Snibe Diagnostic

CE 0123 REF 130262003M:100 tests/kit
130662003M: 50 tests/kit

MAGLUMI® Rubella IgG (CLIA)

INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the quantitative determination of Rubella IgG in human serum and plasma using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer and Biolumi series Integrated System, and the assay is used for an aid in the management of patients with rubella, assess the serological status of an individual and used for pre-natal screening of women.

SUMMARY

Rubella virus belongs to the Togaviridae family[1] and is transmitted through respiratory droplets and direct contact, with initial virus replication occurring in the nasopharyngeal mucosa, followed by spread to regional lymph nodes[2]. It is an enveloped, single-stranded, positive sense ribonucleic acid (RNA) virus[3]. Clinical disease often results in mild illness characterised by fever, a generalised erythematous maculopapular rash, and lymphadenopathy. Fever is typically low grade and can be accompanied by headache, malaise, mild conjunctivitis (particularly in adults), sore throat, cough, and rhinorrhoea[2]. Other manifestations, although rare, include tenosynovitis, carpal tunnel syndrome, thrombocytopenia, post-infectious encephalitis, myocarditis, hepatitis, hemolyticanemia, and hemolytic uremic syndrome[4].

Although rubella virus infection usually produces a mild febrile rash illness in children and adults, infection during pregnancy, especially during the first trimester, can result in miscarriage, fetal death, stillbirth, or an infant born with a constellation of birth defects known as congenital rubella syndrome (CRS)[5]. Common presenting signs and symptoms of congenital rubella syndrome include cataracts, sensorineural hearing impairment, congenital heart disease, hepato-splenomegaly, hepatitis with jaundice, thrombocytopenia with purpura, interstitial pneumonitis, meningoen-cephalitis, and microcephaly[2]. Today, the widespread use of highly effective and safe vaccines dramatically reduced the incidence of rubella and CRS[5,6].

Rubella virus IgM appear within 3 days after the rash and generally disappear in 4 to 12 weeks. Rubella virus IgG appear slightly later (5-8 days after the onset of the rash) and persist throughout life[6]. Diagnosis of rubella can be made by detection of rubella IgM and the detection of a significant rise in rubella specific IgG concentration[7], and a significant rise in IgG antibody or positive IgM antibody test indicates recent infection[8]. IgM is used to diagnose acute and recent rubella infection. A positive serum rubella IgM or a significant rise between acute- and convalescent-phase IgG titers indicates an acute infection. After discussing the potential for reinfection, physicians might recommend acute- and convalescent-phase IgG antibody testing or an IgM antibody test to document whether reinfection has occurred[8].

TEST PRINCIPLE

Indirect chemiluminescence immunoassay.

The sample, diluent, buffer, magnetic microbeads coated with Rubella antigen are mixed thoroughly, incubating and performing a wash cycle after a precipitation in a magnetic field. ABEI labeled with anti-human IgG monoclonal antibody are then added and incubated, reacting to form immuno-complexes. After precipitation in a magnetic field, the supernatant is decanted and then a wash cycle is performed. 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 proportional to the concentration of Rubella IgG present in the sample.

REAGENTS

Kit Contents

Component	Description	100 tests/kit	50 tests/kit
Magnetic Microbeads	Magnetic microbeads coated with Rubella antigen (~1.00 μg/mL) in PBS buffer, NaN_3 (<0.1%).	2.5 mL	1.5 mL
Calibrator Low	A low concentration of Rubella IgG in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL
Calibrator High	A high concentration of Rubella IgG in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL
Buffer	BSA, NaN_3 (<0.1%).	22.5 mL	12.0 mL
ABEI Label	ABEI labeled with anti-human IgG monoclonal antibody (~100 ng/mL) in Tris-HCl buffer, NaN_3 (<0.1%).	22.5 mL	12.0 mL
Diluent	BSA, NaN_3 (<0.1%).	25.0 mL	13.5 mL
Negative Control	PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL
Positive Control	A high concentration of Rubella IgG (40.0 IU/mL) in PBS buffer, NaN_3 (<0.1%).	1.0 mL	1.0 mL
All reagents are provided ready-to-use.			

Warnings and Precautions

- For *in vitro* diagnostic use.
- For professional use only.
- Exercise the normal precautions required for handling all laboratory reagents.
- Personal protective measures should be taken to prevent any part of the human body from contacting samples, reagents, and controls, and should comply with local operating requirements for the assay.
- A skillful technique and strict adherence to the package insert are necessary to obtain reliable results.
- Do not use kit beyond the expiration date indicated on the label.
- Do not interchange reagent components from different reagents or lots.
- Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).
- All waste associated with biological samples, biological reagents and disposable materials used for the assay should be considered potentially infectious and should be disposed of in accordance with local guidelines.
- This product contains sodium azide. Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after disposal, flush with a large volume of water to prevent azide build-up.
- The safety data sheet is available on request.
- Note: If any serious incident has occurred in relation to the device, please report to Shenzhen New Industries Biomedical Engineering Co., Ltd. (Snibe) or our authorized representative and the competent authority of the Member State in which you are established.

Reagent Handling

- To avoid contamination, wear clean gloves when operating with a reagent kit and sample. When handling reagent kit, replace the gloves that have been in contact with samples, since introduction of samples will result in unreliable results.
- Do not use kit in malfunction conditions; e.g., the kit leaking at the sealing film or elsewhere, obviously turbid or precipitation is found in reagents (except for Magnetic Microbeads) or control value is out of the specified range repeatedly. When kit in malfunction conditions, please contact Snibe or our authorized distributor.
- To avoid evaporation of the liquid in the opened reagent kits in refrigerator, it is recommended that the opened reagent kits to be sealed with reagent seals contained within the packaging. The reagent seals are single use, and if more seals are needed, please contact Snibe or our authorized distributor.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.
- Do not transfer opened integral reagents between instruments.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- For further information about the reagent handing during system operation, please refer to Analyzer Operating Instructions.

Storage and Stability

- Do not freeze the integral reagents.
- Store the reagent kit upright to ensure complete availability of the magnetic microbeads.
- Protect from direct sunlight.

Stability of the Reagents	
Unopened at 2-8°C	until the stated expiration date
Opened at 2-8°C	6 weeks
On-board	4 weeks

Stability of Controls	
Unopened at 2-8°C	until the stated expiration date
Opened at 10-30°C	6 hours
Opened at 2-8°C	6 weeks
Frozen at -20°C	3 months
Frozen and thawed cycles	no more than 3 times

SPECIMEN COLLECTION AND PREPARATION

Specimen Types

Only the specimens listed below were tested and found acceptable.

Specimen Types	Collection Tubes
Serum	Tubes without additive, or tubes containing clot activator or clot activator with gel
Plasma	K2-EDTA, Li-heparin or Na-heparin

- The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. Follow tube manufacturers' instructions carefully when using collection tubes.

Specimen Conditions

- Do not use heat-inactivated samples or grossly hemolyzed/hyperlipidaemia specimens and specimens with obvious microbial contamination.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some serum specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the serum 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.
- To prevent cross contamination, use of disposable pipettes or pipette tips are recommended.

Preparation for Analysis

- Inspect all specimens for foam. Remove foam with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.
- Frozen specimens must be completely thawed before mixing. Mix thawed specimens thoroughly by low speed vortexing or by gently inverting. Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous. If specimens are not mixed thoroughly, inconsistent results may be obtained.
- For reliable results, specimens should be free of fibrin, red blood cells, or other particulate matter. Specimens must be centrifuged prior to testing, transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- The sample volume required for a single determination of this assay is 10 μL.

Specimen Storage

Specimens removed from the separator, red blood cells or clot may be stored up to 2 days at 10-30°C or 2 weeks at 2-8°C, or 6 months frozen at -20°C. Frozen specimens subjected to up to 5 freeze/thaw cycles have been evaluated.

Specimen Shipping

- Package and label specimens in compliance with applicable local regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

Specimen Dilution

- Samples, with Rubella IgG concentrations above the analytical measuring interval, can be diluted with Diluent either by following automated dilution protocol or manual dilution procedure. The recommended dilution ratio is 1:10. The concentration of the diluted sample must be >50.0 IU/mL.
- For manual dilution, multiply the result by the dilution factor. For dilution by the analyzers, the analyzer software automatically takes the dilution into account when calculating the sample concentration.

PROCEDURE

Materials Provided

Rubella IgG (CLIA) assay, control barcode labels.

Materials Required (But Not Provided)

- General laboratory equipment.
- Fully-auto chemiluminescence immunoassay analyzer Maglumi 600, Maglumi 800, Maglumi 1000, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000, Maglumi 4000 Plus, MAGLUMI X 3, MAGLUMI X6, MAGLUMI X8, MAGLUMI X10, or Integrated System Biolumi 8000 and Biolumi CX8.
- For Reaction Module, Starter 1+2, Wash Concentrate, Light Check, Tip, and Reaction Cup, please refer to corresponding Analyzer Operating Instructions for catalogue number.
- Please use accessories specified by Snibe to ensure the reliability of the test results.

Assay Procedure

Preparation of the Reagent

- Take the reagent kit out of the box and visually inspect the integral vials for leaking at the sealing film or elsewhere. If there is no leakage, please tear off the sealing film carefully.
- Open the reagent area door; hold the reagent handle to get the RFID label close to the RFID reader (for about 2s); the buzzer will beep; one beep sound indicates successful sensing.
- Keeping the reagent straight insert to the bottom along the blank reagent track.
- Observe whether the reagent information is displayed successfully in the software interface, otherwise repeat the above two steps.
- 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.

Assay Calibration

- Select the assay to be calibrated and execute calibration operation in reagent area interface. For specific information on registrating calibrations, refer to the calibration section of Analyzer Operating Instructions.
- Execute recalibration according to the calibration interval required in this package insert.

Quality Control

- When new lot used, check or edit the quality control information.
- Scan the control barcode, choose corresponding quality control information and execute testing. For specific information on registrating quality controls, refer to the quality control section of the Analyzer Operating Instructions.

Sample Testing

- After successfully loading the sample, select the sample in interface and edit the assay for the sample to be tested and execute testing. For specific information on registrating samples, refer to the sample section of the Analyzer Operating Instructions.

To ensure proper test performance, strictly adhere to Analyzer Operating Instructions.

Calibration

Traceability: This method has been standardized against the WHO 1st International Standard RUBI-1-94.

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the master curve.
Recalibration is recommended as follows:

- Whenever a new lot of Reagent or Starter 1+2 is used.
- Every 28 days.
- The analyzer has been serviced.
- Control values lie outside the specified range.

Quality Control

Controls are recommended for the determination of quality control requirements for this assay and should be run in singlicate to monitor the assay performance. Refer to published guidelines for general quality control recommendations, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24 or other published guidelines[9].
Quality control is recommended once per day of use, or in accordance with local regulations or accreditation requirements and your laboratory's quality control procedures, quality control could be performed by running the Rubella IgG assay:

- Whenever the kit is calibrated.
- Whenever a new lot of Starter 1+2 or Wash Concentrate is used.

The first seven digits of the lot number on the controls must match those of the corresponding reagent kit. For each target value and range refer to the label.
The performance of other controls should be evaluated for compatibility with this assay before they are used. Appropriate value ranges should be established for all quality control materials used.
Control values must lie within the specified range, whenever one of the controls lies outside the specified range, calibration should be repeated and controls retested. If control values lie repeatedly outside the predefined ranges after successful calibration, patient results must not be reported and 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 package insert.
- If necessary, contact Snibe or our authorized distributors for assistance.

If the controls in kit are not enough for use, please order Rubella IgG (CLIA) Controls (REF: 160201478MT) from Snibe or our authorized distributors for more.

RESULTS

Calculation

The analyzer automatically calculates the Rubella IgG 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 IU/mL. For further information please refer to the Analyzer Operating Instructions.

Interpretation of Results

The expected results for the Rubella IgG assay was obtained by testing 277 Rubella IgG positive patients and 582 Rubella IgG negative people in China, gave the following expected value by ROC curve:

- Non-reactive: A result less than 10.0 IU/mL (<10.0 IU/mL) is considered to be negative.
- Reactive: A result greater than or equal to 10.0 IU/mL (≥10.0 IU/mL) is considered to be positive.

Results may differ between laboratories due to variations in population and test method. It is recommended that each laboratory establish its own reference interval.

LIMITATIONS

- The assay is mainly used to prenatal screening and physical examination.
- Results should be used in conjunction with patient's medical history, clinical examination and other findings.
- If the Rubella IgG results are inconsistent with clinical evidence, additional testing is needed to confirm the result.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies[10,11]. Additional information may be required for diagnosis.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or animal serum products can be prone to this interference and anomalous values may be observed[12].
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- A negative test result does not completely rule out the possibility of an infection with Rubella. Individuals may not exhibit any detectable IgG antibodies at the early stage of acute infection.
- The results in HIV patients, in patients undergoing immunosuppressive therapy, or in patients with other disorders leading to immune suppression, should be interpreted with caution.
- Specimens from neonates, cord blood, pretransplant patients or body fluids other than serum and plasma, such as urine, saliva or amniotic fluid have not been tested.

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

Precision

Precision was determined using the assay, samples and controls in a protocol (EP05-A3,EP05-A2) of the CLSI (Clinical and Laboratory Standards Institute): duplicates at two independent runs per day for 20 days at three different sites using three lots of reagent kits (n=720). The following results were obtained:

Sample	Mean (IU/mL) (n=720)	Within-Run		Between-Run		Reproducibility	
		SD (IU/mL)	%CV	SD (IU/mL)	%CV	SD (IU/mL)	%CV
Serum Pool 1	8.068	N/A	N/A	N/A	N/A	N/A	N/A
Serum Pool 2	11.751	0.580	4.93	0.237	2.01	1.035	8.81
Serum Pool 3	102.626	5.392	5.25	2.533	2.47	7.679	7.48
Plasma Pool 1	7.834	N/A	N/A	N/A	N/A	N/A	N/A
Plasma Pool 2	11.649	0.648	5.56	0.296	2.54	1.042	8.95
Plasma Pool 3	99.945	5.084	5.09	2.577	2.58	8.295	8.30
Negative Control	<7.000	N/A	N/A	N/A	N/A	N/A	N/A
Positive Control	40.493	2.186	5.40	0.663	1.64	3.554	8.78

Based on internal testing on the MAGLUMI and Biolumi systems, the test results of negative samples should be negative; the overall repeatability (% CV) is estimated to be ≤ 8% for samples tested, the overall reproducibility (%CV) is estimated to be ≤ 10%. Performance of the assay at individual laboratories may vary.

Linear Range

3.00-500 IU/mL (defined by the Limit of Quantitation and the maximum of the master curve).

Reportable Interval

2.00-5000 IU/mL (defined by the Limit of Detection and the maximum of the master curve×Recommended Dilution Ratio).

Analytical Sensitivity

Limit of Blank (LoB) =0.500 IU/mL.
Limit of Detection (LoD) =2.00 IU/mL.
Limit of Quantitation (LoQ) =3.00 IU/mL.

Analytical Specificity

Interference

Interference was determined using the assay, three samples containing different concentrations of analyte were spiked with potential endogenous and exogenous interferents in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

Interference	No interference up to	Interference	No interference up to
Hemoglobin	2400 mg/dL	Acyclovir	6.6 mg/dL
Intralipid	3000 mg/dL	Interferon α	15000 IU/mL
Bilirubin	50 mg/dL	Levamisole	1.5 mg/mL
HAMA	40 ng/mL	Acetylsalicylic acid	0.65 mg/mL
ANA	398 AU/mL	Ibuprofen	50 mg/dL
Rheumatoid factor	2000 IU/mL	Methylcobalamin	50 μg/mL
Total protein	12 g/dL	Rifampicin	48 μg/mL
Systemic Lupus Erythematosus Plasma	/	Doxycycline	18 μg/mL
Anti-Mitochondrial Antibody	398 RU/mL	Cefoxitin	6600 μg/mL
Total IgG	8000 mg/dL	Cyclosporine	2 μg/mL
Total IgM	2500 mg/dL	Metronidazole	125 μg/mL
K2-EDTA	22.75 μmol/mL	Ascorbic acid	60 μg/mL
Heparin sodium salt	80 IU/mL	Phenylbutazone	330 μg/mL
Heparin lithium salt	80 IU/mL	Vidarabine	1000 μg/mL
Biotin	0.5 mg/dL	Acetaminophen	400 μg/mL
Ribavirin	2 mg/mL	Sodium salicylate	500 μg/mL

Cross-Reactivity

The assay is highly specific for Rubella IgG antibodies, with no observed cross reactivity to Toxo IgG, CMV IgG, HSV-1 IgG, HSV-2 IgG, Rubella IgM, HAV IgG, Anti-HBs, HBeAb IgG, HBcAb IgG, Anti-HCV, Anti-HIV, Anti-Treponema pallidum, EBV EA IgG, EBV NA IgG, EBV VCA IgG, *M.Pneumoniae* IgG, *C.Pneumoniae* IgG, Parvovirus B19 IgG, VZV IgG, Influenza A virus IgG, Influenza B virus IgG, Parainfluenza virus IgG, Adenovirus IgG and COXB IgG.

High-Dose Hook

No high-dose hook effect was seen for Rubella IgG concentrations up to 5000 IU/mL.

Relative Sensitivity

The relative sensitivity of the Rubella IgG assay was determined by testing 303 samples collected from expected positive population with commercial assay confirmation of Rubella IgG positive result.

N of samples	Reactive	Relative Sensitivity	95% CI
303	301	99.34%	97.63%-99.82%

Relative Specificity

The relative specificity of the Rubella IgG assay was determined by testing 547 samples collected from expected negative population with commercial assay confirmation of Rubella IgG negative result.

N of samples	Non-reactive	Relative Specificity	95% CI
547	547	100.00%	99.30%-100.00%

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SYMBOLS EXPLANATIONS

	Consult instructions for use		Manufacturer
2°C 8°C	Temperature limit (Store at 2-8°C)		Use-by date
Σ	Contains sufficient for<n> tests		Keep away from sunlight
	This way up	EC REP	Authorized representative in the European Community
IVD	*In vitro* diagnostic medical device	CONTENTS	Kit component
REF	Catalogue number	LOT	Batch code
CE 0123	CE marking with notified body ID number		

Summary of safety and performance is available at Eudamed.

Shenzhen New Industries Biomedical Engineering Co., Ltd.
No.23, Jinxiu East Road, Pingshan District, 518122 Shenzhen, P.R. China
Tel: +86-755-21536601 Fax:+86-755-28292740

EC REP **Shanghai International Holding Corp. GmbH (Europe)**
Eiffestrasse 80, 20537 Hamburg, Germany
Tel: +49-40-2513175 Fax: +49-40-255726