



Human infections with neglected vector-borne pathogens in China: A systematic review

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Summary

Background Emerging vector-borne pathogens (VBPs) pose a continuous background threat to the global health. Knowledge of the occurrence, distributions and epidemiological characteristics of VBP are lacking in many countries. Outbreaks of novel VBP are of increasing global interest including those arising in China.

Methods A systematic review of published literature was undertaken to characterize the spectrum of VBPs causing human illness in China. We searched five databases for VBP-related articles in English and Chinese published between January 1980 and June 2021, that excluded those listed in the National Notifiable Diseases Surveillance System of China. The study is registered with PROSPERO, CRD42021259540.

Findings A total of 906 articles meeting the selection criteria were included in this study. A total of 44,809 human infections with 82 species of VBPs including 40 viruses, 33 bacteria (20 Rickettsiales bacteria, eight Spirochaetales bacteria, and five other bacteria) and nine parasites, were identified in China. Rickettsiales bacteria were the most common and widely distributed pathogens with 18,042 cases reported in 33 provinces by 347 reviewed articles, followed by Spirochaetales bacteria with 15,745 cases in 32 provinces (299 articles), viruses with 8455 cases in 30 provinces (139 articles), other bacteria with 2053 cases in 19 provinces (65 articles), parasites with 514 cases in 17 provinces (44 articles), and multiple pathogens with 3626 cases in 14 provinces (23 articles). *Coxiella burnetii*, *Bartonella henselae* and *Rickettsia sibirica* were the most frequently reported pathogens. A total of 18 new pathogens were reported in China during this period (these also represented their first identification globally). Based on 419 articles with clinical information, a meta-analysis revealed that flu-like illness was the most common manifestation among infections with VBPs.

Interpretation This review helps improve the understanding of VBPs in China, demonstrating the need to consider a wider surveillance of VBPs in many different settings, thus helping to inform future research and surveillance efforts.

Funding Natural Science Foundation of China.

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Introduction

Emerging infectious diseases (EID) pose a significant burden on global public health and global economies.^{1–3} The majority of emerging and reemerging human infectious diseases are zoonoses,⁴ of which vector-borne diseases

(VBDs) comprise a large percentage.⁵ Arthropods act as vectors for a large array of pathogens (defined here as vector-borne pathogens, VBPs) that consist of viruses, bacteria, and protozoa species, transmitting them between animal or plant hosts.⁶ The direct impact on human health is considerable, such as tick-borne Lyme disease and rickettsioses;⁷ mosquito-borne malaria,^{8,9} dengue,¹⁰ infection with Zika virus and chikungunya virus,¹¹ all representing noteworthy VBDs with wide range health threats.^{12–15} Over the past three decades, the changing distribution and increased incidence of VBD driven by socio-economic,

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The Lancet Regional Health - Western Pacific 2022;22: 100427
Published online xxx
<https://doi.org/10.1016/j.lanwpc.2022.100427>

Research in context

Evidence before this study

Vector-borne diseases (VBDs) have been neglected at a broad societal level in China, not just by primary health-care providers and clinicians. Although an increasing number of human cases have been reported, the study efforts mainly focus on infectious diseases listed in the National Notifiable Diseases Surveillance System (NNDSS) (e.g., malaria, dengue fever, Japanese encephalitis, endemic and epidemic typhus, filariasis, leishmaniasis, scrub typhus, human granulocytic anaplasmosis, severe fever with thrombocytopenia syndrome, and tick-borne encephalitis). We searched PubMed and Web of Science, and GIDEON for articles in English, and China National Knowledge Infrastructure and Wanfang database for articles in Chinese published between January 1980 and June 2021, with the following primary search terms: (“vector-borne”, “tick-borne”, “mosquito-borne”, “flea-borne”, “louse-borne”, “mite-borne”, “sand-fly-borne”) AND “China” and limited to human infection. Eight papers reviewed the occurrence of vector-borne pathogens (VBP) in human, mainly involving the detection of dengue virus, Japanese encephalitis virus, *Borrelia burgdorferi* sensu lato, severe fever with thrombocytopenia syndrome virus, tick-borne encephalitis virus, and emerging tick-borne diseases (TBD). There are no reviews that have described all available vector-borne pathogens in China.

Added value of this study

In this systematic review that made an exhaustive search of published literatures, 906 studies were included and analyzed, revealing a high heterogeneity on the laboratory methods, patient populations, as well as the wide spectrum of pathogens identified. In total 82 species (or sub-species) of VBPs that infected 44,809 human cases in the mainland of China, including 40 viruses, 33 bacteria (20 Rickettsiales bacteria, eight Spirochaetales bacteria, and five other bacteria) and nine parasites. Among them 54 species of VBPs were identified by molecular methods, microscopy or culture methods, and the others were identified by serological methods. A total of 18 novel pathogens including 15 viruses, two parasites and one Rickettsiales bacteria detected in China also represented their first identification in the world. A broad range of VBPs that caused human infection were reported in Yunnan, Heilongjiang and Xinjiang provinces. Clinical information was reported from altogether 419 articles, based on which a meta-analysis revealed flu-like illness to the most common manifestations among all types of VBPs. Six clusters were formed based on the clinical manifestations that could differentiate VBP infections.

Implications of all the available evidence

Our results show the marked etiological diversity of VBPs in causing human infections, underlining the substantial geographical and population heterogeneities

that exist in reported VBD cases. These findings can help attain an enhanced epidemiological understanding of multiple VBDs to inform prevention and control of threat to humans in China. It is hoped that the findings might also generate greater awareness of the clinical picture of VBDs and provide a starting point for actions to better manage these diseases, for example through improved diagnostic and clinical treatment algorithms.

environmental and ecological factors, has created new challenges for public health.^{16–18} The spread of Lyme and emergence of other tick-borne diseases (TBD),¹⁹ the reemergence of many mosquito-borne illnesses including malaria and dengue fever that had been controlled in many areas in Asia and the Americas,^{20,21} the resurgence of chikungunya virus disease in Asia and Africa,^{22,23} the discovery of novel TBDs, severe fever with thrombocytopenia syndrome, all have caused considerable economic, ecological, and public health impacts.^{24,25} Particularly in countries where VBDs are most prevalent yet neglected, limited knowledge on these diseases had hindered the diagnosis and control efforts to be taken.¹⁶

The ongoing geographic expansion of vectors, possibly driven by climatic, socioeconomical and environmental change, has drawn global attention.²⁶ *Haemaphysalis longicornis*-the emerging medically important tick species, which was originally native to East Asia, spread to Australia, New Zealand, and was found in the eastern U.S. The expansion of *Ha. longicornis* has raised public health and veterinary health concerns due to its capability of transmitting tick-borne pathogens, e.g., *Dabie bandavirus* (known as Severe Fever with Thrombocytopenia Syndrome Virus, SFTSV),²⁷ spotted fever group *Rickettsia*, and *Anaplasma phagocytophilum*.²⁸ Another significant mosquito vector-*Aedes albopictus*, which could transmit dengue fever, Chikungunya fever and yellow fever, has been observed movement northward in central and eastern China.²⁹ China is among countries with high disease burden of VBDs. An increasing amount of data on VBDs had been recently generated through field investigation and high-throughput DNA sequencing approaches,^{28,30} which had marginally hastened the recognition of novel VBPs and the related diseases.^{31–33} However, most of the recent studies have been carried out to report the identification of one certain species, within limited geographic scope and recorded sporadically. In addition, the publication in Chinese may limit wider accessibility and understanding. This is far from adequate to attain a complete understanding of the current VBPs. Here in order to attain a complete understanding of the VBPs in China, we performed an exhaustive literature review of the published literatures, explored the occurrence, distribution, epidemiology, and clinical features of emerging and reemerging VBPs that had been neglected, with

focus on those capable of causing human infection. This knowledge can be used to provide epidemiological evidence base for disease control program development and also guide the diagnostic and treatment algorithms for fever of unknown reason, with the potential to improve clinical outcomes.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and has been registered with the international prospective register of systematic reviews (PROSPERO) (International Prospective Register of Ongoing Systematic Reviews) (CRD42021259540).³⁴

Search strategy and selection criteria

A literature search was conducted on Chinese and English databases using a set of terms and Boolean operators, mainly through China National Knowledge Infrastructure (CNKI) (<http://www.cnki.net/>), Wanfang Database (<http://www.wanfangdata.com.cn/>), PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>), ISI Web of Science (WOS) (<http://www.webofscience.com>), and Global Infection Diseases and Epidemiology Online Network (GIDEON) (<https://web.gideononline.com/>), inclusive to reflect the study on emerging and reemerging pathogens identified from human beings in China over the recent 40 years from 1980 to 2021. At the first step, general search terms were applied that included: (“vector-borne”, or “tick-borne”, “mosquito-borne”, or “flea-borne”, or “louse-borne”, or “mite-borne”, or “sandfly-borne”) AND (“human infection” or “patient”) AND “China”. To attain an exhaustive search, a reference list of eligible VBPs was compiled using lists from the World Health Organization (WHO) as well as from the literature-based searches.¹² Further specific search was performed by using this list of eligible VBPs at the lowest level of taxonomy term AND syntax (“China”, “Hongkong”, “Macao”, “Taiwan”) limited to humans. Details of search concept construction are given in the appendix (Appendix Tables S1–S5).

Study selection and validity assessment

Inclusion and exclusion criteria. Comprehensive inclusion and exclusion criteria were predefined to facilitate the screening process (detailed in Appendix Tables S7–S10). For this review, VBD illness is defined as infectious diseases caused by vector-borne pathogens that had not been included in the National Notifiable Diseases Surveillance System (NNDSS), since there has been nation-wide report based on the NNDSS data. Thus the initial screening has excluded 11 diseases in

the NNDSS list (i.e. endemic typhus, epidemic typhus, scrub typhus, malaria, filariasis, dengue fever, Japanese encephalitis, leishmaniasis, human granulocytic anaplasmosis, severe fever with thrombocytopenia syndrome, and tick-borne encephalitis, detailed in Appendix Table S6), which were not within the scope of the current study.³⁵ The diseases that are transmitted to animals or plants without reports in human beings were not within the scope of current study.

Studies were eligible if they described the laboratory detection of VBPs causing human illness (rather than clinical definition alone), and studies that clearly stated the total number of individuals tested and those that were positive for infection. We excluded the following studies: (i) data focusing on the VBDs that were listed as the national reportable diseases or not causing human infection; (ii) data on drug or vaccine trials; (iii) studies conducted in travelers returning to China; and (iv) studies that detected the selected pathogens in patient with immunodepression status (Figure 1).

Title and abstracts of the retrieved studies were screened independently by two reviewers (two of MCL, TTL, and JJC) to identify studies potentially eligible for inclusion. The full texts of the selected studies were retrieved and independently assessed for eligibility by two reviewers (two of YYZ, TLC and FFM).

Data extraction and variable definitions

Full text of all the selected papers were reviewed, and data were extracted into a standardized form that includes the following 24 variables: reference ID, article title, first author, year of publication, study duration, study design (case report or case series, symptomatic series and seroprevalence study³⁶), age range (pediatric <15 years old, adult ≥15 years, all age group encompassing pediatric and adult population), source of tested individuals (inpatients, outpatients, or common healthy population), type of sampled area (urban or rural area), type of pathogen (virus, Rickettsiales bacteria, Spirochaetales bacteria, other bacteria and parasite), type of transmission (tick-borne, mosquito-borne, flea-borne, louse-borne, and sandfly-borne), pathogen name, type of specimen and testing method (molecular, serological, microscopy, or culture), number of patients tested for each pathogen and number of confirmed positive and positive rate of individuals tested, the reported geographic location information (province, prefecture and county), ecological region, clinical presentations and co-infection. Co-infection was defined as simultaneous detection of multiple pathogens of different species in the same individual (Appendix Table S9).³⁷ All conflicts of opinion and uncertainties were discussed and resolved by consensus with third reviewers. Attempts were also made to clarify with the corresponding authors regarding any uncertainties or missing data in selected reports. The PRISMA flow diagram was

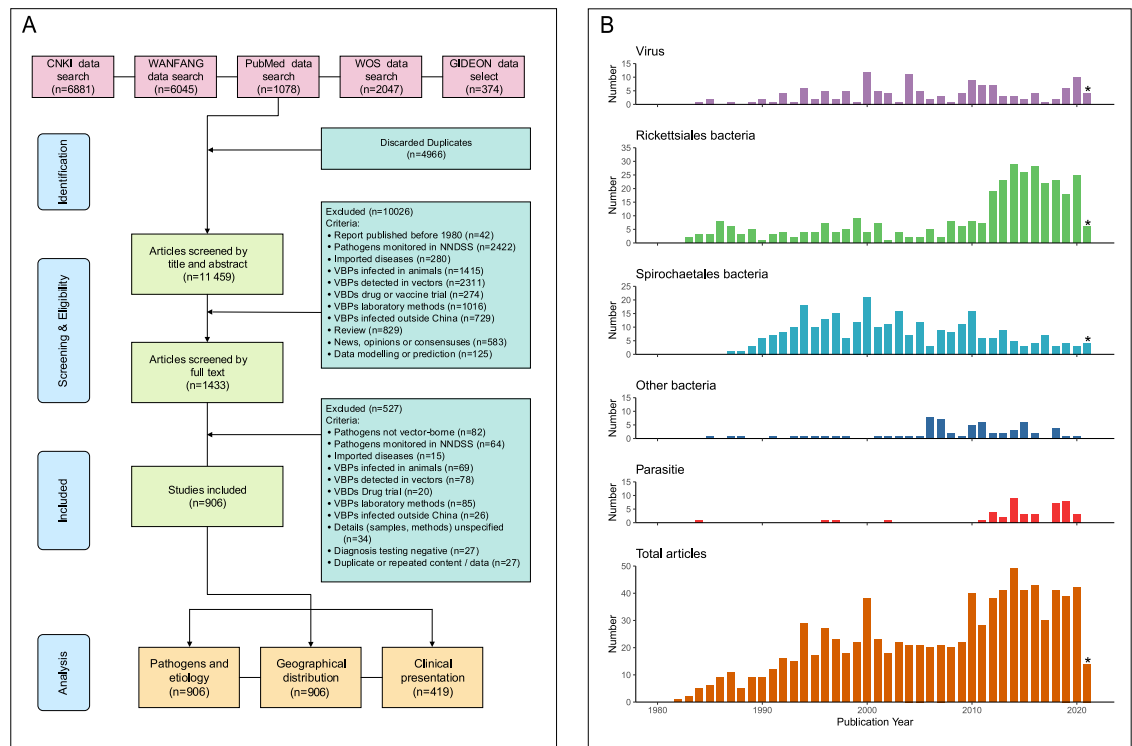


Figure 1. PRISMA flow chart of article assessed for the review (A), and timelines of published articles (B) on neglected vector-borne pathogens in human infection in China. (A) Flowchart outlining the protocol adopted in this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); (B) The bars fill in the blank and marked with “*” represent the article published in 2021.

presented in Figure 1A. As Rickettsiales bacteria are microorganisms that share features of both bacteria and viruses which are comprised of obligate intracellular parasitic bacteria,^{38,39} and Spirochaetales bacteria do not possess bacterial adhesins and differ from most other motile pathogenic bacteria in that the spirochetes miss external appendages that are commonly required for bacterial motility.⁴⁰ In order to distinguish vector-borne diseases caused by different bacteria, we divided vector-borne bacteria into Rickettsiales bacteria, Spirochaetales bacteria and other bacteria in this review.^{41–43}

Since the pathogen names and taxonomy might have changed along the study years, online taxonomy search websites, including International Committee on Taxonomy of Viruses (ICTV) (<https://talk.ictvonline.org/>) and National Center for Biotechnology Information (NCBI) Taxonomy (<https://www.ncbi.nlm.nih.gov/taxonomy/>) were used to update the current taxonomy classification. The available tools for assessing the quality and risk of bias were not met by the current review design,^{44,45} thus we performed quality assessment based on article information and laboratory testing methods, as described in Shrestha et al.³⁶ Among all article types, case report/case series was considered to be at high risk of bias owing to lack of representation, while

seroprevalence study was considered to be at moderate risk of bias, and symptomatic series were considered at low risk of bias because of their typical presentations. Among all testing methods, molecular methods (including PCR, genetic sequencing, Western blot), microscopy and culture method were considered at low risk of bias.

Data analysis

Descriptive statistics were performed with frequencies and percentages estimated for categorical variables and mean/median calculated for continuous variables. For the researches that described clinical symptoms/syndromes of cases diagnosed following standard protocol using robust detection methods (molecular detection, culture, microscopy, a four-fold increase in titer of specific antibodies or seroconversion), we further performed meta-analysis to estimate the frequency of clinical manifestations. Briefly, if there was only one study included for the manifestation of the pathogen, the clinical manifestation proportion was calculated by clinical manifestation cases divided by total cases and without a 95% CI. If the number of studies was two or more, the pooled proportion and 95% CI were estimated using the inverse variance combined with fixed effects

or random effects models depending on the degree of the heterogeneity between studies. Heterogeneity was quantified using the statistic Higgin's I^2 , when its value was greater than 50%, random effects model was used, otherwise, fixed effects model was applied.⁴⁶ A clustered heatmap was used to visualize the pooled proportion of clinical manifestation of each pathogen, and pathogens were divided into different clusters using complete-link hierarchical clustering method which can find similar clusters.⁴⁷ All data analyses were carried out using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), graphical presentations were done using the ggplot2 package, meta-analysis were done using meta and forestplot package.^{48–51} The location of study was used together with all contextual information provided to determine its latitudinal and longitudinal coordinates and overlaid using ArcGIS 10.7 software to compile the maps. For the geo-coded study sites, seven ecological regions (Northeast, North China, Inner Mongolia-Xinjiang, Qinghai-Tibet, Southwest, Central China, and South China) were defined according to the climatic and ecological characteristics,^{42,52,53} and used for the inter-group comparison.

Role of the funding source

This work was supported by Natural Science Foundation of China (No. 81825019). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

Summary of included literatures and study population

The literature search identified a total of 16,425 articles, with 12,926 in Chinese (6881 from CNKI, 6045 from Wanfang), 3499 in English (1078 from PubMed, 2047 from WOS, 374 from GIDEON). Among them 906 (5.52%) were included after full-text review, corresponding to data recorded from 1980 to 2021 (Figure 1A). The annual number of published papers that met inclusion criteria steadily increased between 1980 and 2021. Particularly since 2010, there had been a dramatic increase in the publication of Rickettsiales bacteria, while a decrease in the publication of Spirochaetales bacteria and other bacteria otherwise (Figure 1B). Among these studies, 564 (62.25%) were seroprevalence studies, 244 (26.93%) were case reports or case series and 98 (10.82%) were symptomatic series.

Of the 906 articles, adult population were studied in 281 (31.02%) reports, pediatric population were studied in 104 (11.48%) reports, and all age groups were studied in 306 (33.77%), while age was not specified in 215

(36.79%). Among all-age population, rickettsial infections were the largest proportion of VBPs that were tested (347/906, 38.30% and 80/104, 76.92%, respectively). The clinical type of inpatients was described in 295 (32.56%) reports, outpatients in 17 (1.88%), and mixed groups in 221 (24.39%) reports. Study area of urban was recorded in 47 (5.19%) reports, rural in 234 (25.83%), both areas in 479 (52.87%), while not specified in 146 (16.11%) (Table 1). These data collectively demonstrated a widely and persistently performed studies in China in recent years.

Specimen collection and detection methods

Blood was the most often recorded specimen type, tested in 839 (92.60%) articles, lymph nodes was tested in 25 (2.76%) articles, cerebrospinal fluid (CSF) in six (0.66%) articles, and others (faeces, skin, puncture fluid, bronchoalveolar lavage fluid) in four (0.44%) articles. Multiple specimens were tested in 32 (3.53%) articles, consisted of blood in combination with CSF, bone marrow, skin, and urine in 14, seven, five, five articles and with each of eschar, lymph node, throat swabs in one article, respectively. Serological methods were the main techniques used in 660 (72.85%) of the articles, followed by molecular techniques in 97 (10.71%), microscopy in 40 (4.42%), culture in 8 (0.88%), and multiple methods in 101 (11.15%) (Table 1). When looking in detail, serological methods accounted for 69.78% (97/139) of the detection for viral infections, 79.54% (276/347) for rickettsial infections, 82.99% (239/288) for spirochetal infections, 46.15% (30/65) for other bacterial infections (Table 1).

Pathogen identification and co-infection

In total, 82 pathogen species that belong to three kingdoms, seven phyla, 10 classes, 11 orders, 15 families, and 22 genera were determined in causing human infection, among which the most common were viruses (40 species), followed by 20 Rickettsiales bacteria species, nine parasitic species, five other bacterial species, eight species of Spirochaetales bacteria (Table 2). Seven were uncharacterized that belonged to *Babesia* spp., *Colpodella* spp., *Theileria* spp., spotted fever group *Rickettsia*, tick-borne relapsing fever *Borrelia*, *Borrelia burgdorferi* sensu lato and Coltiviruses-Old World, respectively. As Coltiviruses reported in the references before 2004 actually are seadonavirus and does not match the current taxonomy list, these viruses are termed as Coltiviruses-Old World according to GIDEON.⁵⁴ Among all 906 records within scope of 82 pathogens, the most frequently determined illness were rickettsial infection (38.30%, 347/906) with totally 18,042 cases reported in 33 provinces, followed by spirochetal infections (31.79%, 288/906) with 15,745 cases in 32 provinces, viral infections in 139 (15.34%) with 8455 cases in 30 provinces,

Characteristic	Total	Virus	Rickettsiales bacteria	Spirochaetales bacteria	Other bacteria	Parasite	Multiple etiologies
<i>n</i> (%)	906 (100.00)	139 (15.34)	347 (38.30)	288 (31.79)	65 (7.17)	44 (4.86)	23 (2.54)
Study design, <i>n</i> (%)							
Case report or case series	244 (26.93)	23 (16.55)	67 (19.31)	84 (29.17)	37 (56.92)	31 (70.45)	2 (8.70)
Symptomatic series	98 (10.82)	17 (12.23)	39 (11.24)	22 (7.64)	3 (4.62)	11 (25.00)	6 (26.09)
Seroprevalence studies	564 (62.25)	99(71.22)	241 (69.45)	182 (63.19)	25 (38.46)	2 (4.55)	15 (65.22)
Age range, <i>n</i> (%)							
Pediatric	104 (11.48)	9 (6.47)	80 (23.05)	7 (2.43)	5 (7.69)	2 (4.55)	1 (4.35)
Adult	281 (31.02)	19 (13.67)	106 (30.55)	90 (31.25)	30 (46.15)	31 (70.45)	5 (21.74)
Mixed ages	306 (33.77)	68 (48.92)	94 (27.09)	110 (38.19)	20 (30.77)	4 (9.09)	10 (43.48)
Unspecified	215 (23.73)	43 (30.94)	67 (19.31)	81 (28.12)	10 (15.38)	7 (15.91)	7 (30.43)
Source of tested individuals, <i>n</i> (%)							
Inpatients	295 (32.56)	25 (17.99)	141 (40.63)	66 (22.92)	31 (47.69)	29 (65.91)	3 (13.04)
Outpatients	17 (1.88)	4 (2.88)	4 (1.15)	7 (2.43)	1 (1.54)	0 (0.00)	1 (4.35)
Mixed patients	221 (24.39)	43 (30.94)	114 (32.85)	45 (15.62)	11 (16.92)	7 (15.91)	1 (4.35)
Population-based	326 (35.98)	46 (33.09)	72 (20.75)	166 (57.64)	20 (30.77)	7 (15.91)	15 (65.22)
Multiple origins	47 (5.19)	21 (15.11)	16 (4.61)	4 (1.39)	2 (3.08)	1 (2.27)	3 (13.04)
Type of sampled area, <i>n</i> (%)							
Rural	234 (25.83)	26 (18.71)	65 (18.73)	118 (40.97)	6 (9.23)	14 (31.82)	5 (21.74)
Urban	47 (5.19)	9 (6.47)	8 (2.31)	20 (6.94)	7 (10.77)	2 (4.55)	1 (4.35)
Multiple areas	479 (52.87)	67 (48.20)	228 (65.71)	126 (43.75)	27 (41.54)	19 (43.18)	12 (52.17)
Unspecified	146 (16.11)	37 (26.62)	46 (13.26)	24 (8.33)	25 (38.46)	9 (20.45)	5 (21.74)
Type of testing method, <i>n</i> (%)							
Serological	660 (72.85)	97 (69.78)	276 (79.54)	239 (82.99)	30 (46.15)	3 (6.82)	15 (65.22)
Molecular biology	97 (10.71)	19 (13.67)	36 (10.37)	18 (6.25)	6 (9.23)	18 (40.91)	0 (0.00)
Microscopy	40 (4.42)	0 (0.00)	1 (0.29)	5 (1.74)	26 (40.00)	8 (18.18)	0 (0.00)
Culture	8 (0.88)	5 (3.60)	2 (0.58)	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)
Multiple methods	101 (11.15)	18 (12.95)	32 (9.22)	25 (8.68)	3 (4.62)	15 (34.09)	8 (34.78)

Table 1: Characteristics of emerging and reemerging neglected vector-borne pathogens in human infection in China by etiology.

other bacterial infections in 65 (7.17%) with 2053 cases in 19 provinces, parasitic infections in 44 (4.86%) with 514 cases in 17 provinces, and multiple etiological infection in 23 (2.54%) with 3626 cases in 14 provinces, respectively (Table 1). Among all characterized Rickettsiales bacteria species, the most frequently determined were *Coxiella burnetii* (*n* = 241), followed by *Rickettsia sibirica* (*n* = 38), *Ehrlichia chaffeensis* (*n* = 30), *Rickettsia heilongjiangensis* (*n* = 14), *Rickettsia japonica* (*n* = 10), and *Rickettsia conorii* (*n* = 10). Among all Spirochaetales bacterial infections, only 34 records were characterized for the genotype, composed of 13 with *Borrelia garinii*, 10 with *Borrelia afzelii*, four with *Borrelia valaisiana*, four with *Borrelia recurrentis*, two with *Borrelia miyamotoi*, one with *Borrelia burgdorferi* sensu stricto, and the remaining 277 records were uncharacterised *Borrelia burgdorferi* sensu lato which were determined by serological assay. The most frequently reported viral pathogens were Chikungunya virus (*n* = 36), followed by Crimean-Congo hemorrhagic fever virus (*n* = 25), and Sindbis virus (*n* = 24). *Bartonella henselae* was the most commonly recorded among other bacterial infections (*n* = 51), followed by *Francisella tularensis* (*n* = 22).

Among parasitic infection, *Babesia microti* (*n* = 20) and *Babesia venatorum* (*n* = 5) were the top two parasitic infections, while 14 *Babesia* spp were uncharacterized (Figure 2).

With all detection evidence, 46 of 906 references had evidence of co-infection (Appendix Table S13). Co-infection with multiple VBPs had been determined from 788 patients, mostly occurring between *Borrelia burgdorferi* sensu lato and tick-borne encephalitis virus (*n* = 308), between spotted fever group *Rickettsia* and *Dabie bandavirus* (*n* = 77), and between Coltiviruses-Old World and Japanese encephalitis virus (*n* = 76). All the coinfecting VBPs belonged to the NNDSS list.

Spatial pattern of pathogen type and richness

The majority of reports came from Central China (28.37%, 257/906), particularly in Zhejiang province (*n* = 39), followed by North China (26.93%, 244/906) particularly in Beijing city (*n* = 55), and South China (21.85%, 198/906) especially in Guangdong province (*n* = 54) (Figure 3A). The heterogeneous geographical distribution was observed among five pathogen types,

Pathogen names (Abbreviations) [#]	Classification (family)	Classification (genus)	Transmission types	Types of specimens	Evidence of detection
Virus					
Barmah Forest virus (BFV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood, Cerebrospinal fluid	Molecular, Serological
Bebaru virus (BEBV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Chikungunya virus (CHIKV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne, Vertical Transmission	Blood	Molecular, Culture, Serological
Eastern equine encephalitis virus (EEEV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Getah virus (GETV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Mayaro virus (MAYV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Ross River virus (RRV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood, Cerebrospinal fluid	Molecular, Serological
Sagiyama virus (SAGV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Semliki forest virus (SFV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Sindbis virus (SINV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood, Cerebrospinal fluid	Molecular, Culture, Serological
Venezuelan equine encephalitis virus (VEEV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Western equine encephalitis virus (WEEV)	<i>Togaviridae</i>	<i>Alphavirus</i>	Mosquito-borne	Blood	Serological
Kunjin virus (KUN)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Mosquito-borne	Blood	Serological
Murray Valley encephalitis virus (MVEV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Mosquito-borne	Blood	Serological
Saint Louis encephalitis virus (SLEV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Mosquito-borne	Blood	Serological
West Nile virus (WNV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Mosquito-borne	Blood, Cerebrospinal fluid	Serological
Zika virus (ZIKV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Mosquito-borne	Blood	Molecular, Serological
Kyasanur Forest disease virus (KFDV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Tick-borne	Blood	Molecular, Morphology, Culture, Serological
Langat virus (LGTV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Tick-borne	Blood	Serological
Powassan virus (POWV)	<i>Flaviviridae</i>	<i>Flavivirus</i>	Tick-borne	Blood, Cerebrospinal fluid	Serological
Alongshan virus * (ALSV)	<i>Flaviviridae</i>	<i>unclassified Flaviviridae</i>	Tick-borne	Blood	Molecular
Jingmen tick virus * (JTV)	<i>Flaviviridae</i>	<i>unclassified Flaviviridae</i>	Tick-borne	Blood, Skin	Molecular, Serological
Coltivirus-Old World ^{1,3} (Coltivirus-OW)	<i>Reoviridae</i>	<i>Coltivirus</i>	Mosquito-borne	Blood, Cerebrospinal fluid	Molecular, Culture, Serological
Novel orbivirus *, ¹ (NOBV)	<i>Reoviridae</i>	<i>Orbivirus</i>	Mosquito-borne	Blood	Serological
Tibet orbivirus * (TIBOV)	<i>Reoviridae</i>	<i>Orbivirus</i>	Mosquito-borne	Blood	Serological
Yunnan orbivirus * (YUOV)	<i>Reoviridae</i>	<i>Orbivirus</i>	Mosquito-borne	Blood	Serological
Banna virus * (BAV)	<i>Reoviridae</i>	<i>Seadornavirus</i>	Mosquito-borne	Blood, Cerebrospinal fluid	Molecular, Serological
MD virus *, [†] (MDV)	<i>Reoviridae</i>	<i>Seadornavirus</i>	Mosquito-borne	Blood	Culture
Novel Seadornavirus *, [†] (NSRV)	<i>Reoviridae</i>	<i>Seadornavirus</i>	Mosquito-borne	Blood	Serological
Batai virus (BATV)	<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	Mosquito-borne	Blood	Serological
Ebinur lake virus* (EBIV)	<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	Mosquito-borne	Blood	Molecular, Serological
Snowshoe hare virus (SSHV)	<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	Mosquito-borne	Blood	Serological

Table 2 (Continued)

Pathogen names (Abbreviations) [#]	Classification (family)	Classification (genus)	Transmission types	Types of specimens	Evidence of detection
Tahyna virus (TAHV)	Peribunyaviridae	Orthobunyavirus	Mosquito-borne	Blood	Molecular, Serological
Crimean-Congo hemorrhagic fever virus (CCHFV)	Nairoviridae	Orthonairovirus	Tick-borne, Contact	Blood	Molecular, Culture, Serological
Songling virus * (SGLV)	Nairoviridae	Orthonairovirus	Tick-borne	Blood	Molecular
Tacheng tick virus 1 * (TCTV-1)	Nairoviridae	Orthonairovirus	Tick-borne	Blood, Throat swabs, Urine	Molecular, Serological
Guertu virus * (GTV)	Phenuiviridae	Bandavirus	Tick-borne	Blood	Serological
Wuxiang virus * (WXV)	Phenuiviridae	Phlebovirus	Sandfly-borne	Blood	Serological
Tacheng tick virus 2 * (TCTV-2)	Phenuiviridae	Uukuvirus	Tick-borne	Blood	Molecular, Serological
Nam Dinh virus (NDV)	Mesoniviridae	Alphamesonivirus	Mosquito-borne	Blood	Serological
Rickettsiales bacteria					
<i>Ehrlichia canis</i> (<i>E. canis</i>)	Rickettsiaceae	<i>Ehrlichia</i>	Tick-borne	Blood	Serological
<i>Ehrlichia chaffeensis</i> (<i>E. chaffeensis</i>)	Rickettsiaceae	<i>Ehrlichia</i>	Tick-borne	Blood, Puncture fluid	Molecular, Morphology, Serological
<i>Rickettsia felis</i> (<i>R. felis</i>)	Rickettsiaceae	<i>Rickettsia</i>	Flea-borne	Blood, Cerebrospinal fluid	Molecular, Serological
<i>Rickettsia akari</i> (<i>R. akari</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Molecular, Serological
<i>Rickettsia australis</i> (<i>R. australis</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Serological
<i>Rickettsia conorii</i> (<i>R. conorii</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Molecular, Serological
<i>Rickettsia heilongjiangensis</i> * (<i>R. heilongjiangensis</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood, Eschar	Molecular, Serological
<i>Rickettsia japonica</i> (<i>R. japonica</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Bronchoalveolar lavage fluid, Blood	Molecular, Serological
<i>Rickettsia massiliae</i> (<i>R. massiliae</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Molecular, Serological
<i>Rickettsia monacensis</i> (<i>R. monacensis</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Molecular
<i>Rickettsia raoultii</i> (<i>R. raoultii</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood, Eschar	Molecular, Morphology, Serological
<i>Rickettsia rickettsii</i> (<i>R. rickettsii</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Serological
<i>Rickettsia sibirica</i> (<i>R. sibirica</i>)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood, Eschar	Molecular, Culture, Serological
Candidatus <i>Rickettsia tarasevichiae</i> † (CRT)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood, Eschar	Molecular, Serological
Candidatus <i>Rickettsia xinyangensis</i> *, † (CRX)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Molecular, Serological
Uncharacterised spotted fever group <i>Rickettsia</i> § (SFG <i>Rickettsia</i> spp.)	Rickettsiaceae	<i>Rickettsia</i>	Tick-borne	Blood	Molecular, Culture, Serological
<i>Anaplasma capra</i> (<i>A. capra</i>)	Anaplasmataceae	<i>Anaplasma</i>	Tick-borne	Blood	Molecular, Serological
<i>Anaplasma ovis</i> (<i>A. ovis</i>)	Anaplasmataceae	<i>Anaplasma</i>	Tick-borne	Blood	Molecular, Serological
<i>Coxiella burnetii</i> (<i>C. burnetii</i>)	Coxiellaceae	<i>Coxiella</i>	Tick-borne, Air-borne	Blood	Molecular, Culture, Serological
Candidatus <i>Neoehrlichia mikurensis</i> † (CNM)	Ehrlichieae	<i>Neoehrlichia</i>	Tick-borne	Blood	Molecular
Spirochaetales bacteria					
<i>Borrelia afzelii</i> (<i>Bo. afzelii</i>)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood, Skin, Urine	Molecular, Serological
<i>Borrelia burgdorferi sensu stricto</i> (<i>Bo. burgdorferi s.s.</i>)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood	Serological
<i>Borrelia garinii</i> (<i>Bo. garinii</i>)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood, Cerebrospinal fluid, Skin, Urine	Molecular, Culture, Serological

Table 2 (Continued)

Pathogen names (Abbreviations) [#]	Classification (family)	Classification (genus)	Transmission types	Types of specimens	Evidence of detection
<i>Borrelia miyamotoi</i> (<i>Bo. miyamotoi</i>)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood	Molecular
<i>Borrelia recurrentis</i> (<i>Bo. recurrentis</i>)	Spirochaetaceae	<i>Borrelia</i>	Louse-borne	Blood, Cerebrospinal fluid	Morphology, Serological
<i>Borrelia valaisiana</i> (<i>Bo. valaisiana</i>)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood	Molecular, Serological
Uncharacterised <i>Borrelia burgdorferi sensu lato</i> [§] (<i>Bo. burgdorferi</i> s.l.)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood, Cerebrospinal fluid, Skin, Urine	Molecular, Morphology, Culture, Serological
Uncharacterised tick-borne relapsing fever <i>Borrelia</i> [§] (TBRF <i>Borrelia</i> spp.)	Spirochaetaceae	<i>Borrelia</i>	Tick-borne	Blood	Morphology
Other bacteria					
<i>Bartonella elizabethae</i> (<i>B. elizabethae</i>)	Bartonellaceae	<i>Bartonella</i>	Flea-borne	Blood	Serological
<i>Bartonella henselae</i> (<i>B. henselae</i>)	Bartonellaceae	<i>Bartonella</i>	Flea-borne, Cat-scratch	Blood, Lymph node, Skin	Molecular, Morphology, Serological
<i>Bartonella quintana</i> (<i>B. quintana</i>)	Bartonellaceae	<i>Bartonella</i>	Louse-borne	Blood	Serological
<i>Bartonella birtlesii</i> (<i>B. birtlesii</i>)	Bartonellaceae	<i>Bartonella</i>	Tick-borne	Blood	Molecular
<i>Francisella tularensis</i> (<i>F. tularensis</i>)	Francisellaceae	<i>Francisella</i>	Tick-borne, Contact, Air-borne	Blood, Lymph node	Molecular, Morphology, Serological
Parasite					
<i>Babesia microti</i> (<i>Ba. microti</i>)	Babesiidae	<i>Babesia</i>	Tick-borne, Transfusion-transmitted	Blood, Bone marrow	Molecular, Morphology, Serological
<i>Babesia venatorum</i> (<i>Ba. venatorum</i>)	Babesiidae	<i>Babesia</i>	Tick-borne	Blood	Molecular, Morphology
<i>Babesia bigemina</i> (<i>Ba. bigemina</i>)	Babesiidae	<i>Babesia</i>	Tick-borne, Transfusion-transmitted	Blood	Serological
<i>Babesia divergens</i> (<i>Ba. divergens</i>)	Babesiidae	<i>Babesia</i>	Tick-borne	Blood	Molecular
<i>Babesia</i> sp. MDJ ^{*†} (<i>Ba.</i> sp. MDJ)	Babesiidae	<i>Babesia</i>	Tick-borne	Blood	Molecular, Morphology
<i>Babesia</i> sp. XXB/HangZhou ^{*†} (<i>Ba.</i> sp. HZ)	Babesiidae	<i>Babesia</i>	Tick-borne	Blood	Molecular
Uncharacterised <i>Babesia</i> spp. [§] (<i>Babesia</i> spp.)	Babesiidae	<i>Babesia</i>	Tick-borne	Blood, Bone marrow, Faeces	Molecular, Morphology, Cultures, Serological
Uncharacterised <i>Colpodella</i> spp. [§] (<i>Colpodella</i> spp.)	Colpodellidae	<i>Colpodella</i>	Tick-borne	Blood, Cerebrospinal fluid	Molecular, Morphology
Uncharacterised <i>Theileria</i> spp. [§] (<i>Theileria</i> spp.)	Theileriidae	<i>Theileria</i>	Tick-borne	Blood	Molecular

Table 2: Emerging and reemerging neglected vector-borne pathogens in human infection in China.

* The 18 kinds of novel vector-borne pathogens detected in human infection discovered in China for the first time in the world.

† The 9 kinds of vector-borne pathogens in human infection identified in China tentatively named by the authors.

§ The uncharacterised pathogens. The classification of family and genus of each pathogen was determined by the online taxonomy search websites, including International Committee on Taxonomy of Viruses (ICTV) (<https://talk.ictvonline.org/>) and National Center for Biotechnology Information (NCBI) Taxonomy (<https://www.ncbi.nlm.nih.gov/taxonomy/>).

We excluded vector-borne pathogens (including *Rickettsia mooseri*, *Rickettsia prowazekii*, *Orientia tsutsugamushi*, *Plasmodium*, *Wuchereria bancrofti*, *Brugia malayi*, Dengue virus, Japanese encephalitis virus, *Leishmania* spp., *Anaplasma phagocytophilum*, *Dabie bandavirus*, Tick-borne encephalitis virus) listed in the National Notifiable Diseases Surveillance System of China for the current analysis.

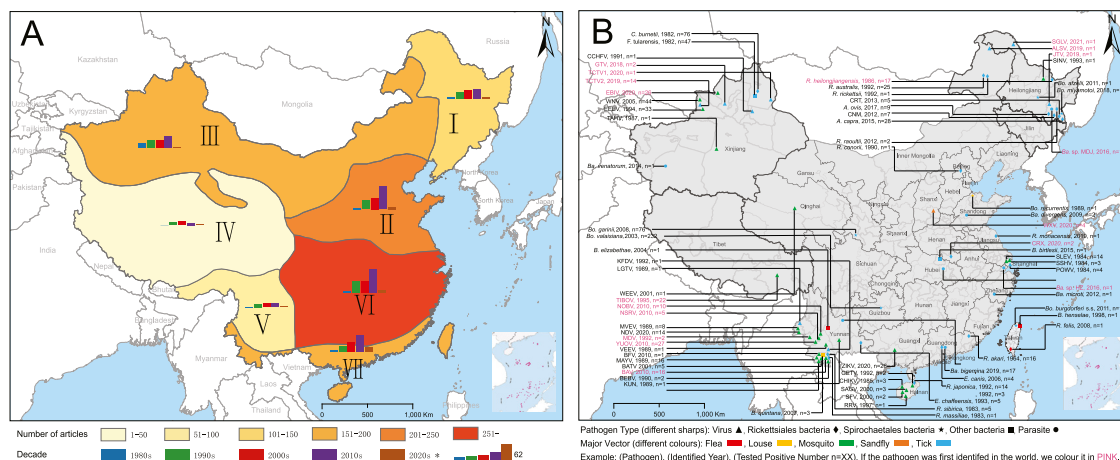


Figure 3. Distribution of extracted records of VBP causing human infection in China from 1980 to 2021 (A), and the first identification site of 75 VBPs causing human infection in China from 1980 to 2021 (B). (A) Records number of extracted literatures in seven ecological regions. Within each ecological region, the bar diagram was used to illustrate the published article number by decade, and the total number was reflected by the background color. The bars fill in the blank and marked with “*” represent the article published in 2020s. I= Northeast region (NE), II=North China region (N), III=Inner Mongolia-Xinjiang region (IMX), IV= Qinghai-Tibet region (QT), V=Southwest region (SW), VI=Central China region (C) and VII=South China region (S); (B) The location where the pathogen was firstly identified in human population is determined at prefecture level as referred to the included literatures. The number of tested positive of each pathogen were extracted from the dataset. The abbreviation of each pathogen was shown in Table 2.

In contrast with the publication number, the highest richness of pathogen was found in Yunnan province in Southwestern where totally 41 pathogens were identified (27 viruses, seven Rickettsiales bacteria, one Spirochaetales bacteria, three other bacteria, three parasites), followed by 27 pathogens in Xinjiang uygur autonomous region in Northwestern China (13 viruses, seven Rickettsiales bacteria, four Spirochaetales bacteria, two other bacteria, one parasite), 26 in Heilongjiang province in Northeastern China (six viruses, 10 Rickettsiales bacteria, five Spirochaetales bacteria, five parasites) (Figure 2). This spatial pattern was highly compatible with that of the firstly-identified region of each pathogen, for example, since the year of 1980, the first-time identification of 22 pathogens had been reported in Yunnan province, followed by 12 in Heilongjiang province and 11 in Xinjiang Uygur autonomous region (Figure 3B, detailed in Appendix Table S11).

Among totally 75 newly identified pathogens in China, 18 represented the first report of human infection in the world as well, which were determined primarily in Yunnan province (six mosquito-borne viruses, e.g. Yunnan orbivirus and Banna virus), Heilongjiang province (two tick-borne viruses, e.g. Songling virus and Jingmen tick virus, one tick-borne rickettsia, e.g. *Rickettsia heilongjiangensis*, and one tick-borne parasite e.g. *Babesia* sp. MDJ) and Xinjiang uygur autonomous region (three tick-borne viruses, e.g. Guertu virus, Tacheng tick virus 1 and Tacheng tick virus 2, and one mosquito-borne virus, e.g. Ebinur lake virus) (Figure 3B). In line with the finding that rickettsial

infection was most frequently reported, it was also the most widely distributed, e.g. *Coxiella burnetii* was the most widely detected in 28 provinces, followed by Sindbis virus in 17 provinces, and *Bartonella henselae* in 17 provinces (Figure 2).

Clinical presentation

In total 419 articles containing clinical data were used for meta-analysis, based on which 21 commonly seen clinical manifestations were reported from 9 866 patients with determined infection of 57 types of VBPs (Figure 4A). Fever was the most common symptom, recorded in almost all VBPs (The proportion of fevers attributed to each pathogen ranged from 14.29% to 100.00%) except for *Anaplasma ovis* where no fever was reported, fatigue was present in 66.67% (38/57), headache in 64.91% (37/57) (Figure 4A). Other common unspecific symptoms included myalgia (57.89%, 33/57), rash (54.39%, 31/57), nausea (49.12%, 28/57), lymphadenopathy (43.86%, 25/57), and chills (43.86%, 25/57). When compared among pathogen types, fever and fatigue was more prevalent among patients with rickettsial infection than others, four main presentations (headache, dizziness, rash, and myalgia) were more prevalent among patients with bacterial infection than others, the presence of chills among patients with parasitic infection than other infections (Figure 4B).

Six clusters were formed that differed in the variety of the clinical manifestation. Flu-like illnesses (fever, fatigue, headache, chills, dizziness, or cough) as the

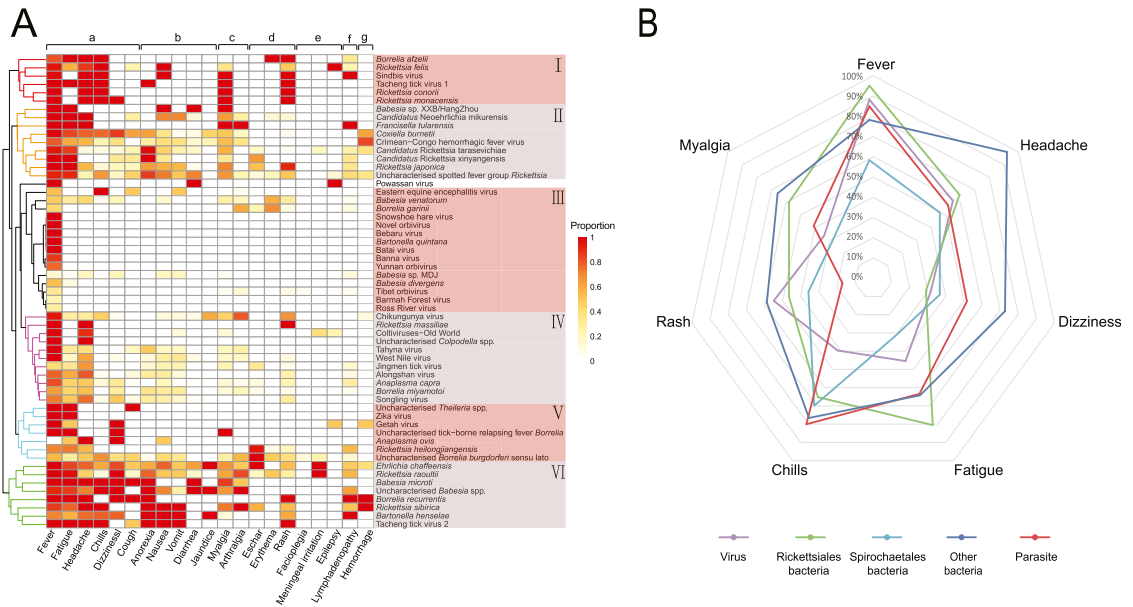


Figure 4. Clustered Heat chart describing the weighed clinical presentations of each pathogen (A), and Radar chart illustrating the seven common clinical presentations by etiology (B). (A) The clinical presentations were divided into: (a) flu-like presentations (fever, headache, dizziness, cough, fatigue, and chills), (b) gastrointestinal presentations (nausea, vomit, diarrhea, and jaundice), (c) motor presentations (myalgia and arthralgia), (d) dermatologic presentations (rash, eschar, erythema), (e) neurological presentations (meningeal irritation, facioplegia and epilepsy), (f) lymphadenopathy, (g) hemorrhage. Six clusters were obtained according to the complete cluster analysis of clinical presentations; (B) Seven clinical presentations: fever, headache, dizziness, fatigue, chills, rash, and myalgia.

common presentation, were featured in all clusters, however, other manifestations differed among clusters, i.e., myalgia/arthralgia and skin presentations (eschar, erythema, or rash) were related to Cluster I; gastrointestinal (anorexia, nausea, vomit, diarrhea, or jaundice), lymphadenopathy, skin and other hemorrhagic illnesses were related to Cluster II; gastrointestinal and skin illnesses were related to Cluster IV; a high complex manifestation including gastrointestinal, skin, lymphadenopathy and hemorrhagic illnesses were related to Cluster VI. Only rare illnesses other than flu-like illnesses were presented in Cluster III or Cluster V (Figure 4A). Further detailed clinical presentation that were estimated for each of the tested pathogen was shown in appendix (Appendix Figure S2).

Risk of bias and precision of distribution. Among 906 articles, 104 articles were evaluated at high risks of bias, 564 at moderate risks, and 238 at low risks. The precision of pathogen distribution was considered to be high in 419, moderate in 398, and low in 89.

Discussion

In China, the variety of VBDs that can cause human infection and their distributions are poorly understood

due to the lack of etiological testing in clinical practice.²⁷ Here by performing the most comprehensive systematic review of literature in China between 1980 and 2021, we have revealed diverse VBDs that cause human infection which are not within the surveillance list, with each occurrence identified by its unique geographical location and time points.

Viral infections were reported with the highest variety, constituting almost half of the reported pathogens during the study period. As has been previously described, viral pathogens accounted for the majority of emerging infectious diseases, especially RNA viruses,⁵⁵ owing to their high rates of nucleotide substitution, poor mutation error-correction ability and therefore higher capacity to adapt to new hosts, including humans.^{2,55-60} In contrast, rickettsial infection was related to the highest number of records, reflecting the high variety of *Rickettsia* species,^{61,62} and of course the elevated interest in the identification and reporting of *Rickettsia*, especially spotted fever group in China. This trend was particularly noteworthy in the 2010s, when rickettsial infection had received much more attention than previous years (Appendix Figure S1). This has been resembled by the most recent study in the Southeast Asia region where rickettsial diseases have been reported to be the second most common cause of non-malarial febrile illness, only after dengue infection,

owing to greater clinical suspicion, case definition and detection test changes, or increase in disease incidence and prevalence.^{36,62,63} Antibiotic therapy proved to be effective in treating infection with most *Rickettsia* species,⁶² therefore empirical application might be a choice in regions with high probability of acquiring tick borne *Rickettsia*, such as in Northeastern China according to the current review. Generally, spotted fever group *Rickettsia* infections are significantly neglected and under-recognized in China,^{64,65} for which disease the affected area continues to expand and the incidence is on the rise in recent years, with major endemic areas focused in Northern China. Alongside this trend, it's noteworthy that records on pediatric infection with VBDs, especially rickettsial infections are increased. Such evidence called for an increased efforts to survey and identify emerging TBPs in pediatric patients, especially when considering their long-term impacts on the child's life.⁶⁶

There were 18 pathogens which had been identified in human infection for the first time in China within global wide range. There is noticeable geographic segregation for some pathogens, with rickettsial infection reported more frequently in Central and North China, and viral infection reported more frequently in Inner Mongolia-Xinjiang and South China (Appendix Figure S1). This cannot be interpreted as an accurate reflection of the distribution of VBPs or their prevalence, as factors such as the diagnostic capacity available and assessment efforts of the likely causes of febrile illness in a specific location could be responsible. It's highly possible that once pathogens are identified in any location, there might be increased awareness of those pathogens, thus contributing to the improved diagnostic efforts in this region. Despite this bias, the spatial pattern of pathogen type could be driven by the hosts and vectors, and the ecology of the transmission. The distribution of vectors determines their contact with vertebrate hosts, which influences in turn the spatial spread of VBPs.¹⁷ The regions which have rich varieties of natural conditions, including a wide range of flora and wild animals, create a spectrum of ecological niches. Areas with thick forest and high mammalian biodiversity are considered as the hotspot of emerging infectious disease. Risk of spillover for the emerging infectious disease from mammal hosts to humans directly or transmitted by vectors has been found to be positively correlated with host species richness.⁶⁷ Ecology environment and climate change all contribute to broad geographic changes both in mammals and vectors.¹⁵ This likely reflects the fact that most VBPs have geographical ranges restricted by the distributions of their vectors and/or reservoir hosts. China is a vast country with a diversity of ecosystems and climatic zones which make areas suitable for vectors (e.g., ticks, mosquitoes, mites, lice and fleas) survival. Zhao et al. conducted a comprehensive review and spatial modelling of tick species in China, and this study revealed

that ticks are abundant in Xinjiang and Yunnan (over 20 tick species in these prefectures).⁴² Yunnan also have the abundant diversity of mosquito, lice and mite species.^{68–70} It's noteworthy that the geographical sites with high richness of pathogen mainly focused in Yunnan, Heilongjiang and Xinjiang at the province level. None of them was among the economically most developed provinces that can support more advanced diagnostic technologies or intensive surveillance efforts than the other provinces. These controversies thus could allow inferences to be made illustrating the hotspot of emerging mosquito-borne and/or TBDs in China. As has been acknowledged, these provinces were featured by complex biological and ecological niche, especially Yunnan province, as a part of Greater Mekong Sub-region, had been featured by rich ecological diversity, subtropical to tropical climate, rapidly urbanizing populations of people and a high degree of livestock production.^{71–73} Similarly, Zhangguangcai Mountain in Heilongjiang and Tian Shan Mountains in Xinjiang, have large areas of forests, abundant natural resources and richness biodiversity. However, increasing evidence indicates that areas of naturally high biodiversity may serve as a source pool for novel pathogens and biodiversity loss frequently increases disease transmission with the urbanization and environmental change.⁷⁴ These factors might have driven high odds of pathogens-vectors-hosts interface, promoted cross-species transmission and rendered generation of a large number of novel VBPs. High priority for the surveillance of novel VBPs were advocated in these provinces, optimally through the high-through sequencing methods.

There is a great challenge in diagnosis of VBDs due to their non-specific clinical manifestations, limited laboratory capacity, seroconversion-based diagnosis methods, especially in resource limited region.^{60,75} These challenges necessitate syndromic approaches for the purpose of patient differentiation and management. Here by aggregating all reported VBP related clinical presentation of the published literature, we could disclose the clinical aspects of VBDs in China at the current stage. Six clusters were formed according to their similarity in clinical aspects, among which Cluster III and V were noteworthy, presenting with mild disease and less presence of clinical manifestations other than influenza like illnesses. Most member of these two groups were *Babesia* species or *Rickettsia* species, which is in sharp contrast with other groups where more viruses were grouped. Although no specific syndrome was linked to certain specific infection, the clustering could provide a starting point for improving differential diagnosis among febrile illnesses of unknown reason.

There are several limitations to this study. The efforts and quality of reporting of VBP infection are inconsistent by region and often biased by difficulties in diagnosis, limited resources for diagnostic testing and the variable reporting capacities of local health systems.

Biases in testing practices for different pathogens in different locations and with different clinical presentations will influence the pathogens looked for, detected and reported. The bias assessments for study representativeness and precision in the description of human infections with neglected VBPs in China reveal that the majority of data points had medium or low risk, and high or moderate precision of pathogen distribution, showing that the characteristics and spatial pattern of VBPs could be high representative, despite using inconsistent laboratory diagnostic methods. Moreover, we could not ignore other biases in this study. All might have biased the comparison results of the current review. Because the purpose of this database is to enable the identification of all known occurrences of human VBP infection nationally, many different types of study design and test methods were used for compiling the database. The heterogeneity prevented a meta-analysis of current research and the incidence or prevalence of VBP are hard to be attained. Given the unavailability of specific confirmation techniques in the earlier years, analyses of historical documents inevitably suffer from such limitations due to the absence of absolute etiologic certainty. Therefore, there have been a large amount of publication that reported uncharacterized pathogen, especially for *Borrelia burgdorferi* sensu lato and spotted fever group *Rickettsia*, which remained as one of the limitations inherent to the retrospective literature review study. Some pathogens were tentatively named by the authors, such as MD virus,⁷⁶ Novel Seadornavirus,⁷⁷ which restricted the comparable study with other studies with similar study design for VBDs in other countries/regions.

Despite the limitations, our study provides a starting point for gaining knowledge and improving awareness of VBPs that are known to contribute to human illnesses, demonstrating the need to consider multiple infections in different settings, thus help inform future research and surveillance efforts in China. VBPs studies offers an opportunity to integrate multiple disciplines (e.g., epidemiology, clinical medicine, veterinary medicine, ecology and geography science). Understanding of the mechanistic processes linking climate change, land use, and socioeconomic conditions with VBDs enables precise prediction of future trends of emerging VBDs and control of its outbreaks.¹⁶ A prioritization scheme should be developed for surveillance, reporting, and assessment of endemic, epidemic, and pandemic VBDs according to their relative health burdens. Our study found it potentially important to expand current field survey of wild hosts and vectors and strengthen diagnostic and treatment capacities in areas where VBPs infectious cases have emerged.

Contributors

The author contributions are as follows. SIH, LQF and WL conceived, designed and supervised the study. YQS,

MCL, TTL, CLL, QX, YYZ, TLC and FFM searched, screened and assessed the publications. YQS, TW, AYT and JJC created data extraction forms and extracted and analyzed the data. YQS, TW, JJC helped with checking data and constructed the figures. BGJ, QX, CLL and NZ provided statistical and clinical expertise in data analysis. YQS wrote the drafts of the manuscript. YQS, TW, and YYZ interpreted the findings. SIH, LQF and WL commented on and revised drafts of the manuscript. All authors read the manuscript, provided feedback, and approved the final version.

Data sharing

Data will be made available upon request made to the corresponding author.

Editor note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

We declare no competing interests.

Acknowledgments

The authors would like to thank all patients who contributed data and clinicians who collected the data.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.lanwpc.2022.100427](https://doi.org/10.1016/j.lanwpc.2022.100427).

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