Tick-borne viruses: moving the dial on diagnostics with diverse technological advances

Lancet Microbe 2025
Published Online
https://doi.org/10.1016/j.lanmic.2025.101234

See Online for appendix

Tick-borne viruses (TBVs) pose an escalating threat to human and animal health, driven by the geographical expansion of endemic pathogens (eg, tick-borne encephalitis virus) and continued spillover of emerging ones (eg, Yezo virus), many of which are associated with substantial morbidity and mortality (appendix pp 2–3).[1–3] Multiroute transmission of TBVs, including tick bites and exposure to infected animal blood, tissues, or unpasteurised dairy in occupational settings (eg, slaughterhouses) and community contexts (eg, sacrificial religious gatherings), may obscure exposure history and hinder early clinical suspicion.[3,4] TBV infections often present with non-specific manifestations (eg, fever), and in the case of Crimean–Congo haemorrhagic fever virus, up to 88% of infections could be asymptomatic, further complicating diagnosis.[1] Furthermore, short-lived viraemia restricts direct detection of virus to a narrow acute-phase window.[5] These challenges call for reliable and efficient detection methods to enhance diagnostic capacity across diverse TBV infections.

Molecular methods for viral nucleic acid detection (eg, reverse transcription-quantitative PCR, RT-qPCR) form a cornerstone in diagnosis, with latest technological advancements improving sensitivity in low-titre samples and reducing thermal cycling times. Nested RT-PCR enhances sensitivity substantially via two-round amplification (appendix pp 4–7). The microfluidic Veri-Q PCR 316 system supports the severe fever with thrombocytopenia syndrome virus assay through accelerated thermal cycling, enabling detection within 55 min while maintaining high sensitivity (limit of detection=5·3 copies per µL; table).[6] Meanwhile, isothermal amplification platforms are advancing field diagnostics. Specifically, reverse transcription recombinase polymerase amplification combined with CRISPR-associated protein 12a enables sensitive detection of severe fever with thrombocytopenia syndrome virus (limit of detection=0·1 copies per µL) and single-base resolution via fluorescence. Results can also be read within 10 min using immunochromatographic strips (limit of detection=1 copy per µL), thus minimising equipment dependency (appendix pp 4–7). Similarly, a field-deployable reverse transcription loop-mediated isothermal amplification assay based on degenerate primers, 1000-fold more sensitive than conventional RT-PCR, achieved the first reverse transcription loop-mediated isothermal amplification-based detection of Crimean–Congo haemorrhagic fever virus in the urine, expanding non-invasive diagnostic capacity (table).[7] These innovative methods are increasingly being integrated into automated multiplex systems, such as the BioFire FilmArray system with its Global Fever Panel (appendix pp 8–10), which promises simultaneous detection of multiple TBVs and could further enhance point-of-care accessibility through simplified workflows. Despite these key advancements, conventional molecular diagnostics rely inherently on pre-identified pathogens, underscoring the need for innovative approaches to detect divergent and novel viruses.

Targeted metagenomics (eg, Crimean–Congo haemorrhagic fever virus hybridisation capture) tolerates minor sequence mismatches and enables sequence recovery across viral lineages, making the technique suitable for detecting divergent viruses (appendix pp 4–7). Notably, unbiased metagenomic next-generation sequencing offers tremendous potential for pathogen discovery, having already identified multiple emerging TBVs associated with human infections and aiding the diagnosis of suspected TBV infections or undifferentiated febrile illnesses (appendix pp 4–7). Nanopore sequencing, with its portability and ultralong reads, partly mitigates the limitations of traditional laboratory-bound workflows. Nanopore sequencing has been used to identify 20 viruses and assemble the coding regions of Alongshan virus from tick samples.[8] Artificial intelligence (AI)-driven approaches could support the analysis of vast metagenomic next-generation sequencing datasets, holding promise for enhancing the accuracy and efficiency of TBV detection.

Serological diagnosis is essential for confirming past exposure to TBVs and establishing infection history, particularly when acute-phase samples are unavailable. However, traditional methods face two persistent challenges: biosafety burdens (eg, plaque reduction neutralisation tests for most TBVs require biosafety level-3 or level-4 facilities) and cross-reactivity, both of which can be mitigated to some extent through novel strategies.

	Virus	Gene type	Detection method	Target	Sensitivity	Specificity	Sample types	Limit of detection	Detection time	Stage
Yoo et al (2020)[6]	SFTSV	3 segments (S, M, and L) negative-strand RNA	One-step real-time RT-PCR based on lab-on-a-chip technology	SFTSV S segment	14 (100%) of 14	103 (100%) of 103	Serum	5·3 RNA copies per µL	55 min	Preclinical
Febrer-Sendra et al (2023)[7]	CCHFV	3 segments (S, M, and L) negative-strand RNA	Colorimetric RT-LAMP	CCHFV S segment	NA	100% (no cross-reactivity with other viruses; eg, ZEBOV and LSSV)	Plasma and urine	50 fg/µL	NA	Preclinical
Ackermann-Gäumann et al (2024)[9]	TBEV	Non-segmented positive-strand RNA	RVP-based SNT	TBEV antibodies	92·3% (95% CI 79·7–97·4)	100% (95% CI 81·6–100)	Serum	NA	<48 h	Preclinical
Kasbergen et al (2025)[5]	TBEV and CCHFV		Multiantigen serology and a diagnostic algorithm*	TBEV and CCHFV RNA; antibodies	NA	NA	Serum	NA	NA	Preclinical

CCHFV=Crimean–Congo haemorrhagic fever virus. CI=confidence interval. L=large genome segments. LSSV=Lassa virus. M=medium genome segments. NA=not applicable. RT-LAMP=reverse transcriptase loop-mediated isothermal amplification. RVP=reporter virus particle. S=small genome segments. SFTSV=severe fever with thrombocytopenia syndrome virus. SNT=seroneutralisation test. TBEV=tick-borne encephalitis virus. TBV=tick-borne virus. ZEBOV=Zaire Ebola virus. *Study combined the use of reverse transcription quantitative PCR, protein microarrays, ELISA, virus neutralisation tests, and indirect immunofluorescence test.

***Table*: Performance comparison of representative detection methods for select TBVs**

The reporter virus particle-based seroneutralisation test for tick-borne encephalitis virus can be performed safely in a biosafety level-2 environment and delivers results within 48 h (as compared with the 5–7 days taken for a plaque reduction neutralisation test), with 92·3% sensitivity and near 100% specificity (table).[9] Protein microarrays, as an innovative alternative, effectively minimise cross-reactivity by targeting the tick-borne encephalitis virus non-structural protein 1 antibodies.[5] Building on this, multiantigen serology combined with a diagnostic algorithm has been proposed to integrate temporal, serological, and molecular data, improving interpretation in the context of incomplete and heterogeneous clinical information (table).[5] Additionally, electrochemical immunoassay using silver nanoparticles allows enzyme-free detection of tick-borne encephalitis virus antibodies at concentrations as low as 90 international units per mL, representing another cutting-edge approach for low-resource settings.[10]

Diagnosing TBVs remains a complex challenge due to factors such as transient viraemia, non-specific symptoms in infected individuals, and low diagnostic accessibility, especially in remote rural areas. To address this limitation, future diagnostic frameworks should incorporate rapid molecular testing, real-time genomic intelligence, and broad serological surveillance to enhance early detection and epidemiological monitoring. Field-deployable innovations—such as CRISPR-enhanced isothermal amplification and paper-based microfluidic assays—hold promise for mass screening in low-resource, tick-endemic regions. For high-risk populations, wearable biosensors could enable early, minimally invasive detection and shift care from reactive to preventive. Systemically, decentralised sequencing networks and AI-driven metagenomics should be embedded within the One Health strategy to support real-time pathogen identification and cross-sector data sharing. Ultimately, the future of TBV diagnostics lies in smart, scalable, and interconnected solutions that improve accessibility and strengthen frontline response.

We declare no competing interests. SS acknowledges support from the Scientific Research Innovation Capability Support Project for Young Faculty (ZYGXQNJSKYCXNLZCXM-116) by the Ministry of Education (U40 project), the Program of Shanghai Academic Research Leader (23XD1420700), Distinguished Researcher Program of Henan Province, and Medical Science Data Center of Fudan University. MK acknowledges support from the Rising-Star Program of Shanghai Science and Technology Innovation Action Plan for 2024 (Yangfan Special Project, 24YF2734300), National Major Science and Technology Project (2023ZD0506502), and Young Sprouts Project of Shanghai General Hospital (CCTR-2025C37).

*Xinyu Wang†, Xinyi Jiao†, Ruihua Dong†, Xiaoling Li†, Di Wang, Zhiwen Jiang, Mei Kang, Andres Merits, Hao Li, Longxian Zhang, *Zhihang Peng‡, *Na He‡, *Shuo Su‡*
zhihangpeng@163.com; nhe@fudan.edu.cn; shuosu@fudan.edu.cn; ssh5658485@163.com

†Contributed equally
‡Joint senior authors

Department of Epidemiology, School of Public Health, Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai 200032, China (XW, XJ, RD, XL, ZJ, MK, NH, SS); Research Center for Frontier Fundamental Studies, Zhejiang Lab, Hangzhou, China (DW); Clinical Research Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (MK); Institute of Bioengineering, University of Tartu, Tartu, Estonia (AM); State Key Laboratory of Pathogen and Biosecurity, Academy of Military Medical Sciences, Beijing, China (HL); College of Veterinary Medicine, Henan Agricultural University, Zhengzhou, China (LZ); National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, Chinese Center for Disease Control and Prevention, Beijing, China (ZP)

1 Semper AE, Olver J, Warner J, et al. Research and product development for Crimean–Congo haemorrhagic fever: priorities for 2024–30. *Lancet Infect Dis* 2025; **25:** e223–34.

2 Zhang MZ, Bian C, Ye RZ, et al. A series of patients infected with the emerging tick-borne Yezo virus in China: an active surveillance and genomic analysis. *Lancet Infect Dis* 2025; **25:** 390–98.

3 US Centers for Disease Control and Prevention. Tick-borne encephalitis. April 23, 2025. https://www.cdc.gov/yellow-book/hcp/travel-associated-infections-diseases/tick-borne-encephalitis.html (accessed Aug 17, 2025).

4 Hawman DW, Feldmann H. Crimean–Congo haemorrhagic fever virus. *Nat Rev Microbiol* 2023; **21:** 463–77.

5 Kasbergen LMR, de Bruin E, Chandler F, et al. Multi-antigen serology and a diagnostic algorithm for the detection of arbovirus infections as novel tools for arbovirus preparedness in southeast Europe (MERMAIDS-ARBO): a prospective observational study. *Lancet Infect Dis* 2025; **25:** 678–89.

6 Yoo IY, Kim JY, Yoon YK, Huh HJ, Lee NY. Comparison between the SFTS-QS kit and the PowerChek SFTSV real-time PCR kit for the detection of severe fever with thrombocytopenia syndrome virus. *Ann Lab Med* 2020; **40:** 317–20.

7 Febrer-Sendra B, Fernández-Soto P, García-Bernalt Diego J, et al. A novel RT-LAMP for the detection of different genotypes of Crimean–Congo haemorrhagic fever virus in patients from Spain. *Int J Mol Sci* 2023; **24:** 6411.

8 Ergunay K, Boldbaatar B, Bourke BP, et al. Metagenomic nanopore sequencing of tickborne pathogens, Mongolia. *Emerg Infect Dis* 2024; **30:** 105–10.

9 Ackermann-Gäumann R, Dentand A, Lienhard R, et al. A reporter virus particle seroneutralization assay for tick-borne encephalitis virus overcomes ELISA limitations. *J Med Virol* 2024; **96:** e29843.

10 Khristunova E, Barek J, Kratochvil B, Korotkova E, Dorozhko E, Vyskočil V. Electrochemical immunoassay for the detection of antibodies to tick-borne encephalitis virus by using various types of bioconjugates based on silver nanoparticles. *Bioelectrochemistry* 2020; **135:** 107576.