

Epstein-Barr virus VCA IgM micro- capture ELISA

Enzyme immunoassay for the qualitative or quantitative determination of IgM antibodies against the viral capsid antigen (VCA) of Epstein-Barr virus in human serum and plasma.

REF **RE57361**

 **96**

   **2-8°C**

EU: **IVD** 



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1. INTENDED USE

Enzyme immunoassay for the qualitative or quantitative determination of IgM antibodies against the viral capsid antigen (VCA) of Epstein-Barr virus (EBV) in human serum and plasma.

2. SUMMARY AND EXPLANATION

Infectious mononucleosis is an acute lymphoproliferative disease that is common in children and young adults and is caused by the Epstein-Barr virus (EBV). The EBV is one of the herpes viruses 4 (gamma).

Characteristic clinical features include:

1. fever, sore throat, and lymphadenopathy
2. an associated absolute lymphocytosis greater than 50%, containing at least 10% of atypical lymphocytes in the peripheral blood
3. development of transient heterophil and persistent antibody responses against EBV
4. abnormal liver function tests.

4% of infected young adults show an icteric manifestation and 50% have splenomegaly. In addition, EBV is implicated in nasopharyngeal carcinoma, Burkitt lymphoma and Hodgkin's disease.

An infectious mononucleosis similar syndrome can be caused by cytomegalovirus, toxoplasmosis and other viral infection; differential diagnosis depends on laboratory results, with only EBV stimulating the production of heterophil antibodies.

EBV is present in saliva of patients with acute infectious mononucleosis, and excretion of the virus from the oropharynx, which persists for several months after the outbreak of the disease, is one of the major ways of virus transmission. Infected persons keep the Epstein-Barr virus for lifetime, but are mostly asymptomatic. In developing countries practically the whole population is infected; in western countries prevalence is about 80 – 90%. Transmission, possibly from the mother, already takes place at child's age and mainly via saliva.

Of great importance for diagnosis is the detection of an increase in relative and absolute number of lymphocytes and atypical lymphocytes. During the disease 50 – 60% of leukocytes in the peripheral blood can be lymphatic cells, of which normally 10% are atypical lymphocytes. In addition, abnormal liver function tests and high titers of heterophil antibodies are seen.

Serological tests like ELISA are very useful for the detection of anti-EBV antibodies, especially if heterophil antibodies are absent. The different stages of an EBV infection (acute, reactivated, past) are characterized by the appearance of different antibodies (IgA, IgG, IgM) against different viral antigens (virus capsid antigen = VCA, early antigen = EA and Epstein-Barr virus nuclear antigen = EBNA).

The six parameters produced by IBL (VCA IgA / IgG / IgM, EA IgA / IgG und EBNA IgG) enable to detect and differentiate all stages of an EBV infection. A well directed selection of antigens for IBL EBV ELISAs results in an extraordinary sensitivity and specificity for the diagnosis of acute diseases and for the detection of past infections.

The assays for the detections of antibodies against EA and EBNA use highly specific recombinant antigens – EA p54 antigen expressed in *E. coli* and EBNA-1 p72 antigen expressed in Sf9 cells; affinity purified VCA gp125 from P3HR1 cells is responsible for the high sensitivity of the VCA ELISAs.

This selection of antigens together with a purposeful regulation of assay characteristics results in a clear distinction between positive and negative samples, i.e. a small grey zone.

The very high sensitivity of the VCA IgA assay and the 100% specificity of the EA IgA ELISA are of particular importance; the combination of these two assays allows the correct detection of reactivated infections with extremely high reliability.

The μ -capture principle applied for the VCA IgM assay results in a higher specificity compared to IgM ELISAs following the sandwich principle, i.e. false positive results are minimized.

Information about antibody combinations that are typical for the different stages of an infection is given in chapter PERFORMANCE.

3. TEST PRINCIPLE

Solid phase enzyme-linked immunosorbent assay (ELISA) based on the μ -capture principle.

Anti-human-IgM-antibodies are bound on the surface of the microtiter strips. Diluted patient serum or ready to use calibrators and controls are pipetted into the wells of the microtiter plate. A binding between the IgM antibodies of the sample and the IgM class-specific antibodies on the microtiter plate takes place during the first incubation.

In the second incubation, ready to use antigen conjugate (biotinylated EBV viral capsid antigen, VCA gp 125 affinity purified from P3HR1-cells, mixed with anti-biotin-peroxidase) is added and binds to specific IgM antibodies captured on the microtiter wells.

Subsequently, substrate (TMB) is pipetted, inducing the development of a blue dye in the wells. The colour development is terminated by the addition of a stop solution, which courses the colour change from blue to yellow. The resulting dye is measured spectrophotometrically at the wavelength of 450 nm. The concentration of the specific IgM antibodies is directly proportional to the intensity of the colour.

4. WARNINGS AND PRECAUTIONS

1. For *in-vitro diagnostic* use only. For professional use only.
2. Before starting the assay, read the instructions completely and carefully. Use the valid version of the package insert provided with the kit. Be sure that everything is understood.
3. In case of severe damage of the kit package please contact IBL or your supplier in written form, latest one week after receiving the kit. Do not use damaged components in test runs, but keep safe for complaint related issues.
4. Obey lot number and expiry date. Do not mix reagents of different lots. Do not use expired reagents.
5. Follow good laboratory practice and safety guidelines. Wear lab coats, disposable latex gloves and protective glasses where necessary.
6. Reagents of this kit containing hazardous material may cause eye and skin irritations. See MATERIALS SUPPLIED and labels for details. Material Safety Data Sheets for this product are available on the IBL-Homepage or upon request directly from IBL.
7. Chemicals and prepared or used reagents have to be treated as hazardous waste according to national biohazard and safety guidelines or regulations.
8. The cleaning staff should be guided by the professionals regarding potential hazards and handling.
9. Avoid contact with Stop solution. It may cause skin irritations and burns.
10. All reagents of this kit containing human serum or plasma have been tested and were found negative for anti-HIV I/II, HBsAg and anti-HCV. However, a presence of these or other infectious agents cannot be excluded absolutely. For this reason reagents should be treated as potential biohazards in use and for disposal.

5. STORAGE AND STABILITY

The kit is shipped at ambient temperature and should be stored at 2-8 °C. Keep away from heat or direct sunlight. The storage and stability of specimens and prepared reagents is stated in the corresponding chapters.

The microtiter strips are stable up to the expiry date of the kit in the broken, but tightly closed bag when stored at 2-8 °C.

6. SPECIMEN COLLECTION AND STORAGE

Serum, Plasma (EDTA, Citrate)

The usual precautions for venipuncture should be observed. It is important to preserve the chemical integrity of a blood specimen from the moment it is collected until it is assayed. Do not use grossly hemolytic, icteric or grossly lipemic specimens. Samples appearing turbid should be centrifuged before testing to remove any particulate material.

Storage:	2-8°C	-20°C	Keep away from heat or direct sunlight. Avoid repeated freeze-thaw cycles.
Stability:	7 days	> 7 days	

7. MATERIALS SUPPLIED

Quantity	Symbol	Component
1 x 12 x 8	MTP	Microtiter Plate Break apart strips. Coated with antibodies against human IgM-Ab.
1 x 12 mL	AG CONJ	Antigen Conjugate Red colored. Contains: EBV VCA antigen, stabilizers.
1 x 200 µL	ENZ TRACER CONC	Enzyme Tracer Concentrate (100x) Contains: antibodies against antigen, conjugated to peroxidase, stabilizers.
1 x 1.5 mL	CONTROL+	Positive Control Red colored. Ready to use. Contains: IgM antibodies against EBV-VCA (Human serum), stabilizers.
1 x 1.5 mL	CONTROL-	Negative Control Green colored. Ready to use. Contains: IgM antibodies against EBV-VCA (Human serum), stabilizers.
1 x 4 x 1.5 mL	CAL A-D	Standard A-D 2; 20; 50; 200 U/mL. Standard B = Cut-Off Control Ready to use. Contains: IgM antibodies against EBV-VCA (Human serum), stabilizers.
1 x 100 mL	DILBUF	Diluent Buffer Blue colored. Ready to use. Contains: PBS Buffer, detergents, BSA, stabilizers.
1 x 100 mL	WASHBUF CONC	Wash Buffer, Concentrate (10x) Contains: PBS Buffer, detergents.
1 x 15 mL	TMB SUBS	TMB Substrate Solution Ready to use. Contains: TMB, Buffer, stabilizers.
1 x 15 mL	TMB STOP	TMB Stop Solution Ready to use. 0.5 M H ₂ SO ₄ .

8. MATERIALS REQUIRED BUT NOT SUPPLIED

1. Micropipettes (Multipette Eppendorf or similar devices, < 3 % CV). Volume: 5; 100; 500 µL
2. Vortex mixer
3. Tubes for sample dilution
4. Incubator, 37 °C
5. 8-Channel Micropipettor with reagent reservoirs
6. Wash bottle, automated or semi-automated microtiter plate washing system
7. Microtiter plate reader capable of reading absorbance at 450 nm (reference wavelength 600-650 nm)
8. Bidistilled or deionised water
9. Paper towels, pipette tips and timer

9. PROCEDURE NOTES

1. Any improper handling of samples or modification of the test procedure may influence the results. The indicated pipetting volumes, incubation times, temperatures and pretreatment steps have to be performed strictly according to the instructions. Use calibrated pipettes and devices only.
2. Once the test has been started, all steps should be completed without interruption. Make sure that required reagents, materials and devices are prepared ready at the appropriate time. Allow all reagents and specimens to reach room temperature (18-25 °C) and gently swirl each vial of liquid reagent and sample before use. Mix reagents without foaming.
3. Avoid contamination of reagents, pipettes and wells/tubes. Use new disposable plastic pipette tips for each component and specimen. Do not interchange caps. Always cap not used vials. Do not reuse wells/tubes or reagents.
4. Use a pipetting scheme to verify an appropriate plate layout.
5. Incubation time affects results. All wells should be handled in the same order and time sequences. It is recommended to use an 8-channel Micropipettor for pipetting of solutions in all wells.
6. Microtiter plate washing is important. Improperly washed wells will give erroneous results. It is recommended to use a multichannel pipette or an automatic microtiter plate washing system. Do not allow the wells to dry between incubations. Do not scratch coated wells during rinsing and aspiration.

Rinse and fill all reagents with care. While rinsing, check that all wells are filled precisely with Wash Buffer, and that there are no residues in the wells.

7. Humidity affects the coated wells/tubes. Do not open the pouch until it reaches room temperature. Unused wells/tubes should be returned immediately to the resealed pouch including the desiccant.

10. PRE-TEST SETUP INSTRUCTIONS

10.1. Preparation of Components

Dilute / dissolve	Component		Diluent	Relation	Remarks	Storage	Stability
100 mL	WASHBUF CONC	ad 1000 mL	bidist. water	1:10	Warm up at 37°C to dissolve crystals, if necessary. Mix vigorously.	2-8°C	8 weeks

Component	to be mixed	with	Relation	Remarks	Storage	Stability
ENZ TRACER CONC	generally	AG CONJ	1:101	e.g. 100 µL ENZ TRACER CONC + 10 mL AG CONJ	2-8 °C	1 day

10.2. Dilution of Samples

Sample	to be diluted	with	Relation	Remarks
Serum / Plasma	generally	DILBUF	1:101	e.g. 5 µL + 500 µL DILBUF

Samples containing concentrations higher than the highest standard have to be diluted further.

11. TEST PROCEDURE

1.	Pipette 100 µL of each Standard, Control and diluted sample into the respective wells of the Microtiter Plate. In the qualitative test only Standard B (Cut-off Standard) is used. The reliability of the analysis can be improved by duplicate determinations.
2.	Cover plate with adhesive foil. Incubate 60 min at 37°C.
3.	Remove adhesive foil. Discard incubation solution. Wash plate 3 x with 300 µL of diluted Wash Buffer . Remove excess solution by tapping the inverted plate on a paper towel.
4.	Pipette 100 µL of Enzyme Conjugate into each well.
5.	Cover plate with new adhesive foil. Incubate 60 min at 37°C.
6.	Remove adhesive foil. Discard incubation solution. Wash plate 3 x with 300 µL of diluted Wash Buffer . Remove excess solution by tapping the inverted plate on a paper towel.
7.	For adding of Substrate and Stop Solution use, if available, an 8-channel Micropipettor. Pipetting should be carried out in the same time intervals for Substrate and Stop Solution. Use positive displacement and avoid formation of air bubbles.
8.	Pipette 100 µL of TMB Substrate Solution into each well.
9.	Incubate 30 min at 18-25°C in the dark (without adhesive foil).
10.	Stop the substrate reaction by adding 100 µL of TMB Stop Solution into each well. Briefly mix contents by gently shaking the plate.
11.	Measure optical density with a photometer at 450 nm (Reference-wavelength: 600-650 nm) within 60 min after pipetting of the Stop Solution.

12. QUALITY CONTROL

The test results are only valid if the test has been performed following the instructions. Moreover the user must strictly adhere to the rules of GLP (Good Laboratory Practice) or other applicable standards/laws. All standards must be found within the acceptable ranges as stated on the QC Certificate. If the criteria are not met, the run is not valid and should be repeated. Each laboratory should use known samples as further controls.

In case of any deviation the following technical issues should be proven: Expiration dates of (prepared) reagents, storage conditions, pipettes, devices, incubation conditions and washing methods.

13. CALCULATION OF RESULTS

The evaluation of the test can be performed either qualitatively or quantitatively.

13.1. Qualitative Evaluation

The Cut-off value is given by the optical density (OD) of the Standard B (Cut-off standard). The Cut-off index (COI) is calculated from the mean optical densities of the sample and Cut-off value. If the optical density of the sample is within a range of 10 % around the Cut-off value (grey zone), the sample has to be considered as borderline. Samples with higher ODs are positive, samples with lower ODs are negative.

For a quantification, the Cut-off index (COI) of the samples can be formed as follows:

$$\text{COI} = \frac{\text{OD Sample}_{\text{measured value}}}{\text{CO}}$$

Typical Example:

Cut-off = OD (Standard B, Cut-off standard) = 0.45

Sample OD = 0.70

Cut-off index (COI): $0.70 / 0.45 = 1.56$. The sample has to be considered positive.

13.2. Quantitative Evaluation

The obtained OD of the standards (y-axis, linear) are plotted against their concentration (x-axis, logarithmic) either on semi-logarithmic graph paper or using an automated method. A good fit is provided with cubic spline, 4 Parameter Logisitics or Logit-Log.

For the calculation of the standard curve, apply each signal of the standards (one obvious outlier of duplicates might be omitted and the more plausible single value might be used).

The concentration of the samples can be read from the standard curve.

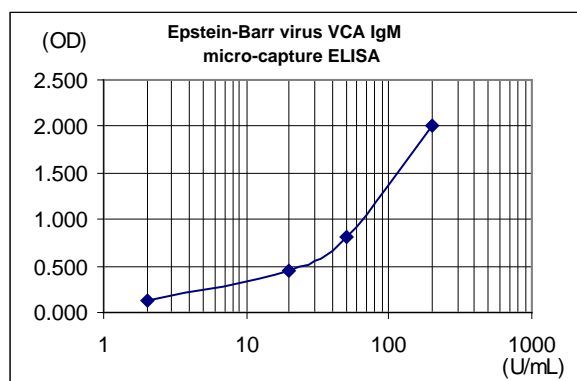
The initial dilution has been taken into consideration when reading the results from the graph. Results of samples of higher predilution have to be multiplied with the dilution factor.

Samples showing concentrations above the highest standard can be diluted as described in PRE-TEST SETUP INSTRUCTIONS and reassayed.

Typical Calibration Curve

(Example. Do not use for calculation!)

Standard	U/mL	OD _{Mean}
A	2	0.131
B	20	0.455
C	50	0.803
D	200	2.001



14. INTERPRETATION OF RESULTS

Method	Range	Interpretation
Quantitative (Standard curve):	> 22 U/mL	positive
	18 – 22 U/mL	borderline
	< 18 U/mL	negative
Qualitative (Cut-off Index, COI):	> 1.1	positive
	0.9 – 1.1	borderline
	< 0.9	negative

The results themselves should not be the only reason for any therapeutical consequences. They have to be correlated to other clinical observations and diagnostic tests.

15. LIMITATIONS OF THE PROCEDURE

Specimen collection and storage have a significant effect on the test results. See SPECIMEN COLLECTION AND STORAGE for details.

Azide and thimerosal at concentrations > 0.1 % interfere in this assay and may lead to false results.

The following blood components do not have a significant effect (+/-20% of expected) on the test results up to the below stated concentrations:

Hemoglobin	2.0 mg/mL
Bilirubin	0.3 mg/mL
Triglyceride	2.5 mg/mL

16. PERFORMANCE

Analytical Specificity (Cross Reactivity)	No cross-reactivities were found to (n=6-14):		Antibodies against Parvovirus B19, Hepatitis C, HSV 1/2, Rubella, CMV, Influenza A/B, VZV, ANA			
	Cross-reactivities were found to (positive tested samples)		Hepatitis B (1/10), RF (1/15), Mumps (2/17), Measles (1/10)			
Precision	Range ± 1xSD (U/mL)	CV (%)	Range ± 1xSD (U/mL)	CV (%)	Range ± 1xSD (U/mL)	CV (%)
Intra-Assay (n = 20)	125 ± 5	4	19 ± 1	3	12 ± 1	8
Inter-Assay (n = 20)	89 ± 6	7	20 ± 2	10	7 ± 2	21
Inter-Lot (n = 20)	100 ± 16	16	20 ± 2	11	18 ± 2	11
Linearity	Range (U/mL)	Dilution Range (sample specific)		Rec. Range (%)		
	7 – 98	1:32 – 1:512		97 – 121		
Automation	This test has been validated with: BEPIII (Dade Behring), TRITURUS (Grifols)					




To determine the clinical sensitivity and specificity of all 6 IBL EBV parameter ELISAs, a sample panel of 242 samples have been tested in all assays. This panel is made up of samples from different phases of an EBV infection:

Seronegative (including samples from children)	n = 64
Acute phase of an infection	n = 48
Reactivated infection	n = 55
Past infection	n = 75

The classification of the samples has been approved by immunofluorescence (IFA), especially the samples for reactivated infection.

For method comparison, the entire panel has been measured with FDA-approved reference ELISAs for EBNA IgG, VCA IgG, VCA IgM and EA IgG. For EA IgA and VCA IgA no FDA-approved reference ELISA exists.

Samples determined as positive (including border-line) with IBL-ELISAs						
n = 242	VCA IgM	VCA IgG	VCA IgA	EA IgA	EA IgG	EBNA IgG
acute infection n = 48	96%	90%	75%	65%	90%	0%
reactivated infection n = 55	0%	100%	96%	76%	93%	100%
past infection n = 75	1%	89%	47%	0%	10%	100%
Seronegative n = 22	5% *	14% *	18% *	0%	0%	0%
children 0-12 month n = 42	2%	36% **	2%	0%	2%	14% **

	almost 100 % positive		almost 100 % negative
	varyingly positive		maternal Ab

* the EBV seronegative group may include very early asymptomatic EBV infections, that lead to positive results for VCA IgM, IgA and IgG

** maternal antibodies are only present for VCA IgG and EBNA IgG in very low concentrations

16.1. Sensitivity and specificity of IBL EBV-ELISAs regarding different phases of an EBV infection

Acute EBV infection: As shown in the table above, an acute EBV infection can be clearly identified by three parameters that are expected to be positive (VCA IgM, VCA IgG and EA IgG) and by EBNA IgG, which was found clearly negative, as expected.

Reactivated EBV infection: In contrast to an acute infection, a reactivated EBV infection with or without tumor development is expected to be 100 % negative for VCA IgM, but clearly positive for VCA IgG, VCA IgA, EA IgG and EBNA IgG, as shown in the table above.

Past infection: Past EBV infections show only two clearly positive parameters, VCA IgG and EBNA IgG. All other parameters are expected to be almost negative, with the exception of VCA IgA, which can persist up to one year in past infections.













Seronegative patients Seronegative patients should have negative results for all six parameters. Single positive results for VCA IgG, VCA IgA or VCA IgM may indicate a very early, still asymptomatic EBV infection. Alternatively, such isolated positive results are a sign of a slight non-specificity of the assays, which may recognize antibodies from polyclonal stimulations due to their very high sensitivity. For clarification it is suggested to repeat the test after 7-10 days.

Maternal antibodies: Maternal antibodies are detectable in very low concentrations only during the first 6-9 months of life and can only be expected to be positive for the two parameters of past infections, VCA IgG and EBNA IgG. All other antibodies should be negative, as shown in the table above. The fact that maternal antibodies can be detected demonstrates the very high sensitivity of the IBL ELISAs for those two parameters.

17. PRODUCT LITERATURE REFERENCES

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Symbols / Symbole / Symbôles / Símbolos / Símbolos / Σύμβολα

	Cat.-No.: / Kat.-Nr.: / No.- Cat.: / Cat.-No.: / N.º Cat.: / N.-Cat.: / Αριθμός-Κατ.:
	Lot-No.: / Chargen-Bez.: / No. Lot: / Lot-No.: / Lote N.º: / Lotto n.: / Αριθμός -Παραγωγή:
	Use by: / Verwendbar bis: / Utiliser à: / Usado por: / Usar até: / Da utilizzare entro: / Χρησιμοποιείται από:
	No. of Tests: / Kitgröße: / Nb. de Tests: / No. de Determ.: / N.º de Testes: / Quantità dei tests: / Αριθμός εξετάσεων:
	Concentrate / Konzentrat / Concentré / Concentrar / Concentrado / Concentrato / Συμπύκνωμα
	Lyophilized / Lyophilisat / Lyophilisé / Liofilizado / Liofilizado / Liofilizzato / Λυοφιλιασμένο
	In Vitro Diagnostic Medical Device. / In-vitro-Diagnostikum. / Appareil Médical pour Diagnostics In Vitro. / Dispositivo Médico para Diagnóstico In Vitro. / Equipamento Médico de Diagnóstico In Vitro. / Dispositivo Medico Diagnostico In vitro. / Ιατρική συσκευή για In-Vitro Διάγνωση.
	Evaluation kit. / Nur für Leistungsbewertungszwecke. / Kit pour évaluation. / Juego de Reactivos para Evaluació. / Kit de avaliação. / Kit di evaluazione. / Κιτ Αξιολόγησης.
	Read instructions before use. / Arbeitsanleitung lesen. / Lire la fiche technique avant emploi. / Lea las instrucciones antes de usar. / Ler as instruções antes de usar. / Leggere le istruzioni prima dell'uso. / Διαβάστε τις οδηγίες πριν την χρήση.
	Keep away from heat or direct sun light. / Vor Hitze und direkter Sonneneinstrahlung schützen. / Garder à l'abri de la chaleur et de toute exposition lumineuse. / Manténgase alejado del calor o la luz solar directa. / Manter longe do calor ou luz solar directa. / Non esporre ai raggi solari. / Να φυλάσσεται μακριά από θερμότητα και άμεση επαφή με το φως του ηλίου.
	Store at: / Lagern bei: / Stocker à: / Almacene a: / Armazemar a: / Conservare a: / Αποθήκευση στους:
	Manufacturer: / Hersteller: / Fabricant: / Productor: / Fabricante: / Fabbicante: / Παραγωγός:
	Caution! / Vorsicht! / Attention! / ¡Precaución! / Cuidado! / Attenzione! / Προσοχή!
<p>Symbols of the kit components see MATERIALS SUPPLIED. Die Symbole der Komponenten sind im Kapitel KOMPONENTEN DES KITS beschrieben. Voir MATERIEL FOURNI pour les symbôles des composants du kit. Símbolos de los componentes del juego de reactivos, vea MATERIALES SUMINISTRADOS. Para símbolos dos componentes do kit ver MATERIAIS FORNECIDOS. Per i simboli dei componenti del kit si veda COMPONENTI DEL KIT. Για τα σύμβολα των συστατικών του κιτ συμβουλευτείτε το ΠΑΡΕΧΟΜΕΝΑ ΥΛΙΚΑ.</p>	

COMPLAINTS: Complaints may be submitted initially written or vocal. Subsequently they need to be filed including the test performance and results in writing in case of analytical reasons.

WARRANTY: The product is warranted to be free from material defects within the specific shelf life and to comply with product specifications delivered with the product. The product must be used according to the Intended use, all instructions given in the instructions for use and within the product specific shelf life. Any modification of the test procedure or exchange or mixing of components of different lots could negatively affect the results. These cases invalidate any claim for replacement.

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