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Roche

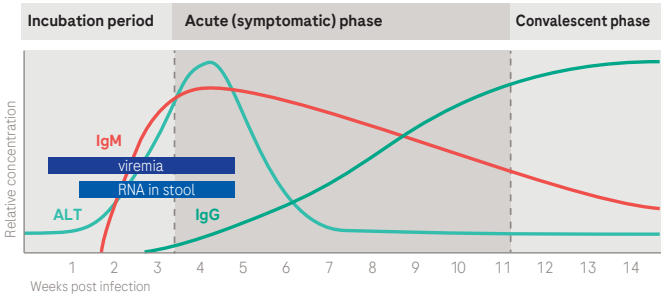
Infectious Diseases Testing

Markers, algorithms & interpretation

Hepatitis A Infection

Course of infection

Serological profile[1-8]



Diagnostic HAV markers and disease stages[1-8]

	Incubation period The average incubation period for HAV is 28 days.	**Acute phase** Fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, abdominal pain, or dark urine, jaundice.	**Convalescent phase** Symptoms can range from asymptomatic or mild to severe. Not everyone who is infected will have all the symptoms. Clinical illness usually does not last longer than 2 months
ALT	(elevated)	elevated	normal
anti-HAV IgM	+	+	(+)*
anti-HAV IgG**	–	(+)	+
anti-HAV total**	+	+	+
HAV RNA	+	(+)	–
Symptoms	–	+	–

*Detection of serum IgM antibodies in the absence of clinical symptoms may reflect prior hepatitis A infection with prolonged persistence of IgM, a false positive result, or asymptomatic infection (which is more common in children <6 years of age than older children or adults). People who test positive for anti-HAV IgM more than 1 year after infection have been reported.

**These markers will also be detected after receiving the HAV vaccine, so they may be used to determine whether a person has developed immunity after vaccination.

(...) = potentially present

Adapted from:

1 Stapleton, J.T. (1995). Host Immune Response to Hepatitis A Virus. ***J Inf Dis 171(suppl 1),*** 89-14.

2 Hollinger, F.B. et al. (2007). Hepatitis A virus. In: ***Fields Virology. Knipe, D.M., Howley, P.M. (eds), 5th ed.,*** Lippincott Williams and Wilkins, Philadelphia, USA. Chapter 27, 911-947.

3 Hadem, J. and Manns, M.P. (2007). Immune Response to Hepatitis A and E Viruses. Role in Disease Pathogenesis and Viral Elimination. In: Gershwin, M.E., Manns, M.P., Vierling, J.M., Springer. Link (Online service), editors. Liver Immunology Principles and Practice. ***Totowa, N.J: Humana Press Inc.,*** 163-77.

4 Roque-Afonso, A.M. et al. (2010). Hepatitis A virus: serology and molecular diagnostics. ***Future Virology 5***(2), 233-242.

5 World Health Organization (2011). The immunological basis for immunization series: module 18: hepatitis A. Available at: https://apps.who.int/iris/bitstream/handle/10665/44570/9789241501422_eng.pdf?sequence=1. Accessed 27Oct2023

6 Salete de Paula, V. (2012). Laboratory diagnosis of hepatitis A. **Future Virol** 7(5), 461-472.

7 U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2020). Hepatitis Serology Training, Hepatitis A. Available at: https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm. Accessed 27Oct2023

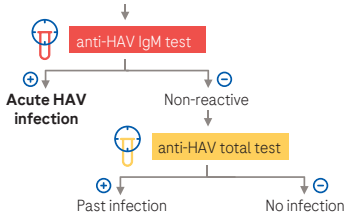
8 Pischke, S. et al. (2018). Hepatitis A. In: Maus, S. et al. ***Hepatology. A Clinical Textbook (9th ed., pp. 31-38).*** Medizin Fokus Verlag. Available at: https://www.hepatologytextbook.com/. Accessed 27Oct2023

Hepatitis A Infection

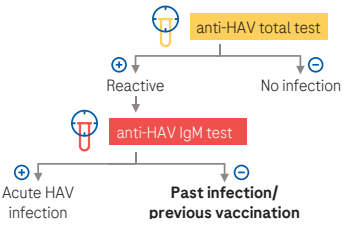
Testing algorithm

Suspected HAV infection[1-4,6]

- symptoms of acute hepatitis
- elevated serum alanine transaminase (ALT) levels
- contact with known HAV cases



Unknown HAV immune status[1-5,7]



Result interpretation

anti-HAV IgM	anti-HAV total	Results indicate
positive	not performed	Acute or recent HAV infection
negative*	positive	No active infection but previous HAV exposure; has developed immunity to HAV or was recently vaccinated for HAV; no further testing required
not performed	positive	Has been exposed to HAV, but does not rule out acute infection
not performed	negative	No current or previous HAV infection; vaccination may be recommended if at risk

*Approximately 3 % of HAV-infected people will be IgM negative if blood is drawn on or before the day of onset of jaundice. Suspicious cases with negative IgM results from such early samples should be retested in 4 – 7 days to rule out the diagnosis.[7]

Adapted from:

1 Hollinger, F.B. et al. (2007). Hepatitis A virus. In: ***Fields Virology. Knipe, D.M., Howley, P.M. (eds), 5th ed.,*** Lippincott Williams and Wilkins, Philadelphia, USA. Chapter 27, 911-947.

2 Roque-Afonso, A.M. et al. (2010). Hepatitis A virus: serology and molecular diagnostics. ***Future Virology 5(2)***, 233-242

3 Salete de Paula V (2012). Laboratory diagnosis of hepatitis A. ***Future Viral*** 7(5), 461-472.

4 Ontario Association of Medical Laboratories (2010). Guidelines for Testing for Viral Hepatitis CLP12 and Interpretation of Viral Hepatitis Laboratory Test Results. Available at: https://oaml.com/guidelines/. Accessed 27Oct2023

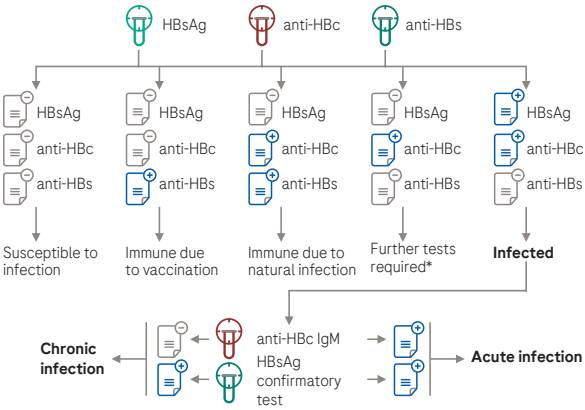
5 U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2015). Epidemiology and Prevention of Vaccine-Preventable Diseases – Hepatitis A. Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/hepa.html. Accessed 27Oct2023

6 Public Health England. UK Standards for Microbiology Investigations: Hepatitis A virus. [illegible] Virology (2019). ***Virology 27***(4). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/[illegible]. Accessed 27Oct2023

7 Oregon Health Authority. Public Health Division. Hepatitis A Investigative Guidelines (2019). Available at: https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/REPORTINGCOMMUNICABLEDISEASE/REPORTINGGUIDELINES/Documents/hepa.pdf. Accessed 27Oct2023

Unknown Hepatitis B status

Testing algorithm[1-3]



*Interpretation unclear, consider testing other markers (anti-HBc IgM, HBeAg, anti-HBe, HBV DNA)

Possible causes:
- Resolved infection (most common)
- False-positive anti-HBc, thus susceptible
- "Low level" chronic infection
- Resolving acute infection

Critical serologic markers in assessment of HBV infection

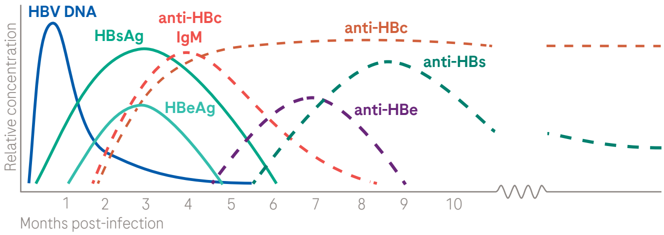
Marker	Definition and diagnostic use
HBsAg	• General marker of active/acute HBV infection • Early viral marker to appear • Persistence for >6 months refers to chronic HBV infection
anti-HBs	• Neutralizing antibody • Develops in response to HBV vaccination and during recovery from acute hepatitis B, indicating past infection and immunity • Only marker detectable after immunity conferred by HBV vaccination
anti-HBc IgM	• Present during acute HBV infection and usually disappears within 6 months • 10 – 20 % of chronically infected with hepatitis flares may also be positive for anti-HBc IgM
anti-HBc	• Indicates a prior exposure to HBV. Infection may be resolved (HBsAg negative) or ongoing (HBsAg positive). • Not a neutralizing antibody • Isolated anti-HBc IgG may indicate occult HBV infection
HBeAg	• Indicator for replication of HBV and high risk of transmission
anti-HBe	• Marker of reduced HBV replication • Indicates decrease of HBV infectivity and remission of disease • Precore/core promoter mutations in HBV genome

Adapted from:
1 Centers for Disease Control and Prevention (CDC). Interpretation of hepatitis serologic [illegible] Available at: https://www.cdc.gov/hepatitis/hbv/pdfs/SerologicChartv8.pdf. Accessed 27Oct2023.
2 Elgouhari, H.M. et al. (2008). Hepatitis B virus infection: understanding its epidemiology, course, and diagnosis. Cleve. *Clin. J. Med. 75*, 881-889.
3 Fourati, S. and Pawlotsky, J.M. (2016). Recent advances in understanding and diagnosing hepatitis B virus infection. *F1000Res 5:F1000 Faculty Rev-2243.*

Acute Hepatitis B Infection

Course of infection

Serological profile of acute and resolved infection[1-5]



The rate of spontaneous recovery from acute HBV infection varies, depending on the patient's age at the time of acquisition and the patient's immune status. Only 5 – 20 % of immunocompetent adults infected with HBV remain chronically infected, whereas up to 90 % of infected infants will remain chronically infected.

Testing algorithm[1-6]

Suspected acute HBV infection
(jaundice, viral illness [low-grade fever, hepatomegaly, and fatigue])

↓

Perform liver function tests (ALT) → Normal: no acute viral hepatitis

↓

Elevated

↓

Perform acute hepatitis test panel
(anti-HAV lgM, anti-HCV, **HBsAg, anti-HBc lgM)**

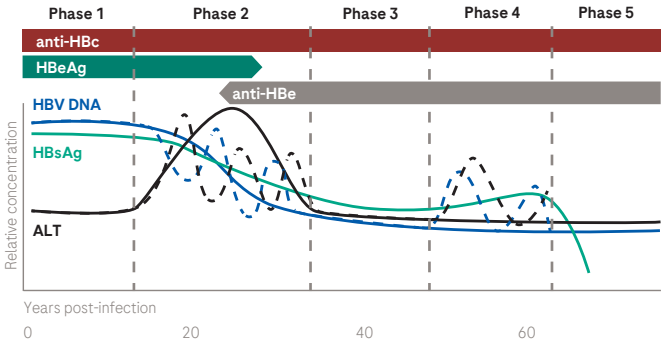
HBsAg	Result	anti-HBc IgM	
⊕	Acute hepatitis B	⊕	→ Repeat test in 4 – 6 weeks, consider testing other HBV markers
⊕	Possibly chronic HBV	⊖	→ Repeat test in 4 – 6 weeks, consider testing other HBV markers
⊖	Infection probably resolving	⊕	
⊖	Consider other etiologies	⊖	

Adapted from:
1 Fourati, S. and Pawlotsky, J.M. (2016). Recent advances in understanding and diagnosing hepatitis B virus infection. F1000Res 5.
2 Petersen, J. (2018). Hepatitis B: diagnostic tests. In: Mauss S, Berg T, Rockstroh J, Sarrazin C, and Wedemeyer H (Eds.), Hepatology – A clinical textbook (9th ed., pp. 151-62). Medizin Fokus Verlag. Available at: https://www.hepatologytextbook.com/. Accessed 27Oct2023
3 Liaw, Y.F., Chu, C.M. (2009). Hepatitis B virus infection. ***Lancet 373,*** 582-592.
4 Davison, S.A. and Strasser, S.I. (2014). Ordering and interpreting hepatitis B serology. ***BMJ 348,*** g2522.
5 Shiffman, M.L. (2010). Management of Acute Hepatitis B. ***Clin Liv Dis 14***(1), 75-91.
6 ARUP Consult (2006). Hepatitis B Virus Testing. Available at: https://arupconsult.com/algorithm/hepatitis-b-virus-testing-algorithm. Accessed 27Oct2023

Chronic Hepatitis B Infection

Course of infection

Serological profile of chronic infection



Diagnostic HBV markers and disease stages

	2017 EASL nomenclature	Previous naming convention	Liver histology
Phase 1	**HBeAg positive chronic HBV infection**	non-inflammatory or **immune-tolerant phase**	Minimal infammation and fibrosis
Phase 2	**HBeAg positive chronic hepatitis B**	inflammatory or **immune-reactive phase**	Moderate-to-severe inflammation or fibrosis
Phase 3	**HBeAg negative chronic HBV infection**	**inactive carrier phase**	Minimal necroinflammation but variable fibrosis
Phase 4	**HBeAg negative chronic hepatitis B**	reactivation or **immune escape phase**	Moderate-to-severe inflammation or fibrosis
Phase 5	**Occult HBV infection (OBI)**		No imflammation, minimal fibrosis

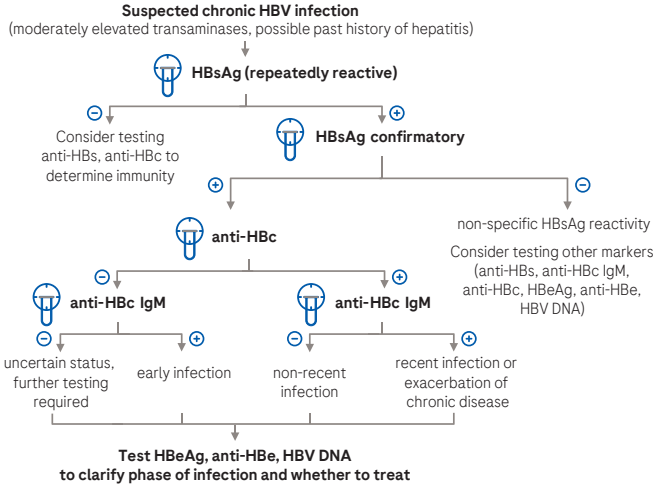
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
ALT	Normal	Elevated	Normal	Fluctuates	Normal
HBsAg	High	High	Low	Low	Un-detectable
HBeAg	Detectable	(Detectable)	Un-detectable	(Detectable)	Un-detectable
anti-HBe	Un-detectable	(Detectable)	Detectable	(Detectable)	(Detectable)
HBV DNA*	High	Fluctuates	Low	Fluctuates	Low

(...) = potentially present / *in serum/plasma

Adapted from:
1 Elgouhari, H.M. et al. (2008). Hepatitis B virus infection: understanding the pathobiology and its consequences. *Cleve Clin J Med 75*, 881-889.
2 Fourati, S. and Pawlotsky, J.M. (2016). Recent advances in understanding and diagnosing chronic HBV infection. *F1000Res 5:F1000 Faculty Rev-2243.*
3 Lok, A.S. et al. (2017). Hepatitis B cure: From discovery to regulatory approval. *J Hepatol 67*, 847-861.
4 European Association for the Study of the Liver (EASL). 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol 67*, 370-398.

Chronic Hepatitis B Infection

Testing algorithm



Result interpretation

	Not infected or vaccinated	Immune: vaccinated	Acute HBV infection: window phase	Acute HBV infection	Immune: resolved infection	Chronic replicative HBV infection	Chronic non-replicative HBV infection	Occult HBV infection (OBI)
HBsAg	–	–	+/–	+	–	+	+	–
anti-HBs	–	+	–	–	+	–	–	+/–
anti-HBc	–	–	+/–	+	+	+	+	+
anti-HBc IgM	–	–	+/–	+	–	–	–	–
HBeAg	–	–	-	+	–	+	–	–
anti-HBe	–	–	–	–	+/–	–	+	+/-
HBV DNA	–	–	+	+	–	+	+	+

Adapted from:

1 Elgouhari, H.M. et al. (2008). Hepatitis B virus infection: understanding the pathobiology and its consequences. *Cleve Clin J Med 75*, 881-889.

2 Fourati, S. and Pawlotsky, J.M. (2016). Recent advances in understanding and diagnosing chronic HBV infection. *F1000Res 5:F1000 Faculty Rev-2243.*

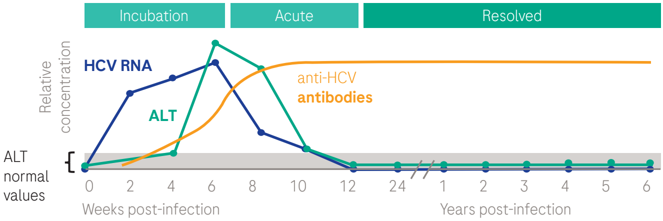
3 Lok, A.S. et al. (2017). Hepatitis B cure: From discovery to regulatory approval. *J Hepatol 67*, 847-861.

4 Davison, S.A. and Strasser, S.I. (2014). Ordering and interpreting hepatitis B serology. *BMJ 348*, g2522.

Hepatitis C Infection

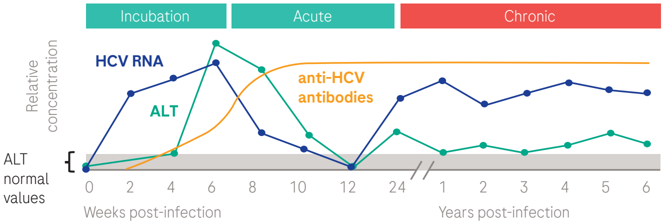
Course of infection[1-6]

Serological profile of acute and resolved infection



~15 – 45 % of infected people spontaneously clear the virus within 6 months of infection without any treatment.

Course of chronic infection



Diagnostic HCV markers and disease stages

	Early stage	Early acute	Acute	Resolved	Chronic	Occult*
ALT	normal	elevated	elevated	normal	elevated	(elevated)
anti-HCV	–	–	(+)	+	+	(+)
HCV RNA	+	+	+	–	+	–
Symptoms	–	(+)	+	–	–	–

* Occult HCV infection is defined as the presence of HCV RNA in liver and in peripheral blood mononuclear cells (PBMCs) in the absence of detectable viral RNA in serum by standard tests[7].

(...) = potentially present

Adapted from:

1 Dufour, D.R. et al. (2001). Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. ***Clin Chem 46***(12), 2027-49.

2 Hoofnagle, J.H. (2002). Course and Outcome of Hepatitis C. ***Hepatology 36,*** S21-S29.

3 U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2015). Viral Hepatitis Serology Training, Hepatitis C. Available at: https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm. Accessed 27Oct2023

4 WHO Guidelines on Hepatitis B and C Testing. Geneva: World Health Organization; 2017 Feb. Fig. 1, Approximate time course for HCV virological and serological markers in chronic HCV infection. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442283/figure/annexe2.fig1/. Accessed 27Oct2023

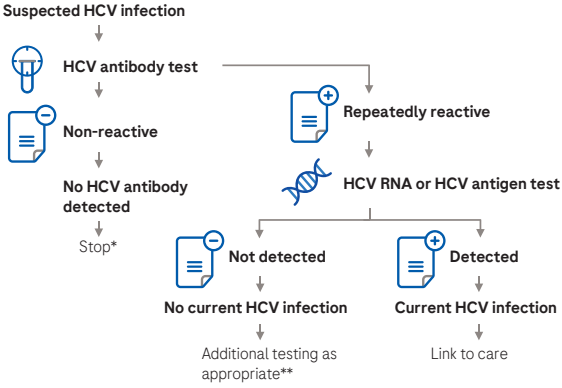
5 Manns, M.P. et al. (2017). Hepatitis C virus infection. ***Nat Rev Dis Prim 3,*** 17006.

6 Ahmad, J. (2017). Hepatitis C. ***BMJ 358,*** j2861.

7 Austria, A. and Wu, G.Y. (2018). Occult Hepatitis C Virus Infection: A Review. ***J Clin Transl Hepatol 6,*** 155-160.

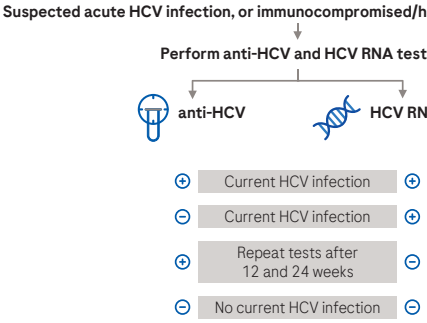
Hepatitis C Infection

Testing algorithm[1-3]



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended.[2]

** Repeat HCV RNA testing 12 and 24 weeks later to confirm definitive clearance and if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test sample.[1,2]



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HBsAg quantitative	
Anti-HBs	🩸
Anti-HBc	🩸
Anti-HBc IgM	
Anti-HBe	
HBeAg quantitative	
HBeAg	
Anti-HCV	🩸
HCV Duo	

cobas® Molecular Assays

Viral Hepatitis	
HBV DNA quantitative	
HCV RNA qualitative	
HCV RNA quantitative	
HCV genotyping	
HEV RNA qualitative	🩸
MPX (HIV/HCV/HBV)	🩸
DPX (B19V/HAV)	🩸

🩸 Bloodscreening solution

MC--03478

Adapted from:

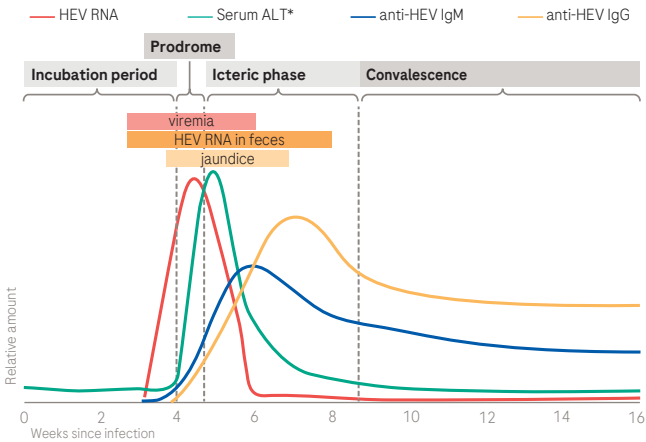
1 EASL Recommendations on Treatment of Hepatitis C (2018). *J Hepatol 69*, 461-511.

2 Centers for Disease Control and Prevention (2013). Testing for HCV Infection: An Update of Guidance for Clinicians and Laboratorians. *MMWR 62*(18), 362-65.

3 AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 27Oct2023

Hepatitis E (HEV)

Course of infection[1-6]



* alanine aminotransferase
(...) = potentially present

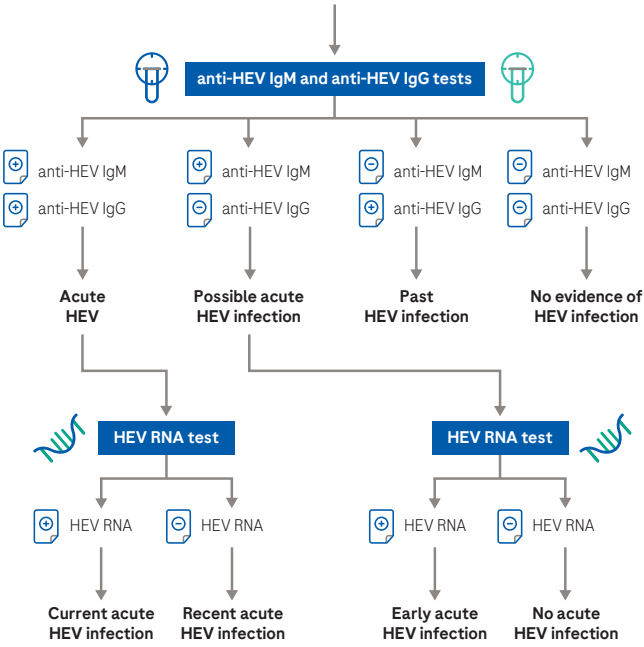
	Incubation period	Prodromic phase	Icteric phase	Convalescent phase
	The incubation period following exposure to HEV ranges from 2 to 10 weeks, with an average of 5 to 6 weeks.	An initial phase of mild fever, reduced appetite (anorexia), nausea and vomiting lasting for a few days; abdominal pain; itching, skin rash, or joint pain; jaundice (yellow colour of the skin), dark urine and pale stools; and a slightly enlarged, tender liver (hepatomegaly).	Jaundice (yellowing of the skin and whites of the eyes) develops Anorexia, nausea and vomiting may worsen Irritated skin lesions may develop Other symptoms may subside	The infection is usually self-limiting and resolves within 2-6 weeks. In rare cases, acute hepatitis E can be severe and result in fulminant hepatitis (acute liver failure).
ALT	normal	(elevated)	elevated	normal
anti-HEV IgM	-	(+)	+	(+)
anti-HEV IgG	-	(+)	+, rising	+
HEV RNA	(+)	+	(+)	-
Symptoms	-	(+)	+	-

References:
1 Aggarwal R, Goel A. Natural History, Clinical Manifestations, and Pathogenesis of Hepatitis E Virus Genotype 1 and 2 Infections. ***Cold Spring Harb Perspect Med.*** 2019;9(7):a032136.
2 Webb GW, Dalton HR. Hepatitis E: an underestimated emerging threat. ***Ther Adv Infect Dis.*** 2019;6:1-18.
3 Lhomme S, et al. Screening, diagnosis and risks associated with Hepatitis E virus infection. ***Expert Rev Anti Infect Ther.*** 2019;17:403-418.
4 Kamar, N., Izopet, J., Pavio, N. et al. Hepatitis E virus infection. ***Nat Rev Dis Primers.*** 2017; 3: 17086.
5 WHO. https://www.who.int/news-room/fact-sheets/detail/hepatitis-e. Accessed 5Feb2024
6 Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/hepatitis/hepatitis-a. Accessed 5Feb2024

Hepatitis E (HEV)

Testing algorithm[1-5]

- symptoms of acute hepatitis
- elevated serum ALT levels
- unexplained flares of chronic liver disease (indicated by e.g. jaundice, fatigue, abdominal pain, loss of appetite, nausea, vomiting, dark urine, pale stools, unexplained weight loss)
- suspected drug-induced liver injury

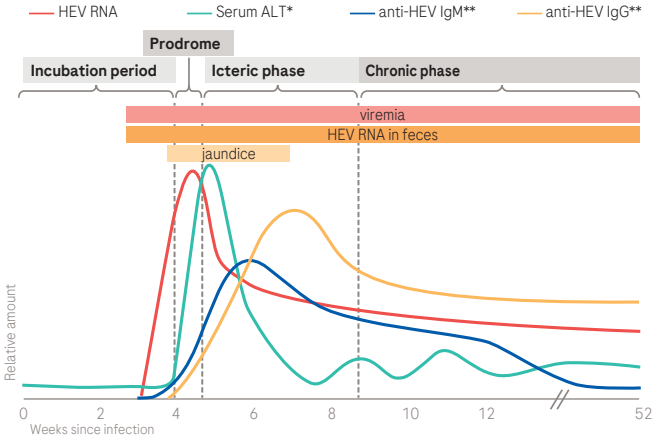


References:
1 Kar, P, Karna R. A Review of the Diagnosis and Management of Hepatitis E. Curr Treat Options ***Infect Dis.*** 2020;12:310–320.
2 Aslan AT, Balaban HY. Hepatitis E virus: Epidemiology, diagnosis, clinical manifestations, and treatment. ***World J Gastroenterol.*** 2020;26:5543-5560.
3 Public Health England. Public health operational guidelines for hepatitis E. Health protection response to reports of hepatitis E infection. 2019 Guidelines. Internet [updated 2019 Sep; cited 2023 May]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/845090/Public_Health_Operational_Guidelines_for_Hepatitis_E-protection_response.pdf.
4 Lhomme S, et al. Screening, diagnosis and risks associated with Hepatitis E virus infection. ***Exp Rev Anti-inf Ther.*** 2019;17:403-418.
5 European Association for the Study of the Liver (EASL). Clinical Practice Guidelines on hepatitis E virus infection. ***J Hepatol*** 2018;68:1256-1271.

Hepatitis E (HEV)

Testing for HEV infection in immunocompromised patients

Course of infection[1-7]



* alanine aminotransferase

** in immunosuppressed patients with chronic hepatitis E, anti-HEV antibodies are often undetectable

(...) = potentially present

	Incubation period	Prodromic phase	Icteric phase	Chronic phase
	The incubation period following exposure to HEV ranges from 2 to 10 weeks, with an average of 5 to 6 weeks.	an initial phase of mild fever, reduced appetite (anorexia), nausea and vomiting lasting for a few days; abdominal pain, itching, skin rash, or joint pain; jaundice (yellow colour of the skin), dark urine and pale stools; and a slightly enlarged, tender liver (hepatomegaly).	Jaundice (yellowing of the skin and whites of the eyes) develops Anorexia, nausea and vomiting may worsen Irritated skin lesions may develop Other symptoms may subside	In rare cases, acute hepatitis E can be severe and result in fulminant hepatitis (acute liver failure).
ALT	normal	(elevated)	elevated	(elevated)
anti-HEV IgM	-	(+)	(+)	-
anti-HEV IgG	-	(+)	(+, rising)	(+)
HEV RNA	(+)	+	+	+
Symptoms	-	(+)	+	(+)

Adapted from:

1 Aggarwal R, Goel A. Natural History, Clinical Manifestations, and Pathogenesis of Hepatitis E Virus Genotype 1 and 2 Infections. *Cold Spring Harb Perspect Med.* 2019;9(7):a032136.

2 Webb GW, Dalton HR. Hepatitis E: an underestimated emerging threat. *Ther Adv Infect Dis.* 2019;6:2049936119844165.

3 Lhomme S, et al. Screening, diagnosis and risks associated with Hepatitis E virus infection. *Exp Rev Anti-inf Ther.* 2019;17:403-418.

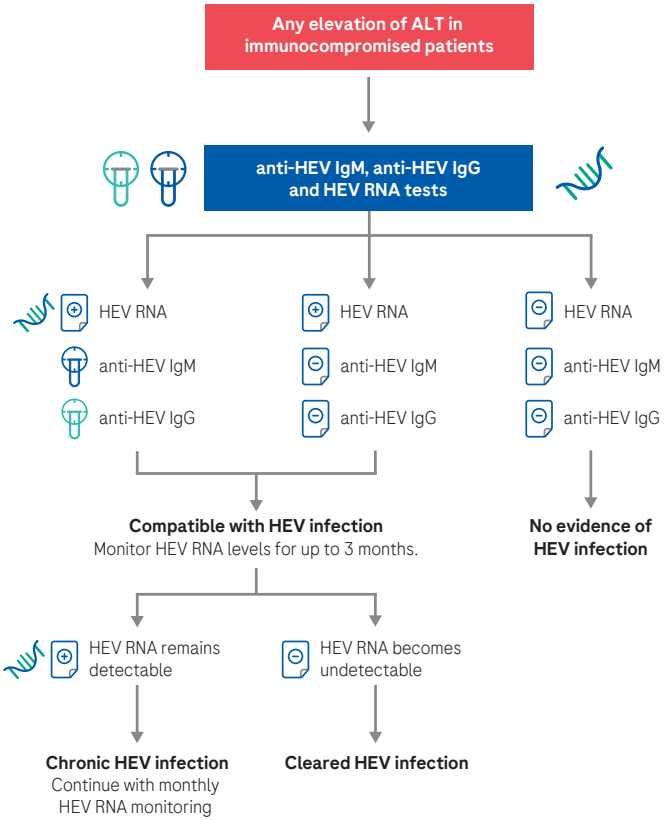
4 Kamar, N., Izopet, J., Pavio, N. et al. Hepatitis E virus infection. *Nat Rev Dis Primers.* 2017;3, 17086 (2017).

5 WHO. https://www.who.int/news-room/fact-sheets/detail/hepatitis-e. Accessed 5Feb2024

6 Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/hepatitis/hepatitis-a. Accessed 5Feb2024

Hepatitis E (HEV)

Testing algorithm for immunocompromised[1-5]



Adapted from:

1 Abravanel F, et al. Diagnostic and management strategies for chronic hepatitis E infection, ***Exp Rev Anti-inf Ther.*** 2023;21:143-148.

2 Kar, P, Karna R. A Review of the Diagnosis and Management of Hepatitis E. ***Curr Treat Options Infect Dis.*** 2020;12:310–320.

3 Aslan AT, Balaban HY. Hepatitis E virus: Epidemiology, diagnosis, clinical manifestations, and treatment. ***World J Gastroenterol.*** 2020;26:5543-5560.

4 Public Health England. Public health operational guidelines for hepatitis E. Health protection response to reports of hepatitis E infection. 2019 Guidelines. Internet [updated 2019 Sep; cited 2023 May]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/845090/Public_Health_Operational_Guidelines_for_Hepatitis_E-protection_response.pdf.

5 Lhomme S, et al. Screening, diagnosis and risks associated with Hepatitis E virus infection. ***Exp Rev Anti-inf Ther.*** 2019;17:403-418.

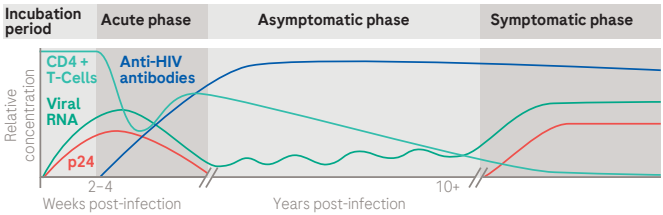
6 European Association for the Study of the Liver (EASL). Clinical Practice Guidelines on hepatitis E virus infection. ***J Hepatol*** 2018;68:1256-1271.

7 Murali AR, et al. Chronic hepatitis E: A brief review. World ***J Hepatol.*** 2015;7:2194-201.

HIV Infection

Course of infection[1-3]

Serological profile



Diagnostic HIV markers and disease stages

	Incubation Period	Acute Phase	Asymptomatic Phase	Symptomatic Phase
Description	2 – 4 weeks	"flu-like" symptoms	• progressive depletion of $CD4^+$ T-cells • can last >10 years	• AIDS develops • Common symptoms: chills, fever, sweats, swollen lymph glands, weakness, and weight loss
$CD4^+$ T-cells	normal	low	declining	low to depleted
p24 antigen	rising	high	–	high
anti-HIV	–	rising	high	high
HIV RNA	rising	high	fluctuating	high
Contagious	–	highly	moderately	highly

Adapted from:

1 Fiebig, E.W. et al. (2003). Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. ***AIDS 17,*** 1871-1879.

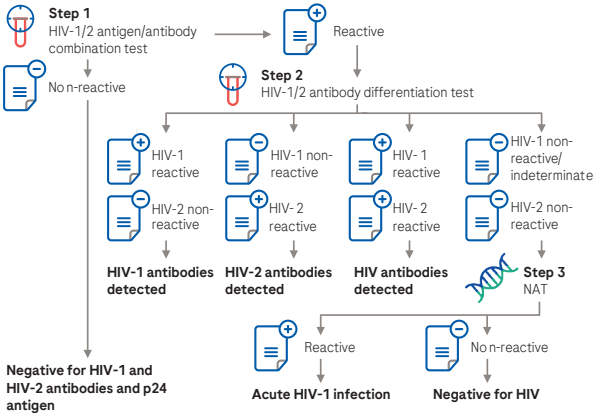
2 Cohen, M.S. et al. (2011). Acute HIV-1 Infection. ***N Engl J Med 364***(20), 1943-1954.

3 De Jong, M.D. et al. (1991). Clinical, virological and immunological features of primary HIV-1 infection. ***Genitourin Med 67***(5), 367-73.

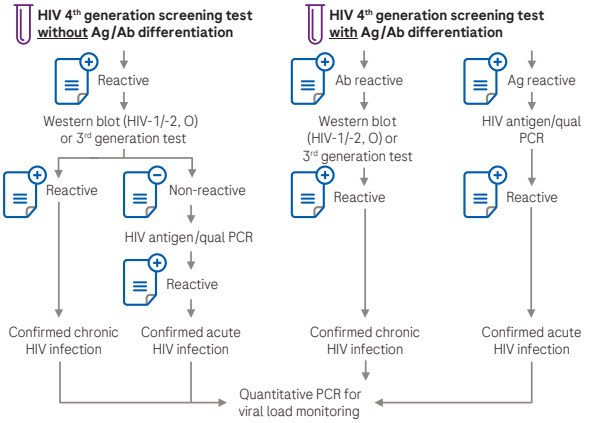
HIV Infection

Testing algorithm[1,2]

Algorithm for HIV diagnosis



4th generation screening test with differentiation between HIV p24 antigen and anti-HIV antibodies



Adapted from:

1 Centers for Disease Control and Prevention (CDC) (2014). New CDC Recommendations for HIV Testing in Laboratories. A step-by-step account of the approach. Available at: https://www.cdc.gov/nchhstp/newsroom/docs/2014/HIV-testing-Labs-Flowchart.pdf. Accessed 27Oct2023

2 Alexander, T.S. (2016). Human Immunodeficiency Virus Diagnostic Testing: 30 Years of Evolution. *Clin Vaccine Immunol 23*, 249-253.

3 European Centre for Disease Prevention and Control (ECDC) (2016). Technical Report HIV testing in Europe. Evaluation of the impact of the ECDC guidance on HIV testing: increasing uptake and effectiveness in the European Union. Available at: https://www.ecdc.europa.eu/en/publications-data/hiv-testing-europe. Accessed 27Oct2023

4 Rijksinstituut voor Volksgezondheid and Milieu (RIVM) (2018). Draaiboek Consult seksuele gezondheid. Available at: https://lci.rivm.nl/draaiboeken/consult-seksuele-gezondheid. Accessed 27Oct2023

5 Haute Autorité de Santé (HAS) (2009). Dépistage de l'infection par le VIH en France. Stratégies et dispositif de dépistage. Available at: https://www.has-sante.fr/jcms/c_866949/fr/depistage-de-l-infection-par-le-vih-en-france-strategies-et-dispositif-de-depistage. Accessed 27Oct2023

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HIV Antigen confirmatory

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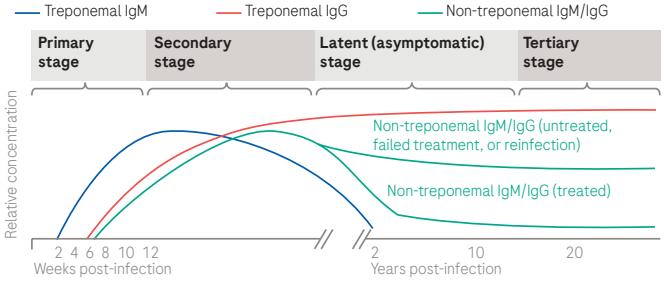
HIV-1 / HIV-2 RNA qualitative

Syphilis Infection

Course of infection[1,2]

Serological profile



Diagnostic Syphilis markers and disease stages

	Primary stage	Secondary stage	Latent stage	Tertiary stage
Symptoms	painless genital ulcers (chancre)	• Skin rash covering the whole body (25 % of infected) • Fever, generalized lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis, and glomerulonephritis are possible	asymptomatic	10 % of untreated patients: • Gummatous syphilis[a] • Late neurosyphilis[b] • Cardiovascular syphilis[c]
Treponemal IgM	rising	high	declining	negative
Treponemal IgG	rising	high	high	high
Non-treponemal IgM/IgG*	rising	high	high (untreated) declining (treated)	high (untreated) low (treated)

*antibodies against cellular lipids (mostly cardiolipin)

a Nodules/plaques or ulcers.

b Meningitis, cranial nerve dysfunction, meningovascular syphilis (stroke, myelitis), and parenchymatous neurosyphilis (general paresis, tabes dorsalis).

c Aortic regurgitation, stenosis of coronary ostia, and aortic aneurysm.

Adapted from:

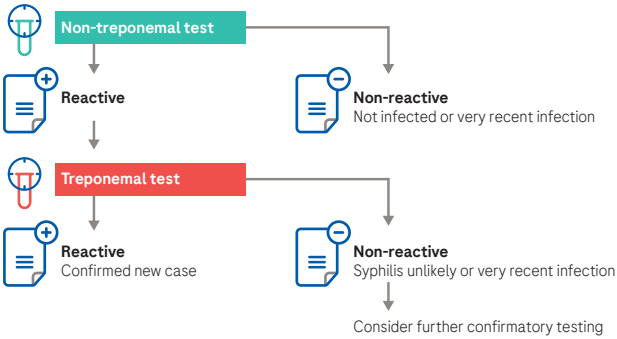
1 Centers for Disease Control and Prevention (CDC) (2017). Syphilis-CDC Fact Sheet. Available from: https://www.cdc.gov/std/syphilis/stdfact-syphilis-detailed.htm. Accessed 27Oct2023

2 Peeling, R.W. and Ye, H. (2004). Tools to prevent and manage maternal and congenital syphilis. Bulletin of World Health Organization. 82:439-446. Available from: http://www.who.int/bulletin/volumes/82/6/439.pdf?ua=1. Accessed 27Oct2023

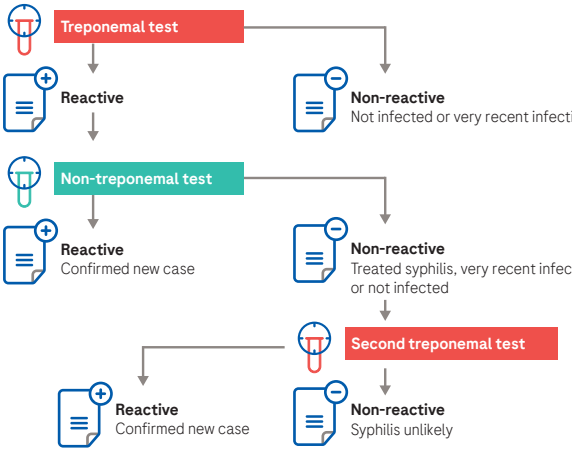
Syphilis Infection

Testing algorithm[1,2]

Traditional algorithm



Reverse algorithm



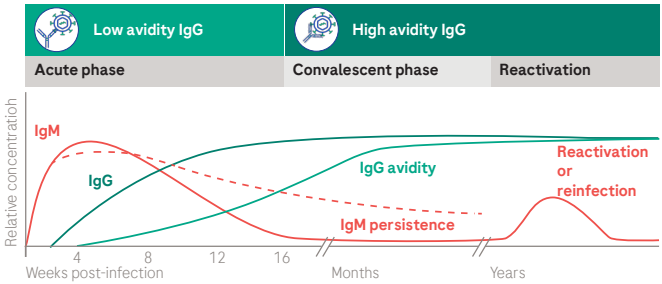
MC--03478

Adapted from:
1 Peeling, R.W. (2017). Syphilis. ***Nat Rev Dis Primers 3,*** 17073.
2 Janier, M. et al. (2014). European Guideline on the Management of Syphilis. ***J Eur Acad Dermatol Venereol 28,*** 1581-93.

Cytomegalovirus (CMV) Infection

Course of infection

Serological profile[1-5]



Result interpretation*[1-5]

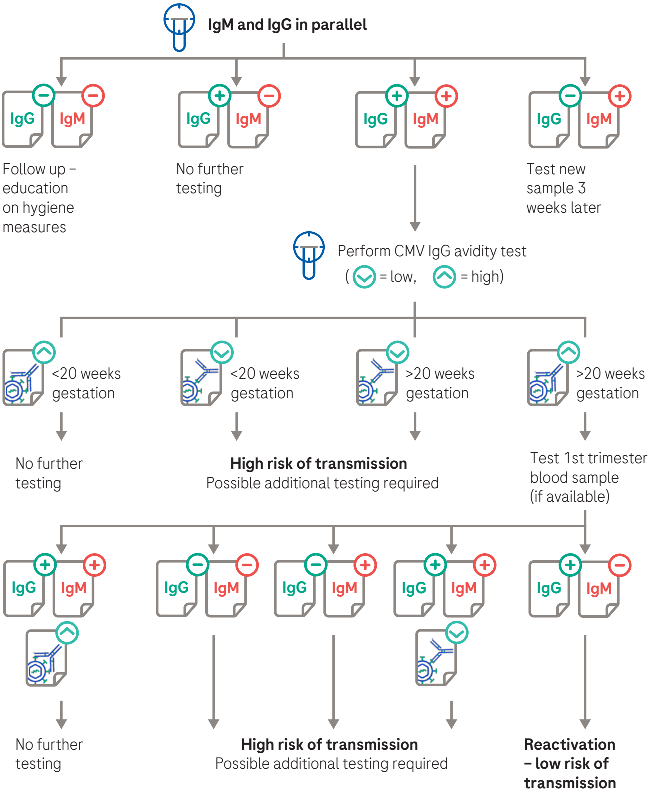
CMV IgM	CMV IgG	CMV IgG Avidity	CMV DNA	Interpretation
1st sample				
–	–	N/A	N/A	Patient is not immune and susceptible to infection. Pregnant women should take preventive measures and be closely monitored during pregnancy.
–	+	N/A	N/A	Infection at least one year previously, and immunity to CMV infection.
+	–	N/A	N/A	Very early stage of infection or false positive (unspecific IgM). Perform follow-up test incl. IgG Avidity (when IgG is reactive) after 2 – 3 weeks to confirm either result.
+	+	N/A	N/A	
2nd sample				
+	+	low	+	Acute infection confirmed
+	+	low	N/A	Acute infection highly suspected – follow-up sample and DNA testing is recommended
+	+	high	N/A or –	Acute infection not confirmed

*for pregnancy/ except infants
N/A: not available or not tested

Adapted from:
1 Prince, H.E. and Lapé-Nixon, M. (2014). Role of Cytomegalovirus (CMV) IgG Avidity Testing in Diagnosing Primary CMV Infection during Pregnancy. *Clin Vaccine Immunol 21(10), 1377-1384.*
2 Revello, M.G. and Gerna, G. (2002). Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. Clin *Microbiol Rev 15*, 680-715.
3 Duff, P. (2010). Diagnosis and management of CMV Infection in Pregnancy. *Fetal Maternal Medicine Review 21(3), 194-210.*
4 Centers for Disease Control (CDC) (2008). Knowledge and Practices among Physicians and Other Providers Regarding Cytomegalovirus Infection During Pregnancy. *MMWR 57(03), 65-68.* Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5703a2.htm Accessed 27Oct2023
5 Davis, N.L. et al. (2017). Cytomegalovirus infection in pregnancy. *Birth Defects Research 109*, 336-346.

CMV Infection

Testing algorithm[1-4]



Adapted from:

1 Munro, S.C. et al. (2005). Diagnosis of and screening for cytomegalovirus infection in pregnant women. *J Clin Microbiol 43,* 4713-4718.

2 Duff, P. (2007). A thoughtful algorithm for the accurate diagnosis of primary CMV infection in pregnancy. *Am J Obstet Gynecol 196,* 196-197.

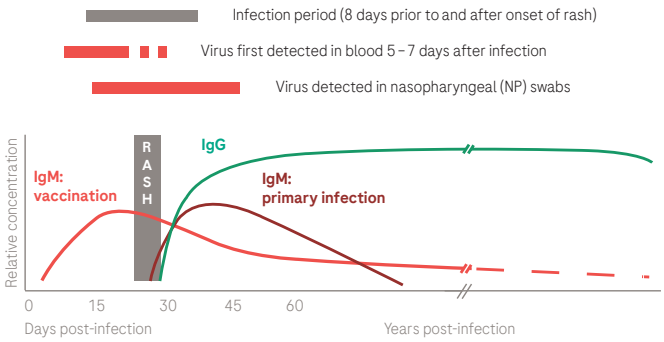
3 Guerra, B. et al. (2007). Impact of diagnostic and confirmatory tests and prenatal counseling on the rate of pregnancy termination among women with positive cytomegalovirus immunoglobulin M antibody titers. *Am J Obstet Gynecol 196,* 221 e221-226.

4 Lazzarotto, T. et al. (2004). Congenital cytomegalovirus infection: recent advances in the diagnosis of maternal infection. *Hum Immunol 65,* 410-415.

Rubella Infection

Course of infection

Serological profile[1-4]



Result interpretation*[5]

Rubella IgM	Rubella IgG	Results indicate
–	–	Susceptible / No current or previous rubella infection; repeat IgM and IgG testing 2 – 3 weeks later; before pregnancy or post-partum vaccination is recommended.
–	+	Immune; no further testing required. The presence of antibodies at any level is sufficient to confirm immunity[6].
+	–	Acute or recent rubella infection or false positive/ unspecific IgM. Best period for testing is in a serum collected within the first few days after rash onset. Test for other causes, e.g. rheumatoid factor, EBV, CMV, Parvovirus B19. Test a second sample 5 – 10 days later, if available, and perform IgG avidity. A significant rise of the rubella IgG titer from a first to a second sample supports the diagnosis of acute rubella infection.
+	+	

*for pregnancy/ except infants

Adapted from:

1 Banatvala, J.E. and Brown, D.W.G. (2004). Rubella. ***Lancet 363***, 1127-1137.

2 Lambert, N. et al. (2015). Rubella. ***Lancet 385***, 2297-2307.

3 Vauloup-Fellous, C. and Grangeot-Keros, L. (2007). Humoral immune response after primary rubella virus infection and after vaccination. ***Clin Vaccine Immunol 14***, 644-647.

4 Abernathy, E. et al. (2009). Confirmation of rubella within 4 days of rash onset: comparison of rubella virus RNA detection in oral fluid with immunoglobulin M detection in serum or oral fluid. ***J Clin Microbiol 47***, 182-188.

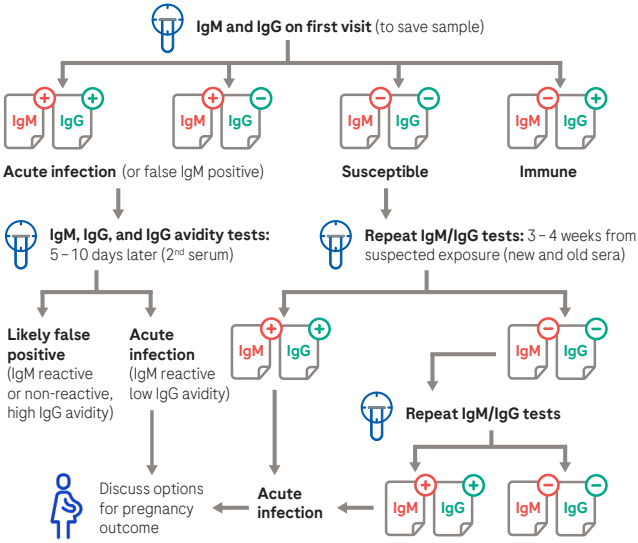
5 Centers for Disease Control and Prevention. (2014). Manual for the Surveillance of Vaccine-Preventable Diseases. Chapter 14: Rubella. Surveillance Manual. Available at: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt14-rubella.html. Accessed: 27Oct2023

6 Iyanger, N. et al. (2019) Guidance on the investigation, diagnosis and management of viral rash illness, or exposure to viral rash illness, in pregnancy. Public Health England publications gateway number GW-231. Available at: https://www.gov.uk/government/publications/viral-rash-in-pregnancy. Accessed 27Oct2023

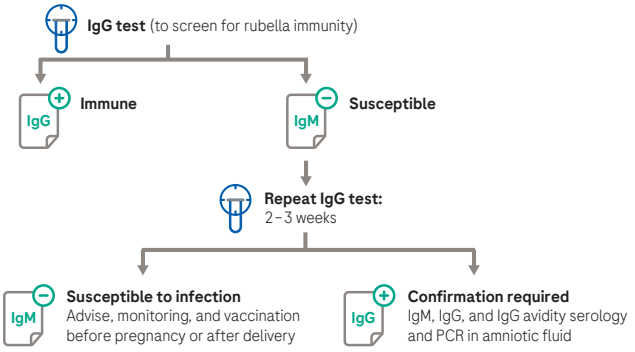
Rubella Infection

Testing algorithm

Serological evaluation of pregnant women exposed to rubella[1,2]



Serological evaluation of pregnant women for rubella immunity[2]



Adapted from:

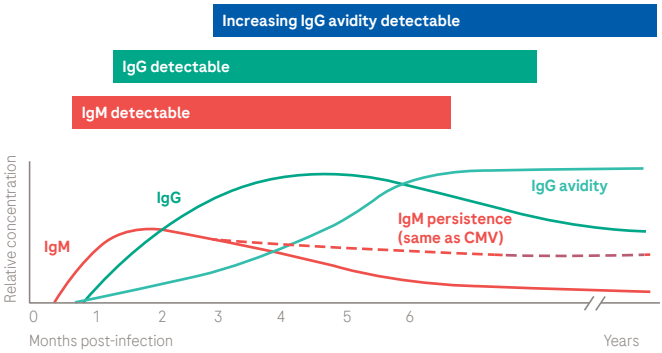
1 Centers for Disease Control and Prevention. (2014). Manual for the Surveillance of Vaccine-Preventable Diseases. Chapter 14: Rubella. Surveillance Manual. Available at: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt14-rubella.html. Accessed 27Oct2023

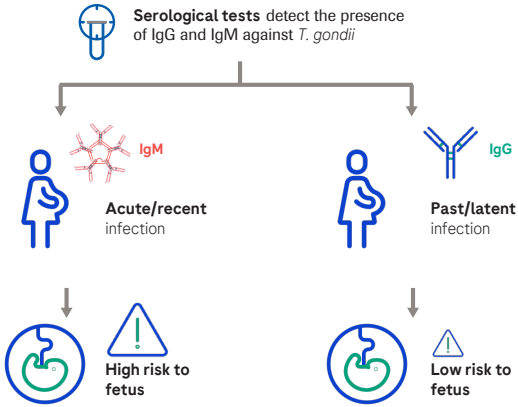
2 Picone, O. and Grangeot-Keros, L. (2005). Rubéole et grossesse. ***EMC-Gynécologie-Obstétrique 2***, 343-353.

Toxoplasma Infection

Course of infection

Serological profile[1-4]



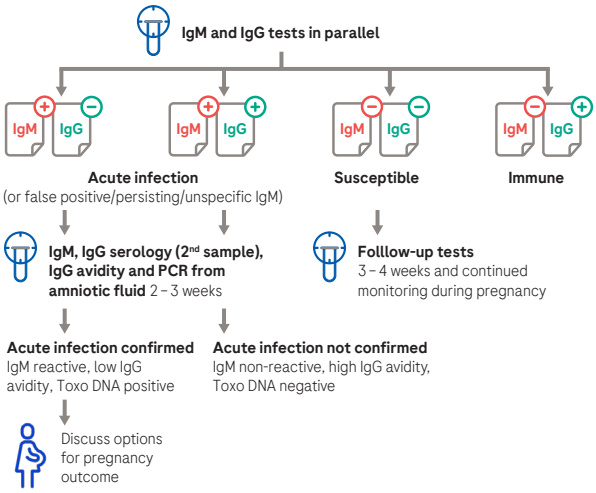


Note: The detection of Toxo IgM antibodies in a single sample is not sufficient to prove an acute toxoplasma infection since elevated IgM antibody levels may persist even for years after initial infection. Further tests or a combination of test methods should be done for clarification (e.g. refer to the following testing algorithm)[5,6].

Adapted from:
1 Robert-Gangneux, F. and Darde, M.L. (2012). Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin Microbiol Rev 25*, 264-296.
2 Montoya, J.G. and Liesenfeld, O. (2004). Toxoplasmosis. *Lancet 363*, 1965-1976.
3 Tekkesin, N. (2012). Diagnosis of toxoplasmosis in pregnancy: a review. *Mikrobiyoloji Bulteni*
4 Lappalainen, M. and Hedman, K. (2004). Serodiagnosis of toxoplasmosis: the impact of measurement of IgG avidity. *Ann Ist Super Sanita 40*, 81-88.
5 Elecsys Toxo IgM Method sheet, 2019-09, V 11.0.
6 Dhakal, R. et al. (2015) Significance of a positive Toxoplasma immunoglobulin M test result in the United States. *J Clin Microbiol 53*, 3601-3605.

Toxoplasma Infection

Testing algorithm[1-4]



Result interpretation*

Toxo IgM	Toxo IgG	Toxo IgG Avidity	Toxo DNA	Interpretation
1st sample				
–	–	N/A	N/A	Patient is not immune and susceptible to infection. Pregnant women should take preventive measures and be closely monitored during pregnancy.
–	+	N/A	N/A	Immunity to toxoplasmosis.
+	–	N/A	N/A	Very early stage of infection or false positive IgM (unspecific IgM). Perform follow-up test incl. IgG Avidity (when IgG is reactive) after 2 – 3 weeks to confirm either result.
+	+	N/A	N/A	
2nd sample				
+	+	low	+	Acute infection confirmed.
+	+	low	N/A	Recently acquired infection not excluded. Test follow-up sample after 3 weeks. PCR on amniotic fluid is recommended.
+	+	high	N/A or –	Acute infection excluded.

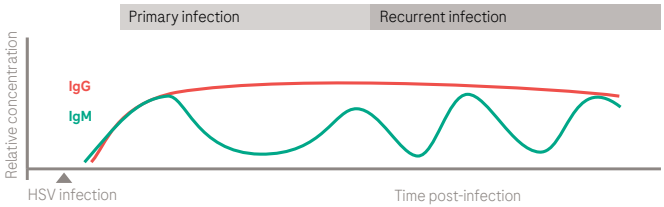
*for pregnancy/ except infants
N/A: not available or not tested

Adapted from:
1 Robert-Gangneux, F. and Darde, M.L. (2012). Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin Microbiol Rev 25*, 264-296.
2 Montoya, J.G. and Liesenfeld, O. (2004). Toxoplasmosis. *Lancet 363*, 1965-1976.
3 Remington, J.S. et al. (2011). Chapter 31: Toxoplasmosis. In (Ed.) Infectious Diseases of the Fetus and Newborn Infant (7th Edition) (ed., pp. 918-1041). Philadelphia: W.B. Saunders.
4 Villard, O. et al. (2016). Serological diagnosis of Toxoplasma gondii infection. Recommendations from the French National Reference Center for Toxoplasmosis. *Diagn Microbiol Inf Dis 84*, 22-33.

Herpes simplex virus (HSV) Infection

Course of infection

Serological profile[1-9]



Antibodies to HSV are detected 2 weeks to 6 months after primary exposure[1,2]. A substantial proportion of newly-infected patients are positive for IgG and IgM, or IgG alone[1,3,4]. Despite the theory that IgM production ceases over time, levels of anti-HSV IgM can vary considerably after the primary infection and can be detected also due to recurrent episodes[3,5]. Approximately one-third of people infected with HSV-2 have detectable IgM with a recurrent infection. In addition, IgM tests cannot accurately distinguish between HSV-1 and HSV-2 antibodies and sometimes cross-react with other viruses in the same family[6]. For these reasons IgM testing is not recommended in routine clinical practice[6,7,8,9].

Result interpretation[1-10]

HSV-1 IgG	HSV-2 IgG	HSV 1/2 DNA	Results indicate
–	–	–	Susceptible; consider at risk of infection to both types.
–	–	+	Profile suggestive of an initial primary first episode of genital herpes.
+	+	Type 1 or 2 +	Profile suggestive of recurrence.
+	–	Type 1 +	
–	+	Type 2 +	
-	+	Type 1 +	Profile suggestive of a non-primary first episode of genital herpes.
+	–	Type 2 +	

Adapted from:

1 Riedel, A. et al. (2013). P5.071 Evaluation of Elecsys Immunoassay System for Determination of Type-Specific IgG Antibodies to HSV-1 and HSV-2. ***Sex Transm Infect 89*** (Suppl 1), A1-A428.

2 Patel, R. et al. (2001). European guideline for the management of genital herpes. ***Int J STD AIDS 12***(Suppl 3), 34-39.

3 Morrow, R. and Friedrich, D. (2006). Performance of a novel test for IgM and IgG antibodies in subjects with culture-documented genital herpes simplex virus-1 or -2 infection. ***Clin Microbiol Infect 12***, 463-469.

4 Whitley, R.J. and Miller, R.L. (2001). Immunologic approach to herpes simplex virus. ***Viral Immunol 14***, 111-118.

5 Gardella, C. and Brown, Z.A. (2007). Managing genital herpes infections in pregnancy. ***Cleve Clin J Med 74***, 217-224.

6 American Sexual Health Association. Herpes resource center: testing. Available at: http://www.ashasexualhealth.org/stdsstis/herpes/herpes-testing. Accessed 27Oct2023

7 Sénat, M.V. et al. (2018). Prevention and management of genital herpes simplex infection during pregnancy and delivery: Guidelines from the French College of Gynaecologists and Obstetricians (CNGOF). ***Eur J Obstet Gynecol Repr Biol 224***, 93-103.

8 Workowski, K.A. et al. (2015). Sexually Transmitted Diseases Treatment Guidelines. ***MMWR Recomm Rep 64***(3), 1-140.

9 Patel, R. et al. (2017). European guideline for the management of genital herpes. ***Int J STD AIDS 28***(14), 1-14.

10 Groves, M.J. (2016). Genital Herpes: A Review. ***Am Fam Physician 93***, 928-934.

HSV Infection

Testing algorithm[1–4]

Perform HSV-1 and HSV-2 IgG tests (type-specific)

HSV-1 and HSV-2 IgG non-reactive

Check the immune status of the partner

Partner is HSV-1 and HSV-2 non-reactive

Counseling

If seronegative woman and her partner are in high risk group, educate them about the potential risks of HSV-2 infections and protection.

Pregnant woman is HSV-1 IgG reactive

Partner is HSV-2 IgG reactive

Proposed management strategy

- Perform PCR from the genital swab sample of the woman
- Educate the woman and her partner:
  - Avoid genital contact
  - Use condoms
  - Antiviral treatment (suppression of the virus)

HSV-2 IgG reactive

Proposed management strategy

- Educate
- Antiviral treatment (suppression of the virus)
- Perform PCR from genital swab samples
- Avoid vaginal delivery

Adapted from:

1 Sénat, M.V. et al. (2018). Prevention and management of genital herpes simplex infection during pregnancy and delivery: Guidelines from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Repr Biol 224*, 93-101.

2 Workowski, K.A. et al. (2015) Sexually Transmitted Diseases Treatment Guidelines, 2015. ***MMWR Recomm Rep 64***(3), 1-140.

3 Brown, Z.A. (2004). Use of Herpes Type-specific Serology to Prevent Neonatal Herpes Simplex Virus Infection. ***NeoReviews 5***(1), e16-e21.

4 Brown, Z.A. et al. (2005). Genital herpes complicating pregnancy. ***Obstet Gynecol 106***, 845-856.

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HIV combi PT	🩸
HIV Antigen	
HIV Antigen confirmatory	
Syphilis	🩸
HSV-1 IgG	
HSV-2 IgG	
HTLV-I/II	🩸

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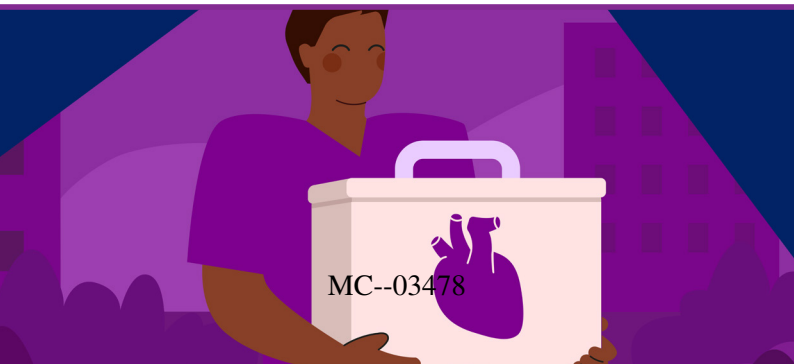
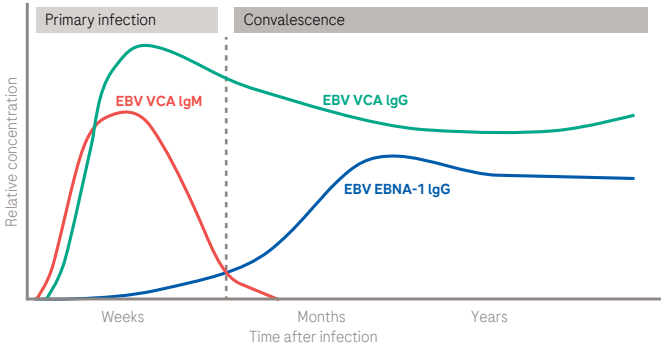
CT/NG DNA	
HSV-1/HSV-2 DNA	
HIV RNA quantitative	
HIV-1/HIV-2 RNA qualitative	
HPV DNA	
HPV genotyping	
MPX (HIV/HCV/HBV)	🩸



Epstein-Barr virus (EBV) Infection

Course of infection

Serological profile[1,2]



Result interpretation*[3,4]

VCA IgM	VCA IgG	EBNA-1 IgG	Interpretation
–	–	–	Seronegative, no immunity
+	–	–	Presumed early phase of infection#
+	+	–	Acute infection
+	+	+	Transient phase of primary infection, or reactivation#
-	+	+	Past infection
-	+	–	Isolated VCA IgG#
–	–	+	Isolated EBNA-1 IgG#

*In immunocompetent patients #Indeterminate EBV serology. Additional testing required.

Adapted from:

1 Hess, R. (2004). Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. ***J Clin Microbiol 42***(8), 3381-7.

2 Middeldrop, J.A. (2015). Epstein-Barr virus-specific humoral immune responses in health and disease. ***In: C. Münz (ed.), Epstein Barr Virus Volume 2, Current Topics in Microbiology and Immunology 391, pp. 289-322.*** Springer International Publishing.

3 De Paschale, M. and Clerici, P. (2012). Serological diagnosis of Epstein-Barr virus infection: problems and solutions. ***World J Virol*** *1*(1), 31-43.

4 Public Health of England (PHE) (2019). UK Standards for Microbiology Investigations. Epstein-Barr virus serology. ***Virology 26***(6), 2-8. Available at: https://www.gov.uk/government/publications/smi-v-26-epstein-barr-virus-serology. Last accessed: [October 29, 2019].

Epstein-Barr virus (EBV) Infection

Testing algorithm

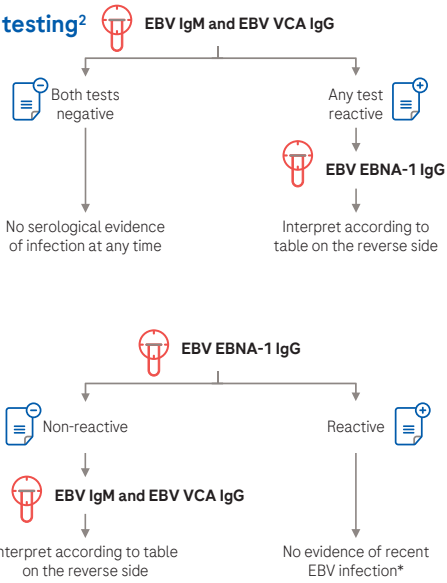
Parallel testing[1]

Perform EBV IgM, EBV VCA IgG, and EBV EBNA-1 IgG tests

↓

Interpret according to table on the reverse side

Sequential testing[2]



*In a small number of cases EBV EBNA-1 IgG may be detectable early (10 days after the onset of illness in <5 %)[3].

Adapted from:

1 De Paschale, M. and Cleirici, P. (2012). Serological diagnosis of Epstein-Barr virus infection: Problems and solutions. ***World J Virol 1***(1), 31-43.

2 Public Health of England (PHE) (2019). UK Standards for Microbiology Investigations. Epstein-Barr virus serology. ***Virology 26***(6), 2-8. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773292/V_26i6.pdf. Last accessed: [October 29, 2019].

3 Henle, G. et al. (1974). Antibodies to Epstein-Barr virus-associated nuclear antigen in infectious mononucleosis. ***J Inf Dis 130***, 231-9.

Not all assays are available for sale in all countries. Contact your local sales representative for details.

Elecsys® Immunoassays

Congenital & *Transplant	
CMV IgG	🩸
CMV IgM	
CMV IgG Avidity	
HSV-1 IgG	
HSV-2 IgG	
Rubella IgG	
Rubella IgM	
Toxo IgG	
Toxo IgM	
Toxo IgG Avidity	
Others	
EBV EBNA IgG	
EBV VCA IgG	
EBV IgM	
Chagas	🩸
Zika IgG	

cobas® Molecular Assays

Congenital & *Transplant	
*ADV DNA quantitative	🩸
*BKV DNA quantitative	
*CMV DNA quantitative	
*EBV DNA quantitative	
Zika RNA	🩸
Others	
Cdiff DNA	
MRSA/SA DNA	
MTB DNA	
MTB-RIF/INH	
MAI DNA	
WNV DNA	🩸
CHIKV/DENV RNA	🩸
Babesia RNA/DNA	🩸
Zika RNA	🩸

The Infectious Diseases assay portfolio from Roche Diagnostics

Elecsys® Immunoassays

Viral Hepatitis	Sexual Health	Congenital & *Transplant	Others
Anti-HAV total	HIV Duo# 🩸	CMV IgG 🩸	EBV EBNA IgG
Anti-HAV IgM	HIV combi PT 🩸	CMV IgM	EBV VCA IgG
HBsAg 🩸	HIV Antigen	CMV IgG Avidity	EBV IgM
HBsAg confirmatory	HIV Antigen confirmatory	HSV-1 IgG	Chagas 🩸
HBsAg quantitative	Syphilis 🩸	HSV-2 IgG	Zika IgG
Anti-HBs 🩸	HSV-1 IgG	Rubella IgG	
Anti-HBc 🩸	HSV-2 IgG	Rubella IgM	
Anti-HBc IgM	HTLV-I/II 🩸	Toxo IgG	
Anti-HBe		Toxo IgM	
HBeAg		Toxo IgG Avidity	
HBeAG quantitative			
Anti-HCV 🩸			
HCV Duo			

cobas® Molecular Assays

HBV DNA quantitative	TV/MG	*ADV DNA quantitative	Cdiff DNA
HCV RNA qualitative	CT/NG DNA	*BKV DNA quantitative	MRSA/SA DNA
HCV RNA quantitative	HSV-1/HSV-2 DNA	*CMV DNA quantitative	MTB DNA
HCV genotyping	HIV RNA quantitative	*EBV DNA quantitative	MTB-RIF/INH
HEV RNA qualitative 🩸	HIV-1/HIV-2 RNA qualitative	Zika RNA 🩸	MAI DNA
MPX (HIV/HCV/HBV) 🩸	HPV DNA		WNV DNA 🩸
DPX (B19V/HAV) 🩸	HPV genotyping		CHIKV/DENV RNA 🩸
	MPX (HIV/HCV/HBV) 🩸		Babesia RNA/DNA 🩸
			Zika RNA 🩸

for use on **cobas e** 801 immunoassay analyzer only

🩸 **Donor Screening:** Part of the Roche Blood Safety Solutions panel

Please check with your local Roche representative on the availablility of the assays and tests in your country.

diagnostics.roche.com

MC--03478

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Other Approval	Dani Schord Marketing Compliance 27-Feb-2024 18:52:09 GMT+0000

Regulatory Approval	Deanna Koon Regulatory Approval 27-Feb-2024 20:46:14 GMT+0000

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