LABORATORY • DIAGNOSTICS

CE

Borrelia ViraStripe® IgM Test Kit

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

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

The Borrelia ViraStripe® IgM Test Kit fulfils the quality standards of the microbiological-infectiological guidelines ("**MiQ" 12/2000**), the general DIN recommendation (**DIN 58967-40**) and can be evaluated according to "**MiQ" 12/2000** (18) and **DIN 58969-44** (5) criteria. These guidelines postulate a one-band criterion for a positive result and describe special requirements for the detection of antibodies against Borrelia burgdorferi.

Principle of the assay

During the serum incubation step Borrelia specific IgM antibodies bind to the immobilised antigens on the test strip. 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 test strip purple. The washing procedures following serum, conjugate and chromogen/substrate incubation steps remove unbound antibodies and reagents.

The green separation line divides the test strip into a control section and an analytical section. The control section contains the **negative control band**, the **serum control, three conjugate controls** (IgG, IgA, IgM) and the **cut off control**.
The test strip code for Borrelia ViraStripe® IgM test strips is **BM**. Test strips are numbered from **01** to **50.** The analytical section contains the Borrelia specific antigens.

Order No.:	**V-BSSMOK**	Order No.:	**V-BSSMDK (Deca Kit)**
Kit size:	**1x 50 test strips**	Kit size:	**10x 50 test strips**
Specimen:	**20 µl serum**	Specimen:	**20 µl serum**
Time for testing:	**approx. 90 minutes**	Time for testing:	**approx. 90 minutes**

Materials provided

1x or 10x 50 test strips	**Borrelia ViraStripe® Antigen Strips (IgM)** Test strips including a control section and Borrelia specific antigens in the analytical section, ready to use	(Prod. No.: V-BSSMAS)
1x or 10x 9 ml	**ViraStripe® / ViraBlot® AP-Anti-Human IgM Conjugate** Concentrate, goat	(Order No.: V-UVNMKI)
1x or 10x 100 ml	**ViraStripe® / ViraBlot® Diluent / Wash Buffer** 10x concentrate	(Order No.: V-UVNUWP)
1x or 10x 5 g	**ViraStripe® / ViraBlot® Diluent / Wash Powder**	(Order No.: V-UVNUMP)
1x or 10x 90 ml	**ViraStripe® / ViraBlot® Chromogen / Substrate Solution** Ready to use	(Order No.: V-UVNUCS)
1 or 10 copies	**Evaluation Protocol** for **Borrelia ViraStripe® IgM Test Kit**	

Additionally available

330 µl	**Borrelia ViraStripe® IgM Positive Control** Human, ready to use	(Order No.: V-BSSMPK)
330 µl	**Borrelia ViraStripe® IgG,A,M Negative Control** Human, ready to use	(Order No.: V-BSSPNK)
50 copies	**Borrelia ViraStripe® IgM evaluation protocols** for automated interpretation with ViraScan® software	(Order No.: V-BSSMEP)

Preparation of reagents and patient samples

Bring all reagents to room temperature (20-25°C) prior to use. Information about stability can be found on page 5.

Diluent / Wash Buffer Working Dilution:	Dilute **Diluent / Wash Buffer Concentrate 1:10** with distilled or deionised water (100 ml concentrate + 900 ml water). Add Diluent / Wash Powder completely and stir well until all powder is dissolved. If needed, place onto a magnetic stirrer for 10-15 minutes. The pH value should be around pH 7.5 at 20°C.
Antigen Strips:	Carefully separate the required number of test strips by use of **forceps** at the **label** and place the test strips in the prepared incubation tray (see assay procedure, step 2). Use test strips directly after removing from packing. Do not touch test strips by hand. Return unused test strips directly into the original packing, seal well and store at 2-8°C.
Patient samples:	Use **20 µl patient serum** undiluted per test strip.
Controls:	Use **100 µl** of **Positive Control** or **100 µl** of **Negative Control** undiluted per test strip respectively.
Conjugate Working Dilution:	Prepare **Conjugate Concentrate 1:10** with Diluent / Wash Buffer Working Dilution (see table 1). Prepare freshly prior to each test run. Do not store for further use.
Chromogen / Substrate Solution:	Ready to use.

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Preparation of Conjugate Working Dilution IgM

Number of strips	Diluent / Wash Buffer Working Dilution		Conjugate Concentrate	Final volume
1	1.35 ml	+	0.15 ml	1.5 ml
2	2.70 ml	+	0.30 ml	3.0 ml
3	4.05 ml	+	0.45 ml	4.5 ml
4	5.40 ml	+	0.60 ml	6.0 ml
5	6.75 ml	+	0.75 ml	7.5 ml
6	8.10 ml	+	0.90 ml	9.0 ml
7	9.45 ml	+	1.05 ml	10.5 ml
8	10.80 ml	+	1.20 ml	12.0 ml
9	12.15 ml	+	1.35 ml	13.5 ml
10	13.50 ml	+	1.50 ml	15.0 ml
11	14.85 ml	+	1.65 ml	16.5 ml
12	16.20 ml	+	1.80 ml	18.0 ml
13	17.55 ml	+	1.95 ml	19.5 ml
14	18.90 ml	+	2.10 ml	21.0 ml
15	20.25 ml	+	2.25 ml	22.5 ml
16	21.60 ml	+	2.40 ml	24.0 ml
17	22.95 ml	+	2.55 ml	25.5 ml
18	24.30 ml	+	2.70 ml	27.0 ml
19	25.65 ml	+	2.85 ml	28.5 ml
20	27.00 ml	+	3.00 ml	30.0 ml
21	28.35 ml	+	3.15 ml	31.5 ml
22	29.70 ml	+	3.30 ml	33.0 ml
23	31.05 ml	+	3.45 ml	34.5 ml
24	32.40 ml	+	3.60 ml	36.0 ml
25	33.75 ml	+	3.75 ml	37.5 ml

Number of strips	Diluent / Wash Buffer Working Dilution		Conjugate Concentrate	Final volume
26	35.10 ml	+	3.90 ml	39.0 ml
27	36.45 ml	+	4.05 ml	40.5 ml
28	37.80 ml	+	4.20 ml	42.0 ml
29	39.15 ml	+	4.35 ml	43.5 ml
30	40.50 ml	+	4.50 ml	45.0 ml
31	41.85 ml	+	4.65 ml	46.5 ml
32	43.20 ml	+	4.80 ml	48.0 ml
33	44.55 ml	+	4.95 ml	49.5 ml
34	45.90 ml	+	5.10 ml	51.0 ml
35	47.25 ml	+	5.25 ml	52.5 ml
36	48.60 ml	+	5.40 ml	54.0 ml
37	49.95 ml	+	5.55 ml	55.5 ml
38	51.30 ml	+	5.70 ml	57.0 ml
39	52.65 ml	+	5.85 ml	58.5 ml
40	54.00 ml	+	6.00 ml	60.0 ml
41	55.35 ml	+	6.15 ml	61.5 ml
42	56.70 ml	+	6.30 ml	63.0 ml
43	58.05 ml	+	6.45 ml	64.5 ml
44	59.40 ml	+	6.60 ml	66.0 ml
45	60.75 ml	+	6.75 ml	67.5 ml
46	62.10 ml	+	6.90 ml	69.0 ml
47	63.45 ml	+	7.05 ml	70.5 ml
48	64.80 ml	+	7.20 ml	72.0 ml
49	66.15 ml	+	7.35 ml	73.5 ml
50	67.50 ml	+	7.50 ml	75.0 ml

Table 1: **1:10** dilution of conjugate concentrate with Diluent / Wash Buffer Working Dilution

Assay procedure

1.	**Rinse incubation tray channels once with 1.5 ml Diluent / Wash Buffer Working Dilution, decant the liquid**	Mark the trays with water-resistant pen. Rinsing removes dust particles.
2.	**Place the needed amount of test strips into the incubation tray - one test strip per channel**	For each patient serum and each control, carefully separate one test strip by use of forceps at the label and place them into the incubation tray channels. **The side showing the green separation line and the label must face up.**
3.	**Add 1.5 ml Diluent / Wash Buffer Working Dilution and incubate by rocking for 5 minutes at room temperature (RT)**	Make sure the test strips are completely covered with liquid. Use a 2D rocker with a rocking frequency of approx. 40/min. Avoid spilling of liquid. **Do not decant the liquid after incubation.**
4.	**Add 20 µl of each patient serum or 100 µl of each control**	Add patient sera and controls directly onto the labelled end of the test strips while the 2D rocker is running or make sure to tilt the incubation tray after adding each serum.
5.	**Incubate by rocking for 30 minutes at RT**	Make sure the test strips are completely covered with liquid. Use a 2D rocker with a rocking frequency of approx. 40/min.
6.	**Decant the liquid**	Carefully tap the incubation tray on absorbent paper to remove the remaining liquid. **Test strips adhere to the incubation tray when liquid is decanted.**
7.	**3 x washing:** **- add 1.5 ml Diluent / Wash Buffer Working Dilution** **- incubate by rocking for 5 minutes at RT** **- decant the liquid**	Wash on the 2D rocker. Carefully tap the incubation tray on absorbent paper to remove the remaining liquid.
8.	**Add 1.5 ml fresh Conjugate Working Dilution**	Make sure the test strips are completely covered with Conjugate Working Dilution
9.	**Incubate by rocking for 15 minutes at RT**	Make sure the test strips are completely covered with liquid. Use a 2D rocker with a rocking frequency of approx. 40/min.
10.	**Decant the liquid**	Carefully tap the incubation tray on absorbent paper.
11.	**3 x washing as in step 7**	Wash on the 2D rocker.
12.	**Add 1.5 ml distilled or deionised water and incubate by rocking for 1 minute at RT**	Make sure the test strips are completely covered with liquid. Use a 2D rocker with a rocking frequency of approx. 40/min.
13.	**Decant the liquid**	Carefully tap the incubation tray on absorbent paper.
14.	**Add 1.5 ml Chromogen / Substrate Solution**	Make sure the test strips are completely covered with liquid.
15.	**Incubate by rocking at RT** **Borrelia ViraStripe® IgM: approx. 5 to 15 minutes**	Stop the reaction as soon as the cut off control becomes visible. **The Cut off control is located in the test strip control section. Caution:** Prolonged incubation causes background staining.
16.	**Stop the reaction by decanting the liquid**	Carefully tap the incubation tray on absorbent paper.
17.	**Wash 3 x with 1.5 ml distilled or deionised water**	Wash without incubation time.
18.	**Dry test strips for interpretation**	Carefully tap the incubation tray on absorbent paper to remove the remaining liquid. Place wet test strips with forceps on unbleached absorbent paper and allow to air dry before interpretation.

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Assay interpretation

1. Evaluation protocol: Record data on the evaluation protocol. Glue the test strips on the evaluation protocol. Place the green separation line of the test strips exactly onto the separation line printed on the evaluation protocol.

2. Validity of test strips: A test strip is considered as valid if the following bands are visible:
   - The **serum control**.
   - The **conjugate control** of the conjugate class being used. If more than one of the three conjugate controls becomes visible, the strongest band must indicate the appropriate conjugate class.
   - The **cut off control**.

   and if the following band is **not** visible:
   - The **negative control band**.

   Do not assess invalid test strips!

3. Assignment of antigen bands: The green separation line of the test strips indicates position and orientation for the assignment of bands with the bandlocator on the evaluation protocol. Assign bands and record results according to 4.

4. Assessment of bands: According to quality laboratory guidelines, the use of a cut off control for each run is recommended (16). **The cut off control of the Borrelia ViraStripe® IgM is located in the control section on each test strip.** The intensity of the cut off control indicates the threshold of which bands are being assessed:

   A band is considered as **distinct** if its intensity is **equal** to or **higher** than the intensity of the cut off control. Mark bands with **X** in the evaluation protocol appropriately.
   A band is not assessed if it is **not present** or if its intensity is **lower** than the intensity of the cut off control.

5. Interpretation of patient bands: Patient bands 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)

   Bands of the following antigens are considered as **highly specific** for Borrelia species:
   p41 (limited specificity)**, p39, OspC, Osp17** and **VlsE**

IgM Interpretation criteria

General note: Distinct bands must have a minimum intensity (≥ cut off), which has to be determined by the cut off control. The cut off control is located in the control section of each test strip.

Identified bands	Result	Interpretation
At least **one distinct** band out of: **p39, OspC, Osp17, VlsE** or **p41 higher** than cut off	**Positive**	Specific antibodies against **Borrelia species** detectable. An infection with **Borrelia species** is probable.
No distinct bands or **p41 equal** to cut off	**Negative**	No specific 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 bands in IgM tests. In the case of unclear band constellation use RF-Absorbent (ViraSorb, 5 ml, Order No.: CB003) **for IgM analysis.**

IgM test strip

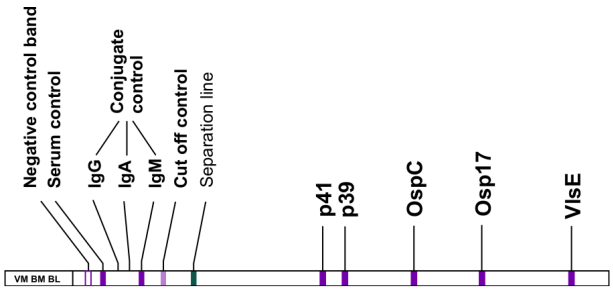

Figure 1: Schematic drawing of a Borrelia ViraStripe® IgM test strip in full scale.

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Nomenclature and description of Borrelia species bands from literature

Band nomenclature:	Antigen:	Comments:
VlsE	**Specific** **VlsE** (Variable major protein (VMP) like sequence Expressed)	Antibodies against VlsE are described as specific. IgG antibodies are already being developed at an early stage and remain until the late stage of the disease. IgM antibodies against VlsE could appear as well in early stages but their serologic detection is less frequent (9).
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).

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 titers decrease gradually during convalescence (22).
2. IgM antibodies usually appear 2-3 weeks after onset of the disease for the first time (22). Antibody titers 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 band pattern differs from patient to patient. As a general rule: The number of antibody types and therefore the number of specific bands 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 an EBV infection needs to be tested for. Cross reactivities in cases of autoimmune diseases, MS, ALS, Influenza and Syphilis are described as well.

IgM performance data

Sensitivity:

156 sera from patients with the Lyme borreliosis manifestations Erythema migrans, Erythema chronicum migrans, multiple Erythemata migrantia, Acrodermatitis chronica atrophicans, Lyme arthritis and neuroborreliosis were assessed to determine the sensitivity of the Borrelia ViraStripe® IgM Test Kit.

Stage of Lyme borreliosis	Borrelia ViraStripe® IgM, % (n)	Borrelia ViraStripe® IgG / IgM, % (n)
Erythema migrans **(n= 29)**	**69% (20)**	**79% (23)**
Multiple Erythemata migrantia **(n= 13)**	**77% (10)**	**85% (11)**
Erythema chronicum migrans **(n= 27)**	**52% (14)**	**96% (26)**
Neuroborreliosis **(n= 24)**	**75% (18)**	**96% (23)**
Acrodermatitis chronica atrophicans **(n= 34)**	**53% (18)**	**97% (33)**
Lyme arthritis **(n= 29)**	**66% (19)**	**100% (29)**

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Specificity:

To determine the specificity of the Borrelia ViraStripe® IgM Test Kit 129 sera from blood donors showing a negative result with a reference test (Borrelia „MiQ“ + VlsE ViraBlot® IgM and IgG Test Kit) were assessed.

Collective	Borrelia ViraStripe® IgM, % (n)	Borrelia ViraStripe® IgG / IgM, % (n)
Blood donors **(n= 129)**	**98% (126)**	**97% (125)**

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. In general, biological and chemical agents should be handled according to „Good Laboratory Practice (GLP)“ guidelines. 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 under humid conditions. 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.

Storage and stability of reagents

1. Test strips: In closed bags stable until the expiration date if stored at 2-8°C.
2. Conjugate Concentrate: Stable until the expiration date if stored at 2-8°C.
3. Conjugate Working Dilution: Prepare freshly prior to each run. Do not store for further use.
4. Diluent / Wash Buffer Concentrate, 10x: Stable until the expiration date if stored at 2-8°C.
5. Diluent / Wash Buffer Working Dilution: Stable for 2 weeks if stored at 2-8°C. For longer storage, aliquot and freeze at -20°C.
6. Diluent / Wash Powder: Stable until the expiration date if stored at 2-8°C.
7. Chromogen / Substrate Solution: Stable until the expiration date if stored at 2-8°C. Avoid exposure to light!

Specimen indications

1. The **Borrelia ViraStripe® IgM Test Kit** must be used with human serum or cerebrospinal fluid.
2. Only clear, non-hemolysed, non-microbially contaminated specimens must be used.
3. Using icteric, lipemic, hemolytic and/or heat-inactivated serum may lead to false 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.

Limitation of the procedure

1. To ensure reliable results, follow carefully the Instruction for Use and “Good Laboratory Practice”.
2. A positive result is based on elevated specific antibody titers 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. Test strips showing a high background level should not be interpreted, especially if band intensities are lighter than the background level.
7. *In vitro* diagnostics must not be used beyond expiration date 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.

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Symbols used

	Manufacturer	REF	Order Number
	Refer to Instructions for Use		Use by / Expiration Date
IVD	*In-Vitro* Diagnostic Medical Device		Temperature Limitation (Storage)
LOT	Test Kit Lot Number	CONTROL +	Positive Serum Control
	Sufficient for 50 Tests	CONTROL -	Negative Serum Control
	Room Temperature in °C	CONTROL	Control
	User	DATE	Date
#	Serum Number		Chromogen/Substrate Incubation Time in Minutes
PROTOCOL	Evaluation Protocol	No	Protocol Number

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