Underrecognized Q Fever and Rickettsial Diseases Across China

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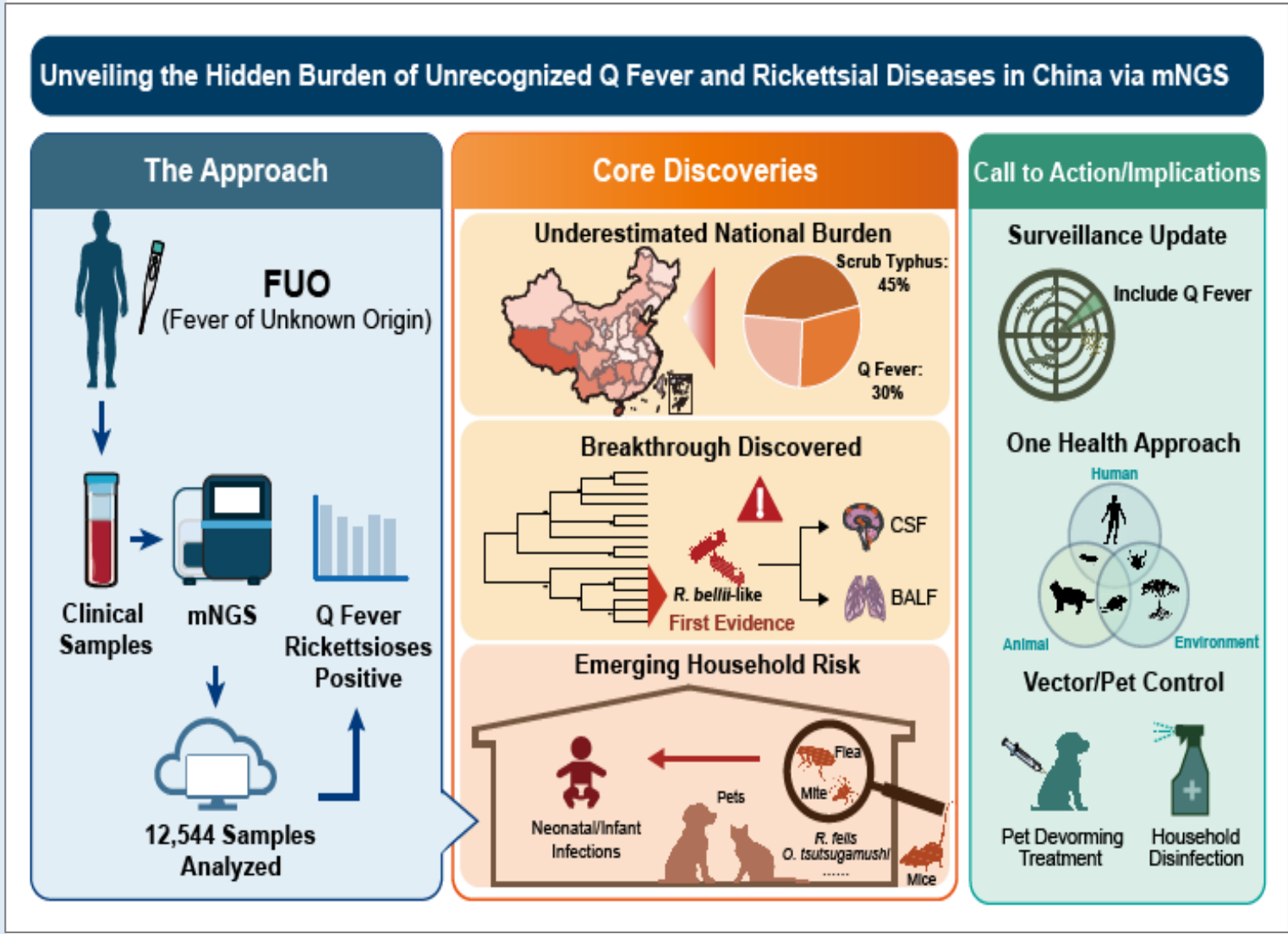
Tian Qin, Zhongqiu Teng, Yamin Sun, Yaoming Liang, Junrong Liang, Ronghua Jin, Jianguo Xu. 2026. Underrecognized Q Fever and Rickettsial Diseases Across China. ***iMetaOmics*** 3: e70149. https://doi.org/10.1002/imo2.70149

Introduction

- **Clinical Dilemma of FUO**: Q fever (*Coxiella burnetii*) and rickettsial diseases are severe zoonoses causing life-threatening complications (endocarditis, meningoencephalitis), yet routinely missed due to nonspecific early symptoms.

- **Surveillance Gap in China**: Statutory surveillance covers only epidemic and endemic typhus; the nationwide burden and true geographic footprint remain undefined.

- **The Power of mNGS**: Metagenomic next-generation sequencing offers unbiased pathogen detection directly from clinical specimens, uncovering neglected etiologies across China.



Highlights

- **Nationwide Clinical Landscape (12,544 FUO Cohort)**: 9.4% positivity rate (1,176 cases) across mainland China, identifying *C. burnetii* (29.5%) and *O. tsutsugamushi* (45.0%) as predominant etiologies.
- **First Clinical Detection of Ancestral *R. bellii*-like Lineage**: Recovered *R. bellii*-like sequences from human CSF, BALF, and blood samples across three provinces, challenging the traditional "non-pathogenic" paradigm.
- **Unexpected Pediatric & Neonatal Detections**: Identified 27 rickettsial infections in children <5 years old (including neonates <1 month), highlighting critical domestic and companion-animal exposure risks.

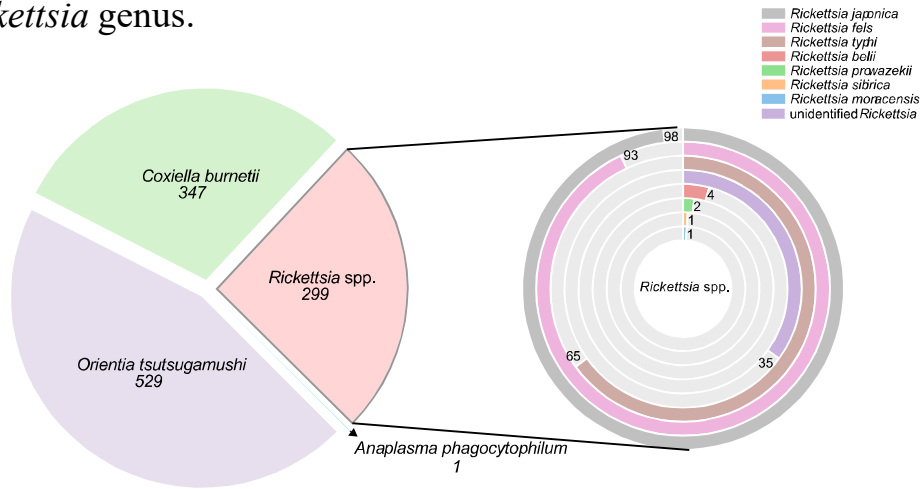
Study Design & Methodology

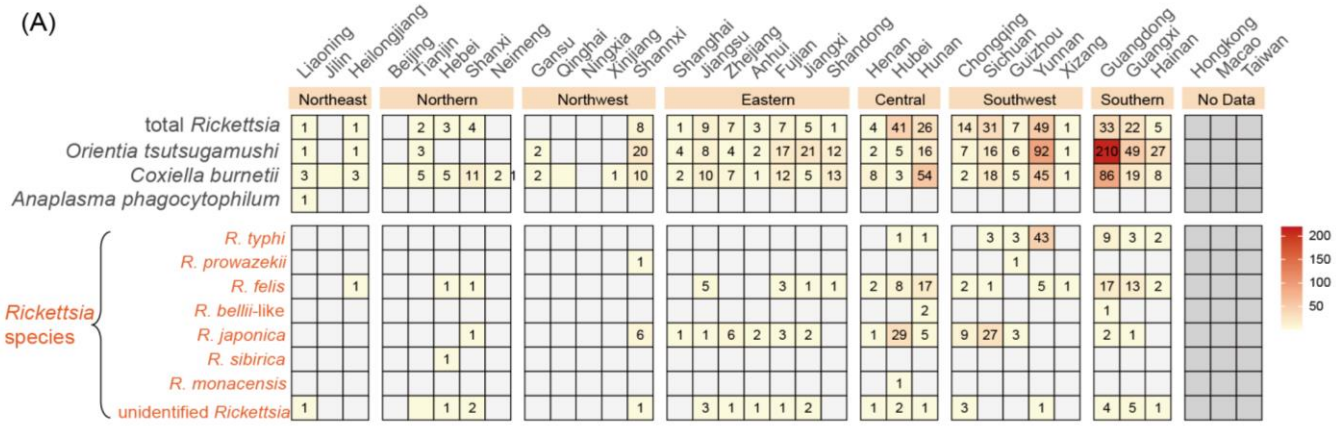
Nationwide Study Design & Independent Validation Pipeline

- **Cohort Recruitment**: 12,544 clinical FUO specimens spanning all 31 provincial-level administrative regions (Dec 2021 – Apr 2025) via KingMed Diagnostics network.
- **Multi-Sample Types**: Encompassed peripheral blood, BALF, CSF, and bone marrow.
- **Independent Bioinformatics Pipeline**:
  - Computational fragmentation into 100-bp specific pathogen tags.
  - Filtering against non-target bacterial genomes (>90% identity removed).
  - Dual verification using Bowtie 2 (>95% identity) and NCBI BLAST.
  - Maximum-likelihood phylogenetic placement (IQ-TREE, 1,000 bootstraps) for *R. bellii*-like reads.

Result 1:Total case counts of Q fever and rickettsial pathogens

Orientia tsutsugamushi accounted for the largest proportion of cases (n = 529), followed by *Coxiella burnetii* (n = 347), *Rickettsia spp.* (n = 299), and *Anaplasma phagocytophilum* (n = 1). The donut chart on the right provides an expanded view of the composition of *Rickettsia spp.*, illustrating the proportional representation of individual species within the *Rickettsia* genus.





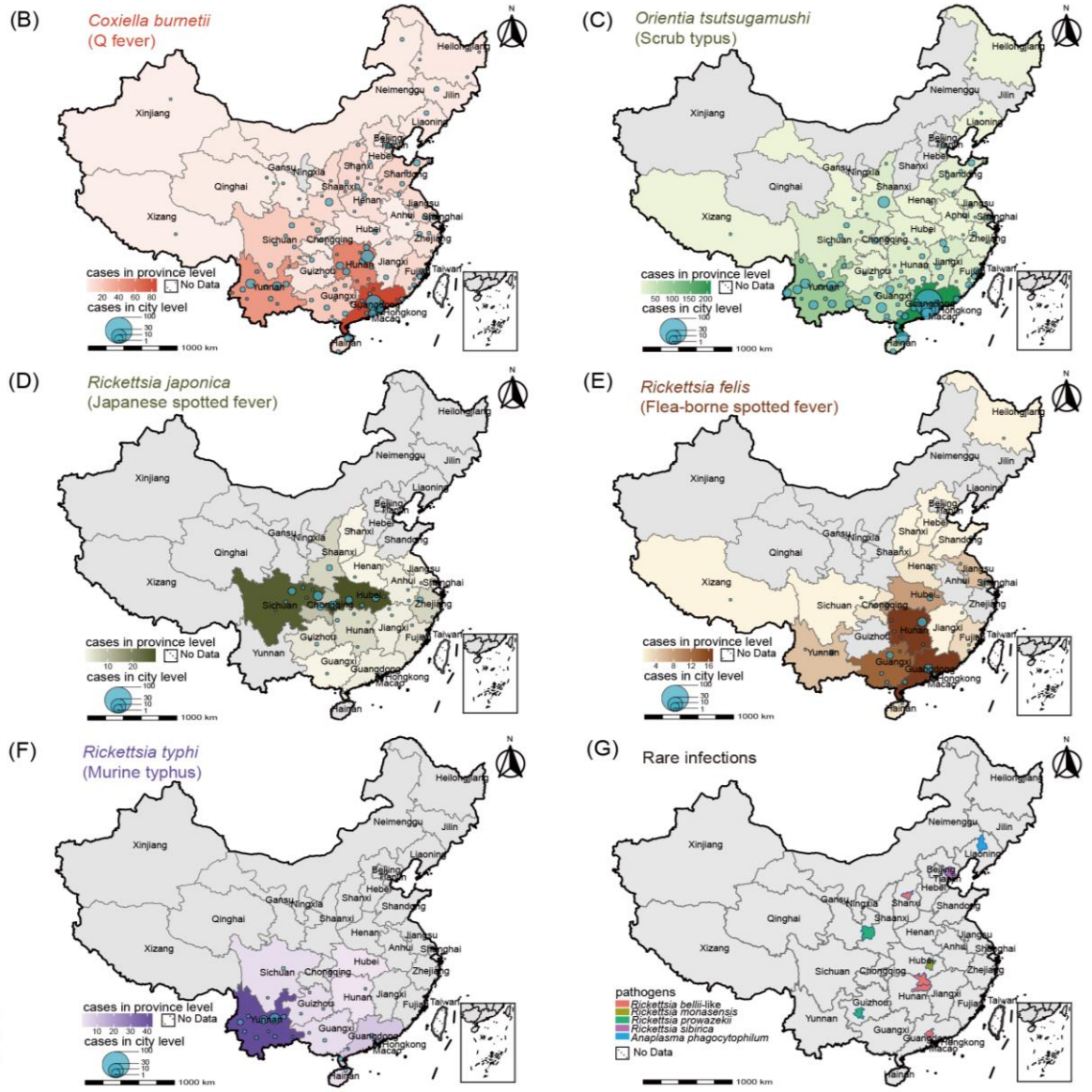
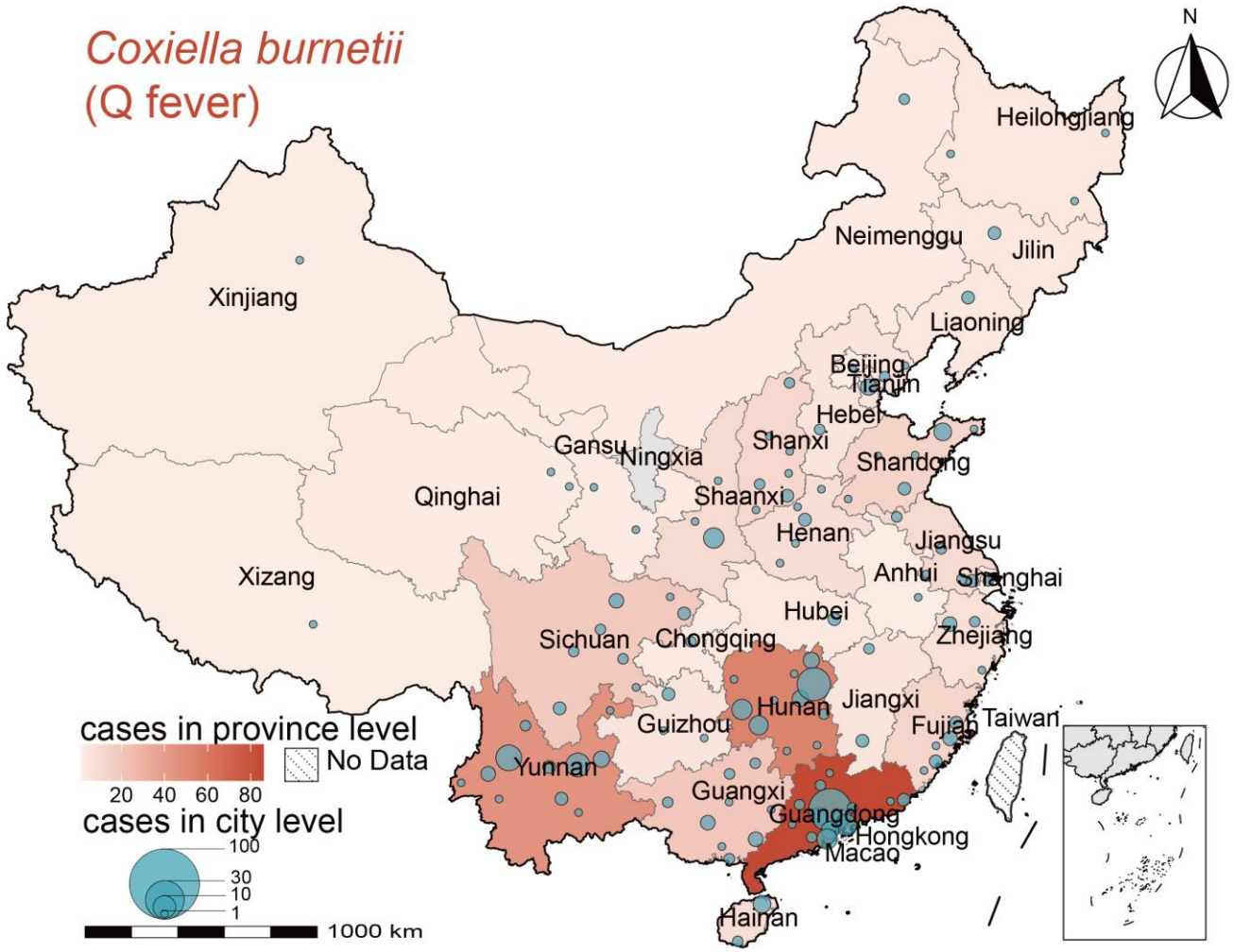


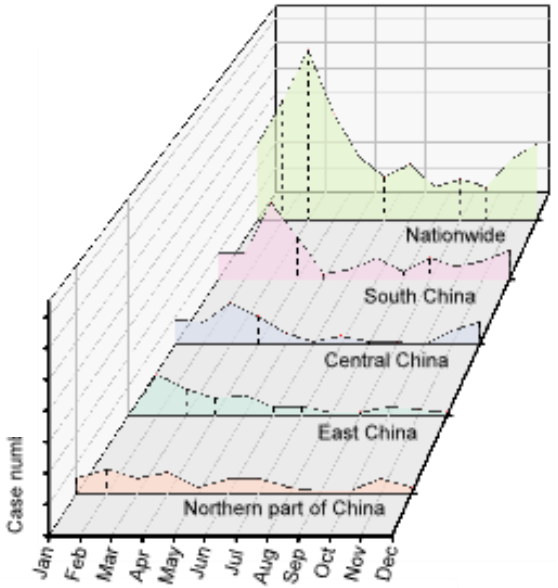
Figure 1. distribution of detected pathogens

Result 2: Nationwide Epidemiology of Q Fever

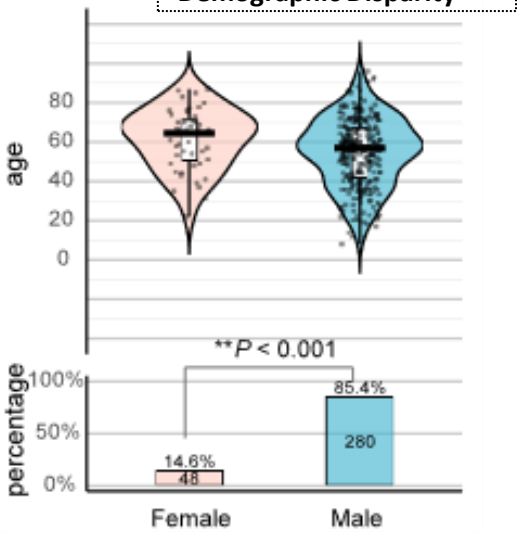


- **Widespread Distribution**: *C. burnetii* detected in 30 provincial divisions, with major case clusters in Guangdong (86), Hunan (54), and Yunnan (45).
- **Seasonal Dynamic**: Peaks nationwide in March (late autumn to spring), aligning with livestock lambing periods and animal housing.
- **Demographic Disparity**: Marked male predominance (81.6% vs. 18.4%) and older age distribution (median 58 years), linked to estrogen protection and occupational risk.

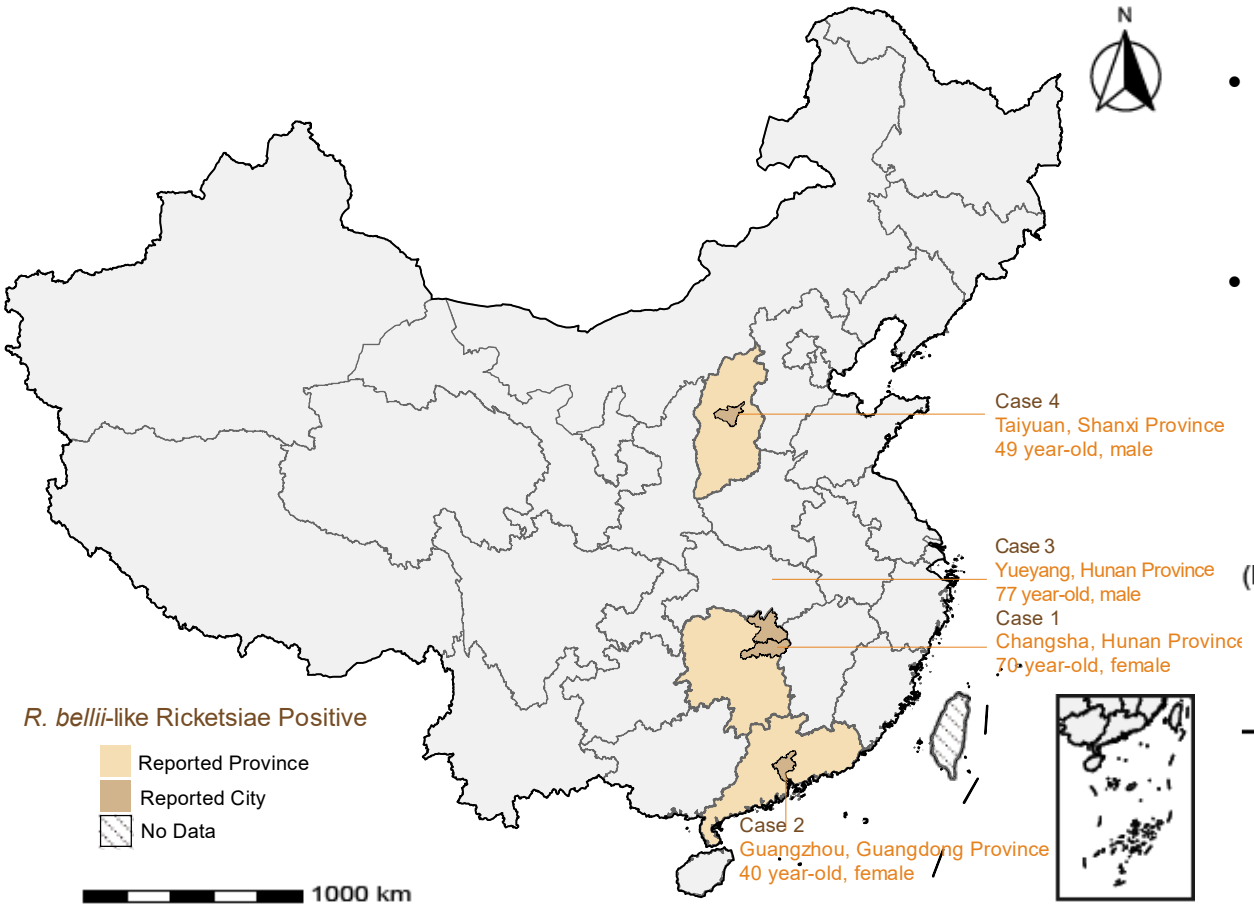
Seasonal Dynamic



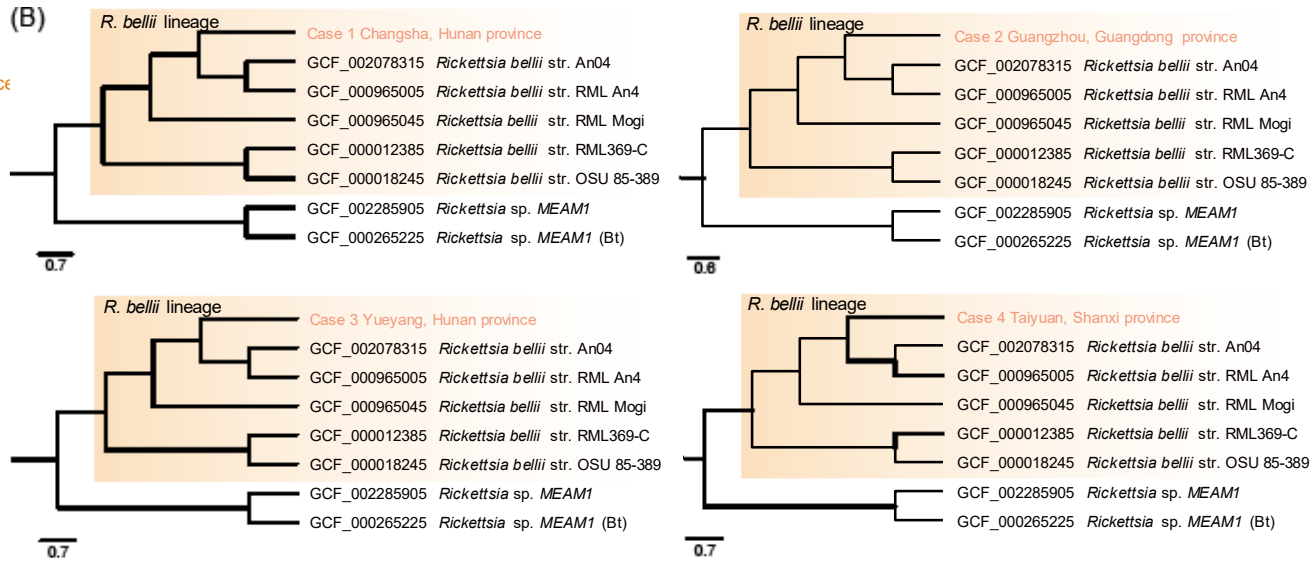
Demographic Disparity



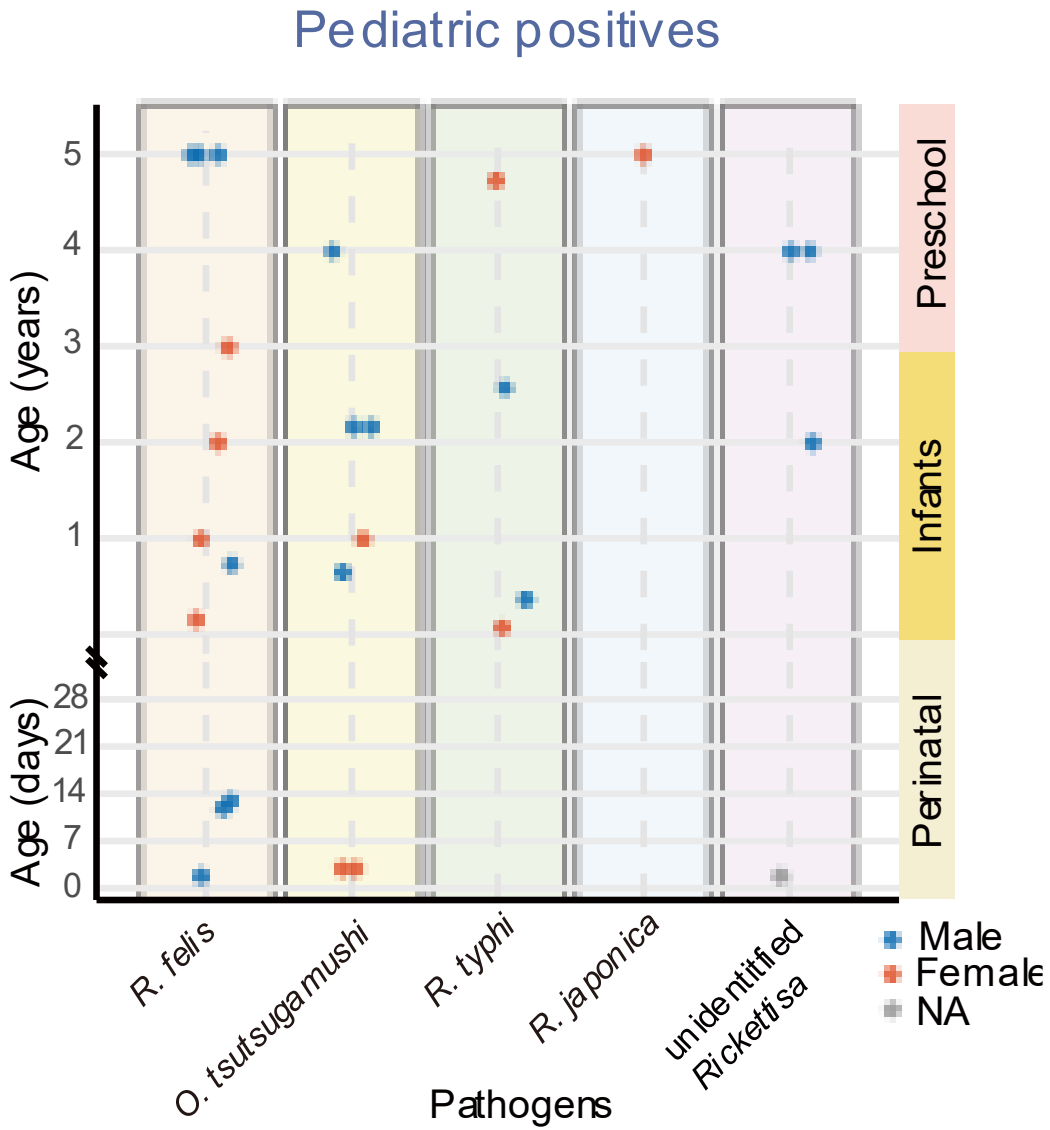
Result 3: Discovery of Ancestral *Rickettsia bellii*-like Sequences



- **First Clinical Metagenomic Evidence**: Four cases identified across Shanxi, Hunan, and Guangdong representing distinct climatic zones.
- **Invasive Specimen Recovery**: Recovered from CSF (2 cases with neurological signs / coma) and BALF (1 case with respiratory distress), with 94.7%–96.0% sequence identity to reference strain.
- **Phylogenetic Robustness**: Rigorous IQ-TREE analysis clustered all clinical reads squarely into the ancestral group rickettsiae (AGR) clade.



Result 4: Unexpected Pediatric Infections



- **Shifting Demographic Paradigm**: 27 cases in children under 5 years; 19 detections in infants <3 years old; documented cases in neonates (<1 month of age).
- **Leading Pediatric Pathogens**: *R. felis* (37.0%), *O. tsutsugamushi* (29.6%), and *R. typhi* (14.8%).
- **Potential Domestic & Perinatal Transmission**: High proportion of indoor flea- and rodent-borne pathogens may points to domestic pet contacts, commensal rodent infestations, or potential perinatal routes.

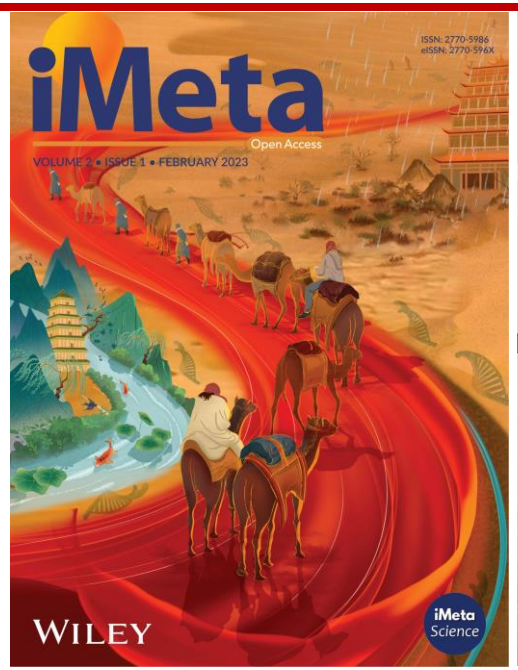
Summary

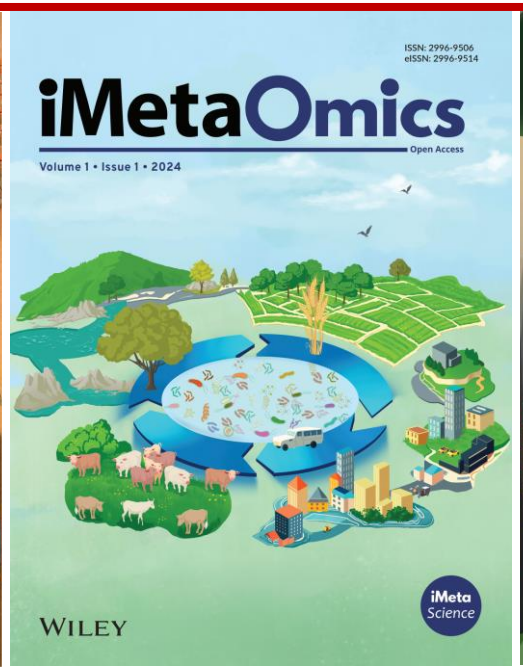
- Q fever and diverse rickettsial diseases represent substantially underrecognized burdens among febrile patients across China.
- We urgently call for strengthening Q fever surveillance in China.
- Heighten clinical awareness for atypical vectors and ancestral rickettsial lineages (*R. bellii*).
- Joint surveillance encompassing human diagnostics, pet/livestock veterinary monitoring, and arthropod vector tracking.

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