LABORATORY · DIAGNOSTICS

Borrelia ViraChip® IgM Test Kit 2.0

Instructions for use

CE

Chip-Immunoblot for the qualitative detection of **IgM** antibodies against specific **Borrelia species** antigens in human serum. For using the **Borrelia ViraChip® IgM Test Kit 2.0** with cerebrospinal fluid (CSF) as sample material the corresponding, separately available instruction for use has to be considered.

The Borrelia ViraChip® IgM Test Kit 2.0 is an immunoblot based on an enzyme-immunoassay in a microarray format, carrying highly purified specific native antigens from Borrelia afzelii (Pko) and Borrelia burgdorferi sensu stricto as well as recombinant VlsE at defined positions. The Borrelia ViraChip® IgM Test Kit 2.0 is manufactured according to the guidelines **98/79/EG** and **DIN 58967-40**.

The Borrelia ViraChip® IgM Test Kit 2.0 fulfils the quality standards of the microbiological-infectiological guidelines (“**MiQ” 12/2017** (18)), the general DIN recommendation (**DIN 58967-40** (5)). These guidelines postulate a *two-band* criterion for a positive result and describe special requirements for the detection of antibodies against Borrelia burgdorferi.

Principle of the assay

A nitrocellulose membrane is fixed at the bottom of each well of a standard microtiter plate (MTP). On this membrane, the antigens are fixed as analyte spots. The wells of these microarrays are single breakable and are stored in a holding frame with 96 positions. During the serum incubation step Borrelia specific IgM antibodies bind to the immobilised antigens, herein after referred to as spots, on the microarray. During the conjugate reaction, AP-conjugate binds to the antigen-antibody complex. The alkaline phosphatase converts the chromogen/substrate and thus, stains the antigen-antibody complex on the microarray purple. The washing procedures following serum, conjugate and chromogen/substrate incubation steps remove unbound antibodies and reagents.

In addition to the analyte spots, each microarray includes the following controls spots: **serum controls, conjugate controls**, **calibrator controls** and a **negative control**. The analyte spots serve to detect antibodies against **p41, p39, OspC, Osp17** and **VlsE**.

For clear assignment, each well is coded by a colour system: Therefore, the Borrelia ViraChip® IgM is marked with a **green quadrant** on the rim of the well.

Order No.:	**V-BSCMOK**	Order No.:	**V-BSCMDK (Deca Kit)**
Kit size:	**1 MTP with 96 single breakable wells**	Kit size:	**10x 1 MTP with 96 single breakable wells**
Specimen:	**10 µl serum**	Specimen:	**10 µl serum**
Time for testing:	**approx. 130 minutes**	Time for testing:	**approx. 130 minutes**

Materials provided

1 or 10 MTP with 96 wells	**Borrelia ViraChip® IgM Antigen Coated Wells** Single breakable wells with ViraChip® Microarrays, ready to use	(Prod. No.: V-BSCMAC)
1x or 10x 12 ml	**ViraChip® AP-Anti-Human IgM Conjugate** Anti-human IgM Conjugate Solution for ViraChip® tests, ready to use	(Order No.: V-UVCMKI)
1x or 10x 100 ml	**ViraChip® / ViraStripe® / ViraBlot® Diluent / Wash Buffer** Wash Buffer Concentrate for ViraChip® tests, 10x	(Order No.: V-UVNUWP)
1x or 10x 12 ml	**ViraChip® Chromogen / Substrate Solution** Chromogen / Substrate solution for ViraChip® tests, ready-to-use	(Order No.: V-UVCUCS)

Sample buffer required for sample dilution, is delivered separately

50 ml	**ViraChip® Sample Buffer** Sample Buffer for ViraChip® tests, ready-to-use	(Order No.: V-UVCUPP)

Additionally, available

1 MTP strip with 8 wells	**Borrelia ViraChip® IgM Antigen Coated Wells (8)** Single breakable wells with ViraChip® Microarrays, ready to use	(Order. No.: V-BSCMRT)
330 µl	**Borrelia ViraChip® IgM Positive Control** Human, ready to use	(Order No.: V-BSCMPK)
330 µl	**Borrelia ViraChip® IgG,A,M Negative Control** Human, ready to use	(Order No.: V-BSCPNK)
96 wells	**Microtiter plate** with 96 empty wells	(Order No.: V-UVNMTP)

Preparation of reagents and patient samples

Bring all reagents and the packed microtiter plate to room temperature (RT, 20-23°C) prior to use and perform the test at room temperature. Mix all reagents thoroughly before use.

Wash Buffer Working Dilution:	Dilute **Wash Buffer Concentrate 1:10** with distilled or deionised water (100 ml concentrate + 900 ml water).
Sample Buffer:	Ready to use.
Conjugate Solution:	Ready to use.
Chromogen / Substrate Solution:	Ready to use.
Wells:	Carefully unpack the microtiter plate (MTP) and place the required number of wells in an empty holding frame (see processing of the test run, step 1). Use wells directly after removing from packing. Return unused wells directly into the original packing, seal accurately and store at 2-8°C.
Patient samples:	Use 100 µl of a **1:76** dilution of patient serum, e.g. **10 µl of patient serum** plus **750 µl Sample Buffer*.**
Controls:	Optionally, use 100 µl of a **1:16** dilution of control serum, e.g. **10 µl of control serum** plus **150 µl Sample Buffer***.

*) Depending on the equipment, dilutions may be performed in several steps.

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Preparation of the test run using the ViraChip® Software

For the preparation of the test run the steps **Assembling** and **Loading** have to be performed in the ViraChip® Software. Afterwards the step **Processing** follows.

- **Assemble**: Test selection and transfer of sample data into the layout.
- **Load**: Scanning of the 2D bar code of the microtiter plate to transfer the lot number of the antigen coated wells and the lot specific factors.
- **Process:** Data transfer to processor **or** manual processing

Processing of the test run#)

1. **Preparation**
   - Place the needed amount of wells into the holding frame.
   - Fill free positions of a column in the holding frame with empty wells.

   Place the wells into the holding frame accordingly to the layout. Pay attention that no plastic particles fall into the wells while breaking the bars.
2. **Preincubation**
   - Add 300 µl Wash Buffer Working Dilution to each well.
   - Incubate by shaking for 5 minutes.
   - Aspirate liquid.
3. **Serum incubation**
   - Add 100 µl of each diluted patient serum or 100 µl of each diluted control serum.
   - Incubate by shaking for 30 minutes at RT.
   - Aspirate liquid.
4. **3 x washing**
   - Add 300 µl Wash Buffer Working Dilution to each well.
   - Incubate by shaking for 5 minutes at RT.
   - Aspirate liquid.
5. **Conjugate incubation**
   - Add 100 µl Conjugate Solution to each well.
   - Incubate by shaking for 30 minutes at RT.
   - Aspirate liquid.

   Make sure the bottoms of the wells are not damaged while adding or aspirate liquid.

   The bottoms of the wells have to be completely covered with liquid during the respective incubation steps.

   During the incubation steps, use an orbital shaker with a shaking frequency of approx. 750 rpm or a linear shaker with a shaking frequency of approx. 20 Hz.
6. **3 x washing**
   - Add 300 µl Wash Buffer Working Dilution to each well.
   - Incubate by shaking for 5 minutes at RT.
   - Aspirate liquid.
7. **1 x washing**
   - Add 300 µl distilled or deionised water to each well.
   - Incubate by shaking for 1 minutes at RT.
   - Aspirate liquid.
8. **Substrate incubation**
   - Add 100 µl Chromogen / Substrate Solution to each well.
   - Incubate by shaking for 15 minutes at RT.
   - Stop the reaction by aspirating the liquid.
9. **3 x rinsing**
   - Add 300 µl distilled or deionised water to each well.
   - No incubation necessary.
   - Aspirate liquid.
10. **Dry wells.**
    Let the wells dry under continuous airflow for 20 minutes at 60 % humidity max.

    At higher humidity levels, the drying time may be extended. Wells dry for 12 hours at RT.
11. **Measure and interpret wells.**

    Measurement of spot intensities has to be performed within 24 hours (store MTP in a dark place) e.g. by the ViraChip® Scanner or the ViraChip® Reader camera system. The subsequent interpretation is done by the ViraChip® Software.

#) For automated processing incubation times and volumes of single steps of the procedure may be adjusted to the respective processor type. Refer to section “Notes to Equipment and Software”.

Assay interpretation with the ViraChip® Software

1. **After measuring the spot intensities, the interpretation of the ViraChip® Microarrays is performed using the ViraChip® Software. A detailed description of each step can be found in the ViraChip® Software Manual (available on request).**

   The next steps in the ViraChip® Software are:
   - **Scan:** Measurement of the single ViraChip® Microarrays e.g. by the ViraChip® Scanner or the ViraChip® Reader camera system.
   - **Analyse:** Calculation of the total result from the data**.**

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2. Check validity of ViraChip® Microarrays.

The validity check is performed by the ViraChip® Software automatically.

A test run is valid, if the following spots are detectable on each ViraChip® Microarray:
- **Serum controls (sc)**
- **Conjugate controls IgM (ccM)**
- **Calibrator controls (cal)**

and if the following spot is **not** visible:
- **Negative control (nc)**

If these validation criteria are not fulfilled, the ViraChip® Microarray is classified as invalid. ViraChip® Microarrays that are invalid must not be interpreted and should be repeated.

If multiple conjugate controls are detectable, the strongest spots must indicate the conjugate class being used.

3. Check spot assignment.

The spot layout is shown in Fig. 1. The spot assignment is performed by the ViraChip® Software automatically.

The visual verification of the spots being detected is done by the user. For implausible assignments or wrongly detected spots the QC selection field of the ViraChip® Software has to be changed to “invalid”. This sample should be repeated.

4. Assessment of ViraChip® Microarrays.

According to quality laboratory guidelines, the use of a calibrator control or cut off control for each run is recommended (16, 25). The calibrator controls of the Borrelia ViraChip® IgM are integrated on the ViraChip® Microarray. The assessment is performed by the ViraChip® Software automatically.

The measured mean intensity of the calibrator controls is multiplied by the lot specific factor for each antigen (spot triplet). The resultant value is used as cut-off for the assessment of the respective antigen.

A spot triplet is considered as **distinct** if its mean intensity is **equal** to or **higher** than the intensity of the respective cut off.
A spot triplet is not assessed if its mean intensity is **lower** than the intensity of the respective cut off or if it is **not present**.

5. Interpretation of patient spots.

The identified spot triplets of each patient sample have to be considered as symptoms of the disease. A final clinical diagnosis should always be made considering anamnesis, clinical manifestations and laboratory data (24).

“If the pattern of reactive bands meets the specific conditions, the result is positive, i.e. the positive result of an EIA or another test of the first step is confirmed. If, despite the presence of specific diagnostic bands, the criteria for a positive result are not fulfilled, the result is considered equivocal. In such a case a follow-up control may be recommended.” (18)

The following antigens of the Borrelia ViraChip® IgM are considered as **highly specific** for Borrelia species for the detection of IgM antibodies: **p41, p39, OspC, p21, Osp17** and **VlsE**.

Figure

Antigens:
Each Borrelia specific antigen (**p41, p39, OspC, Osp17** and **VlsE)** is spotted three times with the same concentration as spot triplet. Each spot triplet corresponds to one band on an immunoblot.
Controls:
The following integrated controls are implemented on the Borrelia ViraChip® IgM:
Serum controls (sc), negative control (nc), conjugate controls (ccG, ccM) and **calibrator controls (cal).**

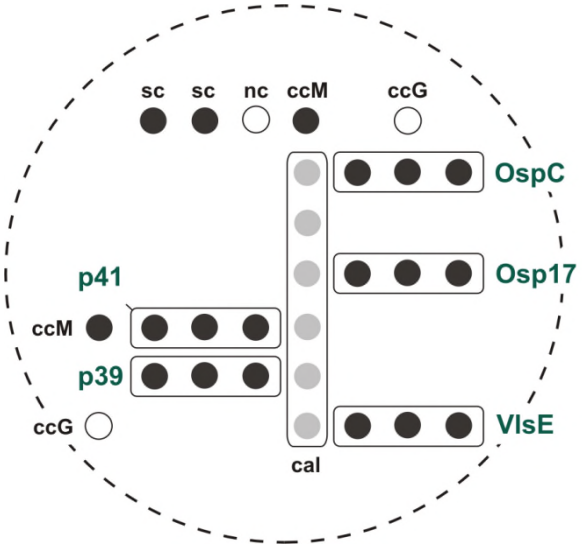

Figure1: Schematic drawing of one well of the microtiter plate with the Borrelia ViraChip® IgM Microarray (magnified). Spot layout for antigens and integrated controls.

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Interpretation criteria

Distinct Borrelia specific spot triplets are calculated in relation to the calibrator control and the lot specific factors by the ViraChip® Software. Calibrator Controls are implemented on each ViraChip® Microarray.

Identified spot triplet	Result	Interpretation
At least **one distinct** spot triplets out of: **p41, p39, OspC, Osp17** or **VlsE**	**Positive**	Specific IgM antibodies against **Borrelia species** detectable. An infection with **Borrelia species** is probable.
No or **only weak** spot triplets	**Negative**	No specific IgM antibodies against **Borrelia species** detectable. If an infection is suspected, check a second sample for IgM and IgG specific antibodies after 2-3 weeks.

Rheumatoid factor can affect the reactivity of antigen spot triplets in IgM tests. In the case of unclear spot triplet constellation use RF-Absorbent (ViraSorb, 5 ml, Order No.: CB003) **for IgM analysis.**

Nomenclature and description of Borrelia species antigens from literature

Nomenclature:	Antigen:	Comments:
p41	**Limited specificity** Flagellum protein	Cross-reactivities with other spirochetes and other flagellum carrying bacteria are described (2,15,22,23).
p39	**Highly specific** **BmpA** (Borrelia membrane protein A)	In many patients antibodies against p39 are already detectable in the early stage of the disease (1,15).
OspC	**Highly specific** **OspC** (Outer surface protein C)	At least 13 different immuno-distinct types of OspC are known. IgM antibodies against OspC are often the first Borrelia specific antibodies detectable in patients and may appear before IgM antibodies against p41(1,8,12,13,21,22).
Osp17	**Specific** **Osp17** (Outer surface protein 17)	Binding to Decorin on the host cell. Antibodies against Osp17 are described as specific. The presence of IgG antibodies is associated among others with Arthritis and Neuroborreliosis. Species specific (9,10,19).
VlsE	**Specific** **VlsE** (Variable major protein (VMP) like sequence Expressed)	Antibodies against VlsE are described as specific. IgM antibodies are already being developed at an early stage and remain until the late stage of the disease (9).

Diagnostic significance of antibodies against Borrelia species

1. IgG antibodies are produced for the first time several weeks to months after infection and are often not detectable in early stages of infection (22). In suspicion of a recent infection, IgM antibodies should be checked and a second sample should be analysed later. Patients in the 2nd or 3rd stage of the disease are usually positive for IgG antibodies. Antibody titres decrease gradually during convalescence (22).

2. IgM antibodies usually appear 2-3 weeks after onset of the disease for the first time (22). Antibody titres often decline several weeks to months after convalescence. But they may also persist up to several years (7,11,20).

3. IgA antibodies are detectable at an early stage of borreliosis in many patients, in some cases earlier than IgM antibodies.

4. The immune response and consequently the spot triplet pattern differ from patient to patient. As a general rule: The number of antibody types and therefore the number of specific spot triplets is increasing with progression of the disease (1).

5. An early antibiotic therapy can suppress the development of antibodies (17).

6. Medication and immunoglobulin therapy can cause unspecific antibody reactions (24).

7. Cross reactivities to Borrelia antigens are described for infections with Treponema, Leptospira and other bacteria with flagella (2,15,22). An acute EBV infection can cause a polyclonal stimulation of Borrelia antibodies (22). If IgM antibodies against OspC or p41 are detected without clinical symptoms for Borreliosis it needs testing for an EBV infection. Cross reactivities in cases of autoimmune diseases, MS, ALS, Influenza and Syphilis are described as well.

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Performance data

Sensitivity

104 sera from patients with the Lyme borreliosis at early stages Erythema migrans, Erythema chronicum migrans, multiple Erythemata migrantia and at late stages Acrodermatitis chronica atrophicans, Lyme arthritis and neuroborreliosis were assessed to determine the sensitivity of the Borrelia ViraChip® IgM.

Stage of Lyme Borreliosis	**Borrelia ViraChip® IgM** positive, % (n)	**Borrelia ViraChip® IgG, IgM** positive / equivocal, % (n)
Erythema migrans **(n= 17)**	**35%** (6)	**71%** (12)
Erythema chronicum migrans **(n= 22)**	**41%** (9)	**82%** (18)
Multiple Erythemata migrantia **(n= 11)**	**82%** (9)	**91%** (10)
Neuroborreliosis **(n= 13)**	**46%** (6)	**92%** (12)
Acrodermatitis chronica atrophicans **(n= 25)**	**36%** (9)	**100%** (25)
Lyme-Arthritis **(n= 16)**	**25%** (4)	**100%** (16)

Specificity

To determine the specificity of the Borrelia ViraChip® IgM 127 sera from blood donors showing a negative result with a reference test (Borrelia ViraStripe® IgG and IgM Test Kit) were assessed.

Collective	**Borrelia ViraChip® IgM** negative, % (n)	**Borrelia ViraChip® IgG, IgM** negative, % (n)
Blood donors **(n= 127)**	**98%** (125)	**97%** (123)

Warnings and precautions

1. All human serum components were tested for HCV, HIV1,2 antibodies and HBs antigens and found to be negative. Nevertheless, all human kit components as well as the patient samples should be considered as potentially infectious and handled according to safety precautions. While working with potentially infectious/hazardous materials, all national and international rules, regulations, guidelines and laws must be taken into account. This also applies to storage and disposal of chemicals and reagents being used.
2. While working with hazardous or toxic substances/ biological agents precautions have to be applied following national biosafety regulations. Precautions among others are:
- Do not pipette by mouth.
- Wear disposable gloves and safety glasses while working.
- Do not eat, drink or smoke in the working area.

3. The chromogen/substrate solution contains BCIP and NBT. Avoid contact with skin and mucous membranes. In case of contact with skin and eyes wash immediately with large quantities of water.
4. Samples and all potentially contaminated materials must be decontaminated using validated laboratory techniques, e.g. by autoclaving 20 minutes at 121°C. Liquid disposals can be mixed with sodium hypochlorite to a final concentration of 1% sodium hypochlorite. Incubate 30 min for complete disinfection.
5. Please refer to material safety data sheets for detailed information on potential risks, first aid guidelines, accidental release measures, handling and storage recommendations, personal protective equipment, directions for disposal and indications to toxicology.
6. Dust and other contaminations in the wells of the MTP have to be avoided, as this might lead to invalid results.

Storage and stability of reagents

1. ViraChip® Microarrays: In closed bags stable until the expiration date if stored at 2-8°C.
2. Wash Buffer Concentrate, 10x: Stable until the expiration date if stored at 2-8°C.
3. Wash Buffer Working Dilution: Stable for 2 weeks if stored at 2-8°C. For longer storage, aliquot and freeze at -20°C.
4. Sample Buffer: Stable until the expiration date if stored at 2-8°C.
5. Conjugate Solution: Stable until the expiration date if stored at 2-8°C.
6. Chromogen / Substrate Solution: Stable until the expiration date if stored at 2-8°C. Avoid exposure to light!

Specimen indications

1. The **Borrelia ViraChip® IgM Test Kit 2.0** must be used with human serum.
2. Specimens must not be microbially contaminated.
3. Using heat-inactivated, haemolytic, icteric or lipemic specimens may lead to invalid results.
4. Normally, human serum can be stored up to 5 days at 2-8°C. Specimens may be stored at -20°C (or below) for long term storage.
5. Prior test processing, specimens should have reached room temperature. Mix specimens carefully after thawing. Precipitates in specimens can be removed by centrifugation.
6. Avoid multiple freeze and thaw cycles.

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Limitations of the procedure

1. To ensure reliable results, follow carefully the Instructions for Use and "Good Laboratory Practice".
2. A positive result is based on elevated specific antibody titres and should be considered as a symptom. The correlation to a disease is only conditionally possible.
3. A negative result does not exclude a contact with the pathogen or the presence of a disease.
4. Adequately trained personnel only should perform the assay procedure.
5. The detection of specific antibodies can vary within different assays from different manufacturers and can lead to different results due to different sensitivity, specificity and assay methodologies.
6. ViraChip® Microarrays showing a high background level should not be interpreted, especially if spot intensities are lighter than the background level.

Notes to Equipment and Software

1. Automatised processing requires usage of processor type specific test procedures which are validated and programmed by Viramed Biotech AG.
2. Usage of processor specific consumables requires approval of the respective configurations according to manufacturer's instructions by Viramed Biotech AG.
3. The equipment and software configuration provided by Viramed Biotech AG must not be changed. Any alteration can lead to false results.
4. Equipment specific software must be used, only. Changes of configuration files must be perfomed by Viramed Biotech AG.
5. Measuring devices approved by Viramed Biotech AG are allowed to be used, only.
6. Assay interpretation of ViraChip® Microarrays has to be performed using the ViraChip® Software. A manual / visual interpretation is not possible.
7. *In vitro* diagnostics must not be used beyond expiration dates, as reliable results may not be possible.
8. Efficient washing after each incubation step is essential for consistent results; insufficient washing may lead to false results.

Literature

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Symbols used

	Manufacturer		Order Number
	Refer to Instructions for Use		Use by / Expiration Date
	*In-Vitro* Diagnostic Medical Device		Temperature Limitation (Storage)
	Lot Number		Positive serum control
	Sufficient for 96 tests		Negative serum control

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