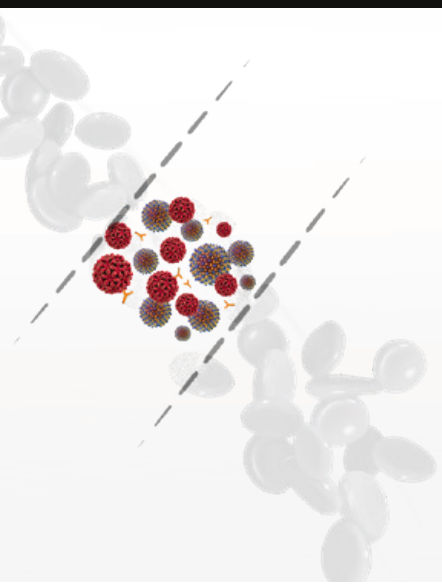

Eradicating HBV: A Global Initiative

Important updates support viral elimination goals and propel test demand

Hepatitis B virus (HBV)

Despite the availability of an effective vaccine, chronic HBV remains a significant global burden.[1-3]

Most HBV infections remain undiagnosed, with approximately 1.2 million new infections occurring yearly.[2,4] Deaths from viral hepatitis increased from 1.1 million in 2019 to 1.3 million in 2022, with 83% associated with chronic HBV.[5] Efficacious therapies for HBV exist and, while not curative, can significantly reduce morbidity, mortality, and onward transmission.[1,4-6] Global programs have set specific targets toward elimination (Table 1), with increased testing to identify infection a vital component.[7,8]

Table 1. Viral hepatitis elimination programs: A global initiative.*

WHO Global Health Sector Strategy (GHSS) on Viral Hepatitis[7]

2030 TARGET:
Reducing deaths from HBV by 65%, an 80% treatment rate for chronic HBV, and a 90% reduction in chronic infections.

Viral Hepatitis National Strategic Plan (U.S.)[8]

2030 TARGET:
Identifying 90% of infections with linkage to care and an 80% treatment rate.

Lack of awareness

39%
INCREASE IN DEATHS
Projected 2015–2030

Even with aggressive elimination goals, annual global deaths from HBV are projected to increase by 39% from 2015 to 2030 without significant improvement in detection and treatment.[5,9] A major barrier to elimination efforts is the existing majority of people unaware of their infection who may unknowingly transmit and/or develop serious liver disease.[1-3] For 2022, the WHO reported only 13% of people living with chronic HBV had been diagnosed and only 3% received antiviral therapy.[2] In many regions, mother-to-child transmission of HBV remains significant source of chronic HBV.[3] While rates of vaccination are generally higher for children, coverage is incomplete, and the majority of adults remain unvaccinated.[1-3,8]

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Expanded HBV serology testing is essential and recommended

To improve detection of unidentified HBV infections, updated testing guidance broadens suggested testing populations as well as the assays recommended (Table 2). Laboratory-based immunoassays are preferred when available.[1]

- The updated U.S. CDC recommendations now advocate for universal testing at least once for HBV for all adults regardless of risk, with repeat testing for those at elevated risk.[1]
- Testing (termed "triple-panel test") for three HBV analytes (HBsAg, Anti-HBs, Total anti-HBc) over prior guidance of HBsAg alone is now advised by the CDC to improve detection and identify those who may benefit from vaccination.[1]

Table 2. Recommended testing for HBV to identify chronic infection.

Recommending Body	Who to Test	Primary Screening Assay(s)† Recommended
WHO[2-6]	All adults in settings with ≥2% prevalence. Repeat testing based on risk. All pregnant women during each pregnancy.	HBsAg
CDC[1]	Adults aged ≥18 years at least once, with repeat testing based on risk. All pregnant women during each pregnancy.	Triple panel (HBsAg, Anti-HBs, Total anti-HBc).
Asian Pacific Association for the Study of the Liver[10]	High-risk individuals and all pregnant women.	HBsAg (Anti-HBs, Total anti-HBc may be used in conjunction.)
EASL[11] (European Association for the Study of Liver Disease)	HBV suspected or high risk.	HBsAg (Anti-HBs, Total anti-HBc may be used in conjunction.)

Table 3 defines the CDC-recommended triple-screen analytes and indications when reactive. Once chronic HBV infection is identified, further testing for HBeAg, anti-HBe, and HBV DNA can provide information on viral replication and infectivity and help guide clinical management.[1,9-11] An HBV Core IgM test is useful to aid cases of suspected acute infection.[1,9-11]

Table 3. Triple screening for HBV (source: CDC).[1]

Assay	Indication
HBsAg	HBV infection‡ (considered chronic if it remains detectable >6 months)
Anti-HBs	Immune§ (from vaccination or resolved infection). Those with low or absent antibody levels may benefit from vaccination.
Total anti-HBc	History of HBV infection (acute, chronic, resolved). May be useful to identify occult infections** or those at higher risk of reactivation.

Economic impact of triple-panel screening

The updated CDC testing recommendations include an analysis of the predicted economic impact of universal testing, identifying expected reductions in cirrhosis, liver cancer, and need for liver transplant.[1] Data indicates the economic impact of universal screening with the triple panel would be cost-effective, with an estimated incremental cost-effectiveness ratio of $11,207 per quality-adjusted life year. Cost-savings are also projected for the WHO HBV elimination efforts.[12]

Focus on testing: Impact of HBV diversity

Mutant HBsAg vs. wildtype infections

HBV's unique replication process and immune pressure are associated with a higher frequency of viral mutations, including in the HBsAg protein targeted by most immunoassays.[13-19] Mutations in the HBsAg region can include one or more changes.

Mutations could result in missed infections (false negatives) if the assay design is incapable of recognizing the altered epitope(s). Many manufacturers of automated HBsAg assays now offer assays capable of broad genotypic wildtype and mutant detection, typically accomplished by targeting more than one epitope in the antigen.[15,17,20,21]

Published and other data (such as manufacturer product inserts) indicate many automated assays are now capable of broad detection, including naturally occurring HBsAg mutants with single, double, and even triple mutations.[15,20,21] In a large head-to-head study comparing routinely available automated HBsAg assays, highly comparable detection was observed across 52 different HBsAg mutants (Table 4).[15]

Table 4. Comparable detection of HBsAg mutants with four automated assays.[15]

HBsAg assay (qualitative)	ADVIA Centaur XP HBsAg II	Abbott ARCHITECT HBsAg II	Roche ELECSYS HBsAg II	DiaSorin LIAISON HBsAg
Detection of 52 known HBsAg diagnostic and escape mutations	100%	100%	100%	100%

Choosing an assay: Comparative performance among commonly available automated HBsAg tests

While HBsAg mutants are well-documented, the majority of HBV infections still involve wildtype surface antigen, so sensitive detection of mutant and wildtype forms of HBsAg is necessary.[13,14,16,18,19] Multiple studies investigating the comparative performance (including mutants and wildtype) of routinely available automated assays indicate similar clinical performance and good concordance, although some differences have been observed (see Tables 5 and 6 for examples).[15,22-24]

- When comparing assays, it's essential to understand the study design when interpreting the data. Study designs vary, including use of samples initially selected by one manufacturer's assay then tested with other assays, or comparison of individual results vs. a consensus agreement (using multiple assays tested with the same samples).
- Other options can include evaluating samples for viral DNA, patients' clinical history, or other HBV markers to help discriminate true positives vs. negatives.

Assessing individual HBsAg assay performance using consensus agreement

To limit potential bias in cases with preselected samples, a consensus approach can be used (correlation of the individual result to the overall group results to assign sample reactivity status). Table 5 shows published data for HBsAg that included a consensus approach and supports the good performance between the assays. Percent agreement refers to the consensus, not individual results (although individual correlations were also included in the study).

Table 5. Correlation to consensus (samples initially selected on Abbott ARCHITECT system).[22]

Platform	Assay	Sensitivity	Specificity	Percent Agreement
Atellica IM	HBsAg II (qual)	100%	100%	100%
ARCHITECT	HBsAg (qual)	100%	92.9%	96.0%
ALINITY i	HBsAg II (qual)	100%	98.2%	99.0%
LIAISON	LIAISON XL HBsAg††	100%	100%	100%

Assessing individual HBsAg assay performance using concordance to a single assay

Another study method used is concordance (agreement) between individual assay results. Samples can either be prospective or previously selected on a specific analyzer/assay. Table 6 shows concordance data from a study using HBsAg samples initially tested on the Abbott ARCHITECT system, then evaluated for HBsAg on the alternate platforms (including the Abbott ALINITY I system).[22] While some minor discordance was noted, the authors observed overall high (>98%) concordance rates between HBsAg assays.

Table 6. Agreement between individual HBsAg assays.[24]

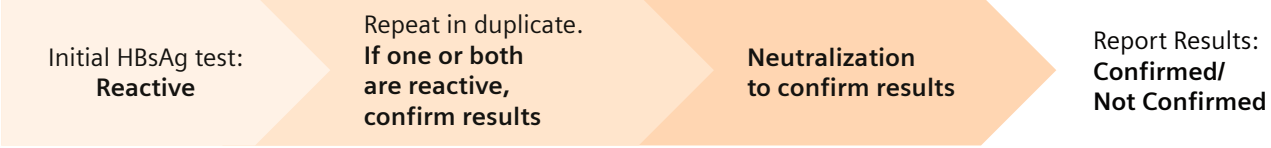
Analyzers (HBsAg assays)	Percent Agreement for Initially Reactive HBsAg Results‡‡
Atellica IM/COBAS e 801	98.6%
ALINITY i/Atellica IM	98.7%
ARCHITECT i2000/Atellica IM	99.3%
ARCHITECT i2000/ALINITY i	99.6%
ALINITY i/COBAS e 801	98.7%
ARCHITECT i2000/COBAS e 801	99.0%

Leveraging workflow to expedite HBsAg testing

Access to high-performing assays is important for clinical accuracy, but with rising test demand, these assays must also offer testing efficiencies, including throughput capacity and turnaround times. Labs are increasingly being asked to do more, often with fewer resources. Workflow advantages associated with the platform or the assay itself can help meet these demands.

Testing volume for HBsAg is often significant in labs offering routine ID immunoassays, associated in part with recommendations for universal testing of adults[1] and in each pregnancy.[1,2-6,10] To improve accuracy when reporting a reactive result, multiple manufacturers of automated HBsAg immunoassays suggest confirming all initially reactive samples in their package inserts.[20,25,26] A commonly recommended approach for automated assays is shown in Figure 1.

Figure 1. Confirmation of initially-reactive HBsAg samples.[20,25,26]



Two unique workflow benefits help mitigate time and cost associated with confirming all initial reactive samples when using Siemens Healthineers HBsAg II:

1 A single-value rule-in (the "Hot Zone") reduces the need for repeat testing

- If the HBsAg II sample is initially >50.0 Index or flagged as "> Index Range," the specimen is reactive (positive) for hepatitis B surface antigen, and no further HBsAg testing is required.[§§ 20]
- While samples initially >50 Index can avoid further testing, samples with an initial Index 1.0–50.0 should be repeated in duplicate and neutralized if one/both repeat reactive.[20]
- **Index >50 represents an additional approved single-value rule-in.** Reactive samples with an Index 1–50 are not considered indeterminate but, like other HBsAg assays, benefit from repeat testing and neutralization to confirm.
- Applying the Hot Zone may significantly reduce the need to repeat and confirm (Table 7).[27]

2 Fully automated HBsAg II testing, from initial reactive samples through confirmation (the "SMART Algorithm")

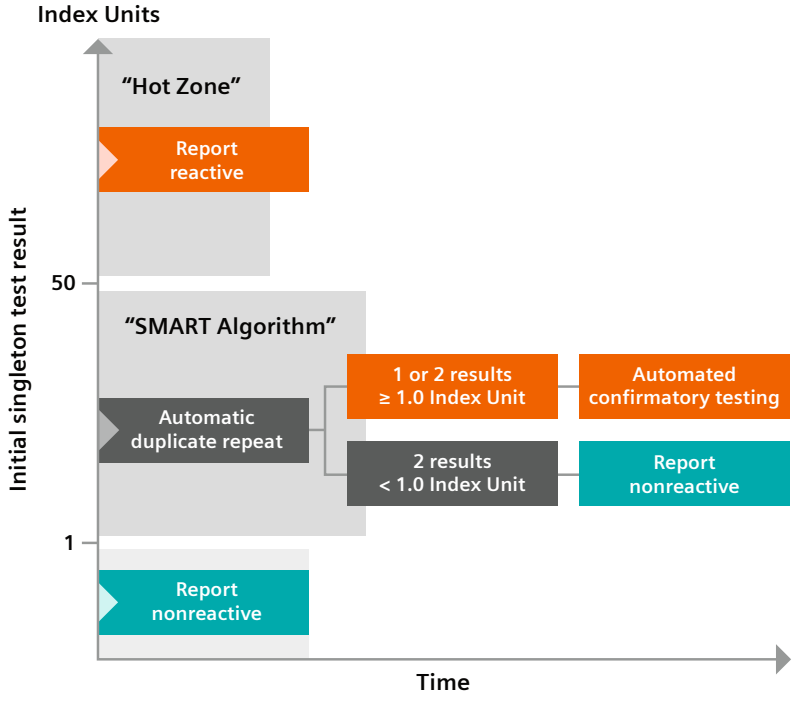
- When using Atellica or ADVIA Centaur IA analyzers, HBsAg II testing can be fully automated, from initial reactive through repeat and confirmatory testing (including dilutions if needed).[27]***
- Time to reportable (initial reactive results confirmed) in as little as 2 hours.[27]†††
- The SMART Algorithm is especially useful when performing higher-volume HBsAg II testing.

Table 7. The HBsAg II "Hot Zone" can reduce the need for additional testing with initially reactive results >50 Index.[27]

ADVIA Centaur HBsAg *Testing Stage*	Without Hot Zone # tests (# samples)	With Hot Zone # tests (# samples)
Initial testing	52 (52)	52 (52)
Repeat testing	104 (52)	4 (2)
Confirmatory testing of neat sample	104 (52)	4 (2)
Confirmatory testing of 1:50 sample dilution	70 (35)	0 (0)
Confirmatory testing of 1:2500 sample dilution	0 (0)	0 (0)
Total tests used	330	60

Application of the Hot Zone and use of the SMART Algorithm can improve efficiencies and mitigate delays in reporting HBsAg results (Figure 2).

Figure 2 (right). Reduce the need for operator intervention and improve reporting times when using the Atellica HBsAg II.



Additional workflow advantages on Atellica IM Analyzer: Consolidation of ID and other testing

- Some ID tests can be longer assays that, on some analyzers, may delay TAT on STAT requests when processing.
- On Atellica IM Analyzer, data show longer assays that include ID can reliably be run on a single analyzer without compromising TAT when a STAT request is added. Data in Table 8 shows minimal impact on time for cardiac troponin even when running a high percent of ID assays.[28]
- ID assays can also be run as STAT when needed, even if routine ID assays are in process.

Table 8. Impact on STAT tests on TAT using the 90th percentile based on percent of ID assays being run.[28]

% ID Tests	0%	1–9%	10–19%	20–29%	30–39%	40–49%
Samples (n)	54,427	20,767	22,425	13,029	6109	2367
90th percentile (min)	11.6	11.3	11.4	11.7	11.4	11.5

Conclusion

Testing and linkage to care are critical to viral hepatitis elimination, including HBV. Comparable performance of the SH HBsAg II assay is demonstrated in clinical studies, supporting routine use. HBsAg II and other infectious disease (ID) assays can be reliably run together on a single Atellica IM platform with minimal impact on TAT for other assays, including STAT.

Workflow benefits such as the HBsAg II single-value rule-in (Hot Zone) and the fully automated SMART Algorithm can enhance productivity and reduce the need for manual intervention.

Talk to your Siemens Healthineers representative to learn how Atellica Solution can support increasing test demand and provide workflow efficiencies while delivering clinical confidence across the ID assay menu.

> Talk to your Siemens Healthineers representative to learn how Atellica Solution can support increasing test demand and provide workflow efficiencies while delivering clinical confidence across the ID assay menu, or visit siemens-healthineers.com

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* Additional information can be found at https://www.globalhep.org/.
† Viral hepatitis assays from Siemens Healthineers are not approved for blood bank screening in the U.S.
‡ HBsAg assays may be transiently positive following HBV vaccination.
§ Immunity generally assessed as levels ≥10 mIU/mL.[1]
** Occult infection defined as replication-competent HBV DNA is present in the liver (may be present or absent in blood), but HBsAg is non-detectable.
†† The LIAISON HBsAg quant is available OUS and was used in this analysis.
‡‡ In cases of discordance, repeat testing was not done due to limited sample availability.
§§ When Atellica IM HBsAg II assay is used as a stand-alone assay (for example, in pregnant women being screened to identify neonates who are at risk for acquiring HBV during the perinatal period), it is suggested that Atellica IM HBsII Conf assay be used to confirm the result.[20]
*** Confirmatory reagents must be onboard.
††† For samples requiring an additional dilution for neutralization, time to reportable is longer.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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