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CURRENT TRENDS IN THE LABORATORY DIAGNOSIS OF HEPATITIS B INFECTIONS

Michael Simidele **ODIMAYO**[1*], Adejoke Kayode **OBAJULUWA**[2,3], Samuel Ihenacho **NWADIOHA**[4], Precious **JEFF-AGBOOLA**[5], Pius Abimbola **OKIKI**[2,3]

[1]State Ministry of Health/ Ondo State Governor's Office; formerly, Department of Microbial Pathology, University of Medical Sciences, Ondo City, Nigeria.
[2]Department of Biological Sciences, College of Sciences, Afe Babalola University, Ado- Ekiti, Nigeria
[3]ABUAD Biotechnology Centre, Afe Babalola University, Ado- Ekiti, Nigeria
[4]Department of Medical Microbiology, Faculty of Basic Clinical Sciences, Benue State University, Makurdi, Nigeria
[5]Department of Microbiology, Faculty of Sciences, University of Medical Sciences, Ondo City, Nigeria
[*]**Corresponding author:** simideledimayo@gmail.com

Abstract

Viral hepatitis remains a major global public health challenge, accounting for approximately 1.4 million deaths annually. Hepatitis B virus (HBV) infection alone contributes substantially to this burden, particularly in low- and middle-income countries where access to timely diagnosis and treatment remains limited. Despite the availability of effective vaccines and antiviral therapies, an estimated 90% of individuals living with HBV worldwide remain unaware of their infection status, perpetuating transmission and increasing the risk of long-term liver complications. This review examines current trends in the laboratory diagnosis of HBV infection, with emphasis on both conventional and emerging diagnostic technologies. A systematic literature review was conducted using PubMed, Scopus, and Google Scholar to identify relevant studies published between 2010 and 2025 on HBV diagnostic methodologies. Traditional diagnostic approaches, including serological markers, biochemical liver function tests, and imaging techniques, remain foundational for assessing infection status, immune response, and liver disease progression. However, molecular diagnostics have become central to HBV management, with quantitative detection of HBV DNA and RNA now regarded as the gold standard for viral load monitoring and therapeutic decision-making. Advances in molecular diagnostics span multiple generations, including real-time quantitative polymerase chain reaction (qPCR), isothermal amplification technologies, HBV RNA quantification, and next-generation sequencing (NGS). These innovations offer enhanced sensitivity and specificity, improved disease monitoring, rapid turnaround times, high-throughput capabilities, and expanded applications such as genotyping and antiviral resistance detection. Despite these advancements, significant challenges persist, notably high costs, infrastructure demands, lack of standardization, and limited accessibility in underserved populations. Achieving the World Health Organization's 2030 hepatitis B elimination targets will require expanding access to affordable, accurate, and simplified diagnostic tools alongside strengthened health systems, workforce training, and public awareness initiatives. Continued technological innovation and global collaboration remain essential to reducing diagnostic gaps and improving outcomes for millions affected by HBV worldwide.

Keywords: Hepatitis B virus; laboratory diagnosis; molecular diagnostics; viral load; current trends

Introduction

Viral hepatitis remains one of the most significant causes of infectious disease–related morbidity and mortality worldwide. It is estimated that viral hepatitis causes approximately 1.4 million deaths annually, rivaling tuberculosis and exceeding human immunodeficiency virus (HIV)–related mortality in many regions (World Health Organization [WHO], 2022). Among the hepatotropic viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV) are responsible for nearly 90% of hepatitis-related deaths, while hepatitis A, D, and E viruses account for the remaining proportion (Jefferies et al., 2018).

HBV is a partially double-stranded DNA virus belonging to the family *Hepadnaviridae*. It is transmitted primarily through exposure to infected blood or body fluids, including perinatal transmission, unsafe injections, sexual contact, and blood transfusion. Globally, an estimated 296 million people were living with chronic HBV infection in 2019, with the highest burden observed in sub-Saharan Africa and East Asia (WHO, 2022). HBV infection is ranked among the top ten causes of infectious disease–related deaths worldwide and is a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC).

Despite the availability of an effective vaccine since the 1980s and potent antiviral therapies, HBV remains underdiagnosed and undertreated. Approximately 90% of infected individuals globally are unaware of their infection status, resulting in delayed treatment initiation and ongoing transmission (WHO, 2022). In resource-limited settings, socioeconomic factors,

limited laboratory infrastructure, and high diagnostic costs further exacerbate this diagnostic gap. For example, a study from Ondo State, Nigeria, reported that only 7.6% of individuals aware of their HBV-positive status could afford treatment, highlighting the critical impact of economic barriers on disease control (Odimayo et al., 2022).

Early and accurate laboratory diagnosis of HBV infection is essential for effective clinical management, prevention of transmission, and reduction of HBV-related complications. Current treatment strategies aim primarily at long-term suppression of viral replication, with loss of hepatitis B surface antigen (HBsAg) regarded as the optimal therapeutic endpoint. According to the European Association for the Study of the Liver (EASL, 2017), treatment is generally indicated in patients with HBV DNA levels exceeding 2,000 IU/mL, elevated alanine aminotransferase (ALT), and/or evidence of moderate liver necroinflammation or fibrosis. All patients with cirrhosis and detectable HBV DNA should receive antiviral therapy regardless of ALT levels. Additional indications include prevention of mother-to-child transmission in pregnant women with high viremia and prevention of HBV reactivation in patients undergoing immunosuppression or chemotherapy.

Given the evolving landscape of diagnostic technologies, this review critically examines current trends in the laboratory diagnosis of HBV infection, encompassing traditional serological and biochemical assays, as well as advanced molecular and genomic approaches. Particular emphasis is placed on innovations that enhance diagnostic accuracy, disease monitoring, and accessibility in resource-poor settings.

Methodology

This review was conducted using a systematic literature search of electronic databases including PubMed, Scopus, and Google Scholar. Peer-reviewed articles published between January 2010 and March 2025 were considered eligible for inclusion. Search terms included combinations of: *Hepatitis B diagnosis*, *HBV molecular diagnostics*, *HBsAg detection*, *HBV viral load quantification*, *HBV RNA*, *HBV biomarkers*, *isothermal amplification*, *next-generation sequencing*, and *point-of-care HBV testing*.

Inclusion criteria comprised original research articles, systematic reviews, meta-analyses, clinical guidelines, and policy documents focusing on laboratory diagnostic technologies for HBV infection, their analytical performance, clinical applications, and innovations. Studies not published in English or lacking relevance to laboratory diagnostics were excluded. Reference lists of included articles were manually screened to identify additional relevant publications. Data were synthesized narratively to provide a comprehensive overview of current diagnostic trends.

Results and Discussion

Traditional Laboratory Diagnosis of HBV Infection

Serological Diagnostic Methods

Serological assays remain the cornerstone of HBV diagnosis and epidemiological surveillance. These tests detect virus-specific antigens and antibodies that appear at different stages of infection, providing valuable insights into infection status, immune response, and disease phase (Vainionpää & Leinikki, 2012). The standard serological panel includes HBsAg, antibody to HBsAg (anti-HBs), hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), and antibody to hepatitis B core antigen (anti-HBc) (Centers for Disease Control and Prevention [CDC], 2023).

Laboratory-based immunoassays, including enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs), and electrochemiluminescence immunoassays (ECLIAs), are widely used due to their high analytical sensitivity and specificity, often exceeding 99% (WHO, 2017). Rapid diagnostic tests (RDTs) provide point-of-care screening, particularly valuable in decentralized and resource-limited settings, although they generally exhibit lower sensitivity compared with laboratory-based assays (Okda *et al.,* 2016).

Detection of Hepatitis B Surface Antigen (HBsAg)

HBsAg is the primary marker for HBV screening and diagnosis. It appears in serum 1–10 weeks after infection and persists in chronic infection (Liaw & Chu, 2009). The presence of HBsAg for more than six months defines chronic HBV infection. Traditional ELISA-based assays remain widely used, while newer ultrasensitive assays, such as immune complex transfer chemiluminescence enzyme immunoassay (ICT-CLEIA), enable detection of very low antigen levels, facilitating early diagnosis and improved treatment monitoring (Tsuge *et al.,* 2019).

Antibody Markers

Anti-HBc antibodies indicate exposure to HBV and are present in both acute and chronic infections but not following vaccination. IgM anti-HBc is a marker of acute or recent infection, whereas IgG anti-HBc persists for life (Terrault *et al.,* 2018). Anti-HBs antibodies indicate immunity, either from vaccination or resolved infection, with protective immunity defined by titers ≥10 mIU/mL (Dini *et al.,* 2017). HBeAg and anti-HBe serve as markers of viral replication and infectivity, aiding in disease phase classification and treatment decisions (EASL, 2017).

Biochemical and Imaging Assessment

Biochemical tests, including ALT, aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase, are routinely used to assess liver injury and disease activity. However, these markers are non-specific and may fluctuate independently of

viral replication. Imaging techniques and non-invasive fibrosis assessment tools, such as transient elastography (FibroScan), complement laboratory diagnostics by evaluating liver fibrosis and cirrhosis. FibroScan measures liver stiffness expressed in kilopascals (kPa), correlating with fibrosis stages and guiding clinical management (WHO, 2022).

Molecular Diagnostic Methods in HBV Infection

Molecular diagnostics have transformed HBV management by enabling direct detection and quantification of viral nucleic acids. Unlike serological methods, molecular assays provide precise measurements of viral replication, disease progression, and treatment response (Liu et al., 2023).

Real-Time Quantitative PCR (qPCR)

Real-time PCR is the clinical gold standard for HBV DNA quantification. It combines amplification and real-time detection using fluorescent probes or dyes, allowing accurate viral load measurement down to 10 IU/mL (Lu *et al.,* 2006). qPCR plays a central role in confirming active infection, guiding treatment initiation, monitoring therapeutic response, and detecting virological breakthrough (Obiomah *et al.,* 2020).

Despite its advantages, qPCR requires costly equipment, skilled personnel, and reliable electricity, limiting its availability in many low-resource settings (Peeling & Mabey, 2010).

Isothermal Amplification Techniques

Isothermal amplification methods amplify nucleic acids at a constant temperature, eliminating the need for thermocyclers. Techniques such as loop-mediated isothermal amplification (LAMP), recombinase polymerase amplification (RPA), transcription-mediated amplification (TMA), nucleic acid sequence-based amplification (NASBA), and helicase-dependent amplification (HDA) offer rapid, sensitive, and potentially low-cost alternatives to PCR (Notomi *et al.,* 2000; Srivastava & Prasad, 2023).

LAMP and RPA have shown promising performance for HBV detection in decentralized settings, with visual readouts and minimal equipment requirements. TMA is widely used in automated commercial platforms, such as the Aptima HBV Quant assay, providing high sensitivity and throughput (Kacian & Fultz, 2016).

HBV RNA Quantification

HBV RNA quantification has emerged as a novel biomarker reflecting transcriptional activity of covalently closed circular DNA (cccDNA). Unlike HBV DNA, which may become undetectable during nucleos(t)ide analogue therapy, HBV RNA can persist, providing insight into residual viral activity and relapse risk (Wang et al., 2021). Techniques such as RT-qPCR, droplet digital PCR (ddPCR), and TMA are employed, although standardization remains a major challenge (Nguyen *et al.,* 2020).

Next-Generation Sequencing (NGS)

NGS enables high-throughput, deep sequencing of HBV genomes, allowing comprehensive genotyping, detection of drug resistance mutations, and analysis of viral quasispecies (Chen *et al.,* 2019). NGS is particularly valuable for detecting occult HBV infection and low-frequency variants associated with immune escape or treatment failure (Seto *et al.,* 2015). However, high costs, bioinformatics complexity, and limited clinical validation restrict routine use in many settings.

Advanced PCR-Based Mutation Detection

Advanced PCR-based techniques, including allele-specific PCR, COLD-PCR, high-resolution melting analysis, digital PCR, and PCR-NGS hybrids, enhance detection of minor variants and resistance mutations (Milbury *et al*., 2011; Khan *et al*., 2025). These methods support personalized therapy but require standardization and integration into clinical workflows.

Serological and molecular markers used in the diagnosis of Hepatitis B virus infection are summarised in Table 1. Table 2 presents the comparison of molecular techniques for HBV detection, while clinical significance of occult Hepatitis B infection (OBI) is presented in Table 3.

Challenges and Future Directions

Despite significant advances, HBV diagnostics face challenges related to cost, infrastructure, technical complexity, and inequitable access. Lack of standardization for emerging biomarkers, such as HBV RNA, further complicates clinical implementation. Addressing these barriers will require investment in affordable point-of-care technologies, workforce training, regulatory harmonization, and integration of diagnostics into primary healthcare systems (Table 4).

Conclusion

Laboratory diagnosis remains central to HBV control and elimination efforts. While traditional serological and biochemical assays provide essential baseline information, molecular diagnostics have revolutionized HBV detection, monitoring, and personalized management. Real-time PCR continues to serve as the clinical backbone, complemented by isothermal amplification, HBV RNA quantification, and next-generation sequencing. Expanding access to accurate, affordable, and simplified diagnostics—particularly in resource-limited settings—is critical to achieving the WHO 2030 hepatitis elimination targets. Continued innovation, global collaboration, and health system strengthening are essential to reducing the global burden of HBV infection.

Table 1 Serological and Molecular Markers Used in the Diagnosis of Hepatitis B Virus Infection

Marker	Type	Clinical Interpretation	Diagnostic Utility
HBsAg	Serological	Active HBV infection	Screening and diagnosis
Anti-HBs	Serological	Immunity (vaccination or recovery)	Post-vaccination assessment
Anti-HBc (Total)	Serological	Previous or ongoing infection	Exposure history
Anti-HBc IgM	Serological	Acute or recent infection	Acute HBV diagnosis
HBeAg	Serological	Active viral replication	Disease activity monitoring
Anti-HBe	Serological	Reduced replication	Treatment response
HBV DNA	Molecular	Viral load	Treatment monitoring
HBV RNA	Molecular	cccDNA transcriptional activity	Emerging biomarker

Table 2: Comparison of Molecular Techniques for HBV Detection

Technique	Target	Sensitivity	Turnaround Time	Advantages
Conventional PCR	HBV DNA	Moderate	4–6 hours	Simple, low cost
Real-Time PCR (qPCR)	HBV DNA	High	2–3 hours	Quantitative, sensitive
Digital PCR (dPCR)	HBV DNA/RNA	Very high	3–4 hours	Absolute quantification
TMA	HBV RNA	Very high	2 hours	Detects low-level RNA
LAMP	HBV DNA	High	<1 hour	Field adaptable
NGS	Whole genome	Ultra-high	Days	Genotyping, mutation detection

Table 3: Clinical Significance of Occult Hepatitis B Infection (OBI)

Feature	Description
Serology	HBsAg negative, Anti-HBc positive
Viral Load	Very low or undetectable HBV DNA
Risk Groups	Immunosuppressed, transfusion recipients
Clinical Risk	Reactivation, hepatocellular carcinoma
Diagnostic Challenge	Requires sensitive molecular assays

Table 4: Barriers to Molecular HBV Diagnostics in Low- and Middle-Income Countries

Barrier	Impact
High equipment cost	Limited access to PCR platforms
Reagent availability	Interrupted testing services
Skilled manpower shortage	Reduced diagnostic accuracy
Infrastructure gaps	Poor cold-chain and power supply
Out-of-pocket payment	Low patient uptake

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