of LBWI mortality rate and the proportion of infant deaths due to LBW. The permutation test was used to determine statistically significant joinpoints. There were 16 data points in this study. Consistent with the model's requirements, the maximum number of joinpoints was two. We determined the annual percentage change (APC) in each time period and the average annual percentage change (AAPC) and their 95% confidence intervals (CIs). APC>0 means that the mortality rate or constituent ratio (proportion of deaths attributed to a specific cause) increases year-by-year in a certain time period; APC<0 means decreasing year-by-year. If there were no joinpoint points, APC=AAPC, indicating that the mortality rate or constituent ratio increased or decreased year-by-year over the whole time period. AAPCs by gender, urban or rural area, and region were compared, and the AAPC differences and their 95% CIs were calculated. If 95% CIs did not include 0, the AAPC difference was statistically significant (*5*). We used a statistical test level, α =0.05.

Mortality rates, constituent ratios, and trends of LBWI during infancy were calculated by gender, area type, and region. According to the classification method of the National Bureau of Statistics, monitoring points were divided into east, central, and west regions, containing 11, 8, and 12 PLADs, respectively. Counties were in rural areas and districts were in urban areas/cities (*6*). LBW was coded as p05–p07 according to the International Classification of Diseases (ICD-10). The mortality rate of LBWI = number of infant deaths due to LBW / total number of infants × 100,000. The constituent ratio of LBW infant deaths was the percentage of infant deaths due to LBW and was defined as the number of infant deaths due to LBW / total number of infant deaths × 100%.

From 2004 to 2019, the mortality rate of LBWI during infancy decreased from 97.66/100,000 to 26.75/100,000 (Figure 1), with a statistically significant AAPC of –8.5% (95% CI: –11.0% to –5.9%). Mortality rates by gender, urban or rural area, and region all decreased significantly. The rural area mortality rate APC was –13.8% (–17.5% to –9.9%) in 2012–2019, a more rapid decline than the –5.1% (–8.5% to –1.6%) mortality rate APC in 2004–2012 (Table 1). Other than in 2004, the mortality rate of LBWI of boys was consistently higher than that of girls (Figure 1).

From 2004 to 2019, the percent of deaths due to LBW among infants increased from 8.5% to 11.12%, with a statistically significant AAPC of 1.4% (95% CI: 0.0% to 2.7%) (Table 2, Figure 2). In 2019, the percentages of infant deaths due to LBW in the eastern, central, and western regions were 11.87%, 11.35%, and 10.25%, respectively, with the largest increase in the western region, from 6.11% to 10.25% (Figure 2). From 2004 to 2019, the AAPCs of infant deaths due to LBW were 3.0% (95% CI: 1.5% to 4.5%) in the western region, 2.3% (95% CI: –0.1% to 4.8%) in the central region, and –0.1% (95% CI: –1.2% to 0.9%) in the eastern region. There was a statistically significant difference in AAPC between the east and west (P<0.05) (Table 2).

DISCUSSION

LBW is an important cause of infant deaths that threatens the life and health of infants. Based on the analyses of causes of death from 2004 to 2019, we found that mortality rates of LBWI decreased overall, and by gender, urban or rural area, and region. Our findings were similar to another study (*7*), and may be due in part to many special maternal and child health projects for pregnant women and newborns implemented by the government of China. These projects include a neonatal resuscitation project and a rural maternal hospital delivery subsidy that improved maternal and child healthcare and newborn resuscitation practices, leading to a reduction in LBWI mortality.

The infant mortality rate in rural areas decreased faster after 2012 than it did before 2012. This may be related to accelerating implementation of the “China Children’s Development Program (2011–2020)”, which increased funding for maternal and child health in rural and remote areas (*8*) and expanded basic coverage of the new rural cooperative system after 2010 (*9*). The Ministry of Health and three other governmental departments pointed out that beginning in 2012, newborns were automatically eligible for the new rural cooperative medical treatment program (*10*), effectively increasing the accessibility of basic health services for LBWI in rural areas.

The infant mortality rate of boys was higher than that of girls, which was consistent with existing research (*7*). Biological factors were a determining factor of sex differences in infant mortality. According to a study, girls are likely to have an innate survival advantage, leading to a lower infant mortality rate compared to boys (*11*).

The percent of infant deaths due to LBW increased during the study period, indicating that LBW still affects the life and health of Chinese infants. This may be related to a relatively insufficient investment in medical and healthcare for LBWI (*12*), as infant mortality from causes other than LBW declined faster than infant mortality due to LBW. Currently, LBW is the most common cause of infant death in China (*13*). A key to reducing child mortality and improving children’s health is to reduce the mortality of LBWI. From 2004 to 2019, the percent of infant deaths due to LBW increased faster in the western region than in the eastern region, suggesting that the western region should focus on LBW prevention and clinical care improvement in the future.

Our study was subject to at least two limitations. The data were extracted from a publicly available cause of death monitoring data system in China. The monitoring system was integrated and expanded in 2013. There may be omissions in reporting data at various monitoring points, especially the expanded monitoring points, so that the mortality of LBWI may

FIGURE 1. Mortality rates of low-birth-weight infants by (A) gender, (B) urban or rural area, and (C) region in China from 2004 to 2019 (1/100,000).

TABLE 1. Trends in mortality of low-birth-weight infants by gender, urban or rural area, and region in China from 2004 to 2019 (%).

Dimension	Trend 1		Trend 2		Trend 3		AAPC (95% CI)	AAPC difference (95% CI)
	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)		
Total	2004−2013	−4.2 (−7.3 to −1.0)*	2013−2019	−14.6 (−19.7 to −9.3)*			−8.5 (−11.0 to −5.9)*	
Gender								
Boy	2004−2012	−2.0 (−5.2 to 1.3)	2012−2019	−14.2 (−17.6 to −10.6)*			−7.9 (−10.0 to −5.7)*	2.0 (−4.2 to 8.1)
Girl	2004−2010	−10.3 (−15.3 to −5.0)*	2010−2013	4.8 (−25.4 to 47.1)	2013−2019	−16.1 (−20.7 to −11.1)*	−9.9 (−15.5 to −3.9)*	
Area type								
Urban	2004−2014	0.0 (−4.5 to 4.8)	2014−2019	−16.4 (−26.8 to −4.5)*			−5.8 (−10.2 to −1.1)*	3.5 (−1.6 to 8.6)
Rural	2004−2012	−5.1 (−8.5 to −1.6)*	2012−2019	−13.8 (−17.5 to −9.9)*			−9.3 (−11.5 to −7.0)*	
Region								
East	2004−2010	−15.1 (−19.8 to −10.2)*	2010−2013	14.2 (−18.2 to 59.4)	2013−2019	−16.2 (−20.8 to −11.4)*	−10.4 (−15.8 to −4.6)*	−3.8 (−11.2 to 3.7)†
Central	2004−2007	10.8 (−15.0 to 44.5)	2007−2019	−10.6 (−13.3 to −7.7)*			−6.6 (−11.4 to −1.6)*	0.8 (−4.6 to 6.2)§
West	2004−2012	−0.1 (−3.5 to 3.4)	2012−2019	−15.2 (−18.7 to −11.5)*			−7.5 (−9.7 to −5.2)*	−2.9 (−9.0 to 3.1)¶

Abbreviations: APC=annual percentage change; AAPC=average annual percentage change; CI=Confidence interval.
* *P*<0.05.
† the AAPC in the eastern region is compared with that in the central region.
§ the AAPC in the central region is compared with that in the western region.
¶ the AAPC in the eastern region is compared with that in the western region.

TABLE 2. Trends in percentages of infant deaths due to low birth weight (constituent ratios) by gender, urban or rural area, and region in China from 2004 to 2019 (%).

Dimension	Trend 1		Trend 2		AAPC (95% CI)	AAPC difference (95% CI)
	Year	APC (95% CI)	Year	APC (95% CI)		
Total	2004−2012	5.7 (3.7 to 7.8)*	2012−2019	−3.4 (−5.7 to −1.1)*	1.4 (0.0 to 2.7)*	
Gender						
Boy	2004−2012	6.3 (3.8 to 9.0)*	2012−2019	−4.2 (−7.1 to −1.3)*	1.3 (−0.5 to 3.0)	−0.0 (−2.3 to 2.3)
Girl	2004−2013	4.5 (2.7 to 6.4)*	2013−2019	−3.3 (−6.4 to −0.1)*	1.3 (−0.2 to 2.8)	
Area type						
Urban	2004−2012	7.5 (4.3 to 10.8)*	2012−2019	−5.3 (−8.7 to −1.7)*	1.3 (−0.8 to 3.5)	0.2 (−2.5 to 2.9)
Rural	2004−2013	4.6 (2.5 to 6.6)*	2013−2019	−3.9 (−7.3 to −0.3)*	1.1 (−0.6 to 2.8)	
Region						
East	2004−2019	−0.1 (−1.2 to 0.9)			−0.1 (−1.2 to 0.9)	−2.5 (−5.1 to 0.2)†
Central	2004−2008	18.0 (8.2 to 28.6)*	2008−2019	−2.9 (−4.6 to −1.1)*	2.3 (−0.1 to 4.8)	−0.7 (−3.6 to 2.2)§
West	2004−2012	8.4 (6.1 to 10.7)*	2012−2019	−2.8 (−5.3 to −0.3)*	3.0 (1.5 to 4.5)*	−3.1 (−4.9 to −1.3)*¶

Abbreviations: APC=annual change percentage; AAPC=average annual change percentage; CI=confidence interval.
* *P*<0.05.
† the AAPC in the eastern region is compared with that in the central region.
§ the AAPC in the central region is compared with that in the western region.
¶ the AAPC in the eastern region is compared with that in the western region.

be underestimated. We could not obtain individual level data, and therefore could not determine the risk factors of LBW. Further targeted research is needed.

A LBW prevention and control system covering pre-marital and pre-pregnancy periods, pregnancy, and newborn and infant care is recommended to be implemented to reduce the occurrence of LBW and its associated death. Health policies that increase investment in the prevention of LBW and improvement in LBWI healthcare should be promoted, especially in the western region of China. Research should actively explore the etiologies of LBW. The

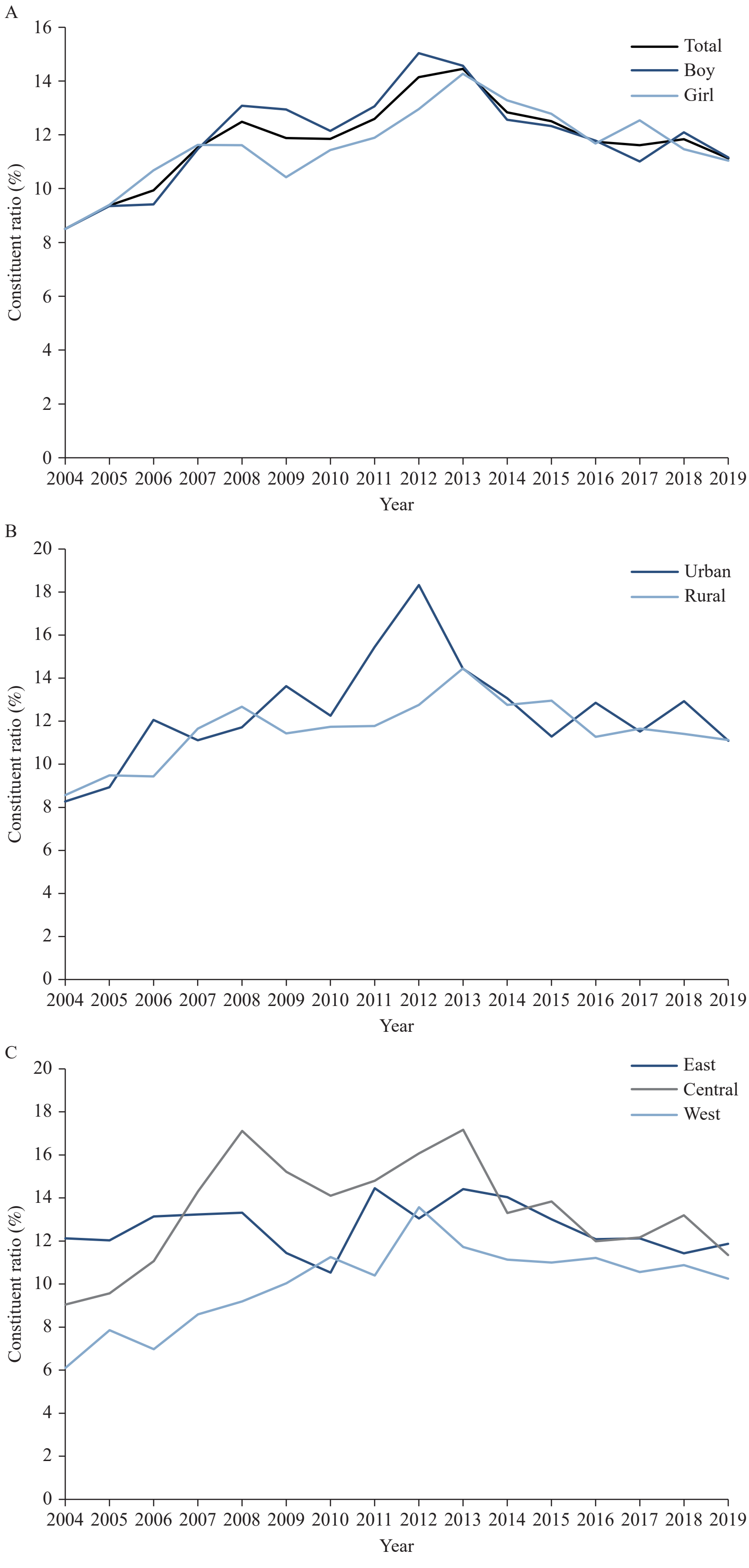

FIGURE 2. Percentages of infant deaths due to low birth weight (constituent ratios) in China from 2004 to 2019 by gender (A), urban or rural area (B), and region (C).

whole society should pay attention to LBWI and take effective measures to improve survival rates and quality of life with the aim of reducing infant mortality and increasing life expectancy.

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Commentary

Realising the Potential of Genomics for *M. tuberculosis*: A Silver Lining to the Pandemic?

Timothy M Walker[1]; Derrick W Crook[2]

The impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic on tuberculosis has been profound. Globally, there were 1.4 million fewer patients receiving tuberculosis treatment in 2020, representing not a fall in the global case load but a failure to serve millions of patients with the disease (*1*–*2*). Morbidity, mortality, and onward transmission are inevitable outcomes of such failure, setting the world back a decade of progress.

Even before the pandemic, there was a severe diagnostic deficit with only 61% of patients with bacteriologically confirmed tuberculosis tested for rifampicin resistance, let alone other drugs relevant to their disease (*3*). Culture-based susceptibility testing is too slow, expensive, and demanding of infrastructure and skills to provide a global solution, not least because the global burden of disease is predominantly found in low- and middle-income countries. Interim molecular solutions have come in cartridge form, but even the widely available MTB/RIF Xpert® and its descendants cannot provide full drug susceptibility testing results that clinicians would optimally want when designing personalised regimens for their patients.

Attention has therefore rightly turned to the potential of genomic solutions. Whole genome sequencing (WGS) has already been adopted as a routine test in a number of high-income settings such as the UK (*4*). It offers not only genome-based drug susceptibility testing for many drugs where we understand the molecular mechanisms of resistance, but also vital information on transmission to inform public health interventions. A remaining disadvantage of this technology is that good quality sequence data generally still requires DNA extraction from culture. Targeted Next Generation Sequencing (tNGS) offers a solution here by amplifying a fraction of the genome directly from the clinical sample and sequencing that to great depth. Clinically useful coverage of the "resistome" is thus generated, but at the cost of losing the potential for identifying genomic relatedness, inferring transmission, and informing public health action focussed on outbreaks.

All molecular assays, whether targeted or not, require interpretation. Whilst there are some canonical mutations conferring resistance to key drugs, there are many more mutations with less supporting data (*5*). The challenge for targeted molecular assays based purely around polymerase chain reaction (PCR) technology has been to identify a small number of high-value mutations restricted to the short target DNA sequence available to the assay. As many mutations outside the target sequence are therefore missed, results need to be interpreted with caution and with regard to the circumstances (*6*). The challenge for sequencing solutions continues to be selecting the infrequent, often more poorly supported, but collectively important mutations to include in an interpretative catalogue of resistance mutations. Catalogue-based approaches to interpretation gained a boost in 2021 after the World Health Organization (WHO) formally endorsed a catalogue of mutations associated with resistance in *M. tuberculosis* in 2021 (*7*). Although this catalogue may not provide more accurate results than other existing lists of mutations, it sets a standard in a field where until now none has been universally worked out.

The challenge with catalogue-based interpretation is that for most anti-tuberculosis drugs a small number of common mutations account for most global resistance, after which a potentially much larger number of rare mutations might collectively explain the remaining 5%–10% of drug resistance. Even in the dataset approaching 40,000 *Mycobacterium tuberculosis* (*M. tuberculosis*) isolates from which the WHO catalogue was generated, many of these mutations were seen too infrequently to confidently grade. Moreover, as some of these mutations may have only an incremental impact on the minimum inhibitory concentration (MIC), the resulting binary phenotype against which they are assessed is so inconsistent that just accumulating ever more data is unlikely to solve the problem. Recognizing that mutations do not all act in isolation but that some combine to have additive, synergistic, or epistatic effects is part of the solution (*8*).

A number of machine learning techniques have been applied to the problem of drug susceptibility testing in *M. tuberculosis*. These avoid the need for a catalogue but do rely on training datasets. They have the potential to exploit features that have no mechanistic role in drug resistance, such as common drug resistance patterns (for example isoniazid resistance being common in the context of rifampicin resistance). The performance of some machine learning models has been excellent, and open-source tools exist for others to implement (*9*–*10*).

Although some machine learning approaches avoid the need for a bioinformatics pipeline, instead of operating more or less directly from the raw sequence data (*11*), a pipeline that maps sequencing reads to a reference genome and filters for variants remains a prerequisite for most of the above approaches. Again, although many different tools are used across academia, health service providers, and industry (*12*), no single global standard exists even though attempts have been made to outline what it may look like (*13*). Moreover, were opinions to coalesce around any one of the existing solutions, none would likely be capable of scaling to process tens of thousands of genomes a day to serve potential global demand. In the absence of a standardised solution, data comparability and data sharing are more burdensome, and progress is stalled.

The SARS-CoV-2 pandemic has led to global interest in genome sequencing as it has been the tool to identify the emergence of new variants and track their transmission locally, regionally, and globally (*14*). Huge efforts have gone into this work in countries around the world, with scientists facing many of the same problems described here: a need for bioinformatics pipelines; a need for global comparability and data sharing; and a need for scalability as samples are sequenced in their many thousands (*15*). The challenge has triggered a large philanthropic donation of cloud computing services and software engineering support from the tech giant ORACLE to the University of Oxford (*16*). The resulting Global Pathogen Analysis System (GPAS) delivered through the University of Oxford has been built in the first instance for an automated “turn-key” analysis service for SARS-CoV-2 genome sequence data agnostic to nucleic acid preparative methods and sequencing technology. Work is already in progress for an automated *M. tuberculosis* bioinformatics solution.

With the support of up to 100 ORACLE and University bioinformaticians and software engineers, GPAS is now a cloud based, industry standard, secure solution that can process around 1 million SARS-CoV-2 genomes per day. The solution provides the user with sovereign control of their own data, but also with the opportunity to share it with the global community (this is not a vehicle for either ORACLE or the University of Oxford to access data for themselves). GPAS will be accessible from anywhere in the world, by anyone with an internet connection, and will be a sequencing platform and able to process both WGS and tNGS data with the ability to accommodate bespoke primer sets. For users who wish to share data, options to upload data to existing global repositories will be offered. Drug susceptibility predictions will be catalogue based, but machine learning approaches are a future possibility. For WGS data, a user-friendly graphical interface will summarize the genomic relatedness to all other samples that have been globally shared to date.

A 10-year agreement with ORACLE provides GPAS free of charge for low- and middle-income countries, with services provided on a non-for-profit basis for high-income countries. GPAS is available for SARS-CoV-2 with a plan to release a parallel solution for *M. tuberculosis* in the third quarter of 2022, and thereafter for other microbial pathogens of importance to public health guided by a user group advising the development group led by the University of Oxford.

Amongst the many losses the fight against tuberculosis has suffered due to the SARS-CoV-2 pandemic, the promise of a secure, industry standard, scalable pipeline solution for *M. tuberculosis* diagnosis and control, accessible by anyone around the world at low or no cost for the global good is a definite silver lining. It opens up the potential for WGS or tNGS technology to be adopted more widely where it has hitherto been held back by the absence of sequencing analytic capability. Many challenges remain, but this unprecedented opportunity for data sharing in the interest of public health may play a role in the solution for some.

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