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Rubella IgM

cobas®

IgM antibodies to Rubella virus

REF	Σ	SYSTEM
04618831 190	100	Elecsys 2010 MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

Please note

The measured anti-Rubella IgM value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the Rubella IgM assay used.

Anti-Rubella IgM values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations.

Therefore, the results reported by the laboratory to the physician should include:

"The following results were obtained with the Elecsys Rubella IgM assay. Results from assays of other manufacturers cannot be used interchangeably."

Intended use

Immunoassay for the in vitro qualitative determination of IgM antibodies to Rubella virus in human serum and plasma.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Summary

References[1,2,3,4,5,6,7]

Rubella virus is the etiological agent of German measles, a commonly mild rash disease which occurs usually during childhood. It is spread by small droplets via the respiratory route. Postnatal acquired infection is seldom associated with complications.

However, Rubella can be a serious disease when a pregnant woman becomes infected especially during the first trimester of pregnancy. Rubella virus can be transmitted through the placenta and can result in fetal death or may cause severe malformations to the fetus, commonly summarized as congenital Rubella syndrome (CRS). CRS is an important cause of blindness, deafness, congenital heart disease and mental retardation. Today infant vaccination programs and the vaccination of women in child-bearing age who are susceptible to Rubella infection have considerably reduced the incidence of acute Rubella infection and the incidence of CRS.

The detection of Rubella-specific antibodies is used to determine the immune status of an individual and to aid in the diagnosis of acute Rubella infection.

The presence of IgG antibodies to Rubella virus indicates a previous exposure either by vaccination or prior Rubella infection and is indicative of presumptive immunity.

The detection of Rubella-specific IgM antibodies is used as an aid in the diagnosis of acute Rubella infection. Seroconversion of specific Rubella antibodies or a significant rise of the IgG antibody titer from a first to a second sample may support the diagnosis of acute Rubella infection.

Recombinant Rubella-like particles (RLP) have proven to replace authentic Rubella virus as an antigen in diagnostic assays.

Test principle

µ-Capture test principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 µL of sample are automatically prediluted 1:20 with Diluent Universal. Biotinylated monoclonal anti-human IgM-specific antibodies and Rubella-specific recombinant antigen are added and react with anti-Rubella IgM antibodies present in the sample to form a complex.
- 2nd incubation: After addition of ruthenium-labeled[a)] Rubella-specific antibodies and streptavidin-coated microparticles the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as RUBIGM.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-h IgM-Ab~biotin; Rubella-specific recombinant antigen (gray cap), 1 bottle, 10 mL:
Biotinylated monoclonal anti-h IgM antibody (mouse) > 500 ng/mL, Rubella-like particles (RLP) approx. 0.1 U/mL; sodium phosphate buffer pH 7.7; preservative.

R2 Anti-Rubella~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL:
Anti-Rubella antibodies labeled with ruthenium complex > 400 ng/mL; sodium phosphate buffer pH 7.7; preservative.

RUBIGM Cal1 Negative calibrator 1 (white cap), 2 bottles of 1.0 mL each:
Human serum, non-reactive for anti-Rubella IgM; preservative.

RUBIGM Cal2 Positive calibrator 2 (black cap), 2 bottles of 1.0 mL each:
Anti-Rubella IgM approx. 700 U/mL (Roche units) in buffer; preservative.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

All human material should be considered potentially infectious.

The negative calibrator (RUBIGM Cal1) has been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

Positive calibrator (RUBIGM Cal2): Materials of human origin were tested for HIV and hepatitis C. The findings were negative.

The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[8,9]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit are ready for use and are supplied in bottles compatible with the system.

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Elecsys 2010 and **cobas e** 411 analyzers: The calibrators should only be left on the analyzers during calibration at 20-25 °C. After use, close the bottles as soon as possible and store at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per bottle set should be performed.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, transfer aliquots of the ready-for-use calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is read in from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the analyzers	2 weeks or 12 weeks if stored alternately in the refrigerator and on the analyzers (up to 84 hours)

Stability of the calibrators	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on Elecsys 2010 and **cobas e** 411 at 20-25 °C	up to 5 hours
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested in a sufficient number and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_3-EDTA and sodium citrate plasma. Do not use plasma treated with sodium fluoride and potassium oxalate.

Criterion: Mean recovery of positive samples within 80-120 % of serum value.

Stable for 3 weeks at 2-8 °C, 3 days at 25 °C, 3 months at -20 °C. The samples may be frozen 6 times.

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. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Specimens should not be subsequently altered with additives (biocides, anti-oxidants or substances that could possibly change the pH of the sample) in order to avoid erroneous findings.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

Centrifuge samples containing precipitates and frozen samples before performing the assay. Lyophilized samples and samples and controls stabilized with azide (up to 1 %) can be used.

Do not use heat-inactivated samples.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See “Reagents – working solutions” section for reagents.

- 2 x 6 bottle labels

Materials required (but not provided)

- REF 04618840190, PreciControl Rubella IgM, 4 x 1 mL each of PreciControl Rubella IgM 1 and 2
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or
  REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

Bring the cooled reagents to approx. 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Place the calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

Calibration

Traceability: This method has been standardized against a Roche standard. The units have been selected arbitrarily.

Rubella IgM

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Calibration frequency: Calibration must be performed once per reagent lot using RUBIGM Cal1, RUBIGM Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings with PreciControl Rubella IgM outside the defined limits
- more frequently when this is required by pertinent regulations

Range for the electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (RUBIGM Cal1): 500-2700 (Elecsys 2010, MODULAR ANALYTICS E170 and **cobas e** analyzers).

Positive calibrator (RUBIGM Cal2): 5500-30000 (Elecsys 2010, MODULAR ANALYTICS E170 and **cobas e** analyzers).

Quality control

For quality control, use PreciControl Rubella IgM.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note:

For technical reasons re-assigned target values valid for a specific reagent and control lot combination only, must be entered manually on all analyzers (except for the **cobas e** 602 analyzer). Therefore, always refer to the value sheet included in the rackpack or PreciControl kit to make sure that the correct target values are used.

When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of RUBIGM Cal1 and RUBIGM Cal2. The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Results obtained with the Elecsys Rubella IgM assay can be interpreted as follows:

Non-reactive: < 0.8 COI

Indeterminate: ≥ 0.8 - < 1.0 COI

Reactive: ≥ 1.0 COI

Samples with a cutoff index < 0.8 are non-reactive in the Elecsys Rubella IgM assay.

Samples with a cutoff index between ≥ 0.8 and < 1.0 are considered indeterminate. The sample should be retested. In case the result is still indeterminate, a second sample should be collected e.g. within 1 week. A significant increase of the Rubella IgG antibody titer from a first to a second sample supports the diagnosis of acute Rubella infection.

Samples with a cutoff index ≥ 1.0 are reactive in the Elecsys Rubella IgM assay.

The magnitude of the measured result above the cutoff is not indicative of the total amount of antibody present in the sample.

The anti-Rubella IgM results in a given specimen, as determined by assays from different manufacturers, can vary due to differences in assay and reagent methods.

Limitations - interference

A negative Rubella IgM test result, also in combination with a positive Rubella IgG result, does not completely rule out the possibility of acute Rubella infection:

- Specimens taken very early in the acute phase of infection may not contain detectable amounts of Rubella IgM antibodies.
- The immune response after Rubella infection varies considerably. Non-reactive results may preferentially occur in the late phase of acute infection by the Elecsys Rubella IgM assay.

The detection of IgM antibodies to Rubella virus in a single sample is not sufficient to prove an acute Rubella infection. Elevated IgM antibody levels may persist after natural infection and also after vaccination for a variable time period. Further tests or a combination of test methods should be done for clarification. The diagnosis of acute Rubella infection may be supported by a significant increase of the Rubella IgG antibody titer from a first to a second sample.

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.

The assay is unaffected by icterus (bilirubin < 428 µmol/L or < 25 mg/dL), hemolysis (Hb < 1.49 mmol/L or < 2.4 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 205 nmol/L or < 50 ng/mL).

Criterion: Mean recovery of positive samples within ± 20 % of initial value.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 6210 IU/mL.

The high-dose hook effect does not lead to false-negative results in the Elecsys Rubella IgM assay.

In vitro tests were performed on 18 commonly used pharmaceuticals and in addition on folic acid. No interference with the assay was found.

As with many µ-capture assays an interference with unspecific human IgM is observed. Increasing amounts of unspecific human IgM may lead to a decrease in the recovery of positive samples with the Elecsys Rubella IgM assay.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, human sera and controls (repeatability n = 21, intermediate precision n = 10); intermediate precision on MODULAR ANALYTICS E170 analyzer was determined in a modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60). The following results were obtained:

Elecsys 2010 and **cobas e** 411 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS[b], negative	0.198	0.005	2.4	0.20	0.006	3.0
HS, weakly positive	1.29	0.016	1.2	1.31	0.024	1.9
HS, positive	3.57	0.037	1.0	6.69	0.271	4.1
PC[c] Rubella IgM 1	0.175	0.003	1.8	0.20	0.008	4.1
PC Rubella IgM 2	1.98	0.036	1.8	1.95	0.080	4.1

b) HS = human serum

c) PC = PreciControl

Rubella IgM

IgM antibodies to Rubella virus

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MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS, negative	0.184	0.004	1.9	0.183	0.017	9.5
HS, weakly positive	1.06	0.011	1.0	1.00	0.027	2.7
HS, positive	4.12	0.049	1.2	3.96	0.108	2.7
PC Rubella IgM 1	0.211	0.003	1.6	0.180	0.020	10.9
PC Rubella IgM 2	1.52	0.033	2.2	1.59	0.053	3.4

Analytical specificity

390 samples containing potentially interfering substances were tested with the Elecsys Rubella IgM assay and commercially available comparison tests comprising specimens:

- containing IgM antibodies against HAV, HBcAg, CMV*, EBV, HSV, Parvo B19*, VZV, Toxoplasma gondii, measles and mumps
- positive for HIV (early infection), HCV (early infection), Treponema pallidum, Gonorrhea and Chlamydia
- containing autoantibodies (AMA, ANA*, SMA*) and elevated titers of rheumatoid factor*
- after vaccination against HBV and influenza

Positive or indeterminate results were verified by a Rubella IgG avidity test or a third commercial Rubella IgM test. 7 false positive and 5 indeterminate samples were found for Elecsys Rubella IgM. The specificity (COI ≥ 0.8) in this group was found 96.9 %. The lower confidence limit was found 95.1 %.

*CMV IgM positive: 1 false positive and 1 indeterminate result out of 30 samples, Parvo B19 IgM: 2 indeterminate results out of 30 samples; patients with autoantibodies: ANA: 2 false positive and 2 indeterminate results out of 47 samples, SMA: 1 false positive result out of 12 samples, RF: 3 false positive results out of 48 samples.

Clinical sensitivity

Acute Rubella infection

Of 109 samples from the early acute phase of Rubella infection (< 30 days after onset of symptoms) which were tested at two sites, 87 samples were found positive with the Elecsys Rubella IgM assay. 4 samples were found indeterminate (reactive) and 18 samples were found negative.

Sensitivity in early acute Rubella infection (< 30 days)

Site	N	Sensitivity Elecsys Rubella IgM (%) COI ≥ 0.8	Sensitivity Comparison Rubella IgM tests (%)
1	84	80 % (67/84)	87 % (73/84)
2	25	96 % (24/25)	96 % (24/25)

Of 17 samples from the late acute phase (≥ 30 days), 6 samples were found positive with the Elecsys Rubella IgM assay, 1 sample was found indeterminate (reactive) and 10 samples were found negative.

Sensitivity in late acute Rubella infection (≥ 30 days)

Site	N	Sensitivity Elecsys Rubella IgM No. of samples detected/ tested COI ≥ 0.8	Sensitivity Comparison Rubella IgM tests No. of samples detected/tested
1	14	6/14	10/14
2	3	1/3	3/3

Persisting IgM after Rubella infection

Of 91 specimens from previously infected pregnant women where an acute Rubella infection was excluded at the time of bleeding, 66 samples were found negative with the Elecsys Rubella IgM assay, 10 samples were found indeterminate (reactive) and 15 samples were found positive.

Rubella vaccination

In 67 individuals comprising 265 samples after Rubella vaccination, Rubella IgM antibodies were detected with the Elecsys Rubella IgM assay up to 60-90 days.

Clinical specificity

Pre-selected negative samples

In 311 pre-selected Rubella IgM negative samples, 2 discordant positive and 3 indeterminate results were found with the Elecsys Rubella IgM assay.

Routine samples (antenatal screening)

A total of 1556 fresh samples obtained from clinical routine (antenatal screening) were tested at 2 different sites in comparison to commercially available Rubella IgM assays. Samples with reactive or indeterminate results were re-tested with a third commercial Rubella IgM test at site 1 and at site 2 in addition with a Rubella IgG avidity test at site 2.

Relative specificity after resolution

Site	N	Relative specificity (%) COI < 0.8	Lower confidence limit (%)
1	557	98.74 (547/554)	97.65
2	999	98.99 (983/993)	98.30

Site 1: 7 samples which were found positive or indeterminate with the Elecsys Rubella IgM assay were found negative with the comparison tests. 3 samples were found reactive with all comparison assays despite lacking signs of Rubella-related symptoms and thus excluded from the calculation of specificity.

Site 2: Of 16 samples which were positive or indeterminate with the Elecsys Rubella IgM assay, an acute Rubella infection was excluded within 10 samples by a Rubella IgG avidity test (index > 60 %). 3 samples with an inconclusive Rubella IgG avidity test result and 3 samples which could not be further examined were excluded from the calculation of specificity.

References

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5 Pustowoit B, Grangéot-Kéros L, Hobman TC, et al. Evaluation of recombinant rubella-like particles in a commercial immunoassay for the detection of anti-rubella IgM. Clin Diagn Virol 1996;5:13-20.

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7 Detection and Quantification of Rubella IgG Antibody: Evaluation and Performance Criteria for Multiple Component Test Products, Specimen Handling, and Use of Test Products in the Clinical Laboratory; Approved Guideline. NCCLS Publication; 1997;Vol17,No17.

8 Occupational Safety and Health Standards: bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

9 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Rubella IgM

IgM antibodies to Rubella virus

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Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Roche