Abbott AxSYM® System

AxSYM CORE-M 2.0
List No. 8B89
66-8429/R1

AxSYM CORE-M™ 2.0

IgM Antibody to Hepatitis B Virus Core Antigen (IgM Anti-HBc)

Customer Service
United States: 1-877-4ABBOTT

This package insert must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

CAUTION:

United States Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to, by, or on the order of a physician.

ABBOTT LABORATORIES
Diagnostics Division
Abbott Park, IL 60064 USA

Printed in USA

34

NAME

AxSYM CORE-M™ 2.0

INTENDED USE

AxSYM CORE-M 2.0 is a microparticle enzyme immunoassay (MEIA) intended for the qualitative detection of IgM antibody to hepatitis B virus core antigen (IgM anti-HBc) in adult and pediatric serum (including serum collected in serum separator tubes) or plasma (collected in potassium EDTA, sodium citrate, sodium heparin, lithium heparin, or plasma separator tubes). The assay is used as an aid in the diagnosis of acute or recent hepatitis B virus (HBV) infection in conjunction with other laboratory results and clinical information.

WARNING: Not intended for use in screening blood, plasma, or tissue donors. The effectiveness of AxSYM CORE-M 2.0 for use in screening blood, plasma, or tissue donors has not been established.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. The user is responsible for establishing their own assay performance characteristics in these populations.

SUMMARY AND EXPLANATION OF THE TEST

Virus specific IgM antibody has been detected in most acute viral infections and is a reliable marker for acute viral disease. High levels of IgM anti-HBc have been detected in patients with acute HBV infection[1-6] and low levels have been detected in some patients with chronic HBV infection.[7,8] Differentiation of acute and chronic HBV infection on the basis of viral markers such as HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc is difficult because most of these markers are seen during both acute and chronic disease.[1] In cases where these markers are present, acute illness with other agents such as hepatitis C, non-A, non-B, non-C hepatitis, and delta hepatitis may confuse the diagnosis.[9] Several studies have demonstrated that IgM anti-HBc is the only specific marker for the diagnosis of acute HBV infection.[4-5,10-13]

Samples with Index Values greater than 1.20 are considered reactive by AxSYM CORE-M 2.0 indicating presumptive evidence of IgM anti-HBc. Samples with Index Values from 0.80 to 1.20 are considered gray zone reactive by AxSYM CORE-M 2.0 and patients should be retested at approximately one-week intervals to distinguish between early and late acute HBV infection. Samples with Index Values less than 0.80 are considered nonreactive by AxSYM CORE-M 2.0. A nonreactive test result does not exclude the possibility of exposure to or infection with HBV.

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

AxSYM CORE-M 2.0 is based on MEIA technology and utilizes the principle of direct binding of the IgM anti-HBc in the sample to anti-human IgM coated microparticles, and detection of the IgM anti-HBc by rHBcAg, followed by anti-HBc (human):alkaline phosphatase conjugate. The AxSYM CORE-M 2.0 reagents and sample are pipetted in the following sequence:

SAMPLING CENTER

- Sample and all AxSYM CORE-M 2.0 reagents required for one test are pipetted by the Sampling Pipettor into various wells of a Reaction Vessel (RV).
- The RV is immediately transferred into the Processing Center. Further pipetting is done in the Processing Center by the Processing Pipettor.

PROCESSING CENTER

- Antibody to Human IgM (Goat) Coated Microparticles are dispensed onto the Matrix Cell. The microparticles bind irreversibly to the glass fiber matrix.
- Sample diluted in Specimen Diluent is dispensed onto the Matrix Cell. IgM present in the sample binds to the Antibody to Human IgM (Goat) Coated Microparticles.
- The Matrix Cell is washed with Matrix Cell Wash to remove materials not bound to the microparticles.
- Hepatitis B Virus Core Antigen (*E. coli*, Recombinant) (rHBcAg) is dispensed onto the Matrix Cell and binds to any IgM anti-HBc present in the sample that has bound to the microparticles, forming an antibody-antigen complex.
- Antibody to Hepatitis B Virus Core Antigen (Human):Alkaline Phosphatase Conjugate is dispensed onto the Matrix Cell and binds with microparticle-bound antibody-antigen complex forming an antibody-antigen-antibody complex.
- The Matrix Cell is washed with Matrix Cell Wash to remove materials not bound to the microparticles.
- The substrate, 4-Methylumbelliferyl Phosphate (MUP), is added to the Matrix Cell, and the fluorescent product is measured by the MEIA optical assembly.

The presence or absence of IgM anti-HBc in the sample is determined by comparing the rate of formation of fluorescent product to the mean Index Calibrator rate, which is calculated from a previous AxSYM CORE-M 2.0 Index Calibration, to determine an Index Value. Samples with Index Values greater than 1.20 are considered reactive by AxSYM CORE-M 2.0. Samples with Index Values from 0.80 to 1.20 are considered gray zone reactive by AxSYM CORE-M 2.0. Samples with Index Values less than 0.80 are considered nonreactive by AxSYM CORE-M 2.0.

For further information regarding MEIA technology, refer to the AxSYM System Operations Manual, Section 3.

REAGENTS

REAGENT KIT, 100 TESTS

AxSYM CORE-M 2.0 Reagent Pack (8B89-20)*

- 1 Bottle (17.6 mL) Hepatitis B Virus Core Antigen (*E. coli*, Recombinant) in TRIS buffer with protein (10% bovine) stabilizer. Minimum concentration: 0.175 µg/mL. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents. (Reagent Bottle 1)
- 1 Bottle (12.2 mL) Antibody to Hepatitis B Virus Core Antigen (Human):Alkaline Phosphatase Conjugate in TRIS buffer with protein (1% bovine) stabilizer. Minimum concentration: 0.1 µg/mL. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents. (Reagent Bottle 2)
- 1 Bottle (10.5 mL) Antibody to Human IgM (Goat) Coated Microparticles in TRIS buffer with protein (0.05% porcine) stabilizer. Minimum concentration: 0.06% solids. Preservative: 0.1% Sodium Azide. (Reagent Bottle 3)
- 1 Bottle (50.2 mL) Specimen Diluent containing 0.3 M Sodium Chloride in TRIS buffer. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents. (Reagent Bottle 4)

Index Calibrator

1 Bottle (5.5 mL) AxSYM CORE-M 2.0 Index Calibrator is recalcified IgM anti-HBc positive human plasma. Minimum titer = 1:1.
Preservative: 0.1% Sodium Azide. Dye: Green (Acid Yellow No. 23 and Acid Blue No. 9).

* 8B89-66 includes the AxSYM CORE-M 2.0 Reagent Pack and Index Calibrator (100 tests), Reaction Vessels (100 each), and Matrix Cells (100 each).

AxSYM CORE-M 2.0 Controls (8B89-10) (sold separately)

2 Bottles (7.4 mL each) of AxSYM CORE-M 2.0 Controls:

- The Negative Control (1 Bottle) is recalcified IgM anti-HBc negative human plasma. Preservative: 0.1% Sodium Azide.
- The Positive Control (1 Bottle) is recalcified IgM anti-HBc positive human plasma in recalcified IgM anti-HBc negative human plasma. Preservative: 0.1% Sodium Azide.

The AxSYM CORE-M 2.0 Controls have the following ranges:

Control	Color	IgM Anti-HBc (Minimum Titer)	Control Range (Index Value)
Negative	Natural	Not Applicable	0.01 – 0.20
Positive	Blue[b]	1:1	1.00 – 2.30

[a] Dye: Acid Blue No. 9

OTHER REAGENTS (sold separately)

AxSYM Probe Cleaning Solution (9A35-05)

2 Bottles (220 mL each) AxSYM Probe Cleaning Solution containing 2% Tetraethylammonium Hydroxide (TEAH).

Solution 1 (MUP) (8A47-04)

4 Bottles (230 mL each) Solution 1 (MUP) containing 4-Methylumbelliferyl Phosphate, 1.2 mM, in AMP buffer. Preservative: 0.1% Sodium Azide.

Solution 3 (Matrix Cell Wash) (8A81-04)

4 Bottles (1000 mL each) Solution 3 (Matrix Cell Wash) containing 0.3 M Sodium Chloride in TRIS buffer. Preservatives: 0.1% Sodium Azide and Antimicrobial Agents.

Solution 4 (Line Diluent) (8A46)

1 Bottle (10 L) Solution 4 (Line Diluent) containing 0.1 M Phosphate buffer. Preservatives: 0.1% Sodium Azide and Antimicrobial Agent.

WARNINGS AND PRECAUTIONS

For *In Vitro* Diagnostic Use.

SAFETY PRECAUTIONS

- **CAUTION:** This product contains human sourced and/or potentially infectious components. NOTE: The AxSYM CORE-M 2.0 Index Calibrator and Positive Control are biohazardous and must be handled as though capable of transmitting HBV. For a specific listing, refer to the **REAGENTS** section of this package insert. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, all human sourced material must be considered potentially infectious. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens.[14] Biosafety Level 2[15] or other appropriate biosafety practices[16,17] should be used for materials that contain or are suspected of containing infectious agents.
- The AxSYM CORE-M 2.0 Index Calibrator is reactive for IgM anti-HBc and nonreactive for HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, and anti-HCV. Plasma is also tested for HBsAg and may be either nonreactive or reactive.
- The AxSYM CORE-M 2.0 Negative Control is nonreactive for HBsAg, HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, anti-HCV, anti-HBc, and anti-HBs.
- The AxSYM CORE-M 2.0 Positive Control is reactive for IgM anti-HBc and nonreactive for HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, and anti-HCV. Plasma is also tested for HBsAg and may be either nonreactive or reactive.
- This product contains Sodium Azide; for a specific listing, refer to the **REAGENTS** section. Contact with acids liberates very toxic gas. This material and its container must be disposed of in a safe way.

HANDLING PRECAUTIONS

- **AxSYM CORE-M 2.0 reagents are susceptible to bubbles/foaming and require inspection and removal of bubbles before loading. Refer to the AxSYM System Operations Manual, Section 9.**
- **Do not use Solution 1 (MUP) beyond the expiration date or a maximum of 14 days on board the AxSYM System. When loading new Solution 1 (MUP), it is important to immediately tighten the instrument cap for MUP to minimize exposure to air. Prolonged exposure of MUP to air may compromise performance.**
- Do not use AxSYM CORE-M 2.0 Reagent Kit beyond the expiration date.
- Do not use AxSYM CORE-M 2.0 Reagent Pack beyond a maximum of 112 cumulative hours on board the AxSYM System.
- Do not mix reagents from different Reagent Packs. Do not mix reagents and index calibrators from different lots.
- Avoid microbial contamination of specimens and reagents. Use of disposable pipettes or pipette tips is recommended.
- Avoid chemical contamination of reagents and equipment.
- Ensure that sufficient sample volume is present. If sample volume is insufficient, the AxSYM System will give an error code and no result will be reported. For a description of the system error codes, refer to the AxSYM System Operations Manual, Section 10.
- Use caution in handling patient specimens to prevent cross contamination.

Refer to the AxSYM System Operations Manual, Sections 7 and 8, for a more detailed discussion of the safety and handling precautions during system operation.

STORAGE INSTRUCTIONS

Upon receipt, the AxSYM CORE-M 2.0 Reagent Pack, Index Calibrator, and Controls must be stored at 2-8°C. They may be used immediately after removal from the refrigerator. Index Calibrator and Controls should be returned to 2-8°C storage immediately after use.

Reagents are stable until the expiration date when stored and handled as directed.

The AxSYM CORE-M 2.0 Reagent Pack may be on board the AxSYM System for a maximum of 112 cumulative hours; for example, 14 eight-hour shifts. After 112 hours, the Reagent Pack and associated Index Calibrator must be discarded. Refer to the AxSYM System Operations Manual, Sections 2 and 5, for further information on tracking onboard time.

Solution 1 (MUP) must be stored at 2-8°C (do not freeze). It may be used immediately after removal from the refrigerator. MUP may be on board the AxSYM System for a maximum of 14 days. After 14 days, it must be discarded.

The AxSYM Probe Cleaning Solution, Solution 3 (Matrix Cell Wash), and Solution 4 (Line Diluent) must be stored at 15-30°C.

INDICATIONS OF INSTABILITY OR DETERIORATION OF REAGENTS

When an AxSYM CORE-M 2.0 Negative or Positive Control value is out of the expected range, it may indicate deterioration of the reagents or errors in technique. The test results of associated specimens are invalid and these specimens must be retested. Assay recalibration may be necessary. Refer to the AxSYM System Operations Manual, Section 10, for further troubleshooting information.

INSTRUMENT PROCEDURE

NOTE: AxSYM CORE-M 2.0 must only be used with AxSYM System Software Version 3.60 or higher.

ASSAY FILE INSTALLATION

The AxSYM CORE-M 2.0 assay file must be installed on the AxSYM System from the AxSYM CORE-M 2.0 Assay Disk, List No. 3C42-01 or higher, prior to performing the AxSYM CORE-M 2.0 assay. Refer to the AxSYM System Operations Manual, Section 2, for proper installation procedures.

AxSYM CORE-M 2.0 ASSAY PARAMETERS

Assay parameters can be displayed and edited according to the procedure in the AxSYM System Operations Manual, Section 2. Selected assay parameters used for the AxSYM CORE-M 2.0 assay are listed below.

	Assay Parameters
1	Long Assay Name (English): CORE-M_2
6	Abbrev Assay Name (English): CORE-M_2
11	Assay Number: 166
43	Default Dilution Protocol > UNDILUTED
44	Default Calibration Method > Index Cal
45	Selected Result Concentration Units > Index
80	Interpretation Option to use > 1

NOTE: Although allowed, Parameters 43, 44, 45, and 80 should not be edited.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

- Human serum (including serum collected in serum separator tubes) or plasma (collected in potassium EDTA, sodium citrate, sodium heparin, lithium heparin, or plasma separator tubes) may be used with the AxSYM CORE-M 2.0 assay. Follow the manufacturer's processing instructions for serum or plasma collection tubes.
- Specimens from heparinized patients may be incompletely coagulated and inconsistent results could occur due to the presence of fibrin. To prevent partially coagulated specimens, draw the specimen prior to heparin therapy or into a plasma collection tube. Serum collection tubes should not be used with heparinized patients.
- The AxSYM System does not provide the capability to verify sample type. It is the responsibility of the operator to verify that the correct sample type is tested with the AxSYM CORE-M 2.0 assay.
- This assay was designed for use with human serum or plasma from individual patient specimens. Pooled specimens must not be used.
- Gravity separation is not sufficient for specimen preparation. Specimens containing clots, red blood cells, or particulate matter may give inconsistent results and must be clarified by centrifugation prior to testing.
- **All patient specimens to be tested in Primary Tubes must be centrifuged to remove red blood cells or particulate matter. Follow the manufacturer's instructions for centrifugation.**
- **Specimens must be transferred to a centrifuge tube and centrifuged at a Relative Centrifugal Force (RCF) of 10,000 x g for 10 minutes if:**
  - **they still contain clots, red blood cells, or particulate matter after being centrifuged according to the collection tube manufacturer's instructions, or**
  - **they have been frozen and thawed.**

  Transfer the clarified specimen to an aliquot tube or sample cup for testing.

  NOTE: AxSYM System Software Version 3.60 and higher offers an "Auto Retest/Auto Dilution" feature. Due to the centrifugation requirements discussed above, this feature must not be used with this assay.
- Centrifuged specimens with a lipid layer on the top of the liquid must be transferred to an aliquot tube or sample cup. Care must be taken to transfer only the clarified specimen and not the lipemic material.
- The Clinical Laboratory Standards Institute (CLSI) provides the following recommendations for storing blood specimens.[18]
  - Store samples at 22°C (72°F) for no longer than 8 hours.
  - If the assay will not be completed within 8 hours, refrigerate the sample at 2-8°C (36-46°F).
  - If the assay will not be completed within 48 hours, freeze at or below –20°C (–4°F).

  Note: Per manufacturer's recommendations, plasma collected in heparin collection tubes should be stored at room temperature to minimize latent fibrin formation promoted by cold temperatures.[19]
  - Specimens that are not tested within the specified time period listed must be removed from the clot or red blood cells, and stored frozen (–20°C or colder).
  - Specimens may be subjected to up to 2 freeze/thaw cycles prior to being tested. Specimens must be mixed **thoroughly** after thawing, by LOW speed vortexing or by gentle inversion, and centrifuged prior to use to remove particulate matter and to ensure consistency in the results.
- Specimens may be shipped at -20°C or colder (dry ice), 2-8°C (wet ice), or 15-30°C and must be packaged and labeled in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances. Do not exceed the storage limitations listed above. It is recommended to ship specimens off the clot or red blood cells.
- For optimal results, specimens should be free of fibrin, red blood cells, or other particulate matter.
- Specimens with obvious microbial contamination should not be used.

- Do not use heat-inactivated specimens.
- Performance has not been established for the use of cadaveric specimens or the use of body fluids other than human serum or plasma.
- Inspect all samples for bubbles. Remove bubbles prior to testing the sample. Refer to the AxSYM System Operations Manual, Section 7, for detailed instructions on removing bubbles.
- To minimize the effects of evaporation, all samples (patient specimens, controls, and index calibrator) should be tested within 3 hours of being placed on board the AxSYM System. Refer to the AxSYM System Operations Manual, Section 5, for a more detailed discussion of onboard sample storage constraints.

SAMPLE VOLUME

The sample volume required to perform a single AxSYM CORE-M 2.0 test on the AxSYM System varies according to the type of sample container used. For sample cups, a ROUTINE test and a STAT test each require 184 µL. For every additional AxSYM CORE-M 2.0 test performed (ROUTINE or STAT) from the same sample container, an additional 134 µL of sample is required.

The sample cup minimum volume for both ROUTINE and STAT tests is calculated by the AxSYM System. They are displayed on the Order screen at the time the test(s) is(are) ordered. The sample cup STAT minimum volume is printed on the Orderlist Report. When using the Host Order Query, the Order screen information and Orderlist Report are not available. Refer to the AxSYM System Operations Manual, Section 5, for a description of the Host Order Query Option.

To obtain the recommended volume requirements for the AxSYM CORE-M 2.0 Index Calibrator and Controls, hold the bottles **vertically** and dispense 8 drops of Index Calibrator or 6 drops (per replicate) of each control into each respective sample cup.

For sample volume requirements in Primary or Aliquot Tubes, and calibrator/control volume requirements for multiple AxSYM CORE-M 2.0 reagent lots, refer to the AxSYM System Operations Manual, Section 5.

AxSYM CORE-M 2.0 PROCEDURE

MATERIALS PROVIDED

- 8B89-66 AxSYM CORE-M 2.0 Reagent Kit, containing:
  - AxSYM CORE-M 2.0 Reagent Pack
  - AxSYM CORE-M 2.0 Index Calibrator
  - 100 Reaction Vessels (RV)
  - 100 Matrix Cells

MATERIALS REQUIRED BUT NOT PROVIDED

- 8B89-10 AxSYM CORE-M 2.0 Controls
- 8A47-04 Solution 1 (MUP)
- 8A81-04 Solution 3 (Matrix Cell Wash)
- 8A46 Solution 4 (Line Diluent)
- 9A35-05 AxSYM Probe Cleaning Solution
- 8A76-01 Sample Cups
- Pipettes or pipette tips (optional) to deliver the volumes specified on the Order screen

CAUTION:

- Mix the AxSYM CORE-M 2.0 Index Calibrator and Controls by gentle inversion prior to use.
- When manually dispensing samples into sample cups, verify that dispensing equipment does not introduce cross contamination and delivers the specified sample volume. Use a separate pipette tip for each sample. Use accurately calibrated equipment.
- For optimal performance, it is important to follow the routine maintenance procedures defined in the AxSYM System Operations Manual, Section 9.

ASSAY PROCEDURE

CAUTION: The System status must be WARMING, PAUSED, READY, or STOPPED before adding or removing sample segments, Reagent Packs, or Reaction Vessels.

NOTE: The AxSYM System "Auto Retest/Auto Dilution" feature must **not** be used for this assay. Refer to the **SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS** section of this package insert.

1. Check for sufficient onboard inventory of Matrix Cells and bulk solutions, and sample segment availability.
2. Check for sufficient waste collection capacity.

   CAUTION: Do not open the Interior Waste Door or the AxSYM Processing Center Cover while any test is in progress. If opened, all processing will stop. All tests will be terminated and must be repeated.
3. Order the AxSYM CORE-M 2.0 Index Calibrator, AxSYM CORE-M 2.0 Controls, and/or patient specimens as required. Assign or modify sample segment position (S/P) for each sample, as necessary. Refer to the **QUALITY CONTROL PROCEDURES** section of this package insert for calibration and control requirements.

   Index Calibration
   Perform AxSYM CORE-M 2.0 calibration by testing 2 replicates of the Index Calibrator. Invert gently to mix and dispense at least 8 drops of the Index Calibrator into a sample cup. Do not simultaneously calibrate more than one AxSYM CORE-M 2.0 reagent lot.

   Controls
   Perform quality control by testing the Negative and Positive Controls (one test each). Invert gently to mix and dispense at least 6* drops each of the Negative and Positive Controls into individual sample cups.

   * When more than one AxSYM CORE-M 2.0 reagent lot is on board the AxSYM System, multiply the control volume by the number of lots.

   Patient Specimens
   Ensure that sufficient volume is present in the sample cups or tubes. The sample cup minimum volume is 184 µL for the first AxSYM CORE-M 2.0 test plus 134 µL for each additional AxSYM CORE-M 2.0 test. For volume requirements in Primary or Aliquot Tubes, refer to the AxSYM System Operations Manual, Section 5.

NOTE: The operator may obtain an Orderlist Report by accessing the Orderlist screen and pressing PRINT. The printout contains sample placement information and minimum STAT sample cup volume requirements for all tests ordered. When using the Host Order Query, the Orderlist Report is not available. Refer to the AxSYM System Operations Manual, Section 5: Ordering Patient Samples, for a description of the Host Query Option.

4. Place sample segments containing the ordered samples into the Sample Carousel.
5. Open Reagent Bottle 4 containing the Specimen Diluent. Place the AxSYM CORE-M 2.0 Reagent Pack into the Reagent Pack Carousel.

NOTE: The cap for Reagent Bottle 4 must be manually opened prior to running an AxSYM CORE-M 2.0 assay. Upon completion of the run, close the Reagent Bottle 4 cap securely.

6. Ensure that RVs are present on the RV Carousel. Additional RVs may be added as needed.
7. Press RUN. All entries on the Orderlist screen are transferred to the Order Status screen for sample processing.
8. When testing is completed, close Reagent Bottle 4 and remove the samples and the AxSYM CORE-M 2.0 Reagent Pack from the Sampling Center. Store reagent pack at 2-8°C.

NOTE: When using the onboard reagent tracking feature, the operator must perform a reagent pack scan after removing any pack from the system in order to maintain the validity of the reagent pack stability time.

Sections 5 and 6 of the AxSYM System Operations Manual contain detailed steps for performing assay calibration and sample testing procedures.

QUALITY CONTROL PROCEDURES

CALIBRATION

A minimum of 2 replicates of the AxSYM CORE-M 2.0 Index Calibrator must be tested for an AxSYM CORE-M 2.0 calibration. A single sample of both the Negative and Positive Controls must be tested as a means of evaluating the assay calibration. Once the AxSYM CORE-M 2.0 calibration is accepted and stored, all subsequent samples may be tested without further calibration unless one or more of the following occur:

- A reagent pack with a new lot number is used.
- Either of the AxSYM CORE-M 2.0 Control values is out of its specified range.
- The MEIA Optics Verification Update has been performed.

Refer to the AxSYM System Operations Manual, Section 6, for additional information on:

- Setting up an assay calibration
- Determining when recalibration may be necessary
- Calibration verification

The operator must verify that the AxSYM CORE-M 2.0 Control values are within the ranges specified in this package insert. Refer to the **REAGENTS** section of this package insert for AxSYM CORE-M 2.0 Control ranges.

The AxSYM System verifies that the results of an assay calibration meet the specifications assigned to selected validity parameters. An error message occurs when the calibration fails to meet a specification. Refer to the AxSYM System Operations Manual, Section 10, for an explanation of the corrective actions for the error code. Refer to the AxSYM System Operations Manual, Appendix E, for an explanation of the calibration validity parameters that may be used by the AxSYM System.

QUALITY CONTROL

The performance of the Abbott AxSYM CORE-M 2.0 Controls has not been established with any other IgM anti-HBc assays.

The AxSYM CORE-M 2.0 controls are in a serum matrix made from recalcified plasma. The user should provide alternate control material for plasma when necessary.

Good laboratory practice recommends the use of positive and negative controls to assure functionality of reagents and proper performance of the assay procedure. Positive control and negative control are intended to monitor for substantial reagent failure. Quality Control requirements must be performed in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's standard quality control procedures. It is recommended that the user refer to CLSI document C24-A2[20], *Statistical Quality Control for Quantitative Measurements: Principles and Definitions:* [Approved Guideline – Second Edition] or other published guidelines for general quality control recommendations. For further guidance on appropriate quality control practices, refer to 42 CFR 493.1202(c).[21]

The minimum control requirement for an AxSYM CORE-M 2.0 assay is a single sample of each of the Negative and Positive Controls tested every 24 hours, each day of use for each reagent lot. Controls may be placed in any position in the Sample Carousel.

Additional controls may be tested in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control procedures.

The operator must verify that the AxSYM CORE-M 2.0 Control values are within the ranges specified in this package insert Refer to the **REAGENTS** section of this package insert for AxSYM CORE-M 2.0 Control ranges. If a control value is out of its specified range, the associated test results are invalid and must be retested. Recalibration may be indicated.

FLUORESCENCE BACKGROUND ACCEPTANCE CRITERIA

Quality control with regard to the MUP substrate blank is automatically determined by the instrument and checked under Assay Parameter 64, Max Intercept-Max MUP intercept, each time a test result is calculated. If the MUP intercept value is greater than the maximum allowable value, the result is invalid. The test request will be moved to the Exceptions List where it will appear with the message "1064 Invalid test result, intercept too high" and the calculated intercept value. Refer to the AxSYM System Operations Manual, Section 10, when this error message is obtained.

Refer to the AxSYM System Operations Manual, Section 2, for further information on this parameter.

RESULTS

CALCULATION

The AxSYM System calculates the mean rate of the Index Calibrator replicates and stores the result. The AxSYM CORE-M 2.0 assay protocol calculates a result based on the ratio of the sample rate to the stored Index Calibrator mean rate for each sample and control.

Index Value = Sample Rate / Index Calibrator Mean Rate

FLAGS

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the AxSYM System Operations Manual, Sections 1 and 2.

INTERPRETATION OF RESULTS

AxSYM CORE-M 2.0		
Index Value	**Instrument Interpretation**	**Interpretation**
> 1.20	REACTIVE	Presumptive evidence of IgM anti-HBc.
0.80 to 1.20	GRAYZONE REACTIVE[a]	Presumptive evidence of IgM anti-HBc. Patients with specimens exhibiting gray zone reactive test results should be retested at approximately one-week intervals.
< 0.80	NONREACTIVE	IgM anti-HBc not detected. Does not exclude the possibility of exposure to or infection with HBV.

[a] The word "GRAYZONE" will appear in the interpretation field on the printout.

- Monitoring the level of IgM anti-HBc by retesting at approximately one-week intervals will distinguish rapidly rising IgM anti-HBc levels associated with early acute hepatitis B infection from gradually decreasing or unchanging IgM anti-HBc levels often associated with late acute stage of HBV infection, 6 to 9 months from the appearance of HBsAg.
- Immunosuppressed or immunocompromised individuals may not produce IgM anti-HBc above the detection limit of the AxSYM CORE-M 2.0 assay.

LIMITATIONS OF THE PROCEDURE

- **WARNING: Not intended for use in screening blood, plasma, or tissue donors.** The effectiveness of AxSYM CORE-M 2.0 for use in screening blood, plasma, or tissue donors has not been established.
- Current methods for the detection of IgM anti-HBc may not detect all potentially infected individuals. A nonreactive test result does not exclude the possibility of exposure to or infection with HBV.
- The AxSYM CORE-M 2.0 assay is limited to the detection of IgM anti-HBc in human serum or plasma. It can be used to determine whether a patient has, or has recently had, acute or subclinical hepatitis B infection. Supportive clinical information, including other hepatitis B markers, should also be evaluated. The test cannot determine a patient's immune status to hepatitis B.

EXPECTED VALUES

Due to geographic locations or demographics, assay results obtained in individual laboratories may vary from data presented.

Of the prospective subjects participating in the clinical investigation, 55.82% (1,313/2,352) were individuals, living in the United States, who were at increased risk of HBV infection. All subjects were at risk of HBV infection due to lifestyle, behavior, occupation, or known exposure event but were asymptomatic and reported no current signs or symptoms of hepatitis. The population was 47.60% Caucasian, 36.25% African American, 12.72% Hispanic, 1.45% Asian, 0.46% American Indian/Alaska Native, with the remaining 1.52% represented by other ethnic groups. The population was 62.15% female and 37.85% male ranging in age from 18 to 75 years. AxSYM CORE-M 2.0 was reactive or gray zone reactive in 0.61% (8/1,313) of the individuals in this population. Table 1 is a summary of the percent of individuals at increased risk of HBV infection enrolled at each location and the percent of AxSYM CORE-M 2.0 reactive results observed from each location. Table 2 is a summary of the percent AxSYM CORE-M 2.0 reactive results by age range and gender.

Table 1
AxSYM CORE-M 2.0 Reactive Results by Specimen Collection Site or Specimen Vendor for Individuals at Increased Risk of HBV Infection

Specimen Collection Site/ Specimen Vendor Location	Percent of Individuals at Increased Risk of HBV Infection Enrolled at Each Location	Percent of AxSYM CORE-M 2.0 Reactive[a] Results Observed From Each Location
Site 1, Galveston, TX	56.51 (742/1,313)	0.54 (4/742)
Site 2, Dallas, TX	4.49 (59/1,313)	0.00 (0/59)
Site 3, Miami, FL	3.96 (52/1,313)	1.92 (1/52)
Site 4, St. Petersburg, FL	4.27 (56/1,313)	1.79 (1/56)
Site 5, Chicago, IL	0.61 (8/1,313)	0.00 (0/8)
Site 6, Denver, CO	2.74 (36/1,313)	0.00 (0/36)
Specimen Vendor Location:		
Colton, CA	5.79 (76/1,313)	0.00 (0/76)
Plymouth, MA	7.54 (99/1,313)	1.01 (1/99)
High Point, NC	14.09 (185/1,313)	0.54 (1/185)

[a] Includes gray zone reactives.

Table 2
AxSYM CORE-M 2.0 Results by Age Range and Gender for Individuals at Increased Risk of HBV Infection

Age Range	Gender	AxSYM CORE-M 2.0 Result + Number of Specimens	GZR Number of Specimens	− Number of Specimens	Total
10 to 19	Female	0	0	14	14
	Male	0	0	11	11
20 to 29	Female	0	1	183	184
	Male	1	0	96	97
30 to 39	Female	0	0	184	184
	Male	1	0	106	107
40 to 49	Female	1	1	249	251
	Male	0	0	159	159
50 to 59	Female	0	1	136	137
	Male	1	1	106	108
60 to 69	Female	0	0	35	35
	Male	0	0	12	12
70 to 79	Female	0	0	8	8
	Male	0	0	3	3
Unknown[a]	Female	0	0	3	3
Total		**4 (0.30%)**	**4 (0.30%)**	**1,305 (99.39%)**	**1,313**

GZR = Gray Zone Reactive

[a] Age was not provided for three subjects.

SPECIFIC PERFORMANCE CHARACTERISTICS

Assay results obtained in individual laboratories may vary from data presented.

PRECISION

System Reproducibility

A five-day precision study was performed based on guidance from the CLSI document EP15-A2[22]. Testing was conducted at three clinical testing sites using three AxSYM CORE-M 2.0 reagent and control lots per site. Testing included two precision runs per day (a minimum of two hours apart) for each reagent lot, on each of five days. Each precision run included four replicates of each of the two panel members and the AxSYM CORE-M 2.0 Index Calibrator, Negative Control, and Positive Control. Panel members were prepared by adding recalcified human plasma reactive for IgM anti-HBc to nonreactive human serum. The overall precision data are summarized in Table 3 and the by-site precision data are summarized in Table 4.

Table 3
AxSYM CORE-M 2.0 System Reproducibility: Overall Precision
Three Reagent Master Lots, Three Clinical Testing Sites

Sample	Total No. Reps	Grand Mean Index Value	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision with Additional Component of Between-Lot		Precision with Additional Component of Between-Site		Precision with Additional Components of Site and Lot (Overall)	
			SD	%CV	SD	%CV	SD	%CV	CL	SD	%CV	SD	%CV	SD	%CV
Panel 1	360	0.65	0.030	4.6	0.052	8.1	0.053	8.1	9.1	0.075	11.6	0.072	11.1	0.084	13.0
Panel 2	360	1.03	0.028	2.8	0.038	3.7	0.042	4.0	4.4	0.082	8.0	0.091	8.8	0.107	10.4
NC	360	0.03	0.003	9.9	0.003	9.9	0.003	10.5	11.3	0.005	18.2	0.003	12.1	0.005	18.6
PC	360	1.58	0.037	2.4	0.049	3.1	0.052	3.3	3.6	0.083	5.2	0.126	8.0	0.126	8.0

Sample	Total No. Reps	Grand Mean Rate	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision with Additional Component of Between-Lot		Precision with Additional Component of Between-Site		Precision with Additional Components of Site and Lot (Overall)	
			SD	%CV	SD	%CV	SD	%CV	CL	SD	%CV	SD	%CV	SD	%CV
IC	360	293.84	8.414	2.9	10.891	3.7	12.334	4.2	4.6	20.841	7.1	25.368	8.6	29.436	10.0

NC = Negative Control, PC = Positive Control, IC = Index Calibrator, Reps = Replicates, SD = Standard Deviation, CV = Coefficient of Variation, CL = Upper One-sided 95% Confidence Limit

Table 4
AxSYM CORE-M 2.0 System Reproducibility: By-Site Precision
Clinical Testing Sites 1, 2, and 3, Three Reagent Master Lots

Clinical Testing Site	Sample	Total No. Reps	Grand Mean Index Value / Rate*	Within-Run		Within-Day		Within-Laboratory Precision (Total)		Precision with Additional Component of Between-Lot	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	Panel 1	120	0.60	0.015	2.4	0.022	3.7	0.024	4.0	0.039	6.4
	Panel 2	120	0.95	0.023	2.5	0.031	3.3	0.034	3.5	0.052	5.5
	NC	120	0.03	0.002	6.7	0.002	6.7	0.002	6.9	0.006	21.9
	PC	120	1.46	0.032	2.2	0.037	2.5	0.045	3.1	0.087	6.0
	IC	120	275.72	7.002	2.5	9.134	3.3	9.383	3.4	13.148	4.8
2	Panel 1	120	0.67	0.046	6.8	0.085	12.7	0.085	12.7	0.115	17.1
	Panel 2	120	1.08	0.036	3.3	0.049	4.6	0.049	4.6	0.114	10.6
	NC	120	0.03	0.003	11.5	0.003	11.5	0.003	11.7	0.004	15.0
	PC	120	1.65	0.044	2.7	0.060	3.6	0.060	3.6	0.102	6.2
	IC	120	288.41	9.990	3.5	12.339	4.3	15.075	5.2	28.821	10.0
3	Panel 1	120	0.67	0.018	2.7	0.020	3.0	0.022	3.3	0.046	6.8
	Panel 2	120	1.07	0.025	2.3	0.031	2.9	0.040	3.8	0.068	6.3
	NC	120	0.03	0.003	10.4	0.003	10.4	0.003	11.7	0.005	17.7
	PC	120	1.63	0.034	2.1	0.044	2.7	0.051	3.1	0.051	3.2
	IC	120	317.40	7.973	2.5	10.962	3.5	11.878	3.7	17.307	5.5

NC = Negative Control, PC = Positive Control, IC = Index Calibrator, Reps = Replicates, SD = Standard Deviation, CV = Coefficient of Variation

* Panel 1, Panel 2, NC, and PC are reported in Grand Mean Index Value. The IC is reported in Grand Mean Rate.

Within-Laboratory Precision

A 20-day precision study was conducted based on guidance from CSLI EP5-A2[23]. Testing was conducted at Abbott Laboratories using two AxSYM CORE-M 2.0 reagent lots, one control lot, and two AxSYM instruments. Testing included two precision runs per day (a minimum of two hours apart) for each reagent lot, on each instrument, on each of 20 days. Each precision run included two replicates of each of the two panel members and the AxSYM CORE-M 2.0 Index Calibrator, Negative Control, and Positive Control. Panel members were prepared by adding recalcified human plasma reactive for IgM anti-HBc to nonreactive human serum. The data are summarized in Table 5.

Table 5
AxSYM CORE-M 2.0 Within-Laboratory Precision

Sample	Total No. Reps	Grand Mean Index Value	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision with Additional Component of Between-Lot		Precision with Additional Component of Between-Instrument	
			SD	%CV	SD	%CV	SD	%CV	CL	SD	%CV	SD	%CV
Panel 1	320	0.62	0.019	3.1	0.022	3.5	0.028	4.6	5.0	0.035	5.6	0.029	4.7
Panel 2	320	0.99	0.026	2.6	0.030	3.0	0.041	4.1	4.5	0.051	5.2	0.043	4.3
NC	320	0.03	0.003	10.2	0.003	10.8	0.004	11.2	12.0	0.004	13.7	0.004	11.2
PC	320	1.55	0.043	2.8	0.047	3.1	0.062	4.0	4.4	0.081	5.2	0.062	4.0

Sample	Total No. Reps	Grand Mean Rate	Within-Run		Within-Day		Within-Laboratory Precision (Total)			Precision with Additional Component of Between-Lot		Precision with Additional Component of Between-Instrument	
			SD	%CV	SD	%CV	SD	%CV	CL	SD	%CV	SD	%CV
IC	320	272.22	7.426	2.7	7.967	2.9	10.632	3.9	4.3	10.632	3.9	10.950	4.0

NC = Negative Control, PC = Positive Control, IC = Index Calibrator, Reps = Replicates, SD = Standard Deviation, CV = Coefficient of Variation, CL = Upper One-sided 95% Confidence Limit

CLINICAL PERFORMANCE

A multi-site study was conducted to evaluate the clinical performance of AxSYM CORE-M 2.0 with serum specimens from 2,016 individuals at increased risk of HBV infection due to lifestyle, behavior, occupation, or known exposure events and individuals with signs and symptoms of hepatitis infection. Specimens were prospectively collected in the United States at specimen collection sites located in Galveston, TX (39.29%); Dallas, TX (5.80%); Miami, FL (4.51%); St. Petersburg, FL (4.17%); Chicago, IL (8.18%); and Denver, CO (6.10%), or were obtained from a specimen vendor at the following three locations: Colton, CA (5.85%); Plymouth, MA (16.91%); and High Point, NC (9.18%) (Population 1). Specimens were also prospectively collected in Vietnam from 300 individuals at increased risk of HBV infection and individuals with signs and symptoms of hepatitis infection (Population 2).

Population 1 was Caucasian (52.83%), African American (28.52%), Hispanic (14.68%), Asian (1.98%), and American Indian/Alaska Native (0.45%), with the remaining 1.54% represented by other ethnic groups. The population was 52.53% female and 47.47% male and ranged in age from 18 to 83 years. Testing of these specimens occurred at clinical testing sites located in Port Jefferson, NY (39.29%); Dallas, TX (40.13%); and Raritan, NJ (20.59%).

Population 2 was Vietnamese (100.00%). The population was 53.33% female and 46.67% male and ranged in age from 18 to 68 years. Testing of these specimens occurred at a clinical testing site located in Raritan, NJ.

The HBV classification for each subject was determined by a serological assessment using an HBV reference marker pattern consisting of four FDA-approved reference assays for the detection of HBsAg, IgM anti-HBc, total anti-HBc, and anti-HBs. All reference assays used were from a single manufacturer.

The specimens were assigned an HBV classification (Tables 6 and 7), and the AxSYM CORE-M 2.0 results were compared to the reference IgM anti-HBc results (Tables 8 and 9). Agreement of the AxSYM CORE-M 2.0 assay was assessed relative to the reference IgM anti-HBc results (Tables 10 and 11).

Results of HBV Classification

Population 1 specimens were assigned an HBV classification using the positive (+) and negative (–) patterns for the four HBV reference markers. Table 6 is a summary of how these classifications were derived and the number of specimens in each classification. There were 16 unique HBV reference marker patterns observed in the AxSYM CORE-M 2.0 clinical investigation.

Table 6
HBV Classification for Individuals at Increased Risk of HBV Infection and Individuals With Signs and Symptoms of Hepatitis Infection—Population 1

HBV Reference Markers					HBV Classification
Number of Specimens	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
2	+	–	–	–	Early Acute
7	+	+	+	–	Acute
1	+	+	+	I	Chronic
2	+	–	+	+	Chronic
35	+	–	+	–	Chronic
1	+	–	–	+	Chronic
2	+	–	+	I	Chronic
1	+	+	+	+	Late Acute/Recovering
4	–	+	+	+	Recovering Acute
3	–	+	+	I	Early Recovery
193	–	–	+	+	Immune Due to Natural Infection
31	–	–	+	I	Distantly Immune/Anti-HBs Unknown
107	–	–	+	–	Distantly Immune/Anti-HBs Not Detected
507	–	–	–	+	Immune Due to HBV Vaccination
66	–	–	–	I	Unknown
1,054	–	–	–	–	Susceptible
2,016					**Total**

I = Indeterminate

Population 2 specimens were assigned an HBV classification using the positive (+) and negative (–) patterns for the four HBV reference markers. Table 7 is a summary of how these classifications were derived and the number of specimens in each classification. There were 10 unique HBV reference marker patterns observed in the AxSYM CORE-M 2.0 clinical investigation.

Table 7
HBV Classification for Individuals at Increased Risk of HBV Infection and Individuals With Signs and Symptoms of Hepatitis Infection—Population 2

HBV Reference Markers					HBV Classification
Number of Specimens	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
1	+	–	–	–	Early Acute
3	+	–	+	+	Chronic
119	+	–	+	–	Chronic
2	+	–	–	+	Chronic
3	+	–	+	I	Chronic
72	–	–	+	+	Immune Due to Natural Infection
5	–	–	+	I	Distantly Immune/Anti-HBs Unknown
15	–	–	+	–	Distantly Immune/Anti-HBs Not Detected
41	–	–	–	+	Immune Due to HBV Vaccination
39	–	–	–	–	Susceptible
300					**Total**

I = Indeterminate

Comparison of Results

Table 8 is a comparison of the AxSYM CORE-M 2.0 results to the reference IgM anti-HBc assay results for Population 1 by HBV classification.

Table 8
Comparison of AxSYM CORE-M 2.0 Results With Reference IgM Anti-HBc Results by HBV Classification—Population 1

	Reference IgM Anti-HBc Result[a]						
	+			–			
	AxSYM CORE-M 2.0 Result						
HBV Classification	+	GZR	–	+	GZR	–	Total
Early Acute	0	0	0	0	0	2	2
Acute	7	0	0	0	0	0	7
Chronic	1	0	0	1[b]	5[c]	34	41
Late Acute/Recovering	1	0	0	0	0	0	1
Recovering Acute	3	1	0	0	0	0	4
Early Recovery	3	0	0	0	0	0	3
Immune Due to Natural Infection	0	0	0	0	2[d]	191	193
Distantly Immune/Anti-HBs Unknown	0	0	0	0	0	31	31
Distantly Immune/Anti-HBs Not Detected	0	0	0	0	1[e]	106	107
Immune Due to HBV Vaccination	0	0	0	0	0	507	507
Unknown	0	0	0	0	1[f]	65	66
Susceptible	0	0	0	0	0	1,054	1,054
Total	**15**	**1**	**0**	**1**	**9**	**1,990**	**2,016**

GZR = Gray Zone Reactive

[a] Includes retesting performed according to the package insert as required.
[b] This specimen was tested and determined to be positive for anti-HBe and HBV DNA.
[c] Three specimens were tested and determined to be positive for HBeAg and HBV DNA; two specimens were positive for anti-HBe and HBV DNA.
[d] These specimens were tested and determined to be positive for anti-HBe and gray zone reactive by an FDA-approved IgM anti-HBc assay.
[e] This specimen was tested and determined to be positive for anti-HBe and gray zone reactive by an FDA-approved IgM anti-HBc assay.
[f] This specimen was tested and determined to be gray zone reactive by an FDA-approved IgM anti-HBc assay.

Table 9 is a comparison of the AxSYM CORE-M 2.0 results to the reference IgM anti-HBc assay results for Population 2 by HBV classification.

Table 9

Comparison of AxSYM CORE-M 2.0 Results With Reference IgM Anti-HBc Results by HBV Classification—Population 2

	Reference IgM Anti-HBc Result[a]						
	+			–			
	AxSYM CORE-M 2.0 Result						
HBV Classification	+	GZR	–	+	GZR	–	Total
Early Acute	0	0	0	0	0	1	1
Chronic	0	0	0	0	3[b]	124	127
Immune Due to Natural Infection	0	0	0	0	0	72	72
Distantly Immune/Anti-HBs Unknown	0	0	0	0	0	5	5
Distantly Immune/Anti-HBs Not Detected	0	0	0	0	0	15	15
Immune Due to HBV Vaccination	0	0	0	0	0	41	41
Susceptible	0	0	0	0	0	39	39
Total	**0**	**0**	**0**	**0**	**3**	**297**	**300**

GZR = Gray Zone Reactive

[a] Includes retesting performed according to the package insert as required.

[b] Two specimens were tested and determined to be positive for HBeAg and HBV DNA; one specimen was positive for anti-HBe and HBV DNA.

Percent Agreement

Table 10 is a summary, for each HBV classification, of the percent agreement between AxSYM CORE-M 2.0 and the reference IgM anti-HBc assay for Population 1.

Table 10

Percent Agreement Between AxSYM CORE-M 2.0 Results and Reference IgM Anti-HBc Results Summarized by HBV Classification—Population 1

HBV Classification	Positive Percent Agreement (%)	95% Confidence Interval (%)	Negative Percent Agreement (%)	95% Confidence Interval (%)
Early Acute	NA	NA	2/2 (100.00)	[15.81, 100.00]
Acute	7/7 (100.00)	[59.04, 100.00]	NA	NA
Chronic	1/1 (100.00)	[2.50, 100.00]	34/40 (85.00)	[70.16, 94.29]
Late Acute/Recovering	1/1 (100.00)	[2.50, 100.00]	NA	NA
Recovering Acute	4/4 (100.00)	[39.76, 100.00]	NA	NA
Early Recovery	3/3 (100.00)	[29.24, 100.00]	NA	NA
Immune Due to Natural Infection	NA	NA	191/193 (98.96)	[96.31, 99.87]
Distantly Immune/Anti-HBs Unknown	NA	NA	31/31 (100.00)	[88.78, 100.00]
Distantly Immune/Anti-HBs Not Detected	NA	NA	106/107 (99.07)	[94.90, 99.98]
Immune Due to HBV Vaccination	NA	NA	507/507 (100.00)	[99.28, 100.00]
Unknown	NA	NA	65/66 (98.48)	[91.84, 99.96]
Susceptible	NA	NA	1,054/1,054 (100.00)	[99.65, 100.00]
Overall	16/16 (100.00)	[79.41, 100.00]	1,990/2,000 (99.50)	[99.08, 99.76]

NA = Not Applicable

Table 11 is a summary, for each HBV classification, of the percent agreement between AxSYM CORE-M 2.0 and the reference IgM anti-HBc assay for Population 2.

Table 11

Percent Agreement Between AxSYM CORE-M 2.0 Results and Reference IgM Anti-HBc Results Summarized by HBV Classification—Population 2

HBV Classification	Positive Percent Agreement (%)	95% Confidence Interval (%)	Negative Percent Agreement (%)	95% Confidence Interval (%)
Early Acute	NA	NA	1/1 (100.00)	[2.50, 100.00]
Chronic	NA	NA	124/127 (97.64)	[93.25, 99.51]
Immune Due to Natural Infection	NA	NA	72/72 (100.00)	[95.01, 100.00]
Distantly Immune/Anti-HBs Unknown	NA	NA	5/5 (100.00)	[47.82, 100.00]
Distantly Immune/Anti-HBs Not Detected	NA	NA	15/15 (100.00)	[78.20, 100.00]
Immune Due to HBV Vaccination	NA	NA	41/41 (100.00)	[91.40, 100.00]
Susceptible	NA	NA	39/39 (100.00)	[90.97, 100.00]
Overall	NA	NA	297/300 (99.00)	[97.11, 99.79]

NA = Not Applicable

Percent of Positive Specimens for Individuals Diagnosed With Acute HBV Infection

AxSYM CORE-M 2.0 performance was evaluated by testing prospectively-collected serum specimens from individuals diagnosed with acute HBV infection. Table 12 is a summary of the percent of AxSYM CORE-M 2.0 positive specimens from subjects with documented acute HBV infection. Acute status was defined by four-marker HBV reference testing.

Table 12
Percent of Positive Specimens—Individuals Diagnosed With Acute HBV Infection

Specimen Category	Number of Specimens	Number of Positive Specimens (%)	95% Confidence Interval (%)
Individuals Diagnosed With Acute HBV Infection	11	11 (100.00)	[71.51, 100.00]

Percent Agreement for Preselected IgM Anti-HBc Positive Specimens

AxSYM CORE-M 2.0 performance was further evaluated by testing prospectively-collected, preselected IgM anti-HBc positive serum specimens. The positive percent agreement between the AxSYM CORE-M 2.0 assay and the reference IgM anti-HBc assay was 100.00% (23/23) with a 95% confidence interval of 85.18% to 100.00%. Negative percent agreement was 0.00% (0/2) with a 95% confidence interval of 0.00% to 84.19%.

The specimens were assigned an HBV classification using the positive (+) and negative (–) patterns for the four HBV reference markers. Table 13 is summary of how these classifications were derived and the number of specimens in each classification. There were 2 unique HBV reference marker patterns observed in the AxSYM CORE-M 2.0 clinical investigation for this population.

Table 13
HBV Classification Preselected IgM Anti-HBc Positive Specimens

HBV Reference Markers					HBV Classification
Number of Specimens	HBsAg	Anti-HBc IgM	Total Anti-HBc	Anti-HBs	
23	+	+	+	–	Acute
2	+	–	+	–	Chronic
25					**Total**

Clinical Performance in a Pediatric Population

The performance of AxSYM CORE-M 2.0 in a pediatric population was evaluated by testing specimens from a surplus pediatric population (n = 100) collected in Fall River, MA, by a specimen vendor, and from the pediatric subjects (n = 109) from Population 1 and Population 2, as shown in the Clinical Performance section of this package insert. The negative percent agreement between the AxSYM CORE-M 2.0 assay and the reference IgM anti-HBc assay was calculated. Table 14 is a demographic summary of the surplus population by age range and gender with AxSYM CORE-M 2.0 results. The negative percent agreement was 100.00% (100/100) with a 95% confidence interval of 96.38% to 100.00%.

Table 14
Demographic Summary With AxSYM CORE-M 2.0 Results for a Surplus Pediatric Population

		AxSYM CORE-M 2.0 Result			
		+	GZR	–	
Age Range	Gender	Number of Specimens	Number of Specimens	Number of Specimens	Total
> 2 to 12 Years	Female	0	0	28	28
	Male	0	0	22	22
> 12 to 19 Years	Female	0	0	39	39
	Male	0	0	11	11
Total		**0**	**0**	**100 (100.00%)**	**100**

GZR = Gray Zone Reactive

Table 15 is a demographic summary of the prospectively collected population (Population 1 and Population 2) by age range and gender with AxSYM CORE-M 2.0 results. The negative percent agreement was 100.00% (109/109) with a 95% confidence interval of 96.67% to 100.00%.

Table 15
Demographic Summary With AxSYM CORE-M 2.0 Results for a Prospectively Collected Pediatric Population

		AxSYM CORE-M 2.0 Result			
		+	GZR	–	
Age Range	Gender	Number of Specimens	Number of Specimens	Number of Specimens	Total
> 18 to 21 Years	Female	0	0	50	50
	Male	0	0	59	59
Total		**0**	**0**	**109 (100.00%)**	**109**

GZR = Gray Zone Reactive

ANALYTICAL SPECIFICITY

A study was conducted to evaluate the potential for cross-reactivity in the AxSYM CORE-M 2.0 assay when used to test specimens from individuals with medical conditions unrelated to HBV infection. A total of 185 specimens from 19 different categories were tested. All 185 specimens were nonreactive (100.0%) by AxSYM CORE-M 2.0. The data are summarized in Table 16.

Table 16
Cross-reactivity of AxSYM CORE-M 2.0
in Specimens from Individuals with Medical Conditions Unrelated to HBV Infection

Specimen Category[a]	Number of Specimens Tested	AxSYM CORE-M 2.0		
		Nonreactive	Gray Zone Reactive	Reactive
Hepatitis A Virus[b]	12	12	0	0
Hepatitis C Virus[b]	10	10	0	0
Human Immunodeficiency Virus	10	10	0	0
Human T-Lymphotropic Virus[b]	9	9	0	0
Cytomegalovirus[b]	10	10	0	0
Epstein-Barr Virus[b]	10	10	0	0
Herpes Simplex Virus[b]	10	10	0	0
Rubella[b]	10	10	0	0
Systemic Lupus Erythematosus	10	10	0	0
Rheumatoid Factor Positive[c]	10	10	0	0
Elevated IgG	10	10	0	0
Elevated IgM	10	10	0	0
Influenza Vaccine Recipients	10	10	0	0
HBV Vaccine Recipients	5	5	0	0
Toxoplasmosis[b]	4	4	0	0
Alcoholic Liver Disease	10	10	0	0
Fatty Liver Disease	15	15	0	0
Obstructive Jaundice	15	15	0	0
Hepatocellular Carcinoma	5	5	0	0
Total (%)	**185**	**185/185 (100.0%)**	**0/185 (0.0%)**	**0/185 (0.0%)**

[a] Information about age and gender of the individuals is not available.
[b] Only IgG antibodies present.
[c] Both IgG and IgM antibodies present for eight of the ten total specimens. The remaining two specimens were categorized based on clinical diagnosis.

SEROCONVERSION DETECTION

The ability of the AxSYM CORE-M 2.0 assay to detect IgM anti-HBc was evaluated by testing seven seroconversion panels obtained from two commercial vendors. The results were compared to the results of an FDA-approved IgM anti-HBc assay (reference). IgM anti-HBc was detected by AxSYM CORE-M 2.0 coincident with the reference IgM anti-HBc assay in six panels and two days later than the reference IgM anti-HBc assay in one panel. In this panel, the initial IgM anti-HBc reactive specimen was also reactive for HBsAg.

One seroconversion panel showed sustained HBsAg reactivity for longer than six months without detectable anti-HBs, which is indicative of an acute HBV infection progressing to a potential chronic HBV infection. The profiles of the remaining six seroconversion panels were characteristic of an acute HBV infection progressing to eventual recovery and immunity to HBV. AxSYM CORE-M 2.0 detected IgM anti-HBc following detection of HBsAg in all panels during the acute stage of disease. IgM anti-HBc remained detectable over a period of seven months after the appearance of HBsAg in the single panel from an acute HBV infection progressing to a potential chronic infection, and over a range of two to eleven months in the other six panels. The overall AxSYM CORE-M 2.0 results were consistent with the known serological profile of each panel.

INTERFERENCE

At the concentrations listed below, total bilirubin (unconjugated), hemoglobin, total protein, and triglycerides showed less than 0.08 index value interference in the AxSYM CORE-M 2.0 assay for high negative (0.6 Index Value target) serum samples and less than or equal to 10% interference in the AxSYM CORE-M 2.0 assay for low positive (1.0 Index Value target) serum samples:

- Total Bilirubin ≤ 20 mg/dL
- Hemoglobin ≤ 500 mg/dL
- Total Protein ≤ 12 g/dL
- Triglycerides ≤ 3,000 mg/dL

50

TUBE TYPE MATRIX COMPARISON

The following tube types are acceptable for use with the AxSYM CORE-M 2.0 assay:

- Glass: serum and serum separator
- Plastic: serum, serum separator, plasma separator, potassium EDTA, sodium citrate, sodium heparin, and lithium heparin.

On average, the tube types evaluated showed less than a 10% difference when compared to the control tube type (Glass Serum), with the exception of sodium citrate, which showed a 12% difference when compared to the control tube type. The distribution of the percent differences per tube type is listed in the following table.

Table 17
Sample Type (Serum and Plasma) Study of AxSYM CORE-M 2.0
Distribution of % Differences by Sample Type

	Distribution of %Differences		
Evaluation Tube Type	**0% to ≤ 10%**	**> 10% to ≤ 20%**	**> 20%**
Plastic Serum	83.3% (35/42)	9.5% (4/42)	7.1% (3/42)
Glass Serum Separator	88.1% (37/42)	7.1% (3/42)	4.8% (2/42)
Plastic Serum Separator	88.1% (37/42)	4.8% (2/42)	7.1% (3/42)
Plastic Plasma Separator	90.5% (38/42)	4.8% (2/42)	4.8% (2/42)
Plastic Potassium EDTA	85.7% (36/42)	7.1% (3/42)	7.1% (3/42)
Plastic Sodium Citrate[a]	61.9% (26/42)	26.2% (11/42)	11.9% (5/42)
Plastic Sodium Heparin	90.5% (38/42)	4.8% (2/42)	4.8% (2/42)
Plastic Lithium Heparin	88.1% (37/42)	7.1% (3/42)	4.8% (2/42)

[a] Note: Sodium citrate tubes have been shown to increase the Index values in specimens near the assay cutoff in a positive direction. Low positive specimens (0.80 to 0.90 Index Value) obtained on samples collected with this anticoagulant should be interpreted accordingly.

BIBLIOGRAPHY

1. Overby LR, Ling C-M, Decker RH, *et al.* Serodiagnostic profiles of viral hepatitis. In: Szmuness W, Alter HJ, Maynard JE, editors. *Viral Hepatitis.* Philadelphia, PA: Franklin Institute Press, 1981:169–82.
2. Kryger P, Aldershvile J, Mathiesen LR, *et al.* Acute type B hepatitis among HBsAg negative patients detected by anti-HBc IgM. *Hepatology* 1982;2(1):50–3.
3. Mortimer PP, Vandervelde EM, Parry JV, *et al.* The anti-HBc IgM response in the acute and convalescent phases of acute hepatitis. *J Infect* 1981;3:339–47.
4. Lemon SM, Gates NL, Simms TE, *et al.* IgM antibody to hepatitis B core antigen as a diagnostic parameter of acute infection with hepatitis B virus. *J Infect Dis* 1981;143(6):803–9.
5. Chau KH, Hargie MP, Decker RH, *et al.* Serodiagnosis of recent hepatitis B infection by IgM class anti-HBc. *Hepatology* 1983;3(2):142–9.
6. Hoofnagle JH, Ponzetto A, Mathiesen LR, *et al.* Serological diagnosis of acute viral hepatitis. *Dig Dis Sci* 1985;30:1022–7.
7. Sjogren M, Hoofnagle JH. Immunoglobulin M antibody to hepatitis B core antigen in patients with chronic type B hepatitis. *Gastroenterology* 1985;89:252–8.
8. Surrenti C, Ambu S, Patussi V, *et al.* Diagnostic significance of anti-HBc IgM (RIA) in healthy HBsAg carriers and in chronic hepatitis B. *J Med Virol* 1986;18:229–34.
9. Perrillo RP, Chau KH, Overby LR, *et al.* Anti-hepatitis B core immunoglobulin M in the serologic evaluation of hepatitis B virus infection and simultaneous infection with type B, delta agent, and non-A, non-B viruses. *Gastroenterology* 1983;85:163–7.
10. Hawkes RA, Boughton CR, Ferguson V, *et al.* Use of immunoglobulin M antibody to hepatitis B core antigen in diagnosis of viral hepatitis. *J Clin Microbiol* 1980;11(6)581–3.
11. Roggendorf M, Deinhardt F, Frösner GG, *et al.* Immunoglobulin M antibodies to hepatitis B core antigen: Evaluation of enzyme immunoassay for diagnosis of hepatitis B virus infection. *J Clin Microbiol* 1981;13(4):618–26.
12. Kryger P. Significance of anti-HBc IgM in the differential diagnosis of viral hepatitis. *J Virol Methods* 1985;10:283–9.
13. Govindarajan S, Ashcavai M, Chau KH, *et al.* Evaluation of enzyme immunoassay for anti-HBc IgM in the diagnosis of acute hepatitis B virus infection. *Am J Clin Pathol* 1984;82(3):323–5.
14. US Department of Labor, Occupational Safety and Health Administration, 29 CFR Part 1910.1030, Occupational exposure to bloodborne pathogens.
15. US Department of Health and Human Services. *Biosafety in Microbiological and Biomedical Laboratories.* 4th ed. Washington, DC: US Government Printing Office; May 1999.
16. World Health Organization. *Laboratory Biosafety Manual.* Geneva: World Health Organization; 2004.
17. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections: Approved Guideline—Third Edition.* CLSI Document M29-A3. Wayne, PA: CLSI; 2005.
18. Clinical and Laboratory Standards Institute. *Procedures for the Handling and Processing of Blood Specimens: Approved Guideline – Third Edition.* CLSI Document H18-A3. Wayne, PA: CLSI, 2004;24(38):1–39.
19. Bush V. Why Doesn't My Heparinized Plasma Specimen Remain Anticoagulated? *LabNotes* (a newsletter from BD Vacutainer Systems) 2003;13(2):9–10,12.
20. Clinical and Laboratory Standards Institute. *Statistical Quality Control for Quantitative Measurements: Principles and Definitions: Approved Guideline – Second Edition.* CLSI Document C24-A2. Wayne, PA: CLSI, 1999.
21. 42 CFR Part 493.1202(c), Laboratory Requirements;2002;3:1021. Available at: http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2002/octqtr/42cfr493.1202.htm. Accessed November 22, 2005.
22. Clinical and Laboratory Standards Institute. *User Verification of Performance for Precision and Trueness: Approved Guideline – Second Edition.* CSLI Document EP15-A2. Wayne, PA: CSLI, 2005.
23. Clinical and Laboratory Standards Institute. *Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline – Second Edition.* CLSI Document EP5-A2. Wayne, PA: CLSI, 2004.

August 2006

52

Abbott AxSYM® System

***In Vitro* Test**
List No. 8B89-10
XX-XXXX/RX

AxSYM CORE-M™ 2.0
Controls

ABBOTT LABORATORIES
Abbott Park, IL 60064 USA

Printed in USA

53

INTENDED USE

The AxSYM CORE-M™ 2.0 Controls are used for monitoring the performance of the AxSYM® System (reagent and instrument) when used for the qualitative detection of IgM antibody to hepatitis B virus core antigen (IgM anti-HBc) when using the AxSYM CORE-M 2.0 Reagent Pack. The performance of the AxSYM CORE-M 2.0 Controls has not been established with any other IgM anti-HBc assays.

WARNINGS AND PRECAUTIONS

For *In Vitro* Diagnostic Use.

- **CAUTION: This product contains human sourced and/or potentially infectious components. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens.[1] Biosafety Level 2[2] or other appropriate biosafety practices[3,4] should be used for materials that contain or are suspected of containing infectious agents.**
- The AxSYM CORE-M 2.0 Negative Control is nonreactive for HBsAg, HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, anti-HCV, anti-HBc, and anti-HBs.
- The AxSYM CORE-M 2.0 Positive Control is reactive for IgM anti-HBc and nonreactive for HIV-1 Ag or HIV-1 RNA, anti-HIV-1/HIV-2, and anti-HCV. Plasma is also tested for HBsAg and may be either nonreactive or reactive.
- This product contains Sodium Azide; for a specific listing, refer to the **MATERIALS PROVIDED** section of this package insert. Contact with acids liberates very toxic gas. This material and its container must be disposed of in a safe way.

MATERIALS PROVIDED

2 Bottles (7.4 mL each) of AxSYM CORE-M 2.0 Controls:

- The Negative Control (1 Bottle) is recalcified IgM anti-HBc negative human plasma. Preservative: 0.1% Sodium Azide.
- The Positive Control (1 Bottle) is recalcified IgM anti-HBc positive human plasma in recalcified IgM anti-HBc negative human plasma. Preservative: 0.1% Sodium Azide.

PREPARATION AND STORAGE

- Controls are liquid ready-to-use. No preparation is required.
- When stored and handled as directed, the controls are stable until the expiration date.
- The controls must be stored at 2-8°C and may be used immediately after removal from 2-8°C storage.

Refer to the AxSYM CORE-M 2.0 assay reagent package insert for the maximum on board stability requirements.

Store at 2-8°C

QUALITY CONTROL PROCEDURES

Refer to the AxSYM CORE-M 2.0 assay package insert and the AxSYM System Operations Manual for additional information.
The minimum control requirement for the AxSYM CORE-M 2.0 assay is a single sample of each of the Negative and Positive Controls tested every 24 hours each day of use for each reagent lot. Additional controls may be tested in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control procedure.

PROCEDURE

- AxSYM CORE-M 2.0 Controls must be mixed by gentle inversion before use.
- To obtain the recommended volume requirements for the AxSYM CORE-M 2.0 Controls, hold the bottles **vertically** and dispense 6 drops of each control into each respective sample cup.

EXPECTED RESULTS

The AxSYM CORE-M 2.0 Controls have the following ranges:

Control	Color	IgM Anti-HBc (Minimum Titer)	Control Range (Index Value)
Negative	Natural	Not Applicable	0.01 – 0.20
Positive	Blue[a]	1:1	1.00 – 2.30

[a] Dye: Acid Blue No. 9

LIMITATIONS

- Control values have not been established for assays other than the AxSYM CORE-M 2.0 assay. If the user wishes to use this control material with other assays, it is their responsibility to establish the appropriate ranges.
- The AxSYM CORE-M 2.0 Controls are in a serum matrix made from recalcified plasma. The user should provide alternate control material for plasma when necessary.
- The controls are not calibrators and should not be used for assay calibration.

BIBLIOGRAPHY

1. US Department of Labor, Occupational Safety and Health Administration, 29 CFR Part 1910.1030, Occupational exposure to bloodborne pathogens.
2. US Department of Health and Human Services. *Biosafety in Microbiological and Biomedical Laboratories*. 4th ed. Washington, DC: US Government Printing Office; May 1999.
3. World Health Organization. Laboratory Biosafety Manual. Geneva: World Health Organization; 2004.
4. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections: Approved Guideline—Third Edition.* CLSI Document M29-A3. Wayne, PA: CLSI; 2005.

August 2006

55