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Cover Photo: Alveolar Echinococcosis Medical Screening in Tashilhunpo Monastery, Tibet Autonomous Region, China, 2016 (photographer: Gang Xu from Shandong Provincial Medical Team for Tibet Autonomous Region).

Preplanned Studies

Investigation on the Management for Patients with Echinococcosis Treated with Albendazole — Three PLADs, China, 2019

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Summary

What is already known about this topic?

In China, patients with echinococcosis receive complimentary healthcare services, such as medical treatment, diagnostic examinations, and follow-up care. Despite this, no studies have been conducted to assess the quality of patient management to date.

What is added by this report?

This study reviewed the medical records of 899 patients who underwent albendazole treatment across 10 endemic counties. Out of 634 evaluable patient files, the proportion of patients with a ratio of actual follow-up and reexamination times to theoretical follow-up and reexamination times ≥0.8 were both low (21.92% and 23.19%, respectively).

What are the implications for public health practices?

This study identified weaknesses and specific issues in patient management and proposed feasible recommendations to enhance patient file documentation, follow-up, and reexamination.

Echinococcosis is a parasitic disease that poses a significant threat to human health and constitutes a global public health concern (*1*). Medication serves as one of the primary treatments, with albendazole considered the first-line drug (*2–3*). Present evidence indicates that Chinese mainland experiences the highest prevalence of echinococcosis (*4*). To alleviate the economic burden on patients and enhance treatment efficacy, China initiated "The National Project for Echinococcosis Control and Prevention" in 2008, offering free albendazole for patients undergoing medical treatment and mandating regular patient management. This study examined and investigated 899 patient files of individuals receiving and having received albendazole treatment, registered at the CDC across 10 endemic counties in Sichuan, Gansu, and Xinjiang provincial-level administrative divisions (PLADs) in 2019. The objective was to evaluate patient management quality, identify issues, and recommend viable strategies and measures. Among 634 assessable patient files, 71.60% of patients demonstrated a ratio of actual follow-up times to theoretical times below 0.8, and 71.46% of patients exhibited a ratio of actual reexamination times to theoretical times below 0.8. The proportion of individuals with a ratio of actual follow-up times to theoretical times decreased as the duration of albendazole treatment increased (χ^2=229.394, P<0.001), as did reexamination rates (χ^2=195.144, P<0.001). These findings suggest that relevant authorities should focus on improving the quality of patient management.

According to "The National Project for Echinococcosis Control and Prevention," the CDC is responsible for establishing patient files upon initial diagnosis of echinococcosis. These files should include basic personal information, disease characteristics, and the date of initial diagnosis. Furthermore, it is mandated to record all follow-ups and reexaminations during the treatment period. Based on these findings, the therapeutic effects are evaluated, and the medical treatment plan may be adjusted as necessary (*5*). Follow-up assessments are conducted every three months to monitor patient medication adherence and to encourage corresponding reexaminations. Additionally, imaging reexaminations for patients undergoing albendazole treatment are recommended every six months.

In this study, we randomly selected 10 endemic counties in 2019 to examine the treatment of patients with relatively complete patient files. The selected counties included Daofu County, Ganzi County, and Ruoergai County in Sichuan Province; Huining County, Tianzhu County, Zhang County, and Maqu County in Gansu Province; and Gaochang District,

Jimusar County, and Fukang City in Xinjiang Uygur Autonomous Region. We employed cluster sampling to investigate all patients treated with albendazole in these endemic counties. Data were collected from patient files, including administrative entry dates, actual follow-up occurrences, imaging reexaminations, and the duration of albendazole therapy.

The duration of albendazole therapy was calculated in months based on administrative entry dates and investigation dates. Durations of less than 15 days were excluded from the analysis. Due to missing mandatory data (e.g., administrative entry dates), we were unable to calculate the duration of albendazole therapy for some patients. Theoretical follow-up occurrences were computed based on follow-up frequency every three months. To evaluate follow-up, we calculated the ratio of actual to theoretical follow-up occurrences (R_f). The assessment of imaging reexaminations was calculated similarly by determining R_r. Additionally, we calculated the ratio of the actual duration of albendazole therapy to the recommended duration of therapy (R_m).

For statistical analysis, we utilized Epidata (version 3.1, EpiData Association, Odense, Denmark) and SPSS (version 22.0, IBM Corporation, Armonk, US).

In this study, a total of 899 patients from 10 endemic counties received albendazole treatment. The integrity of each patient file was assessed during the evaluation process. Out of the 899 patient files, 265 (29.48%) were found to have missing mandatory information and were consequently excluded from statistical analysis. Ultimately, 634 valid patient files (70.52%) were considered for further examination in this research.

Among the 634 files analyzed, 41 were found to be without follow-up records, resulting in a follow-up rate of 93.53% (593/634). The majority of R_f values fell within the range of $0.3 \leq R_f < 0.5$, accounting for 35.17%, followed by the range $0.5 \leq R_f < 0.8$, accounting for 25.55%. Only 21.92% of patients had R_f values ≥ 0.8. When stratified according to the theoretical duration of albendazole treatment, R_f values ≥ 0.8 were observed in 95.24% (20/21), 88.00% (44/50), 69.39% (34/49), 12.75% (26/204), 5.12% (15/293), and 0 (0/17) of patients for those treated with albendazole for less than 1 year, 1–2 years, 3–4 years, 5–6 years, 7–9 years, and ≥10 years, respectively. The proportion of patients with R_f values ≥ 0.8 significantly decreased as the duration of albendazole treatment increased ($\chi^2_{trend}=229.394$, $P<0.001$) (Table 1). The recorded rate of reexamination was 94.64% (600/634). The R_r was mainly concentrated $0.3 \leq R_r < 0.5$, accounting for 41.17%, and $0.5 \leq R_r < 0.8$, accounting for 21.61%. Only 23.19% of patients had $R_r \geq 0.8$. Among patients taking albendazole for less than 1 year, 1–2 years, 3–4 years, 5–6 years, 7–9 years, and ≥10 years, the percentages of patients with $R_r \geq 0.8$ were 100.00% (21/21), 84.00% (42/50), 57.14% (28/49), 10.78% (22/204), 11.26% (33/293), and 5.88% (1/17), respectively. As the treatment duration increased, the proportion of patients with $R_r \geq 0.8$ significantly decreased ($\chi^2_{trend}=195.144$, $P<0.001$) (Table 1).

Among 593 patients with follow-up records, 65.94% (91/138) of patients with $R_f \geq 0.8$ had the $R_m \geq 0.8$, which was significantly higher than that of patients with other ratios ($\chi^2=281.745$, $P<0.001$) (Table 2). For reexamination, 87.05% (121/139) of the patients with $R_f \geq 0.8$ had the $R_r \geq 0.8$, which was significantly higher than that of patients with other ratios ($\chi^2=825.136$, $P<0.001$) (Table 3).

DISCUSSION

Since the initiation of "The National Project for Echinococcosis Control and Prevention," China has invested significant funds in treating and curing patients with echinococcosis. However, the present study revealed that there are serious issues in the management of this patient population, which may considerably impact the effectiveness of echinococcosis prevention and treatment in China.

The data were incomplete, with invalid or empty files containing only the patient's name. Most counties continue to use a paper-based record management system, which proves to be inefficient and inconvenient for real-time access. For patients with incomplete records, it becomes impossible to determine whether they are being appropriately monitored and supervised, thereby revealing gaps in the management efforts. Indeed, comprehensive patient records can reflect the quality of patient management and evaluate their treatment outcomes.

The ratio of actual follow-up and reexamination times to theoretical follow-up and reexamination times was higher in cases involving early medication. However, this study found that the follow-up and reexamination ratio decreased as the duration of patients' medication increased. This observation suggests that not only do patients neglect their condition, but also the relevant follow-up personnel may disregard their management responsibilities or fail to record pertinent information due to oversight.

TABLE 1. Number and percentage (%) of echinococcosis patients treated with albendazole, stratified by duration of therapy, across ten endemic counties in 2019.

Duration of albendazole therapy (year)	Total (*N*)	Follow-up (*N*, %)					Reexamination (*N*, %)				
		R_f<0.3	0.3≤R_f<0.5	0.5≤R_f<0.8	R_f≥0.8	Unrecorded	R<0.3	0.3≤R_r<0.5	0.5≤R_r<0.8	R_r≥0.8	Unrecorded
<1	21	0 (0.00)	0 (0.00)	1 (4.76)	20 (95.24)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	21 (100.00)	0 (0.00)
1−	50	0 (0.00)	0 (0.00)	4 (8.00)	44 (88.00)	2 (2.00)	0 (0.00)	1 (2.00)	4 (8.00)	42 (84.00)	3 (6.00)
3−	49	0 (0.00)	4 (8.16)	7 (14.29)	34 (69.39)	4 (8.16)	3 (6.12)	4 (8.16)	10 (20.41)	28 (57.14)	4 (8.16)
5−	204	35 (17.16)	76 (37.25)	56 (27.45)	26 (12.75)	11 (5.39)	14 (6.86)	99 (48.53)	59 (28.92)	22 (10.78)	10 (4.90)
7−	293	28 (9.56)	135 (46.08)	94 (32.08)	15 (5.12)	21 (7.17)	22 (7.51)	157 (53.58)	64 (21.84)	33 (11.26)	17 (5.80)
≥10	17	6 (35.29)	8 (47.06)	0 (0.00)	0 (0.00)	3 (17.65)	16 (94.12)	0 (0.00)	0 (0.00)	1(5.88)	0 (0.00)
Total	634	69 (10.88)	223 (35.17)	162 (25.55)	139 (21.92)	41 (6.47)	55 (8.68)	261 (41.17)	137 (21.61)	147 (23.19)	34 (5.36)
χ^2		229.394					195.144				
P-value*		<0.001					<0.001				

Note: *N* represents the total number of patients.
Abbreviation: *CI*=confidence interval; R_f=the ratio of actual to theoretical follow-up occurrences; R_r=the ratio of actual to theoretical reexamination occurrences.
* *P*-values were compared at a significance level of 0.05.

TABLE 2. Follow-up and medication analysis for echinococcosis patients treated with albendazole in ten endemic counties, 2019.

Follow-up	Total (*N*)	Medication (*N*, %, 95% *CI*)						χ^2	*P**
		R_m=0	0<R_m<0.3	0.3≤R_m<0.5	0.5≤R_m<0.8	R_m≥0.8	Unrecorded		
R_f<0.3	69	8 (12.50, 4.17–20.83)	27 (42.19, 29.75–54.62)	23 (35.94, 23.86–48.02)	6 (9.38, 2.04–16.71)	0	5	281.745	<0.001
0.3≤R_f<0.5	223	15 (8.29, 4.23–12.34)	35 (19.34, 13.53–25.15)	63 (34.81, 27.80–41.81)	60 (33.15, 26.23–40.07)	8 (4.42, 1.40–7.44)	42		
0.5≤R_f<0.8	162	21 (13.13, 7.84–18.41)	15 (9.38, 4.81–13.94)	42 (26.25, 19.36–33.14)	53 (33.13, 25.75–40.50)	29 (18.13, 12.09–24.16)	2		
R_f≥0.8	139	0	0	2 (1.45, 0.57–3.47)	45 (32.61, 24.69–40.53)	91 (65.94, 57.94–73.95)	1		
Total	593	44 (8.10, 5.80–10.41)	77 (14.18, 11.24–17.12)	130 (23.94, 20.34–27.54)	164 (30.20, 26.33–34.08)	128 (23.57, 19.99–27.15)	50		

Note: *N* represents the total number of patients. "Unrecorded" indicates a lack of medication records with corresponding follow-up data. Chi-square tests were utilized to determine the significance levels across varying ratio distributions.
Abbreviation: *CI*=confidence interval; R_f=the ratio of actual to theoretical follow-up occurrences; R_m=the ratio of the actual duration of albendazole therapy to the recommended duration of therapy.
* *P*-values were compared at the 0.05 significance level.

TABLE 3. Analysis of Follow-up and reexamination for echinococcosis patients treated with albendazole in 10 endemic counties, 2019.

Follow-up	Total (*N*)	Reexamination (*N*, %, 95% *CI*)				Unrecorded	χ^2	*P**
		R_f<0.3	0.3≤R_f<0.5	0.5≤R_f<0.8	R_f≥0.8			
R_f<0.3	69	29 (42.65, 30.59–54.71)	39 (57.35, 45.29–69.41)	0	0	1		
0.3≤R_f<0.5	223	22 (10.50, 6.03–14.06)	191 (87.21, 82.76–91.67)	5 (2.28, 0.29–4.28)	1 (0.46, 0.04–1.36)	4		
0.5≤R_f<0.8	162	4 (2.50, 0.05–4.95)	22 (13.75, 8.36–19.14)	115 (71.88, 64.83–78.92)	19 (11.88, 6.81–16.94)	2	825.136	<0.001
R_f≥0.8	139	0	1 (0.72, 0.07–2.14)	17 (12.23, 6.72–17.74)	121 (87.05, 81.40–92.70)	0		
Total	593	55 (9.39, 7.02–11.75)	253 (43.17, 39.15–47.20)	137 (23.38, 19.94–26.82)	141 (24.06, 20.59–27.53)	7		

Note: *N* represents the total number of patients. "Unrecorded" indicates the absence of reexamination and follow-up records. Chi-square tests were utilized to determine the significance levels among various ratio distributions.
Abbreviation: *CI*=confidence interval; R_f=the ratio of actual to theoretical follow-up occurrences; R_f=the ratio of actual to theoretical reexamination occurrences.
* *P*-values were compared at the 0.05 significance level.

The inadequate follow-up and reexamination information makes it challenging to assess medication compliance, current disease and health status, and accurately evaluate treatment outcomes. This issue, while easily overlooked, necessitates proper attention. Reexamination serves the purpose of understanding therapeutic effects and preventing recurrence (*5*–*7*). Although the records indicate that patients taking albendazole for extended periods are still undergoing treatment, their follow-up and reexamination numbers fall significantly below the requirements. As a result, it remains unclear whether these patients are adhering to their medication regimen and what the treatment outcomes are.

This study revealed poor patient compliance with medication, indicating that these problems require urgent attention and resolution.

We conducted a comparison of the limited research available on the management of patients with echinococcosis (*8*–*9*). A consistent challenge identified in these studies is the long-term follow-up of patients treated with albendazole for echinococcosis, as few individuals consistently undergo regular reexaminations.

This study was subject to certain limitations. The results were primarily based on patient medical records, potentially introducing information bias. We propose the following recommendations to address these issues:

1) Patients with incomplete records or insufficient follow-up should be thoroughly investigated to determine their current status, medication usage, and potential loss to follow-up. If lost, try reconnecting with them through village leaders and schedule re-examinations. Adjust treatment plans to the development of their lesions and establish regular management records.

2) Improve the training of follow-up personnel to enhance awareness of echinococcosis and their professional competence, ensuring no patients are overlooked during follow-up. Our findings indicate that patients with a high follow-up ratio (R_f≥0.8) demonstrated better medication and re-examination compliance, emphasizing the importance of regular follow-ups.

3) Develop a unified national scheme and implementation rules for file records to address incomplete patient medical records. We also recommend establishing a standardized electronic information platform for echinococcosis patient management to enable real-time data entry, online

verification, and patient information supervision.

4) Improve patients' accessibility to re-examinations by providing portable B-ultrasound examination instruments in local township health centers or village clinics, and train medical staff to use them effectively.

5) Consider adjusting follow-up intervals based on patients' disease duration and severity in different endemic counties. Prioritize patients with severe conditions and prompt medication adherence to improve treatment effectiveness.

6) Regularly conduct health education activities to promote active patient compliance and cooperation, particularly for patients taking albendazole for extended periods.

In conclusion, more emphasis should be placed on the management of patients with echinococcosis. Implementing these recommendations may result in better patient outcomes and reduce the limitations faced in this study.

Conflicts of interest: No conflicts of interest.

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Preplanned Studies

Identification of Novel *Bartonella washoensis* Sequence Type 22 in *Marmota himalayana* — Jiuquan City, Gansu Province, China, 2021–2022

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Summary

What is already known about this topic?

The prevalence of rodent-adapted *Bartonella* species has been increasing significantly. However, the specific *Bartonella* species carried by *Marmota himalayana* (*M. himalayana*), a large rodent species, and the potential risk it poses to human populations remain unknown.

What is added by this report?

Bartonella washoensis (*B. washoensis*), associated with human endocarditis, was initially identified in *M. himalayana*, exhibiting a detection rate of approximately one-third and demonstrating a predilection for the heart and lungs. The discovery of the novel Sequence Type 22 has expanded both the isolation source and genetic lineage of *B. washoensis*.

What are the implications for public health practice?

Individuals residing within the *M. himalayana* plague focus are at an elevated risk for *B. washoensis* infection. Consequently, there is a pressing need for public health warnings and efficient clinical case identification in this population.

The emergence of *Bartonella* species has been identified as a cause of blood-culture-negative endocarditis. While the list of *Bartonella* species carried by rodents has rapidly expanded, species carried by *Marmota himalayana* (*M. himalayana*) remain unknown. To investigate this, *Bartonella washoensis* (*B. washoensis*) screening was conducted using samples obtained from both deceased and captured marmots during plague surveillance in Jiuquan City, Gansu Province from 2021 to 2022. The *B. washoensis* species were identified through 16s rRNA gene and multi-locus sequence typing (MLST), with phylogenetic trees constructed using the neighbor-joining method.

The detection rate of *B. washoensis* in captured marmots (29.58%, 21/71) was found to be significantly higher than that of deceased marmots (10.28%, 11/107), with relatively high rates observed in marmot heart and lung samples. The new sequence type, Sequence Type 22 (ST22), discovered in marmots, possessed five loci of novel sequences and clustered between *B. washoensis* from *Spermophilus dauricus* in China and *Spermophilus columbianus* in the United States. Importantly, human endocarditis-associated *B. washoensis* was identified for the first time and demonstrated a high prevalence in *M. himalayana*.

Our findings suggest that *B. washoensis* in marmots may have a preference for heart and lung tissue, and individuals in specific areas may be at risk of *B. washoensis* infection. Consequently, there is a pressing need for continued surveillance of *B. washoensis* and identification of clinical cases.

Overall, 13 of the 45 known *Bartonella* species are documented to infect humans. Species such as *Bartonella quintana* (*B. quintana*), *Bartonella henselae* (*B. henselae*), *B. washoensis*, *Bartonella koehlerae* (*B. koehlerae*), *Bartonella alsatica*, *Bartonella elizabethae*, and others have emerged as causes of blood-culture-negative endocarditis (*1*). Among these species, *B. henselae* and *B. quintana* are the most frequent causes of infectious endocarditis in humans (*2–3*). Recently, the list of *Bartonella* species carried by rodents has rapidly expanded. *M. himalayana* is the primary host of *Yersinia pestis* (*Y. pestis*) and is also known to carry a variety of bacteria and parasites pathogenic to humans (*4–5*). Although *Bartonella* has been reported in *M. himalayana* in China, the specific infecting species of *Bartonella* remains unidentified (*6*). In this study, human endocarditis-associated *B. washoensis* was initially identified in *M. himalayana* during the plague surveillance conducted from 2021 to 2022, and its public health risks were analyzed.

Peripheral blood mononuclear cells (PBMCs) were isolated from *M. himalayana* blood samples collected during plague surveillance in the Altun Mountains,

which is part of the *M. himalayana* plague focus in the Qinghai-Tibet Plateau (*7*). DNA was extracted from the samples using the DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany). The 16S rRNA gene (27F, 1492R) was amplified, sequenced, and aligned using BLASTn. Additionally, six housekeeping loci of *B. washoensis* (16S rRNA gene, *ftsZ*, *gltA*, *groEL*, *ribC*, and *rpoB*) were amplified and sequenced (*8*). Allele numbers and sequence type (ST) assignments were determined through pubMLST (*9*).

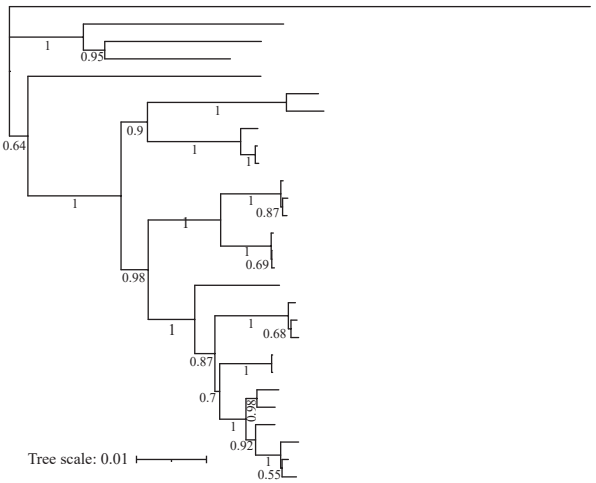
Sequences were extracted from the reference genome of 40 *Bartonella* species by aligning with six housekeeping genes from *B. washoensis*. A phylogenetic tree was constructed using the neighbor-joining (NJ) method based on the concatenated sequence of these six housekeeping genes. NJ trees were generated for both the *Bartonella* genus and the *B. washoensis* species. In the *B. washoensis* species tree, four *Bartonella* species closely related to *B. washoensis* (*B. quintana, Bartonella senegalensis*, *B. henselae*, and *B. koehlerae*) were also incorporated.

During the 2021–2022 plague surveillance in the Altun Mountains, samples were collected from six organs (heart, liver, spleen, lung, kidney, and bone) of 107 *M. himalayana* found dead in the environment and 71 live-captured marmots. These findings were within the *M. himalayana* plague focus of Qinghai-Tibet Plateau. The *B. washoensis gltA* gene was screened, sequenced, and aligned according to a previously published method (*10*). Detection rates were compared between deceased and live marmots, among the six sampled organs, and between *B. washoensis* and *Y. pestis*.

Chi-squared tests were used to compare the differences between groups, with *P*-values<0.05 considered statistically significant. Fisher's exact test was employed if the theoretical frequency ranged between 1<T<5. Statistical analyses were conducted using the SPSS software (version 19.0, IBM Corp., NY, USA).

The highest BLASTn match for the 16S rRNA gene from marmots in our study was *B. washoensis* (GenBank: AB519060.1), exhibiting 100% coverage and 100% identity. Other *Bartonella* species, such as *Bartonella volans* (GenBank: EU294521.1), were identified with 100% coverage and 99.77% identity, surpassing the species identification threshold (*10*). Based on the NJ tree of 40 *Bartonella* species, which was constructed using concatenated sequences of housekeeping genes, the sequences derived from marmots formed a cluster on the same branch as *B. washoensis*. Neighboring branches included *B. quintana*, *B. senegalensis*, *B. henselae*, and *B. koehlerae* (Supplementary Figure S1, available in http://weekly.chinacdc.cn).

The housekeeping gene allele numbers of *B. washoensis* in marmots were identified as 2-15-18-20-20-18 for the 16S rRNA gene, *ftsZ*, *gltA*, *groEL*, *ribC*, and *rpoB*, which collectively formed the novel ST 22. Excluding the 16S rRNA gene, the other five genes displayed at least 5, 8, 18, 14, and 26 base differences from known sequences. The NJ trees for *B. washoensis* (Figure 1) revealed that *B. washoensis* isolates from marmots clustered together with those from ground squirrels (*Spermophilus*), showing the greatest similarity to *B. washoensis* from *S. columbianus*. The other four



	Country	Year	Host	Source
1487_18	Germany	2018	*Homo sapiens*	Mitral valve
ER14-3	China	2007	*Sciurus vulgaris orientis*	Blood
SR22-1	China	2007	*Tamias sibiricus*	Blood
SR25-1	China	2007	*Tamias sibiricus*	Blood
SR24-1	China	2007	*Tamias sibiricus*	Blood
AR4-1	USA	2007	*Tamiasciurus hudsonicus*	Blood
AR15-2	USA	2007	*Tamiasciurus hudsonicus*	Blood
AR2-2	USA	2007	*Tamiasciurus hudsonicus*	Blood
AM9-1	USA	2007	*Glaucomys volans*	Blood
AM5-1	USA	2007	*Glaucomys volans*	Blood
AM2-1	USA	2007	*Glaucomys volans*	Blood
Sb944nv	USA	2000	*Spermophilus beecheyi*	Blood
DR10-1	China	2007	*Spermophilus dauricus*	Blood
DR3-1	China	2007	*Spermophilus dauricus*	Blood
DR1-1	China	2007	*Spermophilus dauricus*	Blood
A22-731	China	2022	*Marmota Himalayana*	Blood
A22-727	China	2022	*Marmota Himalayana*	Blood
CJ25-1	USA	2007	*Spermophilus columbianus*	Blood
CJ23-2	USA	2007	*Spermophilus columbianus*	Blood
CJ22-1	USA	2007	*Spermophilus columbianus*	Blood
RJ21-1	USA	2007	*Spermophilus richardsonii*	Blood
RJ33-1	USA	2007	*Spermophilus richardsonii*	Blood
RJ30-1	USA	2007	*Spermophilus richardsonii*	Blood

FIGURE 1. Phylogenetic trees of *B. washoensis* based on concatenated sequences of housekeeping genes.
Note: Red means in this study.

Bartonella species (*B. quintana, B. senegalensis, B. henselae,* and *B. koehlerae*) formed separate clusters outside the *B. washoensis* strains.

The detection rate of *B. washoensis* in captured marmots (29.58%, 21/71) was found to be significantly higher than that in self-dead marmots (10.28%, 11/107, χ^2=10.778; *P*=0.001). In the captured marmots, the top four positive organs were bone (29.27%, 12/41), spleen (15.52%, 9/58), lung (13.56%, 8/59), and heart (9.30%, 4/43) (Table 1). Statistical differences were observed between the highest rate in the bone (29.27%) and the lowest in the liver (1.72%, χ^2=19.159; *P*<0.002). For self-dead marmots, the top four positive organs included spleen (17.50%, 7/40), lung (9.76%, 4/41), heart (7.69%, 3/39), and bone (4.00%, 4/100), with no significant differences between different organs (Fisher exact test, χ^2=9.573; *P*=0.059). The detection rate was also lowest in the liver (2.38%, 1/42) in self-dead marmots. Moreover, *B. washoensis* positive rates showed no differences between marmots with or without *Y. pestis* (Supplementary Table S1, available in https://weekly.chinacdc.cn/) (χ^2=0.628; *P*=0.428). *B. washoensis* was detected in 7.84% (4/51) of *Y. pestis*-negative self-dead marmots, and in 12.5% (7/56) of *Y. pestis*-positive self-dead marmots. The 77 *B. washoensis*-positive samples revealed three different *gltA* sequence types, displaying one to three single nucleotide polymorphisms (SNPs), all of which were synonymous mutations.

DISCUSSION

In the current study, the first identification of human endocarditis-associated *B. washoensis* was observed with a relatively high detection rate in *M. himalayana* (approximately 1/3 in captured marmots and 1/10 in self-dead marmots). An increasing number of *Bartonella* species have been found to contribute to blood culture-negative endocarditis, with *B. henselae* and *B. quintana* being the most common causes of human cases (*2–3*) (Supplementary Figure S1, available in http://weekly.chinacdc.cn) (double asterisk). *B. washoensis* has recently been associated with human and dog endocarditis (*10–11*) and exhibits a close relationship with *B. quintana* and *B. henselae* in the NJ tree, based on housekeeping gene sequences. *B. washoensis* was detected in six types of marmot organs, suggesting a systemic distribution in its carriers. The spleen, heart, lung, and bone displayed the highest detection rates. The order of rates in captured and self-dead marmots varies, which may be attributable to sample freshness or other causes of death. Nonetheless, higher rates were detected in the heart and lung of marmots, implying that *B. washoensis* may exhibit a preference for these organs. In light of its phylogenetic position in the NJ tree, it is suggested that *B. washoensis* from *M. himalayana* closely resembles human-endocarditis-related *Bartonella*. Moreover, the presence of *Y. pestis* does not impact *B. washoensis*, and *B. washoensis* may serve as a cause of marmot mortality independent of *Y. pestis*. Lastly, the detection rate of *B. washoensis* is lowest in the liver of marmots, rendering the spleen the recommended site for detection.

The detection of *B. washoensis* in *M. himalayana* has expanded the known range of rodent species that carry this bacterium, while the discovery of the novel ST22 has enhanced its genetic lineage by adding a marmot-origin branch between *S. columbianus* and *S. dauricus*. *B. washoensis* has been previously identified in squirrels from the provinces of Hebei and Zhejiang in China (*12*). However, the housekeeping gene sequences of *B. washoensis* in marmots and squirrels exhibit significant differences. Five of the six housekeeping genes, excluding the 16S rRNA gene, have 5–26 SNPs when

TABLE 1. Detection rates of *B. washoensis* in six organs of marmots.

Sample	Captured marmot			Self-dead marmot		
	Positive	Total	Positive rate (%)	Positive	Total	Positive rate (%)
Bone	12	41	29.27*	4	100	4.00
Spleen	9	58	15.52	7	40	17.50
Lung	8	59	13.56	4	41	9.76
Heart	4	43	9.30	3	39	7.69
Kidney	3	43	6.98	1	37	2.70
Liver	1	58	1.72*	1	42	2.38

* means statistical significance between positive rates of bone and liver in captured marmots.

compared with the closest known sequences. Most *gltA* genes of *B. washoensis* observed in marmots differ by two bases, suggesting their close relationship with the ST22 type. The geographical isolation of the Qinghai-Tibet Plateau may contribute to the divergence of pathogens in *M. himalayana*, such as the new bacterial species *Streptococcus respiraculi* (*13*), *Helicobacter himalayensis* (*14*), and the novel parasite species *Enterocytozoon bieneusi* (*5*). Our research team will continue efforts to isolate and purify *B. washoensis* from marmots in order to further elucidate its biological and genomic characteristics.

In this study, we identified human endocarditis-associated *B. washoensis* for the first time, with a relatively high detection rate in *M. himalayana* and even higher in the heart and lungs of marmots. The new sequence type, ST22, of *M. himalayana*-derived *B. washoensis* is considerably different from the previously reported housekeeping gene sequence, expanding the isolation source and genetic lineage of *B. washoensis. Bartonella* has become an emerging cause of human endocarditis worldwide; however, related monitoring, detection, and diagnosis are insufficient in our country. Our findings suggest that individuals in high-risk areas are susceptible to *B. washoensis* infection, necessitating public health warnings and enhanced clinical case identification.

Conflicts of interest: No conflicts of interest.

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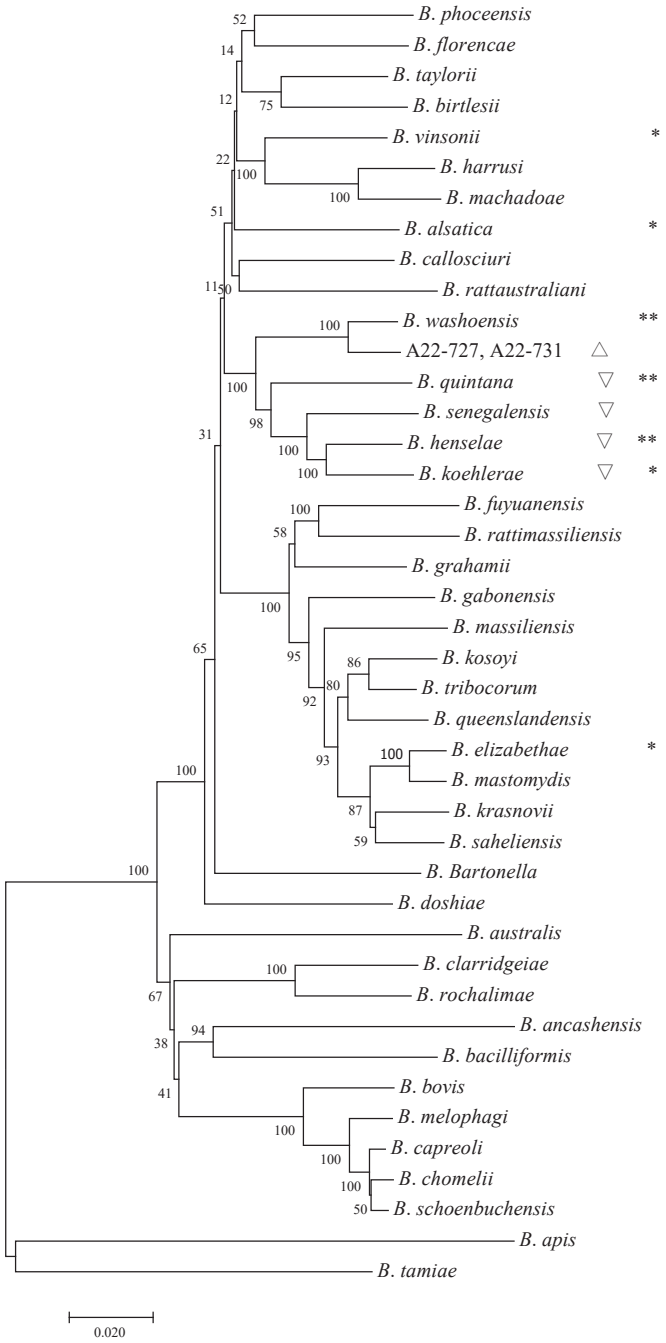

SUPPLEMENTARY FIGURE S1. *Bartonella* phylogenetic trees based on the concatenated sequence of *B. washoensis* housekeeping genes.
Note: △ means in this study; ▽ means four *Bartonella* species close to *B. washoensis*; * means animal endocarditis-related species; ** means human endocarditis-related species.

SUPPLEMENTARY TABLE S1. Prevalence of *Bartonella washoensis* in deceased marmots with and without *Yersinia pestis* infection.

Yersinia pestis	***Bartonella washoensis***		
	+	**–**	**Positive rates (%)**
–	4	47	7.84
+	7	49	12.50

Note: "+" means positive; "–" means negative.

Preplanned Studies

Associations of Occupational Stress and Coping Styles with Well-Being Among Couriers — Three Cities, Zhejiang Province, China, 2021

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Summary

What is already known about this topic?

Prior research has primarily concentrated on occupational health concerns, including injuries and heatstroke, among couriers. Nevertheless, there has been a scarcity of emphasis on mental health aspects, with existing studies predominantly addressing the risk factors associated with occupational stress.

What is added by this report?

The present study demonstrated a significant association between occupational stress and well-being among couriers, with positive coping strategies acting as a mediating factor. Furthermore, the results indicate that implementing a positive coping style may mitigate the impact of occupational stress on well-being.

What are the implications for public health practice?

Future public policy initiatives should focus on promoting the well-being of couriers by fostering improvements in the workplace environment, reevaluating the organization of work, and delivering support to couriers in managing occupational stress.

In recent years, the rapid development of the express industry in China has led to an increase in occupational stress among couriers, potentially contributing to poor well-being (*1*). A positive attitude in the workplace significantly impacts reducing occupational stress, and coping styles are crucial factors in well-being (*2*–*3*). This study aimed to investigate the association between occupational stress, coping styles, and well-being and explore the intermediary effect of coping styles on the relationship between occupational stress and well-being among couriers. The research used a cluster random sampling method to select 1,200 couriers from mainstream express companies in three cities (Ningbo, Jiaxing, and Taizhou) within Zhejiang Province, China. The Core Occupational Stress Scale (COSS) was employed to assess occupational stress, the World Health Organization's five-item Well-Being Index (WHO-5) scale to measure well-being, and the Trait Coping Style Questionnaire (TCSQ) to evaluate coping styles. Poor well-being was found to be relatively common among couriers in the three cities within Zhejiang Province, accounting for 43.5% in this study. Couriers' well-being was correlated with occupational stress (r_s=−0.142, P<0.01) and positive coping styles (r_s=0.059, P<0.05), with occupational stress exhibiting a direct effect on well-being and an indirect effect through positive coping styles. The findings of this study emphasize the need for a coordinated, multi-level effort to control the prevalence of occupational stress among couriers and actively guide them in managing stressors to promote their mental health.

This cross-sectional study was conducted from September to November 2021 and included 1,200 employees aged 18 years or older, with at least one year of work experience from 20 leading express companies in Ningbo, Jiaxing, and Taizhou cities in Zhejiang Province. An anonymous, self-administered questionnaire was employed for data collection, and all investigators underwent uniform training prior to conducting the survey. The study received approval from the Medical Ethics Committee of the National Institute of Occupational Health and Poison Control, and informed consent was provided by all participants. A total of 1,161 valid questionnaires were collected, yielding a response rate of 96.8%.

The WHO-5 scale was employed to assess subjective well-being (*4*), with a total score below 13 indicating poor well-being. Occupational stress was evaluated using the COSS (*5*), which consists of four subscales: social support, organization and return, demand and pay, and autonomy. A total score exceeding 50 denotes occupational stress. The TCSQ, comprising 20 items, is divided into positive coping and negative coping

aspects, each containing 10 items. The scores for both coping styles are determined by summing up their respective items. Data analysis was conducted using SPSS (version 25.0, IBM Corporation, Armonk, NY, USA) and AMOS (version 24.0, IBM Corporation, Armonk, NY, USA). The relationship between occupational stress, coping styles, and well-being was examined via Spearman's rank correlation analysis. To further investigate the associations among occupational stress, coping styles, and well-being, structural equation modeling (SEM) was implemented. Two-tailed *P* values <0.05 were deemed statistically significant.

The study sample included 1,161 couriers, primarily aged between 31 and 40 years and with 1–5 years of work experience (Table 1). The prevalence of occupational stress among these couriers was found to be 52.9%. A majority (72.5%) of the couriers exhibited a predominantly positive coping style, whereas 19.6% displayed a negative coping style. Poor well-being was reported by 43.5% of the participants.

A significant difference in the prevalence of poor well-being was observed between couriers with different education levels (χ^2=10.932, *P*=0.027). Additionally, a statistically significant difference was found in the prevalence of poor well-being among couriers with various working hours (χ^2=23.416, *P*<0.001).

Table 2 presents the results of the correlation analysis between occupational stress, coping styles, and well-being. Couriers' well-being was found to be negatively correlated with occupational stress (r_s=−0.142, *P*<0.01) and positively correlated with the positive coping style (r_s=0.059, *P*<0.05). However, no significant correlation was observed between well-being and negative coping style (r_s=0.011, *P*>0.05).

The final output model illustrated research variables' correlations and effect paths (Figure 1). It can be observed that occupational stress was negatively related to the positive coping style (β =−0.107, *P*<0.05), and the positive coping style was positively related to well-being (β =0.010, *P*<0.001).The 95% confidence interval (*CI*) of the estimation of the two-mediation path does not include 0, which means that the total effect of occupational stress on well-being was statistically significant, and occupational stress had significant indirect effects through the positive coping style on well-being (Supplementary Table S1, available in http://weekly.chinacdc.cn). However, the negative coping style did not demonstrate direct or indirect effects on well-being (*P*>0.05).

DISCUSSION

This study investigated the relationship between occupational stress, coping styles, and well-being among Chinese couriers. The results indicated a prevalence of poor well-being in 43.5% of the participants, with occupational stress and positive coping styles being associated with well-being. Well-being encompasses individuals' emotional responses and satisfaction in various life domains. Couriers often experience a heavy workload, frequent overtime, and time constraints related to delivery tasks, leading to increased occupational stress. The long-term accumulation of stress can contribute to mental health deterioration.

In recent years, a growing number of studies have focused on the connection between well-being and occupational stress in diverse professions, examining the mediating role of coping styles. For instance, Ryu et al. (*6*) identified coping styles as significant mediating factors between occupational stress and well-being among police officers in the Republic of Korea. Similar results were observed in a study involving nurses (*7*). However, few studies have specifically examined couriers in this context.

Occupational stress was found to be inversely correlated with well-being in this study, with positive coping styles mediating the relationship between the two. Coping styles refer to individuals' cognitive and behavioral efforts or strategies used to regulate their emotions and reduce adverse effects when faced with stressful events. Individuals experiencing stress often adopt coping styles to mitigate its impact on well-being (*8*). Positive coping styles can generate a more positive mood, thus reducing the effects of occupational stress (*9*). Consequently, couriers with high levels of positive coping styles can effectively resist occupational stress, maintaining a positive and resilient approach to life.

However, our findings only revealed a moderating role for positive coping styles in the relationship between occupational stress and well-being. The association between negative coping styles and well-being requires further investigation. It is possible that compared to a negative coping style, a positive coping style actively alleviates personal psychological stress through emotion regulation, whereas a negative coping style hampers well-being improvement.

These findings suggest that the well-being of couriers could be enhanced by both reducing their occupational stress and encouraging the adoption of

TABLE 1. Prevalence of occupational stress, coping styles, and poor well-being among couriers in three cities in Zhejiang Province, China, 2021.

Characteristic	Total, *n* (%)	Occupational stress			Positive coping style			Negative coping style			Poor well-being		
		n (%)	χ^2	*P*	*n* (%)	χ^2	*P*	*n* (%)	χ^2	*P*	*n* (%)	χ^2	*P*
Total	1,161 (100)	614 (52.9)			842 (72.5)			228 (19.6)			505 (43.5)		
Gender			6.186	0.023		6.500	0.011		4.533	0.033		2.024	0.155
Male	835 (71.9)	459 (55.0)			623 (74.6)			151 (18.1)			374 (44.8)		
Female	326 (28.1)	155 (47.5)			219 (67.2)			77 (23.6)			131 (40.2)		
Age (years)			24.305	<0.001		6.113	0.191		5.075	0.280		3.097	0.542
18–25	206 (17.7)	103 (50.0)			151 (73.3)			40 (19.4)			89 (43.2)		
26–30	297 (25.6)	179 (60.3)			206 (69.4)			61 (20.5)			133 (44.8)		
31–40	428 (36.9)	240 (56.1)			306 (71.5)			91 (21.3)			194 (45.3)		
41–50	191 (16.5)	77 (40.3)			146 (76.4)			33 (17.3)			75 (39.3)		
>50	39 (3.4)	15 (38.5)			33 (84.6)			3 (7.7)			14 (35.9)		
Education level			42.431	<0.001		13.466	0.009		16.638	0.002		10.932	0.027
≤Middle school	265 (22.8)	95 (35.8)			198 (74.7)			45 (17.0)			105 (39.6)		
High school	506 (43.6)	282 (55.7)			377 (74.5)			89 (17.6)			244 (48.2)		
College	241 (20.8)	145 (60.2)			168 (69.7)			53 (22.0)			104 (43.2)		
University	129 (11.1)	79 (61.2)			91 (70.5)			31 (24.0)			46 (35.7)		
≥Graduate school	20 (1.7)	13 (65.0)			8 (40.0)			10 (50.0)			6 (30.0)		
Marital status			4.976	0.290		15.853	0.003		11.976	0.018		2.385	0.665
Unmarried	301 (25.9)	151 (50.2)			215 (71.4)			60 (19.9)			126 (41.9)		
Married	676 (58.2)	370 (54.7)			495 (73.2)			135 (20.0)			292 (43.2)		
Separated	104 (9.0)	47 (45.2)			85 (81.7)			11 (10.6)			50 (48.1)		
Widowed	61 (5.3)	35 (57.4)			39 (63.9)			14 (23.0)			30 (49.2)		
Divorced and others	19 (1.6)	11 (57.9)			8 (42.1)			8 (42.1)			7 (36.8)		
Monthly income (CNY)			25.912	<0.001		11.582	0.041		10.105	0.072		6.615	0.251
<3,000	56 (4.8)	18 (32.1)			39 (69.6)			11 (19.6)			25 (44.6)		
3,000–4,999	363 (31.3)	183 (50.4)			246 (67.8)			87 (24.0)			146 (40.2)		
5,000–6,999	398 (34.3)	200 (50.3)			286 (71.9)			80 (20.1)			185 (46.5)		
7,000–9,000	214 (18.4)	135 (63.1)			169 (79.0)			32 (15.0)			101 (47.2)		
9,000–10,999	86 (7.4)	56 (65.1)			66 (76.7)			12 (14.0)			31 (36.0)		
≥11,000	44 (3.8)	22 (50.0)			36 (81.8)			6 (13.6)			17 (38.6)		

TABLE 1. (Continued)

Characteristic	Total, *n* (%)	Occupational stress			Positive coping style			Negative coping style			Poor well-being		
		n (%)	χ^2	*P*	*n* (%)	χ^2	*P*	*n* (%)	χ^2	*P*	*n* (%)	χ^2	*P*
Working age (years)			19.551	<0.001		13.018	0.005		11.573	0.009		7.047	0.070
1–5	564 (48.6)	286 (50.7)			395 (70.0)			115 (20.4)			250 (44.3)		
6–10	227 (19.6)	141 (62.1)			163 (71.8)			47 (20.7)			103 (45.4)		
11–15	172 (14.8)	102 (59.3)			120 (69.8)			43 (25.0)			82 (47.7)		
>15	198 (17.1)	85 (42.9)			164 (82.8)			23 (11.6)			70 (35.4)		
Smoking			13.903	<0.001		8.049	0.017		8.876	0.012		5.254	0.072
No	488 (42.0)	234 (48.0)			371 (76.0)			85 (17.4)			197 (40.4)		
Yes	551 (47.5)	323 (58.6)			378 (68.6)			127 (23.0)			259 (47.0)		
Quit smoking	122 (10.5)	57 (46.7)			93 (76.2)			16 (13.1)			49 (40.2)		
Alcohol drinking			8.639	0.003		18.994	<0.001		20.425	<0.001		0.765	0.382
No	414 (35.7)	195 (47.1)			332 (80.2)			52 (12.6)			173 (41.8)		
Yes	747 (64.3)	419 (56.1)			510 (68.3)			176 (23.6)			332 (44.4)		
Physical exercise			0.492	0.483		1.377	0.241		1.122	0.290		0.762	0.092
Lack of exercise	622 (53.6)	323 (51.9)			460 (74.0)			115 (18.5)			268 (43.1)		
Often exercise	539 (46.4)	291 (54.0)			382 (70.9)			113 (21.0)			237 (44.0)		
Working hour (per week)			0.233	0.629		0.011	0.918		0.053	0.817		23.416	<0.001
≤40	122 (10.5)	62 (50.8)			88 (72.1)			23 (18.9)			28 (23.0)		
>40	1,039 (89.5)	552 (53.1)			754 (72.6)			205 (19.7)			477 (45.9)		
Shiftwork status			0.053	0.871		21.112	<0.001		24.442	<0.001		0.168	0.682
No	758 (65.3)	399 (52.6)			583 (76.9)			117 (15.4)			333 (43.9)		
Yes	403 (34.7)	215 (53.3)			259 (64.3)			111 (27.5)			172 (42.7)		

Note: The three cities were Ningbo, Jiaxing, and Taizhou.
Abbreviation: CNY=Chinese Yuan.

TABLE 2. Correlation analysis of occupational stress, coping styles, and well-being among couriers in three cities in Zhejiang Province, China, 2021.

Variables	Occupational stress	Positive coping style	Negative coping style	Well-being
Occupational stress	1.000			
Positive coping style	−0.163**	1.000		
Negative coping style	0.092**	−0.449**	1.000	
Well-being	−0.142**	0.059*	0.011	1.000

Note: The three cities were Ningbo, Jiaxing, and Taizhou.
* P<0.05.
** P<0.01.

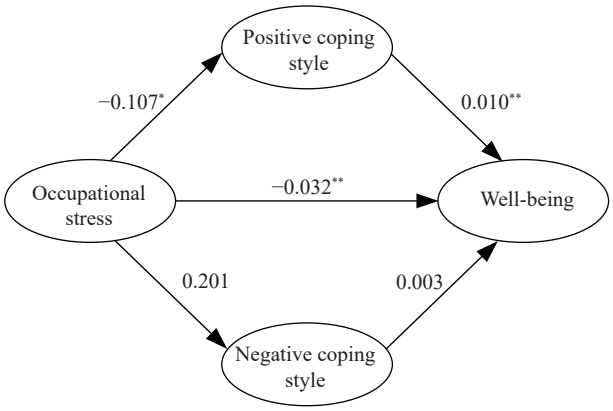

FIGURE 1. Standardized path analysis illustrating the relationships among occupational stress, coping styles, and well-being among couriers in three cities in Zhejiang Province, China, 2021.
Note: The three cities included in the study were Ningbo, Jiaxing, and Taizhou. The fit indices for the structural model were as follows: χ^2=37.576; df=11; χ^2/df=3.416; P<0.001; CFI=0.981, GFI=0.991, AGFI=0.976; NFI=0.986; RMSEA=0.046. A model is considered to have a good fit if it meets the following criteria: RMSEA<0.08, CFI>0.90, and NFI>0.90. Based on these results, the structural model demonstrated a good fit with the data in this study.
Abbreviation: CFI=comparative fit index; GFI=goodness-of-fit index; AGFI=adjusted goodness-of-fit index; NFI=normed fit index; RMSEA=root-mean-square error of approximation.
* P<0.05.
** P<0.001.

active coping strategies. This study provides evidence on how to implement effective interventions in promoting mental health among couriers during their working hours.

The study was subject to several limitations. First, due to the cross-sectional design, the causal relationship between occupational stress, coping strategies, and well-being could not be established. Second, the use of self-administered questionnaires to collect data might have introduced recall bias, potentially impacting the findings. Last, the investigation was conducted in only three cities in Zhejiang Province, thereby not offering a comprehensive representation of the courier industry within the province. Therefore, future research is warranted to expand the scope of the study.

The results of this study indicate that addressing occupational stress and coping strategies may serve as interventions to enhance the well-being of couriers. To foster the healthy development of the express industry, future policies could be enacted at the government level, focusing on refining laws and regulations related to occupational health protection for couriers and establishing a multi-tiered protection system. Professional occupational health prevention and treatment institutions should consider couriers as an emerging occupational group, guiding enterprises to enhance their occupational health management systems and implementing mental health interventions such as providing stress-reduction coping skills and techniques.

Enterprises can potentially mitigate couriers' occupational stress by improving their work environment and modifying their work organization, including advocating for workload adjustments based on employees' capabilities and clearly delineating job roles and responsibilities, ultimately bolstering the well-being of couriers. Additionally, considering the difficulty in achieving drastic improvements in their working conditions and work pressure in a short period, mental health interventions can effectively regulate the couriers' mental state, thereby enhancing their well-being in the foreseeable future.

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SUPPLEMENTARY TABLE S1. Characteristics and the distributions of well-being, occupational stress and coping styles of participants.

Variables	Total	Well-being		Positive coping style		Negative coping style		Occupational stress	
	n (%)	M±SD	*P*	M±SD	*P*	M±SD	*P*	M±SD	*P*
Gender			0.086		0.168		<0.001		0.002
Male	835 (71.9)	13.04±4.54		31.15±7.74		24.20±8.18		50.08±5.6	
Female	326 (28.1)	13.54±4.48		31.89±8.49		26.79±9.81		48.92±5.55	
Age (years)			0.093		0.396		0.214		<0.001
18–25	206 (17.7)	13.42±4.72		30.52±7.19		23.69±6.86		49.36±6.17	
26–30	297 (25.6)	12.84±4.23		31.11±8.78		25.23±9.52		50.51±5.6	
31–40	428 (36.9)	13.00±4.31		31.81±8.14		25.30±9.32		50.36±5.32	
41–50	191 (16.5)	13.60±4.61		31.55±7.49		25.14±8.44		47.96±5.22	
>50	39 (3.4)	14.44±3.91		31.67±4.69		24.03±5.46		48.28±5.31	
Education level			0.026		0.031		<0.001		<0.001
≤Middle school	265 (22.8)	13.68±4.27		30.69±7.71		24.12±7.66		47.34±5.19	
High school	506 (43.6)	12.77±4.54		31.15±7.92		23.83±8.26		50.37±5.86	
College	241 (20.8)	13.09±4.32		31.36±7.85		25.94±9.22		50.54±5.31	
University	129 (11.1)	13.86±4.32		33.35±8.16		27.87±9.94		50.78±4.53	
≥Graduate school	20 (1.7)	13.65±3.70		32.40±10.78		32.25±11.31		50.2±5.47	
Marital status			0.52		0.002		<0.001		0.261
Unmarried	301 (25.9)	13.24±4.52		30.05±7.30		23.58±6.77		49.7±5.86	
Married	676 (58.2)	13.29±4.43		32.04±7.80		25.34±9.16		49.91±5.56	
Separated	104 (9.0)	12.50±4.06		30.72±7.63		23.77±7.34		48.63±5.31	
Widowed	61 (5.3)	12.95±4.34		30.44±10.70		26.15±11.25		49.92±5.53	
Divorced and others	19 (1.6)	12.84±4.37		34.11±11.77		33.89±12.35		50.68±4.85	
Monthly income (CNY)			0.229		0.024		0.116		<0.001
<3,000	56 (4.8)	13.21±4.16		32.09±7.84		27.46±9.54		47.64±4.87	
3,000–4,999	363 (31.3)	13.60±4.46		30.66±8.21		25.40±8.90		48.86±5.67	
5,000–6,999	398 (34.3)	13.13±4.45		31.25±7.83		24.61±8.68		49.88±5.96	
7,000–9,000	214 (18.4)	12.63±4.58		31.66±7.60		24.30±8.31		51.12±4.86	
9,000–10,999	86 (7.4)	13.12±3.52		33.92±7.37		25.14±9.08		50.85±4.4	
≥11,000	44 (3.8)	12.91±4.61		30.68±9.23		23.39±7.84		49.98±6.33	
Working age			0.082		0.801		0.003		0.001
0–5	564 (48.6)	13.20±4.54		31.35±8.10		25.55±8.75		49.46±5.78	
6–10	227 (19.6)	12.94±4.48		31.73±8.46		25.40±10.04		50.57±5.36	
11–15	172 (14.8)	12.71±4.18		30.92±8.30		24.55±9.07		50.67±5.33	
>15	198 (17.1)	13.81±4.11		31.33±6.59		22.93±6.21		48.85±5.43	
Smoking			0.167		0.001		<0.001		0.167
No	488 (42.0)	13.46±4.50		30.51±7.13		23.36±7.01		49.04±5.68	
Yes	551 (47.5)	12.95±4.33		32.30±8.73		26.73±10.10		50.45±5.41	
Quit smoking	122 (10.5)	13.12±4.42		30.47±6.97		23.07±6.50		49.5±5.89	
Drinking alcohol			0.091		0.059		<0.001		0.007
No	414 (35.7)	12.95±4.34		30.79±7.13		23.07±6.75		49.16±5.83	
Yes	747 (64.3)	13.48±4.49		31.67±8.38		25.96±9.52		50.09±5.46	
Physical exercise			0.697		0.105		<0.001		0.160
Lack of exercise	622 (53.6)	13.02±4.36		31.00±7.45		24.06±7.68		49.54±5.82	
Often exercise	539 (46.4)	13.14±4.54		31.77±8.50		25.93±9.73		50.00±5.34	
Weekly working hours			<0.001		0.078		0.249		0.027
≤40	122 (10.5)	15.55±4.30		30.16±7.79		24.07±7.69		48.70±6.04	
>40	1,039 (34.7)	12.90±4.34		31.50±7.97		25.03±8.85		49.88±5.55	
Shiftwork status			0.412		<0.001		<0.001		0.289
No	758 (65.3)	13.10±4.42		30.53±7.25		23.11±6.97		49.88±5.51	
Yes	403 (34.7)	13.33±4.40		32.91±8.96		28.34±10.54		49.52±5.79	

Abbreviation: CNY=Chinese Yuan; M±SD=mean±standard deviation.

Preplanned Studies

Impact of Influenza and Pneumococcal Polysaccharide Vaccination on Economic Burden from Acute Exacerbations of Chronic Obstructive Pulmonary Disease — Hebei Province, China, November 2018 to November 2020

Yan Li[1]; Pingshu Zhang[2]; Zhijie An[1]; Ying Ma[2]; Yamin Wang[1]; Liye Wang[2]; Yunqiu Liu[2]; Xiaodong Yuan[2]; Keli Li[1]; Zundong Yin[1]; Huaqing Wang[1,#]

Summary

What is already known on this topic?

Chronic obstructive pulmonary disease (COPD) exacerbations increase household economic burden, but there is limited evidence from prospective cohort studies in China about the impact of vaccination on economic burden.

What is added by this report?

This study demonstrated the economic burden of COPD exacerbations, pneumonia, and hospitalization in COPD patients in China is substantial. Influenza vaccine and 23-valent pneumococcal polysaccharide vaccine (PPSV23), separately or together, were significantly associated with decreased economic burden.

What are the implications for public health practice?

Our study supports evidence on recommendations that COPD patients in China are offered both influenza vaccine and PPSV23.

The economic burden caused by chronic obstructive pulmonary disease (COPD) exacerbation in patients can lead to significant financial strain. However, limited evidence is available from cohort studies that examine the economic burden of exacerbations and the potential cost savings associated with vaccination in China. To address this gap, we conducted a prospective intervention cohort study to determine the economic burden of three adverse outcomes in COPD patients. We also estimated the cost savings associated with influenza and 23-valent pneumococcal polysaccharide vaccine (PPSV23) vaccination, as well as their combined use. Trivalent influenza vaccine (TIV) is a synthetic vaccine composed of three inactivated influenza viruses, including two types of influenza type A strains and one influenza type B strain, while PPSV23 protects against 23 different types of pneumococcus that cause pneumococcal disease. Our study showed that COPD patients experienced a high economic burden due to exacerbations and pneumonia, particularly hospitalization cases. However, vaccination with influenza vaccine and PPSV23, either separately or in combination, was associated with significantly reduced costs. These findings support the current vaccination recommendations for COPD patients and highlight the potential value of vaccination programs for disease management.

COPD is a chronic respiratory disease that is preventable and treatable. The disease burden of COPD is significant worldwide and in China (*1*–*2*). Patients with COPD frequently have acute exacerbations [acute exacerbation of chronic obstructive pulmonary disease (AECOPD)], which can lead to a further decline in lung function, aggravating the progression of the disease, increasing the risk of death, and creating a financial burden for families (*3*). AECOPD often result from infections with pneumococcus and influenza viruses (*3*). Immunization against influenza and pneumococcal diseases can reduce the risk and severity of these infections, easing the burden of AECOPD, pneumonia, and hospitalizations in COPD patients (*4*).

A prospective intervention study was conducted in Tangshan City, Hebei Province, China from November 2018 to November 2020. Vaccination was offered in November 2019. In this study, doctors from the respiratory outpatient clinics of ten hospitals recruited eligible patients between September and October 2018. The patients had a ratio of post-bronchodilator one-second forced expiratory volume (FEV1) to forced vital capacity (FVC) of less than 0.70 (*1*). Those who had received influenza vaccine during

the 2018–2019 influenza season or PPSV23 in the past 5 years were excluded.

Our study utilized standardized questionnaires to collect data on fundamental characteristics, such as age, gender, occupation, COPD severity, comorbidities, and smoking status, as well as the occurrence and associated costs of three outcomes: AECOPD, pneumonia, and hospitalization related to these conditions during a 2-year period. We defined coal miners as individuals who worked or had worked in coal mining. Severity ratings for COPD were consistent with international standards (*1*). Comorbidities were defined as any other diagnosed diseases except COPD. Smoking was defined as the act of smoking at the time of participation in the study. The case definitions for AECOPD, pneumonia, and related hospitalization can be found in our previously published paper (*4*). To ensure data accuracy, we cross-checked outcome occurrences and associated cost data according to medical records of subjects' medical visits and hospitalizations, health insurance reimbursement records, and original invoices. Cost information included outpatient expenses, hospitalization expenses, self-purchased medicine expenses, work-loss expenses (as calculated by salary per day multiplied by the number of work-loss days), and other related expenses. One year into the 2-year study, we offered TIV and PPSV23. Subjects chose to receive either, both, or neither vaccine, resulting in four distinct groups: TIV group, PPSV23 group, TIV&PPSV23 group, and an unvaccinated group. The Sanofi Pasteur and Merck Corporation produced the TIV and PPSV23 used in this study, respectively (Figure 1).

The software programs EpiData (version 3.1,

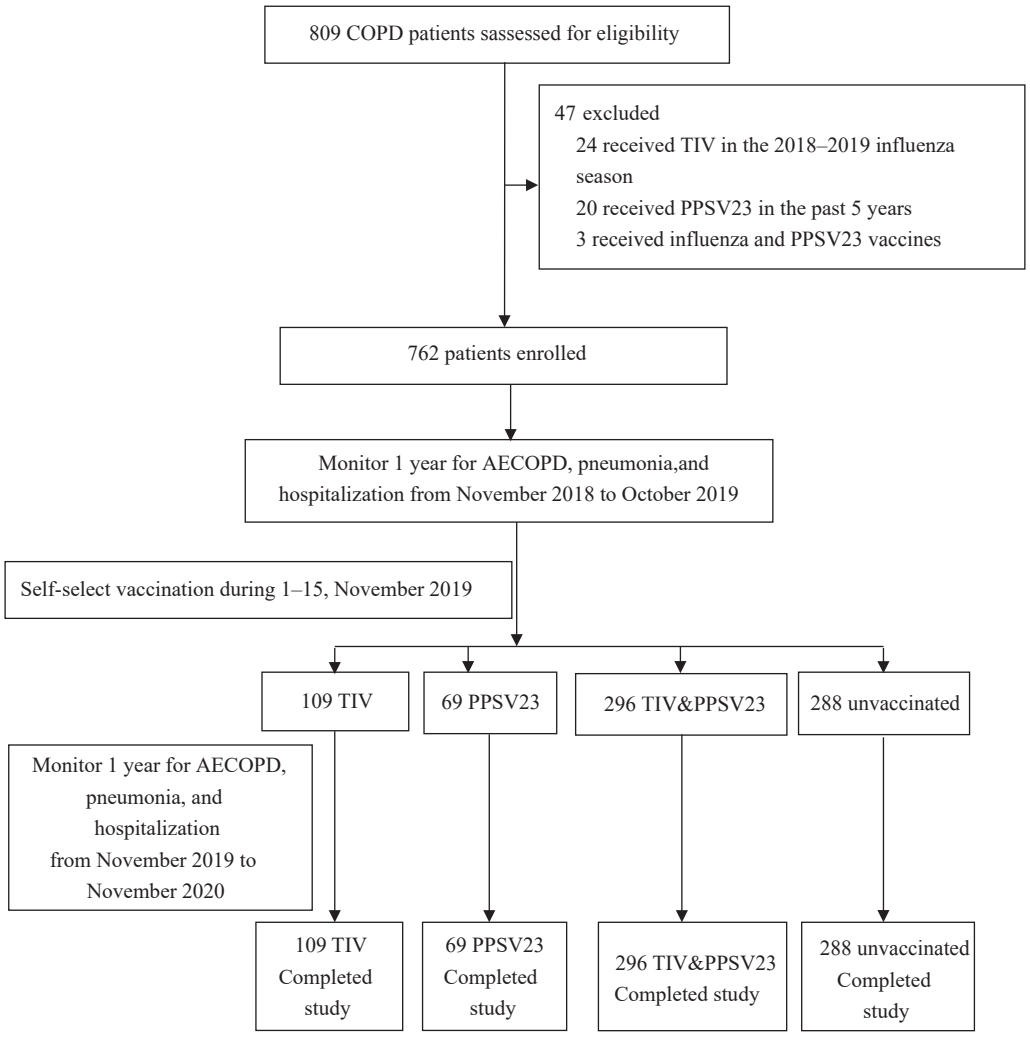

FIGURE 1. The study flow chart.
Abbreviation: COPD=chronic obstructive pulmonary disease; TIV=trivalent influenza vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; AECOPD=acute exacerbation of chronic obstructive pulmonary disease.

EpiData Software, Epi Info V6, Denmark) and SAS (version 9.4, SAS Institute, Cary, NC, USA) were utilized for data entry and statistical analyses. The basic characteristics of subjects were compared using either chi-squared or Fisher's exact probability testing. Non-parametric testing was conducted to compare the cost per person and cost per instance of different outcomes. Statistical significance was considered for *P*-values<0.05.

The Ethical Review Committee of the Chinese Center for Disease Control and Prevention provided the necessary approval for this study (Ethical Approval Notification Nos. 201826 and 201940). Prior to enrollment and vaccination, all participants provided written informed consent.

The study included 762 subjects who completed the study, with 109 receiving TIV, 69 receiving PPSV23, 296 receiving both vaccines, and 288 receiving no vaccine. Significant differences between groups were noted regarding age, occupation, comorbidities, and current smoking (Supplementary Table S1, available in https://weekly.chinacdc.cn/). The unvaccinated group had the lowest average age, the lowest percentage of subjects with comorbidities, and the highest percentage of non-smokers.

During the 2-year follow-up study period, a total of 486 cases of AECOPD, 223 cases of pneumonia, and 368 COPD-related hospitalizations were reported. Among these, 355 (73%) AECOPDs, 161 (72%) cases of pneumonia, and 250 (68%) COPD-related hospitalizations occurred in the year prior to vaccination. The frequency of AECOPDs, pneumonia, and related hospitalizations varied by month, with the highest frequency occurring from October to December and the lowest frequency from August to September (Figure 2). A previous publication reported on the incidence densities of AECOPD, pneumonia, and related hospitalization before and after vaccination within three vaccination groups (*4*). For the unvaccinated group, the number of AECOPD, pneumonia, and related hospitalization outcomes before and after vaccination were 52 and 30, 27 and 15, and 42 and 28, respectively. The corresponding incidence densities were 18.06/100 person-year and 10.42/100 person-year, 9.38/100 person-year and 5.21/100 person-year, 14.58/100 person-year and 9.72/100 person-year.

The study results showed that the total cost incurred by subjects who experienced AECOPD, pneumonia, and related hospitalization was 3,912,985 CNY. Outpatient visits accounted for 3.10% of the total cost,

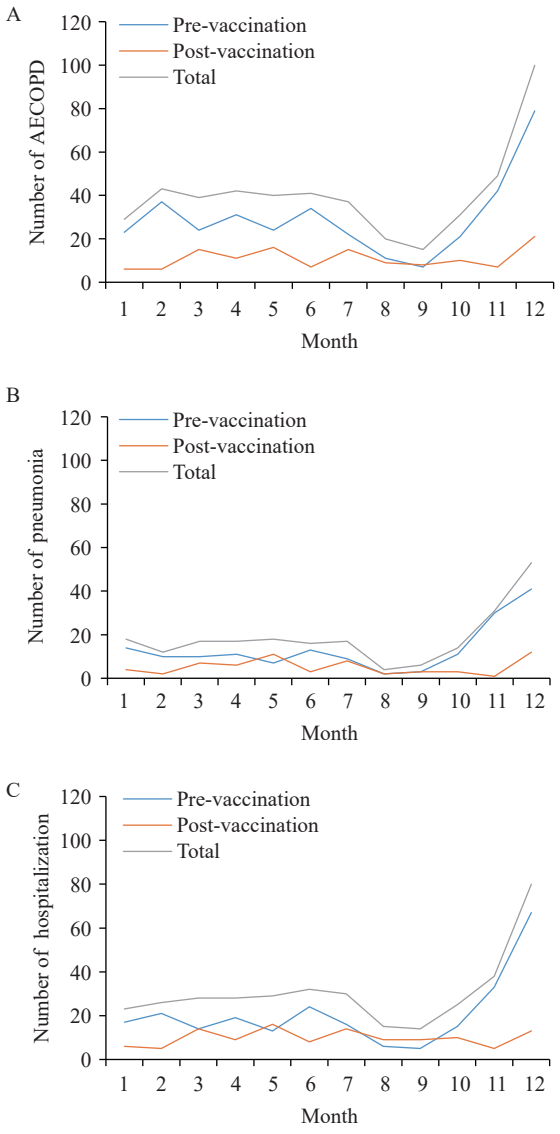

FIGURE 2. Distribution of incidence of AECOPDs, pneumonia, and hospitalizations by month. (A) Month distribution of AECOPDs, (B) Month distribution of pneumonia, (C) Month distribution of hospitalizations.
Abbreviation: AECOPD=acute exacerbation of chronic obstructive pulmonary disease.

while hospitalizations, self-purchased medication, work-loss, and other related expenses accounted for 83.47%, 0.91%, 8.43%, and 4.09%, respectively. A breakdown of these costs by study group and period is provided in Table 1.

The study also found that in the year after vaccination, the total expenses, outpatient expenses, and other related expenses in the TIV group were statistically lower compared to the year before vaccination. Similarly, all types of expenses in the TIV&PPSV23 group and outpatient expenses, self-purchased drug expenses, and work-loss expenses in the

PPSV23 group were also significantly lower in the year after vaccination compared to the year before vaccination (Table 1).

During the 2-year follow-up, 505 outcome-related events were reported. Of those, 92 were AECOPD alone, 4 were pneumonia alone, 41 were AECOPD and pneumonia, 190 were AECOPD and hospitalization, 15 were pneumonia and hospitalization, and 163 were AECOPD, pneumonia, and hospitalization. Among them, 82 AECOPD alone, 4 pneumonia alone, 36 AECOPD and pneumonia, 129 AECOPD and hospitalization, 13 pneumonia and hospitalization, and 108 AECOPD, pneumonia, and hospitalization occurred during the year prior to vaccination. Meanwhile, 10 AECOPD alone, 0 pneumonia alone, 5 AECOPD and pneumonia, 61 AECOPD and hospitalization, 2 pneumonia and hospitalization, and 55 AECOPD, pneumonia, and hospitalization occurred during the year following vaccination. The costs per instance of the six outcome combinations were 770.0 CNY for AECOPD alone, 1,423.5 CNY for pneumonia alone, 1,054.9 CNY for AECOPD and pneumonia, 1,0650.0 CNY for AECOPD and hospitalization, 9,047.2 CNY for pneumonia and hospitalization, and 10,007.5 CNY for AECOPD, pneumonia, and hospitalization, respectively. There were no significant differences in most of the costs per instance of the six outcome combinations before and after vaccination (Table 2). However, the costs per instance of the outcome combinations that involved hospitalization were significantly higher (P<0.001).

The average costs per person before and after vaccination were analyzed across four groups: TIV, PPSV23, TIV&PPSV23, and unvaccinated. In the TIV group, the average costs per person before and after vaccination were 4,115.2 CNY and 1,932.5 CNY respectively. In the PPSV23 group, the average costs per person before and after vaccination were 4,330.8 CNY and 3,440.1 CNY respectively. For the TIV&PPSV23 group, the average costs per person before and after vaccination were 4,032.0 CNY and 2,114.5 CNY respectively, while for the unvaccinated group, the average costs per person before and after vaccination were 1,696.7 CNY and 1,422.1 CNY respectively. For the TIV group and TIV&PPSV23 group, costs per person after vaccination were significantly lower than before vaccination (P=0.04, P<0.001). However, for the PPSV23 and unvaccinated groups, there were no significant differences observed between year 1 and year 2 (P=0.23, P=0.26), as shown in Table 3. In the TIV&PPSV23 group, the cost savings between different COPD severity levels were statistically different (P=0.008, P>0.005). However, there were no other statistically significant differences observed among different age groups, genders, occupations, COPD severity, comorbidities, and smoking status, in different groups. We observed a trend of lower cost savings with increasing age and COPD severity, and higher cost savings in COPD patients without comorbidities.

DISCUSSION

The prevention of AECOPD in patients with COPD can be facilitated through influenza and pneumococcal vaccination. The World Health Organization (*5*), the United States Centers for Disease Control and Prevention (CDC) (*6*–*7*), and the expert consensus in China (*2*) all recommend the use of both TIV and PPSV23 in COPD patients. Our study is a prospective, before-and-after vaccination, cohort study which aims to determine the burden of illness and impact of TIV and PPSV23 vaccination in COPD patients. Our study findings demonstrate that the economic burden of AECOPD, pneumonia, hospitalization in COPD patients is high. Costs are highest when hospitalization is necessary. Additionally, the economic burdens of these outcomes were significantly decreased following vaccination. These results support the current recommendations for influenza and pneumococcal polysaccharide vaccination in COPD patients.

Seasonal variations in the exacerbation of COPD, pneumonia, and hospitalizations were observed among COPD patients, with the highest occurrences in winter and the lowest in summer and autumn. The most significant reductions associated with vaccination were observed during the winter season. These results corroborate a previous study conducted by Wang et al. (*3*), which identified a higher incidence of AECOPD during winter, attributed to an increased prevalence of respiratory viral infections associated with colder outdoor temperatures.

Hospitalization costs accounted for over 80% of all outcome costs, which is consistent with the findings of a previous economic study on COPD conducted in India (*8*). Our study revealed a higher proportion of costs due to work-loss (over 8%) compared to the Indian study (4%). The average cost of outpatient visits in our cohort was approximately 1,000 CNY, while the average cost of hospitalization was

TABLE 1. Composition of total expenses (in CNY) across different groups, one year prior to and following vaccination.

Groups	Total expenses	Outpatient expenses	Proportion (%)	Hospitalization expenses	Proportion (%)	Self-purchased medicine expenses	Proportion (%)	Work-loss expenses	Proportion (%)	Other related expenses	Proportion (%)
TIV group											
Pre-	448,553.9	13,082.7	2.92	378,732.5	84.43	3,530.0	0.79	33,158.7	7.39	20,050.0	4.47
Post-	210,646.9	2,650.0	1.26	177,715.9	84.37	1,861.0	0.88	19,800.0	9.40	8,620.0	4.09
P	0.04	<0.001		0.12		0.24		0.19		0.01	
PPSV23 group											
Pre-	298,823.0	20,335.3	6.81	208,316.0	69.71	5,085.0	1.70	54,416.7	18.21	10,670.0	3.57
Post-	237,367.6	5,148.6	2.17	191,599.0	80.72	2,620.0	1.10	31,170.0	13.13	6,830.0	2.88
P	0.23	0.001		0.56		0.04		0.02		0.20	
TIV&PPSV23 group											
Pre-	1,193,468.4	33,564.4	2.81	1,008,669.9	84.52	8,106.0	0.68	83,688.0	7.01	59,440.0	4.98
Post-	625,897.3	28,570.8	4.56	507,948.9	81.16	2,476.0	0.40	52,811.7	8.44	34,090.0	5.45
P	<0.001	<0.001		<0.0001		<0.001		0.001		<0.001	
Unvaccinated group											
Pre-	488,660.3	9,354.5	1.91	434,474.8	88.91	5,221.0	1.07	29,990.0	6.14	9,620.0	1.97
Post-	409,567.3	8,446.7	2.06	358,754.9	87.59	6,558.0	1.60	24,927.7	6.09	10,880.0	2.66
P	0.26	0.44		0.49		0.50		0.43		0.92	

Abbreviation: TIV=trivalent influenza vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine.

TABLE 2. Cost (in CNY) per instance of different outcomes, pre-vaccination, and post-vaccination.

Group	Pre-vaccination						Post-vaccination				
	AECOPD	Pneumonia	AECOPD& pneumonia	AECOPD& Hospitalization	Pneumonia& hospitalization	AECOPD& pneumonia& hospitalization	AECOPD	AECOPD& pneumonia	AECOPD& hospitalization	Pneumonia& hospitalization	AECOPD& pneumonia& hospitalization
TIV group	701.1	–	1,069.1	13,146.5	5,433.3	9,549.7	–	1,566.7	10,903.1	18,617.2	11,633.2
PPSV23 group	1,103.6	–	1,363.9	6,667.4*	–	8,449.1	722.2	2,500.0	11,147.6*	–	10,102.1
TIV&PPSV23 group	649.3	1,231.3	805.5	8,810.2	9,140.6	8,134.6	1,057.4	1,343.3	11,877.6	14,276.4	12,777.0
Unvaccinated group	550.5	2,000.0	1,276.9	12,509.2†	7,510.0	10,591.5§	716.0	1,000.0	15,098.8†	–	13,962.0§
Total	751.4	1,423.5	986.0	9,852.1	7,908.8	8,814.9¶	922.7	1,550.7	12,337.4	16,446.8	12,349.5¶

Note: "–" means no outcome was reported.

Abbreviation: TIV=trivalent influenza vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; AECOPD=acute exacerbation of chronic obstructive pulmonary disease.

* *P*=0.01;

† *P*=0.004;

§ *P*<0.001;

¶ *P*=0.04.

TABLE 3. Costs (in CNY) per person of AECOPD, pneumonia, and related hospitalization pre-vaccination and post-vaccination.

variable	TIV group			PPSV23 group			TIV&PPSV23 group			Unvaccinated group		
	No. of cases	Pre-	Post-	No. of cases	Pre-	Post-	No. of cases	Pre-	Post-	No. of cases	Pre-	Post-
Age (years)												
<65	41	4,337.3	509.4	23	3,015.8	2,327.3	125	3,815.9	1,550.8	151	1,402.5	1,103.2
≥65	68	3,981.2	2,790.6	46	4,988.2	3,996.5	171	4,189.9	2,526.6	137	2,021.1	1,773.6
Gender												
Male	94	4,668.2	2,148.4	52	5,433.3	4,541.7	226	4,419.3	2,769.5	214	1,992.2	1,724.4
Female	15	649.7	579.8	17	958.2	70.6	70	2,781.6	0.0	74	842.3	547.9
Occupation												
Coal miner	79	5,532.3	2,666.4	41	6,435.2	4,887.2	230	4,460.6	2,717.3	202	1,873.3	1,818.0
Other	30	383.3	0.0	28	1,249.3	1,321.1	66	2,538.2	13.8	86	1,281.9	492.3
Severity of COPD												
Mild	12	1,965.5	2,534.1	13	639.5	3,311.2	39	1,073.8	479.2	43	362.6	739.8
Moderate	40	3,817.0	952.4	18	3,083.9	2,469.4	120	4,417.7	1,717.2	105	1,687.0	771.4
Severe	40	4,866.5	2,676.7	21	8,755.9	6,622.5	101	5,075.2	2,200.5	82	1,862.5	2,027.3
Very severe	17	4,566.3	2,063.2	17	3,007.3	635.3	36	3,024.2	4,969.5	58	2,469.2	2,250.3
Comorbidities												
Yes	76	3,531.7	2,164.7	42	4,512.6	4,005.5	193	3,788.1	2,310.4	134	2,474.4	1,746.0
No	33	5,459.0	1,397.9	27	4,047.9	2,560.6	103	4,489.0	1,747.5	154	1,020.0	1,140.3
Smoking												
Yes	53	5,353.8	2,081.2	26	4,234.6	2,404.5	100	4,581.2	2,112.0	82	1,791.4	1,096.7
No	56	2,942.9	1,791.8	43	4,388.9	4,066.3	196	3,751.8	2,115.8	206	1,659.1	1,551.7
Total	109	4,115.2	1,932.5	69	4,330.8	3,440.1	296	4,032.0	2,114.5	288	1,696.7	1,422.1

Abbreviation: TIV=trivalent influenza vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; AECOPD=acute exacerbation of chronic obstructive pulmonary disease.

approximately 10,000 CNY. Interestingly, the costs per hospitalization in our study were lower than those observed in two studies conducted in Beijing (*9*–*10*), indicating regional variations within China. Additionally, the hospitalization costs we found were lower than those reported in the United States (*11*) and Canada (*12*), but higher than those in India (*8*), Italy (*13*), Türkiye (*14*), and Vietnam (*15*). This comparison suggests that the economic burden caused by AECOPD in China is relatively high. Our study demonstrated that vaccination was associated with the greatest reduction in hospitalization costs due to the decreased number of hospitalizations.

In both the TIV group and the TIV&PPSV23 group, costs decreased significantly following vaccination, providing evidence that vaccination is correlated with a reduction in COPD-related expenses. This outcome aligns with findings from other studies (*16*–*17*). Research has identified risk factors for AECOPD, including smoking, the presence of comorbidities, and the severity of COPD (*1*,*3*). In our study, we observed an upward trend in costs with increasing COPD severity, while COPD patients without comorbidities exhibited lower costs.

The present study has several strengths. First, we utilized a self-controlled pre-and-post design to estimate the economic burden associated with exacerbation, pneumonia, and related hospitalizations in COPD patients. Second, the comparable epidemic intensity of pre- and post-vaccination influenza (*18*) made our study design particularly meaningful. Lastly, our study offered cost-savings evaluations for three vaccination groups — an influenza vaccine group, a PPSV23 group, and an influenza&PPSV23 group — within a single study.

That being said, our study also has limitations. One potential issue relates to the accuracy of cost estimates. Although we verified the bulk of costs associated with the project, some expenses were ultimately estimated by study participants; thus the accuracy of these costs

may be questionable. Nevertheless, we believe the impact of incomplete estimates will be negligible. Additionally, it is worth noting that COVID-19 interventions since February 2020 may impact the effect of vaccination. However, since AECOPD, pneumonia, and hospitalizations occur most frequently in the winter, the influence of COVID-19 interventions may be limited. Lastly, the small size of the PPSV23 group and sub-groups in all groups precluded accurate estimates for desirable comparisons — such as the vaccination impact by COPD severity.

In conclusion, the economic burden of AECOPD, pneumonia, and hospitalization related to COPD in patients residing in China is substantial. Immunization with influenza vaccine and PPSV23, either individually or in combination, can yield substantial reductions in costs, thereby lending support to extant vaccination guidance for patients with COPD.

Conflicts of interest: No conflicts of interest reported.

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SUPPLEMENTAL MATERIALS

SUPPLEMENTARY TABLE S1. Basic characteristics of four groups.

Variable	TIV group	PPSV23 group	TIV&PPSV23 group	Unvaccinated group	*P*
Age (years)					
<65	41	23	125	151	0.004
≥65	68	46	171	137	
Gender					
Male	94	52	226	214	0.09
Female	15	17	70	74	
Occupation					
Coal miner	79	41	230	202	0.01
Other	30	28	66	86	
Severity					
Mild	12	13	39	43	0.07
Moderate	40	18	120	105	
Severe	40	21	101	82	
Very severe	17	17	36	58	
Comorbidities					
Yes	76	42	193	134	0.003
No	33	27	103	154	
Smoking					
Yes	53	26	100	82	0.002
No	56	43	196	206	
Total	109	69	296	288	

Abbreviation: TIV=trivalent influenza vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine.

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