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Preplanned Studies

The Spectrum and Age-Sex Patterns Among Outpatients with Allergic Diseases — Yichang City, Hubei Province, China, 2018–2021

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Summary

What is already known about this topic?

Allergic diseases have affected an estimated 40% of the population in China. However, our understanding of the full spectrum of these diseases remains insufficient.

What is added by this report?

Between 2018 and 2021, Yichang City documented 625,929 outpatient visits mainly related to skin and mucous membrane allergies (77.90%) and allergic respiratory conditions (19.64%). In 2021, the occurrence of outpatient visits for conditions such as allergic rhinitis, acute atopic conjunctivitis, and atopic dermatitis increased. The demographic analysis revealed that male patients comprised the majority of the under 18 age bracket (56.05%), while female patients were predominantly represented in the 18 to 65 age bracket (61.79%).

What are the implications for public health practice?

This constitutes the first analysis of the spectrum of allergic diseases, utilizing regional outpatient data, which has substantial implications for understanding the disease burden.

Approximately 40% of the Chinese population is affected by allergic diseases, which pose potential threats to the respiratory system, skin, and digestive tract and may even be life-threatening (*1*). These common diseases include allergic rhinitis (AR), asthma, urticaria, atopic dermatitis (AD), and allergic contact dermatitis (ACD). Currently, most research within the country on allergic diseases concentrates specifically on major diseases and distinct age groups, leading to the unclear picture of the disease spectrum. Particularly, the majority of prior studies have employed cross-sectional designs and are lacking in longitudinal data on dynamic changes in these diseases (*2*–*3*). However, the era of big data in healthcare presents new possibilities. The utilization of regional healthcare big data can facilitate easier access to and analysis of medical data. This study applied the Yichang Healthcare Big Data Platform to elucidate the spectrum and distribution characteristics of allergy-related outpatients during the years 2018–2021 in Yichang City, Hubei Province. The findings demonstrated that the augmentation of allergic respiratory disease (ARD) visits in 2021 was primarily due to an uptick in AR, along with acute atopic conjunctivitis (AAC) and AD. For patients under 18, allergy outpatient visits were predominantly male, whereas those aged 18–65 were primarily female. Due attention should be directed toward AR, AAC, and AD, and future disease control and preventive measures should be optimized according to the age-sex specific pattern of allergic diseases.

This research study utilized allergy-related outpatient data derived from the Yichang Healthcare Big Data Platform, which accumulates data from all health institutions within its urban locales. Yichang City has accomplished active automated scrutiny, risk analysis, and consistent tracking of diverse diseases and health risk factors using this medical data. In relation to innovation and application in scientific research, approximately 20 research projects have been undertaken utilizing this medical data, encompassing epidemic features, environmental risk factors, medical expenditure, and genetic characteristics of diseases, among others. The information assembled includes demographic attributes, disease names, International Statistical Classification of Diseases' 10th revision (ICD-10) codes, and diagnosis timelines. This study incorporated all healthcare institutions in Yichang's urban regions (comprising 9 tertiary hospitals, 2 secondary hospitals, and 18 community health service institutions). The frequency data (excluding personal information) of primary diagnoses of allergic diseases in outpatient services were extracted employing the ICD-10. Supplementary Table S1 (available in https://weekly.chinacdc.cn) contains the specific ICD-10 codes for each disease studied. Quantitative

normal distribution data was defined by the mean and standard deviations, while non-normal distributions were reported through the median and interquartile range (IQR). Frequencies and percentages were highlighted for categorical variables, and the Mann-Kendall test was utilized for trend analysis. Differences in gender and age distributions were assessed using the chi-squared (χ^2) test. Data analysis was conducted using the R software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria).

Between 2018 and 2021, the Yichang City recorded a total of 625,929 outpatient visits attributable to allergic diseases. The male-to-female patient ratio was 0.84∶1, and the average frequency of visits for each individual was 2.01. The median age was 31 years for males (IQR: 7–55) and 34 years for females (IQR: 18–51), with an overall median of 33 years (IQR: 10–52).

The highest proportion of outpatient visits was attributed to allergic diseases of the skin and mucous membranes (77.90%). This was followed by ARD at 19.64%, severe anaphylaxis at 1.32%, ocular allergies (OA) at 0.86%, allergic diseases of the digestive tract at 0.02%, and other allergies at 0.25%.

A slight decrease in visits concerning skin-related and mucous membrane-related allergic diseases was noted over the four-year period, dropping from 78.81% to 76.28% (Mann-Kendall test, Z=−1.019, P=0.308). Conversely, visits involving ARD increased from 18.56% to 21.13% (Z=1.698, P=0.089) (Figure 1).

The predominant characterizations of allergic diseases affecting the skin and mucous membranes were other types of dermatitis (65.59%) and urticaria (13.81%). Similarly, ARDs primarily comprised of AR (59.30%) and asthma (40.42%). Among severe anaphylaxis cases, allergic purpura was significantly prevalent, accounting for 91.27%. In 2021, there was a substantial rise in outpatient visits for AD, AR, and AAC compared to preceding years (Table 1).

Age and gender distribution significantly affected the proportion of allergic diseases (χ^2=19,636.111, P<0.001). Amongst outpatients diagnosed with allergies, those under the age of 18 constituted 30.57% with males (56.05%) making up the majority. A significantly larger proportion (57.73%) fell within the age bracket of 18–65 years, with a predominance of females (61.79%), while 11.70% were individuals over 65 years of age, primarily males (56.10%). Allergic diseases that impacted the skin and mucous membranes were predominantly found among adults between 18 and 65 years (60.18%), with females forming the majority (62.19%). ARDs were most prevalent among adults of the same age group (50.02%) with a higher proportion of afflicted individuals being women (59.45%), while 41.76% were children under 18 years old, primarily male (64.70%). An overwhelming majority of severe anaphylaxis cases (61.74%), OA cases (51.44%), and allergic diseases affecting the digestive tract (60.54%) were found in children below 18 years old (Figure 2A).

The twelve leading disease subcategories were identified, ranked by the frequency of outpatient visits. We observed greater proportions of male patients under 18 years old for each category of allergic disease, while for the 18–65 age group, the proportions were

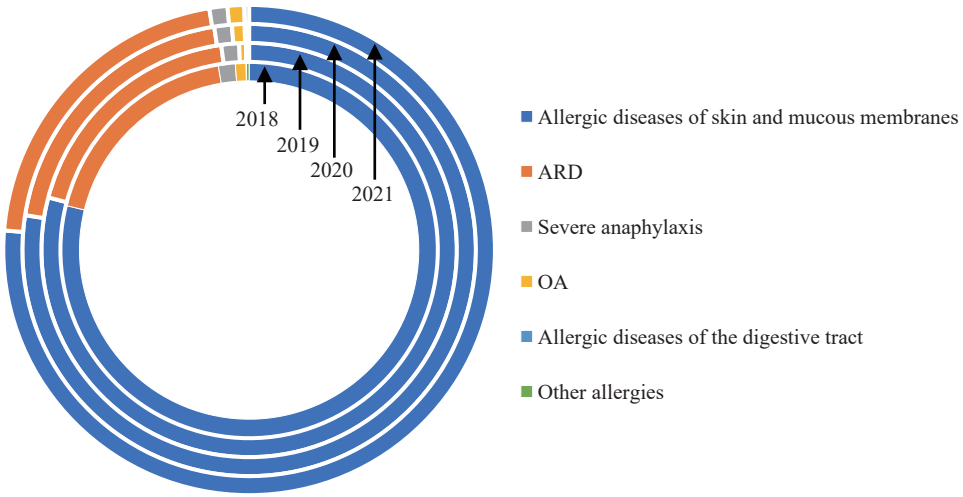

FIGURE 1. Composition of outpatient visits for various allergic diseases in Yichang City, Hubei Province, 2018–2021.
Abbreviation: ARD=allergic respiratory diseases; OA=ocular allergy.

TABLE 1. Number of outpatient visits for allergic disease in Yichang City, Hubei Province, 2018–2021.

Categories	2018	2019	2020	2021	Total
Allergic diseases of the skin and mucous membranes (*n*=487,615)					
Other dermatitis	76,322	89,964	65,284	88,275	319,845
Urticaria	16,748	19,425	13,461	17,688	67,322
Lichen simplex chronicus and prurigo	9,571	10,188	6,429	9,219	35,407
Allergic contact dermatitis	6,988	9,437	6,214	9,858	32,497
Unspecified contact dermatitis	2,514	2,734	1,790	2,504	9,542
AD	1,741	1,968	1,437	3,393	8,539
ARD (*n*=122,951)					
AR	15,635	17,659	15,492	24,127	72,913
Asthma	11,912	14,926	9,721	13,138	49,700
Upper respiratory tract hypersensitivity reaction, site unspecified	53	44	19	16	132
Allergic bronchopulmonary aspergillosis	21	24	32	53	130
Hypersensitivity pneumonitis due to organic dust	21	29	8	11	69
Allergic bronchopulmonary disorders	2	2	0	3	7
Severe anaphylaxis (*n*=8,252)					
Allergic purpura	1,997	2,178	1,412	1,945	7,532
Drug hypersensitivity reactions	122	162	82	85	451
Anaphylactic shock, unspecified	30	43	54	23	150
Food-related allergic reactions	15	9	26	42	92
Anaphylactic shock due to adverse effect of correct drug or medicament properly administered	2	5	5	7	19
Anaphylactic shock due to adverse food reaction	1	3	2	1	7
OA (*n*=5,371)					
AAC	1,376	921	1,133	1,941	5,371
Allergic diseases of the digestive tract (*n*=147)					
Allergic gastroenteritis and colitis	32	36	39	40	147
Other allergies (*n*=1,593)	344	391	354	504	1593
Total	148,962	174,252	125,951	176,764	625,929

Abbreviation: AD=atopic dermatitis; ARD=allergic respiratory diseases; AR=allergic rhinitis; OA=ocular allergy; AAC=acute atopic conjunctivitis.

higher for females. AR (50.92%), AD (55.09%), allergic purpura (65.60%), and AAC (51.44%) were prevalently noted in patients under 18 years of age. Interestingly, 65% of the children diagnosed with AR and AAC were male.

In contrast to other conditions, dermatitis (59.90%), urticaria (59.90%), asthma (56.86%), lichen simplex chronicus and prurigo (56.60%), allergic contact dermatitis (69.91%), unspecified contact dermatitis (59.89%), irritant contact dermatitis (76.18%) and dermatitis due to substances taken internally (72.77%) were primarily seen in adults aged 18–65 years. Furthermore, more than 66% of adults diagnosed with urticaria and allergic contact dermatitis were female (Figure 2B).

DISCUSSION

The total population of Yichang City as of 2021 stood at 3.91 million, with 1.60 million accounting for its urban populace. This investigation unveiled that the highest number of allergy-involved outpatient appointments in the Yichang City from 2018 to 2021 were due to skin and mucous membrane allergies (77.90%), with ARD forming the next largest category (19.64%). Main subsets of allergic diseases included other forms of dermatitis, AR, asthma, and urticaria. Further differences in age and gender regarding outpatient visits for specific allergic diseases were highlighted. A distinct retrospective cross-sectional investigation conducted on children's outpatient cases

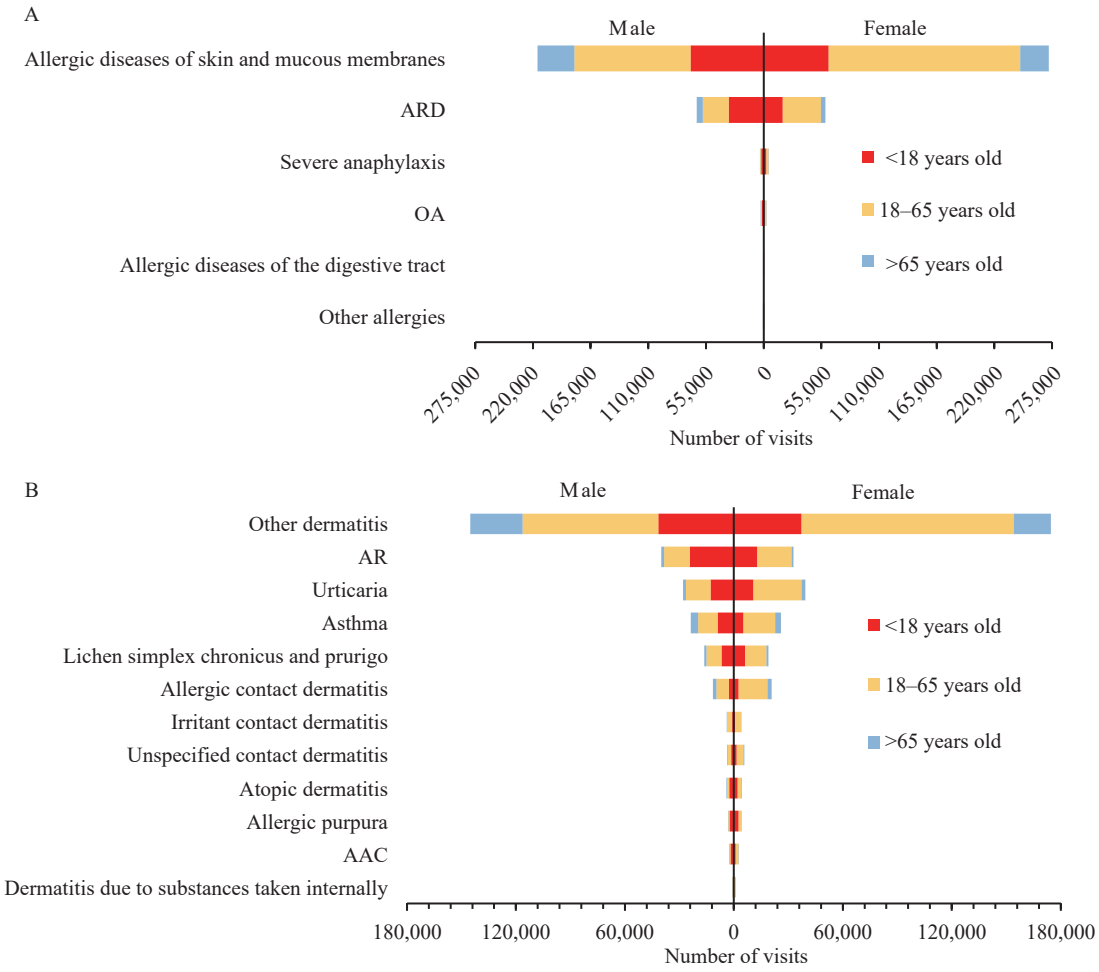

FIGURE 2. Age-sex patterns of outpatient visits for various allergic diseases in Yichang City, Hubei Province, 2018–2021. (A) Age-sex patterns for different disease categories; (B) Age-sex patterns for primary disease subcategories.
Abbreviation: AR=allergic rhinitis; AAC=acute atopic conjunctivitis; ARD=allergic respiratory diseases; OA=ocular allergy

with allergic diseases in a tertiary hospital in Botswana revealed asthma to be the most common disease, representing 61.2%, followed by AR, AD, AC, and food allergies (*2*). These findings differ from those of the Yichang study, which could be attributed to varying genetic and environmental prompts of allergic diseases across different populations, or potential disparities in age structure and sample size. Epidemiological research focusing on the spectrum of allergic diseases remains scarce globally (*2–3*). The acquisition of such insights is crucial for understanding which allergic diseases pose a significant risk to population health and for establishing healthcare service priorities.

The observed increase in outpatient visits for ARD from 2018 to 2021 can primarily be attributed to the surge in visits for AR in 2021, along with AAC and AD. This can be reasoned by the direct exposure of nasal mucosa, conjunctiva, and skin to the exterior environment — such exposure potentially makes these regions more prone to irritation and sensitization from ambient allergens, resulting in a heightened number of outpatient visits for AR, AAC, and AD. AD, a chronic, relapsing inflammatory skin condition akin to eczema, is frequently diagnosed. Current research indicates that direct skin contact with airborne allergens can prompt skin reactions in those with AD (*4*).

Owing to its subtropical location, the city of Yichang retains high humidity throughout the year, which engenders a favorable condition for dust mite proliferation. Dust mites, the main airborne allergens, rise concurrently with the increase in humidity levels (*5*). Prior research illuminates the frequent co-occurrence of AR and AC, owing to exposure to perennial airborne allergens such as dust mites, molds, and animal dander, or seasonal allergens like pollen. Over half of AR patients also experience symptoms of AC or conjunctivitis. This is presumably due to the

shared properties of the conjunctiva and nasal mucosa — they have the same type of epithelial cells, they show similar allergen reactivity, and both play a role in Immunoglobulin E (IgE)-mediated allergic inflammation, indicating shared pathological mechanisms. Plus, the presence of an anatomical link between the eyes and nasal mucosa through the nasolacrimal duct enables allergic reactions to spread from the conjunctiva to the nose (*6*).

In addition, the number of outpatient visits for asthma in Yichang City did not reveal a significant surge. The intricate interrelationship among asthma, allergies, and bronchial hyperreactivity is rapidly becoming clear, with multiple factors apart from allergens contributing to the development of asthma. The mechanisms implicated in asthma potentially exhibit more complexity when compared with AR, AC, and AD. Research conducted in Hong Kong Special Administrative Region (SAR), China, unveiled a substantial escalation in the prevalence of allergic rhinoconjunctivitis and atopic eczema among school-aged children between 1995 and 2001, positively correlating with frequent upper respiratory tract infections. However, the prevalence of asthma largely remained consistent (*7*). Future research is warranted to explore the correlation between the rise in the number of allergy-related visits and potential contributing factors like environmental allergens and upper respiratory tract infections.

Furthermore, in the population of allergic outpatients under 18 years, males superseded the females. Conversely, among those aged 18–65 years, females were more prominent. Studies have demonstrated that testosterone can suppress immune memory responses, inhibiting reactivity to the same antigen. Both epidemiological and experimental studies suggest that female hormones, often amplify the immune memory response, potentially intensifying allergic diseases. Estrogen, specifically, has been shown to bolster humoral immunity, antibody synthesis, and the activation and sensitization of mast cells. Such findings might underscore the predisposition of male children and female adults to allergies. Existing research indicates a shift in the prevalence of AR in Asia — from being predominantly male during childhood to becoming predominantly female in adulthood. A similar trend has been documented concerning asthma. Males exhibit higher total serum IgE levels and rates of allergic sensitization than females during the first year of life. These rates persistently rise in males through adolescence but decrease in adulthood, whereas rates in females remain steady (*8*). Besides hormonal influences, differential lifestyle factors, microbial diversity, dietary habits, and occupational preferences between males and females could drive this disparity and warrant further research (*8*).

Our study primarily found AD and allergic purpura in outpatient children under the age of 18. This observation mirrors findings from previous studies where AD predominantly surfaces in early life, affecting approximately 20%–30% of children compared to only 3% of adults. Longitudinal studies suggest that allergic conditions tend to manifest in a specific sequence, typically transitioning from AD in infancy to allergic asthma and AR later in life (*9*). Allergic purpura, a systemic vasculitis largely mediated by immunoglobulin IgA, is found in almost 90% of child cases. Moreover, the prevalence amongst children is 2–33 times higher than in adults (*10*).

The present study was subjected to certain limitations. First, there was a noticeable decline in the number of outpatient visits for allergic diseases during the coronavirus disease 2019 pandemic in 2020. This decrease may be attributed to fears of contracting the virus or stricter control measures implemented during this period. As a result, the total number of outpatient visits could potentially be an underestimation. Regardless, this research employed relative composition ratios for comparative reasons. Second, this study utilized the widely recognized ICD-10 codes. However, it is noteworthy that the ICD-10 falls short in providing an intricate classification system for diseases related to food allergies, possibly leading to some conditions being misclassified. Lastly, to maintain the integrity of the dataset, this study only incorporated data from urban-based medical institutions in Yichang City, primarily comprising urban residents.

In conclusion, considering the substantial rise in outpatient visits for AR, AAC, and AD during 2021, it is imperative that future efforts concentrate on the prevention and treatment of these three significant allergic diseases, along with investigating their root causes in Yichang. Further, attention ought to be directed towards examining the gender propensity of allergic diseases across diverse age groups.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE S1. Detailed listing of ICD-10 codes for allergic diseases.

Categories	Subcategories of diseases and corresponding ICD-10 codes
Allergic diseases of skin and mucous membranes	Other dermatitis (L30), urticaria (L50), lichen simplex chronicus and prurigo (L28), allergic contact dermatitis (L23), unspecified contact dermatitis (L25), atopic dermatitis (L20), irritant contact dermatitis (L24), dermatitis due to substances taken internally (L27), unspecified erythema multiforme (L51.9), angioneurotic oedema (T78.3), diaper dermatitis (L22), toxic epidermal necrolysis [Lyell] (L51.2), eczematous external otitis (H60.501), allergic rash (R21.X01), radiodermatitis (L58), eyelid dermatitis (H01.101), exfoliative dermatitis (L26), photocontact dermatitis [berloque dermatitis] (L56.2), solar urticaria (L56.3), erosive erythema multiforme (L51.800), lichenoid drug reaction (L43.2), acute skin change due to ultraviolet radiation (L56.9), nonbullous erythema multiforme (L51.0), serum-reactive urticaria (T80.603), allergic dermatitis of the eyelid (H01.154), and drug photoallergic response (L56.1)
Allergic respiratory diseases	Allergic rhinitis (J30.1, J30.2, J30.3, J30.4), asthma (J45, J46), upper respiratory tract hypersensitivity reactions at unspecified sites (J39.3), allergic bronchopulmonary aspergillosis (B44.101), hypersensitivity pneumonitis due to organic dust exposure (J67), and other allergic bronchopulmonary disorders (J98.413)
Severe anaphylaxis	Allergic purpura (D69.0), drug hypersensitivity reactions (T88.701), unspecified anaphylactic shock (T78.2), food-related allergic reactions (T78.101), anaphylactic shock due to the adverse effect of a correctly administered drug or medicament (T88.6), anaphylactic shock resulting from adverse food reactions (T78.0), and anaphylactic shock due to serum (T80.5)
Ocular allergy	Acute atopic conjunctivitis (H10.1)
Allergic diseases of the digestive tract	Allergic gastroenteritis and colitis (K52.200, K52.201, K52.202, K52.203, K52.204)
Other allergies	Unspecified allergy (T78.4), allergic otitis media (H65.101, H65.102)

Review

Advancements in the Worldwide Detection of Severe Fever with Thrombocytopenia Syndrome Virus Infection from 2009 to 2023

Lin Ai[1,&]; Wei Wang[2,&]; Zheng Teng[1,2,#]

ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) is a growing concern as an emerging tick-borne infectious disease originating from the SFTS virus (SFTSV), a recent addition to the *Phlebovirus* genus under the family of bunyaviruses. SFTS is typically identified by symptoms such as fever, thrombocytopenia, leukopenia, and gastrointestinal problems, accompanied by a potentially high case fatality rate. Thus, early and accurate diagnosis is essential for effective treatment and disease management. This review delves into the existing methodologies for SFTS detection, including pathogenic, molecular, and immunological technologies.

SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME

The severe fever with thrombocytopenia syndrome virus (SFTSV) is an emergent tick-borne virus causing severe fever and thrombocytopenia, accompanied by high mortality rates (*1*–*2*). Identified initially in 2009 within the Hubei Province, China, this virus fits into the *Bandavirus* genus of the *Phenuiviridae* family (*3*). It was later detected in Taiwan, China (*4*), Japan (*5*), the Republic of Korea (*6*), and Vietnam (*7*). Transmission of the SFTS disease is primarily via the arthropod vector, notably through tick bites (*8*). Transmission through animals such as cats (*9*), dogs (*10*), and cheetahs (*11*) is also reported. Cases of human-to-human transmission of SFTSV have been noted, involving contact with blood and bodily fluids, even in hospital settings (*12*–*13*). The potential for SFTSV transmission from pets to humans presents a risk to pet owners and veterinary professionals alike (*9*,*14*).

The clinical manifestation of SFTS typically presents with fever, thrombocytopenia, and leukocytopenia. Patients may also experience fatigue, chills, headaches, lymphadenopathy, and gastrointestinal symptoms, among other systemic manifestations like muscular symptoms and coagulopathy (*15*). The case fatality rate of SFTS patients varies across China, the Republic of Korea, and Japan, ranging from approximately 6% to over 40% (*2*,*16*–*17*). The case fatality rate can escalate to 75% in cases complicated by hemophagocytic syndrome (*18*). The world is yet without an effective clinical treatment for this condition, and work on the development of an inactivated vaccine against SFTS is still in progress. Consequently, the World Health Organization has designated SFTSV as a priority pathogen that requires urgent attention (*19*).

A variety of detection methods for SFTSV have been developed, encompassing pathogenic, molecular, and immunological approaches. Pathogenic detection includes virus isolation via cell culture and electron microscopy techniques (*3*,*20*–*21*). Nucleic acid amplification techniques such as reverse transcription-polymerase chain reaction (RT-PCR) (*22*–*23*), loop-mediated isothermal amplification (LAMP) (*24*), and recombinase polymerase amplification (RPA) (*25*). Rapid diagnostic tests, such as lateral flow assays, provide prompt results and prove beneficial in resource-limited environments (*3*). Serological assays, including enzyme-linked immunosorbent assays (ELISAs) (*26*), indirect immunofluorescence assays (IFAs) (*27*), and immunochromatographic tests (ICTs) (*28*), remain the most extensively used methods for identifying SFTSV-specific antibodies in patient serum or plasma.

This review will summarize the current landscape of SFTSV detection methods, The critical importance of prompt and precise diagnosis of SFTSV infection in patient management and disease control underscores the necessity for the development of rapid, sensitive, and specific diagnostic methods.

PATHOGENIC CHARACTERISTICS OF SFTSV

Structural and Genetic Analysis of SFTSV

SFTSV, a negative-sense RNA virus from the

Phenuiviridae family, typically possesses a spherical or pleomorphic structure, with a diameter measuring between 80 and 120 nm. It is an enveloped virus, characterized by a lipid bilayer and surface glycoproteins that form spike-like features (*20*–*21*). The genome of SFTSV is segmented into three distinct negative-sense RNA strands, specifically designated as small (S), medium (M), and large (L) segments (*20*). The S segment, containing 1,744 nucleotides, codes for the nucleocapsid protein (N) (*29*–*30*). The M segment, made up of 3,378 nucleotides, is responsible for coding the glycoprotein precursor (GPC) (*31*). Lastly, the L segment, with 6,368 nucleotides, codes for the RNA-dependent RNA polymerase (RdRp) (*32*).

The SFTSV N protein is a highly conserved 116-amino acid protein that forms the nucleocapsid through its interaction with the viral RNA. The N protein is composed of two domains: the N-terminal domain that interacts with the RNA, and the C-terminal domain that is involved in oligomerization and protein-protein interactions (*30*).

The glycoprotein precursor of SFTSV undergoes post-translational cleavage, forming spikes on the surface of the virus. The Gn protein plays a critical role in attaching to the receptors of the host cell, while the Gc protein facilitates fusion with the membranes of the host cell (*31*).

The SFTSV RdRp is a large protein with multiple domains. The N-terminal region contains the RNA-binding and capping domains, while the C-terminal region contains the polymerase domain, responsible for catalyzing the RNA replication and transcription (*32*).

Electron Microscopy (EM) for SFTSV

SFTSV presents as spherical or pleomorphic particles, with diameters ranging between 80 and 120 nm. The virus also features a lipid envelope with prominent surface spikes, approximately 12–20 nm in length, and houses a dense core protecting the vital genomic material, which was conducted by EM analysis (*3*). Then, the full-length structure and 3D model of SFTSV L protein by cryogenic EM were reported (*28*,*33*–*34*).

Virus Isolation

This process of isolating SFTSV often includes the introduction of clinical samples or cell culture supernatants into susceptible cell lines. This is then followed by observing cytopathic effects (CPE) and the verification of viral replication via molecular techniques (*3*). Numerous studies have reported success in isolating SFTSV from a range of sources, including patient samples, ticks, and animals that have been experimentally infected (*3*,*35*–*39*).

It's important to note that SFTSV can infect a variety of cells, including L929, Vero E6, Vero, and DH82 cells. However, CPEs were only identified in DH82 cells (*3*). Furthermore, Vero cells were employed to isolate SFTS at temperatures of 37 °C and 39 °C, suggesting that the SFTSV strain ZJ2013-06 from a patient demonstrated limited replication at 39 °C as per the research conducted by Feng et al. (*35*).

Ten infective SFTSVs were isolated successfully from various tick species in one 2021 study (*38*). Moreover, the viral sequences extracted from the ticks demonstrated remarkable homology to the sequences previously isolated from SFTS patients from the same region of sample collection.

Wei et al. (*39*) conducted a study on the ability of SFTSV to infect BEAS-2B cells. Utilizing cell culture techniques, they assessed the overall antibody production in the serum as well as the viral load in the tissue of mice infected with SFTSV via aerosol exposure.

Virus isolation has been utilized in the SFTSV transmission cycle. According to a study by Jiao et al., goats inoculated with SFTSV showed no disease signs and did not expel the virus through either respiratory or digestive routes. This finding suggests that without specific arthropod species as carriers, an efficacious viral transmission cycle cannot be established in natural conditions (*36*).

NUCLEIC ACID DETECTION

Detection of SFTSV genome could be achieved by different nucleic acid detection techniques such as RT-PCR (*13*,*40*–*43*), real-time RT-PCR (*23*,*28*,*41*, *44*–*48*), LAMP (*24*,*49*–*50*), as well as RPA (*25*,*51*–*52*).

Conventional Nucleic Acid Detection

The S segment codes for the nucleocapsid protein — a crucial element for the processes of viral assembly and replication (*29*). A two-tube multiplex real-time RT-PCR assay, designed for the identification of four hemorrhagic fever viruses: SFTSV, Hantaan virus, Seoul virus, and the dengue virus. It targets the nucleocapsid protein in the SFTSV genome (*47*).

The ability to differentiate between SFTSV strains can be facilitated by the M segment. A one-step RT-PCR assay targeting this M segment was developed by Sun et al. (*23*), which exhibited high specificity and sensitivity and was capable of detecting as few as 10 copies of the viral RNA per reaction.

The L segment — responsible for encoding the RNA-dependent RNA polymerase — is frequently targeted in SFTSV RT-PCR assays due to its relatively preserved characteristics. This focus on the L segment affords significant specificity in the detection of SFTSV (*32*).

RT-PCR and real-time RT-PCR assays are widely used for the detection and quantification of SFTSV in clinical samples, such as blood, serum, and cerebrospinal fluid (*43*,*53*–*55*). They are also employed in epidemiological investigations, such as tick and animal infected surveillance, analysis of viral genetic diversity, as well as a crucial role in the evaluation of antiviral drugs and vaccines against SFTSV (*9*,*36*,*56*–*61*).

Rapid Nucleic Acid Detection

The method of LAMP exhibits considerable potential for SFTSV detection given its efficiency, rapidity, and economic feasibility (*62*–*63*). The one-step, single-tube reverse transcription LAMP assay for rapid identification of RNA from SFTSV with a detection limit of 10×50% tissue culture infective dose ($TCID_{50}$) per mL, demonstrated high specificity and sensitivity. After combining with the fluorescent detection reagent (FDR) method, results could be determined by observing a color change within 30 min (*64*). Jang et al. developed a multiplex RT-LAMP to identify larger segments and GroES genes for SFTSV and *Orientia tsutsugamushi* (OT) (*24*). The sensitivity of the multiplex SFTSV/OT/Internal control (IC) RT-LAMP assay proved comparable to that of the commercial PowerChek™ SFTSV Real-time PCR (91.3% *vs*. 95.6%). Moreover, it displayed a higher sensitivity (91.6%) than the LiliF™ TSUTSU nested PCR (75%), with the multiplex SFTSV/OT RT-LAMP assay exhibited 100% specificity. The LAMP assay has been successfully implemented in clinical specimens from both humans (*50*,*64*–*66*) and cats (*67*), indicating promising applications.

RPA is a novel isothermal nucleic acid amplification technique that offers rapid, sensitive, and specific detection of SFTSV with constant temperature between 37 and 42 °C as well as eliminates the need for thermal cycling equipment (*68*–*70*). RPA assays can be combined with various detection methods, such as fluorescence, lateral flow, or colorimetric detection, to facilitate rapid and straightforward readouts (*71*–*72*).

Zhou et al. implemented the RT-RPA assay to detect SFTSV in serum samples (*25*). The detection limit was illustrated to be 241 copies per reaction at a 95% probability, with a sensitivity and specificity rate of approximately 96.00% and 98.95% respectively. Thus, the rapid RT-RPA assay presents itself as a promising candidate for point-of-care detection methods of SFTSV.

The advent of molecular technology has facilitated the development of novel detection methods for SFTSV, utilizing CRISPR-Cas13a (*73*). Huang et al. (*52*) and Park et al. (*74*) applied CRISPR-Cas12a system combined with RT-RPA to detect SFTS. In Huang et al.'s report, three copies of the L gene from the SFTSV genome per reaction were enough to ensure stable detection within 40 min. In Park et al. research, it successfully diagnosed SFTSV infections with the reaction time of 50 min from blood plasma without cross-reactivity to other viruses.

IMMUNOLOGICAL TEST

Serological assays, which detect SFTSV-specific antibodies in patients' or animals' serum or plasma, have been extensively utilized. These assays comprise ELISAs (*26*,*35*,*75*–*78*), IFAs (*45*,*78*), and ICTs (*28*).

ELISAs for SFTSV Detection

Various SFTSV-specific antigens have been employed in ELISAs, encompassing SFTSV nucleocapsid protein (NP), glycoprotein (GP), and non-structural protein (NSs). Predominantly, NP-based ELISA is utilized and has demonstrated superior diagnostic precision for SFTSV serodiagnosis (*26*,*79*).

A sandwich ELISA predicated on recombinant N protein for the detection of total antibodies targeting this virus in humans and animals (*36*). SFTSV-specific IgM antibodies detectable in patient serum merely three days post-symptom onset, peaking approximately two weeks later, have also been revealed (*78*). Furthermore, SFTSV-specific IgG antibodies became detectable about six days post-symptom onset, persisting up to six months. In a report by Yu, recombinant SFTSV-N (rSFTSV-N) protein was produced using an *Escherichia coli* expression system and purified (*80*). Additionally, Yu established

rSFTSV-N protein-based IgG ELISA and IgM ELISA systems.

ELISA methods are currently being extensively utilized to monitor SFTSV infection in humans as well as animals. According to a report by Tran et al. (*78*), the seroprevalence of anti-SFTSV IgM or IgG was recorded at 3.64% (26 out of 714) with a high IgM antibodies positivity titer >80 (0.28%, 2 out of 714). Lee et al. (*75*) developed a competitive ELISA for diagnosing STFV in bovine sera using a monoclonal antibody where lab-immunized positive sera exhibited a 98.1% consistency with IFA results. A 2020 study by Duan et al. (*81*) introduced enzyme-antibody-modified gold nanoparticle probes for the ultrasensitive detection of the nucleocapsid protein in SFTSV, where the detection limit for NP was 0.9 pg/mL, demonstrating good specificity and reproducibility.

Utilizing IFAs for the Detection of SFTSV

The IFA technique, which is recombinant antigen-based, utilizes recombinant viral proteins from a heterologous system as the source of the antigen. A case in point is the research conducted by Tran et al. whereby serum samples from 714 healthy Vietnamese residents were collected (*78*). To assess the SFTSV seroprevalence, the samples underwent IFA, ELISA, and the 50% focus reduction neutralization test (FRNT50) assay. The neutralizing antibodies against SFTSV recorded a range of 15.5 to 55.9 in terms of titer.

Utilizing ICAs for SFTSV Detection

Upholding the principle of antigen-antibody interaction, immunochromatographic tests employ capillary action to transport the sample along the strip, where either antibodies or antigens are immobilized and labeled. (*28*).

Wang et al. (*28*) implemented the ICA method, which involves the use of gold nanoparticles coated with recombinant SFTSV to simultaneously detect both IgG and IgM antibodies to SFTSV. This method was developed and assessed using 245 positive serum samples from China CDC of SFTSV infection. The ensuing results revealed positive and negative coincidence rates of 98.4% and 100% for IgM, as well as 96.7% and 98.6% for IgG, respectively.

DISCUSSION

In conclusion, a myriad of diagnostic methods have emerged and have been implemented for recognizing SFTSV infection. This includes etiological, immunological, and molecular methodologies. While strides have been made in detecting SFTSV, substantial efforts remain regarding standardization and automation, along with the cultivation of multiplex assays for enhancing detection efficiency and accuracy. As a result, forthcoming research should prioritize resolving these challenges, whilst seeking novel diagnostic approaches that will aid us in battling this lethal disease.

For consistent and trustworthy results vital for patient care, it is essential that all labs adopt uniform methodologies and procedures for detecting SFTSV. Without such standardization, the validity and reliability of SFTSV detection can fluctuate across different labs, impeding effective identification and containment of virus outbreaks. Automating these techniques could enhance efficiency, minimize costs, and allow labs to tackle larger volumes of samples in less time. Moreover, automation mitigates the risk of human errors, thereby enhancing the accuracy and reliability of the results obtained. Implementing multiplex assays could notably enhance the effectiveness and accuracy of SFTSV detection. These assays allow for the simultaneous detection of multiple pathogens in a single sample. Consequently, labs could identify SFTSV as well as other tick-borne diseases with similar symptoms, such as *Anaplasma phagocytophilum* and *Borrelia burgdorferi*. Multiplex assays would be especially beneficial in environments where multiple tick-borne diseases are prevalent.

SFTSV represents a significant health threat that necessitates prompt and precise identification to facilitate appropriate treatment and manage potential outbreaks. It is recommended that standardization and automation be prioritized in conjunction with the development of multiplex assays to enhance the detection effectiveness and precision. The introduction of innovative diagnostic approaches, such as next-generation sequencing and biomarker recognition, could potentially yield more meticulous and sensitive detection methods for SFTSV. Undertaking these challenges is integral to the effective containment and prevention of this virus' spread.

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Recollections

The "Paired Learning by Doing" Approach for Capacity Building Derived from the China-UK-Tanzania Pilot Project on Malaria Control During 2015–2018

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BACKGROUND

China's growing prosperity has led to an increased role in international affairs, particularly in global health cooperation. Alongside sending medical teams abroad, China's health authority is gradually expanding its South-South cooperation in public health. However, due to a late start in global health initiatives and limited experience in organizing, coordinating, and implementing intervention projects overseas, China still faces significant challenges in global health, particularly in the local context. Recognizing the longstanding partnership between the Chinese and British governments, they have identified global health as a new area of strategic cooperation. In 2012, the former UK Department for International Development (DFID) initiated a new type of health development cooperation project named the China-UK Global Health Support Programme (GHSP).

Malaria is a highly prevalent infectious disease that poses a significant threat to nearly half of the global population. The African Region of the World Health Organization (WHO) is especially susceptible, with approximately 95% of all malaria cases occurring in this region. Tanzania is among the four African countries that contribute to more than half of all malaria-related deaths, with a mortality rate of 4% (*1*). As a result, Tanzania faces substantial obstacles in the prevention and control of malaria. With the remarkable achievement in malaria control and elimination, China's extensive expertise in this field has played a pivotal role in shaping the basis of China-Africa collaboration.

The China-UK-Tanzania Pilot Project on Malaria Control signifies China's inaugural endeavor in public health cooperation in Africa. This project represents a significant milestone in the adoption of China's "going global" approach, building on the initial outputs of the GHSP. The primary aim of the pilot project is to apply China's wealth of public health expertise and best practices in collaboration with developing nations. The project seeks to accomplish three main objectives: 1) document the lessons learned and experiences gained in implementing China's novel health cooperation model, 2) serve as a successful model for future bilateral and multilateral collaborations, and 3) support partner countries in enhancing global health capacities. The National Institute of Parasitic Diseases (NIPD) at the China CDC and the Chinese Center for Tropical Diseases Research (NIPD-CTDR) lead the pilot project, which engages 11 institutions in China and abroad, including the Ifakara Health Institute (IHI) (*2*). Following approximately three years of implementation, malaria cases in the intervention areas have reduced by over 80% (*3*). Additionally, the project has facilitated the development of an effective intervention strategy known as the "1,7-malaria Reactive Community-based Testing and Response" (1,7-mRCTR) approach through the sharing of Chinese anti-malaria technology and practices (*4*).

To accomplish its objectives, the pilot project implemented a novel approach to capacity building known as "Paired Learning by Doing". This method involved close collaboration between Chinese employees, local experts, and staff members, with the goal of enhancing the capabilities of all individuals involved. Specifically, Chinese staff were paired with partners from the National Malaria Control Programme (NMCP), the IHI, and the local health system (*5*).

The project coordination committee and expert team provided technical assistance and evaluated the progress of the project. The "Learning by Doing" approach, specifically the "paired approach," has been widely utilized and has significantly strengthened the capacity of Chinese healthcare professionals to engage in global health activities. Moreover, this approach has played a pivotal role in training a local team for malaria

prevention and control, thus ensuring the long-term sustainability of the project.

Steps Towards Implementing a "Paired Learning by Doing" Approach in a Pilot Project

Recruitment of Chinese team members and pre-assignment training organization. According to the project work plan, young professionals recommended by provincial disease prevention and control centers or institutes of parasitic diseases, which are partners of the NIPD, underwent a series of interviews and evaluations. A total of 17 young experts, holding a bachelor's degree or higher in public health or sociology, were selected for the project from various provincial centers for disease control and prevention (CDCs) or institutes of parasitic disease. These included the Shandong Institute of Parasitic Disease, the Yunnan Institute of Parasitic Disease, Anhui Provincial CDC, Guangxi Zhuang Autonomous Region CDC, Chongqing CDC, and Sichuan CDC. The selected candidates possessed undergraduate or higher degrees in various fields such as malaria laboratories, epidemiology, vector biology, pathogen biology, information systems, and geographic systems. They were also proficient in foreign languages, facilitating effective communication and professional academic writing. All participants had prior experience in malaria control, either through working with the Global Fund to Fight Malaria or studying abroad, and were eager to contribute to global health. Prior to their departure from their respective locations, these professionals underwent training in China. The training sessions focused on the project's objectives, specific targets, and task assignment. Emphasis was placed on teamwork, effective communication and collaboration with local colleagues, as well as respect for local customs and culture. An annual project wrap-up meeting was held in Shanghai to review and summarize the project's progress and outcomes.

Assembling the Tanzania teams and pairing them with the Chinese teams in the field. Tanzania formed teams comprised of local experts in various disciplines, such as epidemiology, health statistics, vector biology, computer informatics, pathogenesis, and clinical medicine, to ensure efficient fieldwork. To promote ongoing collaboration and sustainability, Chinese professionals were paired with their Tanzanian counterparts. Team grouping was based on professional backgrounds including epidemiology, health statistics, pathogen biology, vector biology, computer informatics, and financial auditing. This pairing facilitated joint discussions on implementation protocols, fieldwork participation, data analysis, and collaborative problem-solving for activities such as malaria surveillance, case testing, case treatment, and vector control. Each group worked in Tanzania for a period of 2–3 months and received 1–2 weeks of quarterly training to enhance their foreign aid capabilities. Training sessions allowed teams to update fieldwork progress, share experiences, discuss future plans and actions, analyze data, and negotiate solutions to project challenges. This approach fostered knowledge sharing and training opportunities between teams in both countries.

Training the paired trainer and local community health workers. During the initial phase, a total of 37 highly skilled young volunteers were recruited by the experts. This group included 21 field researchers, 4 microscopists, 8 community nurses, and 4 community doctors who had previous experience in community malaria control. The volunteers underwent a comprehensive training program consisting of 6 days of theoretical training followed by 8 days of practical training focused on malaria prevention and control. The training covered important aspects such as the objectives of the project, technological roadmaps, and fundamental intervention skills, including case management, vector control, and health education. This training served as a strong foundation for conducting baseline surveys, monitoring activities, and implementing interventions in the project areas.

During the Pilot Project, the support of the Talented Young Scientist Program (TYSP) of the Chinese Ministry of Science and Technology enabled a Tanzanian entomologist, Tegemeo Gavana, to work for one year in the laboratory of the NIPD. During this time, Gavana gained expertise in laboratory techniques of molecular biology, specifically in the identification of *Anopheles* species and testing for *Plasmodium* parasite infection from these mosquitoes. This knowledge and skill set laid a solid foundation for conducting vector tests in the project.

Throughout the interventions, the project also provided comprehensive training on malaria prevention and control techniques for healthcare professionals. This training covered various aspects, including laboratory testing for malaria, standardized case treatment, follow-up management, vector surveillance, parasite control, and information reporting. The primary objective of this training was to

enhance the skills of healthcare professionals in malaria prevention and control and to establish a local team capable of providing continuous and effective services in the community.

Rotation and management of Chinese field teams. Each year, teams comprised of 5 to 6 Chinese members are sent to Tanzania for a period of approximately 3 months, targeting the peak season of malaria transmission. At the conclusion of each rotation, the majority of the Chinese field team members are replaced while a selected few remain. From 2016 to 2018, a total of 32 individuals comprising 6 groups were deployed to provide on-site technical support in the country. The team leader is responsible for overseeing all activities in the field, ensuring adherence to the work plan, and fostering problem-solving skills among team members. Weekly team meetings are held to allow for progress reporting, analysis of collected data, discussion of field results, and resolution of project-related issues.

The Effects and Implications of the "Paired Learning by Doing" Approach

The novel "Learning by Doing" approach, specifically in the form of "paired," has proven to be an essential and effective element contributing to the success of the Pilot Project. This approach can be utilized when cooperation partners are able to establish mutual understanding from the outset. By fostering close collaboration and mutual learning through paired interactions in the field, the approach has significantly enhanced the capacity of both Chinese and Tanzanian members. Consequently, upon their return home, many Chinese team members received promotions. Notably, following their participation in multiple aid projects in Africa, some members from the Anhui and Shandong provinces assumed leadership positions within their respective organizations, while others became recognized experts in China's foreign aid programs.

In addition to the aforementioned outcomes, there are broader implications of the "Learning by Doing" approach in the context of pairing individuals.

Establishment of a global health talent pool in China. This initiative involved the selection of highly skilled professionals from various provincial centers for disease control and prevention, such as the NIPD, Shandong Institute of Parasitic Disease, Yunnan Institute of Parasitic Disease, Anhui Provincial CDC, Guangxi Zhuang Autonomous Region CDC, and Chongqing CDC. These experts were carefully chosen for their comprehensive perspective and practical experience in healthcare. By actively addressing real-world challenges within the project and engaging in on-site communication and coordination with the WHO, Tanzanian experts, and non-governmental organizations, they gained invaluable knowledge and expanded their horizons. To ensure efficient project management and foster the professional growth of the team, the project implemented a robust project management framework which included expert committees, a project officer, field working groups, and community volunteer teams.

Improvement of the capacity of local healthcare services. The successful implementation of the Pilot Project owes much to the efforts of 37 dedicated and talented young volunteers who formed a community worker team in Rufiji District, Tanzania. Their contribution laid a strong foundation for the project's seamless progress and subsequent effective malaria control measures. In addition, 50 local staff members received comprehensive training on indoor residual spraying (IRS) techniques to control infected areas and eliminate Anopheles larvae. Furthermore, 37 clinicians, medical workers, and volunteers underwent training in case management, vector control, and health education. These interventions resulted in the development of a cadre of skilled professionals and technical staff members. Notably, two Tanzanian experts were given the opportunity to study and work in China, thanks to funding from the Chinese government's TYSP. After completing their diplomas, they returned to their homeland to spearhead efforts in training local personnel on malaria control techniques.

Enhancement of local capacity for malaria control and strategic implementation. In order to align with the infrastructure and health conditions of the local community, expert discussions were held between Chinese and Tanzanian professionals to modify the Chinese "1-3-7" approach to the 1,7-mRCTR approach for malaria prevention and control. This collaboration involved local institutions engaged in malaria prevention and control, as well as the establishment of mobile microscopic examination stations. Furthermore, a locally-tailored electronic reporting system was developed based on the Open Data Kit (*6*), which is similar to the Chinese disease surveillance system. Researchers in the field can now utilize this system to gather epidemiological information on reported malaria cases, enabling prompt detection and reporting. The implementation

of this system has not only boosted the efficiency and effectiveness of malaria control efforts but has also bolstered the monitoring and management capabilities of local institutions. This adaptation has resulted in a significant reduction in malaria cases and has reinforced the capacity for local control (*7*–*8*).

Leveraging the Involvement of Private Sectors

Moreover, a productive platform for international cooperation has been established, facilitating successful collaboration among various stakeholders. By means of active communication and coordination, Fosun Pharma was engaged in the cooperation and donated 500,000 Chinese Yuan worth of Dihydroartemisinin and Phosphate Piperaquine (D-ARTEP), an oral artemisinin-based medication. This initiative has not only rescued numerous local patients but also elevated the standardized cure rate for malaria (*3*,*9*).

CONCLUSION

The successful implementation and sustainable development of the Pilot Project rely on the capacity building approach known as "Learning by Doing" through the "paired" method. This approach has effectively facilitated mutual learning between personnel from China and Tanzania, enabling them to collaboratively address local challenges. Additionally, it equips the project team with the necessary skills, knowledge, and resources to deliver the project and ensure its long-term sustainability.

Building upon the achievements of the Pilot Project, a follow-up initiative called the China-Tanzania Demonstration Project on Malaria Control, funded by the BMGF, was carried out from 2019 to 2023. The aim is to replicate the success and extend the work beyond the Pilot Project. This inclusive approach of "Learning by Doing" through "paired" collaboration has the potential to serve as a model for future South-South health development cooperation projects.

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Methods and Applications

An Autoregressive Integrated Moving Average Model for Predicting Varicella Outbreaks — China, 2019

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ABSTRACT

Introduction: Varicella, a prevalent respiratory infection among children, has become an escalating public health issue in China. The potential to considerably mitigate and control these outbreaks lies in surveillance-based early warning systems. This research employed an autoregressive integrated moving average (ARIMA) model with the objective of predicting future varicella outbreaks in the country.

Methods: An ARIMA model was developed and fine-tuned using historical data on the monthly instances of varicella outbreaks reported in China from 2005 to 2018. To determine statistically significant models, parameter and Ljung-Box tests were employed. The coefficients of determination (R^2) and the normalized Bayesian Information Criterion (BIC) were compared to selecting an optimal model. This chosen model was subsequently utilized to forecast varicella outbreak cases for the year 2019.

Results: Four models passed parameter (all $P<0.05$) and Ljung-Box tests (all $P>0.05$). ARIMA $(1, 1, 1)\times(0, 1, 1)_{12}$ was determined to be the optimal model based on its coefficient of determination R^2 (0.271) and standardized BIC (14.970). Fitted values made by the ARIMA $(1, 1, 1)\times(0, 1, 1)_{12}$ model closely followed the values observed in 2019, the average relative error between the actual value and the predicted value is 15.2%.

Conclusion: The ARIMA model can be employed to predict impending trends in varicella outbreaks. This serves to offer a scientific benchmark for strategies concerning varicella prevention and control.

Varicella, or chickenpox, is a prevalent childhood disease resulting from varicella-zoster virus infection. As the third most reported vaccine-preventable infectious disease in China, varicella imposes a substantial socio-economic burden (*1*). The disease is notable for its tendency to cause outbreaks and epidemics. Since 2006, these outbreaks have been reported through the Public Health Emergency Management Information System in China (*2*). Utilizing this system facilitates the timely detection of epidemiological trends associated with varicella outbreaks offering vital early warning signals. Such early warnings are particularly crucial for the prevention and control of varicella outbreaks, hence highlighting their significant role in public health.

The autoregressive integrated moving average (ARIMA) models, accommodating alterations in trends, variations in periodicity, and random disturbances within a time series, have seen extensive application in predicting infectious diseases (*3*–*5*). Our study aimed to depict the temporal patterns of varicella outbreak cases in China spanning 2005–2018, assess the practicality of employing ARIMA models to project upcoming monthly varicella outbreak cases, and contribute empirical evidence for early alarms and effective prevention measures to suppress varicella outbreaks.

METHODS

Data Source

Per the "*National Public Health Emergency Related Information Reporting Management Standards*" distributed by the Ministry of Health's General Office on December 27, 2005, any instance of more than ten varicella cases within the same school, kindergarten, and other related units in a single week is classified as a varicella outbreak. Such outbreaks are mandated to be reported via the public health emergency information reporting system. Our research involved the extraction of varicella outbreak surveillance data from January 2005 to November 2019. This data was divided into segments for model development and model validation. We used the monthly varicella outbreak cases from 2005 to 2018 to construct the model, while the 2019 monthly data was employed to validate the

model and generate predictions.

Development of the ARIMA Model

ARIMA models take the form of ARIMA (p, d, q)×(P, D, Q)s. Parameters d (the degree of differencing) and D (moving average) are numbers of differences required to stabilize the time series. Parameters p (the order of autoregression) and q (the order of moving average) are simple numeric parameters. Parameters P (seasonal autoregression) and Q (seasonal integration) are seasonal parameters, and s is the length of the seasonal period.

The construction and prediction of the ARIMA model consist of three steps. First, *Time series stabilization*: we assessed stationarity and seasonality by graphing a time series plot of the monthly varicella outbreak cases. The trend and seasonality of the initial sequence were eliminated by taking the ordinary and seasonal differences. The time series' stationarity was then determined through the analysis of the stabilized sequence graph as well as the autocorrelation function (ACF) and partial autocorrelation function (PACF). Second, *model identification and diagnosis*: the values of d and D were determined based on the trend differences and seasonal variations. The values for p and q, and P and Q were permitted to vary between 0 and 2, and were assessed individually in model construction. Each proposed model had to pass the Ljung–Box and parameter tests. The most suitable model was subsequently selected based on the highest coefficients of determination (R^2) and the lowest normalized Bayesian Information Criterion (BIC). Lastly, *prediction*: the fitted model was used to project the number of monthly varicella outbreaks for 2019 (*4*).

Data Analysis

The analysis of the data was performed utilizing the SPSS software (version 26.0, IBM, Armonk, NY, USA). The Mann-Kendall trend test was utilized to evaluate the outbreak trends. A significance level was established at $P<0.05$.

RESULTS

Temporal Analysis

From 2005 to 2018, China reported 246,772 outbreak cases in 8,545 varicella outbreaks. The time series mapping of these cases revealed a statistically significant decline from 2007 to 2011 ($Z=-2.25$, $P<0.05$). However, from 2012 to 2018, there was a notable increase ($Z=2.63$, $P<0.05$). When decomposed, the time series exhibited three components: random errors, periodic factors, and long-term trend factors. The data demonstrated seasonal characteristics, with major and minor epidemic peaks recurring annually (Figure 1).

Stabilization of Time Series

The ARIMA model was developed using monthly instances of varicella outbreaks spanning from January 2005 to December 2018. Upon inspection of Figure 1, it became apparent that the series displayed non-stationary characteristics, thus necessitating the stabilization of the series through the incorporation of one-order ordinal and seasonal differences. The stabilized sequence, as depicted in Supplementary Figure S1 (available in https://weekly.chinacdc.cn/), did not exhibit a pronounced upward or downward trend. Supplementary Figure S2 (available in https://weekly.chinacdc.cn/) illustrates the autocorrelation coefficient of the stationary series experiencing a swift decrease following a brief delay period. This observation suggests that the modified time series tended toward stationarity subsequent to differencing adjustment. Consequently, this procedure assigned the parameters d and D as 1.

Model Identification and Diagnosis

The initial model was designated as ARIMA (p, 1, q)×$(P, 1, Q)_{12}$. The individual values for p, q, P, and Q were adjusted independently, ranging from 0 to 2. Following this iterative adjustment, four models successfully passed the parameter tests, all with $P<0.05$, and the Ljung-Box tests, all with $P>0.05$: ARIMA (2, 1, 0)×$(0, 1, 1)_{12}$, ARIMA (1, 1, 0)×$(0, 1, 1)_{12}$, ARIMA (1, 1, 1)×$(0, 1, 1)_{12}$, and ARIMA (1, 1, 1)×$(2, 1, 0)_{12}$. Due to its superior R^2 and the minimal standardized BIC, ARIMA (1, 1, 1)×$(0, 1, 1)_{12}$ was selected as the optimal model (Table 1). The autoregressive coefficients of the model residuals all fell within the control line, as depicted in Supplementary Figure 3 (available in https://weekly.chinacdc.cn/), suggesting that the residual error was random and affirming the validity of the chosen model.

Prediction

Utilizing the optimal ARIMA (1, 1, 1)×$(0, 1, 1)_{12}$ model, we predicted varicella outbreak cases from January through November 2019. The actual values

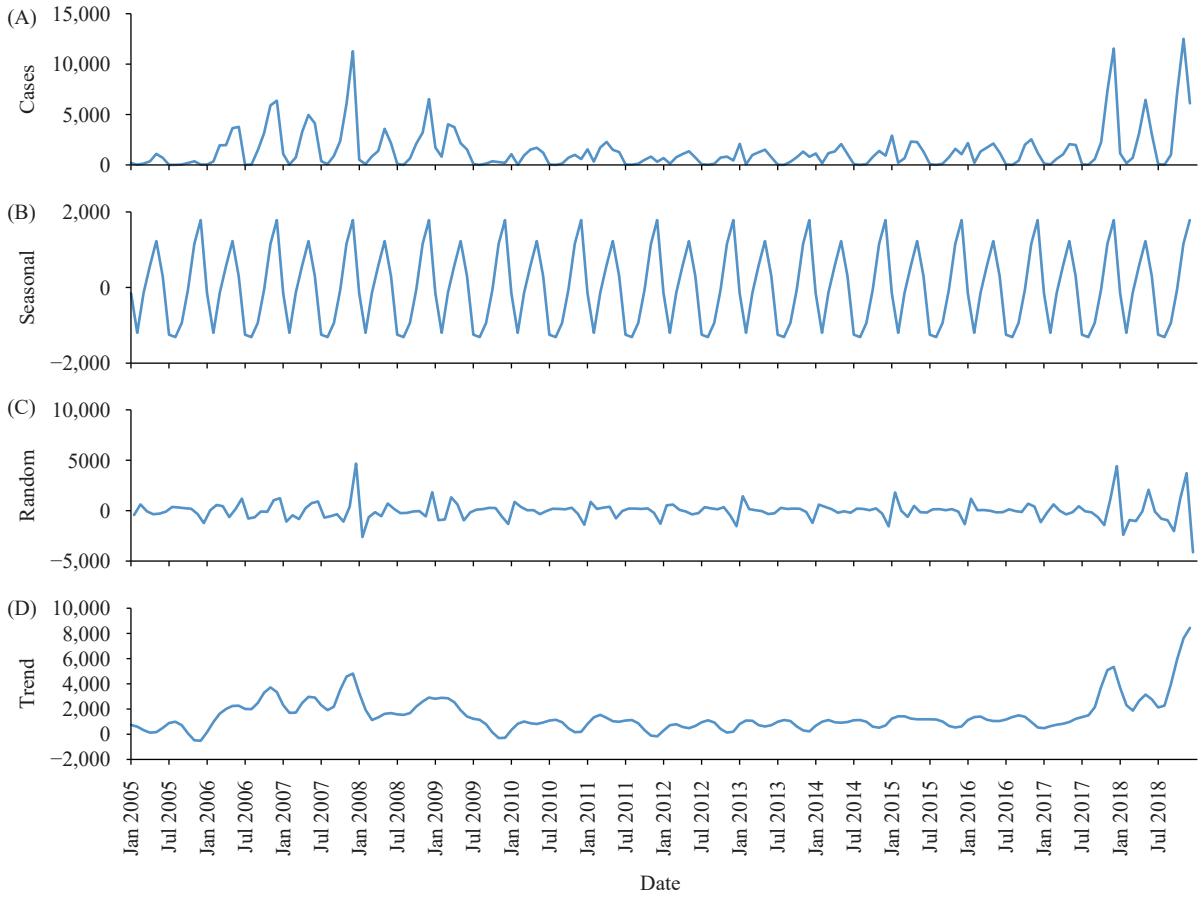

FIGURE 1. The time series graph of monthly varicella outbreak cases in China, 2005–2018. (A) Original time series; (B) seasonal effect; (C) random fluctuation effect; (D) long-term trend effect.

TABLE 1. Estimation of parameters and verification of the ARIMA model.

Variable	ARIMA (2, 1, 0)×(0, 1, 1)$_{12}$		ARIMA (1, 1, 0)×(0, 1, 1)$_{12}$		ARIMA (1, 1, 1)×(0, 1, 1)$_{12}$		ARIMA (1, 1, 1)×(2, 1, 0)$_{12}$	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
AR	−0.346	0	−0.168	0.052	0.379	0	0.381	0
MA	–	–	–	–	0.933	0	0.940	0
Seasonal AR	–	–	–	–	–	–	−0.308	0.006
Seasonal MA	0.306	0.003	0.402	0	0.357	0	–	–
Ling-Box p	0		0		0.005		0.007	
Stationary R^2	0.147		0.048		0.271		0.287	
Normalized BIC	15.127		15.198		14.970		14.987	

Note: "–" represents null values.
Abbreviation: ARIMA=autoregressive integrated moving average; AR=autoregression; MA=moving average; BIC=Bayesian Information Criterion.

aligned closely with the fitted values preceding October 2019 (Figure 2). Even though the subsequent fitted values did not align as closely, they remained within the predicted 95% confidence intervals. The average relative error between the predicted and actual values was 15.2% (Table 2), inferring that the model was deemed suitable for prediction purposes.

DISCUSSION

This study may be the premiere use of an ARIMA model to delineate the epidemic trajectory of varicella outbreaks in China, as it offers a predictive overview of imminent varicella trends. This provides valuable insight for preemptive measures and public health

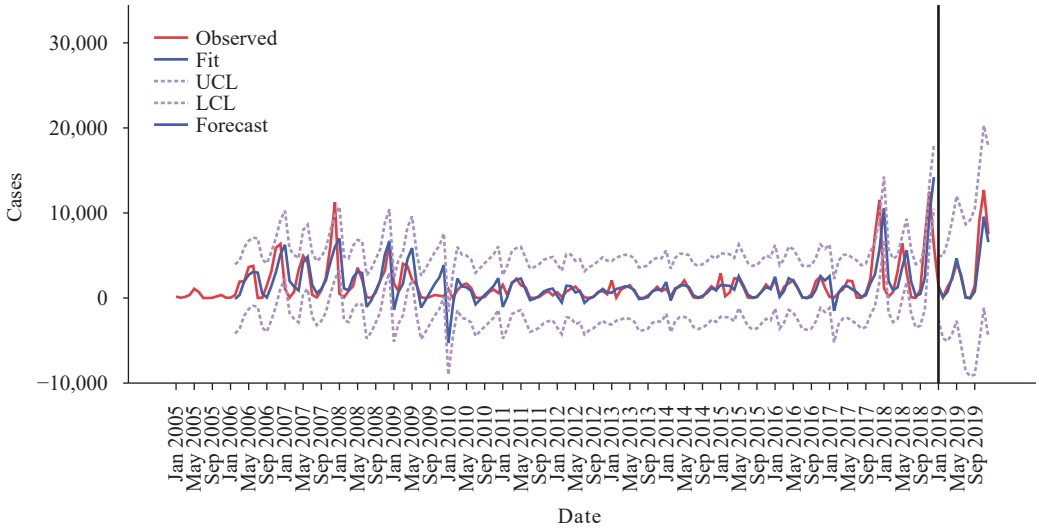

FIGURE 2. Time-series plots of predicted monthly varicella outbreak cases using the ARIMA model, January 2005–December 2019.
Note: The dotted lines represent the 95% *CI*s, with UCL denoting the upper limit and LCL indicating the lower limit of the 95% *CI*.
Abbreviation: ARIMA=autoregressive integrated moving average model; *CI*=confidence interval; UCL=upper confidence limit; LCL=lower confidence limit.

TABLE 2. Comparison between predicted and actual values using ARIMA (1, 1, 1) × $(0, 1, 1)_{12}$ model.

Outbreak cases	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Dec	Nov	Mean relative error
Actual	1,459	91	1,318	2,196	4,038	2,736	93	0	1,428	9,091	12,707	7,492	3,554.083
Predicted	1,256	91	1,335	2,407	4,665	2,421	43	17	745	5,032	9,565	6,570	2,845.583
Absolute error	−203	0	17	211	627	−315	−50	17	−683	−4,059	−3,142	−922	−708.500
Relative error	−0.139	0	0.013	0.096	0.155	−0.115	−0.538	0	−0.478	−0.446	−0.247	−0.123	−0.152

guidance (*5*). Our research reveals an uninterrupted increase in reported varicella outbreak cases since 2012, with a significant surge from 2017 that peaked in 2018. Projections for 2019 continue this rising trend, suggesting that varicella outbreaks have not been fully contained. The low Varicella vaccine (VarV) coverage in China could be a potential catalyst for these increases (*6*). Previous research supports the efficacy of both single and double dose varicella vaccination schedules in mitigating varicella outbreaks (*7*–*9*). A separate study conducted in China (*10*) utilized a modified Delphi technique to gather expert opinions on the potential inclusion of non-program vaccines into China's Expanded Program on Immunization (EPI). VarV emerged as the top non-program vaccine recommended for incorporation into the EPI. Thus, these findings underscore the importance and urgency of integrating VarV into the national immunization framework.

After conducting numerous adjustments to the parameters and running goodness-of-fit tests, it was conclusively determined that the ARIMA (1, 1, 1)× $(0, 1, 1)_{12}$ model was the most compatible with the original time-series data of monthly varicella outbreak cases gathered from 2005 to 2018. This optimal model was subsequently used to predict monthly varicella outbreak cases in 2019. The results revealed that the estimated cases of outbreaks were congruent with the actual reported cases, particularly from January to September. This correspondence indicated the model's ability to accurately predict varicella outbreak cases. From October 2019 onwards, the fitted values did not align as closely, albeit still falling within the 95% confidence intervals. This points to potential influences of large seasonal fluctuations or changes in policy on the model's accuracy, a factor which warrants further analysis. Consequently, it is recommended that the model's data be regularly updated with the most current information to ensure optimal accuracy.

Time series models are instrumental in the prediction of varying trends in infectious diseases such as hand foot and mouth disease (HFMD) (*11*),

coronavirus disease 2019 (COVID-19) (*12*), and influenza (*3*). Our research reinforces the scientific consensus deeming the ARIMA models as proficient tools for synchronous surveillance and forecasting of evolving trends in infectious diseases. Notably, a study conducted in Bulgaria (*13*) illustrated the appropriateness of an ARIMA model in describing varicella incidence trends, and its suitability in projecting near-future disease dynamics, although it didn't account for varicella seasonality. In relation to China, there have been limited studies conducted on varicella incidence prediction, with existing studies only forecasting sporadic varicella incidence in specific regions. For the first time, our study utilizes varicella outbreak data to forecast varicella outbreak occurrences in China on a monthly basis, effectively eliminating the influence of seasonality.

Our study is subject to some limitations. Initially, the use of passive surveillance data can potentially result in an underestimation of the disease burden, which could consequently impact the precision and accuracy of our analyses. Furthermore, the accuracy of our ARIMA model might be subjected to the dynamic changes in key influencing factors such as policy alterations and climate changes. Therefore, the establishment of a dynamic adjustment model is essential to enhance the accuracy of long-term predictions.

In conclusion, the findings from our research indicate the practicality of employing ARIMA models for predicting varicella outbreaks in China. Consequently, these models pose a valuable tool for enhancing varicella prevention and control measures, offering forecasting capabilities for future varicella outbreaks and trend identification within the nation.

Conflicts of interest: No conflicts of interest.

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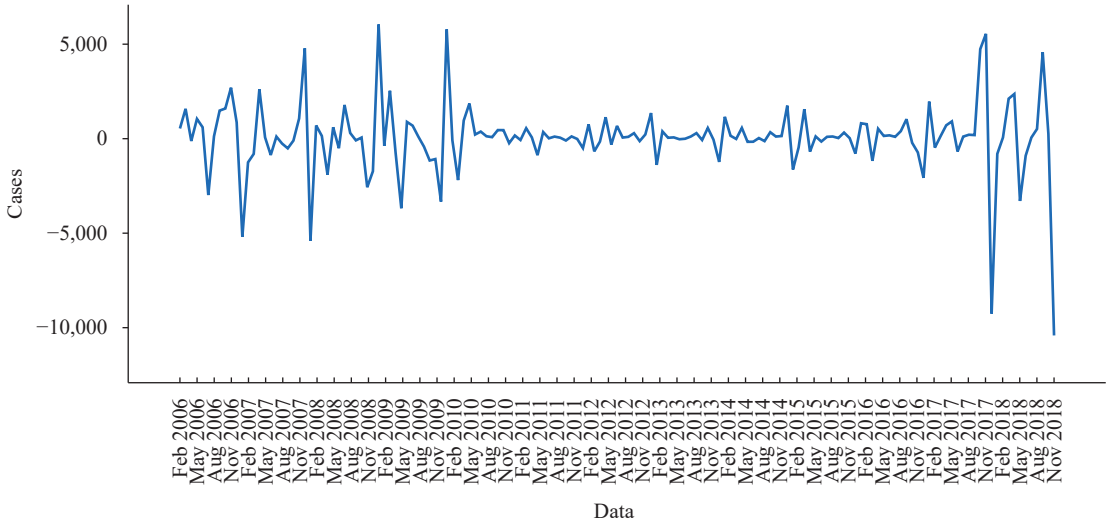
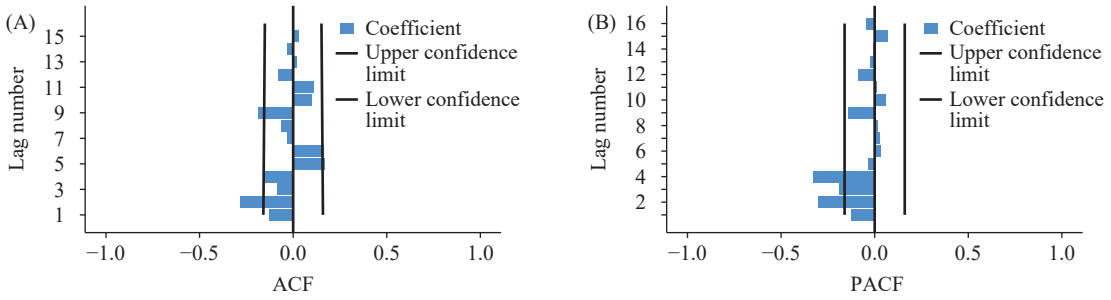
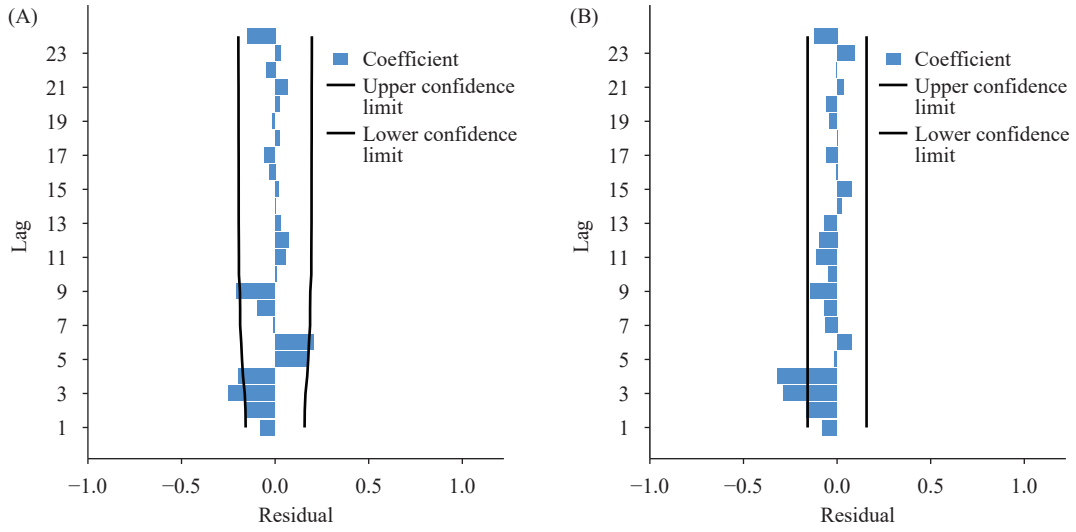
SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE S1. The sequence following initial ordinary and seasonal first-order differences.



SUPPLEMENTARY FIGURE S2. Diagrams of outbreak cases in China from 2005 to 2018 after first-order differencing and seasonal differencing. (A) ACF; (B) PACF.
Abbreviation: ACF=autocorrelation function; PACF=partial autocorrelation function.



SUPPLEMENTARY FIGURE S3. ACF and PACF graphs of the residuals for the ARIMA (1, 1, 1)×(0, 1, 1)$_{12}$ model. (A) ACF; (B) PACF.

Note: Given that the correlation values fell within the 95% *CI* limits, it can be inferred that the residuals are most likely white noise. This suggests that this model is suitable for prediction.

Abbreviation: ARIMA=autoregressive integrated moving average model; ACF=autocorrelation function; PACF=partial autocorrelation function; *CI*=confidence interval.

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