Access
Immunoassay Systems

HBc IgM
REF 34250

Intended Use

The Access HBc IgM assay is a paramagnetic-particle, chemiluminescent immunoassay for the detection of IgM antibody to core antigen of hepatitis B virus in human serum and plasma using the Access Immunoassay Systems.

Summary and Explanation

In the course of a primary infection by hepatitis B virus, the anti-HBc antibodies are the first to appear after the HBs and Hbe antigens. IgM antibodies are synthesized in first, they persist for a few weeks to a few months then disappear progressively during the convalescence when IgG remain for several years after recovery.

Therefore anti-HBc IgM are admitted to be a specific marker to viral hepatitis B in acute phase. Low levels can be detected in the course of chronic hepatitis but their significance remains unclear.[1,2,3,4,5,6,7,8,9]

Therefore the detection of anti-HBc IgM antibody allows to establish the diagnosis of a recent infection by hepatitis B virus, all the more when the HBs and HBe antigens are not any more detected before even the appearance of anti-HBs antibodies (serological "window").[1,5,10,11] The presence of this marker allows also to differentiate an acute hepatitis and a chronic hepatitis.[2,5,6,9,10]

Principles of the Procedure

The Access HBc IgM assay is a qualitative two-step enzyme immunoassay based on the principle of serum IgM immunocapture on the solid phase. In the first step, the sample (serum, plasma or control) is added to the reaction vessel with paramagnetic particles coated with anti-human antibody (chain μ). The specific and non specific IgM in the sample are captured by the solid phase during the first incubation. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. In the second step, IgM specific to the virus B core are identified by the corresponding HBc antigen - alkaline phosphatase conjugate. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is proportional to the amount of enzyme conjugate present at the end of the reaction, therefore to the anti-HBc IgM antibody level present in the tested sample. By comparison of the light intensity with the cut-off value determined during the test calibration on the instrument, it is thus possible to determine the presence or absence of anti-HBc IgM antibody in the sample.

Product Information

Access HBc IgM Reagent Pack

Cat. No. 34250: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 28 days after initial use.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.
- Signs of possible deterioration are a broken elastomeric layer on the Pack or quality control values out of range.

R1a:	Paramagnetic particles coated with sheep anti-human IgM antibody suspended in TRIS saline, with surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	Special wash buffer with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1c:	Recombinant (E. coli) HBc antigen - alkaline phosphatase (bovine) conjugate in PBS with surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patients samples may be routinely processed with minimum risk if the presented procedure is followed. However, handle these products as potentially infectious, regardless of their origin, treatment or prior certification. Follow universal laboratory precautions in storing, handling and disposing of these material and their containers.[12]
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[13]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum or plasma (heparin, EDTA or citrate) are the recommended samples. The blood preservatives ACD, CPD and CPDA are compatible with the assay.
2. Observe the following recommendations for handling, processing, and storing blood samples:[14]
   - Collect all blood samples observing routine precautions for venipuncture.
   - Allow serum samples to clot completely before centrifugation.
   - Keep tubes stoppered at all times.
   - Within two hours after centrifugation, transfer at least 500 µL of cell-free sample to a storage tube. Tightly stopper the tube immediately.
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than eight hours.
   - If the assay will not be completed within eight hours, refrigerate the sample at 2 to 8°C.
   - If the assay will not be completed within 48 hours, or for shipment of samples, freeze at -20°C or colder.
   - Thaw samples only once.
3. Use the following guidelines when preparing specimens:
   - Ensure residual fibrin and cellular matter have been removed prior to analysis.
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
4. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
5. Samples containing up to 80 mg/L bilirubin, lipemic samples containing the equivalent of 36 g/L triolein and hemolyzed samples containing up to 10 g/L hemoglobin do not affect the result. However, it is recommended to use clear and non hemolyzed samples.
6. Do not use heat-inactivated samples for this assay.

Materials Provided

R1 Access HBc IgM Reagent Packs

Materials Required But Not Provided

1. Access HBc IgM Calibrators
   Negative and positive for anti-HBc IgM antibody.
   Cat. No. 34255
2. Quality control materials: Access HBc IgM QC
   Cat. No. 34259
3. Access Substrate
   Cat. No. 81906
4. **Access, Access 2:**
   Access Wash Buffer II, Cat. No. A16792
   UniCel DxI:
   UniCel DxI Wash Buffer II, Cat. No. A16793

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use ten (10) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The first result is obtained within 35 minutes.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

Calibration data determining the assay cut-off value is valid for 28 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality controls are recommended at least every 24 hours and upon system start-up prior to running patient samples. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Use the suggested product, Access HBc IgM QC, or include quality control sera from other sources. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Results of the Access HBc IgM assay performed on the patient samples are automatically calculated by the system software using the cut-off value determined by the active calibration. Results are reported as "reactive" or "non-reactive" in function of their ratio with the cut-off value (signal greater than and equal to or lower than the cut-off value). However, results located 20% below the cut-off value should be carefully interpreted and retested in duplicate. This gray zone (0.8–1.0) must be saved in memory by the user (refer to the appropriate system manuals and/or Help system for complete instructions on gray zone for a qualitative assay). A flag ("equivocal"), which is automatically reported, allows the user to quickly spot a result

located within the gray zone. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing results.

Any sample found reactive in the first test should be re-tested in duplicate. If the initial result is repeated, the sample is considered positive for the Access HBc IgM assay.

If a result is found within the grey zone for a sample ("equivocal"), it is recommended that the patient be closely monitored. New samples should be collected and tested at approximately weekly intervals to distinguish rising levels of anti-HBc IgM (associated with acute hepatitis B infections) from falling or unchanging levels (consistent with recovery or a possible evolution towards chronic infection).

Limitations of the Procedure

1. The Access HBc IgM assay is strictly limited to the detection of anti-HBc IgM antibody in human serum or plasma.
2. The serological diagnosis of acute hepatitis B can not be only based on the IgM antibody detection using the Access HBc IgM. A positive result must be compared with symptoms and the patient history and other biological markers (associated serological markers of hepatitis B; load of viral DNA) are necessary to establish such a diagnosis. This assay does absolutely not reflect the patient immune status, because the anti-HBc IgM antibody are not measured for that purpose.
3. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[15,16]
   Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
4. The Access HBc IgM results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests and other appropriate information.

Specific Performance Characteristics

Results below were generated in internal and external studies.

Intra-Assay Imprecision

Intra-assay imprecision was determined with a panel of 4 sera defined as follows:

S1	negative serum
S2	low positive serum
S3	positive serum
S4	high positive serum

Each serum was tested 30 times in the same run and results are expressed in ratio: S/CO. The variation coefficients obtained are lower than 7% (Table 1).

Table 1: Intra-assay imprecision of the Access HBc IgM assay

Panel	Mean (n = 30) S/CO ratio	CV%
Serum 1	0.01	6.87
Serum 2	2.08	6.34
Serum 3	3.87	4.32
Serum 4	8.23	3.02

Reproducibility

The reproducibility (samples tested in triplicate twice a day, 5 different days) performed on the same sera provided variation coefficient values ranging from 2.7%–13.2%. The variation coefficient of the positive sera is lower than 4% (Table 2).

Table 2: Reproducibility of the Access HBc IgM assay

Panel	Mean (n = 30) S/CO ratio	CV%
Serum 1	0.01	13.2
Serum 2	1.90	3.13
Serum 3	3.95	3.51
Serum 4	8.30	2.71

Sensitivity

Acute hepatitis diagnosis

The sensitivity of the Access HBc IgM assay was evaluated after the analysis of 220 samples from patients with an acute or recent hepatitis B infection and tested in our laboratories and in an external evaluation site. The studied population consisted of 37 follow-ups of acute hepatitis and 9 seroconversions as well as samples isolated and clinically documented.

In all the studied seroconversion samples, the detection of anti-HBc IgM antibody was early and in perfect accordance with other clinical and biological data, which ensures the effectiveness of the Access HBc IgM technique for the acute hepatitis diagnosis. Results obtained for all the samples, compared with a second commercially available EIA technique, demonstrated a 97% agreement (213/220) between the two techniques. The observed discrepancies corresponded to sera collected at the end of the acute phase or during the convalescence period. A very good correlation between the analytical results and the clinical biological data associated with these sera attests to the ability of the Access HBc IgM assay to confirm acute or resolved infections due to the hepatitis B virus with a good sensitivity.

Chronic hepatitis follow-up

Samples from 130 patients with chronic hepatitis B, including 18 follow-up and 38 isolated and documented samples, were tested. In 98% of the samples (127/130), the obtained results correlated perfectly with the comparative EIA. Fifteen samples were found positive with the Access HBc IgM assay and 18 with the comparative assay.

With regard to the discrepant results, three hepatitis B follow-ups, the detection of low titer IgM due to hepatitis B reactivation is proven by the presence of viral DNA in these samples. Nevertheless, the absence of IgM demonstrated by the Access HBc IgM assay is consistent with the absence of hepatic cytolysis.

Globally, the Access HBc IgM assay shows very good sensitivity, ensuring the early detection of anti-HBc IgM during the infection with the hepatitis B virus. It allows confirmation of an acute or a recent infection in association with the other hepatitis B markers.

Specificity

The assay specificity was estimated on a population considered negative, called run-of-the-mill. Among all the tested samples, 1000 samples from blood donors were tested in our laboratories and 551 samples from hospitalized patients were tested in an external evaluation site, no reactive result was found. This study demonstrates a 100% specificity (1551/1551).

Specificity – selected populations

The specificity of the Access HBc IgM assay was also evaluated on samples positive for rheumatoid factor and autoantibodies, on samples positive for different viral and parasitic infections, on samples from groups at risk (drug addicts, hemodialysed patients, etc.) or other origins with an interference potential. The results of this cross-reactivity study, made with 603 sera, tested in our research center and in an external evaluation site, are summarized in Table 3.

Table 3: Specificity of the Access HBc IgM assay (selected populations)

Pathology	Number of samples tested (†)	Reactive samples	Specificity %
Autoimmune diseases	**55**	**0**	**100%**
Antinuclear factors	21	0	
Rheumatoid factor	34	0	
Viral and parasitic infections including:	**219**	**0**	**100%**
HAV (IgM, IgG)	20	0	
HCV	10	0	
HEV (IgM, IgG)	10	0	
CMV (IgM, IgG)	20	0	
EBV (IgM, IgG)	20	0	
HSV (IgM, IgG)	22	0	
VZV (IgM, IgG)	20	0	
Yellow Fever	12	0	
Mumps (IgM, IgG)	20	0	
Rubella (IgM, IgG)	20	0	
Poliomyelitis	35	0	
Toxoplasmosis (IgM)	10	0	
Groups at risk	**67**	**1 (equiv)**	**98.5%**
Hemodialized	14	1 (equiv)	
Hemophilic	15	0	
HIV positive	25	0	
Drug addicts	13	0	
Other origins	**262**	**0**	**100%**
Myeloma	15	0	
Hepatocellular carcinoma	5	0	
Pregnant women	107	0	
Vaccinated patients	135	0	
TOTAL	**603**	**1**	**99.8%**

(†) Retrospective samples frozen and thawed several times

In conclusion, the specificity estimated during the analysis of healthy adult subjects or hospitalized patients with various pathology is excellent.

Interference

A study on the possible influence of anticoagulant agents was also made: 248 serum and plasma samples were tested and no significant difference was demonstrated between the raw signals obtained from the plasma samples and the corresponding serum samples (19 analyses using serum and the corresponding plasma types: heparin, citrate, ACD, CPDA, and CPD; plus 69 serum/EDTA plasma pairs.)

Access
Immunoassay Systems

HBc IgM CALIBRATORS

REF 34255

Intended Use

The Access HBc IgM Calibrators are intended for use with the Access HBc IgM assay for the detection of IgM antibody to core antigen of hepatitis B virus in human serum and plasma using the Access Immunoassay Systems.

Summary and Explanation

The Access HBc IgM Calibrators are used to establish calibration (determine the cut-off value) for the Access HBc IgM assay. By comparing the light intensity generated by a sample to the cut-off value, it is possible to determine the presence or absence of anti-HBc IgM antibody in the sample.

Traceability

The measurand (analyte) in the Access HBc IgM Calibrators is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access HBc IgM Calibrators
Cat. No. 34255: C0 and C1, 1.0 mL/vial

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Mix contents by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Open vial stability is typically until the expiration date stated on the vial label when properly stored and handled.
- Signs of possible deterioration are quality control values out of range.

C0:	Negative calibrator: human serum negative for anti-HBc IgM antibody, < 0.1% sodium azide and 0.5% ProClin** 300.
C1:	Positive calibrator: human defibrinated plasma and serum, positive for anti-HBc IgM antibody, < 0.1% sodium azide and 0.5% ProClin 300.
Calibration Card:	1

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- C0: Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis B, Hepatitis C (HCV), and Human Immunodeficiency Virus (HIV-1 and HIV-2). Because no known test method can offer complete assurance that

infectious agents are absent, handle reagents and patient samples as if capable of transmitting infectious disease.[12]

- C1: The positive calibrator, containing HBs Ag and HBe Ag, was inactivated by a photoinactivation procedure in presence of methylene blue.[17,18,19] Because the inactivation method being used and the verification of the treatment effectiveness cannot offer complete assurance, handle this reagent with usual precautions.[12] Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV-1 and HIV-2).
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[13]
- Xi. Irritant: 0.5% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

The Access HBc IgM Calibrators are provided as:

C0	negative (non-reactive) for anti-HBc IgM antibody
C1	positive (reactive) for anti-HBc IgM antibody.

The Access HBc IgM assay requires a calibration (determination of the cut-off value) every 28 days in order to have an active calibration. A calibration of the Access HBc IgM assay requires approximately 150 µL (4 drops per sample cup) of each HBc IgM Calibrator (cut-off value determined by running C0 in duplicate and C1 in triplicate).

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Access
Immunoassay Systems

HBc IgM QC
REF 34259

Intended Use

The Access HBc IgM QC is intended for monitoring system performance of the Access HBc IgM assay.

Summary and Explanation

The Access HBc IgM QC is intended for monitoring system performance of the Access HBc IgM assay. It is recommended to use a quality control to detect and correct procedure errors inherent to kit handling, quality or to the instrument being used. In addition, they are an integral part of good laboratory practices.[20,21,22,23,24,25] Negative and positive quality controls are provided to allow performance monitoring in the most relevant areas of the assay range.

Traceability

The measurand (analyte) in the Access HBc IgM QC is traceable to the manufacturer's working calibrators. Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of QC and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access HBc IgM QC

Cat. No. 34259: 2.5 mL/vial, 3 vials each level

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Mix contents by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- After initial use, vials are stable for 30 days when correctly handled and stored.
- Signs of possible deterioration are quality control values out of range.

QC 1:	Human serum negative (non-reactive) for anti-HBc IgM antibody, < 0.1% sodium azide and 0.5% ProClin** 300.
QC 2:	Human defibrinated plasma and serum, positive (reactive) for anti-HBc IgM antibody, < 0.1% sodium azide and 0.5% ProClin 300.
QC Value Card:	1

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- QC 1: Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis B, Hepatitis C (HCV), and Human Immunodeficiency Virus (HIV-1 and HIV-2). Because no known test method can offer

complete assurance that infectious agents are absent, handle reagents and patient samples as if capable of transmitting infectious disease.[12]

- QC 2: The positive QC 2, containing HBs Ag and HBe Ag, was inactivated by a photoinactivation procedure in presence of methylene blue.[17,18,19] Because the inactivation method being used and the verification of the treatment effectiveness cannot offer complete assurance, handle this reagent with usual precautions.[12] Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV-1 and HIV-2).
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[13]
- Xi. Irritant: 0.5% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

The Access HBc IgM QC should be treated in the same manner as patient specimens and run in accordance with the instructions accompanying the instrument being used. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[23] More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws.

Note: Refer to the appropriate system manuals and/or Help system for information on quality control theory, configuring quality controls, quality control sample test request entry, and reviewing quality control data.

To process a single determination of the Access HBc IgM QC on the Access Immunoassay System, a minimum of 150 µL per sample cup (4 drops) is required for each level.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Expected Values

The expected values for the Access HBc IgM QC are provided on the QC value card contained in the Access HBc IgM QC kit. Results obtained by the user laboratories should fall within the stated ranges. Variations, such as in technique, equipment, or reagents may result in values different from those listed. However, each laboratory should establish its own mean value and acceptable ranges after sufficient data has been collected.[25]

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