Elecsys Rubella IgM

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REF		Σ	SYSTEM
07027796190	07027796500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
RUBIGM	10021

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 **cobas e** immunoassay analyzers.

Summary

Rubella virus is the etiological agent of German measles, a commonly mild rash disease which occurs usually during childhood.[1,2] It is spread by small droplets via the respiratory route.[1,2,3,4] Postnatal acquired infection is seldom associated with complications.[1,2]

However, Rubella can be a serious disease when a pregnant woman becomes infected especially during the first trimester of pregnancy.[1,2,3,4] Rubella virus can be transmitted through the placenta and results in fetal death or causes severe malformations to the fetus, commonly summarized as congenital Rubella syndrome (CRS).[1,3] CRS can manifest with blindness, deafness, congenital heart disease and/or mental retardation.[2,3,4]

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 that of CRS.[1,2,3,4]

Detection of Rubella-specific antibodies is used to determine the immune status of an individual and contribute to the diagnosis of acute Rubella infection.[4]

The presence of IgG antibodies to Rubella virus indicates a previous exposure either by vaccination or prior Rubella infection and is indicative of immunity.[5]

Detection of Rubella-specific IgM antibodies can be indicative of acute or recent Rubella infection.[4,5] Seroconversion of specific Rubella antibodies or a significant rise of the Rubella IgG antibody titer from a first to a second sample may further 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: 6 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 II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- 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 **cobas e** pack (M, R1, R2) is labeled as RUBIGM.

M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-h-IgM-Ab~biotin; Rubella-specific recombinant antigen, 1 bottle, 21.0 mL:
Biotinylated monoclonal anti-human-IgM antibody (mouse) > 500 µg/L, Rubella-like particles (RLP) approximately 0.1 U/mL; sodium phosphate buffer, pH 7.7; preservative.

R2 Anti-Rubella-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 21.0 mL:
Anti-Rubella antibodies labeled with ruthenium complex > 400 ng/mL; sodium phosphate buffer pH 7.7; preservative.

RUBIGM Cal1 Negative calibrator 1, 1 bottle of 1.0 mL:
Human serum, non-reactive for anti-Rubella IgM; preservative.

RUBIGM Cal2 Positive calibrator 2, 1 bottle of 1.0 mL:
Anti-Rubella IgM approximately 700 U/mL (Roche units) in buffer; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing mist or vapours.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

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P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved by the FDA or that are in compliance with the legal rules applicable to placing in vitro diagnostic medical devices for human use on the market in the European Union.
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.[6,7]

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.

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

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators

The calibrators are supplied ready-for-use in bottles compatible with the system.

Unless the entire volume is necessary for calibration on the analyzer, 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 available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	16 weeks
on the analyzers at 20-25 °C	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 and found acceptable.

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

Li-heparin, Na-heparin, K_2-EDTA, K_3-EDTA and Na-citrate plasma.

Plasma tubes containing separating gel can be used.

Criterion: Correct assignment of positive and negative samples. Samples with a COI (cutoff index) ≥ 1.0: 80-140 % recovery; samples with a COI < 1.0: ≤ ± 0.25 recovery.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower values (COI) for individual patient specimens. In order to minimize dilution effects it is essential that respective sampling devices are filled completely according to manufacturer's instructions.

Stable for 3 days at 20-25 °C, 21 days at 2-8 °C, 3 months at -20 °C (± 5 °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 thawed samples before performing the assay.

Do not use heat-inactivated samples.

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

Due to possible evaporation effects, samples and calibrators 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, 8 x 1.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- REF 07299001190, Diluent Universal, 45.2 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/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.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibrators:

Place the calibrators in the sample zone.

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Read in all the information necessary for calibrating the assay.

Calibration

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

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 **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (RUBIGM Cal1): 400-2000
Positive calibrator (RUBIGM Cal2): 4600-25000

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 **cobas e** pack, 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.

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

Numeric result	Result message	Interpretation/ further steps
COI < 0.8	Non-reactive	Negative for anti-Rubella IgM.
COI ≥ 0.8 to < 1.0	Borderline	Sample should be retested. In case the result is still borderline, a second sample should be collected (e.g. within 1 week) and testing should be repeated.
COI ≥ 1.0	Reactive	Positive for anti-Rubella IgM.

A significant increase of the anti-Rubella IgG titer from a first to a second sample supports the diagnosis of acute Rubella infection.
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 reagents and assay 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 anti-Rubella IgM in a single sample is not sufficient to prove an acute Rubella infection. Elevated Rubella 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 anti-Rubella IgG 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 effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 428 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 205 nmol/L or ≤ 50 ng/mL
Albumin	≤ 7 g/dL
IgG	≤ 7 g/dL
IgA	≤ 1.4 g/dL

Criterion: Samples with a COI ≥ 1.0: ≤ ± 20 % recovery; samples with a COI < 1.0: ≤ ± 0.2 recovery.

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.

There were no false positive results caused by rheumatoid factors.

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

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special drug was tested. No interference with the assay was found.

Special drug

Drug	Concentration tested
Folic acid	≤ 3 mg/L

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, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

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cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[b)], negative	0.233	0.003	1.3	0.009	3.9
HS, weakly positive	1.10	0.010	0.9	0.017	1.5
HS, high positive	2.99	0.036	1.2	0.051	1.7
PC[c)] Rubella IgM 1	0.235	0.003	1.4	0.010	4.2
PC Rubella IgM 2	2.32	0.022	0.9	0.036	1.6

b) HS = human serum

c) PC = PreciControl

Analytical specificity

392 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, Parvovirus 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 borderline results were verified by a Rubella IgG avidity test or a third commercial Rubella IgM test. 8 false positive and 5 borderline samples were found for Elecsys Rubella IgM. The specificity (COI ≥ 0.8) in this group was found 96.7 % and 98.0 % (COI ≥ 1.0). The lower confidence limit was found 94.8 % (COI ≥ 0.8) and 96.4 % (COI ≥ 1.0).

*CMV IgM: 1 false positive and 1 borderline result out of 29 samples, Parvovirus B19 IgM: 2 borderline results out of 30 samples; patients with autoantibodies: ANA: 2 false positive and 2 borderline results out of 47 samples, SMA: 1 false positive result out of 12 samples, RF: 4 false positive results out of 58 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 borderline (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)	85 % (71/84)
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 borderline (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 borderline (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 borderline 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 borderline 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 borderline 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 borderline 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

1 Edlich RF, Winters KL, Long WB 3rd, et al. Rubella and congenital rubella (German measles). J Long Term Eff Med Implants 2005;15:319-328.

2 Best JM. Rubella. Semin Fetal Neonatal Med 2007;12:182-192.

3 Duszak RS. Congenital rubella syndrome--major review. Optometry 2009;80:36-43.

4 De Santis M, Cavaliere AF, Straface G, et al. Rubella infection in pregnancy. Reprod Toxicol 2006;21:390-398.

5 Tipples GA. Rubella diagnostic issues in Canada. J Infect Dis 2011;204(Suppl2):659-663.

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

7 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 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.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

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Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

CE 0123

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