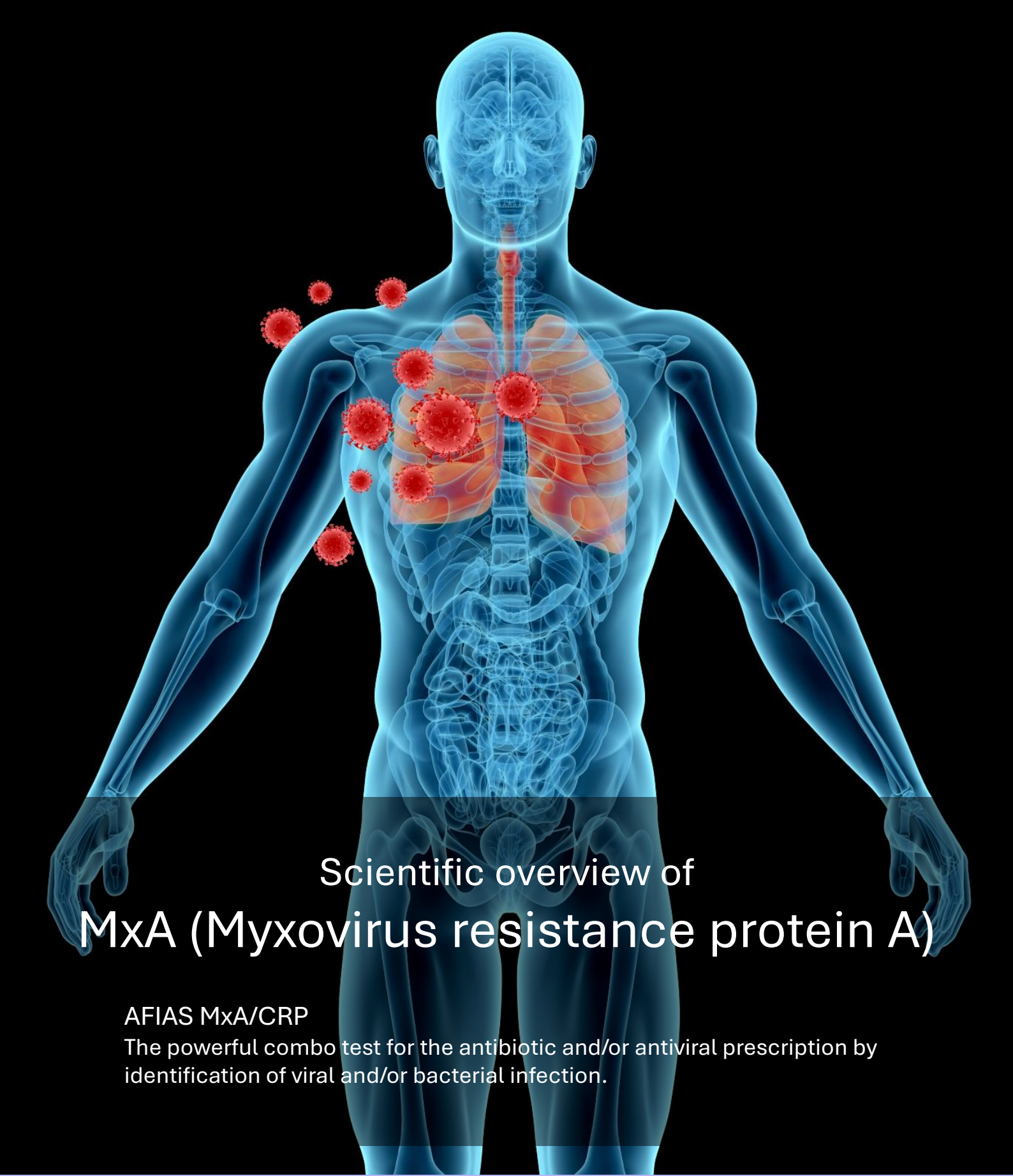


Scientific overview of
MxA (Myxovirus resistance protein A)

AFIAS MxA/CRP

The powerful combo test for the antibiotic and/or antiviral prescription by identification of viral and/or bacterial infection.

BIO TECHNOLOGY boditech

ⓒ 2022 Boditech Med Inc.

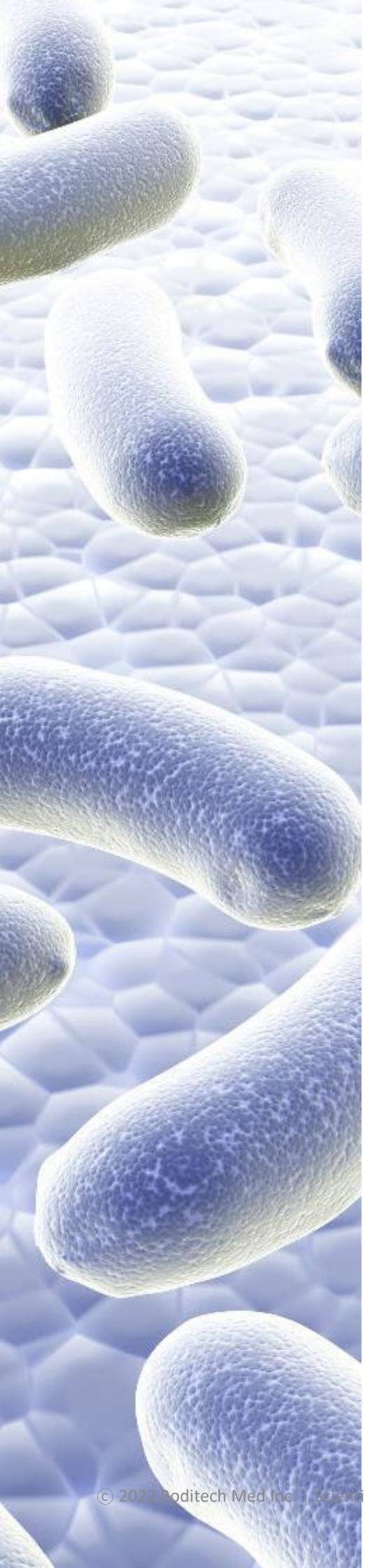


Table of Contents

List of Definitions

AMR
Antimicrobial resistance

ARI
Acute respiratory infection

AUC
Area under cover

CBC
Complete blood cell

CFS
Cerebrospinal fluid

CRP
C-reactive protein

ED
Emergency department

GBP
Guanylate binding protein

HMPV
Human metapneumovirus

INF
Interferon

IFNAR
Interferon-α/ß receptor

IFNLR
Interferon lambda receptor

IRG
Immunity-related GTPases

ISGs
Interferon stimulated genes

ISRE
Interferon stimulated response elements

JAK
Janus activated kinase

LRTI
Lower respiratory tack infection

OAS
Oligoadenylate synthetases

PCR
Polymerase chain reaction

PCT
Procalcitonin

PIV
Parainfluenza virus

POC
Point of care

PKR
Protein kinase R

RSV
Respiratory syncytial virus

RV
Rhinovirus

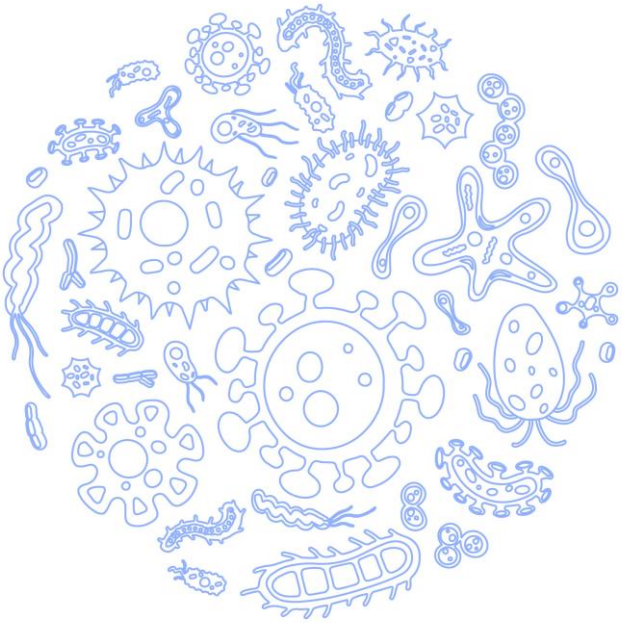
SBIs
Serious bacterial infections

STAT
Signal transducer and activator of transcription

TRAIL
TNF-related apoptosis-inducing ligand

VLIG
Very large inducible GTPase proteins

Introduction



Acute respiratory infections (sinusitis, pharyngitis, common cold, acute bronchitis, etc.) caused by viral or bacterial infection are the most common cause of visiting hospitals and prescribing antibiotics. Most of the patients who visit the hospital for acute respiratory infection are prescribed antibiotics, however, about 50% of them are unnecessary. About 5-25% of patients who have been prescribed antibiotics have side effects, and serious cases can occur 1 of 1,000.

In addition, unnecessary prescription of antibiotics causes antimicrobial resistance, which leads to increased medical costs, antibiotic-related side effects, and serious diseases. Furthermore, the global mortality rate due to antimicrobial resistance is going to surpass cancer in 2050 and cost $100 trillion in medical expenses. [1]

Therefore, it is very important to distinguish whether the cause of infection is a virus or bacteria to prescribe an appropriate antibiotic.

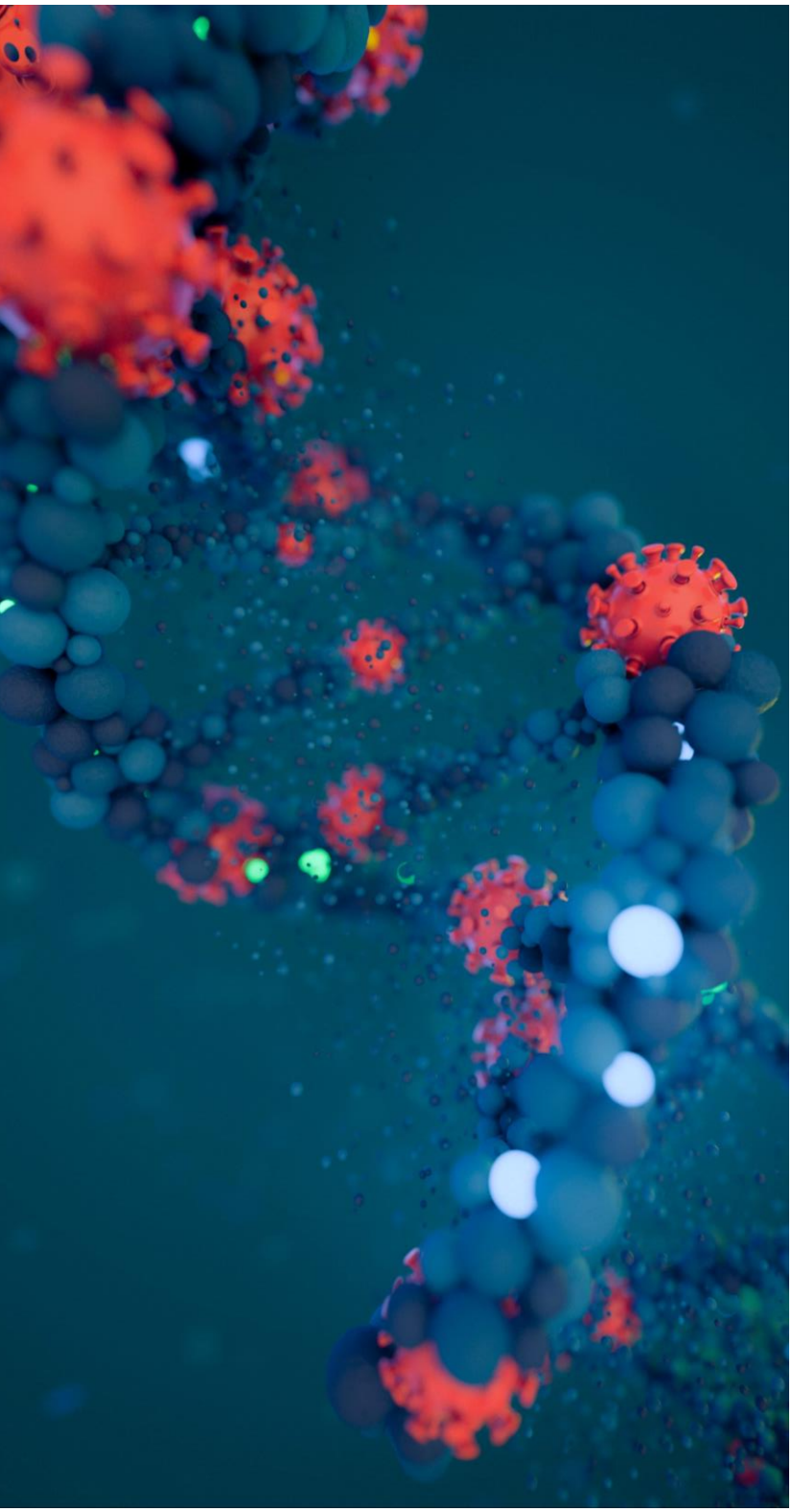
Human myxovirus resistance protein 1 (MxA) is an interferon-induced dynamin-like GTPase that acts as a cell-autonomous host restriction factor [2] against a broad spectrum of RNA and DNA viruses. With this broad antiviral activity, MxA has been widely studied as a potential biomarker for virus infections. To avoid antibiotic abuse, clinical studies have shown that the combined interpretation of MxA with C-reactive protein (CRP) dramatically improves the clinical sensitivity and specificity in discriminating between viral and bacterial infections. [3], [4], [5]

Based on rising social concerns and unrivaled technology prowess, Boditech Med launched AFIAS MxA/CRP. AFIAS MxA/CRP detects human MxA level and CRP level simultaneously with the CE-IVD marked quantitative immunoassays and the point-of-care (POC) AFIAS system.

In the summary, AFIAS MxA/CRP expects to reduce antibiotic misuse and overuse rate even in the primary care system which doesn't have laboratory system with comparatively low cost and simple operation.

Overview of MxA

(Myxovirus resistance protein A)



Historical findings of IFN and MxA

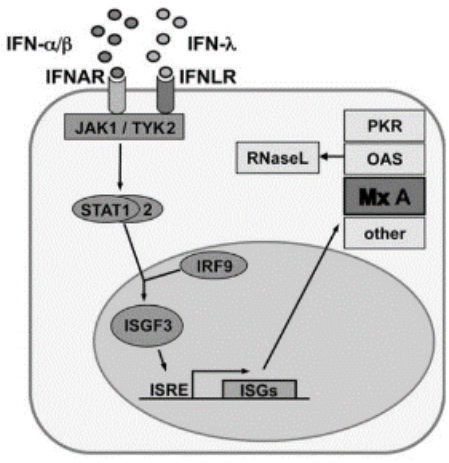
Interferons (IFNs) are produced in response to viral infection and contribute to host defense by establishing an anti-viral state in target cells.

The interferon (IFN)-regulated Mx proteins were discovered in studies on genetically determined resistance of mice to influenza virus (Lindenmann 1962; Horisberger and others 1983; Staeheli and others 1986). Virus induces predominantly two classes of INFs, namely INF-α, and INF-ß, collectively called type I IFNs.

The type III IFNs (IFN-γ) were described (Kotenko and others 2003; Sheppard and others 2003) and it became clear that these novel cytokines also activate the MxA gene (Holzinger and others 2007). [6], [7]

Expression of MxA

Type I and type III IFNs bind to their cognate receptors [IFNAR and IFNLR (also called IL28R), respectively] and activate the expression of MxA and other IFN-stimulated genes (ISGs) via the Janus-activated kinase/signal transducer and activator of transcription (STAT) pathway. As a result, the IFN-stimulated gene factor 3 complex is formed and binds to the IFN-stimulated response elements (ISRE) in the promoter regions of ISGs, such as MxA. [7]

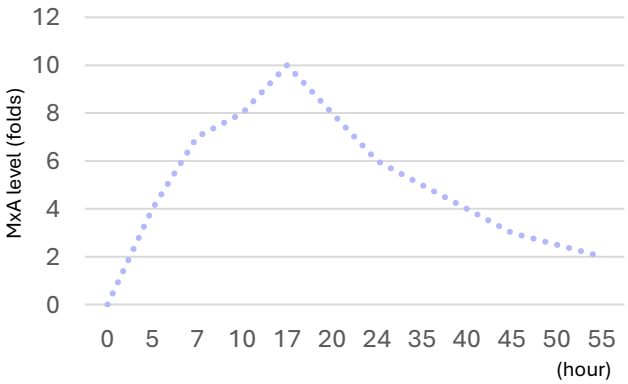


MxA gene expression depends on type I and type III interferon signaling [7]

A characteristic feature of MxA

In most cases of acute viral infections, type I IFN and MxA are released into the peripheral blood. Detection of interferons in serum is difficult and unreliable, mainly due to their short half-life.[8] MxA is detectable within 5 hours after infection and peaked at 17 hours, [9] and have 2.3 days of half-life. [10]

The MxA gene does not respond to other cytokines such as IL-1 or TNF-α. Neither type I IFN nor MxA elevates in healthy patients or those presenting with bacterial infections. [11]



Kinetic of MxA expression
(schematic based on Mattew E. Abrams)

MxA's exclusive expression by type I IFNs, and its relatively long half-life and stable characteristic make it an excellent biomarker for systemic IFN-α/β production in viral infections.

Comparison of MxA with other IFN-induced antiviral protein

IFNs activate the expression of several hundreds ISG products which have viral, antiproliferative, and immunomodulatory functions, such as,

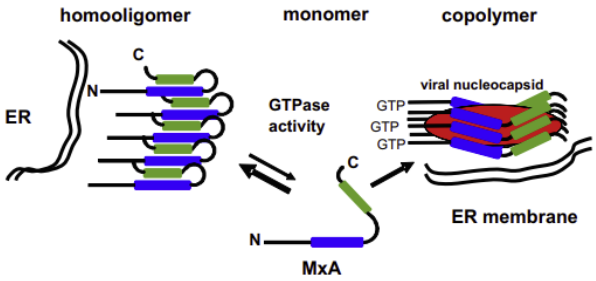
- 2' ,5' oligoadenylate synthetases (2-5 OAS)
- dsRNA-dependent protein kinase (PKR)
- GBP-1

Unlike Mx protein, 2-5 OAS and PKR constitutively express in normal cells in a latent, inactivated form. GBP-1 belongs to the dynamin superfamily of large GTPases like Mx. However, it is predominantly induced by IFN- γ and its antiviral activity against VSV (vesicular stomatitis virus) is comparatively weak. [7]

Therefore, MxA is key component of the antiviral state induced by interferons.

Antiviral activity of MxA

When MxA-expressing cells were microinjected with purified viral nucleocapsids, MxA blocked their movement into the nucleus. How exactly MxA prevents viral replication at the molecular level is not known. Most likely, MxA recognizes incoming viral nucleocapsids and inactivates their function by wrapping around the viral structures there by forming MxA/nucleocapsid oligomers.



Hypothetical model of MxA antiviral action [12]

Other biomarkers? (TRAIL, IP-10)

Recent studies show that other viral biomarkers, such as TNF-related apoptosis-inducing ligand (TRAIL) and IP-10, are less effective than MxA at differentiating viral infection. TRAIL and IP-10 show area under the curve (AUC) specifically for viral infection of 0.72 and IP-10 of 0.72. [13], [14]

MxA's antiviral act against numerous viruses

MxA protein is an important antiviral factor with broad activity against diverse RNA viruses such as influenza virus, vesicular stomatitis virus, measles virus, and other viruses belonging to the family Bunyaviridae. In addition, it has been found that MxA transfected cells were protected against Semliki Forest virus, a togavirus with a single-stranded RNA genome of positive polarity.

MxA protein also manifests antiviral activity to a few DNA viruses like the vaccinia virus (VACV), the monkey pox virus, and the African swine fever virus. [15]

Below table is the list of various viruses activate MxA protein as antiviral factor.

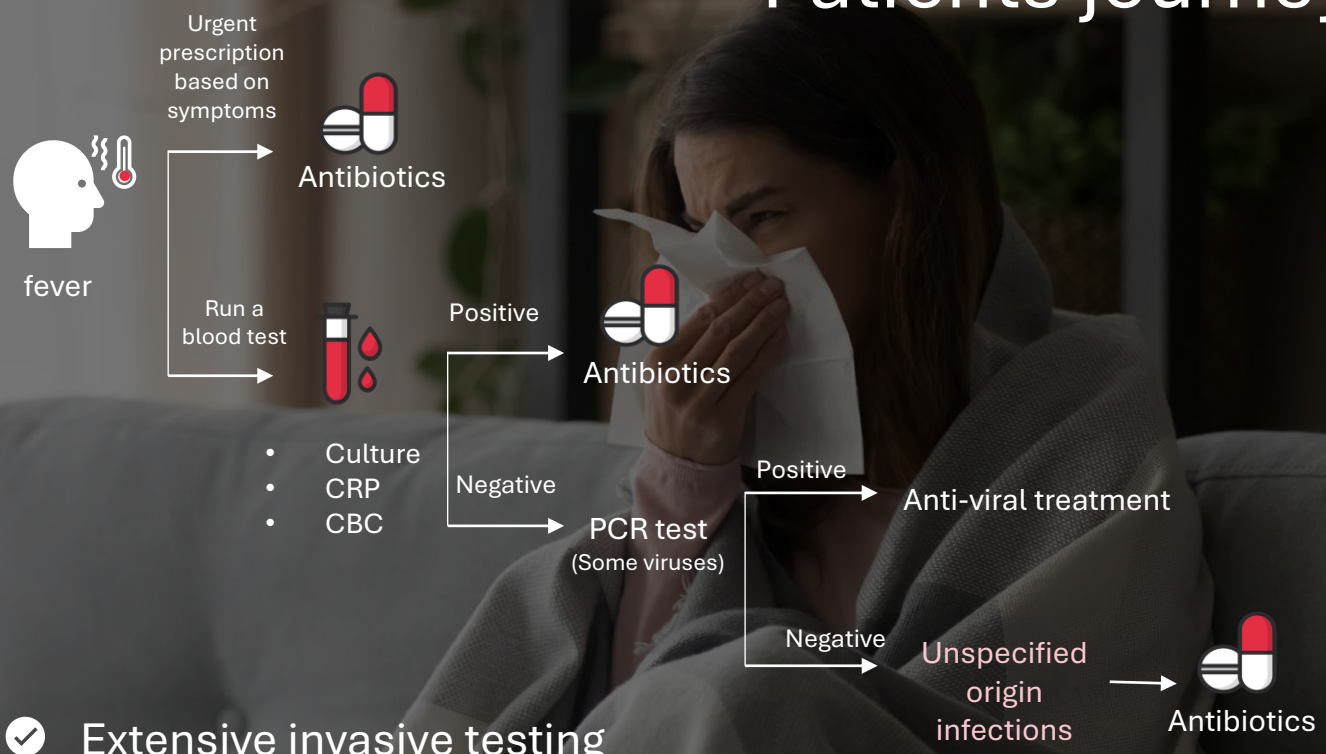
Respiratory infectious viruses
Influenza A virus (Flu A)
Influenza B virus (Flu B)
Influenza C virus (Flu C)
Respiratory Syncytial virus (RSV)
Rhinovirus (RV)
Metapneumovirus (hMPV)
Parainfluenza virus 1 (PIV 1)
Parainfluenza virus 2 (PIV 2)
Parainfluenza virus 3 (PIV 3)
Bocavirus (HBoV)
Coronavirus (229E/NL63/OC43/HKU1)
SarS-CoV-2
Hepatitis virus
Hepatitis B virus (HBV)
Hepatitis C virus (HCV)
Gastroenteritis virus
Rotavirus (Rotv)
Adenovirus (AdV)
Enterovirus (HEV)
Human Papillomavirus
Human Papillomavirus (HPV)
Sexually Transmitted virus
Cytomegalovirus (CMV)
Herpes simplex virus (HSV)
Human Immunodeficiency virus (HIV)
Human herpes virus (HHV)
Flavivirus
Zika virus (ZIKV)
West Nile virus (WNV)
Other viruses
Parvovirus B19 (B19V)
Monkeypox virus (MPXV)
Chikungunya virus (CHIKV)
Epstein-Barr virus
African swine fever virus (ASFV)
Crimean-Congo hemorrhagic fever virus (CCHFV)
Coxsackie virus B (CVB)
Hepatitis B virus (HBV)
Infectious bursal disease virus (IBVD)
Infectious pancreatic necrosis virus (ISAV)
Infectious salmon anemia virus (LACV)
LaCrosse virus (LACV)
Rift Vally fever virus
Vesicular stomatitis virus (VSV)
Measles virus
Selmliki Forest virus
Togavirus

Clinical Utility

Because of the difficulties in differentiating viral from bacterial infections, ill-appearing patients suffer from extensive invasive testing and unnecessary usage of antibiotics. This is a great concern, as inappropriate usage of antibiotics contributes to not only the emerging threat of antimicrobial resistance but also a significant burden on the health care system and large economic consequences both for the family and society.

Therefore, there is an urgent need for more specific and reliable diagnostic tools for the identification of antibiotic-requiring bacterial infections.

Patients journey



- Extensive invasive testing
- Inappropriate usage of antibiotic
- Economic burden

There are many bacterial infection markers, but **why not viral?**

Is it sufficient only a bacterial infection test?

To reduce morbidity and mortality and improve the usage of antibiotics, there is an urgent need for better diagnostic tools in the clinic. An ideal biomarker should not only identify serious infections but also accurately exclude non-infectious causes of inflammation to be able to guide the clinician in the important decision of whether or not to prescribe antibiotics.

While most commercially available biomarkers have been focused on the identification of serious bacterial infections (SBIs), there is currently an increasing interest in viral biomarkers. As novel antiviral therapeutic possibilities arise and new vaccines targeting viruses are developed, the accurate identification of viral infections will be Pivotal, especially for children.

Viral biomarkers and combination tests have the potential to improve the accuracy of identifying bacterial infections as compared with old inflammatory single biomarkers

Our health care team always cares about using antibiotics and tries to participate in antimicrobial stewardship. We test CBC and CRP routinely. Why do we need another test?

Existing test methods (16)

WBC

WBC (White blood counts) have been used for decades to identify severe bacterial infections. However, in the post-vaccine era, the bacterial spectrum has changed and the usefulness of WBC as a predictor for bacterial infections has been questioned especially in infants, as most studies have shown a low predictive value.

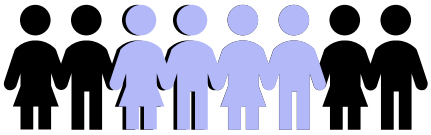
CRP

CRP (C-reactive protein) is a commonly used biomarker for infection worldwide. CRP levels increase at the time of infection, but elevated levels are also seen in other diseases, such as inflammatory disorders, cancer, and trauma. The diagnostic accuracy for discriminating viral from bacterial etiologies is limited, especially in the early stages.

PCT

PCT (Procalcitonin) has, in most studies, been shown to be a superior biomarker as compared with CRP for the differentiation between infectious and non-infectious inflammation, however, the specificity for distinguishing between viral and bacterial infections is limited.

Bacterial cultures from sterile sites are still considered the golden standard for the establishment of bacterial etiology, but the sensitivity is low, and the results may take several days. (16)



Molecular-based methods such as PCR have widely been introduced during the last decade for viral detection. However, the interpretation of the results is complicated by the fact that certain respiratory viruses have been detected in up to 40% of asymptomatic children. (17)

The high sensitivity of PCR allows the detection of minimal amounts of viral nucleic acids, but there are questions concerning the clinical relevance of positive test results. For example, small amounts of a respiratory virus could represent asymptomatic colonization or postinfectious shedding. Appraisal of asymptomatic persons, in comparison to patients with respiratory illnesses, is essential for better understanding the significance of detected viral nucleic acids and for improved interpretation of diagnostic results. (18)

It is also a challenge to obtain representative specimens from the source of infection in children, such as from the lower respiratory tract.

MxA (Myxovirus resistance protein A)

- Promising biomarker for viral infection
- Assist in the distinction between active infection and asymptomatic detection
- Synergy with existing marker for distinguish bacterial and viral infection

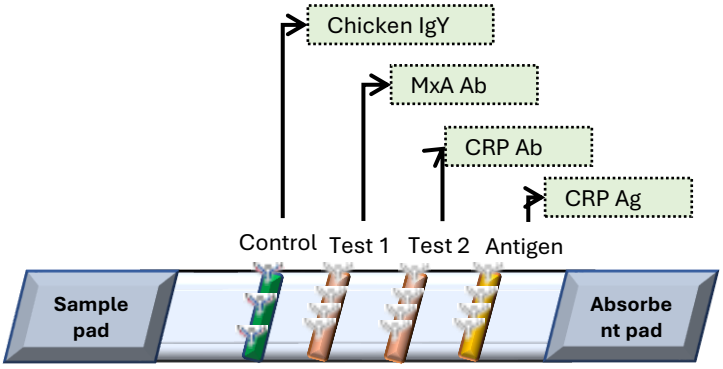
Given the complexity of the host immune response to infections and the increasingly recognized importance of viral–bacterial interactions, it is likely unrealistic to think that one single biomarker would be able to accurately identify with antibiotic-requiring bacterial infections.

Viral biomarkers and combination tests have the potential to improve the accuracy of identifying viral-bacterial infections. MxA is promising biomarker for differentiating between these two etiologies. In addition, MxA levels assist in the distinction between active infection and asymptomatic detection, which is a common clinical problem when interpreting PCR data of certain respiratory viruses.

The combination test of MxA and CRP does not only increase the specificity of differentiating viral-bacterial infection but also can improve medical workflow by saving time and cost.

AFIAS MxA/CRP

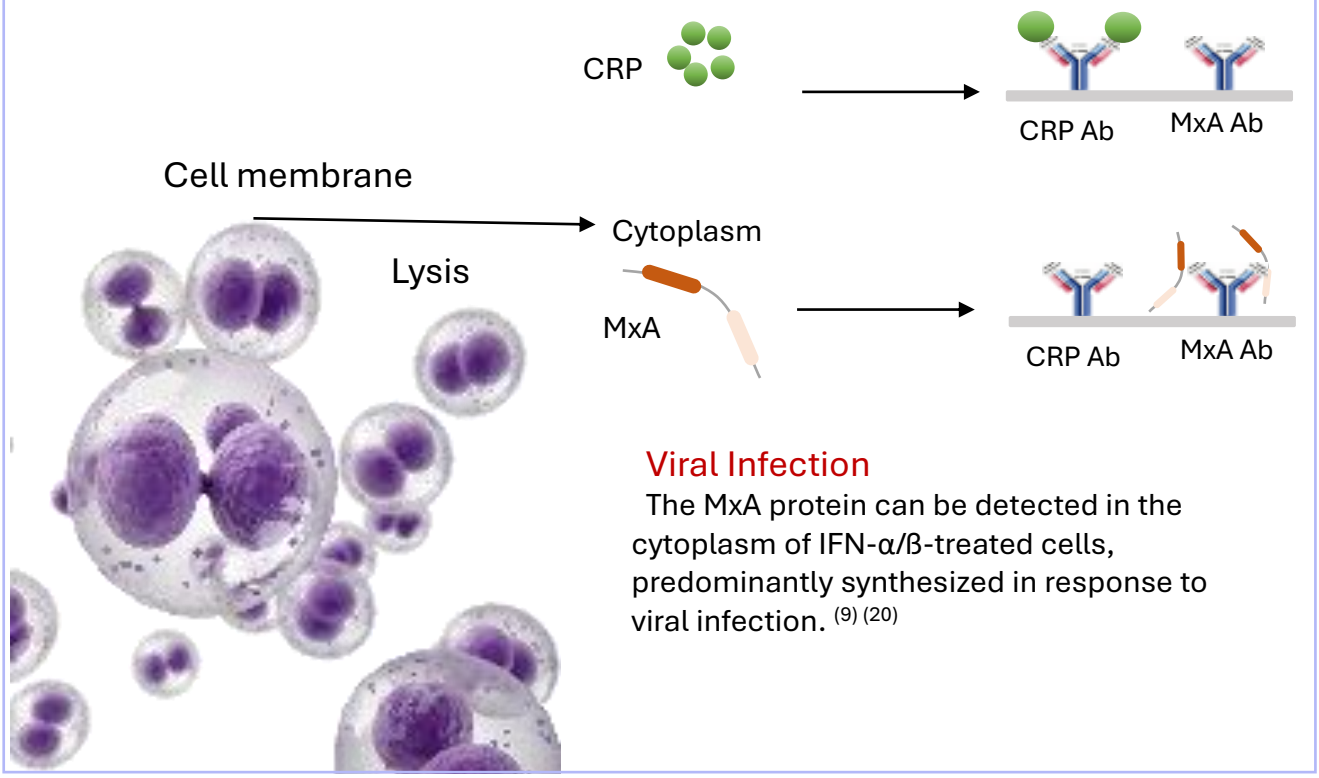
AFIAS MxA/CRP is an in vitro diagnostic medical device that quantitatively measures MxA and CRP in human whole blood specimens using fluorescence immunoassay (FIA). AFIAS MxA/CRP detects 2 proteins simultaneously, which have a considerable difference in concentration, more than 1,000 times in the body, with small peripheral blood.



Measurement principle

Bacterial Infection

CRP is an acute-phase protein, the main biological function is a host defense against bacterial pathogens and clearance of apoptotic and necrotic cells. (19)



Viral Infection

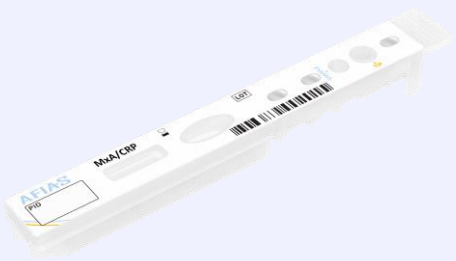
The MxA protein can be detected in the cytoplasm of IFN-α/ß-treated cells, predominantly synthesized in response to viral infection. (9) (20)

Measurement platform

AFIAS-1 / AFIAS-3 / AFIAS-6 / AFIAS-10

Full automated immunoassay analyzer
Rapid and user-friendly
Point-of-care for bedside testing
Small to large size of devices

Test result: in 12 minutes



AFIAS MxA/CRP all in one cartridge

Capillary tip for fingertip blood
No need pipetting, sample pretreatment
Storage at room temperature

Require sample volume: 10 µL for C-tip
150 µL for general mode

Specification

Sample type	Whole blood
Sample volume	General tip 150 uL / C-tip 10 uL
Reaction time	12 minutes
Storage condition	2 - 30℃ (Room temperature)
Expiration date	20 months
Anticoagulant	EDTA(K^2-, K^3-) Heparin(Na-, Li-) Sodium citrate
Working range	MxA: 10.0 – 300.0 ng/mL CRP: 1.0 – 200.0 mg/L
Limit of detection	MxA 5.7 ng/mL CRP 0.4 mg/L
Cut-off	MxA 15.0 ng/mL CRP 10.0 mg/L
Available analyzer	AFIAS-1, AFIAS-3, AFIAS-6, AFIAS-10
Contents	24T/box
Cat no.	SMFP-102

What is the existing problem?

Major disease burden for children

Major cause of antimicrobial Resistance [20]

Increase cost of family and society

Misdiagnosis or delayed diagnosis

What is the cause of the problem?

Clinical findings often provide Insufficient information [5]

low-resource setting (diagnostic laboratory services are often lacking)

Considerable heterogeneity, by geography, season, and comorbidities (ex. HIV) [21]

Limitation of the gold standard [16]

Who need the test?

Acute febrile illnesses adults/ children [21] [22]

Acute respiratory infection adults / children [23]

Lower respiratory infection Common cold to pneumonia [17]

Where need the test?

80% of all antimicrobials prescribed in primary care [11]

Emergency Department / Pediatric Emergency Department (reported probabilities of serious bacterial infection vary from 7 to 16%) [16]

Why AFIAS MxA/CRP?

In the fastest time
AFIAS MxA/CRP combo test provide test result within 12 minutes

With a smallest blood
With C-tip, 10 uL whole blood required for the 2 test

In the most convenient way
Automated - drop and go system

The most efficient method
Economic and compact point-of-care solution

More information for clinician's decision
MxA/CRP test at once, higher the sensitivity and specificity to distinguish viral-bacterial infection

Internal Evaluation

The result of AFIAS MxA/CRP evaluation shows high sensitivity and specificity. For virus infection, sensitivity 88%, specificity 94.4% / for bacterial infection, sensitivity 87.2%, specificity 88%.

Performance

Viral infection

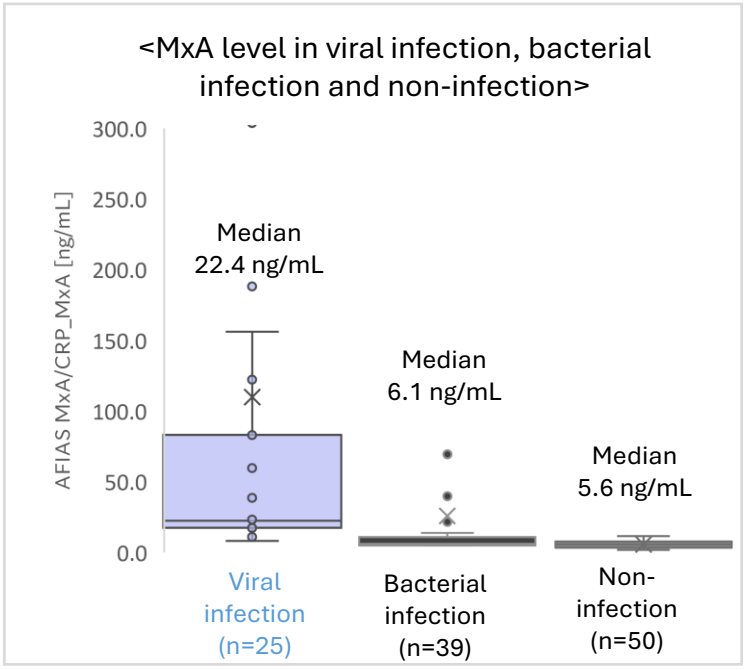
88%

Sensitivity

94.9%

Specificity

<MxA level in viral infection, bacterial infection and non-infection>



Bacterial infection

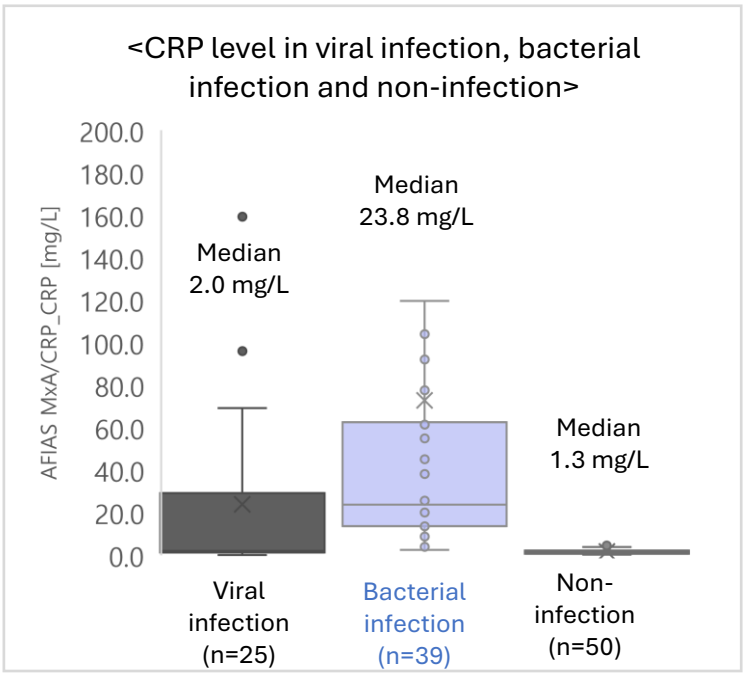
87.2%

Sensitivity

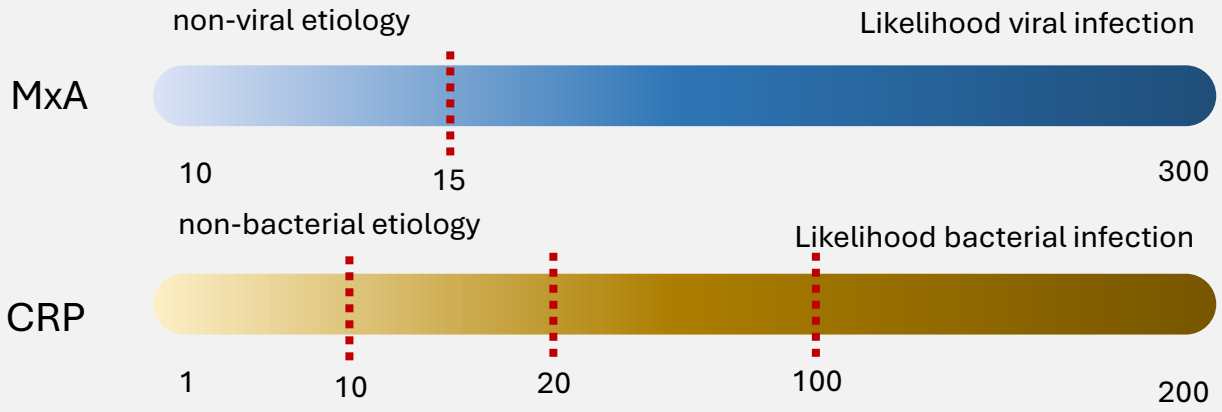
88%

Specificity

<CRP level in viral infection, bacterial infection and non-infection>



Clinical interpretation treatment & considerations



MxA [ng/mL]	CRP [mg/L]	Interpretation
MxA ≥ 15.00	CRP < 10.00	Viral inifection
	10.00 ≤ CRP < 20.00	Viral infection and low likelihodd of bacterial infection
	20.00 ≤ CRP < 100.00	Viral infection and bacterial infection likely
	CRP ≥ 100.00	Viral infection and bacterial infection very likely
MxA < 15.00	10.00 ≤ CRP < 20.00	Likelihodd of bacterial infection
	20.00 ≤ CRP < 100.00	Bacterial infection likely
	CRP ≥ 100.00	Bacterial infection very likely
	CRP < 10.00	Non-infection

FAQ

Does WBC concentration have any effect on the MxA level?

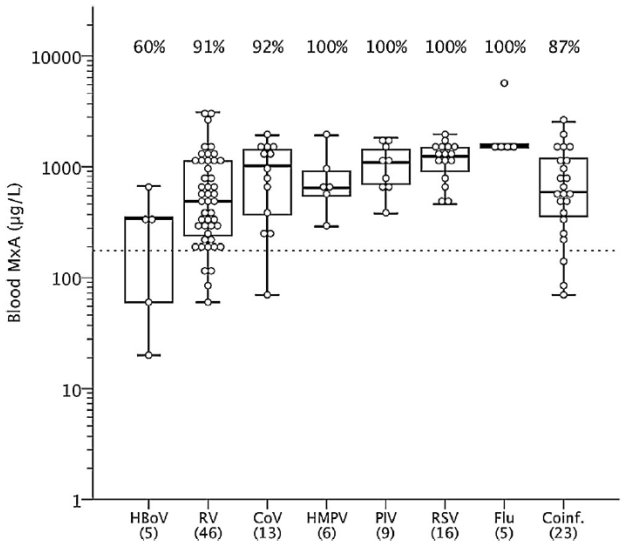
There are no data directly showing correlation of blood WBC and MxA protein concentration. Some research (Piri *et al.*, 2022) show that there is a difference in MxA concentration in virus-infected/non-infected patients based on the age of 2 years. [24]
However, WBC concentration is no significant effect to the test result as MxA is a protein occurs specifically during viral infection (RNA virus, some DNA viruses).

Is MxA measurable in CFS (Cerebrospinal Fluid)?

Since most of the research data on MxA are conducted with blood sample, there are no MxA research data on CFS. We recommend MxA/CRP uses only blood (whole blood) as a test sample.

Is there a difference in detection sensitivity for each virus?

The MxA response varied according to the causative virus. In RSV, PIV, Flu and HMPV the disease was associated with high MxA levels while in RV and CoV infections MxA levels remained at a lower but yet clearly higher levels as compared to samples obtained from patients suffering from asymptomatic or non-viral infections.



Blood MxA protein levels in virus-positive children according to detected viruses. [25]

Does MxA reflects the concentration of the virus and the severity of the disease?

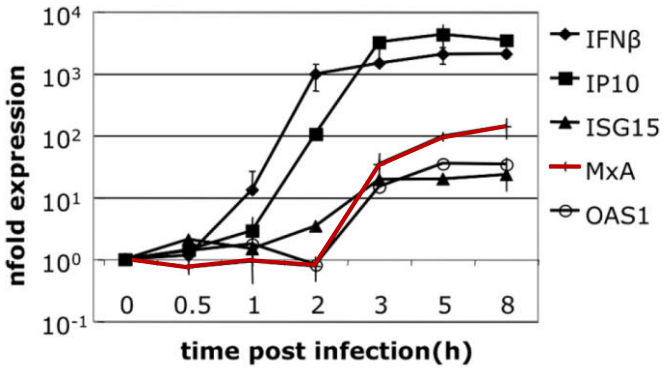
According to the L. Toivonen *et al*., there is no significant correlation between the RV or RSV RNA copy numbers and the blood MxA levels (RV log of copies vs. MxA, Spearman's rho −0.259, p 0.064 and RSV log of copies vs. MxA, Spearman's rho −0.112, p 0.56). [25]
Co-infections or high viral loads in single virus infections were not associated with higher MxA levels in this study.

In recent study, there is association between COVID-19 severity and MxA concentration, also MxA level can predict the need for supplemental oxygen in patients with COVID-19. [26]
But this study result can be applied only to the COVID-19 patient. As we saw in the previous question, MxA level shows different concentration in each viruses, it could not be enough explanation for the association of disease severity and MxA level for all viruses.

AFIAS MxA/CRP purpose to distinguish viral-bacterial infection in the early stage of the infection. More detailed studies on the immune response in these conditions, as well as on MxA response during viral-bacterial co-infections, are warranted.

When MxA can detect in peripheral blood after virus infection?

In in-vitro study, IFN-beta mRNA expression reaches a maximum after 2 hour while prototype ISGs, such as IFN-gamma-inducible protein 10(IP-10), OAS1, or MxA, are expressed in slightly delayed kinetics as expected. [28]



Time course of H5N1-induced genes [28]

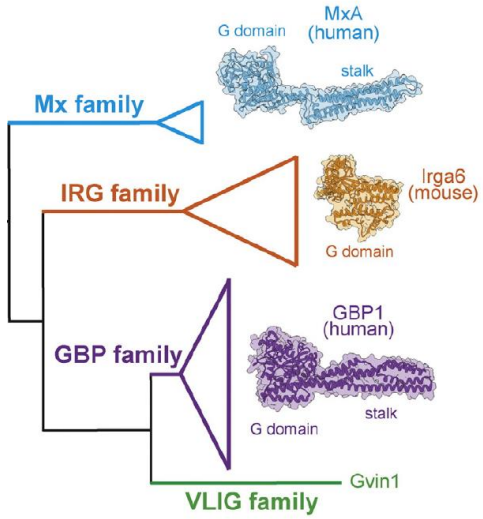
In mononuclear cells stimulated with high doses of leukocyte IFN-alpha concentrations, the amount of MxA mRNA was induced 10-fold at 4 hour after IFN induction (T Ronnie et al,) also according to E. Abrams et al., MxA is detectable within 5 hours after infection.
In conclusion, MxA can detect 2~5 hours after virus infection. [9], [10]

Is MxA detected in recovery period?

According to Micro Schmolke, [28] it is reported that MxA is expressed from 2 hours after infection, but there is no literature related to monitoring MxA level in the recovery period.

For reference, when AFIAS MxA/CRP was regularly tested for COVID-19 patients and the MxA concentration was monitored, the MxA concentration continued to decrease after the peak, and the normal MxA concentration level was observed after 2 weeks.

What can make false-negative and false-positive?



Interferon Inducible GTPase [27]

In cross-reactivity testing with interferon-inducible GTPase, no cross-reactivity was observed. (For cross-reaction test, please refer AFIAS MxA/CRP IFU)

Some false-positive cases, for example, PCR negative but MxA positive cases, we should consider that PCR test cannot run for all kind of viruses, and there is a possibility infected with another viruses. This case should be considered when running MxA test.

Clinical interpretation and treatment consideration of AFIAS MxA/CRP test.

Since it is difficult to identify a viral infection or a bacterial infection based on clinical symptoms only, AFIAS MxA/CRP test can assist clinician's decision.
This test run simultaneously a wide range of virus-specific markers, MxA, and bacterial infection-specific markers, CRP, to help identify bacterial and/or viral infection.

[Interpretation of result]
MxA < cut off value & CRP ≥ cut off value : High probability bacterial infection
MxA ≥ cut off value & CRP ≥ cut off value : High probability of viral infection
MxA ≥ cut off value & CRP < cut off value : High probability of viral infection
MxA < cut off value & CRP < cut off value : Negative

AFIAS MxA/CRP is an invitro diagnostic reagent that assist clinician can take appropriate decision and follow-up treatment. In general, clinician can determine whether to prescribe antibiotics and/or related additional tests when a bacterial infection is confirmed, and whether to prescribe antiviral drugs when a virus or an unknown infection is suspected and/or request a related additional inspection.

References

(1) Antimicrobial Resistance Collaborators, Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, *Lancet*, 2022

(2) Song Gao, *et al*., Structure of Myxovirus Resistance Protein A Reveals Intra- and Intermolecular Domain Interactions Required for the Antiviral Function, *Cell*, 2011

(3) Lika Englemann, *et al*., Diagnosis of Viral Infections Using Myxovirus Resistance Protein A (MxA), *Pediatrics*, 2015

(4) Vincent Chieux *et al*., MxA Protein in Capillary Blood of Children with Viral Infections, *Journal of Medical Virology*, 1999

(5) Dan Coster *et al*., Using the kinetics of C-reactive protein response to improve the differential diagnosis between acute bacterial and viral infections, *A Journal of Infectious disease*, 2019

(6) Stertz S *et al*., Interferon-induced, antiviral human MxA protein localizes to a distinct subcompartment of the smooth endoplasmic reticulum, *Journal of Interferon and Cytokine Research*. 2006

(7) Otto Haller and Georg Kochs, Human MxA Protein: An Interferon-Induced Dynamin-Like GTPase with Broad Antiviral Activity, *Journal of Interferon and Cytokine Research*, 2011

(8) Halminen M *et al*., Expression of MxA protein in blood lymphocytes discriminates between viral and bacterial infections in febrile children, *Pediatr Res,* 1997

(9) Abrams M *et al*., IFN- Induces MxA Gene Expression in Cultured Human Corneal Fibroblasts , *Experimental Eye Research*, 1995

(10) T Ronnie *et al*., Control of IFN-inducible MxA gene expression in human cells, *J Immunol*, 1993

(11) Sambursky R , Shapiro N, Evaluation of a combined MxA and CRP point-of-care immunoassay to identify viral and/or bacterial immune response in patients with acute febrile respiratory infection, *Eur Clin Respir J,* 2015

(12) Otto Haller, Peter Staeheli, Georg Kochs, Interferon-induced Mx proteins in antiviral host defense, *Biochimie*, 2007

(13) Patrick Joseph and Eliot Godofsky, Outpatient Antibiotic Stewardship: A Growing Frontier—Combining Myxovirus Resistance Protein A With Other Biomarkers to Improve Antibiotic Use, *Open Forum Infectious Diseases*, 2018

(14) Yuri van der Does *et al*., TRAIL and IP-10 as biomarkers of viral infections in the emergency department, *J infect*, 2016

(15) Vladimir P. Zav'yalov *et al*., Interferon-Inducible Myxovirus Resistance Proteins: Potential Biomarkers for Differentiating Viral from Bacterial Infections, *Clinical Chemistry*, 2019

(16) Samuel Rhedine *et al*., Novel Biomarkers Differentiating Viral from Bacterial Infection in Febrile Children: Future Perspectives for Management in Clinical Praxis, *Children*, 2021

(17) Samuel Rhedine *et al*., Clinical Utility of PCR for Common Viruses in Acute Respiratory Illness, *Pediatrics*, 2014

(18) Rogier R. Jansen *et al*., Frequent Detection of Respiratory Viruses without Symptoms: Toward Defining Clinically Relevant Cutoff Values, *Journal of Clinical Microbiology*, 2011

(19) John E. Volanakis, Human C-reactive protein: expression, structure, and function, *Molecular Immunology*, 2001

(20) A. Roers, MxA Gene Expression after Live Virus Vaccination: A Sensitive Marker for Endogenous Type I Interferon, *The Journal of Infectious Disease*, 1994

(21) B. Leticia Fernandez-Carballo *et al*., Distinguishing bacterial versus non-bacterial causes of febrile illness –A systematic review of host biomarker, *Journal of infection*, 2021

(22) Yibeltal Akelew *et al*., Evaluation of C-reactive protein and myxovirus resistance protein A to guide the rational use of antibiotics among acute febrile adult patients in Northwest Ethiopia, *International Journal of Infectious Disease*, 2020

(23) Samuel Rhedi *et al*., Myxovirus resistance protein A for discriminating between viral and bacterial lower respiratory tract infections in children e The TREND Study, *Clinical Microbiology and infection*, 2022

(24) Ruut Piri *et al*., Myxovirus Resistance Protein A as a Marker of Viral Cause of Illness in Children Hospitalized with an Acute Infection, *Microbiology Spectrum*, 2022

(25) Laura Toivonen *et al*., Blood MxA protein as a marker for respiratory virus infections in young children, *Journal of Clinical Virology*, 2014

(26) Norikazu Mataki *et al*., Myxovirus resistance protein A in peripheral blood predicts supplemental oxygen need in COVID-19, *Journal of Infection*, 2021

(27) Danielle Pilla-Moffett *et al*., Interferon-Inducible GTPases in Host Resistance, Inflammation and Disease, *Journal of Molecular Biology*, 2016

(28) Mirco Schmolke *et al*., Essential Impact of NF-kB Signaling on the H5N1 Influenza A Virus-Induced Transcriptome, *The Journal of Immunology*, 2022

APPENDIX

(Myxovirus resistance protein A inducible viruses list and references)

(Family) DNA/RNA virus	Virus	MxA express	Reference
(Orthomyxoviridae) Negative-sense single-stranded RNA virus	Influenza A virus (Flu A)	Yes	Halminen et al. Kawamura et al.
	Influenza B virus (Flu B)	Yes	Forster et al.
	Influenza C virus (Flu C)	Yes	Marschall et al.
(Pnemoviridae) Negative-sense,single-strand RNA virus	Respiratory Syncytial virus (RSV)	Yes	Forster et al. Halminen et al. Chieux et al.
(Adenoviridae) Double-strand DNA virus	Adenovirus (AdV)	Yes	Halminen et al. Chieux et al. Nakabayashi et al.
(Picornaviridae) Positive-sense, single-strand RNA virus	Enterovirus (HEV)	Yes	Piri et al. Zhang et al.
	Rhinovirus (RV)	Yes	Toivonen et al. Rhedine et al.
	Coxsackie virus B (CVB)	Yes	Haller et al.
(Pneumoviridae) Positive-sense, single-strand RNA virus	Metapneumovirus (hMPV)	Yes	Toivonen et al. Rhedine et al.
(Paramyxoviridae) Negative-strand RNA	Parainfluenza virus 1 (PIV 1)	Yes	Toivonen et al.
	Parainfluenza virus 2 (PIV 2)	Yes	Forster et al.
	Parainfluenza virus 3 (PIV 3)	Yes	Forster et al. Zhao et al.
(Parvoviridae) Single-strand DNA virus	Bocavirus (HBoV)	Yes	Toivonen et al. Piri et al.
	Parvovirus B19 (B19V)	Yes	Wu et al.
(Coronaviridae) Positive-sense, single-stranded RNA virus	Coronavirus (229E/NL63/OC43/HKU1)	Yes	Rhedine et al. Piri et al.
	SarS-CoV-2	Yes	Bizzotto et al. Tong-Minh et al. Mataki et al.

APPENDIX

(Myxovirus resistance protein A inducible viruses list and references)

(Family) DNA/RNA virus	Virus	MxA express	Reference
(Reoviridae) Double-strand RNA virus	Rotavirus (Rotv)	Yes	Halminen et al. Chieux et al. Nakabayashi et al.
(Papilomaviridae) DNA virus	Human Papillomavirus (HPV)	Yes	Saadeh et al.
(Herpesviridae) DNA virus	Cytomegalovirus (CMV)	Yes	Chieux et al. Nakabayashi et al. Yosimasu et al.
	Herpes simplex virus (HSV)	Yes	Ku et al. Mossman et al.
	Human herpes virus (HHV)	Yes	Yusimasu et al.
	Epstein-Barr virus	Yes	Yoshimasu et al.
(Poxiviridae) Double-stranded DNA virus	Monkeypox virus (MPXV)	Yes	Johnston et al.
(Togaviridae) Postivie-sense single stranded RAN virus	Chikungunya virus (CHIKV)	Yes	Kaur et al.
	Togavirus	Yes	
(Flaviviradae) Single positive-stranded RNA virus	Dengue virus (DENV)	Yes	Akelew et al.
	West Nile virus (WNV)	Yes	Hoenen et al. (2007 and 2014)
	Zika virus (ZIKV)	Yes	Ren et al.
	Hepatitis C virus (HCV)	Yes	Shi et al.
(Retroviridae) Single-stranded, positive sense RNA virus	Human Immunodeficiency Virus (HIV)	Yes	Baldolato et al.

APPENDIX

(Myxovirus resistance protein A inducible viruses list and references)

	Other viruses	MxA express	Reference
(Hepadnaviridae) Double-stranded DNA virus	Hepatitis B virus (HBV)	Yes	Gordien et al.
(Asfarviridae) Double-stranded DNA virus	African swine fever virus (ASFV)	Yes	Haller et al. Netherton et al.
(Nairoviridae) Negative sense RNA virus	Crimean-Congo hemorrhagic fever virus (CCHFV)	Yes	Haller et al. Andresson et al.
(Birnaviridae) Double-stranded RNA virus	Infectious bursal disease virus (IBVD)	Yes	Haller et al.
	Infectious pancreatic necrosis virus (ISAV)	Yes	Haller et al.
(Orthomixoviridae) RNA virus	Infectious salmon anemia virus (LACV)	Yes	Haller et al.
	Thogoto virus	Yes	Haller et al.
	Dhori virus	Yes	Haller et al.
(Peribunyaviridae) RNA virus	LaCrosse virus (LACV)	Yes	Haller et al.
(Hantaviridae) Single-stranded, negative-sense RNA virus	Hantann virus	Yes	Haller et al.
	Puumala virus	Yes	Haller et al.
Rhabdovirus (negative-strand RNA)	Vesicular stomatitis virus (VSV)	Yes	Haller et al. Pavlovic et al.
(Paramyxoviridae) Single-stranded, negative sense RNA virus	Measles virus	Yes	Haller et al.
(Togaviridae) Positive-strand RNA virus	Semliki forest virus	Yes	Heinrich Landis et al.

43, Geodudanji 1-gil, Dongnae-myeon, Chuncheon-si, Gang-won-do 24398, Korea
Tel: +82-33-243-1400 | Fax: +82-33-243-9373 | www.boditech.co.kr/en

Marketing
marketing@boditech.co.kr

Sales
sales@boditech.co.kr

ⓒ 2022 Boditech Med Inc.