CE

Declaration of Conformity

EUROIMMUN Medizinische Labordiagnostika AG
Seekamp 31, D-23560 Lübeck, Germany

declare under our sole responsibility that the products

No. 1 to No. 5448, listed on the attached pages 1 to 53

Digitally signed by Ceaicovschi Tudor
Date: 2022.03.17 10:55:12 EET
Reason: MoldSign Signature
Location: Moldova

meets the demands of

Directive 98/79/EC on in vitro diagnostic medical devices of 27 October 1998 and its transpositions in national laws which apply to it.

Conformity assessment procedure: Annex III

Lübeck, 16.12.2016
(Place and date of issue)

Susanne Aleksandrowicz
- Member of the Board -

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- Head of Quality Management -

EUROIMMUN
Medizinische Labordiagnostika AG

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Order No.	Name
DP 3790-1601 E	EUROLINE Atopy Screen (IgE)
DP 3711-1601 E	EUROLINE pollen-food cross reactions (IgE)
DP 3712-1601 E	EUROLINE Pediatrics (IgE)
DP 3712-6401 E	EUROLINE Pediatrics (IgE)
DP 3712-1601 SE	EUROLINE-SC Pediatric (IgE)
DP 3713-1601 E	EUROLINE Atopy China (IgE)
DP 3713-6401 E	EUROLINE Atopy China (IgE)
DP 3713-1601-3 E	EUROLINE Atopy (China 3) (IgE)
DP 3713-1601-4 E	EUROLINE Atopy (China 4) (IgE)
DP 3713-1601-5 E	EUROLINE Atopy (China 5) (IgE)
DP 3713-1601-6 E	EUROLINE Atopy (China 6) (IgE)
DP 3713-1601-7 E	EUROLINE Atopy (China 7) (IgE)
DP 3713-1601-8 E	EUROLINE Atopy "China 8" (IgE)
DP 3713-6401-8 E	EUROLINE Atopy "China 8" (IgE)
DP 3713-1601-9 E	EUROLINE Atopy "China 9" (IgE)
DP 3713-6401-9 E	EUROLINE Atopy "China 9" (IgE)
DP 3716-1601 E	EUROLINE Atopy (Peru) (IgE)
DP 3717-1601 E	EUROLINE Mix "France" (IgE)
DP 3717-6401 E	EUROLINE Mix "France" (IgE)
DP 3717-1601-2 E	EUROLINE Mix "France 2" (IgE)
DP 3717-6401-2 E	EUROLINE Mix "France 2" (IgE)
DP 3718-1601 E	EUROLINE Atopy "Lithuania" (IgE)
DP 3718-1601 SE	EUROLINE-SC Atopy "Lithuania" (IgE)
DP 3720-1601 E	EUROLINE Insect venoms (IgE)
DP 3812-1601-1 E	EUROLINE DPA-Dx Paediatrics 1 (IgE)
DP 3850-1601-1 E	EUROLINE DPA-Dx Insect venoms 1 (IgE)
DP 3850-1601-2 E	EUROLINE DPA-Dx Insect venoms 2 (IgE)
DW 1111-1601-2 G	Anti-Neuronal Antigen EUROLINE-WB (IgG)
DW 1111-2401-2 G	Anti-Neuronal Antigen EUROLINE-WB (IgG)
DW 1520-1601-3 G	Anti-HEp-2 Cell Antigen EUROLINE-WB (IgG)
DW 1520-3001-3 G	Anti-HEp-2 Cell Antigen EUROLINE-WB (IgG)
DY 2080-1601 A	Anti-Helicobacter pylori Westernblot (IgA)
DY 2080-3001 A	Anti-Helicobacter pylori Westernblot (IgA)
DY 2080-1601 G	Anti-Helicobacter pylori Westernblot (IgG)
DY 2080-3001 G	Anti-Helicobacter pylori Westernblot (IgG)
DY 2080-1601-1 A	Anti-Helicobacter pylori EUROLINE-Westernblot (IgA)
DY 2080-3001-1 A	Anti-Helicobacter pylori EUROLINE-Westernblot (IgA)
DY 2080-1601-1 G	Anti-Helicobacter pylori EUROLINE-Westernblot (IgG)
DY 2080-3001-1 G	Anti-Helicobacter pylori EUROLINE-Westernblot (IgG)
DY 2111-1601 G	Anti-Treponema pallidum Westernblot (IgG)
DY 2111-2401 G	Anti-Treponema pallidum Westernblot (IgG)
DY 2111-1601 M	Anti-Treponema pallidum Westernblot (IgM)
DY 2111-2401 M	Anti-Treponema pallidum Westernblot (IgM)
DY 2111-1601-1 G	Anti-Treponema pallidum EUROLINE-WB (IgG)
DY 2111-2401-1 G	Anti-Treponema pallidum EUROLINE-WB (IgG)
DY 2111-1601-1 M	Anti-Treponema pallidum EUROLINE-WB (IgM)
DY 2111-2401-1 M	Anti-Treponema pallidum EUROLINE-WB (IgM)
DY 2131-1601 G	Anti-Borrelia afzelii Westernblot (IgG)
DY 2131-3001 G	Anti-Borrelia afzelii Westernblot (IgG)
DY 2131-3201 G	Anti-Borrelia afzelii Westernblot (IgG)
DY 2131-24001 G	Anti-Borrelia afzelii Westernblot (IgG)
DY 2131-1601 M	Anti-Borrelia afzelii Westernblot (IgM)
DY 2131-3001 M	Anti-Borrelia afzelii Westernblot (IgM)
DY 2131-3201 M	Anti-Borrelia afzelii Westernblot (IgM)
DY 2131-24001 M	Anti-Borrelia afzelii Westernblot (IgM)
DY 2131-1601-1 G	Anti-Borrelia EUROLINE-WB (IgG)
DY 2131-3001-1 G	Anti-Borrelia EUROLINE-WB (IgG)
DY 2131-24001-1 G	Anti-Borrelia EUROLINE-WB (IgG)
DY 2131-1601-1 M	Anti-Borrelia EUROLINE-WB (IgM)
DY 2131-3001-1 M	Anti-Borrelia EUROLINE-WB (IgM)
DY 2131-24001-1 M	Anti-Borrelia EUROLINE-WB (IgM)
DY 2132-1601 G	Anti-Borrelia burgdorferi Westernblot (IgG)
DY 2132-3001 G	Anti-Borrelia burgdorferi Westernblot (IgG)
DY 2132-3201 G	Anti-Borrelia burgdorferi Westernblot (IgG)
DY 2132-24001 G	Anti-Borrelia burgdorferi Westernblot (IgG)
DY 2132-1601 M	Anti-Borrelia burgdorferi Westernblot (IgM)
DY 2132-3001 M	Anti-Borrelia burgdorferi Westernblot (IgM)
DY 2132-3201 M	Anti-Borrelia burgdorferi Westernblot (IgM)
DY 2132-24001 M	Anti-Borrelia burgdorferi Westernblot (IgM)
DY 2134-1601 G	Anti-Borrelia garinii Westernblot (IgG)
DY 2134-3001 G	Anti-Borrelia garinii Westernblot (IgG)
DY 2134-3201 G	Anti-Borrelia garinii Westernblot (IgG)
DY 2134-24001 G	Anti-Borrelia garinii Westernblot (IgG)
DY 2134-1601 M	Anti-Borrelia garinii Westernblot (IgM)
DY 2134-3001 M	Anti-Borrelia garinii Westernblot (IgM)
DY 2134-3201 M	Anti-Borrelia garinii Westernblot (IgM)
DY 2134-24001 M	Anti-Borrelia garinii Westernblot (IgM)
DY 2173-1601 A	Anti-Yersinia enterocolitica Westernblot (IgA)
DY 2173-3001 A	Anti-Yersinia enterocolitica Westernblot (IgA)
DY 2173-1601 G	Anti-Yersinia enterocolitica Westernblot (IgG)
DY 2173-3001 G	Anti-Yersinia enterocolitica Westernblot (IgG)
DY 2320-0401 G	Anti-Echinococcus granulosus Westernblot (IgG)
DY 2320-1601 G	Anti-Echinococcus granulosus Westernblot (IgG)
DY 2320-2401 G	Anti-Echinococcus granulosus Westernblot (IgG)
DY 2321-1601-1 G	Anti-Echinococcus EUROLINE WB (IgG)
DY 2531-1601-1 G	Anti-HSV-1 / HSV-2 gG-2 EUROLINE-WB (IgG)
DY 2531-2401-1 G	Anti-HSV-1 / HSV-2 gG-2 EUROLINE-WB (IgG)
DY 2531-1601-1 M	Anti-HSV-1 / HSV-2 gG-2 EUROLINE-WB (IgM)
DY 2531-2401-1 M	Anti-HSV-1 / HSV-2 gG-2 EUROLINE-WB (IgM)
DY 2790-1601 G	Anti-EBV Westernblot (IgG)
DY 2790-2401 G	Anti-EBV Westernblot (IgG)
DY 2790-1601 M	Anti-EBV Westernblot (IgM)
DY 2790-2401 M	Anti-EBV Westernblot (IgM)
EA 1012-9601 G	Anti-TPO ELISA (IgG)
EA 1013-9601 G	Anti-TG ELISA (IgG)
EA 1015-9601 G	Anti-TSH Receptor ELISA (IgG)
EA 1015-9601-1 G	Anti-TSH Receptor (TRAb) Fast ELISA (IgG)
EA 1022-9601 G	Anti-GAD ELISA (IgG)
EA 1022-9601-1 G	Anti-GAD/IA2 Pool ELISA (IgG)
EA 1023-9601 G	Anti-IA2 ELISA (IgG)
EA 1060-9601 P	Anti-Ovary ELISA
EA 1063-9601 P	Anti-Zona Pellucida ELISA
EA 1086-9601	Anti-Spermatozoa ELISA (Ig typing)
EA 1086-9601 P	Anti-Spermatozoa ELISA

Order No.	*Name*
EA 1086-9601-R P	Anti-Spermatozoa ELISA (Seminal fluid)
EA 1200-1208-1 G	ANCA Profile ELISA (IgG)
EA 1201-9601-1 G	Anti-PR3 Capture ELISA (IgG)
EA 1201-9601-2 G	Anti-PR3-hn-hr ELISA (IgG)
EA 1211-9601 G	Anti-MPO ELISA (IgG)
EA 1251-9601 G	Anti-GBM ELISA (IgG)
EA 1254-9601 G	Anti-PLA2R ELISA (IgG)
EA 1302-9601 G	Anti-SLA/LP ELISA (IgG)
EA 1307-9601 G	Anti-LC-1 ELISA (IgG)
EA 1321-9601 G	Anti-LKM-1 ELISA (IgG)
EA 1361-9601 G	Anti-PCA ELISA (IgG)
EA 1362-9601 G	Anti-Intrinsic Factor ELISA (IgG)
EA 1435-9601 G	Anti-Acetylcholine Receptor ELISA (IgG)
EA 1490-1208-1 G	Dermatology Profile ELISA (IgG)
EA 1491-4801 G	Anti-Envoplakin ELISA (IgG)
EA 1495-4801 G	Anti-Desmoglein 1 ELISA (IgG)
EA 1496-4801 G	Anti-Desmoglein 3 ELISA (IgG)
EA 1502-4801-1 G	Anti-BP230-CF ELISA (IgG)
EA 1502-4801-2 G	Anti-BP180-NC16A-4X ELISA (IgG)
EA 1505-9601 G	Anti-CCP ELISA (IgG)
EA 151a-4802 G	Anti-Sa ELISA (IgG)
EA 151b-9601 G	Anti-CEP-1 ELISA (IgG)
EA 1560-9601 G	Anti-Histones ELISA (IgG)
EA 1571-9601 G	Anti-dsDNA ELISA (IgG)
EA 1572-9601 G	Anti-dsDNA-NcX ELISA (IgG)
EA 1573-9601 G	Anti-C1q ELISA (IgG)
EA 1574-9601 G	Anti-Nucleosomes ELISA (IgG)
EA 1576-9601 G	Anti-ssDNA ELISA (IgG)
EA 1584-9601 G	Anti-PM-Scl ELISA (IgG)
EA 159z-9601 G	Anti-DFS70 ELISA (IgG)
EA 1590-1208-1 G	Anti-ENA ProfilePlus 1 ELISA (IgG)
EA 1590-1208-2 G	Anti-ENA ProfilePlus 2 ELISA (IgG)
EA 1590-9601-7 G	Anti-ENA PoolPlus ELISA (IgG)
EA 1590-9601-8 G	ANA Screen ELISA (IgG)
EA 1590-9601-9 G	Anti-ENA Pool ELISA (IgG)
EA 1590-9601-11 G	ANA-Screen 11-ELISA (IgG)
EA 1590-1208-12 G	Anti-ENA SLE Profile 2 ELISA (IgG)
EA 1590-9601-14 G	ANA Screen 9 ELISA (IgG)
EA 1591-9601 G	Anti-nRNP/Sm ELISA (IgG)
EA 1593-9601 G	Anti-Sm ELISA (IgG)
EA 1595-9601 G	Anti-SS-A ELISA (IgG)
EA 1597-9601 G	Anti-SS-B ELISA (IgG)
EA 1599-9601 G	Anti-Scl-70 ELISA (IgG)
EA 1611-9601 G	Anti-Centromeres ELISA (IgG)
EA 1621-9601 A	Anti-Cardiolipin ELISA (IgA)
EA 1621-9601 G	Anti-Cardiolipin ELISA (IgG)
EA 1621-9601 M	Anti-Cardiolipin ELISA (IgM)
EA 1621-9601 P	Anti-Cardiolipin ELISA (IgAGM)
EA 162a-9601 A	Anti-Phosphatidylserine ELISA (IgA)
EA 162a-9601 G	Anti-Phosphatidylserine ELISA (IgG)
EA 162a-9601 M	Anti-Phosphatidylserine ELISA (IgM)
EA 162a-9601 P	Anti-Phosphatidylserine ELISA (IgAGM)
EA 1622-9601 G	Anti-M2-3E ELISA (IgG)
EA 1632-9601 A	Anti-ß2-Glycoprotein 1 ELISA (IgA)
EA 1632-9601 G	Anti-ß2-Glycoprotein 1 ELISA (IgG)
EA 1632-9601 M	Anti-ß2-Glycoprotein 1 ELISA (IgM)
EA 1632-9601 P	Anti-ß2-Glycoprotein 1 ELISA (IgAGM)
EA 1641-9601 G	Anti-ribosomal P Proteins ELISA (IgG)
EA 1661-9601 G	Anti-Jo-1 ELISA (IgG)
EA 1675-4801 G	Anti-cN-1A ELISA (IgG)
EA 1814-9601 A	IgA-Rheumatoid Factor ELISA
EA 1814-9601 G	IgG-Rheumatoid Factor ELISA
EA 1814-9601 M	IgM-Rheumatoid Factor ELISA
EA 1818-9601 G	CIC-C1q ELISA (IgG)
EA 1910-9601 A	Anti-Tissue Transglutaminase ELISA (IgA)
EA 1910-9601 G	Anti-Tissue Transglutaminase ELISA (IgG)
EA 1947-4801 G	Anti-Collagen type VII ELISA (IgG)
EI 2040-9601 G	Anti-Diphtheria Toxoid ELISA (IgG)
EI 2050-9601 A	Anti-Bordetella pertussis toxin ELISA (IgA)
EI 2050-9601 G	Anti-Bordetella pertussis toxin ELISA (IgG)
EI 2050-9601 M	Anti-Bordetella pertussis ELISA (IgM)
EI 2050-9601-3 A	Anti-Bordetella FHA ELISA (IgA)
EI 2050-9601-3 G	Anti-Bordetella FHA ELISA (IgG)
EI 2050-9601-4 G	Anti-Bordetella Pertactin ELISA (IgG)
EI 2060-9601 G	Anti-Tetanus Toxoid ELISA (IgG)
EI 2080-9601 A	Anti-Helicobacter pylori ELISA (IgA)
EI 2080-9601 G	Anti-Helicobacter pylori ELISA (IgG)
EI 2081-9601 A	Anti-Helicobacter pylori ELISA CagA (IgA)
EI 2081-9601 G	Anti-Helicobacter pylori ELISA CagA (IgG)
EI 2091-9601 A	Anti-Campylobacter jejuni ELISA (IgA)
EI 2091-9601 G	Anti-Campylobacter jejuni ELISA (IgG)
EI 2111-9601 G	Anti-Treponema pallidum ELISA (IgG)
EI 2111-9601 M	Anti-Treponema pallidum ELISA (IgM)
EI 2111-9601 O	Anti-Treponema pallidum Screen ELISA (IgGM)
EI 2111-9601-L G	CSF: Anti-T. pallidum ELISA (IgG)
EI 2132-9601 M	Anti-Borrelia burgdorferi ELISA (IgM)
EI 2132-9601 O	Lyme Screen ELISA (IgGM)
EI 2132-9601-1 G	Anti-Borrelia burgdorferi VlsE ELISA (IgG)
EI 2132-9601-2 G	Anti-Borrelia plus VlsE ELISA (IgG)
EI 2132-9601-24 O	Lyme ELISA (IgG/IgM)
EI 2132-9601-5 G	Anti-Borrelia Select ELISA (IgG)
EI 2132-9601-5 M	Anti-Borrelia Select ELISA (IgM)
EI 2132-9601-L G	CSF: Anti-Borrelia plus VlsE ELISA (IgG)
EI 2132-9601-L M	CSF: Anti-Borrelia ELISA (IgM)
EI 2132-9601-10 G	Lyme Trace ELISA (IgG)
EI 2150-9601 A	Anti-Legionella pneumophila ELISA (IgA)
EI 2150-9601 G	Anti-Legionella pneumophila ELISA (IgG)
EI 2150-9601 M	Anti-Legionella pneumophila ELISA (IgM)
EI 2173-9601 A	Anti-Yersinia enterocolitica ELISA (IgA)
EI 2173-9601 G	Anti-Yersinia enterocolitica ELISA (IgG)
EI 2189-9601 A	Anti-Brucella abortus ELISA (IgA)
EI 2189-9601 G	Anti-Brucella abortus ELISA (IgG)
EI 2189-9601 M	Anti-Brucella abortus ELISA (IgM)
EI 2202-9601 A	Anti Mycoplasma pneumoniae ELISA (IgA)

Order No.	Name
EI 2202-9601 G	Anti Mycoplasma pneumoniae ELISA (IgG)
EI 2202-9601 M	Anti Mycoplasma pneumoniae ELISA (IgM)
EI 2212-9601 G	Anti-Trypanosoma cruzi ELISA (IgG)
EI 2260-9601 G	Anti-Plasmodium ELISA (IgG)
EI 2320-9601-1 G	Anti-Echinococcus ELISA (IgG)
EI 2525-9601 A	Anti-Hepatitis E Virus (HEV) ELISA (IgA)
EI 2525-9601 G	Anti-Hepatitis E Virus (HEV) ELISA (IgG)
EI 2525-9601 M	Anti-Hepatitis E Virus (HEV) ELISA (IgM)
EI 2525-9601 P	Anti-Hepatitis E Virus (HEV) ELISA (IgAGM)
EI 2531-9601-1 A	Anti-HSV-1/2 Pool ELISA (IgA)
EI 2531-9601-1 G	Anti-HSV-1/2 Pool ELISA (IgG)
EI 2531-9601-1 M	Anti-HSV-1/2 Pool ELISA (IgM)
EI 2531-9601-1 L G	CSF: Anti-HSV-1/2 Pool ELISA (CSF)
EI 2531-9601-2 G	Anti-HSV-1 (gC1) ELISA (IgG)
EI 2531-9601-2 M	Anti-HSV-1 (gC1) ELISA (IgM)
EI 2531-9601-24 G	Anti-HSV-1 (gC1) ELISA (IgG)
EI 2531-9601-L G	CSF: Anti-HSV-1 (gC1) ELISA (IgG)
EI 2532-9601-24 G	Anti-HSV-2 (gG2) ELISA (IgG)
EI 2532-9601-2 G	Anti-HSV-2 (gG2) ELISA (IgG)
EI 2532-9601-2 M	Anti-HSV-2 (gG2) ELISA (IgM)
EI 2532-9601-L G	CSF: Anti-HSV-2 (gG2) ELISA (IgG)
EI 2580-9601 G	Anti-Parvovirus B19 ELISA (IgG)
EI 2580-9601 M	Anti-Parvovirus B19 ELISA (IgM)
EI 2604-9601 G	Anti-MERS-CoV ELISA (IgG)
EI 2610-9601 G	Anti-Measles Virus ELISA (IgG)
EI 2610-9601 M	Anti-Measles Virus ELISA (IgM)
EI 2610-9601-1 G	Avidity: Anti-Measles Virus ELISA (IgG)
EI 2610-9601-4 M	Anti-Measles Virus NP ELISA (IgM)
EI 2610-9601-L G	CSF: Anti-Measles Virus ELISA (IgG)
EI 2630-9601 G	Anti-Mumps Virus ELISA (IgG)
EI 2630-9601 M	Anti-Mumps Virus ELISA (IgM)
EI 2630-9601-L G	CSF: Anti-Mumps Virus ELISA (IgG)
EI 2630-9601-3 G	Anti-Mumps Virus AT ELISA (IgG)
EI 2630-9601-5 M	Anti-Mumps Virus ELISA (G5) (IgM)
EI 2650-9601 A	Anti-VZV ELISA (IgA)
EI 2650-9601 G	Anti-VZV ELISA (IgG)
EI 2650-9601 M	Anti-VZV ELISA (IgM)
EI 2650-9601-1 G	Avidity: Anti-VZV ELISA (IgG)
EI 2650-9601-L A	CSF: Anti-VZV-ELISA (IgA)
EI 2650-9601-L G	CSF: Anti-VZV ELISA (IgG)
EI 2650-9601-L M	CSF: Anti-VZV-ELISA (IgM)
EI 2650-9601-2 M	Anti-VZV Glycoprotein ELISA (IgM)
EI 2661-9601 G	Anti-TBE Virus ELISA (IgG)
EI 2661-9601 M	Anti-TBE Virus ELISA (IgM)
EI 2661-9601-L G	CSF: Anti-TBE Virus ELISA (IgG)
EI 2661-9601-L M	CSF: Anti-TBE Virus ELISA (IgM)
EI 2661-9601-1 G	Avidity: Anti-TBE Virus ELISA (IgG)
EI 2661-9601-9 G	Anti-TBE Virus ELISA "Vienna" (IgG)
EI 2662-9601 G	Anti-West Nile Virus ELISA (IgG)
EI 2662-9601 M	Anti-West Nile Virus ELISA (IgM)
EI 2662-9601-1 G	Avidity: Anti-West Nile Virus ELISA (IgG)
EI 2663-9601 G	Anti-JEV ELISA (IgG)
EI 2663-9601 M	Anti-JEV ELISA (IgM)
EI 2668-9601 G	Anti-Zika Virus ELISA (IgG)
EI 2668-9601 M	Anti-Zika Virus ELISA (IgM)
EI 266b-9601 A	Anti-Dengue Virus ELISA (IgA)
EI 266b-9601 G	Anti-Dengue Virus ELISA (IgG)
EI 266b-9601 M	Anti-Dengue Virus ELISA (IgM)
EI 2667-9601 G	Anti-Usutu Virus ELISA (IgG)
EI 2670-9601 A	Anti-RSV ELISA (IgA)
EI 2670-9601 G	Anti-RSV ELISA (IgG)
EI 2670-9601 M	Anti-RSV ELISA (IgM)
EI 2680-9601 A	Anti-Adenovirus ELISA (IgA)
EI 2680-9601 G	Anti-Adenovirus ELISA (IgG)
EI 2680-9601 M	Anti-Adenovirus ELISA (IgM)
EI 2691-9601 A	Anti-Influenza A Virus ELISA (IgA)
EI 2691-9601 G	Anti-Influenza A Virus ELISA (IgG)
EI 2691-9601 M	Anti-Influenza A Virus ELISA (IgM)
EI 2691-9601-1 A	Anti-Influenza A/B Virus Pool ELISA (IgA)
EI 2691-9601-1 G	Anti-Influenza A/B Virus Pool ELISA (IgG)
EI 2691-9601-1 M	Anti-Influenza A/B Virus Pool ELISA (IgM)
EI 2692-9601 A	Anti-Influenza B Virus ELISA (IgA)
EI 2692-9601 G	Anti-Influenza B Virus ELISA (IgG)
EI 2692-9601 M	Anti-Influenza B Virus ELISA (IgM)
EI 2721-9601-1 A	Anti-Parainfluenza Virus Pool ELISA (IgA)
EI 2721-9601-1 G	Anti-Parainfluenza Virus Pool ELISA (IgG)
EI 2721-9601-1 M	Anti-Parainfluenza Virus Pool ELISA (IgM)
EI 2730-9601-1 A	Anti-Enterovirus ELISA (IgA)
EI 2730-9601-1 G	Anti-Enterovirus ELISA (IgG)
EI 2730-9601-1 M	Anti-Enterovirus ELISA (IgM)
EI 278h-9601-1 G	Anti-Hanta Virus Pool 1 "Eurasia" ELISA (IgG)
EI 278h-9601-1 M	Anti-Hanta Virus Pool 1 "Eurasia" ELISA (IgM)
EI 278h-9601-2 G	Anti-Hanta Virus Pool 2 "America" ELISA (IgG)
EI 278h-9601-2 M	Anti-Hanta Virus Pool 2 "America" ELISA (IgM)
EI 2791-9601 A	Anti-EBV-CA ELISA (IgA)
EI 2791-9601 G	Anti-EBV-CA ELISA (IgG)
EI 2791-9601 M	Anti-EBV-CA ELISA (IgM)
EI 2791-9601-1 G	Avidity: Anti-EBV-CA ELISA (IgG)
EI 2791-9601-21 G	Avidity: Anti-EBV-CA-ELISA (IgG) 2
EI 2791-9601-L G	CSF: Anti-EBV-CA ELISA (IgG)
EI 2793-9601 G	Anti-EBNA-1 ELISA (IgG)
EI 2795-9601 A	Anti-EBV-EA-D ELISA (IgA)
EI 2795-9601 G	Anti-EBV-EA-D ELISA (IgG)
EI 2795-9601 M	Anti-EBV-EA-D ELISA (IgM)
EI 293a-9601 G	Anti-Chikungunya Virus ELISA (IgG)
EI 293a-9601 M	Anti-Chikungunya Virus ELISA (IgM)
EP 9901-0101	Allergen rings preassembled
EP C000-0110	HSA Human serum albumin
EP C001-0110	C1 Penicilloyl G - HSA
EP C002-0110	C2 Penicilloyl V - HSA
EP C003-0110	C3 A.C.T.H.
EP C004-0110	C4 Chymopapain (Discase)
EP C005-0110	C5 Chymopapain
EP C006-0110	C6 Cephalosporin - HSA

Avidity determination of antibodies against Measles Viruses (IgG)
Test instruction

ORDER NO.	ANTIBODIES AGAINST	IG CLASS	SUBSTRATE	FORMAT
EI 2610-9601-1 G	Measles viruses	IgG	Ag-coated microplate wells	96 x 01 (96)

Background

The differentiation between fresh and long-standing infections is one of the greatest challenges in serology. Until now this was based mainly on determination of specific antibodies of the immunoglobulin class IgM, which generally only appear initially. However, the detection of these antibodies is often unreliable and problematic due to interfering factors such as persistence of the IgM response, too weak or delayed IgM production, and unspecific IgM production through polyclonal B-cell stimulation.

In recent years additional determination of the antibody avidity has become an established method for identifcation of primary infections. The immune system reacts to an infection by first forming low-avidity antibodies. With continued disease duration, IgG that are more precisely adapted to the antigens are produced – the avidity increases. If high-avidity IgG are detectable in the serum, it can be assumed that the infection is at a late stage.

Contents of the test system: EI 2610-9601-1 G:

Component	Colour	Format	Symbol
1. Test kit Anti-Measles Viruses ELISA (IgG, order number EI 2610-9601 G)	---	---	---
2. Positive control HA High-avidity anti-Measles (IgG, human), ready for use	red	1 x 1.3 ml	POS CONTROL HA
3. Positive control LA Low-avidity anti-Measles (IgG, human), ready for use	blue	1 x 1.3 ml	POS CONTROL LA
4. Urea solution for Anti-Measles ELISA, ready for use	yellow	1 x 12 ml	UREA
5. Phosphate buffer ready for use	light blue	1 x 12 ml	PBS BUFFER
6. Test instruction	---	1 booklet	---

LOT Lot — CE — Storage temperature

IVD In-vitro determination — Unopened usable until

Storage and stability: The test kit has to be stored at a temperature between 2°C to +8°C. Do not freeze. Unopened, all test kit components are stable until the indicated expiry date.

Waste disposal: Patient samples, calibrators, controls and incubated microplate strips should be handled as infectious waste. All reagents are to be disposed of according to official regulations.

Preparation and stability of the reagents

Note: All reagents must be brought to room temperature (+18 C to +25 C) approx. 30 minutes before use. After first use, the reagents are stable until the indicated expiry date if stored at +2 C to +8 C and protected from contamination, unless stated otherwise below.

- **Controls:** Ready for use. The reagents must be mixed thoroughly before use.

- **Urea solution:** Ready for use. The urea solution included in this test system may only be used for the avidity determination of antibodies against Measles.

- **Phosphate buffer:** Ready for use.

Warning: The calibrators and controls used have been tested negative for HBsAg, anti-HCV, anti-HIV-1 and anti-HIV-2 using enzyme immunoassays and indirect immunofluorescence methods. Nonetheless, all materials should be treated as being a potential infection hazard and should be handled with care. Some of the reagents contain the toxic agent sodium azide. Avoid skin contact.

Preparation and stability of the patient samples

Sample material: Human serum or EDTA, heparin or citrate plasma.

Stability: Patient samples to be investigated can generally be stored at +2°C to +8 C for up to 14 days. Diluted samples should be incubated within one working day.

Sample dilution: Patient samples are diluted **1:101** sample buffer. For example: dilute 10 µl serum to 1.0 ml sample buffer and mix well by vortexing (sample pipettes are not suitable for mixing).

NOTE: The controls are prediluted and ready for use, do not dilute them.

Incubation

Sample incubation: (1. step)
Transfer 100 µl of the controls or diluted patient samples into the individual microplate wells according to the pipetting protocol.
Incubate for **30 minutes** at room temperature (+18°C to +25°C).

Wash:
Manual: Empty the wells and subsequently wash **1 time** using 300 µl of working strength wash buffer.
Automatic: Wash reagent wells **1 time** with 450 µl of working strength wash buffer (program setting: e.g. TECAN Columbus Washer "Overflow Modus").

Leave the wash buffer in each well for 30 to 60 seconds per washing cycle, then empty the wells. After washing (manual and automated tests), thoroughly dispose of all liquid from the microplate by tapping it on absorbent paper with the openings facing downwards to remove all residual wash buffer. Free positions on the microplate strip should be filled with blank wells of the same plate format as that of the parameter to be investigated.

Urea incubation: (2. step)
Pipette 200 µl of urea solution into each of the microplate wells of the first microtiter strip and 200 µl of phosphate buffer into each of the microplate wells of the second microtiter strip.
Incubate for **10 minutes** at room temperature (+18°C to +25°C).

Wash:
Empty the wells. Wash as described above, but wash **3 times** using working strength wash buffer for each wash.

Attention: Residual liquid (> 10 µl) in the reagent wells after washing can interfere with the substrate and lead to false low extinction values.
Insufficient washing (e.g., less than 3 wash cycles, too small wash buffer volumes, or too short reaction times) can lead to false high extinction values.

Conjugate incubation: (3. step)
Pipette 100 µl of enzyme conjugate (peroxidase-labelled anti-human IgG) into each of the microplate wells.
Incubate for **30 minutes** at room temperature.

Wash:
Empty the wells. Wash as described above, but wash **3 times** using working strength wash buffer for each wash.

Substrate incubation: (4. step)
Pipette 100 µl of chromogen/substrate solution into each of the microplate wells.
Incubate for **15 minutes** at room temperature (+18°C to +25°C) protect from direct sunlight.

Stopping the reaction:
Pipette 100 µl of stop solution into each of the microplate wells in the same order and at the same speed as the chromogen/substrate solution was introduced.

Measurement:
Photometric measurement of the colour intensity should be made at a **wavelength of 450 nm** and a reference wavelength between 620 nm and 650 nm **within 30 minutes of adding the stop solution**. Prior to measuring, slightly shake the microplate to ensure a homogeneous distribution of the solution.

Pipetting protocol

	1	2	3	4	5	6	7	8	9	10	11	12
A	pos HA	pos HA	P 7	P 7	P 15	P 15						
B	pos LA	pos LA	P 8	P 8	P 16	P 16						
C	P 1	P 1	P 9	P 9	P 17	P 17						
D	P 2	P 2	P 10	P 10	P 18	P 18						
E	P 3	P 3	P 11	P 11								
F	P 4	P 4	P 12	P 12								
G	P 5	P 5	P 13	P 13								
H	P 6	P 6	P 14	P 14								

The above pipetting protocol is an example of the avidity determination of IgG antibodies in 18 patient samples (P 1 to P 18).

Controls (pos HA and pos LA) as well as the patient samples have been incubated in duplicate in one well each of two different microtiter strips. The reagent wells of the microtiter strips 1, 3, 5 etc. are treated with urea solution after the incubation with patients samples, the reagent wells of the microtiter strips 2, 4, 6 etc. are treated with phosphate buffer.
The wells can be broken off individually from the strips. This makes it possible to adjust the number of test substrates used to the number of samples to be examined and minimises reagent wastage.

Both positive controls with high-avidity and low-avidity antibodies serve as internal controls for the reliability of the test procedure. They should be assayed with each test run.

Calculation of results

The presence of low-avidity antibodies in a patient's serum has been proved if the ELISA extinction value is considerably reduced by urea treatment. For an objective interpretation the relative avidity index (RAI) is calculated and expressed in percent using the extinction values with and without urea treatment.

$$\frac{\textbf{Extinction of the sample with urea treatment x 100}}{\textbf{Extinction of the sample without urea treatment}} = \textbf{relative avidity index (RAI) in \%}$$

The upper limit of the range of low-avidity antibodies (**cut-off value**) recommended by EUROIMMUN is 40% RAI. Values below the indicated cut-off are to be considered as an indication of low-avidity antibodies, values between 40% and 60% RAI as equivocal, values above 60% RAI as an indication of high-avidity antibodies. If a result is classified as equivocal, it is recommended to collect a second sample not less than 7 days later and to test it together with the first sample.

RAI < 40%:	indication of low-avidity antibodies
RAI 40% - 60%:	equivocal
RAI > 60%:	indication of high-avidity antibodies

Reliable results in the the measurement of IgG antibody avidity can only be yielded if the patient sample contains a diagnostically significant concentration of specific antibodies.

Generally, the determination of the relative avidity index is not helpful in samples which have an O.D. of <0.140 after incubation without urea treatment.

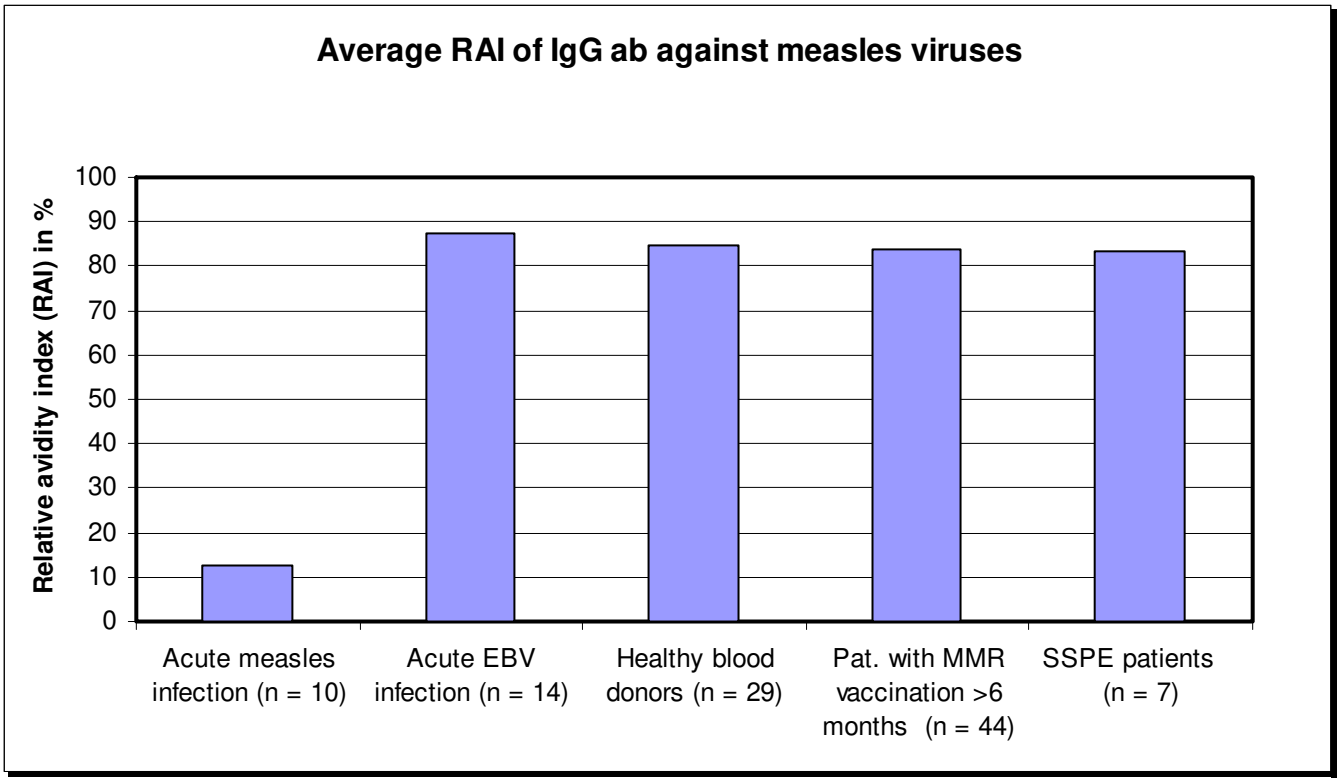
For diagnosis, the clinical symptoms of the patient should always be taken into account along with the serological results.

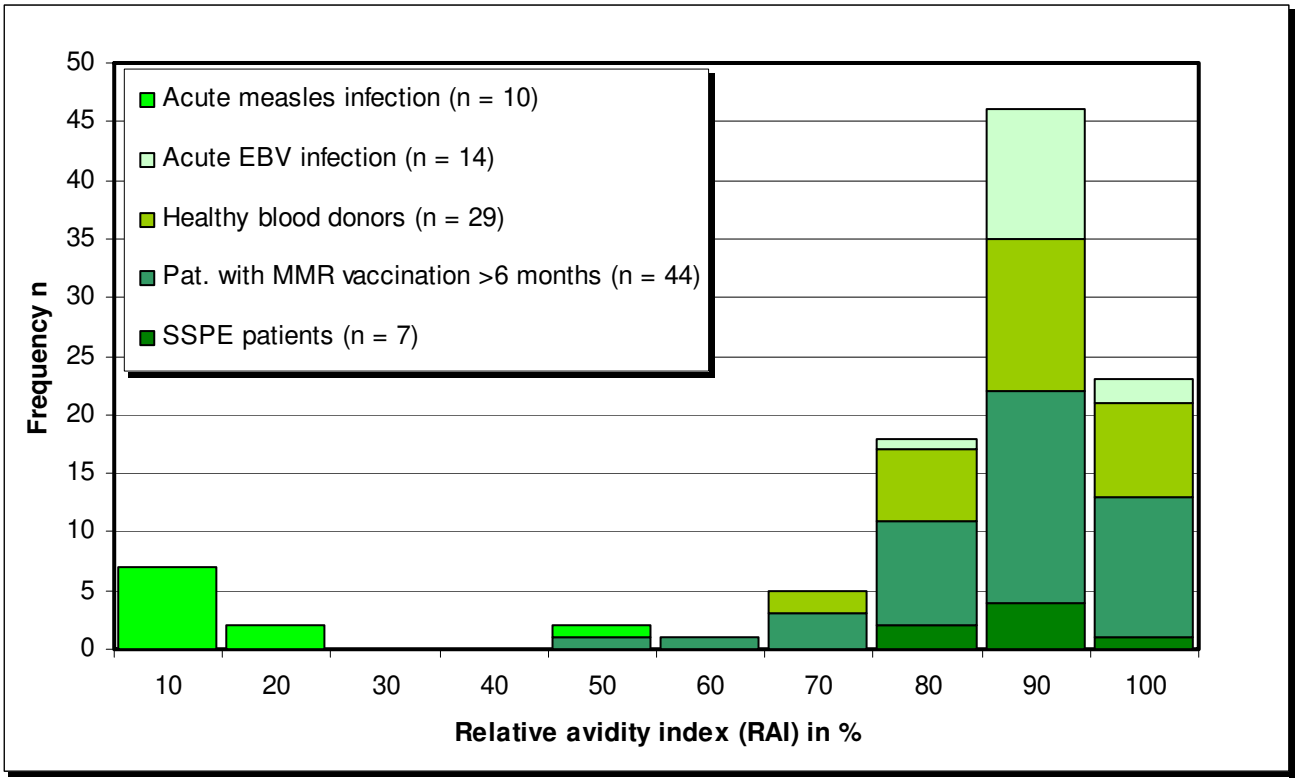
Attention:
In some patients with an acute infection, very high titers of IgG antibodies can be found. Even though the specific IgG antibody population is in different maturation stages, both, high-avidity and low-avidity, the vacant antigen epitopes are predominantly occupied by high-avidity antibodies in high titer samples. The determination of the avidity of the whole specific IgG antibody population can lead to false high RAI values in results.
False high RAI values were found in some cases of acute infections when the extinction value of the IgG measurement without urea treatment was >1.200.
It is recommended for samples with extinction values of >1.200 to repeat the avidity determination with a higher sample dilution (e. g. 1:401). If low avidity of IgG antibodies is already found at extinction values of >1.200, no further testing is necessary.

Test characteristics

A panel of 104 sera from patients with the following diseases was investigated:
10 patients with clinically and serologically diagnosed acute measles infection
14 patients with acute EBV infection and resulting polyclonal stimulation
29 healthy blood donors
44 patients with MMR vaccination more than 6 months ago
7 patients with SSPE after measles infection

In these panels patients with acute infection showed an average RAI of 13%, whereas the RAI determined for the remaining patients without acute measles infection was > 80%.





Clinical significance

The **measles virus (MV)** is the most instantly recognisable member of Morbilliviruses, a group of viruses belonging to the Paramyxoviridae family [1]. No animal reservoir is known. The measles virus causes an acute feverish illness which occurs mainly in childhood and is very infectious [2, 3]. In 1999, measles still caused worldwide 873,000 deaths per year [1, 4, 5]. Today they are less frequent because of vaccination, especially in the western hemisphere [6, 7]. However, measles epidemics are still observed in some countries [2, 3, 4, 5, 6, 8, 9]. Individuals acutely infected with the virus exhibit a wide range of clinical symptoms ranging from a characteristic mild self-limiting infection to death [1, 2, 8, 10].

MV infections are characterised by an incubation period of about 10 days, flue-like symptoms with fever, malaise, catarrh of the upper respiratory tract, cough, congestion and conjunctivitis. Soon afterwards the measles rash, a typical exanthema, appears first near the ears, then on the forehead, in the face and over the rest of the body [1, 5, 8, 11].

Complications arising from MV infections include secondary bacterial pneumonia, otitis media (approx. 1%), encephalitis (approx. 1%), myocarditis, miscarriage and a condition called subacute sclerosing pan-encephalitis (SSPE) [5, 12, 13]. Persistent MV infection of the otic capsule is an aetiologic factor in otosclerosis [9, 14]. Anti-measles IgG for the serological diagnosis of otoslcerotic hearing loss has a high specificity and sensitivity [15]. SSPE is a progressive, generally fatal brain disorder caused by chronic measles virus infection. It occurs about 7 to 10 years after the infection and generally kills within 3 years from the onset of the symptoms. The patients suffer from behavioural changes, cognitive deterioration, vision problems and eventually advanced neurological symptoms, such as severe spasms, and finally severe physical and mental impairment that leads to death [13]. Males are more commonly affected than females.

The risk of SSPE from measles was underestimated according to older data [12]. Actual papers put it at closer to 6.5 to 11 cases of SSPE per 100,000 measles infections; that means 7 to 13 times higher than the earlier estimates [1, 9, 12].

Women with acute measles infection during pregnancy and a negative result for measles-specific antibodies were observed e.g. in Japan, India, Thailand, Kenya and Brazil: 3 of 4 pregnancies ended in preterm delivery, spontaneous abortion or stillbirth; 2 of 4 neonates were found to have congenital measles with a positive result for IgM antibodies [5].

Antibodies against MV can be found in the serum of almost all patients during and after a measles infection. IgM antibodies develop soon after the onset of symptoms and can be measured using ELISA or indirect immunofluorescence tests (IIFT) [16, 20, 21, 22]. 50% of patients have IgM antibodies within three days, more than 90% within 10 days after occurrence of the rash [15, 17]. The Anti-Measles Virus IgM ELISA is more rapid and sensitive for the serological diagnosis of measles infections than other tests [15, 18, 19]. MV infections often cause an increase in heterologic antibodies. The statistically evaluated detection rate for antibodies is significantly higher for ELISA and IIFT in comparison with e.g. neutralisation tests [16, 20]. IgG and IgM antibodies against MV are reliable markers to confirm suspected measles infections.

Measles myelitis or encephalitis can be verified by detecting antibodies against measles in the cerebrospinal fluid (CSF) [23, 24, 25, 26]. These specific antibodies are synthesised in the brain [24]. The CSF-serum quotient (LSQ) allows to differenciate between a blood-derived and a pathological, brain-derived specific antibody fraction in CSF, taking into account individual changes in the blood/CSF barrier function [24, 25, 26, 27]. Therefore it is necessary to confirm the presence of antibodies against MV using ELISA both in CSF and in the serum. During measles myelitis or encephalitis an intrathecal synthesis of antibodies against MV in CFS takes place. Due to the fact that specific antibodies can pass the blood-cerebrospinal fluid barrier by diffusion from serum to CSF it is necessary to determine the relative CSF/serum quotient ($CSQ_{rel.}$, synonym: antibody specificity index) [24, 25, 26]. The quotient is calculated from the amount of specific anti-measles virus IgG antibodies in total CSF IgG in proportion to the amount of specific IgG antibodies in total serum IgG. During conversion the CSF/serum quotient of the pathogen-specific IgG-antibody concentrations $CSQ_{path.-spec.}$ (IgG) is put into relation to the CSF/serum quotient of the total IgG concentrations CSQ_{total} (IgG) [27]. A relative CSQ result above 1.5 indicates the production of specific antibodies in the central nervous system (CNS) and the involvement of the CNS in the disease [25, 26].

With respect to the severe complications known from measles infections, the Robert Koch Institute in Germany recommends vaccinating small children, with a first shot between the age of 11 to 14 months and a second between 15 and 23 months [2, 4, 10, 11]. Neutralisation activity and persistence of antibodies are induced in response to the immunisation [6, 15].

Life-long immunity is generally developed. However, antibody levels are 8 to 10 times lower in post-vaccination sera than in convalescent sera [6, 19, 28]. A passive immunisation with specific immunoglobulin concentrates is usually given to immunosuppressed seronegative individuals, such as tumour patients and recipients of transplants, as well as to seronegative pregnant women after exposure to the virus.

The European Regional Office of the WHO aims at eliminating measles from the region in the following years by area-wide vaccination campaigns [4, 9, 10]. This is expected to limit the number of apparent infections and especially of severe courses of the disease. For the diagnosis of the remaining cases of measles infection and of infections acquired outside Europe as well as for the clarification of atypical courses of the disease in partly immunised patients the antibody determination in serum and CSF will be of growing importance [3, 5, 8, 9].

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Anti-Measles Virus ELISA (IgG)
Test instruction

ORDER NO.	ANTIBODIES AGAINST	IG CLASS	SUBSTRATE	FORMAT
EI 2610-9601 G	Measles virus	IgG	Ag-coated microplate wells	96 x 01 (96)

Indication: measles

Principles of the test: The ELISA test kit provides a quantitative or semiquantitative in vitro assay for human antibodies of the IgG class against measles virus in serum or plasma. The test kit contains microtiter strips each with 8 break-off reagent wells coated with measles virus antigens. In the first reaction step, diluted patient samples are incubated in the wells. In the case of positive samples, specific IgG antibodies (also IgA and IgM) will bind to the antigens. To detect the bound antibodies, a second incubation is carried out using an enzyme-labelled anti-human IgG (enzyme conjugate) catalysing a colour reaction.

Contents of the test kit:

Component	Colour	Format	Symbol
1. Microplate wells coated with antigens: 12 microplate strips each containing 8 individual break-off wells in a frame, ready for use	---	12 x 8	STRIPS
2. Calibrator 1 5000 IU/l (IgG, human), ready for use	red coloured in decreasing intensity	1 x 2.0 ml	CAL 1
3. Calibrator 2 1000 IU/l (IgG, human), ready for use		1 x 2.0 ml	CAL 2
4. Calibrator 3 250 IU/l (IgG, human), ready for use		1 x 2.0 ml	CAL 3
5. Calibrator 4 50 IU/l (IgG, human), ready for use		1 x 2.0 ml	CAL 4
6. Positive control (IgG, human), ready for use	blue	1 x 2.0 ml	POS CONTROL
7. Negative control (IgG, human), ready for use	green	1 x 2.0 ml	NEG CONTROL
8. Enzyme conjugate peroxidase-labelled anti-human IgG (rabbit), ready for use	green	1 x 12 ml	CONJUGATE
9. Sample buffer ready for use	light blue	1 x 100 ml	SAMPLE BUFFER
10. Wash buffer 10x concentrate	colourless	1 x 100 ml	WASH BUFFER 10x
11. Chromogen/substrate solution TMB/H_2O_2, ready for use	colourless	1 x 12 ml	SUBSTRATE
12. Stop solution 0.5 M sulphuric acid, ready for use	colourless	1 x 12 ml	STOP SOLUTION
13. Test instruction	---	1 booklet	
14. Quality control certificate	---	1 protocol	

LOT Lot — CE — Storage temperature

IVD In vitro determination — Unopened usable until

Storage and stability: The test kit has to be stored at a temperature between +2°C to +8°C. Do not freeze. Unopened, all test kit components are stable until the indicated expiry date.

Waste disposal: Patient samples, calibrators, controls and incubated microplate strips should be handled as infectious waste. All reagents must be disposed of in accordance with local disposal regulations.

Preparation and stability of the reagents

Note: All reagents must be brought to room temperature (+18°C to +25°C) approx. 30 minutes before use. After first use, the reagents are stable until the indicated expiry date if stored at +2°C to +8°C and protected from contamination, unless stated otherwise below.

- **Coated wells:** Ready for use. Tear open the resealable protective wrapping of the microplate at the recesses above the grip seam. Do not open until the microplate has reached room temperature to prevent the individual strips from moistening. Immediately replace the remaining wells of a partly used microplate in the protective wrapping and tightly seal with the integrated grip seam (Do not remove the desiccant bag).
  Once the protective wrapping has been opened for the first time, the wells coated with antigens can be stored in a dry place and at a temperature between +2°C and +8°C for 4 months.

- **Calibrators and controls:** Ready for use. The reagents must be mixed thoroughly before use.

- **Enzyme conjugate:** Ready for use. The enzyme conjugate must be mixed thoroughly before use.

- **Sample buffer:** Ready for use.

- **Wash buffer:** The wash buffer is a 10x concentrate. If crystallization occurs in the concentrated buffer, warm it to 37°C and mix well before diluting. The quantity required should be removed from the bottle using a clean pipette and diluted with deionized or distilled water (1 part reagent plus 9 parts distilled water).
  For example: For 1 microplate strip, 5 ml concentrate plus 45 ml water.
  The working strength wash buffer is stable for 4 weeks when stored at +2°C to +8°C and handled properly.

- **Chromogen/substrate solution:** Ready for use. Close the bottle immediately after use, as the contents are sensitive to light. The Chromogen/substrate solution must be clear on use. Do not use the solution if it is blue coloured.

- **Stop solution:** Ready for use.

Warning: The controls and calibrators used have been tested negative for HBsAg, anti-HCV, anti-HIV-1 and anti-HIV-2 using enzyme immunoassays and indirect immunofluorescence methods. Nonetheless, all materials should be treated as being a potential infection hazard and should be handled with care. Some of the reagents contain the toxic agent sodium azide. Avoid skin contact.

Preparation and stability of the patient samples

Samples: Human serum or EDTA, heparin or citrate plasma.

Stability: Patient samples to be investigated can generally be stored at +2°C to +8°C for up to 14 days. Diluted samples should be incubated within one working day.

Sample dilution: Patient samples are diluted **1:101** in sample buffer. For example: dilute 10 µl serum in 1.0 ml sample buffer and mix well by votexing (sample pipettes are not suitable for mixing).

NOTE: Calibrators and controls are prediluted and ready for use, do not dilute them.

Incubation

For **semiquantative analysis** incubate **calibrator 3** along with the positive and negative controls and patient samples. For **quantitative analysis** incubate **calibrators 1 to 4** along with the positive and negative controls and patient samples.

(Partly) manual test performance

Sample incubation: (1st step)
Transfer 100 µl of the calibrators, positive and negative controls or diluted patient samples into the individual microplate wells according to the pipetting protocol. Incubate for **30 minutes** at room temperature (+18°C to +25°C).

Washing:
Manual: Empty the wells and subsequently wash 3 times using 300 µl of working strength wash buffer for each wash.
Automatic: Wash reagent wells 3 times with 450 µl of working strength wash buffer (program setting: e.g. TECAN Columbus Washer "Overflow Modus").

Leave the wash buffer in each well for 30 to 60 seconds per washing cycle, then empty the wells. After washing (manual and automated tests), thoroughly dispose of all liquid from the microplate by tapping it on absorbent paper with the openings facing downwards to remove all residual wash buffer.

Note: Residual liquid (> 10 µl) in the reagent wells after washing can interfere with the substrate and lead to false low extinction values. Insufficient washing (e.g., less than 3 wash cycles, too small wash buffer volumes, or too short reaction times) can lead to false high extinction values.
Free positions on the microplate strip should be filled with blank wells of the same plate format as that of the parameter to be investigated.

Conjugate incubation: (2nd step)
Pipette 100 µl of enzyme conjugate (peroxidase-labelled anti-human IgG) into each of the microplate wells. Incubate for **30 minutes** at room temperature (+18°C to +25°C).

Washing:
Empty the wells. Wash as described above.

Substrate incubation: (3rd step)
Pipette 100 µl of chromogen/substrate solution into each of the microplate wells. Incubate for **15 minutes** at room temperature (+18°C to +25°C) (protect from direct sunlight).

Stopping the reaction:
Pipette 100 µl of stop solution into each of the microplate wells in the same order and at the same speed as the chromogen/substrate solution was introduced.

Measurement:
Photometric measurement of the colour intensity should be made at a wavelength of 450 nm and a reference wavelength between 620 nm and 650 nm **within 30 minutes of adding the stop solution.** Prior to measuring, slightly shake the microplate to ensure a homogeneous distribution of the solution.

Test performance using fully automated analysis devices

Sample dilution and test performance are carried out fully automatically using the analysis device. The incubation conditions programmed in the respective software authorised by EUROIMMUN may deviate slightly from the specifications given in the ELISA test instruction. However, these conditions were validated in respect of the combination of the EUROIMMUN Analyzer I or the DSX from Dynex and this EUROIMMUN ELISA. Validation documents are available on inquiry.
Automated test performance using other fully automated, open system analysis devices is possible, however, the combination should be validated by the user.

Pipetting protocol

	1	2	3	4	5	6	7	8	9	10	11	12
A	**C 3**	**P 6**	**P 14**	**P 22**			**C 1**	**P 3**	**P 11**	**P 19**		
B	**pos.**	**P 7**	**P 15**	**P 23**			**C 2**	**P 4**	**P 12**	**P 20**		
C	**neg.**	**P 8**	**P 16**	**P 24**			**C 3**	**P 5**	**P 13**	**P 21**		
D	**P 1**	**P 9**	**P 17**				**C 4**	**P 6**	**P 14**	**P 22**		
E	**P 2**	**P 10**	**P 18**				**pos.**	**P 7**	**P 15**	**P 23**		
F	**P 3**	**P 11**	**P 19**				**neg.**	**P 8**	**P 16**	**P 24**		
G	**P 4**	**P 12**	**P 20**				**P 1**	**P 9**	**P 17**			
H	**P 5**	**P 13**	**P 21**				**P 2**	**P 10**	**P 18**			

The pipetting protocol for microtiter strips 1-4 is an example for the **semiquantitative analysis** of 24 patient samples (P 1 to P 24).
The pipetting protocol for microtiter strips 7-10 is an example for the **quantitative analysis** of 24 patient samples (P 1 to P 24).

The calibrators (C 1 to C 4), the positive (pos.) and negative (neg.) controls, and the patient samples have each been incubated in one well. The reliability of the ELISA test can be improved by duplicate determinations for each sample.
The reagent wells are break-off format. Therefore, the number of tests performed can be matched to the number of samples, minimizing reagent wastage.
Both positive and negative controls serve as internal controls for the reliability of the test procedure. They should be assayed with each test run.

Calculation of results

Semiquantitative: Results can be evaluated semiquantitatively by calculating a ratio of the extinction value of the control or patient sample over the extinction value of calibrator 3. Calculate the ratio according to the following formula:

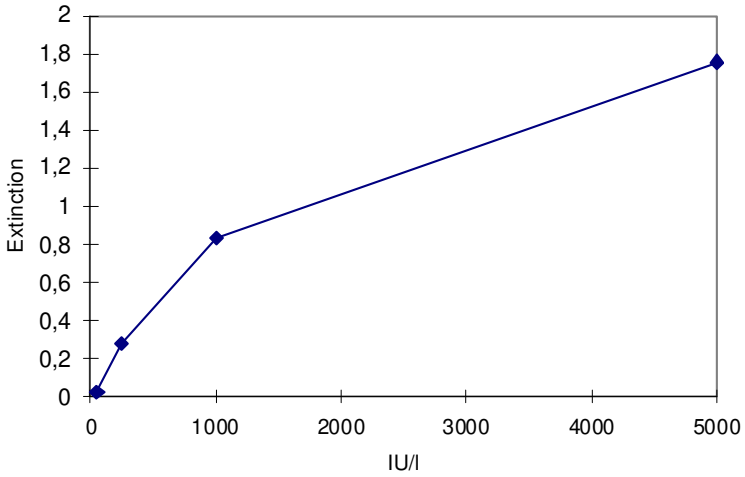
$$\frac{\textbf{Extinction of the control or patient sample}}{\textbf{Extinction of calibrator 3}} = \textbf{Ratio}$$

EUROIMMUN recommends interpreting results as follows:

Ratio <0.8:	**negative**
Ratio ≥0.8 to <1.1:	**borderline**
Ratio ≥1.1:	**positive**

In cases of borderline test results, an additional patient sample should be taken 7 days later and re-tested in parallel with the first patient sample. The results of both samples allow proper evaluation of titer changes.

Quantitative: The standard curve from which the concentration of antibodies in the patient samples can be taken is obtained by point-to-point plotting of the extinction values measured for the 4 calibrators against the corresponding units (linear/linear). Use “point-to-point” plotting for calculation of the standard curve by computer. The following plot is an example of a typical calibration curve. Please do not use this curve for the determination of antibody concentrations in patient samples.



If the extinction of a serum sample lies above the value of calibrator 1 (5000 IU/l), the result should be given as ">5000 IU/l". It is recommended that the sample be re-tested at a dilution of 1:400. The result in IU/l read from the calibration curve for this sample must then be multiplied by a factor of 4.

The upper limit of the reference range of non-infected persons (**cut-off value**) recommended by EUROIMMUN is **250 International Units (IU/l)**. EUROIMMUN recommends interpreting results as follows:

<200 IU/l:	**negative**
≥200 to <275 IU/l:	**borderline**
≥275 IU/l:	**positive**

Evaluation information: For duplicate determinations the mean of the two values should be taken. If the two values deviate substantially from one another the sample should be retested.

For the interpretation of borderline results an investigation using further tests (e.g. avidity determination of antibody class IgG) can be helpful. Diagnosis can be secured by the determination of the titer change in two serum samples taken at an interval of at least 7 days and analysed in parallel.

For diagnosis, the clinical symptoms of the patient should always be taken into account along with the serological results.

Test characteristics

Calibration: The controls of the Anti-Measles Virus ELISA (IgG) were calibrated using the 3rd international standard serum NIBSC 97/648 (anti-measles and anti-polio virus serum, National Institute for Biological Standards and Control, Hertfordshire, England; approved as international reference preparation by the WHO Expert Committee on Biological Standardization). The NIBSC 97/648 serum contains 3 International Units (IU) per ampoule by definition and was resuspended in a concentration of 3 IU/ml.

For every group of tests performed, the extinction values of the calibrators and the international units determined for the positive and negative controls must lie within the limits stated for the relevant test kit lot. A quality control certificate containing these reference values is included. If the values specified for the controls are not achieved, the test results may be inaccurate and the test should be repeated.

The activity of the enzyme used is temperature-dependent and the extinction values may vary if a thermostat is not used. The higher the room temperature during substrate incubation, the greater will be the extinction values. Corresponding variations apply also to the incubation times. However, the calibrators are subject to the same influences, with the result that such variations will be largely compensated in the calculation of the result.

Antigen: The antigen source is provided by inactivated cell lysates of Vero cells infected with the "Edmonston" strain of measles viruses.

Linearity: The linearity of the anti-measles viruses ELISA (IgG) was determined by assaying 4 serial dilutions of different patient samples. The coefficient of determination R^2 for all sera was > 0.95. The Anti-Measles Virus ELISA (IgG) is linear at least in the tested concentration range (52 IU/l - 4865 IU/l).

Detection limit: The lower detection limit is defined as the mean value of an analyte-free sample plus three times the standard deviation and is the smallest detectable antibody titer. The lower detection limit of the Anti-Measles Virus ELISA (IgG) is 8 IU/l.

Cross reactivity: The quality of the antigen used ensures a high specificity of the ELISA. Sera from patients with infections caused by various agents were investigated with the EUROIMMUN Anti-measles virus ELISA (IgG)

Antibodies against	**n**	**Anti-Measles virus ELISA (IgG)**
Adenovirus	8	0%
CMV	6	0%
EBV-CA	11	0%
HSV-1	3	0%
Influenza virus type A	5	0%
Influenza virus type B	11	0%
Mumps virus	4	0%
Mycoplasma pneumoniae	4	0%
Parainfluenza virus types 1-4	11	0%
RSV	9	0%
Rubella virus	6	0%
Toxoplasma	3	0%
VZV	5	0%

Interference: Haemolytic, lipaemic and icteric samples showed no influence on the result up to a concentration of 10 mg/ml for hemoglobin, 20 mg/ml for triglycerides and 0.4 mg/ml for bilirubin in this ELISA.

Reproducibility: The reproducibility of the test was investigated by determining the intra- and inter-assay coefficients of variation using 3 sera. The intra-assay CVs are based on 20 determinations and the inter-assay CVs on 4 determinations performed in 6 different test runs.

Intra-assay variation, n = 20		
Serum	**Mean value (IU/l)**	**CV (%)**
1	830	8.0
2	3410	6.6
3	3725	5.6

Inter-assay variation, n = 4 x 6		
Serum	**Mean value (IU/l)**	**CV (%)**
1	796	11.6
2	3635	5.0
3	3946	6.8

Specificity and sensitivity: 112 clinically characterized patient samples (interlaboratory test samples from INSTAND, Germany, Labquality, Finland and NEQAS, UK) were examined with the EUROIMMUN Anti-Measles Virus ELISA (IgG). The test showed a specificity and a sensitivity of 100% each.

n = 112		**INSTAND / Labquality / NEQAS (IgG)**		
		positive	borderline	negative
EUROIMMUN Anti-Measles Virus ELISA (IgG)	positive	89	1	0
	borderline	0	0	0
	negative	0	0	22

Reference range: The levels of anti-measles virus antibodies (IgG) were analyzed with this EUROIMMUN ELISA in a panel of 500 healthy blood donors. With a cut-off of 250 IU/l, 94% of the blood donors were anti-measles virus positive (IgG), which reflects the known percentage of infections in adults.

Clinical significance

The measles virus (MV) is the most instantly recognizable member of Morbilliviruses, a group of viruses belonging to the Paramyxoviridae family [1]. No animal reservoir is known. The measles virus causes an acute feverish illness which occurs mainly in childhood and is very infectious [2, 3]. In 1999, measles still caused worldwide 873,000 deaths per year [1, 4, 5]. Today they are less frequent because of vaccination, especially in the western hemisphere [6, 7]. However, measles epidemics are still observed in some countries [2, 3, 4, 5, 6, 8, 9]. Individuals acutely infected with the virus exhibit a wide range of clinical symptoms ranging from a characteristic mild self-limiting infection to death [1, 2, 8, 10].

MV infections are characterised by an incubation period of about 10 days, flue-like symptoms with fever, malaise, catarrh of the upper respiratory tract, cough, congestion and conjunctivitis. Soon afterwards the measles rash, a typical exanthema, appears first near the ears, then on the forehead, in the face and over the rest of the body [1, 5, 8, 11].

Complications arising from MV infections include secondary bacterial pneumonia, otitis media (approx. 1%), encephalitis (approx. 1%), myocarditis, miscarriage and a condition called subacute sclerosing panencephalitis (SSPE) [5, 12, 13]. Persistent MV infection of the otic capsule is an aetiologic factor in otosclerosis [9, 14]. Anti-measles IgG for the serological diagnosis of otoslcerotic hearing loss has a high specificity and sensitivity [15]. SSPE is a progressive, generally fatal brain disorder caused by chronic measles virus infection. It occurs about 7 to 10 years after the infection and generally kills within 3 years from the onset of the symptoms. The patients suffer from behavioural changes, cognitive deterioration, vision problems and eventually advanced neurological symptoms, such as severe spasms, and finally severe physical and mental impairment that leads to death [13]. Males are more commonly affected than females. The risk of SSPE from measles was underestimated according to older data [12]. Actual papers put it at closer to 6.5 to 11 cases of SSPE per 100,000 measles infections; that means 7 to 13 times higher than the earlier estimates [1, 9, 12].

Women with acute measles infection during pregnancy and a negative result for measles-specific antibodies were observed e.g. in Japan, India, Thailand, Kenya and Brazil: 3 of 4 pregnancies ended in preterm delivery, spontaneous abortion or stillbirth; 2 of 4 neonates were found to have congenital measles with a positive result for IgM antibodies [5].

Antibodies against MV can be found in the serum of almost all patients during and after a measles infection. IgM antibodies develop soon after the onset of symptoms and can be measured using ELISA or indirect immunofluorescence tests (IIFT) [16, 20, 21, 22]. 50% of patients have IgM antibodies within three days, more than 90% within 10 days after occurrence of the rash [15, 17]. The Anti-Measles Virus IgM ELISA is more rapid and sensitive for the serological diagnosis of measles infections than other tests [15, 18, 19].

MV infections often cause an increase in heterologic antibodies. The statistically evaluated detection rate for antibodies is significantly higher for ELISA and IIFT in comparison with e.g. neutralisation tests [16, 20]. IgG and IgM antibodies against MV are reliable markers to confirm suspected measles infections.

Measles myelitis or encephalitis can be verified by detecting antibodies against measles in the cerebrospinal fluid (CSF) [23, 24, 25, 26]. These specific antibodies are synthesised in the brain [24]. The CSF-serum quotient (LSQ) allows to differentiate between a blood-derived and a pathological, brain-derived specific antibody fraction in CSF, taking into account individual changes in the blood/CSF barrier function [24, 25, 26, 27]. Therefore it is necessary to confirm the presence of antibodies against MV using ELISA both in CSF and in the serum. During measles myelitis or encephalitis an intrathecal synthesis of antibodies against MV in CFS takes place. Due to the fact that specific antibodies can pass the blood-cerebrospinal fluid barrier by diffusion from serum to CSF it is necessary to determine the relative CSF/serum quotient (CSQrel., synonym: antibody specificity index) [24, 25, 26]. The quotient is calculated from the amount of specific anti-measles virus IgG antibodies in total CSF IgG in proportion to the amount of specific IgG antibodies in total serum IgG. During conversion the CSF/serum quotient of the pathogen-specific IgG-antibody concentrations CSQpath.-spec. (IgG) is put into relation to the CSF/serum quotient of the total IgG concentrations CSQtotal (IgG) [27]. A relative CSQ result above 1.5 indicates the production of specific antibodies in the central nervous system (CNS) and the involvement of the CNS in the disease [25, 26].

With respect to the severe complications known from measles infections, the Robert Koch Institute in Germany recommends vaccinating small children, with a first shot between the age of 11 to 14 months and a second between 15 and 23 months [2, 4, 10, 11]. Neutralisation activity and persistence of antibodies are induced in response to the immunisation [6, 15].

Life-long immunity is generally developed. However, antibody levels are 8 to 10 times lower in post-vaccination sera than in convalescent sera [6, 19, 28]. A passive immunisation with specific immunoglobulin concentrates is usually given to immunosuppressed seronegative individuals, such as tumour patients and recipients of transplants, as well as to seronegative pregnant women after exposure to the virus.

The European Regional Office of the WHO aims at eliminating measles from the region in the following years by area-wide vaccination campaigns [4, 9, 10]. This is expected to limit the number of apparent infections and especially of severe courses of the disease. For the diagnosis of the remaining cases of measles infection and of infections acquired outside Europe as well as for the clarification of atypical courses of the disease in partly immunised patients the antibody determination in serum and CSF will be of growing importance [3, 5, 8, 9].

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Anti-Measles Virus ELISA (IgM)
Test instruction

ORDER NO.	ANTIBODIES AGAINST	IG CLASS	SUBSTRATE	FORMAT
EI 2610-9601 M	Measles virus	IgM	Ag-coated microplate wells	96 x 01 (96)

Principles of the test: The ELISA test kit provides a semiquantitative in vitro assay for human antibodies of the IgM class against measles virus in serum or plasma. The test kit contains microtiter strips each with 8 break-off reagent wells coated with measles virus antigens. In the first reaction step, diluted patient samples are incubated in the wells. In the case of positive samples, specific IgM antibodies (also IgA and IgG) will bind to the antigens. To detect the bound antibodies, a second incubation is carried out using an enzyme-labelled anti-human IgM (enzyme conjugate) catalysing a colour reaction.

Contents of the test kit:

Component	Colour	Format	Symbol
1. Microplate wells coated with antigens: 12 microplate strips each containing 8 individual break-off wells in a frame, ready for use	---	12 x 8	STRIPS
2. Calibrator (IgM, human), ready for use	dark red	1 x 2.0 ml	CAL
3. Positive control (IgM, human), ready for use	blue	1 x 2.0 ml	POS CONTROL
4. Negative control (IgM, human), ready for use	green	1 x 2.0 ml	NEG CONTROL
5. Enzyme conjugate peroxidase-labelled anti-human IgM (goat), ready for use	red	1 x 12 ml	CONJUGATE
6. Sample buffer containing IgG/RF absorbent (anti-human IgG antibody preparation obtained from goat), ready for use	green	1 x 100 ml	SAMPLE BUFFER
7. Wash buffer 10x concentrate	colourless	1 x 100 ml	WASH BUFFER 10x
8. Chromogen/substrate solution TMB/H_2O_2, ready for use	colourless	1 x 12 ml	SUBSTRATE
9. Stop solution 0.5 M sulphuric acid, ready for use	colourless	1 x 12 ml	STOP SOLUTION
10. Test instruction	---	1 booklet	
11. Quality control certificate	---	1 protocol	

LOT Lot
IVD In vitro determination
CE
Storage temperature
Unopened usable until

Storage and stability: The test kit has to be stored at a temperature between +2°C to +8°C. Do not freeze. Unopened, all test kit components are stable until the indicated expiry date.

Waste disposal: Patient samples, calibrators, controls and incubated microplate strips should be handled as infectious waste. All reagents must be disposed of in accordance with local disposal regulations.

Preparation and stability of the reagents

Note: All reagents must be brought to room temperature (+18°C to +25°C) approx. 30 minutes before use. After first use, the reagents are stable until the indicated expiry date if stored at +2°C to +8°C and protected from contamination, unless stated otherwise below.

- **Coated wells:** Ready for use. Tear open the resealable protective wrapping of the microplate at the recesses above the grip seam. Do not open until the microplate has reached room temperature to prevent the individual strips from moistening. Immediately replace the remaining wells of a partly used microplate in the protective wrapping and tightly seal with the integrated grip seam (Do not remove the desiccant bag).
  Once the protective wrapping has been opened for the first time, the wells coated with antigens can be stored in a dry place and at a temperature between +2°C and +8°C for 4 months.

- **Calibrator and controls:** Ready for use. The reagents must be mixed thoroughly before use.

- **Enzyme conjugate:** Ready for use. The enzyme conjugate must be mixed thoroughly before use.

- **Sample buffer:** Ready for use. The green coloured sample buffer contains IgG/RF absorbent. Serum or plasma samples diluted with this sample buffer are only to be used for the determination of IgM antibodies.

- **Wash buffer:** The wash buffer is a 10x concentrate. If crystallization occurs in the concentrated buffer, warm it to 37°C and mix well before diluting. The quantity required should be removed from the bottle using a clean pipette and diluted with deionized or distilled water (1 part reagent plus 9 parts distilled water).
  For example: For 1 microplate strip, 5 ml concentrate plus 45 ml water.
  The working strength wash buffer is stable for 4 weeks when stored at +2°C to +8°C and handled properly.

- **Chromogen/substrate solution:** Ready for use. Close the bottle immediately after use, as the contents are sensitive to light. The Chromogen/substrate solution must be clear on use. Do not use the solution if it is blue coloured.

- **Stop solution:** Ready for use.

Warning: The controls and calibrators used have been tested negative for HBsAg, anti-HCV, anti-HIV-1 and anti-HIV-2 using enzyme immunoassays and indirect immunofluorescence methods. Nonetheless, all materials should be treated as being a potential infection hazard and should be handled with care. Some of the reagents contain the toxic agent sodium azide. Avoid skin contact.

Preparation and stability of the patient samples

Samples: Human serum or EDTA, heparin or citrate plasma.

Stability: Patient samples to be investigated can generally be stored at +2°C to +8°C for up to 14 days. Diluted samples should be incubated within one working day.

Introduction: Before the determination of specific antibodies of class IgM, antibodies of class IgG should be removed from the patient sample. This procedure must be carried out in order to prevent any rheumatoid factors from reacting with specifically bound IgG, which would lead to false positive IgM test results, and to prevent specific IgG displacing IgM from the antigen, which would lead to false IgM negative test results.

Functional principle: The sample buffer (green coloured!) contains an anti-human antibody preparation from goat. IgG from a serum sample is bound with high specificity by these antibodies and precipitated. If the sample also contains rheumatoid factors, these will be absorbed by the IgG/anti-human IgG complex.

Separation properties:
- All IgG subclasses are bound and precipitated by the anti-human IgG antibodies.
- Human serum IgG in concentrations of up to 15 mg per ml are removed (average serum IgG concentration in adults: 12 mg per ml).
- Rheumatoid factors are also removed.
- The recovery rate of the IgM fraction is almost 100%.

Performance: The **patient samples** for analysis are diluted **1:101** with sample buffer. For example, add 10 µl sample to 1.0 ml sample buffer and mix well. Incubate the mixture for at least **10 minutes** at room temperature. Subsequently, it can be pipetted into the microplate wells according to the pipetting protocol.

Notes:
- Antibodies of the class IgG should not be analyzed with this mixture.
- It is possible to check the efficacy of the IgG/RF absorbent for an individual patient sample by performing an IgG test in parallel to the IgM test using the mixture. If the IgG test is negative, the IgM result can be considered as reliable.
- The calibrator and controls containing IgM antibodies are pre-diluted and ready for use, do not dilute them.

Incubation

(Partly) manual test performance

Sample incubation: (1st step)
Transfer 100 µl of the calibrator, positive and negative controls or diluted patient samples into the individual microplate wells according to the pipetting protocol. Incubate for **30 minutes** at room temperature (+18°C to +25°C).

Washing:
Manual: Empty the wells and subsequently wash 3 times using 300 µl of working strength wash buffer for each wash.
Automatic: Wash reagent wells 3 times with 450 µl working strength wash buffer (program setting: e.g. TECAN Columbus Washer "Overflow Modus").

Leave the wash buffer in each well for 30 to 60 seconds per washing cycle, then empty the wells. After washing (manual and automated tests), thoroughly dispose of all liquid from the microplate by tapping it on absorbent paper with the openings facing downwards to remove all residual wash buffer.

Note: Residual liquid (> 10 µl) in the reagent wells after washing can interfere with the substrate and lead to false low extinction values. Insufficient washing (e.g., less than 3 wash cycles, too small wash buffer volumes, or too short reaction times) can lead to false high extinction values.
Free positions on the microplate strip should be filled with blank wells of the same plate format as that of the parameter to be investigated.

Conjugate incubation: (2nd step)
Pipette 100 µl of enzyme conjugate (peroxidase-labelled anti-human IgM) into each of the microplate wells. Incubate for **30 minutes** at room temperature (+18°C to +25°C).

Washing:
Empty the wells. Wash as described above.

Substrate incubation: (3rd step)
Pipette 100 µl of chromogen/substrate solution into each of the microplate wells. Incubate for **15 minutes** at room temperature (+18°C to +25°C) (protect from direct sunlight).

Stopping the reaction:
Pipette 100 µl of stop solution into each of the microplate wells in the same order and at the same speed as the chromogen/substrate solution was introduced.

Measurement:
Photometric measurement of the colour intensity should be made at a wavelength of 450 nm and a reference wavelength between 620 nm and 650 nm **within 30 minutes of adding the stop solution.** Prior to measuring, slightly shake the microplate to ensure a homogeneous distribution of the solution.

Test performance using fully automated analysis devices

Sample dilution and test performance are carried out fully automatically using the analysis device. The incubation conditions programmed in the respective software authorised by EUROIMMUN may deviate slightly from the specifications given in the ELISA test instruction. However, these conditions were validated in respect of the combination of the EUROIMMUN Analyzer I, Analyzer I-2P or the DSX from Dynex and this EUROIMMUN ELISA. Validation documents are available on inquiry.
Automated test performance using other fully automated, open system analysis devices is possible, however, the combination should be validated by the user.

Pipetting protocol

	1	2	3	4	5	6	7	8	9	10	11	12
A	C	P 6	P 14	P 22								
B	pos.	P 7	P 15	P 23								
C	neg.	P 8	P 16	P 24								
D	P 1	P 9	P 17									
E	P 2	P 10	P 18									
F	P 3	P 11	P 19									
G	P 4	P 12	P 20									
H	P 5	P 13	P 21									

The above pipetting protocol is an example of the **semiquantitative analysis** of antibodies in 24 patient samples (P 1 to P 24).

Calibrator (C), positive (pos.) and negative (neg.) control as well as the patient samples have been incubated in one well each. The reliability of the ELISA test can be improved by duplicate determinations of each sample.
The wells can be broken off individually from the strips. This makes it possible to adjust the number of test substrates used to the number of samples to be examined and minimizes reagent wastage.
Both positive and negative controls serve as internal controls for the reliability of the test procedure. They should be assayed with each test run.

Calculation of results

The extinction value of the calibrator defines the upper limit of the reference range of non-infected persons (**cut-off**) recommended by EUROIMMUN. Values above the indicated cut-off are to be considered as positive, those below as negative.

Semiquantitative: Results can be evaluated semiquantitatively by calculating a ratio of the extinction value of the control or patient sample over the extinction value of calibrator. Use the following formula to calculate the ratio:

$$\frac{\text{Extinction of the control or patient sample}}{\text{Extinction of calibrator}} = \text{Ratio}$$

EUROIMMUN recommends interpreting results as follows:

Ratio <0.8:	**negative**
Ratio ≥0.8 to <1.1:	**borderline**
Ratio ≥1.1:	**positive**

Evaluation information: For duplicate determinations the mean of the two values should be taken. If the two values deviate substantially from one another the sample should be retested.

For the interpretation of borderline results an investigation using further tests (e.g. avidity determination of antibody class IgG) can be helpful. Diagnosis can be secured by the determination of the titer change in two serum samples taken at an interval of at least 7 days and analysed in parallel.

For diagnosis, the clinical symptoms of the patient should always be taken into account along with the serological results.

Test characteristics

Calibration: As no international reference serum exists for antibodies of the IgM class against measles virus, results are provided in the form of ratios which are a relative measure for the concentration of antibodies.

For every group of tests performed, the extinction values of the calibrator and the ratios of the positive and negative controls must lie within the limits stated for the relevant test kit lot. A quality control certificate containing these reference values is included. If the values specified for the controls are not achieved, the test results may be inaccurate and the test should be repeated.

The activity of the enzyme used is temperature-dependent and the extinction values may vary if a thermostat is not used. The higher the room temperature during substrate incubation, the greater will be the extinction values. Corresponding variations apply also to the incubation times. However, the calibrators are subject to the same influences, with the result that such variations will be largely compensated in the calculation of the result.

Antigen: The antigen source is provided by inactivated cell lysates of Vero cells infected with the "Edmonston" strain of measles viruses.

Detection limit: The lower detection limit is defined as the mean value of an analyte-free sample plus three times the standard deviation and is the smallest detectable antibody titer. The lower detection limit of the Anti-Measles Virus ELISA (IgM) is ratio 0.02.

Cross reactivity: The quality of the antigen used ensures a high specificity of the ELISA. Sera from patients with infections caused by various agents were investigated with the EUROIMMUN Anti-Measles Virus ELISA (IgM).

Antibodies against	n	Anti-Measles Virus ELISA (IgM)
Borrelia burgdorferi	10	0%
CMV	7	0%
EBV CA	17	0%
Mumps virus	8	0%
Parvovirus B19	9	0%
Rubella virus	10	0%
Toxoplasma gondii	10	0%
VZV	5	0%

Interference: Haemolytic, lipaemic and icteric samples showed no influence on the result up to a concentration of 10 mg/ml for hemoglobin, 20 mg/ml for triglycerides and 0.4 mg/ml for bilirubin in this ELISA.

Reproducibility: The reproducibility of the test was investigated by determining the intra- and inter-assay coefficients of variation using 3 sera. The intra-assay CVs are based on 20 determinations and the inter-assay CVs on 4 determinations performed in 6 different test runs.

Intra-assay variation, n = 20		
Serum	**Mean value (Ratio)**	**CV (%)**
1	2.6	7.9
2	4.6	2.5
3	7.0	2.3

Inter-assay variation, n = 4 x 6		
Serum	**Mean value (Ratio)**	**CV (%)**
1	2.4	8.0
2	4.1	4.4
3	6.6	4.4

Specificity and sensitivity: 72 clinically characterized patient samples (interlaboratory test samples from INSTAND, Germany) were examined with the EUROIMMUN Anti-Measles Virus ELISA (IgM). The test showed a specificity of 98% and a sensitivity of 100%.

n = 72		INSTAND	
		positive	negative
ELISA	positive	26	1
	cut-off	0	1
	negative	0	44

Reference range: The levels of the anti-measles virus antibodies (IgM) were analyzed with this EUROIMMUN ELISA in a panel of 300 healthy blood donors. With a cut-off ratio of 1.0, 0.3% of the blood donors were anti-measles viruses positive (IgM).

Clinical significance

The **measles virus (MV)** is the most instantly recognizable member of Morbilliviruses, a group of viruses belonging to the Paramyxoviridae family [1]. No animal reservoir is known. The measles virus causes an acute feverish illness which occurs mainly in childhood and is very infectious [2, 3]. In 1999, measles still caused worldwide 873,000 deaths per year [1, 4, 5]. Today they are less frequent because of vaccination, especially in the western hemisphere [6, 7]. However, measles epidemics are still observed in some countries [2, 3, 4, 5, 6, 8, 9]. Individuals acutely infected with the virus exhibit a wide range of clinical symptoms ranging from a characteristic mild self-limiting infection to death [1, 2, 8, 10].

MV infections are characterised by an incubation period of about 10 days, flue-like symptoms with fever, malaise, catarrh of the upper respiratory tract, cough, congestion and conjunctivitis. Soon afterwards the measles rash, a typical exanthema, appears first near the ears, then on the forehead, in the face and over the rest of the body [1, 5, 8, 11].

Complications arising from MV infections include secondary bacterial pneumonia, otitis media (approx. 1%), encephalitis (approx. 1%), myocarditis, miscarriage and a condition called subacute sclerosing panencephalitis (SSPE) [5, 12, 13]. Persistent MV infection of the otic capsule is an aetiologic factor in otosclerosis [9, 14]. Anti-measles IgG for the serological diagnosis of otoslcerotic hearing loss has a high specificity and sensitivity [15]. SSPE is a progressive, generally fatal brain disorder caused by chronic measles virus infection. It occurs about 7 to 10 years after the infection and generally kills within 3 years from the onset of the symptoms. The patients suffer from behavioural changes, cognitive deterioration, vision problems and eventually advanced neurological symptoms, such as severe spasms, and finally severe physical and mental impairment that leads to death [13]. Males are more commonly affected than females. The risk of SSPE from measles was underestimated according to older data [12]. Actual papers put it at closer to 6.5 to 11 cases of SSPE per 100,000 measles infections; that means 7 to 13 times higher than the earlier estimates [1, 9, 12].

Women with acute measles infection during pregnancy and a negative result for measles-specific antibodies were observed e.g. in Japan, India, Thailand, Kenya and Brazil: 3 of 4 pregnancies ended in preterm delivery, spontaneous abortion or stillbirth; 2 of 4 neonates were found to have congenital measles with a positive result for IgM antibodies [5].

Antibodies against MV can be found in the serum of almost all patients during and after a measles infection. IgM antibodies develop soon after the onset of symptoms and can be measured using ELISA or indirect immunofluorescence tests (IIFT) [16, 20, 21, 22]. 50% of patients have IgM antibodies within three days, more than 90% within 10 days after occurrence of the rash [15, 17]. The Anti-Measles Virus IgM ELISA is more rapid and sensitive for the serological diagnosis of measles infections than other tests [15, 18, 19]. MV infections often cause an increase in heterologic antibodies. The statistically evaluated detection rate for antibodies is significantly higher for ELISA and IIFT in comparison with e.g. neutralisation tests [16, 20]. IgG and IgM antibodies against MV are reliable markers to confirm suspected measles infections.

Measles myelitis or encephalitis can be verified by detecting antibodies against measles in the cerebrospinal fluid (CSF) [23, 24, 25, 26]. These specific antibodies are synthesised in the brain [24]. The CSF-serum quotient (LSQ) allows to differentiate between a blood-derived and a pathological, brain-derived specific antibody fraction in CSF, taking into account individual changes in the blood/CSF barrier function [24, 25, 26, 27]. Therefore it is necessary to confirm the presence of antibodies against MV using ELISA both in CSF and in the serum. During measles myelitis or encephalitis an intrathecal synthesis of antibodies against MV in CFS takes place. Due to the fact that specific antibodies can pass the blood-cerebrospinal fluid barrier by diffusion from serum to CSF it is necessary to determine the relative CSF/serum quotient (CSQrel., synonym: antibody specificity index) [24, 25, 26]. The quotient is calculated from the amount of specific anti-measles virus IgG antibodies in total CSF IgG in proportion to the amount of specific IgG antibodies in total serum IgG. During conversion the CSF/serum quotient of the pathogen-specific IgG-antibody concentrations CSQpath.-spec. (IgG) is put into relation to the CSF/serum quotient of the total IgG concentrations CSQtotal (IgG) [27]. A relative CSQ result above 1.5 indicates the production of specific antibodies in the central nervous system (CNS) and the involvement of the CNS in the disease [25, 26].

With respect to the severe complications known from measles infections, the Robert Koch Institute in Germany recommends vaccinating small children, with a first shot between the age of 11 to 14 months and a second between 15 and 23 months [2, 4, 10, 11]. Neutralisation activity and persistence of antibodies are induced in response to the immunisation [6, 15].

Life-long immunity is generally developed. However, antibody levels are 8 to 10 times lower in post-vaccination sera than in convalescent sera [6, 19, 28]. A passive immunisation with specific immunoglobulin concentrates is usually given to immunosuppressed seronegative individuals, such as tumour patients and recipients of transplants, as well as to seronegative pregnant women after exposure to the virus.

The European Regional Office of the WHO aims at eliminating measles from the region in the following years by area-wide vaccination campaigns [4, 9, 10]. This is expected to limit the number of apparent infections and especially of severe courses of the disease. For the diagnosis of the remaining cases of measles infection and of infections acquired outside Europe as well as for the clarification of atypical courses of the disease in partly immunised patients the antibody determination in serum and CSF will be of growing importance [3, 5, 8, 9].

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