Snibe Diagnostic

CE 0123 REF 130212004M: 100 tests
130612004M: 50 tests

MAGLUMI® Rubella IgM (CLIA)

INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the qualitative determination of Rubella IgM in human serum to aid in the determination of an acute or recent rubella virus infection using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer (including Maglumi 600, Maglumi 800, Maglumi 1000, Maglumi 1000 Plus, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000, Maglumi 4000 Plus and MAGLUMI X8).

SUMMARY AND EXPLANATION OF THE TEST

Rubella is a viral exanthematous infectious disease caused by rubella virus, a single-stranded RNA virus belonging to the Togavirus group. The illness follows a typically benign clinical course with rare complications and is subclinical in a large proportion of cases. Symptomatology is generally mild, characterized by fever, malaise, a maculopapular rash of three to five days' duration and, possibly, coryza and conjunctivitis. The disease is usually accompanied by lymphadenopathy. Infection confers lifelong immunity.

Infection from rubella virus is particularly disastrous if contracted during the first four months of gestation. If not immunologically protected, women infected during pregnancy run a high risk of damage to embryo or foetus. Congenital rubella causes a wide range of severe defects, many of which are permanent and adversely affect later development (cataract, deafness, hepatosplenomegaly, psychomotor retardation, bone alterations, cardiopathies, and neuropathies). Pathological consequences on the foetus or newborn depend on teratogenicity of the virus and on the stage of pregnancy when the infection is contracted. Gestational age at the time of maternal infection is considered the most important determinant of intrauterine trans- mission and foetal damage. It is generally accepted that the risk decreases with increasing gestational age: it is the highest in case of infection during the first two months of pregnancy (40-60%) and progressively decreases during the fourth and fifth months (10-20%). Clinical findings in newborns and virus isolation studies have demonstrated that foetal infection is rare be- yond the second trimester of gestation.

Rubella virus is transmitted in utero during the course of primary maternal infection, whether apparent or inapparent, when the virus in the bloodstream infects the placenta and, subsequently, the foetus. Intrauterine transmission of virus associated with maternal re-infection is extremely rare, indicating that maternal immunity (whether naturally derived or vaccine-induced) protects against intrauterine infection. Maternal infection may result in (a) no infection of the embryo; (b) resorption of the embryo (seen only with infections occurring in the earliest stages of gestation); (c) miscarriage; (d) stillbirth; (e) infection of placenta without foetal involvement or (f) infection of both the placenta and foetus. Infected infants may present obvious multiple organ involvement or, as is frequently observed, no immediately evident disease. However, after long-term follow-up, many of these seemingly unaffected infants have evidence of hearing loss, or central nervous system lesions, or other defects.

The first humoral immune response to infection is the synthesis of specific anti-rubella virus IgM antibody which reaches high serum levels two weeks after the rash and lasts in the circulation for one to two month(s). Specific IgG antibody generally appears a few days after the onset of rash, about one week after IgM develops. It rapidly increases to reach a plateau six to ten weeks after the onset of symptoms and then progressively decreases to a level (15-200 IU/mL) lasting for the whole life. Re-infection, completely asymptomatic, is accompanied by moderately increased levels of specific IgG.

The determination of Rubella IgM antibodies, can aid in the diagnosis of diseases caused by rubella virus, is used to assess the serological status of an individual and is indicative for an acute or past infection, together with the detection of Rubella IgG. This is particularly important in order to adopt suitable prophylaxis in susceptible individuals.

PRINCIPLE OF THE TEST

The Rubella IgM assay is an indirect chemiluminescence immunoassay.

The sample (or calibrator/control, if applicable), buffer (including goat Anti-human IgG, goat Anti-human IgA), magnetic microbeads coated with purified Rubella antigen are mixed thoroughly and incubated, forming antibody-antigen complexes. After precipitation in a magnetic field, decant the supernatant, and perform a wash cycle. Then add ABEI labeled with mouse anti-human IgM antibody, and incubate to form sandwich complexes. After precipitation in a magnetic field, decant the supernatant, and then perform another wash cycle. Subsequently, the Starter 1+2 are added to initiate a chemiluminescent reaction. The light signal is measured by a photomultiplier as relative light units (RLUs), which is indicative to the concentration of Rubella IgM present in the sample (or calibrator/control, if applicable).

KIT COMPONENTS

Material Provided

Components	Contents	100 tests (REF: 130212004M)	50 tests (REF: 130612004M)
Magnetic Microbeads	Magnetic microbeads coated with Rubella antigen containing BSA, NaN_3 (<0.1%).	2.5 mL	2.0 mL
Calibrator Low	Low concentration of Rubella IgM, containing bovine serum, NaN_3 (<0.1%).	2.5 mL	2.0 mL
Calibrator High	High concentration of Rubella IgM, containing bovine serum, NaN_3 (<0.1%).	2.5 mL	2.0 mL
Buffer	Goat anti-human IgA, goat anti-human IgG, containing BSA, NaN_3 (<0.1%).	25.0 mL	13.5 mL
ABEI Label	Mouse anti-human IgM labeled with ABEI, containing BSA, NaN_3 (<0.1%).	22.5 mL	12.5mL
Diluent	Containing BSA, NaN_3 (<0.1%).	25.0 mL	13.5 mL
Internal Quality Control	Rubella IgM, containing bovine serum, NaN_3 (<0.1%).	2.0 mL	2.0 mL
All reagents are provided ready-to-use.			

Accessories Required But Not Provided

MAGLUMI Series:

Reaction Module	REF: 630003
Starter 1+2	REF: 130299004M, 130299027M
Wash Concentrate	REF: 130299005M
Light Check	REF: 130299006M
Reaction Cup	REF: 130105000101

Please order accessories from Shenzhen New Industries Biomedical Engineering Co., Ltd. (SNIBE) or our authorized representatives.

CALIBRATION

Traceability: This method has been standardized against the SNIBE internal reference substance.

Test of assay specific calibrators allows the RLU values to adjust the assigned master curve. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve (10 calibrations) provided via the reagent Radio Frequency Identification (RFID) CHIP.

Recalibration is recommended if any of the following conditions occurs:

- After each change of lots (Reagent or Starter 1+2).
- Every week and/or each time a new reagent kit is used (recommended).
- After instrument service is required.
- If controls lie outside the expected range.

QUALITY CONTROL

Follow government regulations or accreditation requirements for quality control frequency.

Internal quality control is only applicable with MAGLUMI system. For instructions for use and target value refer to ***Rubella IgM (CLIA) Quality Control Information***. User needs to judge results with their own standards and knowledge.

For detailed information about entering quality control values, refer to the operating instructions of MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer.

To monitor system performance and chart trends, commercially available quality control materials are required. Treat all quality control samples the same as patient samples. A satisfactory level of performance is achieved when analyte values obtained are within the acceptable Control Range for the system or within your range, as determined by an appropriate internal laboratory quality control scheme. If the quality control results do not fall within the Expected Values or within the laboratory's established values, do not report results. Take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the instructions for use.
- Rerun the assay with fresh quality control samples.
- If necessary, contact your local technical supporters or distributors for assistance.

SPECIMEN COLLECTION AND PREPARATION

- Use standard sampling tubes or tubes containing separating gel. Collect blood aseptically following the universal precautions for venipuncture.
- Ensure that complete clot formation in specimens has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time.
- If the specimen is centrifuged before a complete clotting, the presence of fibrin may cause erroneous results. Samples must be free of fibrin and other particulate matter.
- Do not use hemolyzed or grossly lipemic specimens as well as specimens containing particulate substance or exhibiting obvious microbial contamination. Inspect all specimens for bubbles, and remove bubbles before analysis for optimal results.
- Avoid repeated freezing and thawing. The serum sample can be frozen and thawed for only two times. Stored samples should be thoroughly mixed prior to use (Vortex mixer). Frozen specimens must be mixed THOROUGHLY after thawing by LOW speed vortexing. Please ask local representative of SNIBE for more derails if you have any doubt.
- Centrifuged specimens with a lipid layer on the top must be transferred to a sample cup or a secondary tube. Care should be taken to transfer only the clarified specimen without the lipaemic material.
- All samples (patient specimens and controls) should be tested within 3 hours when placed on board the MAGLUMI System. Refer to the SNIBE service for more details of onboard sample storage constraints.
- Specimens removed from the separator, red blood cells or clot may be stored up to 7 days at 2-8°C, and stored up to 3 months frozen at -20°C or colder.
- Before shipping specimens, it is recommended that specimens be removed from the clot, red blood cells, or separator. When shipped, specimens should be packaged and labeled in compliance with applicable state, federal and international regulations covering the transport of clinical specimens and infectious substances. Specimens should be shipped frozen.
- The sample volume required for a single determination of Rubella IgM is 10 µL.

WARNING AND PRECAUTIONS FOR USERS

- IVD
- For *In Vitro* Diagnostic Use.
- Follow the package insert carefully. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Safety Precautions

- **CAUTION:** This product requires the handling of human specimens. It is recommended that all human sourced materials be considered potentially infectious and handled in accordance with the 29 CFR 1910.1030 Occupational exposure to bloodborne pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.
- All samples, biological reagents and materials used in the assay should be considered potentially able to transmit infectious agents. They should therefore be disposed in accordance with the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.
- This product contains Sodium Azide. Dispose of contents and containers must be in accordance with all local, regional and national regulations.
- Refer to safety data sheets which are available on request.

Handling Precautions

- Do not use reagent kits beyond the expiration date.
- Do not interchange reagent components from different reagents or lots.
- Prior to loading the reagent kit on the system for the first time, the reagent kit requires mixing to re-suspend magnetic microbeads that have

settled during shipment.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- To avoid contamination, wear clean gloves when operating with a reagent kit and samples.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts which have no effect on assay efficacy.
- For detailed discussion of handling precautions during system operation, refer to the SNIBE service information.

STORAGE AND STABILITY

- Sealed: Stored at 2-8°C until the expiration date.
- Opened at 2-8°C: Minimum stability is 4 weeks.
- On-board: Minimum stability is 4 weeks.
- To ensure the best kit performance, it is recommended to place opened kits in the refrigerator after the end of the intraday test work.
- Keep upright for storage to facilitate later proper resuspension of magnetic microbeads.
- Keep away from sunlight.

TEST PROCEDURE

Preparation of the Reagent

- Resuspension of the magnetic microbeads takes place automatically when the kit is loaded successfully, ensuring the magnetic microbeads are totally resuspended homogenous prior to use.
- To ensure proper test performance, strictly adhere to the operating instructions of MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer. Each test parameter is identified via a RFID tag on the Reagent kit. For further information please refer to the operating instructions of MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer.

DILUTION

Samples with concentrations above the measuring range can be diluted.
After manual dilution, multiply the result by the dilution factor. After dilution by the analyzers, the analyzer software automatically takes the dilution into account when calculating the sample concentration.
The automatic sample dilution is available after dilution settings are done in the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer user software. Please refer to the operating instructions of MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer.

High-Dose Hook

Whenever samples containing extremely high antibody concentrations are tested, the saturation effect can mimic concentrations lower than real. However, a well-optimized two-step method excludes grossly underestimated results, because the analytical signals remain consistently high (saturation curve).
No false negative result due to high-dose hook effect was found with the Rubella IgM assay.

LIMITATIONS

- A skillful technique and strict adherence to the instructions are necessary to obtain reliable results.
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- A result within the expected range does not rule out the presence of disease and should be interpreted together with the patient's clinical picture and other diagnostic procedures.
- Diagnosis of a disease should not be based on the result of a single test, but should be determined in conjunction with clinical findings in association with medical judgement.
- Any therapeutical decision should also be taken on a case-by-case basis.
- Patient samples containing human anti-mouse antibodies (HAMA) may give falsely elevated or decreased values. Although HAMA-neutralizing agents are added, extremely high HAMA serum concentrations may occasionally influence results.

RESULTS

Calculation of Results

The analyzer automatically calculates the concentration in each sample by means of a calibration curve which is generated by a 2-point calibration master curve procedure. The results are expressed in AU/mL. For further information please refer to the operating instructions of MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer.

Interpretation of Results

Results obtained with the Rubella IgM assay can be interpreted as follows:
- Non-reactive: A result less than 2 AU/mL (<2 AU/mL) is considered to be negative. Individuals with such results are presumed to be not currently infected with Rubella.
- Gray zone: A result in the interval between 2 and 3 (2≤ x<3 AU/mL) is considered to be equivocal.
- Reactive: A result greater than or equal to 3 AU/mL is (≥3 AU/mL) considered to be positive. Reactivity for IgM antibodies to Rubella may indicate current infection, reactivation or recent vaccination.

NOTE:

- It is recommended to confirm results of specimens in gray zone by testing Rubella IgG.
- Consider to take a second sample, if possible, within an appropriate period of time (e.g., two weeks) to confirm levels of IgM and IgG.

Since there is no international standard material for Rubella IgM yet, different IVD manufacturer have different traceability chain. Therefore results from assays of other manufacturers cannot be used interchangeably.

PERFORMANCE CHARACTERISTICS

Precision

Precision for the Rubella IgM assay was determined as described in the CLSI EP5-A2, 2 controls and 3 human serum pools containing different concentration of analyte were assayed in duplicate at two independent runs per day for 20 testing days. The results are summarized in the following table:

Sample	Mean(AU/mL) (N=80)	Within-Run		Between-Run		Total	
		SD(AU/mL)	%CV	SD(AU/mL)	%CV	SD(AU/mL)	%CV
Negative Serum Pool	1.203	0.089	7.40	0.063	5.24	0.109	9.06
Low Positive Serum Pool	5.005	0.300	5.99	0.146	2.92	0.334	6.67
High Positive Serum Pool	24.939	1.063	4.26	0.692	2.77	1.269	5.09
Control 1	5.994	0.316	5.27	0.158	2.64	0.353	5.89
Control 2	19.654	0.840	4.27	0.424	2.16	0.941	4.79

Analytical Sensitivity

<0.25 AU/mL

The Analytical Sensitivity represents the lowest analyte level that can be distinguished from zero.

Recovery

Consider calibrator high of known concentration as a sample, dilute it by 1:2 ratio with diluents, and measure its diluted concentration for 10 times. Then calculate the expected concentration and recovery of measured concentration. The recovery should be within 90% -110%.

Expected (AU/mL)	Mean Measuring (AU/mL)	%Recovery
9.805	9.693	98.86

Analytical Specificity

Clinical Rubella IgM negative samples, which contain potential cross-reactants including HAV, HBV, HCV, HIV, Syphilis, EBV, CMV IgM, Rubella IgG, Toxo IgM, HSV-1/2 IgM, RF, HAMA, ANA approved by commercially available CE-marked assay, were used to evaluate the cross-reactivity of Rubella IgM assay. Of all the potential cross-reactants, none were found to cause false positive in the Rubella IgM assay.

Endogenous Interference

Substances up to the following concentrations did not interfere with the assay:

- Bilirubin 40 mg/dL
- Hemoglobin 1000 mg/dL
- Triglyceride 2000 mg/dL

Drug Interference

Drugs up to the following concentrations did not interfere with the assay:

Drugs	Concentration
N-acetylcysteine	150 µg/mL
Methyldopa	25 µg/mL
Theophylline	60 µg/mL
Metformin	12 µg/mL
Isosorbide dinitrate	6 µg/mL
Rifampicin	48 µg/mL
Doxycycline	18 µg/mL
Cefoxitin	6600 µg/mL
Cyclosporine	2 µg/mL
Metronidazole	125 µg/mL
Ascorbic acid	60 µg/mL
Phenylbutazone	200 µg/mL
Aspirin	1000 µg/mL
Acetaminophen	400 µg/mL
Ibuprofen	500 µg/mL
Sodium salicylate	500 µg/mL

REFERENCES

1. Best, J. M., S. O'Shea, G. Tipples, N. Davies, S. M. Al Khusaiby, A. Krause, L. M. Hesketh, L. Jin, and G. Enders. 2002. Interpretation of rubella serology in pregnancy—pitfalls and problems. BMJ 325:147-148.
2. Dwyer, D. E., P. W. Robertson, and P. R. Fields. 2001. Broadsheet: clinical and laboratory features of rubella. Pathology 33:322-328.
3. Field, P. R., V. Sintchenko, and G. L. Gilbert. 1998. Confirmation of rubella infection: review of 10 years' experience at ICPMR. Inoculum 7:1-3.
4. Francis, B. H., A. K. Thomas, and C. A. McCarty. 2003. The impact of rubella immunization on the serological status of women of childbearing age: a retrospective longitudinal study in Melbourne, Australia. Am. J. Public Health 93:1274-1276
5. Gutiérrez, A., M. J. Rodríguez, F. De Ory, G. Piédrola, and M. C. Maroto. 1999. Reliability of low-avidity IgG and of IgA in the diagnosis of primary infection by rubella virus with an adaptation of a commercial test. J. Clin. Lab. Anal. 13:1-4.

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SYMBOLS EXPLANATIONS

	Consult instructions for use		Manufacturer
8 °C 2 °C	Temperature limit (Store at 2-8 °C)		Use-by date
Σ	Contains sufficient for		Keep away from sunlight
	This way up	EC REP	Authorized representative in the European Community
IVD	*In vitro* diagnostic medical device	CONTENTS	Kit components
REF	Catalogue number	LOT	Batch code