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SENTINEL SURVEILLANCE



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Perspectives

Improving Risk Communication and Community Engagement for Public Health Emergencies in China: A State-guided Cooperative Trust Model

Yi Cai[1]; Jie Zhu[2,#]

ABSTRACT

Risk communication and community engagement (RCCE) constitutes a mandatory core capacity under the International Health Regulations (IHR 2005). However, dominant RCCE frameworks are rooted in Western institutional contexts and lack theoretical adaptation to China's state-led governance system. Drawing on an integrated multi-theoretical RCCE framework, this paper systematically examines the context-specific features and the limitations of China's present RCCE model in public health emergencies (PHEs). It identifies critical institutional, adaptive, and trust-related gaps by implementing literature review, policy analysis and case studies in China's RCCE practice, and proposes a state-guided cooperative trust model to reconstruct China's RCCE system. This study addresses the theoretical misalignment between global RCCE frameworks and China's institutional context, providing actionable implications for PHE preparedness and global health security.

Risk communication and community engagement (RCCE) are mandatory core capacities under the International Health Regulations (IHR 2005) and are widely acknowledged as a foundational pillar of effective prevention, preparedness, response, and recovery (PPRR) for public health emergencies (PHEs) (*1*). Pandemics delivered a pivotal global lesson: Even surveillance and emergency response systems may falter when RCCE implementation is insufficient, communities lack meaningful engagement, and response strategies are misaligned with local social, cultural, and institutional contexts (*2*).

RCCE effectiveness is shaped by a country's political institutions, cultural norms, resource availability, and state-society relations. In 2023, WHO released the IHR benchmarks for PHEs, which suggest actions to adapt to the country's context (*3*), and address the limitations of the one-size-fits-all model used in previous guidelines (*4*). These IHR guidelines offer valuable insights tailored to the countries whose RCCE systems remain under-theorized and under-examined.

China's response to large-scale PHEs has fostered a distinct state-led RCCE model (*5*). This model exhibits unparalleled scalability and implementation efficiency in rolling out nationwide public health and social measures (PHSMs). Nevertheless, it also reveals deep-seated systemic challenges, including inadequate institutionalization of community engagement, structural gaps in vulnerable group coverage, and intermittent trust deficits between authorities and local communities (*6*–*8*). The study employed legal policy analysis, systematic evidence synthesis, and comparative institutional analysis to draw on the WHO normative guidelines, China's national health statutes and policy documents, and peer-reviewed empirical literature published between 2020 and 2025 to examine the contextual fit of global RCCE frameworks within China's state-led governance system.

Theoretical Evolution of RCCE in PHEs

The theoretical RCCE underpinnings have undergone three sequential paradigm shifts. Aligned with Arnstein's ladder of citizen participation, these shifts have fundamentally redefined the role of communities in crisis responses, from passive recipients of top-down guidance to active collaborative stakeholders, and ultimately to equal co-producers of sustained crisis resilience (*9*). Early RCCE models were dominated by the knowledge deficit model, which attributed low public compliance with public health measures to insufficient scientific literacy and prescribed one-way factual communication (*10*). It prioritizes short-term behavioral compliance over long-term trust-building.

A paradigmatic turning point in RCCE was driven by empirical evidence from responses to PHEs, which demonstrated that the partnership-centered, two-way

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RCCE consistently outperformed the command-and-control model in enhancing PHE response effectiveness. Building on these insights, the WHO's RCCE framework established four core principles — trust, transparency, early announcement, and respect for public concerns — to be implemented through community-centered, inclusive participatory approaches during PHEs (*3*). Despite the standardized guidelines in the WHO framework, RCCE systems across member states and local communities exhibit significant heterogeneity.

This cross-contextual heterogeneity in RCCE warrants systematic delineation and contextual explanation at the national and community levels to unpack social capital, foster trust, and sustain community resilience within an integrated multi-theoretical framework (Figure 1) (*11*–*13*). Analytically, this framework is constructed along dual logical axes. Trust theory was adopted as the vertical analytical thread, connecting the interactions across dimensions of institutional trust in governmental authorities, epistemic trust in scientific evidence and public health guidance, and interpersonal trust in neighbors, frontline community workers, and local leaders; social capital theories were used as the horizontal analytical foundation. Thus, this analytical framework characterizes the specific social context of RCCE from three domains: relational structure, institutional norms, and trust cognition.

To enhance the equity orientation and sustainability of the framework, the Community Cultural Wealth (CCW) framework reframes marginalized communities not as resource-deprived intervention targets but as bearers of context-specific endogenous assets (*13*). Most critically, community resilience — defined as a community's capacity to resist, absorb, adapt to, and recover from acute shocks while sustaining essential core functions — elevates RCCE from a peripheral element of the PHE response to a core strategic pillar of long-term pandemic PPRR and health system strengthening, serving as the ultimate outcome dimension of the entire integrated framework. Accordingly, this integrated multi-theoretical framework provides a foundational analytical tool for identifying gaps in real-world RCCE practices for PHEs in China.

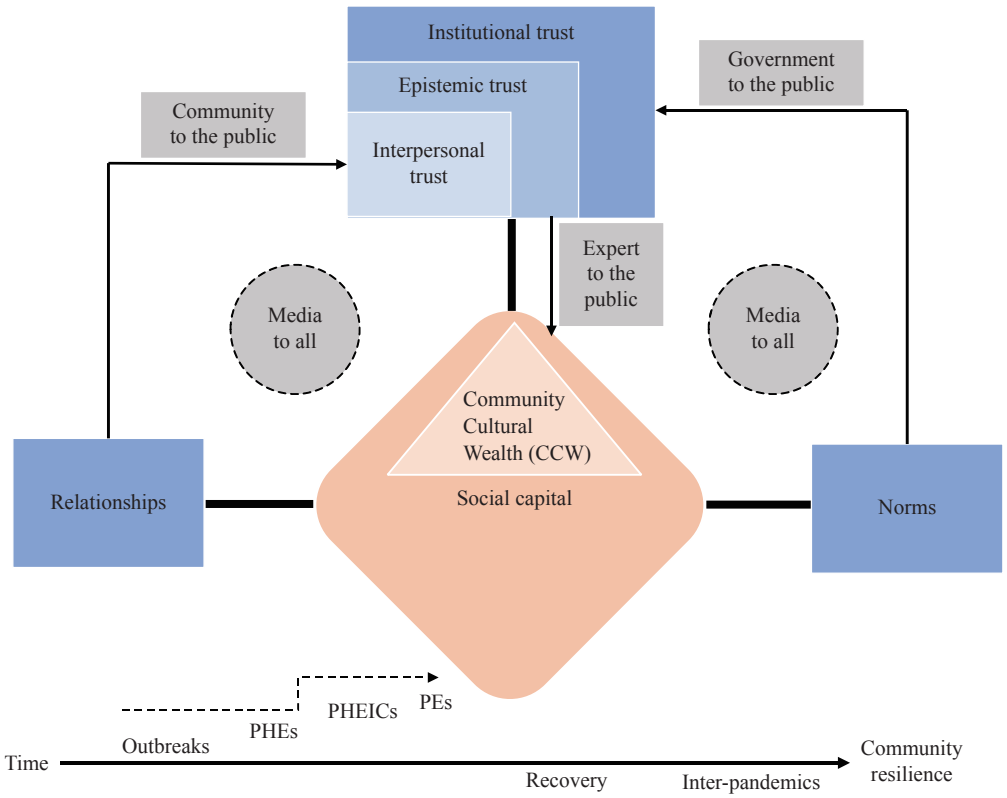


FIGURE 1. An integrated multi-theoretical framework: Three-level trust, social capital, and community resilience across the PHE cycle.
Abbreviation: PHE=public health emergencies; PHEICs=public health emergencies of international concerns; PEs=pandemic emergencies.

China's RCCE in PHEs: Features and Challenges

Building on an integrated multi-theoretical framework, this study diagnoses the structural features and practical gaps in China's RCCE system along three interlocking analytical dimensions: institutional and resilience, social capital and networks, and three forms of trust.

Context-specific features. China's RCCE in PHEs exhibits three interconnected, institutionally embedded features that adapt global guidelines to local contexts. First, it is underpinned by a state-led and party-guided organizational system anchored in community grid-based governance, which operates as a formalized bridging social capital infrastructure aligned with the social capital dimensions of the integrated framework. Second, the model employs collectivist-oriented civic mobilization through culturally congruent risk communication, a strategy built on and sustained by high institutional trust (the foundational pillar of the three-dimensional trust framework) to foster high public adherence. Third, pervasive crosscutting digital technology enablement constructs a decentralized and rapid information diffusion network that aligns with the social network theory dimension and the dynamic communication domain of the integrated framework.

Taken together, these three features endow China's RCCE model with distinctive strengths in scalability, implementation speed, and nationwide coordination during acute emergency responses; however, they also generate corresponding structural limitations that manifest over sustained governance horizons across trust building, social capital adaptation, and resilience, which are systematically discussed in the following section.

Gaps of China's RCCE practice against the integrated theoretical framework. China's hierarchical top-down governance structure delivers exceptionally high implementation efficiency. However, when assessed against an integrated framework and its own institutional and cultural context, China's RCCE system lacks institutionalized bottom-up feedback mechanisms and incentives for community engagement, confining community stakeholders solely to the implementation stage of the decision-making cycle. Communities lack formal avenues for participating in the full cycle of policy formulation, implementation, evaluation, and adjustment, thereby creating structural constraints that undermine the model's long-term effectiveness and equity.

Institutional and resilience dimension: Full-cycle implementation gaps and weak long-term resilience. From the perspective of community resilience theory, China's RCCE system prioritizes acute-phase implementation efficiency but lacks institutionalized mechanisms for full-cycle governance and building long-term community resilience. The study identified structural institutional gaps across the legal governance system that are skewed heavily toward emergency responses. China's RCCE operations rely on a clear hierarchical statutory foundation anchored in its national legal system, providing supreme legal legitimacy, a standardized implementation framework, dedicated emergency provisions, infection control-specific regulations, and overarching institutional support for RCCE practices.

However, the legal system offers a top-down governance framework and guiding principles for the RCCE, it fails to stipulate operational rules for full-cycle implementation, particularly clear provisions for empowering and facilitating community engagement. This creates a notable legal gap and leaves an insufficiently enforceable legal basis for implementing RCCE-related statutory requirements. Beyond statutory provisions, the system also lacks institutionalized routine capacity-building for frontline RCCE personnel. This preparedness gap further undermines the structural foundation of long-term community resilience.

Social capital dimension: Adaptive deficit across heterogeneous community contexts. As predicted by the social capital domain, the one-size-fits-all RCCE strategy fails to account for divergent social capital endowments and network structures across community types, resulting in highly uneven mobilization outcomes. China's culturally congruent collectivist framework cannot accommodate fundamental disparities in population structure, social relations, lifestyles, and governance foundations across four distinct types of residential communities in China.

In urban communities, this homogeneous strategy fails to adapt to the dual engagement logic driven by bonding social capital for internal community affairs and bridging social capital for external public affairs, hindering broad-based grassroots mobilization (*14*). In rural communities, top-down mobilization cannot adapt to the collapse of traditional acquaintance societies and the erosion of bonding social capital caused by the large-scale outmigration of young adults, failing to mobilize the residual social capital of left-behind groups (*15*). In rural-to-urban resettlement communities, the standardized RCCE model fails to

address the "field-habitus mismatch" that describes the disjuncture between residents' internalized behavioral dispositions and their new urban living environment, resulting in pervasive long-term engagement apathy (*16*). In multi-ethnic inter-embedded communities, the administrative mobilization model cannot accommodate diverse cultural norms and differentiated needs, leading to superficial mobilization and a lack of broad-based public engagement (*17*).

Trust dimension: erosion of three-form trust and cognitive bias. China's RCCE practices exhibit structural weaknesses across three forms of trust. First, top-down official risk communication weakens responsiveness to institutional trust. Without formalized bottom-up feedback channels, unmet public concerns gradually erode confidence in governance authorities, thereby holding out the institutional trust foundation for large-scale RCCE mobilization. Second, the disconnection between expert technical discourse and practical public demand drives the persistent erosion of epistemic trust. Driven by technological elitism bias among technical experts, communication strategies prioritize scientific rigor and normative correctness over public acceptance and emotional needs. Third, fragmented information spreads in a fission-like manner across social media during PHEs and disrupts interpersonal trust at the community level. Digital tools enable fast and timely risk communication, efficient service delivery, and real-time situational awareness. However, they also act as major infodemic vectors. These structural trust deficits are further amplified by cognitive biases across the four stakeholder groups: the power-centric bias of governments, excessive self-interest bias of enterprises, technological elitism of technical experts, and irrational fear bias of residents.

Reshaping China's RCCE in PHEs

Based on integrated theoretical frameworks and a diagnosis of China's context-specific challenges, this study proposes a state-guided cooperative trust model representing a systematic context-adaptive reconstruction tailored to China's legal, political, and social institutional settings (Figure 2).

Domestic multi-layered reciprocal trust building. This module embeds a closed-loop, bottom-up feedback system into the existing state-led governance hierarchy. Vertically, the system connects four types of stakeholders with three interdependent trust dimensions as its core pillars: interpersonal trust built between the public and community workers, which forms the micro-foundation of community collective action; epistemic trust fostered by translating scientific evidence from experts into context-specific solutions that address public concerns; and institutional trust strengthened when expert insights inform evidence-based decision-making and government policies are transparently communicated back to the public. Complementing this vertical trust chain, a dual-track media system facilitates horizontal information flow: official media serve as an authoritative channel for government announcements and public feedback collection, whereas social media enable real-time communication and community self-organization.

Embedded safeguard mechanism for infodemic governance. Tailored to China's state-led internet regulatory context, infodemic governance is embedded as a cross-cutting safeguarding mechanism to mitigate trust erosion caused by misinformation diffusion. The government exercises normative oversight over social media platforms through two complementary pathways: one is by formulating targeted legislation to clarify the full-chain responsibilities of social media platforms, including mandatory real-time traceability mechanisms for public health misinformation and hierarchical accountability for core accounts that disseminate false content; the other is by guiding platforms to establish priority dissemination channels for evidence-based authoritative information and incentive mechanisms for verified content sharing. This regulatory framework not only mitigates infodemic risks, but also safeguards the public's right to accurate health information, thereby sustaining the three-tiered trust system.

International mutual communication mechanism. Institutional trust acts as a critical bridge connecting China's domestic RCCE system with the international community. The model embeds parallel two-way communication channels with a broad range of international stakeholders, including foreign governments, the WHO in line with the IHR, academic institutions, medical and public health agencies, and international media. These channels address long-standing communication barriers such as linguistic discrepancies and information asymmetry, enabling mutual learning and coordinated global responses to PHEs.

Theoretical innovation and model positioning. China's RCCE practice has exposed four core theoretical misalignments between global frameworks and their context: the misfit of the binary state-society presupposition, normative mismatch of the linear

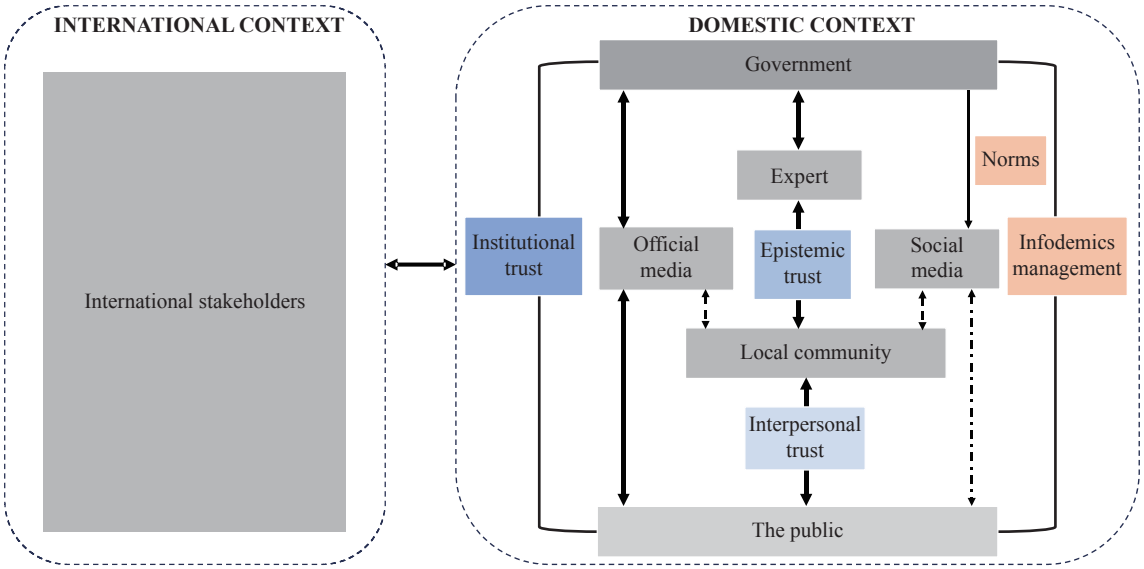


FIGURE 2. A state-guided cooperative trust model: Multi-stakeholder trust building, dual-track media, and infodemic governance across international and domestic contexts.

participation ladder, generalized trust theory's neglect of China's differential mode of association, and insufficient localization of the CCW framework for China's diverse communities. Anchored in a localized integrated theory of state-guided cooperativism and differential trust-building, this framework aims to retain the core strengths of China's hierarchical coordination model, address its structural weaknesses, advance health equity and community resilience, and contribute to China's experience in global health security governance.

CONCLUSION

As an exploratory theoretical analysis aligned with the context-adaptation principle of global RCCE frameworks, this study develops an integrated multi-theoretical analytical lens to diagnose practical gaps in China's RCCE system and proposes a context-adapted state-guided cooperative trust model tailored to China's governance context. This study has the notable limitation of not using primary field data or on-the-ground pilot verifications. Follow-up research will include empirical testing, pilot validation, indicator refinement, scale development, and cross-regional surveys to enhance the theoretical rigor and practical policy relevance.

Conflicts of interest: No conflicts of interest.

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Preplanned Studies

Construction and Application of A Quality Control Indicator System for the Sentinel Surveillance Project for Major Nutrition and Chronic Disease Issues — China, 2022–2025

Zhiwei Xia[1]; Xin Xin[2]; Jingjing Pan[2]; Xiuying Liu[1]; Li Zhang[3]; Kuke Ding[3]; Xiaozhe Tang[3,#]

Summary

What is already known about this topic?

The National Health Commission established a sentinel surveillance project for major nutrition and chronic disease issues in 2022, with a four-tiered full-process quality control (QC) system, monitoring Healthy China Action 2030 indicators.

What is added by this report?

A 68-indicator QC system was developed through two Delphi expert consultation rounds. Application across 38 surveillance sites (2023–2025) showed 95.67% (2,472/2,584) overall compliance. Physical measurement was the weakest dimension. Regional disparities narrowed after targeted interventions.

What are the implications for public health practice?

This system identifies surveillance weaknesses, guides targeted improvements, and provides a replicable reference for QC in other population-based surveillance programs.

ABSTRACT

Introduction: The National Sentinel Surveillance Project for Specific Health Problems was launched in 2021 to monitor overweight, obesity, anemia, and Healthy China 2030 indicators in 101 counties. Ensuring surveillance quality requires a scientific quality control (QC) indicator system.

Methods: A QC indicator system was developed through a literature review and two rounds of Delphi expert consultation with 15 experts. Indicator screening was guided by mean importance scores, coefficients of variation, and feasibility ratings for each indicator. The analytic hierarchy process and expert scoring determined weights. The system was applied to 2,584 QC inspections at 38 sites (2023–2025). Data were analyzed using chi-square tests and the Cochran–Armitage trend test.

Results: The system comprised 6 first-level, 19 second-level, and 68 third-level indicators. Overall compliance was 95.67% (2,472/2,584), increasing from 94.24% (769/816) in 2023 to 96.53% (919/952) in 2025 (χ^2=5.42, P=0.02). Compliance was highest for equipment and materials 98.54% (674/684) and lowest for physical measurement 92.76% (705/760) (P<0.01).

Conclusion: The QC indicator system is scientific and feasible. Physical measurement and questionnaire surveys require improvement, with weaknesses in northeastern provinces. This system is useful for evaluating similar surveillance programs.

In 2021, the National Health Commission launched the Sentinel Surveillance Project for Specific Health Problems, focusing on major nutrition and chronic disease issues in China. The project selected 101 sentinel districts/counties in 31 provincial-level administrative divisions (PLADs) and Xinjiang Uygur Autonomous Region starting in 2022. The annual sample of ≥170,000 persons comprises four population groups (0–5, 6–17, 18–59, and ≥60 years). Surveillance includes questionnaires on Healthy China Action indicators, anthropometric measurements (height, weight, waist circumference), and on-site hemoglobin testing.

Data accuracy requires strict adherence to the four-level quality control (QC) system throughout the process. This process includes pre-implementation training, material preparation, on-site QC, and post-implementation data review. Other public health surveillance programs, such as those for chronic diseases and nutrition, common student diseases, and infectious diseases, emphasize that reliable QC systems are required for data utilization (*1*–*3*). Unlike single-domain surveillance programs, this cross-sectoral initiative under the Healthy China Action framework integrates monitoring requirements across chronic diseases, nutrition, maternal and child health, and

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school health. It covers all age groups and involves multiple data collection modalities. Each domain has its own QC requirements based on different standards (*1*–*4*), which no single QC framework can address simultaneously. This study aimed to develop a scientific QC indicator system and evaluate its application using on-site QC data from 2023 to 2025.

Based on China's nutrition and chronic disease surveillance systems and common student disease surveillance QC indicator systems (*3*–*4*), combined with a literature review, a preliminary on-site QC framework was developed comprising six dimensions: organizational management, sampling implementation, physical measurement, questionnaire survey, on-site hemoglobin testing, and equipment/materials management.

Fifteen experts were purposively selected from national and provincial Centers for Disease Control and Prevention (CDCs) and universities across four regions. Their disciplinary backgrounds included chronic disease epidemiology (n=4), nutrition (n=4), school health (n=1), biostatistics (n=2), public health management (n=2), and grassroots frontline staff (n=2). Five experts held associate senior titles and ten held senior titles, all with bachelor's degrees or above. Their experience included 5–10 (n=4), 10–20 (n=9), and over 20 years (n=2). Expert authority was assessed using a standardized matrix.

Two Delphi consultation rounds were conducted during the 2022 national project training sessions. In Round 1, experts used 5-point Likert scales to rate importance (1=not important to 5=very important), familiarity (1=very unfamiliar to 5=very familiar), judgment basis, and feasibility (1=very poor to 5=very good). Indicator retention criteria were as follows: 1) mean importance score ≥3.5, 2) coefficient of variation (CV) ≤25%, and 3) feasibility rated as "good" or "very good" by ≥80% of experts. Experts could suggest modifications or new indicators. Round 2 presented summarized results from Round 1, and the experts re-rated indicators using stricter criteria (CV≤20%). The initial pool comprised 78 indicators. After Round 1, 8 indicators were deleted, 12 modified, and 5 added, yielding 75 indicators. After Round 2, 7 were deleted, 6 further modified, and 68 retained as the final system (Supplementary Table S1, available at https://weekly.chinacdc.cn). The Delphi rounds and retention criteria were consistent with other Delphi-based studies (*5*–*9*), which have typically employed two to three rounds with similar statistical thresholds.

First-level indicator weights were calculated using the analytic hierarchy process (AHP) with consistency checked (CR<0.1). Second- and third-level indicators were weighted using expert scoring based on importance and feasibility, followed by normalization.

Stratified by four geographic regions, one to five provincial-level administrative divisions (PLADs) were selected annually. In 2023 and 2024, 12 PLADs were selected annually. In 2025, the remaining 8 PLADs and 6 previously weak areas were included, totaling 14 PLADs. Over three years, full coverage of 31 PLADs and the Xinjiang Production and Construction Corps was achieved. One representative surveillance site was randomly selected from each sampled PLAD, yielding 38 total sites. Sampled PLADs did not overlap between 2023 and 2024. Annual training was provided to QC experts. Each year, from May to August, the National Project Management Office coordinated cross-supervision, with 120 expert person-times over three years, following the National Sentinel Surveillance Work Manual. QC verification covered on-site guidance, document reviews, data verification, personnel interviews, and spot checks.

Frequencies, composition ratios, and compliance rates described QC performance. Chi-square tests compared inter-group differences. Cochran–Armitage trend tests analyzed annual trends (α=0.05). SPSS (version 25.0; IBM Corp., Armonk, NY, USA) was used.

Both Delphi rounds had 100% (15/15) response rates. The mean expert authority coefficient was 0.85, and Kendall's W increased from 0.21 in Round 1 to 0.28 in Round 2 (P<0.01). The mean importance score across indicators was 4.31 (standard deviation: 0.52), with CVs ranging from 9.80% to 18.50%. The final QC system comprised 6 first-level dimensions, 19 second-level indicators, and 68 third-level indicators (Supplementary Table S2, available at https://weekly.chinacdc.cn).

Of 2,584 inspections, 2,472 were qualified, yielding an overall compliance of 95.67% (2,472/2,584), increasing significantly from 94.24% (769/816) in 2023 to 96.53% (919/952) in 2025 (P=0.02) (Table 1). Cumulative compliance rates were 96.11% (915/952), 95.88% (652/680), 95.22% (777/816), and 94.11% (128/136) in western, central, eastern, and northeastern China, respectively (P=0.63). However, eastern China showed steady yearly improvement (P=0.04), and northeastern China (2024–2025) increased from 89.71% (61/68) to 98.53% (67/68) (P=0.03), highlighting the effectiveness of targeted supervision (Table 2).

TABLE 1. Comparison of compliance rates for on-site quality control evaluations across four geographic regions in China, 2023−2025 [*n* (%)].

Regions	2023		2024		2025		Total		χ^2_{trend}	*P*
	Items	Compliance Items	Items	Compliance Items	Items	Compliance Items	Items	Compliance Items		
Eastern	272	253 (93.01)	136	130 (95.59)	408	394 (96.57)	816	777 (95.22)	4.42	0.04
Central	272	254 (93.38)	272	268 (98.53)	136	130 (95.59)	680	652 (95.88)	2.72	0.01
Western	272	262 (96.32)	340	325 (95.59)	340	328 (96.47)	952	915 (96.11)	0.02	0.89
Northeastern*	−	−	68	61 (89.71)	68	67 (98.53)	136	128 (94.11)	4.75	0.03
Total	816	769 (94.24)	816	784 (96.08)	952	919 (96.53)	2,584	2,472 (95.67)	5.42	0.02
χ^2		3.30		11.97		1.16		1.71		
P		0.19		0.01		0.76		0.63		

Note: χ^2_{trend} and *P* were obtained from the Cochran–Armitage trend test comparing compliance rates across four geographic regions of China, 2023–2025. Eastern China (Beijing, Tianjin, Hebei, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, Hainan); Central China (Shanxi, Anhui, Jiangxi, Henan, Hubei, Hunan); Western China (Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang); and Northeastern China (Liaoning, Jilin, Heilongjiang). *P*<0.05 indicates a statistically significant difference. − means no data.
* Northeastern China was evaluated in 2024–2025 only.

TABLE 2. Comparison of compliance rates among six quality control dimensions of the sentinel surveillance project for major nutrition and chronic disease issues — China, 2023−2025 [*n* (%)].

Domain	2023	2024	2025	Total	χ^2_{trend}	*P*
Organizational management	91 (94.79)	93 (96.88)	106 (94.64)	290 (95.39)	0.01	0.93
Sampling	82 (97.62)	84 (100.00)	95 (96.94)	261 (98.12)	0.16	0.69
Physical measurement	221 (92.08)	217 (90.42)	267 (95.36)	705 (92.76)	2.27	0.13
Questionnaire survey	67 (93.06)	70 (97.22)	77 (91.67)	214 (93.86)	0.18	0.67
Hemoglobin testing	99 (91.67)	105 (97.22)	124 (98.41)	328 (95.91)	6.52	0.01
Equipment and materials	209 (96.76)	215 (99.54)	250 (99.21)	674 (98.54)	4.54	0.03
Total	769 (94.24)	784 (96.08)	919 (96.53)	2,472 (95.67)	5.42	0.02
χ^2	7.99	28.48	15.33	34.81		
P	0.15	< 0.01	0.01	< 0.01		

Note: χ^2_{trend} and *P* were obtained from the Cochran–Armitage trend test comparing compliance rates across six quality control dimensions from 2023 to 2025 in China.
P<0.05 indicates a statistically significant difference.

The six dimensions differed significantly. Compliance was highest for equipment and materials 98.54% (674/684) and lowest for physical measurement 92.76% (705/760) (*P*<0.01). Hemoglobin testing and equipment and materials management trended upward (*P*<0.05) (Table 2). Regionally (Table 3), eastern China exhibited weaknesses in questionnaires 90.28% (65/72) and physical measurement 90.83% (218/240). Western China showed deficiencies in physical measurement 93.21% (261/280), questionnaires 95.24% (80/84), and hemoglobin testing 95.24% (120/126). Physical measurement compliance was lowest in northeastern China 82.50% (33/40) and highest in central China 96.50% (193/200); all *P*<0.05.

DISCUSSION

The methodological rigor of this study includes two Delphi rounds, 100% (15/15) response rate, authority coefficient of 0.85, Kendall's W ranging from 0.21 to 0.28, and importance scores across all indicators. These metrics are consistent with or exceed recent Delphi-based studies (*5*–*9*).

A hybrid weighting strategy was selected because the six first-level dimensions are conceptually distinct and few in number, making AHP pairwise comparisons feasible. Lower-level indicators are operationally specific, and expert scoring allows for more direct and practical weight assignment. This two-tiered approach balances methodological rigor with operational

TABLE 3. Comparison of on-site quality control compliance rates by six quality control dimensions across four geographic regions of China [*n* (%)].

Region	Organizational management	Sampling	Physical measurement	Questionnaire survey	Hemoglobin testing	Equipment and materials	Total	χ^2	*P*
Eastern	92 (95.83)	84 (100.00)	218 (90.83)	65 (90.28)	104 (96.30)	214 (99.07)	777 (95.22)	26.42	<0.01
Central	74 (92.50)	65 (92.86)	193 (96.50)	57 (95.00)	87 (96.67)	176 (97.78)	652 (95.88)	6.18	0.26
Western	108 (96.43)	98 (100.00)	261 (93.21)	80 (95.24)	120 (95.24)	248 (98.41)	915 (96.11)	14.94	0.01
Northeastern	16 (100.00)	14 (100.00)	33 (82.50)	12 (100.00)	17 (94.44)	36 (100.00)	128 (94.11)	9.84	0.02
Total	290 (95.39)	261 (98.12)	705 (92.76)	214 (93.86)	328 (95.91)	674 (98.54)	2,472 (95.67)	34.81	<0.01
χ^2	2.61	9.71	11.32	1.97	0.83	1.21	1.71	—	—
P	0.46	0.04	0.01	0.54	0.86	0.78	0.63	—	—

Note: χ^2 and *P* were obtained from the chi-square tests comparing the compliance rates among six quality control dimensions across four geographic regions of China. Data are cumulative across 2023–2025. Eastern China (Beijing, Tianjin, Hebei, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, Hainan); Central China (Shanxi, Anhui, Jiangxi, Henan, Hubei, Hunan); Western China (Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang); and Northeastern China (Liaoning, Jilin, Heilongjiang).
P<0.05 indicates a statistically significant difference.
"–" means no data.

feasibility and has been used in previous Delphi-based indicator studies (*10*).

The QC system was established in 2022, with a baseline compliance rate of 94.24% (769/816). This indicates strong initial QC from the outset. Compliance rates continued to increase through training and repeated implementation, providing a valuable reference for large-scale surveillance QC. The 8.82-percentage-point increase in northeastern China has practical public health significance. This demonstrates that applying the QC system in weak areas can effectively promote QC and ensure more reliable data.

Physical measurement had the lowest three-year average compliance. Reasons include high operator turnover, limited staffing, suboptimal field conditions, and inadequate privacy protection. Common problems were insufficient privacy during waist circumference measurement and improper weight instruments calibration. Other issues included insufficient inter-departmental collaboration, unjustified invalid sampling entries, failure to refrigerate hemoglobin QC solution, and insufficiently detailed secondary review of questionnaires.

Five recommendations are proposed. First, strengthen physical measurement training, incorporating daily calibration, standardized procedures, and privacy protection into mandatory assessments. Uniformly provide privacy screens and standard weights. Second, improve the full-process questionnaire review mechanism with double review and standardized informed consent. Third, enhance regional collaboration by leveraging high-performing PLADs for routine on-site guidance. Fourth, refine hierarchical QC assessment by designating persistently low-compliance items and PLADs as annual priority targets. Fifth, given high operator turnover as a key contributor to low physical measurement compliance, incorporate this work into institutional performance evaluation systems, including awards and recognition for frontline staff. Personnel stability (i.e., proportion of trained staff who participate in subsequent surveys) should be added as a supplementary indicator in the organizational management dimension.

The findings of this report are subject to at least three limitations. First, on-site supervision involved point-in-time evaluations, which may not fully reflect routine daily work levels owing to the Hawthorne effect. Future QC efforts could mitigate this with remote real-time monitoring, including photo and audio documentation, combined with unannounced inspections. Observer bias was minimized using standardized checklists (68 indicators) and annual expert training. Second, indicators were primarily designed for nutrition and chronic disease surveillance and may require adaptation for other health domains. Future studies could apply this system to other population-based surveillance programs to test its generalizability (*6*,*9*). Third, the 15-expert Delphi panel may not fully reflect the views of grassroots frontline staff across regions.

Establishing a standardized QC evaluation indicator system and conducting annual cross-regional mutual inspections can accurately assess program strengths and implementation difficulties. Continuous QC evaluations are essential for improving surveillance data quality. This system provides a reference for QC methods in other population surveillance programs.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1 provides the complete 68-item QC indicator framework across six domains (A–F): Organizational Management (8 items), Sampling Implementation (7 items), Physical Measurements (20 items), Questionnaire Surveys (6 items), Hemoglobin Testing (9 items), and Equipment and Materials (18 items).

Supplementary Table S2 summarizes the QC indicator system, including six first-level dimensions, AHP weights, representative second-level indicators, and the number of third-level indicators per dimension.

The tool was validated by experts in epidemiology, nutrition, public health, and information technology to ensure systematic, comprehensive, and scientific validity. This framework was developed through literature review and two rounds of Delphi expert consultation (2022) and applied to on-site QC inspections across 38 surveillance sites in China from 2023 to 2025.

SUPPLEMENTARY TABLE S1. Quality control indicator system for the sentinel surveillance project for major nutrition and chronic disease issues — China, 2023−2025.

First-level dimension (AHP weight)	Representative second-level indicators	Number of third-level indicators
Organizational management (0.16)	Work plan, training, supervision, and data review	8
Sampling implementation (0.19)	Sampling frame, sample size, and age/sex distribution	7
Physical measurement (0.14)	Equipment calibration, measurement environment, operation procedure, and privacy protection	20
Questionnaire survey (0.15)	Informed consent, interview method, primary review, and secondary review	6
On-site hemoglobin testing (0.17)	Quality control slides, sample testing time, and record completeness	9
Equipment and materials management (0.19)	Equipment type, calibration status, supplies, and records	18

Note: Weights of first-level dimensions were calculated via AHP pairwise comparison. Second-level and third-level indicators were weighted by integrated expert scoring based on indicator importance and operational feasibility.
Abbreviation: AHP=analytic hierarchy process.

SUPPLEMENTARY TABLE S2. The 68-item quality control indicator framework for the sentinel surveillance project for major nutrition and chronic disease issues — China, 2022−2025.

Domain	Item	Description	Domain	Item	Description
Organizational Management	A1	Provincial CDC established monitoring working group for guidance and coordination	Questionnaire Surveys	D1	Staff explained project purpose, significance, potential risks and benefits, survey content, completion requirements, and precautions to respondents
	A2	Provincial CDC organized training and assessment for surveillance site staff		D2	Respondents signed informed consent forms
	A3	Provincial CDC arranged on-site quality control visits within its jurisdiction		D3	Food frequency questionnaire completed by interviewer inquiry
	A4	Provincial-level designated personnel responsible for project data review		D4	Staff conducted primary review of completed questionnaire information
	A5	Prefectural-level designated personnel responsible for project data review		D5	Site supervisor conducted secondary review of questionnaire information
	A6	Prefectural or county-level CDC organized training and assessment for surveillance site staff		D6	Survey site well-organized, with reasonable setup and adequate preparation
	A7	Surveillance site developed and implemented quality control plan	Hemoglobin Testing	E1	Quality control slides and blind samples tested before testing began
	A8	Surveillance site designated personnel responsible for full-process quality control		E2	Quality control slides and quality control solution tested as required during testing
Sampling	B1	Sampling frame information (townships, administrative villages, schools, maternal and child health institutions) completely entered into monitoring system		E3	Standardized training and assessment provided to testing personnel before testing
	B2	No invalid sampling processes occurred in the monitoring system		E4	Samples tested within 40 seconds after blood collection
	B3	Sample size met requirement		E5	Blood samples completely absorbed onto test strip
	B4	Age distribution and sex ratio of sampled population complied with requirements		E6	Original records of hemoglobin testing complete
	B5	Survey respondents consistent with sampled individuals; if not, reasons justified		E7	Quality control slide measurements met requirements
	B6	All documents and related information generated during sampling organized and archived		E8	Hemoglobin quality control solution stored at low temperature
	B7	Sampling schedule met progress requirements		E9	Urine laboratory testing quality control records available
Physical Measurements	C1	Supine length measuring board met metrological certification (graduation 0.1 cm, headboard swing ≤0.5 cm)	Equipment and Materials	F1	Supine length measuring board
	C2	Measurement environment: quiet, spacious, level and firm floor, room temperature ≤25 °C		F2	Stadiometer
	C3	Infants removed shoes, hats, and thick clothing		F3	Scale

Preplanned Studies

Pilot Surveillance Program on Pneumonia with Public Health Risk — Shanghai Municipality, China, 2024–2025

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Summary

What is already known about this topic?

China's surveillance for pneumonia of unknown etiology, established in 2004, is vital for identifying novel pathogens early. However, limited cases have been reported, indicating potential challenges regarding sensitivity and operational efficiency.

What is added by this report?

A pilot surveillance program to detect pneumonia with public health risk was implemented in Shanghai between October 2024 and July 2025. The system was established using an optimized workflow involving refined case definitions, tiered laboratory testing network, and joint expert risk assessment process. Forty-six cases were identified in medical institutions at different levels, demonstrating the system's operational feasibility.

What are the implications for public health practice?

The pilot provides a framework for a proactive paradigm for monitoring emerging respiratory threats. Future surveillance should prioritize identifying case clusters and specific epidemiological links (e.g., suspicious animal contact and travel history). Applying advanced diagnostics, including metagenomic sequencing, and integrating multi-source data with information technology are crucial next steps for building a more responsive surveillance system.

ABSTRACT

Introduction: A pilot surveillance program on pneumonia with public health risk was conducted in Shanghai to provide a practical reference for monitoring emerging respiratory infectious diseases.

Methods: A refined risk pneumonia surveillance system was implemented in 14 sentinel hospitals across nine districts between October 2024 and July 2025. Case definitions emphasized individual severity, clustering potential, and novel pathogen detection. Systematic laboratory tests, including multiplex polymerase chain reaction (PCR) and metagenomic sequencing, were conducted. Experts specializing in clinical diagnostics, laboratory tests, and epidemiology performed joint risk assessments. Surveillance data were descriptively analyzed.

Results: Forty-six risk pneumonia cases met the case definition across participating medical institutions. Reporting departments differed by hospital tier (P<0.001). Median time intervals from visit to report were comparable (H=2.261, P=0.323). Severe or critical pneumonia constituted 93.48% of cases, and 6.52% were associated with two distinct clusters. Common indicators of severe pneumonia were shortness of breath (60.47%, 26/43) and oxygen saturation ≤93% (58.14%, 25/43). Most patients (76.09%) were aged ≥60 years. Joint risk assessment showed no evidence of emerging major infectious disease among reported cases, with 33 attributed to common respiratory pathogens detected through multiplex PCR, 11 without emerging/rare pathogens being detected by metagenomic sequencing, and 2 with inadequate samples showing no evidence of major infectious disease at follow-up. The etiologic spectrum included viruses (30.43%), mixed infections (21.74%), bacteria (10.87%), and other pathogens (8.70%).

Conclusion: This pilot demonstrated the feasibility of a surveillance framework for risk pneumonia by identifying 46 cases across medical institution tiers and departments. Integrating multiplex PCR enabled rapid etiologic clarification. Tiered laboratory testing and joint risk assessment provided closed-loop management. No evidence of emerging major infectious diseases was found. Future efforts should refine case definitions to prioritize cluster detection, standardize advanced laboratory techniques, and integrate information technology to improve early warning capabilities.

The global public health landscape increasingly faces challenges from emerging and re-emerging respiratory infectious diseases, such as the 2003 severe acute

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respiratory syndrome (SARS) outbreak and coronavirus disease 2019 (COVID-19) pandemic. These major public health incidents mainly originate from clustered severe pneumonia cases of unknown etiology (*1*–*4*). In China, a national surveillance system for such cases, based on the 2007 surveillance protocol issued by the Ministry of Health, aims to screen for potential SARS cases, human infections of avian influenza viruses, and clusters of respiratory diseases primarily presenting as pneumonia in healthcare institutions at all levels nationwide (*5*). This system has been crucial for detecting and reporting human avian influenza cases (*6*). However, challenges persist in its operation, including suboptimal sensitivity, reporting delays, and susceptibility to external non-technical factors, leading to scarce case reports (*7*–*8*). To address these limitations and shift from a reactive focus on *unknown etiology* to a more proactive, risk-based early warning approach, this study established a surveillance system for pneumonia cases with public health risk by refining case definitions and operational protocols of the current surveillance workflow. Its feasibility was evaluated through an on-site pilot in Shanghai.

This pilot surveillance program was conducted between October 2024 and July 2025. Patients were recruited from 14 sentinel hospitals (5 Level-3A, 6 Level-3B, and 3 Level-2A), which were medical institutions encompassing urban, suburban, and semi-urban areas from 9 districts in Shanghai, ensuring broad geographic representation, alongside considerations related to patient volume and clinical capacity.

Surveillance cases were patients with acute-onset pneumonia of suspected infectious origin, presenting with fever (≥38℃) and compatible imaging or clinical diagnosis who met at least one of the following criteria:

First, individual severity. Severe (critical) pneumonia or pneumonia with a tendency toward rapidly progressing severity and was unresponsive to empirical treatment.

Second, population transmission risk. Pneumonia cases with suspicious epidemiological links were identified within two weeks.

Third, novel pathogen risk. Suspected emerging rare pathogens or novel pathogens were detected in specimens from patients.

Cases that could be explained by infection with common respiratory pathogens through routine diagnosis and management at medical institutions were excluded.

Hospital staff received standardized training on case identification and reporting procedures under the pilot protocol [Work Plan for the Pilot Surveillance and Early-Warning Program for Pneumonia of Unknown Etiology in Shanghai; Shanghai Disease Control and Prevention Administration (2024) No.3]. Standardized checklists were used for case reporting. Attending physicians at each hospital determined which patients to enroll based on clinical judgment, mainly referencing clinical protocols. Respiratory specimens were collected if patients met the surveillance case definition. Twenty-one common respiratory pathogens (Figure 1) were tested at district CDCs within 24 hours using a commercial Multiplex Respiratory Pathogen Nucleic Acid Detection Kit [Fluorescent Polymerase Chain Reaction (PCR) Method] (Shanghai GeneoDx Biotech Co., Ltd., China). When multiplex PCR results were negative, metagenomic sequencing was performed at the municipal CDC on a DNBSEQ-G99 platform (SE100) using the MGI PFI pipeline.

Epidemiological investigations were conducted for all eligible cases to collect information on demographics, clinical presentations, and epidemiological characteristics. A joint risk assessment was conducted based on laboratory tests and epidemiological investigations by experts specializing in clinical diagnostics, laboratory tests, and epidemiology (Figure 1).

All data were collected using standardized case report forms. Descriptive analyses were performed using Excel 2021 and R software (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria). Categorical comparisons were performed using chi-square or Fisher's exact tests (if expected counts were <5). Median comparisons were performed using Kruskal–Wallis tests. For key proportions, 95% Wilson confidence intervals (*CI*s) were calculated. Significance was defined as two-sided $P<0.05$.

Between October 2024 and July 2025, 14 sentinel hospitals recorded 21,650,289 outpatient and emergency visits; 871,164 inpatient admissions; and 221,168 pneumonia cases, of which 46 surveillance cases met the definition. All surveillance cases were hospitalized. Most cases (76.09%, 35/46, 95% *CI*: 62.06%, 86.09%) were aged 60 years or older (Table 1), including 63.04% (29/46) men and 36.96% (17/46) women. Severe or critical cases constituted 93.48% (43/46, 95% *CI*: 82.50%, 97.76%), and 6.52% (3/46) were part of two distinct clusters. One cluster included two family members visiting the hospital. The third clustered case was identified through routine clinical investigations of an individual

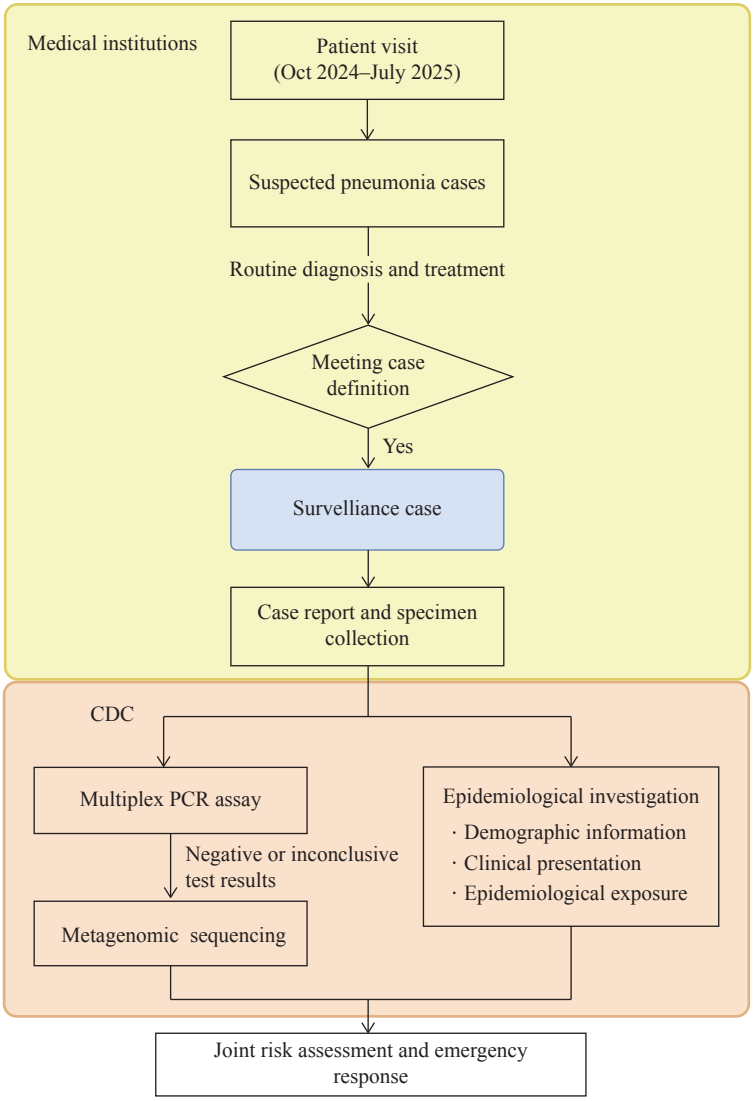


FIGURE 1. Workflow of the pilot surveillance system for pneumonia cases with public health risk.
Note: Multiplex PCR assay detected 21 common respiratory pathogens simultaneously, including SARS-CoV-2, IFV [including A(H1N1)pdm09, A(H3N2), B/Victoria, and B/Yamagata lineages], RSV (including subtypes A and B), HAdV, HMPV, HPIV (including subtypes 1–4), HCoV (including types OC43, 229E, NL63, and HKU1), HBoV, HRV, EV, *S. pyogenes* (Group A *Streptococcus*), *B. pertussis*, *S. pneumoniae, H. influenzae*, *L. pneumophila*, *K. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *C. psittaci, Aspergillus* spp. and *Cryptococcus* spp.
Abbreviation: PCR=Polymerase Chain Reaction; CDC=Center for Disease Control and Prevention; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; IFV=influenza virus; RSV=respiratory syncytial virus; HAdV=human adenovirus; HMPV=human metapneumovirus; HPIV=human parainfluenza virus; HCoV=human coronavirus; HBoV=human bocavirus; HRV=human rhinovirus; EV=enterovirus;*S. pyogenes=Streptococcus pyogenes; B. pertussis=Bordetella pertussis; S. pneumoniae=Streptococcus pneumoniae; H. influenzae=Haemophilus influenzae; L. pneumophila=Legionella pneumophila; K. pneumoniae=Klebsiella pneumoniae; M. pneumoniae=Mycoplasma pneumoniae; C. pneumoniae=Chlamydia pneumoniae; C. psittaci =Chlamydia psittaci;* spp.=species.

with a family member with pneumonia without visiting the sentinel hospital. Common severity indicators for severe or critical cases included shortness of breath (60.47%, 26/43) and oxygen saturation ≤ 93% (58.14%, 25/43). The most frequently reported initial symptoms were fever (71.74%, 33/46), coughing (60.87%, 28/46), and expectoration (45.65%, 21/46). Most patients (82.61%, 38/46) were retirees. Suspicious animal contact and travel histories were reported in 13.04% (6/46) and 8.70% (4/46) of cases, respectively.

Excluding 16 cases with initial medical visits at non-senital hospitals and thus the initial visit time for senital hospitals could not be accurately determined,

TABLE 1. Characteristics of surveillance cases identified through the pilot surveillance system in Shanghai.

Characteristics	All cases (*N*=46)	Case type	
		Severe cases (*N*=43)	Clustered cases (*N*=3)
Gender, *N* (%)			
Male	29 (63.04)	28 (65.12)	1 (33.33)
Female	17 (36.96)	15 (34.88)	2 (66.67)
Age group, *N* (%)			
Adult (18–59 years)	11 (23.91)	9 (20.93)	2 (66.67)
Older adults (≥60 years)	35 (76.09)	34 (79.07)	1 (33.33)
Medical Institution Grade, *N* (%)			
Level 3A	9 (19.57)	9 (20.93)	0 (0)
Level 3B	22 (47.83)	19 (44.19)	3 (100.00)
Level 2A	15 (32.61)	15 (34.88)	0 (0)
Initial symptoms, *N* (%)			
Fever	33 (71.74)	31 (72.09)	2 (66.67)
Coughing	28 (60.87)	27 (62.79)	1 (33.33)
Expectoration	21 (45.65)	21 (48.84)	0 (0)
Shortness of breath	9 (19.57)	9 (20.93)	0 (0)
Aching	5 (10.87)	5 (11.63)	0 (0)
Fatigue	5 (10.87)	5 (11.63)	0 (0)
Chills	4 (8.70)	4 (9.30)	0 (0)
Chest distress	3 (6.52)	3 (6.98)	0 (0)
Throat discomfort	2 (4.35)	2 (4.65)	0 (0)
Running nose	1 (2.17)	1 (2.33)	0 (0)
Sweating	1 (2.17)	1 (2.33)	0 (0)
Diarrhea	1 (2.17)	1 (2.33)	0 (0)
Indicators reflecting severity, *N* (%)			
Shortness of breath	27 (58.70)	26 (60.47)	1 (33.33)
Oxygen saturation ≤93%	25 (54.35)	25 (58.14)	0 (0)
Oxygenation index ≤300 mmHg	9 (19.57)	9 (20.93)	0 (0)
Rapid symptom progression	8 (17.39)	8 (18.60)	0 (0)
Respiratory failure	8 (17.39)	8 (18.60)	0 (0)
Occupation, *N* (%)			
Retiree	38 (82.61)	36 (83.72)	2 (66.67)
Office worker	2 (4.35)	2 (4.65)	0 (0)
Construction worker/Dust-related production line worker	2 (4.34)	1 (2.33)	1 (33.33)
Unemployed	2 (4.34)	2 (4.66)	0 (0)
Student	1 (2.17)	1 (2.33)	0 (0)
Unknown	1 (2.17)	1 (2.33)	0 (0)
Epidemiological exposure, *N* (%)			
None	38 (82.61)	36 (83.72)	2 (66.67)
Suspicious animal contact history	6 (13.04)	6 (13.95)	0 (0)
Travel history	4 (8.70)	4 (9.30)	0 (0)

the median time interval from symptom onset to hospital visit [interquartile range (IQR): 2–5 days] and from hospital visit to case report (IQR: 1.25–5.75 days) were 3 days. Reporting departments varied by hospital grade (P<0.001). Most (66.67%, 6/9) were reported by critical care medicine departments at Level 3A hospitals, whereas reporting was more balanced between infectious disease (45.45%, 10/22) and respiratory medicine (45.45%, 10/22) departments at Level 3B hospitals. Infectious disease departments were dominant, reporting 66.67% (10/15) of the cases at Level 2A hospitals.

Pathogens were detected in 71.74% of cases (33/46; 95% *CI*: 57.45%, 82.68%) through multiplex PCR assay. The three most frequently identified pathogens were Influenza A(H1N1) virus (8 cases), Haemophilus influenzae (7 cases), and Human rhinovirus (5 cases). Viral infections were identified in 30.43% (14/46) of cases. Mixed infections (more than one pathogen) accounted for 21.74% (10/46). Bacterial infections were detected in 10.87% (5/46), and other pathogens (e.g., Mycoplasma and Chlamydia) in 8.70% (4/46). No pathogens were identified in 28.26% (13/46; 95% *CI*: 17.32%, 42.55%) of the cases after multiplex PCR and metagenomic sequencing where feasible, including two cases for which metagenomic testing could not be conducted because of unqualified sample quality (Table 2).

TABLE 2. Characteristics of surveillance cases reported by different levels of medical institutions*.

Characteristics	All cases (*N*=46)	Medical Institution Grade†			H	*P*
		Level 3A (*N*=9)	Level 3B (*N*=22)	Level 2A (*N*=15)		
Report and investigation, Median (Q1, Q3)						
Onset-to-visit interval (days)§	3.00 (2.00–5.00)	3.00 (3.00–3.00)	3.00 (2.00–4.50)	3.00 (1.00–5.00)	0.009	0.996
Visit-to-report interval (days)§	3.00 (1.25–5.75)	6.00 (6.00–6.00)	3.50 (2.00–5.25)	2.00 (1.00–4.00)	2.261	0.323
Reporting department, *N* (%)					–	<0.001
Infectious Disease	20 (43.48)	0 (0.00)	10 (45.45)	10 (66.67)		
Respiratory Medicine	13 (28.26)	2 (22.22)	10 (45.45)	1 (6.67)		
Critical Care Medicine	11 (23.91)	6 (66.67)	2 (9.09)	3 (20.00)		
Others	2 (4.35)	1 (11.11)	0 (0)	2 (4.35)		
Pathogen detected, *N* (%)					–	0.080
Virus detected	14 (30.43)	5 (55.56)	4 (18.18)	5 (33.33)		
No pathogen detected	13 (28.26)	2 (22.22)	6 (27.27)	5 (33.33)		
Mixed infection¶	10 (21.74)	2 (22.22)	8 (36.36)	0 (0)		
Bacteria detected	5 (10.87)	0 (0)	3 (13.64)	2 (13.33)		
Others detected**	4 (8.70)	0 (0)	1 (4.55)	3 (20.00)		
Specimen type, *N* (%)					–	0.212
Oropharyngeal swab	23 (50.00)	2 (22.22)	12 (54.55)	9 (60.00)		
Nasopharyngeal swab	13 (28.26)	2 (22.22)	6 (27.27)	5 (33.33)		
Sputum	6 (13.04)	3 (33.33)	2 (9.09)	1 (6.67)		
Nasal swab	3 (6.52)	1 (11.11)	2 (9.09)	0 (0)		
Bronchoalveolar lavage fluid	1 (2.17)	1 (11.11)	0 (0)	0 (0)		
Assay performed, *N* (%)					–	0.834
Multiplex PCR+Metagenomic sequencing	13 (28.26)	2 (22.22)	6 (27.27)	5 (33.33)		
Multiplex PCR only	33 (71.74)	7 (77.78)	16 (72.73)	10 (66.67)		

* Categorical variables are presented as *N* (%); Comparisons across hospital grades use Fisher's exact tests because of small expected cell counts; Median intervals are compared using the Kruskal–Wallis test. All tests are two-sided with α=0.05.

† Medical institution grade is defined under the Chinese hospital grading system, Level-3 and Level-2 denote tertiary and secondary hospitals by service scope, and Grade A/B (e.g., Level-3A, Level-3B, Level-2A) denotes the accreditation ranking within each level.

§ Sixteen patients with a history of seeking medical care at non-pilot hospitals before visiting the pilot hospital are excluded (including eight cases reported as level-3A, six as level-3B, and two as level-2A).

¶ Mixed infection refers to the detection of more than one pathogen.

** "Others" refers to infections caused by pathogens other than viruses or bacteria (e.g., mycoplasma, chlamydia).

Abbreviation: PCR=polymerase chain reaction.

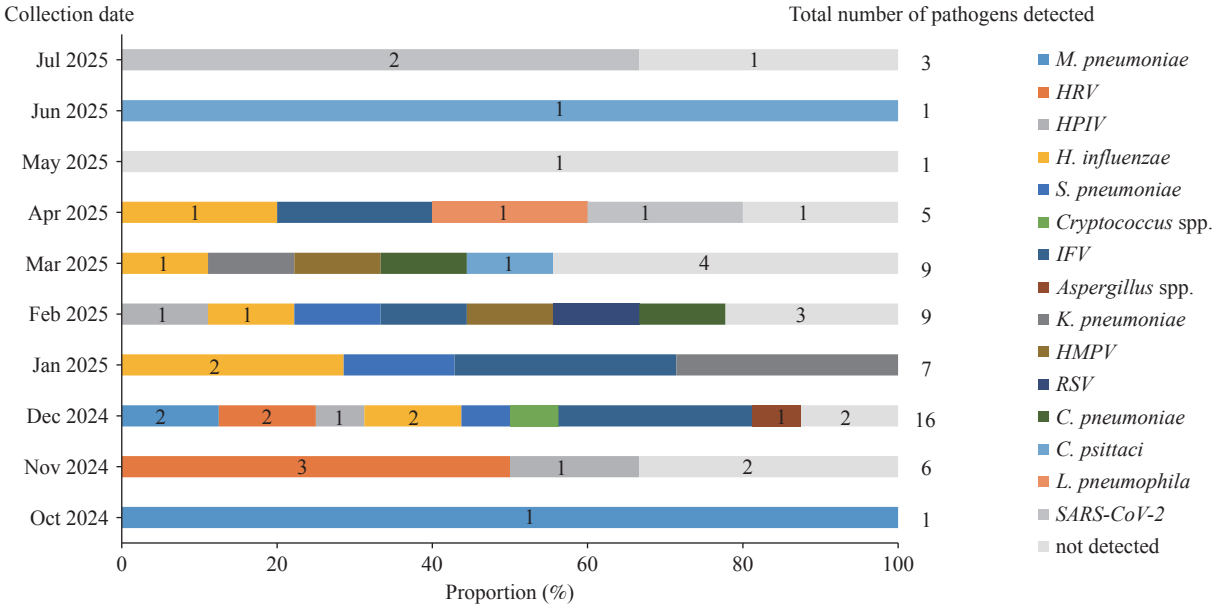


FIGURE 2. Proportion of different pathogens detected from October 2024 to July 2025.
Note: The proportion of each pathogen was calculated as the number of specific pathogen detections divided by the total number of pathogens detected by month. Absolute counts of each detected pathogen are shown in the bar. The undetected category represents cases in which no pathogen was identified by multiplex PCR or subsequent metagenomic sequencing.
Abbreviation: *M. pneumoniae=Mycoplasma pneumoniae;* HRV=human rhinovirus; HPIV=human parainfluenza virus; *H. influenzae=Haemophilus influenzae; S. pneumoniae=Streptococcus pneumoniae;*IFV=influenza virus; *K. pneumoniae=Klebsiella pneumoniae;* HMPV=*human metapneumovirus*; RSV=respiratory syncytial virus; *C. pneumoniae=Chlamydia pneumoniae; C. psittaci =Chlamydia psittaci; L. pneumophila=Legionella pneumophila;* SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; spp.=species*;* PCR=polymerase chain reaction.

Based on the monthly proportion of pathogens detected from pilot surveillance (Figure 2), the most frequently detected Influenza A(H1N1) virus was identified in eight cases over four months (December 2024, January 2025, February 2025, and April 2025). Other common respiratory viruses, such as Human rhinovirus (5 cases) and Human metapneumovirus (3 cases), were also primarily detected in winter (November 2024 to February 2025). Haemophilus influenzae (7 cases) and Streptococcus pneumoniae (3 cases) were the most common bacterial pathogens. Both cases detected with Chlamydia psittaci had a history of suspicious bird contact. *Aspergillus* spp., *Cryptococcus* spp., and *L. pneumophila* were detected in cases of mixed infections.

Risk assessments by epidemiological, laboratory testing, and clinical experts were conducted for all 46 reported cases. Combined with laboratory tests and epidemiological investigation results, 33 were considered to be caused by common respiratory tract pathogens, and 11 were excluded from emerging or rare pathogen infection through metagenomic sequencing. Metagenomic sequencing could not be performed in 2 cases because of poor sample quality. As for the 2 cases, given the following three findings- no suspicious sequences were detected, no secondary transmission was observed among close contacts at follow-up, the clinical course and response to standard care were consistent overall, no evidence of a major infectious disease was identified during the pilot period.

DISCUSSION

This pilot risk pneumonia surveillance system demonstrated operational feasibility by examining a structured framework for early identification of severe and clustered pneumonia cases with potential public health risk. The system's integration of multifaceted case definitions, systematic laboratory testing, and joint risk assessment effectively captured cases that met severity or clustering criteria, establishing a closed-loop monitoring and management process.

Although the pilot program significantly improved surveillance sensitivity, the demographic profiles revealed that most (76.09%) reported cases were aged 60 years or older. This likely reflects the higher background incidence of severe pneumonia in the older adult population owing to comorbidities and age-related immune decline. Although severe disease

monitoring in vulnerable groups is clinically important, from a public health perspective focused on detecting emerging major respiratory infectious diseases, an over-representation of sporadic cases among older adults may dilute the signal for real threats. This concern is particularly notable considering that historical pandemics (e.g., SARS and COVID-19) have often manifested significantly in younger populations at an early stage (*2*,*9*). Future iterations of surveillance system should strategically enhance the focus on cases with greater epidemic potential, including those involving clusters (e.g., in familial settings, workplaces, schools, or healthcare facilities) or unusual epidemiological links, such as suspicious animal contact or travel history. Recalibrating resources and alert thresholds to prioritize investigating such target populations could improve the system's efficiency in detecting genuine public health emergencies. The cross-tier differences in reporting departments found in this study can inform where surveillance capacity and targeted training should be prioritized in resource-constrained settings.

The high proportion (71.74%) of cases infected with common respiratory pathogens underscores the importance of implementing multiplex molecular diagnostics within the surveillance system. This enables timely differentiation between known pathogens and truly unexplained cases, enabling more efficient distribution of public health resources. Influenza A(H1N1) virus was the most frequently detected pathogen, aligning with seasonal influenza activity. Detection of Chlamydia psittaci in cases with a history of bird contact illustrates the system's sensitivity to zoonotic links. However, the persistent fraction of cases (28.26%) with no identified pathogens, even after metagenomic sequencing, highlights ongoing diagnostic challenges and the importance of joint risk assessment by experts from related disciplines. This undetected fraction may be related to factors such as specimen type and quality, suboptimal sampling timing relative to illness onset, prior antimicrobial use, and limitations of reference databases, warranting closer attention.

Interpreting metagenomic sequencing results requires considerable clinical and microbiological expertise to distinguish true infection from colonization or environmental contamination, and epidemiological exposure should be considered (*10*). Operationally, a tiered approach rather than sequencing every PCR-negative specimen is recommended, given the high cost of metagenomic sequencing. The following factors could be assessed: 1) case-level public health risk (preferring cases with strong epidemiological links to clusters or outbreaks and severe clinical manifestations); 2) specimen quality and type (preferring lower respiratory tract specimens); 3) prior antimicrobial use (potentially reducing bacterial detection), and 4) collection timing relative to symptom onset.

This study was subject to at least two limitations. First, surveillance was limited to 14 sentinel hospitals, which may not have captured the complete spectrum of pneumonia cases with public health risk. Without data on the catchment population and estimated coverage, selection bias related to hospital participation and demographic profiles cannot be excluded. Therefore, this pilot supports conclusions regarding operational feasibility rather than citywide representativeness. Variations in reporting patterns across hospital tiers suggest potential differences in clinical pathways and diagnostic practices that warrant further standardization. Second, surveillance currently relies heavily on manual case identification and reporting by clinicians. For example, physician-based judgments used to apply the severity-tendency and common-pathogen exclusion criteria may vary across clinicians and hospitals and could introduce selection bias in case ascertainment. Despite facilitating an established initial workflow, this manual approach requires a shift toward more automated and active surveillance.

Future efforts should 1) refine case definitions emphasizing cluster detection to enhance sensitivity for novel outbreaks that could lead to significant public health hazards; 2) standardize the application of advanced laboratory technologies, such as metagenomic sequencing, in the surveillance of major emerging infectious diseases; 3) strengthen integration of multi-source data and application of information technologies, such as artificial intelligence, to improve the surveillance system's sensitivity; and 4) develop region-specific early warning thresholds based on different districts' epidemiological characteristics and capacities.

This pilot demonstrated the operational feasibility and value of a proactive multidimensional risk framework for pneumonia surveillance. By integrating syndromic screening, tiered laboratory testing, and joint risk assessment, it provides a feasible model for enhancing the sensitivity and timeliness of early warning systems for emerging respiratory infections. Refining this model will be crucial for building a more

resilient, intelligent, and precise national surveillance system capable of meeting the evolving challenges of infectious disease prevention and control.

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Methods and Applications

Environmental Mixture–Health Associations: Current Analytical Practice and Reporting Recommendations

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ABSTRACT

Introduction: Analytical decisions for environmental mixture exposure remain under-standardized. The aim was to outline current analytical practice across studies and propose a reporting checklist.

Methods: An empirical methodological review was conducted for original environmental mixture-exposure studies using Bayesian kernel machine regression (BKMR), weighted quantile sum (WQS), or quantile-based g-computation (QGC), published in four high-impact journals between 2021 and 2025 for exposure types, sample size, and statistical methods. A three-stage analytical framework was outlined. Summaries were analyzed using R software, and descriptive statistics were used to characterize methodological usage and preferences.

Results: Of the 97 studies, the median sample size was 729 [interquartile range (IQR): 396–1,992], and the median number of exposures analyzed was 9 (IQR: 6–15). Most studies focused on internal exposures 86/97 (88.7%); 58/86 (67.4%) reported an explicit detection-rate threshold. Feature reduction was performed in 25/97 studies (25.8%). BKMR, WQS, and QGC were used in 78/97 (80.4%), 35/97 (36.1%), and 30/97 (30.9%) studies, respectively. Overall, 41/97 studies (42.3%) used at least two methods. Post-hoc analyses were common, with 87/97 (89.7%) studies assessing variable importance, 78/97 (80.4%) examining interactions, and 87/97 (89.7%) assessing nonlinearity. Common reporting gaps included incomplete model-parameter specification, insufficient documentation of preprocessing decisions, and limited justification for mixture-method selection.

Conclusion: Among published studies, analytical choices were heterogeneous, and key reporting details were incomplete. Justification of method choice, transparent documentation of preprocessing decisions, and standardized reporting are required to improve reproducibility and interpretability. The checklist supports planning and reporting environmental mixture analyses, and provides transparency in analytical decisions, model specifications, and post-hoc interpretations.

The exposome concept was introduced to capture diverse life-course exposures, including environmental, psychosocial, physical, and lifestyle factors, and their health consequences (*1*–*2*) and has received increasing attention in public-health research in recent years (*3*–*5*). Exposomics typically examines the health effects of multiple simultaneous exposures, usually involving at least three independent chemicals or chemical groups (*6*). Environmental epidemiologists have largely been guided by the "one-exposure–one-disease" paradigm (*7*–*9*). Although conventional regression can adjust for co-pollutants or include prespecified interactions, it may not capture complex correlations, nonlinearities, and joint effects within real-world mixtures (*10*).

The U.S. National Institute of Environmental Health Sciences has prioritized mixed-exposure research through workshops held in 2011 and 2015 (*11*–*12*). In 2017, the institute launched the *Powering Research through Innovative Methods for Mixtures in Epidemiology* program, to accelerate methodological innovations for mixed-exposure analyses (*13*). Dedicated statistical techniques were developed, including weighted quantile sum (WQS) regression in 2013 (*14*), Bayesian kernel machine regression (BKMR) in 2015 (*10*), and quantile-based g-computation (QGC) in 2020 (*15*). User-friendly R packages (e.g., *gWQS*, *bkmr*, and *qgcomp*) have promoted their application (*15*–*17*).

Despite methodological advances, real-world mixture analyses remain challenging because researchers must handle high-dimensional exposure data, correlated pollutants, nonlinear exposure–response (ER) relationships, interactions, and multiple

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competing statistical methods (*18–19*). This often leads to analytical strategies being chosen based on precedent or personal preference. Such choices can introduce bias, compromise reproducibility (*20*), and mislead conclusions. Because exposome research is fundamentally rooted in observational-study designs, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) provides an important general framework for reporting (*21*). However, publications often omit these details. Advanced methods such as WQS, BKMR, and QGC require transparent reporting of model selection, parameter settings, variable reduction strategies, and interpretation (*19*). However, these critical details are often omitted from publications. Such incomplete reporting can limit reproducibility and interpretation, underscoring the need for practical guidance to standardize the analysis and reporting of environmental mixture studies.

To address these challenges, an empirical methodological review was conducted for recent environmental mixture studies from leading journals. Current analytical and reporting practices were summarized and organized into a three-stage framework covering data preparation, association analysis, and post-hoc interpretation, and a reporting checklist was developed to complement STROBE. The aim was to provide practical guidance for researchers to plan, conduct, and report mixture analyses more transparently and consistently.

METHODS

Literature Review

Firstly, a review was performed for analytical approaches used in environmental mixture-exposure studies published in four high-impact journals: Environmental Health Perspectives (EHP), Journal of Hazardous Materials (JHM), Environment International (EI), and Environmental Science & Technology (EST), selected because they are widely recognized as leading outlets in environmental health, exposure science, and epidemiology. Search keywords included "environmental pollutants," "mixed exposure analysis," "BKMR," "WQS," and "QGC." Studies published from 2021 to 2025 were included (Supplementary Material, available at https://weekly.chinacdc.cn/). Reviews, comments, and methodological studies were excluded. Supplementary Material provides more details regarding the literature search.

Analytical Framework in Current Literature

The analytical framework comprised three main stages. 1) Data preparation, referring to analytical steps conducted before fitting mixture models, including exposure screening based on detection rate, handling of values below the limit of detection (LOD) (*22–23*), transformation or standardization of exposure variables, correlation assessment, and feature reduction (*24–25*). 2) Association analysis, which is the core stage of environmental mixture research and may include both single-exposure models (exposome-wide association studies) (*26*), and mixture methods such as WQS, QGC, and BKMR. Single-exposure models assess each exposure separately, whereas mixture methods are more appropriate when exposures are correlated and the research question concerns joint or overall mixture effects. Notably, BKMR emerged as the most widely used method, appearing in over 200 studies since 2022 (Figure 1). 3) Post-hoc analysis, which further characterizes mixture findings by identifying influential components (*27*) and examining whether associations vary through nonlinear ER patterns (*28*) or interactions (*29*). These analyses clarify individual contributions and overall mixture complexity. Supplementary Material provides further details.

RESULTS

In the current analysis, 97 studies were included, comprising 19, 22, 39, and 17 from EHP, JHM, EI, and EST, respectively. Fifty-five studies had a sample size below 1,000, while only 11 studies had a sample size exceeding 5,000. Sample sizes varied considerably across studies, ranging from 76 to over 54.5 million (median: 729; interquartile range [IQR]: 396–1,992). Studies were categorized as examining external exposures (e.g., O_3, NO_2, $PM_{2.5}$, and its components) or internal exposures (e.g., per- and polyfluoroalkyl substances (PFAS), persistent organic pollutants (POPs), organochlorine pesticides (OCPs), and endocrine-disrupting chemicals (EDCs) measured in blood or urine). All included studies employed mixed exposure association methods, and the findings indicate that these methods are predominantly applied in internal exposure research, accounting for 86 of the 97 studies (88.7%), with generally similar proportions observed across the four journals (Table 1).

Data-preparation and model-selection practices

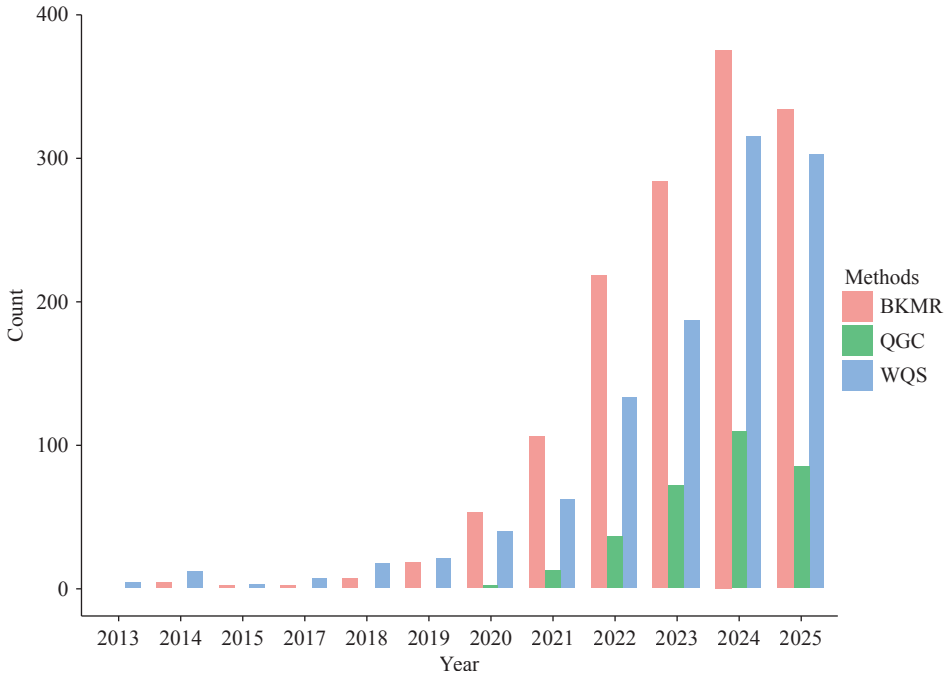


FIGURE 1. Publications using BKMR, WQS, and QGC from 2013 to 2025.
Abbreviation: BKMR=Bayesian kernel machine regression; WQS=weighted quantile sum; QGC=quantile-based g-computation.

varied substantially across studies. Among the 86 internal-exposure studies, 28 (32.6%) did not report a clear detection-rate exclusion threshold, whereas 58 (67.4%) applied a threshold of at least 50% for exposure inclusion. The number of exposures ranged from 3 to 98 (median: 9; IQR: 6–15), and 25 studies performed feature reduction, mainly with large initial exposure sets (Supplementary Material, Supplementary Tables S1–S4, available at https://weekly.chinacdc.cn/).

In the main association analyses, most studies (93/97, 95.9%) employed single-exposure–outcome association analysis, among which 26 (26.8%) applied false-discovery-rate correction to decrease false-positive findings. Regarding methods for mixed-exposure association analyses, BKMR was predominantly used, featuring in 78 studies (80.4%), owing to its versatility in capturing complex interactions and nonlinear relationships among exposures. Contrastingly, WQS and QGC were used in 35 (36.1%) and 30 (30.9%) studies, respectively. Notably, multimodel analyses were used in 41/97 studies (42.3%). The most common combinations were BKMR plus QGC (16/97, 16.5%) and BKMR plus WQS (15/97, 15.5%), followed by WQS plus QGC (5/97, 5.2%) and the use of all three methods (5/97, 5.2%). In stratified analyses, multimodel use was not restricted to studies with larger sample sizes or greater numbers of pollutants, suggesting that multiple mixture methods were often used as a robustness or triangulation strategy (Table 1).

Patterns in the use of BKMR, WQS, and QGC were further examined in relation to sample size and the number of exposures (after feature reduction, if applied). BKMR remained the dominant method in studies with sample sizes below 2,000 and was also commonly used in studies with sample sizes between 2,000 and 6,000 (Figure 2A). In contrast, among studies with sample sizes exceeding 8,000, WQS and QGC were more frequently applied, with WQS becoming the most commonly used method in this subgroup. Regarding the number of exposures, BKMR was favored when fewer than five exposures were included, whereas WQS and QGC were more frequently applied when the number of exposures exceeded 18. For studies involving 5–18 exposures, no clear preference was observed, and the use of all three methods was similarly distributed (Figure 2B).

Post-hoc analyses were common, including variable importance assessment in 87 studies (89.7%), interaction assessment in 78 (80.4%), and nonlinearity assessment in 87 (89.7%). These analyses were most often conducted using the corresponding mixture method, with BKMR frequently used for variable

TABLE 1. Characteristics of included studies using mixed-exposure association approaches.

Characteristics	Overall (*n*=97)	EI (*n*=39)	EHP (*n*=19)	EST (*n*=17)	JHM (*n*=22)
Sample size, median (IQR)	729 (396, 1,992)	1,136 (377.0, 2,959.5)	943 (590, 1,192)	396 (326, 479)	810 (457.2, 2,380.2)
Sample size (%)					
≤200	10 (10.3)	5 (12.8)	1 (5.3)	2 (11.8)	2 (9.1)
201–500	28 (28.9)	9 (23.1)	3 (15.8)	11 (64.7)	5 (22.7)
501–1,000	17 (17.5)	5 (12.8)	6 (31.6)	0 (0.0)	6 (27.3)
1,001– 2,000	18 (18.6)	7 (17.9)	6 (31.6)	3 (17.6)	2 (9.1)
2,001– 5,000	13 (13.4)	6 (15.4)	2 (10.5)	0 (0.0)	5 (22.7)
>5,000	11 (11.3)	7 (17.9)	1 (5.3)	1 (5.9)	2 (9.1)
Study type (%)					
Internal	86 (88.7)	34 (87.2)	17 (89.5)	16 (94.1)	19 (86.4)
External	11 (11.3)	5 (12.8)	2 (10.5)	1 (5.9)	3 (13.6)
No. of exposures, median (IQR)	9 (6,15)	9 (6,13)	8 (6,15)	14 (10,17)	7 (6,12)
No. of exposures (%)					
≤5	15 (15.5)	6 (15.4)	4 (21.1)	2 (11.8)	3 (13.6)
6–10	45 (46.4)	20 (51.3)	8 (42.1)	4 (23.5)	13 (59.1)
11–15	14 (14.4)	6 (15.4)	3 (15.8)	3 (17.6)	2 (9.1)
16–20	14 (14.4)	3 (7.7)	3 (15.8)	4 (23.5)	4 (18.2)
>20	9 (9.3)	4 (10.3)	1 (5.3)	4 (23.5)	0 (0.0)
Feature reduction (%)					
Not performed	72 (74.2)	35 (89.7)	17 (89.5)	4 (23.5)	16 (72.7)
Performed	25 (25.8)	4 (10.3)	2 (10.5)	13 (76.5)	6 (27.3)
Single exposure analysis (%)					
Not performed	4 (4.1)	1 (2.6)	0 (0.0)	2 (11.8)	1 (4.5)
Performed	93 (95.9)	38 (97.4)	19 (100.0)	15 (88.2)	21 (95.5)
FDR (%)					
Not performed	71 (73.2)	29 (74.4)	14 (73.7)	12 (70.6)	16 (72.7)
Performed	26 (26.8)	10 (25.6)	5 (26.3)	5 (29.4)	6 (27.3)
BKMR (%)					
Not performed	19 (19.6)	10 (25.6)	3 (15.8)	3 (17.6)	3 (13.6)
Performed	78 (80.4)	29 (74.4)	16 (84.2)	14 (82.4)	19 (86.4)
WQS (%)					
Not performed	62 (63.9)	23 (59.0)	15 (78.9)	9 (52.9)	15 (68.2)
Performed	35 (36.1)	16 (41.0)	4 (21.1)	8 (47.1)	7 (31.8)
QGC (%)					
Not performed	67 (69.1)	23 (59.0)	15 (78.9)	14 (82.4)	15 (68.2)
Performed	30 (30.9)	16 (41.0)	4 (21.1)	3 (17.6)	7 (31.8)
BKMR & WQS (%)					
Not performed	82 (84.5)	32 (82.1)	18 (94.7)	13 (76.5)	19 (86.4)
Performed	15 (15.5)	7 (17.9)	1 (5.3)	4 (23.5)	3 (13.6)
BKMR & QGC (%)					
Not performed	81 (83.5)	33 (84.6)	15 (78.9)	15 (88.2)	18 (81.8)
Performed	16 (16.5)	6 (15.4)	4 (21.1)	2 (11.8)	4 (18.2)

Continued

Characteristics	Overall (*n*=97)	EI (*n*=39)	EHP (*n*=19)	EST (*n*=17)	JHM (*n*=22)
WQS & QGC (%)					
Not performed	92 (94.8)	36 (92.3)	19 (100.0)	17 (100.0)	20 (90.9)
Performed	5 (5.2)	3 (7.7)	0 (0.0)	0 (0.0)	2 (9.1)
WQS & QGC & BKMR (%)					
Not performed	92 (94.8)	36 (92.3)	19 (100.0)	16 (94.1)	21 (95.5)
Performed	5 (5.2)	3 (7.7)	0 (0.0)	1 (5.9)	1 (4.5)
Variable Importance (%)					
Not performed	10 (10.3)	6 (15.4)	1 (5.3)	0 (0.0)	3 (13.6)
Performed	87 (89.7)	33 (84.6)	18 (94.7)	17 (100.0)	19 (86.4)
Interaction (%)					
Not performed	19 (19.6)	7 (17.9)	3 (15.8)	4 (23.5)	5 (22.7)
Performed	78 (80.4)	32 (82.1)	16 (84.2)	13 (76.5)	17 (77.3)
Nonlinear (%)					
Not performed	10 (10.3)	7 (17.9)	3 (15.8)	0 (0.0)	0 (0.0)
Performed	87 (89.7)	32 (82.1)	16 (84.2)	17 (100.0)	22 (100.0)

Abbreviation: No.=number; EHP=Environmental Health Perspectives; EST=Environmental Science & Technology; JHM=Journal of Hazardous Materials; EI=Environment International; FDR=false discovery rate; BKMR=Bayesian Kernel Machine Regression; WQS=Weighted Quantile Sum; QGC=quantile-based g-computation.

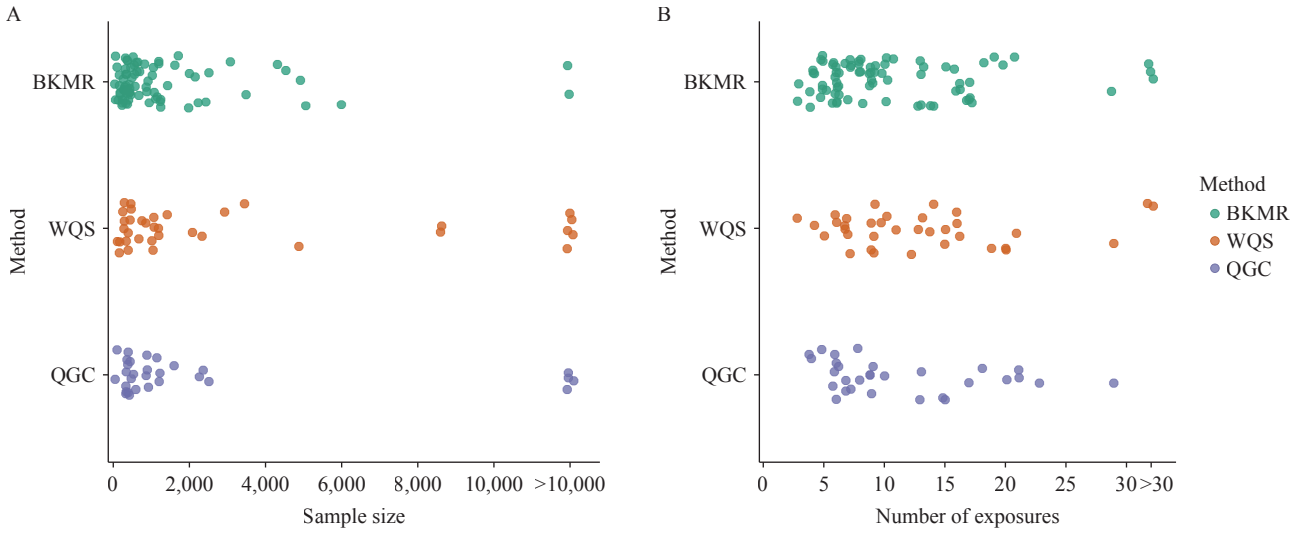


FIGURE 2. Motives for choosing BKMR, WQS, and QGC in relation to (A) sample size and (B) number of exposures.
Abbreviation: BKMR=Bayesian kernel machine regression; WQS=weighted quantile sum; QGC=quantile-based g-computation.

importance, interaction, and nonlinearity assessments, whereas restricted cubic splines were mainly used for single-exposure nonlinearity analyses (Supplementary Material, Supplementary Table S1–S3). Notably, one study used the Relative Excess Risk due to Interaction to enhance the practical interpretability of interaction effects (*30*), and three studies used QGC to investigate nonlinear associations (*31–33*).

DISCUSSION

Large-scale environmental health data and advances in mixture methods have created new opportunities for exposome research (*34*); however, the lack of mixture-specific reporting guidance limits transparency and reproducibility (*35*). Based on studies published in leading journals, current analytical practices were organized into three stages, namely data preparation,

association analysis, and post-hoc evaluation, and used this structure to develop practical reporting recommendations.

Principal Findings and Methodological Implications

Most (86/97, 88.7%) included studies focused on internal exposure biomarkers, reflecting both their biological relevance and the analytical challenges posed by correlated biomarker data. These studies require careful preprocessing as detection-rate thresholds, LOD handling (*36*), and feature reduction may influence results when missingness or exposure dimensionality is high (*37*). Contrastingly, external-exposure studies often involved very large populations but fewer exposures, increasing computational burdens. These differences highlight the need to tailor preprocessing and model-selection strategies to study design, exposure dimension, and data structure.

Method selection should be guided by the research question and data structure. WQS, QGC, and BKMR are designed for mixture analyses, but they differ in assumptions, interpretability, and computational burden: WQS is efficient and interpretable, QGC allows mixed effect directions, and BKMR flexibly models nonlinear and interactive relationships but is computationally intensive (*6*,*19*,*24*–*25*). Single-pollutant models may identify priority pollutants, but mixture methods should play a central role rather than being used only as supplementary analyses (*38*–*40*). Multimodel analyses may strengthen interpretations when findings are consistent; discrepant results should be reported transparently and interpreted according to each method's assumptions and target estimand (*41*–*44*).

Post-hoc analyses were frequently used to interpret mixture findings, including variable importance (89.7%), interaction (80.4%), and nonlinearity (89.7%) assessments. Therefore, recent mixture studies have increasingly aimed not only to estimate overall mixture effects but also to identify influential components and characterize complex risk patterns, including potential nonlinear and interactive relationships (*45*).

Reporting Gaps and the Need for STROBE Extension

As exposome research is largely observational, analytical decisions should be reported transparently to evaluate validity and reproducibility (*46*–*47*). Several recurring reporting gaps were identified: incomplete documentation of detection-rate thresholds and other preprocessing decisions; limited justification for mixture-method selection; and insufficient reporting of key model specifications such as BKMR parameters, WQS bootstrap settings, and QGC assumptions. These gaps hinder assessment of model appropriateness, reproducibility, and interpretation of discrepant findings (*48*). Similarly, a considerable number of studies relied on restricted cubic splines to assess nonlinearity, which is designed to model the nonlinear relationship of a single continuous variable (*49*–*50*). When analyzing multiple correlated pollutants, this approach may still misrepresent the true overall ER relationship.

Although STROBE provides essential guidance for observational studies (*51*), it does not address mixture-specific reporting needs, including exposure screening, LOD handling, feature reduction, method selection, model settings, multimodel interpretation, and post-hoc analyses. We therefore developed a reporting checklist distinguishing core and method-specific items for BKMR, WQS, QGC, and other approaches to improve reporting transparency and facilitate peer review (Supplementary Table S5, available at https://weekly.chinacdc.cn/).

Several limitations should be noted. First, because the analysis focused on studies published in several leading journals, the findings reflect analytical and reporting practices within these influential journals rather than the entire exposome literature. Second, the extraction was based on published reports; therefore, incompletely reported practices may have been underestimated. Finally, this was a descriptive methodological review; individual-level data were not re-analyzed, nor were simulations conducted to determine which practices produced the most valid estimates.

Environmental mixture studies have made substantial methodological progress; however, greater standardization and transparency are still needed. The empirical review of studies published in several leading journals summarizes current analytical practices and provides practical reporting recommendations for researchers conducting mixture analyses. Because no single method can address all mixture-related questions, the method selection should be guided by the research objective, data structure, and target estimand. Researchers should justify mixture-method selection, report preprocessing, and model-specification decisions; interpret multimodel findings transparently; and use reporting guidance such as the

checklist proposed here to improve reproducibility, interpretability, and peer review efficiency.

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SUPPLEMENTARY MATERIALS

METHODS

Literature Search and Data Extraction

PubMed was searched for original studies published between July 2021 and July 2025 in the four selected journals. The search combined mixture-method terms with journal restrictions. For example, the search syntax for Environmental Science & Technology was:

((bkmr OR qgc OR wqs) AND ("Environmental Science & Technology"[Journal]) AND ("2021/7"[Date - Publication] : "2025/7"[Date - Publication])).

The same syntax was applied to Environmental Health Perspectives, Environment International, and Journal of Hazardous Materials by replacing the journal name.

The design characteristics (year of publication, outcome, type of exposure, covariates, and sample size) and the statistical methodologies (including data management, association, interaction, non-linear analysis, and variable importance) were extracted. Each study was treated as the unit of analysis. For studies that used multiple mixture methods, each method was recorded separately using binary indicators for Bayesian Kernel Machine Regression (BKMR), Weighted Quantile Sum (WQS), and quantile-based g-computation. Multimodel use was defined as the use of at least two of the three main mixture methods.

The extracted results were further double-checked, and any identified discrepancies were resolved through discussion until a consensus was reached. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as medians and interquartile ranges (IQRs). Statistical analyses were performed using R (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Analytical Framework in Current Literature

Data Preparation: In this study, data preprocessing referred to analytical steps conducted before fitting mixture models, including exposure screening based on detection rate, handling of values below the limit of detection (LOD), transformation or standardization of exposure variables, correlation assessment, and feature reduction (*1*–*2*). Of note, although both the exclusion of exposures with low detection rates and feature reduction result in a reduced set of exposure variables, they serve distinct purposes. The former is used to identify which exposures are qualified for analysis, as those with very low detection rates may not be analytically reliable; the latter aims to reduce dimensionality among the qualified exposures owing to the limited samples or computation burdens.

Association Analysis: This constitutes the core of the analytical process. Based on the review, most studies employed multiple methods to examine the associations between exposures and health outcomes. The most common approach is single-exposure association analysis, sometimes referred to as exposome-wide association studies (*3*), which assesses the relationship between each exposure and the outcome under the assumption of independence among exposures. It is then advisable to conduct a correlation analysis among the exposures to evaluate whether this independence assumption holds. When strong correlations are found, multi-exposure analysis methods, including WQS regression, QGC, and BKMR are recommended. In fact, the application of WQS, QGC, and BKMR increased significantly after they were developed. Notably, BKMR emerged as the most widely used method, appearing in over 200 studies since 2022 (Figure 1).

In summary, WQS estimates a weighted index of exposure and tests its association with the outcome, offering interpretability but assuming directional homogeneity; that is, all exposures act in the same direction. QGC, a more flexible extension of WQS, relaxes this assumption and allows for mixed directional effects, although it is fundamentally a generalized linear model and computationally efficient. BKMR uses a kernel function to capture complex effects within the mixture in a Bayesian framework, offering high flexibility and the ability to estimate the overall mixture effect and individual exposure–response (ER) functions. However, BKMR is computationally intensive, particularly with a large sample size.

Further Analyses: This stage involves more in-depth post-hoc examinations to elucidate complex relationships within the mixture. The first step is to identify the most important components within the mixture, which is

achieved by calculating the variable importance (*2*,*4*,*5*). Researchers often examine potential interactions among exposures by assessing both the direction and magnitude of these interactive effects on health outcomes. Furthermore, this phase frequently incorporates investigations into non-linear ER relationships, which may reveal threshold effects or other complex patterns that are not captured by linear models. Collectively, these analyses provide a more comprehensive understanding of the overall effects of the mixture and the roles of its components.

1) Variable Importance: WQS, QGC and BKMR can be used to evaluate the importance of exposure. In both WQS and QGC, the relative importance of each exposure was assessed using weights assigned to individual components. In BKMR, variable importance is evaluated using posterior inclusion probability (PIP). A notable advantage of BKMR is its ability to support hierarchical or grouped variables. This allows exposures to be categorized into predefined groups prior to analysis, enabling the simultaneous estimation of both group- and within-group exposure-specific importance.

2) Non-linear Effect: The most common approach for investigating the potential non-linear ER curve for single-exposure analyses is to apply restricted cubic splines (RCS). The key parameter of RCS is the number of knots, with default values typically ranging from three to five, depending on the sample size and R packages used (*6*). It is recommended to explicitly specify the number and location of knots in the analysis and conduct sensitivity analyses using different knots to verify that the non-linear ER shapes remain robust.

3) Interaction Effect: An interaction effect occurs when the effect of one exposure on the outcome varies across different levels of another independent variable. In other words, the association between an exposure and an outcome is modified by a third variable—the modifier or effect modifier. Specifically, interaction effects can be categorized into multiplicative and additive interactions. Multiplicative interactions are commonly evaluated by including a product term in a regression model. Alternatively, stratified (subgroup) analysis can be performed to assess whether the exposure effect differs significantly across subgroups. Additive interactions, on the other hand, exist when the combined effect of two exposures deviates from the sum of their individual effects, and it is assessed using metrics such as the Relative Excess Risk due to Interaction. Additive interaction is especially important in public health and epidemiological research, as it helps determine whether combined interventions targeting multiple risk factors may produce greater benefits than those targeting each factor individually (*7*).

Mixture Association Analysis Methods:

WQS regression: The WQS formula is:

$$g(\mu) = \beta_0 + \beta_1\left(\sum_{i=1}^{m} w_i q_i\right) + \boldsymbol{z}'\boldsymbol{\varphi}$$

$$\mathrm{WQS} = \sum_{j=1}^{m} \overline{w}_j q_j$$

where m exposure components are transformed into quartiles (q_i = 0,1,2,3), w_i denotes component weights, $\overline{w}_j$ is the average weight after bootstrap sampling, β_0 is the intercept, β_1 represents the regression coefficient for the WQS (interpretable as the outcome change per quartile increase in the overall mixture exposure), $\boldsymbol{z}$ is the covariate matrix, and $\boldsymbol{\phi}$ contains covariate coefficients. The link function $g(\cdot)$ accommodates various generalized linear model (GLM) specifications. The WQS model mitigates overfitting and multicollinearity by aggregating mixture effects, but it has several limitations: the restriction of unidirectional effects, need for predefined effect directionality, and inability to evaluate nonlinearity or interactions among the mixture components.

QGC: To address these limitations, researchers developed the QGC, a method that allows mixture components to have both negative and positive directions. Like WQS regression, QGC combines multiple exposures into a single index; however, it does not assume directional homogeneity, offering greater flexibility in real-world scenarios where exposures may have opposing effects on the outcome. Furthermore, QGC supports the modeling of non-linear ER relationships and interaction effects among mixture components, enhancing its ability to capture complex toxicological dynamics. Computationally, QGC is highly efficient and requires relatively limited resources, making it particularly advantageous for large-scale studies where traditional methods would impose a substantial computational burden.

In the QGC framework, the coefficient ψ represents the g-computation estimator derived from a marginal

structural model. It quantifies the change in the outcome associated with a simultaneous one-quantile increase in all exposures. The analytical procedure involves three key steps: 1) transformation of exposures into quantiles, 2) specification of a GLM for the outcome as a function of the exposure quantiles, and 3) estimation of the mixture effect and optional component weights. For statistical robustness, both QGC and WQS typically employ bootstrapping to estimate standard errors and confidence intervals. However, unlike WQS, which requires data splitting and repeated bootstrapping for weight estimation, QGC estimates the joint effect directly in a single GLM model, thereby significantly reducing the computational burden.

BKMR: BKMR is a Bayesian method that models complex exposure–response relationships using kernel-based techniques. The BKMR model is given below:

$$Y_i = h(\boldsymbol{z}_i) + \boldsymbol{x}_i^T \boldsymbol{\beta} + \epsilon_i$$

where Y_i denotes the health outcome, $\boldsymbol{z}_i = (z_{i1}, \ldots, z_{iM})^T$ represents a vector of M exposure variables, and x_i is the matrix of potential covariates (assuming a linear relationship between covariates and outcomes). The term β denotes the regression coefficients, and $h(\cdot)$ is the high-dimensional ER function to be estimated, which may incorporate nonlinearities or interactions among the exposure variables. The core assumption is that individuals with similar exposure characteristics may share similar ER functions $h(\cdot)$. To ensure robust model fitting, a substantial number of Markov chain Monte Carlo iterations is required (for example, ***iter*** ≥10,000).

Notably, BKMR is a flexible, semiparametric method to understand: 1) the overall mixture effect: The change in the outcome when all exposures are fixed at a certain percentile (e.g., 25th percentile) compared to when all of the factors are fixed at their medians; 2) the univariate effect: the change in the outcome associated with increasing a single exposure from a low (e.g., 25th) to a high (e.g., 75th) percentile, while all other exposures are held constant at a fixed level (e.g., their medians) and covariates held constant; 3) bivariate ER: the pairwise dose–response relationship for each exposure on the outcome at varying levels of a second exposure, when remaining exposures are fixed at their medians.

Relation to Existing Literature

Several studies have reviewed statistical methods for assessing the health effects of environmental mixtures, often focusing on specific classes of chemicals. For instance, Pan *et al.* and Gibson *et al.* summarized methods for investigating persistent organic pollutants (POPs) (*1*,*5*), while Lazarevic *et al.* focused on endocrine-disrupting chemicals (*2*), and Billionnet *et al.* examined air pollution (*8*). All the reviews reported the most prevalent exposure components and health outcomes within their respective domains. Additionally, Pan *et al.* identified 23 distinct methods for estimating the overall effect of POP mixtures, highlighting that BKMR and its combination with WQS were the most frequently used approaches. The study by Gibson *et al.* compared supervised methods (e.g. WQS and BKMR) to unsupervised methods (clustering, principal component analysis, and exploratory-factor analysis). Meanwhile, Lazarevic *et al.* and Billionnet *et al.* detailed the strengths and limitations of available approaches, particularly in feature reduction and association analyses, and provided guidance on their software implementation. For researchers seeking detailed instructions on method applications using R software, a recent comprehensive review offers step-by-step workflows and R codes (*9*).

In contrast, the present study specially focused on the application of three specially proposed methods for analyzing mixed-exposure associations and adopted a broader exposome perspective, incorporating both internal and external chemical exposures in terms of study scope. The present study also differed in terms of research objectives and methodological emphasis, thus contributing different insights to the field. The analytical process was summarized into three distinct stages: data preparation, association analysis, and post-hoc analysis. Importantly, the present study emphasizes that both the selection of analytical methods and the detailed reporting of these methods (alongside related findings) are critical to rigorous research. To address these unmet demands, this study developed a structured analytical framework and a practical checklist aimed at improving both the efficiency of peer review and the overall quality of publications in this field. The proposed three-stage framework should be interpreted as a synthesis and organization of existing analytical practices observed in the reviewed studies, rather than as a novel statistical method. Its purpose is to provide a practical structure for researchers to plan, conduct, and report environmental mixture analyses more transparently and consistently.

SUPPLEMENTARY TABLE S1. Current analytical practices in environmental mixture studies a reporting of detection-rate threshold in internal exposure studies.

Detection-rate threshold (%)	Overall (*n*=86)	EI (*n*=34)	EHP (*n*=17)	EST (*n*=16)	JHM (*n*=19)
Not reported	28 (32.6)	10 (29.4)	4 (23.5)	8 (50.0)	6 (31.6)
0.5–0.7	25 (29.1)	17 (50.0)	3 (17.6)	2 (12.5)	3 (15.8)
0.7–0.8	14 (16.3)	4 (11.8)	3 (17.6)	2 (12.5)	5 (26.3)
0.8–0.9	7 (8.1)	0 (0.0)	4 (23.5)	1 (6.2)	2 (10.5)
≥0.9	12 (14.0)	3 (8.8)	3 (17.6)	3 (18.8)	3 (15.8)

SUPPLEMENTARY TABLE S2. Comparison of methods used for analyzing interaction effects in mixed-exposure studies.

Method	Overall (*n*=78)	EI (*n*=32)	EHP (*n*=16)	EST (*n*=13)	JHM (*n*=17)
BKMR (%)					
Not performed	27 (34.6)	17 (53.1)	2 (12.5)	3 (23.1)	5 (29.4)
Performed	51 (65.4)	15 (46.9)	14 (87.5)	10 (76.9)	12 (70.6)
Interaction term (%)					
Not performed	43 (55.1)	13 (40.6)	13 (81.2)	9 (69.2)	8 (47.1)
Performed	35 (44.9)	19 (59.4)	3 (18.8)	4 (30.8)	9 (52.9)

SUPPLEMENTARY TABLE S3. Comparison of methods used for nonlinear associations in mixed-exposure studies.

Method	Overall (*n*=87)	EI (*n*=32)	EHP (*n*=16)	EST (n=17)	JHM (*n*=22)
BKMR (%)					
Not performed	18 (20.7)	9 (28.1)	1 (6.2)	4 (23.5)	4 (18.2)
Performed	69 (79.3)	23 (71.9)	15 (93.8)	13 (76.5)	18 (81.8)
RCS (%)					
Not performed	57 (65.5)	19 (59.4)	11 (68.8)	14 (82.4)	13 (59.1)
Performed	30 (34.5)	13 (40.6)	5 (31.2)	3 (17.6)	9 (40.9)

Abbreviations: EHP=Environmental Health Perspectives; EST=Environmental Science & Technology; JHM=Journal of Hazardous Materials; EI=Environment International; BKMR=Bayesian Kernel Machine Regression; WQS=Weighted Quantile Sum; QGC=quantile-based g-computation; RCS=Restricted Cubic Spline.

SUPPLEMENTARY TABLE S4. Comparison of feature reduction methods used in different initial numbers of exposure.

Feature Reduction (%)	Initial number of exposures	
	≤10 (*n*=49)	>10 (*n*=48)
Not performed	48 (98.0)	24 (50.0)
Performed	1 (2.0)	24 (50.0)

Analytical Framework and Reporting Checklist for Environmental Mixture Health Effects Studies

Primary Objective (Required): (For example:) To systematically evaluate the complex relationships between multiple environmental exposures (mixtures) and a health outcome.

Secondary Objectives (Optional): 1) To identify the most important risky exposure(s), 2) explore the potential non-linear associations, and 3) explore the potential interaction effects.

Three-stage Analytical Framework: 1) Data Preparation: Data preprocessing steps conducted before model fitting, including exposure screening, handling values below the LOD, transformation or standardization, correlation assessment, and confirmation of the final analytical dataset. 2) Association Analysis: The core analytical phase, including single-exposure models, assessment of exposure correlations, and formal mixture models selected according to the research question and data structure. 3) Further Analyses: Post-hoc and sensitivity analyses used to interpret mixture findings, including identification of important components, assessment of nonlinearity or interaction, and robustness checks when appropriate.

Analytical Procedure Checklist: In the checklist below, core items apply broadly to environmental mixture analyses, whereas method-specific items apply to particular approaches such as BKMR, WQS, or QGC.

SUPPLEMENTARY TABLE S5. Analytical framework and reporting checklist for environmental mixture health effects studies.

No.	Task description	Key considerations	Reporting recommendation	Applicability
Stage 1: Data Preparation				
1.1	Exclusion of exposures with low detection frequencies	Determine and justify the minimum detection-frequency threshold used to include exposures in the mixture. Very low detection frequencies (e.g., <50%) generally limit interpretability; thresholds of 70% or 80% are commonly used but should be justified according to the study context.	Report the threshold, number of exposures before and after exclusion, and rationale for the selected threshold.	Core item: broadly applicable to all mixture analyses.
1.2	Handling of values below the limit of detection (LOD) and missing values	Describe how values below the limit of detection and other missing values are handled. Common approaches include substitution using LOD/2 or $\mathrm{LOD}/\sqrt{2}$, multiple imputation, or model-based methods.	Specify the approach used for values below the LOD and missing data, and consider sensitivity analyses using alternative approaches.	Core item: broadly applicable to all mixture analyses.
1.3	Variable transformation	Assess exposure distributions and apply transformation if needed, such as log transformation or square-root transformation, to reduce skewness or improve model fit.	Report whether raw or transformed exposure variables were used, and describe the transformation applied to each exposure.	Core item: broadly applicable to all mixture analyses.
1.4	Standardization or scaling	Scale or standardize exposure variables when required by the selected method or needed for comparability across pollutants. WQS and QGC typically use quantile-based exposure scores, whereas BKMR and regression-based models often require careful scaling or standardization.	Report whether exposures were standardized, scaled, or converted to quantiles, and describe the specific procedure used.	Core item, with method-dependent scaling requirements.
1.5	Feature reduction or exposure selection	Consider feature reduction or exposure selection when the number of exposures is large, when collinearity is substantial, or when the scientific question requires a focused mixture. This step may not be necessary for a small number of prespecified exposures.	If feature reduction or exposure selection is performed, report the rationale, method, and number of exposures retained.	Conditional item: mainly relevant for high-dimensional mixtures or highly correlated exposure sets.
1.6	Final analytical dataset confirmation	Prepare the dataset used for formal analyses after preprocessing decisions have been applied.	Report the final sample size, the final number of exposures included in the mixture analysis, and any exclusions from the analytical sample.	Core item: broadly applicable to all mixture analyses.
Stage 2: Association Analysis				
2.1	Single-exposure analysis	Fit separate regression models for individual exposures when relevant for comparison, screening, or interpretation. These models should be interpreted cautiously because they do not directly estimate the joint effect of correlated exposures.	Report model specification, covariate adjustment, raw p-values, and, if multiple testing correction is used, q-values and the significance threshold.	Contextual item: useful for comparison or preliminary assessment, but not a mixture method.
2.2	Correlation analysis among exposures	Assess correlations or other dependence structures among exposures before mixture modeling. Spearman correlation is commonly used when distributions are skewed or monotonic but not necessarily linear.	Report the correlation metric used and present the exposure-correlation structure (for example, using a heatmap or correlation matrix).	Core item: broadly applicable to all mixture analyses.
2.3	Multi-exposure mixture analysis	Select a mixture method according to the research question, exposure structure, sample size, and method assumptions. Common approaches include BKMR, WQS, and QGC.	Report the mixture method, software or R package, version if available, and key method-specific parameters, such as MCMC iterations for BKMR, bootstrap samples and directionality for WQS, and quantile construction for QGC.	Core mixture item: method-specific parameters should be reported for BKMR, WQS, QGC, or other approaches.

Continued

No.	Task description	Key considerations	Reporting recommendation	Applicability
Stage 3: Further Analyses				
3.1	Identification of important components	Use method-specific metrics to identify exposures that contribute most to the mixture association, such as weights in WQS, posterior inclusion probabilities in BKMR, and positive or negative partial effects in QGC.	Report whether component importance was evaluated, which metric was used, and how the metric was interpreted.	Method-specific item: WQS weights, BKMR PIPs, QGC positive/negative partial effects, or analogous metrics.
3.2	Assessment of interaction effects	Assess potential interactions among mixture components when supported by the research question, sample size, and selected method. For example, BKMR can be used to explore interaction patterns between exposures.	Report whether interactions were examined, how they were assessed, and whether the analysis was prespecified or exploratory.	Method-specific or optional item: particularly relevant for BKMR or models with explicit interaction terms.
3.3	Assessment of non-linear relationships	Examine non-linear associations for the overall mixture or individual exposures when the selected method allows such interpretation, such as BKMR exposure–response functions or spline-based models.	Report whether nonlinearity was examined, the method used, and how non-linear patterns were interpreted.	Method-specific or optional item: particularly relevant for BKMR response functions, splines, or other non-linear models.
3.4	Sensitivity and robustness checks	Evaluate the robustness of key findings using analyses such as alternative covariate adjustment sets, alternative LOD or missing-data handling methods, different exposure-selection thresholds, or alternative mixture methods.	Report the sensitivity analyses performed and whether the main conclusions were materially changed.	Core item: broadly applicable when sensitivity analyses are feasible.

Abbreviations: BKMR=Bayesian Kernel Machine Regression; WQS=Weighted Quantile Sum; QGC=quantile-based g-computation.

Instructions for Use

Sequential Execution: It is recommended to sequentially proceed through Stages 1, 2, and 3.

Method Selection: The choice of specific methods should be justified based on the data characteristics, research question, target estimand, and assumptions of the selected mixture method.

Items in Stage 3 should be applied according to the research question, sample size, model capability, and interpretability, rather than treated as mandatory analyses for every study.

Documentation: Use the "Reporting Recommendation" and "Applicability" columns to report key decisions, methods, assumptions, and parameters. This is critical for ensuring reproducibility and transparency.

NA Option: If a step is not applicable to your study (e.g., Feature Reduction for Step 1.5), mark it as "N/A" and provide a brief reason.

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Outbreak Reports

First Local Cluster of Clonorchiasis Caused by Consumption of Raw Freshwater Fish — Zhengzhou City, Henan Province, China, 2026

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Summary

What is already known about this topic?

Clonorchiasis, a major foodborne parasitic disease in China, is transmitted by eating raw or undercooked freshwater fish and shrimp containing metacercariae. Although prevalent in southeastern and northeastern China, it remains low-endemic in Henan, where raw freshwater fish is not traditionally eaten; indigenous cases are rare and most infections are imported.

What is added by this report?

This report is China's first local clonorchiasis cluster in a low-endemic region. The Zhengzhou outbreak was linked to raw freshwater fish eaten at a dinner and drew online public concern. Three symptomatic and two asymptomatic patients were confirmed by the provincial CDC, and all recovered after anthelmintic treatment.

What are the implications for public health practice?

Rising popularity of raw freshwater fish has raised clonorchiasis risk in low-endemic regions. Authorities should strengthen public health education, train medical staff, and improve collaboration with market supervision agencies. Standardized surveillance of aquatic products, regular release of results, and coordinated responses to clusters and online public concern are essential.

ABSTRACT

Objective: To describe a clonorchiasis outbreak associated with consumption of raw freshwater fish in Zhengzhou, Henan Province, China, in 2026 and highlight the public health risks in low-endemic regions.

Methods: We conducted an epidemiological investigation and laboratory examinations, and analyzed findings in relation to health awareness, medical services, and food safety supervision.

Results: Five diners who consumed raw freshwater fish were diagnosed with clonorchiasis, corresponding to an attack rate of 100%. Patients presented with fever, abdominal pain, and other symptoms; two patients were asymptomatic. All patients had markedly elevated eosinophil counts, and four had impaired liver function. After praziquantel treatment, all patients fully recovered, and follow-up stool tests were negative. The outbreak was attributed to consumption of raw freshwater fish.

Conclusion: Consumption of raw freshwater fish caused this outbreak. Insufficient public awareness, limited clinical capacity, and regulatory gaps were major risk factors. Integrated prevention and control measures are needed to avert similar outbreaks.

On February 10, 2026, Henan CDC received a report of a suspected clonorchiasis case. The patient had consumed raw freshwater fish at a dinner party and presented with eosinophilia, recurrent fever, and abdominal pain. The provincial and municipal CDCs jointly investigated. Based on exposure history, clinical symptoms, and laboratory findings, the event was confirmed as a clonorchiasis outbreak caused by consumption of raw freshwater fish.

INVESTIGATION AND RESULTS

A patient with markedly elevated eosinophil counts presented to the Henan CDC. He had developed a fever and abdominal pain on January 24, 2026 and was treated for gastroenteritis. His condition worsened on February 1, when he developed a fever of 39.2 ℃, abdominal distension, chest tightness, and palpitations. Ten days of combination therapy did not relieve his symptoms. He reported consuming raw freshwater fish at a local Cantonese restaurant on December 31, 2025. *Clonorchis sinensis* (*C. sinensis*) eggs were detected in his stool using the modified Kato–Katz method (Figure 1), confirming infection. Anthelmintic treatment was

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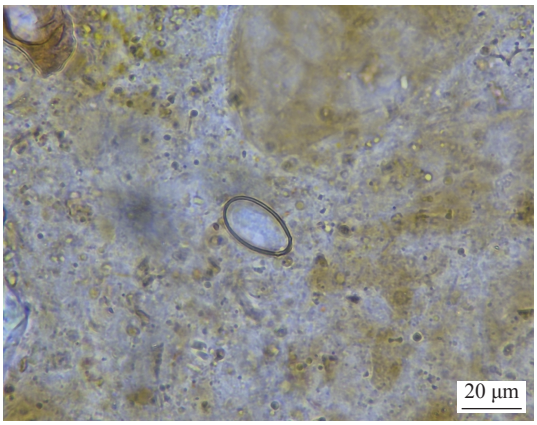


FIGURE 1. *Clonorchis sinensis* egg in a Kato–Katz thick-smear preparation at 400× magnification.
Note: The specimen was prepared using the modified Kato–Katz thick-smear method. The main morphological features of the eggs are a sesame-seed shape, an operculum with shoulder-like elevations at the narrow end, and a small protuberance at the opposite end.

arranged under Henan CDC guidance.

The Henan and Zhengzhou CDCs investigated the index patient's fellow diners. Of the seven attendees, five had consumed raw freshwater fish. One diner developed a fever on February 8 and took ibuprofen; he developed high fever again on February 11 and tested positive for *C. sinensis* eggs. The remaining diners were asymptomatic. Although informed of the risk of clonorchiasis and advised to undergo testing, they initially did not consider it necessary.

On March 11, 2026, a second fellow diner visited the Henan CDC. He had experienced abdominal pain without fever since mid-February but had not sought care promptly; stool testing later confirmed clonorchiasis. After the third case was confirmed, the four remaining diners underwent stool testing on March 12. Two were diagnosed with clonorchiasis. The two diners who had not consumed raw fish were asymptomatic, had normal laboratory findings, and were considered uninfected. All patients were treated with praziquantel at 75 mg/kg per day for 3 days. One month later, follow-up stool tests were negative. All patients recovered completely, with no severe outcomes or deaths.

Five premises were surveyed: the implicated restaurant and four other raw fish restaurants in Zhengzhou. Raw fish slices were mainly prepared from *Ctenopharyngodon idella*, *Squaliobarbus curriculus*, and *Spinibarbus denticulatus*, all purchased from two Zhengzhou aquatic product markets and sourced from Guangdong and Guangxi. Fish served at the implicated restaurant were sourced from Shunde District, Foshan; the origins of other batches were not recorded. The fish came from large-scale aquaculture farms, earthen ponds, or wild catches, and they were held in restaurants before processing. Slaughtering, filleting, and plating were performed in one area, whereas side dishes were prepared in another. Separate knives were allocated for raw and cooked foods; however, no disinfection was performed, and utensils were rinsed only with tap water.

This was not the first clonorchiasis cluster reported in Henan. In November 2024, an imported outbreak occurred in Anyang: all seven tourists who consumed raw freshwater fish in Foshan were tested, and five were positive, corresponding to an attack rate of 71.43%. Both outbreaks were associated with consumption of raw freshwater fish during group dinners. Patients presented with typical symptoms, mainly fever and gastrointestinal discomfort, accompanied by marked eosinophilia and liver injury. Early misdiagnosis was common; patients were initially treated for upper respiratory infection or gastroenteritis without symptom relief (Table 1).

PUBLIC HEALTH RESPONSE

After the outbreak was identified, CDCs at the provincial, municipal, and district levels launched joint interventions. First, all seven dinner attendees were identified through the epidemiological investigation, and testing and follow-up were completed for all exposed persons. Second, health education and management of public concern were implemented. On February 14, 2026, the Henan CDC published a popular-science article on its WeChat account to disseminate clonorchiasis prevention information and reduce infection risk. On March 22, 2026, videos and media reports about patients with clonorchiasis seeking redress circulated online. The Henan CDC immediately notified the Zhengzhou CDC and guided multi-departmental consultations, patient management, risk assessment, and health education. A risk alert was issued to address public concern and mitigate online risk. Because the restaurant declined to release diner records, customers who had consumed raw fish during other service periods could not be screened. Two health advisories urged people who had consumed raw fish to undergo screening at the Henan CDC. Twenty people were tested; five newly-identified individuals had positive stool results. All five infections were associated with raw fish consumed in Guangdong, and no additional local infections have been identified to

TABLE 1. Comparison of epidemiological indicators, clinical characteristics, and laboratory findings among patients with clonorchiasis in two cluster outbreaks in Henan Province.

Features	Local outbreak		Imported outbreak	
	n	Value range	*n*	Value range
Gender				
Male	2	–	3	–
Female	3	–	2	–
Age (y)	–	11–36	–	33–59
Location of exposure	–	Zhengzhou, Henan	–	Foshan, Guangdong
Food source	–	Guangdong	–	Guangdong
Attack rate	–	5/5	–	5/7
Incubation period (d)	3	24–46	4	19–25
Exposure-to-diagnosis interval (d)	5	41–70	5	49
Chief complaints				
Fever	2	–	3	–
Nausea	1	–	3	–
Loss of appetite	1	–	4	–
Abdominal pain	2	–	4	–
No symptoms	2	–	1	–
Parameters				
Eosinophil percentage (%)	5	10.1–61.1	5	23.2–76.5
Alanine aminotransferase (U/L)	4	60–122	2	137–323
Aspartate aminotransferase (U/L)	1	82	2	60–137
Alkaline phosphatase (U/L)	3	110–396	2	326–650
γ-glutamyl transferase (U/L)	1	166	2	313–534
Eggs per gram of stool	5	48–144	5	120–360

Note: All cases identified in the imported outbreak were diagnosed on the same day.
"–" means that the data are no applicable or no available for this group.

date. Sampling at the implicated restaurant could not be performed because raw fish dishes had been removed and no fish stock was available. Third, all confirmed patients remained under follow-up to ensure standardized treatment and re-examination until full recovery.

DISCUSSION

Henan remains a low-endemic region for clonorchiasis, with an infection rate of only 0.01% (5/42,759) reported in a 2015 survey (*2*). However, the two recent clusters indicate increasing risks of foodborne clonorchiasis in Henan. Together with imported exposure, the growing local popularity of raw freshwater fish sourced from high-endemic regions may make sporadic cases and clusters a long-term concern. These outbreaks highlight several important public health issues.

First, public health awareness remains insufficient. Local residents have limited knowledge of the transmission, hazards, and prevention of clonorchiasis and may underestimate the risk of consuming raw freshwater fish. This lack of awareness promotes risky dietary behavior and may facilitate local transmission. Most people with mild or asymptomatic infections do not seek screening or medical care, allowing infections to remain undetected in the community. Long-term infection can cause irreversible liver damage and markedly increase the risks of cholelithiasis, cirrhosis, and cholangiocarcinoma (*3*). Targeted health education is urgently needed to discourage raw fish consumption, interrupt community transmission (*4*), and encourage active screening and early treatment among high-risk populations.

Second, hospitals face major challenges in clonorchiasis management. Clinicians in low-endemic regions may have limited awareness of diagnostic clues,

such as eosinophilia and a history of raw fish consumption, which can lead to delayed diagnosis or misdiagnosis as gastrointestinal or respiratory disease. Laboratory tests at primary-level medical institutions have limited sensitivity for detecting *C. sinensis* eggs and may miss mild infections. Most hospitals in Henan do not routinely stock antiparasitic drugs; therefore, patients with confirmed infection may need to obtain medication from CDCs or online pharmacies, delaying treatment and prolonging the transmission period. In addition, no official clinical guidelines are available, leaving clinicians uncertain about treatment regimens. Hospitals should establish prioritized specimen referral pathways, use provincial and municipal parasitology laboratory networks and CDC diagnostic capacity (*5*), develop rapid response mechanisms, and improve diagnosis and management of clonorchiasis. Although clonorchiasis is managed as an infectious disease requiring focused surveillance and statutory reporting under Category C requirements, formal designation as a Category C notifiable disease should be considered when appropriate.

Third, food safety supervision is inadequate. These surveys indicate major gaps in source control. Aquaculture quarantine and regular snail control in ponds should be strengthened in endemic regions, full traceability implemented in aquatic product markets, and certificate verification required of vendors, to reduce clonorchiasis transmission at the source. These processing practices create a high risk of cross-contamination during raw fish preparation. National Standard GB 2733–2015, Fresh and Frozen Aquatic Products (*6*), covers unprocessed aquatic raw materials but does not specify parasite limits for ready-to-eat products. In contrast, GB 10136–2015, Aquatic Animal Products (*7*), applies to edible raw fish and prohibits trematode metacercariae and nematode larvae. This outbreak reflects weak enforcement of GB 10136–2015 and a regulatory loophole that allows raw fish compliant with GB 2733–2015 to be sold for direct consumption. Market regulators should require any freshwater fish product intended for raw consumption to comply with GB 10136–2015, rather than permitting market entry based on GB 2733–2015 alone. Such products should be clearly labeled as "suitable for raw consumption" or "ready-to-eat."

Fourth, low-endemic regions may adopt mature, replicable full-chain management standards for raw freshwater fish developed in Hengxian and Shunde. Agricultural authorities should conduct seasonal snail control and parasite surveillance at fish farms that supply products intended for raw consumption. Market regulators should increase random sampling and routine testing of high-risk species, such as grass carp and barbel chub, to reduce source-related hazards. Restaurants serving raw fish should be subject to special registration and required to use separate utensils for raw and cooked foods and to follow standardized disinfection protocols. CDCs should provide regular technical training and health education to improve public awareness. When clonorchiasis outbreaks occur, a multi-departmental joint response should include source tracing, standardized treatment of patients, exposure investigation, screening of all diners, and management of public concern to interrupt transmission rapidly.

This study has several limitations. Although supply-chain tracing and on-site hygiene investigations suggested that contamination originated during the upstream aquaculture stage, no cross-provincial investigation was conducted; therefore, the supply sources, aquaculture environments, and contamination conditions could not be determined. Because the incubation period was prolonged, no residual fish samples from the implicated restaurant were available for testing. Because no formal request for regulatory intervention was submitted to market supervision authorities, parasitological examination was limited to diners in the outbreak cluster, and catering staff and other customers were not screened. Large-scale population surveys were not conducted locally; therefore, the infection prevalence among residents could not be accurately quantified.

This is the first local cluster of clonorchiasis caused by consumption of raw freshwater fish in Zhengzhou city of Henan province. It raised the importance of rising popularity of raw freshwater fish with clonorchiasis risk in low-endemic regions.

Conflicts of interest: No conflicts of interest.

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