# FebriDx®

an RPS diagnostic solution

The FebriDx test is a rapid, in-office point-of-care test that uses a fingerstick blood sample to provide clinicians with a simple, fast, and easy-to-use assessment of the body's immune response to an acute respiratory infection




**Microbial resistance to antibiotics has increased alarmingly over recent decades, prompting the World Health Organization to declare this a global public health crisis.[1]**

The FebriDx test altered clinical management in 48% of patients presenting to a primary care clinic and reduced unnecessary antibiotic prescriptions in 80% of cases.[2]



*Improving antibiotic stewardship into the outpatient setting -*

**THE PATHWAY TO DIAGNOSIS STARTS HERE.**

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RPS diagnostics

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## THE PATHWAY TO DIAGNOSIS STARTS HERE

The FebriDx test is a rapid, in-office point-of-care (POC) test that uses a fingerstick blood sample to provide clinicians with a simple, fast, and easy-to-use assessment of the body's immune response to an acute respiratory infection (ARI). The single use, disposable test identifies patients within 10 minutes that have a clinically significant underlying infection and aids in the differentiation of viral and bacterial ARIs through the rapid, in-vitro detection of both Myxovirus resistance protein A (MxA) and c-reactive protein (CRP) directly from a fingerstick blood sample. MxA is an intracellular protein that becomes elevated in the presence of acute viral infection and CRP is an acute-phase inflammatory protein that is elevated in the presence of a clinically significant infection.[3]

The FebriDx test requires no additional equipment to perform or to interpret results. The timely test results provide clinicians the ability to formulate a targeted clinical management and treatment plan during the initial patient encounter, helping to improve antimicrobial stewardship in the outpatient setting.[3] FebriDx may identify immune responses that are more likely to benefit from a watchful waiting antibiotic prescribing strategy or require immediate therapeutic intervention.[2,3]

## REDUCE UNNECESSARY ANTIBIOTICS THAT CONTRIBUTE TO MICROBIAL RESISTANCE

ARI's are one of the most common reasons patients seek medical attention worldwide. ARI refers to otitis media, sinusitis, pharyngitis, bronchitis, and pneumonia. The substantial overlap in symptoms and signs presents a challenge for healthcare providers to identify clinically significant infections as well as to differentiate viral from bacterial infection in the outpatient setting. Diagnostic uncertainty[4] and pressure, from both patients or parents of patients,[5] to prescribe antibiotics results in more than 50% unnecessary antibiotic prescriptions.[6] Recent antibiotic use in primary care is the single most important risk factor for an infection with a resistant organism.[7-8] Antibiotics are frequently prescribed for patients with probable viral illnesses, including upper respiratory infections (URI) inclusive of acute bronchitis, despite their lack of effectiveness in treating these illnesses.[9] According to the European Centre for Disease Prevention and Control, 25,000 people in Europe die each year as a direct result of resistant infection.[10] It is estimated that complications associated with antibiotic resistance cost €9 billion annually in Europe.[11] Prescribing antibiotics incurs direct and indirect costs for adverse events, increases reconsultation rates for subsequent episodes, and medicalizes self-limiting illnesses.[12-13]

Antibiotics are responsible for the largest number of medication-related adverse events and are implicated in 1 of every 5 visits to emergency departments.[15] Adverse events range in severity from mild (e.g. nausea, diarrhea and rash) to severe life-threatening (e.g. C. difficile colitis, Stevens–Johnson syndrome, anaphylaxis).[14] Delayed antibiotic prescribing strategies result in a significant reduction in the consumption of antibiotics.[15]



Negative FebriDx results may indicate patients with a microbiologically unconfirmed respiratory illness (MURI). MURI represents symptomatic patients without confirmed etiology of infection, with a less vigorous immune response, and potentially less clinically significant underlying disease (e.g. allergies, COPD, or asthma, etc). Patients with MURI are less likely to benefit from antibiotic therapy.

# ACUTE RESPIRATORY INFECTION

A FebriDx test is used FIRST to triage patients suffering from an acute respiratory infection, providing physicians with data to diagnose and manage clinically significant infections. FebriDx identifies the cause of infection as viral or bacterial, as opposed to a specific pathogen, and has the capacity to detect a broad range of ARIs, increasing its utility in the outpatient setting.

## VIRAL OR BACTERIAL?

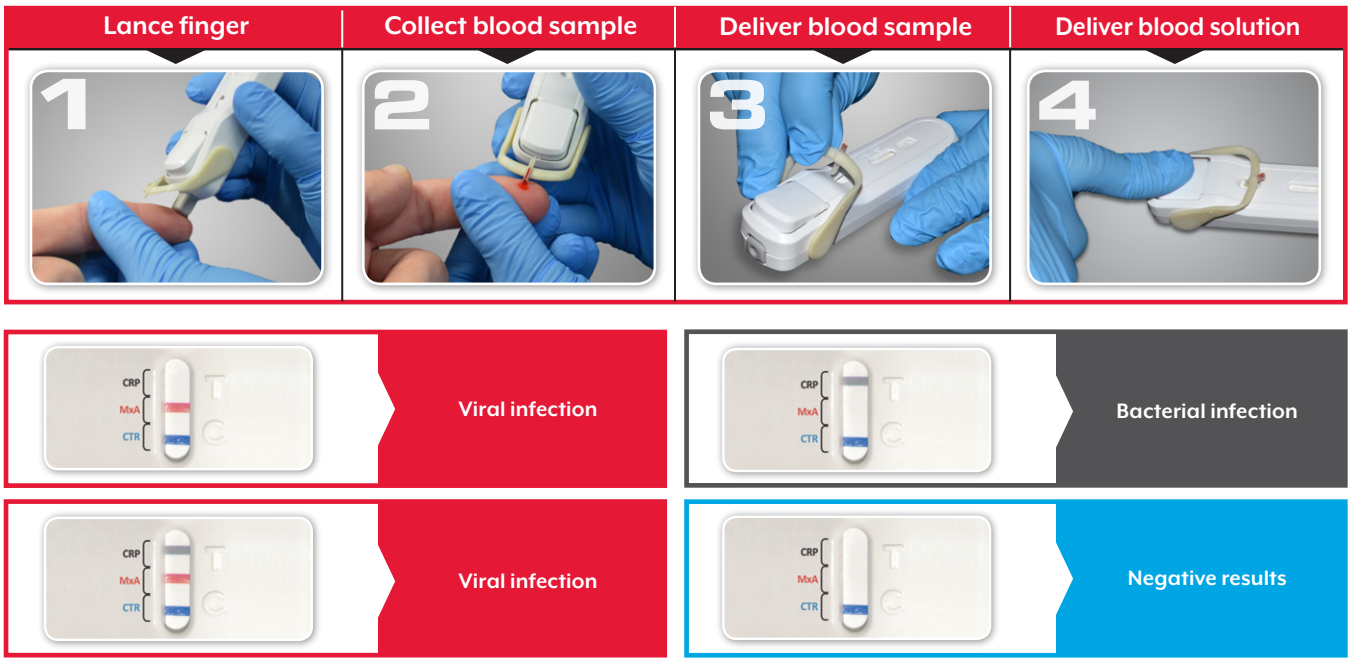
Common symptoms of BOTH viral and bacterial acute respiratory infections are shown below.




FebriDx identifies patients with a CRP concentration ≥ 20 mg/L and MxA ≥ 40 ng/ml. Previous studies conclude that patients with infectious respiratory symptoms and a CRP below this 20 mg/L threshold are likely to have non-bacterial, or self-limited infections. CRP levels above this threshold identify a clinically significant immune response but cannot reliably differentiate between viral and bacterial etiology; therefore, FebriDx also includes the highly specific viral biomarker, MxA, to distinguish patients with a viral infection associated with an elevated CRP.

The ability of FebriDx to rapidly and accurately identify contagious patients may help prevent the spread of disease as well as reduce antibiotic resistance, allergic reactions, and adverse events; empowering physicians to make immune response-directed therapeutic decisions at the point of care.

## FEBRIDX TEST PROCEDURE



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## ACCURATE RESULTS WITHIN 10 MINUTES

Two U.S. prospective, multicenter clinical trials 1) 220 patients enrolled, 100% reported fever ≥ 100.5F within the last 72 hours while 121 patients (55%) had a confirmed fever at the time of enrollment; and 2) 370 patients enrolled consisting of 205 patients 1 year or older that reported a fever within the previous 72 hours and exhibited respiratory tract symptoms/signs (13% febrile at time of enrollment) as well as 165 asymptomatic controls.[3] These studies evaluated the FebriDx test's clinical performance at identifying a clinically significant immune response to viral and/or bacterial acute URI [nonspecific URI, sinusitis, pharyngitis, and bronchitis]. FebriDx results were compared against expert clinical reviewers' evaluation of standardized clinical microbiological (e.g. viral and atypical bacterial polymerase chain reaction [PCR], bacterial cell culture) and laboratory testing (e.g. WBC, PCT). The FebriDx performance values are shown below:




| Sample size (n) | Fever (hyperthermia) | Clinical diagnosis | Sensitivity [95% CI] | Specificity [95% CI] | PPV [95% CI] | NPV [95% CI] |
|---|---|---|---|---|---|---|
| 121<br>Shapiro et al.[2] | *Exhibited* on enrollment (100% febrile) | Bacterial | 95% [77-100] | 94% [88-98] | 76% [59-87] | 99% [93-100] |
| | | Viral | 90% [82-96] | 82% [66-92] | 91% [84-95] | 80% [80-93] |
| 220<br>Shapiro et al.[2] | *Reported* within last 3 days (55% febrile) | Bacterial | 85% [69-95] | 93% [89-96] | 69% [56-79] | 97% [94-99] |
| | | Viral | 90% [83-94] | 84% [75-91] | 88% [83-92] | 86% [78-91] |
| 205<br>Self et al.[3] | *Reported* within last 3 days (13% febrile) | Bacterial | 80% [61-91] | 93% [89-97] | 62% [47-79] | 97% [94-99] |
| | | Viral | 86% [75-94] | 88% [76-88] | 78% [52-74] | 93% [90-97] |

FebriDx Package Insert. Fever defined as a temperature ≥ 100.5F; Inclusion of rhinovirus or coronavirus as a true pathogen and not colonization required confirmation by PCR associated with an elevated WBC, lymphcytosis, bands, or an elevated MxA ≥ 15 ng/ml; Sensitivity = Positive Agreement; Specificity = Negative Agreement

## STRONG CLINICAL PERFORMANCE

A retrospective chart review was performed on 21 patients that presented to an outpatient general practice in the UK with symptoms of an acute respiratory infection and were tested with FebriDx after receiving a clinical diagnosis of nonspecific URI and lower respiratory tract infection (LRTI). Patients had a mean age of 46.3 years, and ranged from age from 3 years to 84 years old. **FebriDx altered clinical management in 48% (10/21) and reduced unnecessary antibiotic prescriptions in 80% (8/10).**[2] All of the patients demonstrated full clinical recovery without additional unscheduled medical consultations or subsequent newly initiated antibiotic prescriptions. FebriDx test results improved clinical management decisions and resulted in a reduction in antibiotic therapy without any subsequent adverse events.[2]



# SIMULTANEOUS DETECTION OF MxA AND CRP BIOMARKERS

## What is Myxovirus resistance protein A (MxA)?

- MxA is an intracellular blood protein that is stimulated by type I interferon (IFN-α and IFN-β).
- Interferons are naturally occurring proteins that are released by cells in response to viruses.
- Type I interferon levels remain within normal limits in healthy patients and in severe bacterial infections.[16,17]
- MxA protein becomes elevated in the presence of acute viral infection, but is not specific to a particular type of virus.
- Numerous clinical studies demonstrate that MxA expression in peripheral blood is a sensitive and specific marker for viral infection.[18-23]
- MxA has a low basal concentration, a fast induction time of 1-2 hours, and a long half-life of 2.3 days.[24,25]

## What is C-reactive protein (CRP)?

- CRP is a nonspecific, acute-phase protein that increases during an inflammatory process, especially following a severe infection.
- Bacterial infection is a potent stimulus of marked CRP elevation, which occurs within 4-6 hours of infection and peaks after 36 hours.[26]
- Bacterial infections dramatically elevate CRP levels while having no impact on MxA levels.
- Normal CRP serum concentration is less than 3 mg/L,[26] and in the presence of severe inflammation or infection, CRP levels can rise above 500 mg/L.[27]
- Viral infections may cause CRP to elevate above 20 mg/L;[3] invasive Adenovirus and Influenza can raise CRP levels above 80 mg/L.[27]
- The administration of antibiotics causes CRP levels to fall rapidly.[28-29]

## Multiplexed Pattern of Results

Independently, neither MxA nor CRP alone is sensitive or specific enough to differentiate viral from bacterial infection. A study shows that CRP guidance alone – at the National Institute for Health and Care Excellence (NICE) Pneumonia Guidelines recommended cut-off value of 20 mg/L[30] – may lead to over treatment of more than 38-56% of patients with ARI.[2,3]

The FebriDx test produces a multiplexed pattern of results combining an MxA value and CRP to help identify clinically significant viral and bacterial immune responses as well as aid in the differentiation of infectious etiology.







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## RESULTS DRIVEN SOLUTION

# OUTPATIENT MANAGEMENT OF ACUTE RESPIRATORY INFECTION

**PATIENT PRESENTS WITH SYMPTOMS AND SIGNS OF ACUTE RESPIRATORY INFECTION**
(Primary care offices, urgent care centers, pharmacies, government [biodefense, border and migration control])

**SYMPTOMS AND SIGNS**
Sore throat, cough, runny nose/nasal congestion, ear ache, difficulty breathing, sinus pressure, fatigue, chills, malaise, anorexia; Tonsillar erythema/swelling, lymphadenopathy, sinus tenderness, rhonchi, rales, wheezes, increased respiratory rate, reduction in $O_2$ saturation

**Fever**

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Differential Diagnostic Testing (fingerstick blood sample)

### NEGATIVE




**NO antibiotics required**

**Supportive care**
**Over-the-counter medications**
(cough suppressant, pain relievers, inhaler, nasal decongestant, etc.)

If no improvement in 48 hours, consider re-evaluation

Consider repeating FebriDx if symptoms persist or worsen

### VIRAL INFECTION





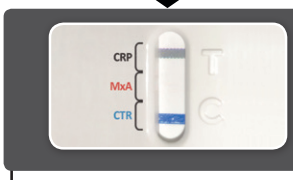


*Cannot preclude co-infection

**NO antibiotics required**

**Consider watchful waiting and supportive care**
Over-the-counter medications

### BACTERIAL INFECTION




**Antibiotics recommended**

**If no clinical improvement in 48 hours, consider changing antibiotic therapy**

**Consider additional lab tests**
Bacterial throat, sputum, or blood cultures







# FEBRIDX REDUCES UNNECESSARY ANTIBIOTICS, IMPROVES OUTCOMES, AND SAVES COSTS

## Identify clinically significant bacterial infections

- Diagnose bacterial infection and treat early to avoid worsening disease or complications

## Reduce antibiotic overuse

- More than 50% of antibiotics are unnecessary[6]
- Reduce the risk of antibiotic related adverse events
- Identify contagious patients and allow for isolation to reduce spread of disease
- Reduce direct costs associated with unnecessary antibiotics and subsequent antibiotic related medical consultations
- Limit development of antimicrobial resistance

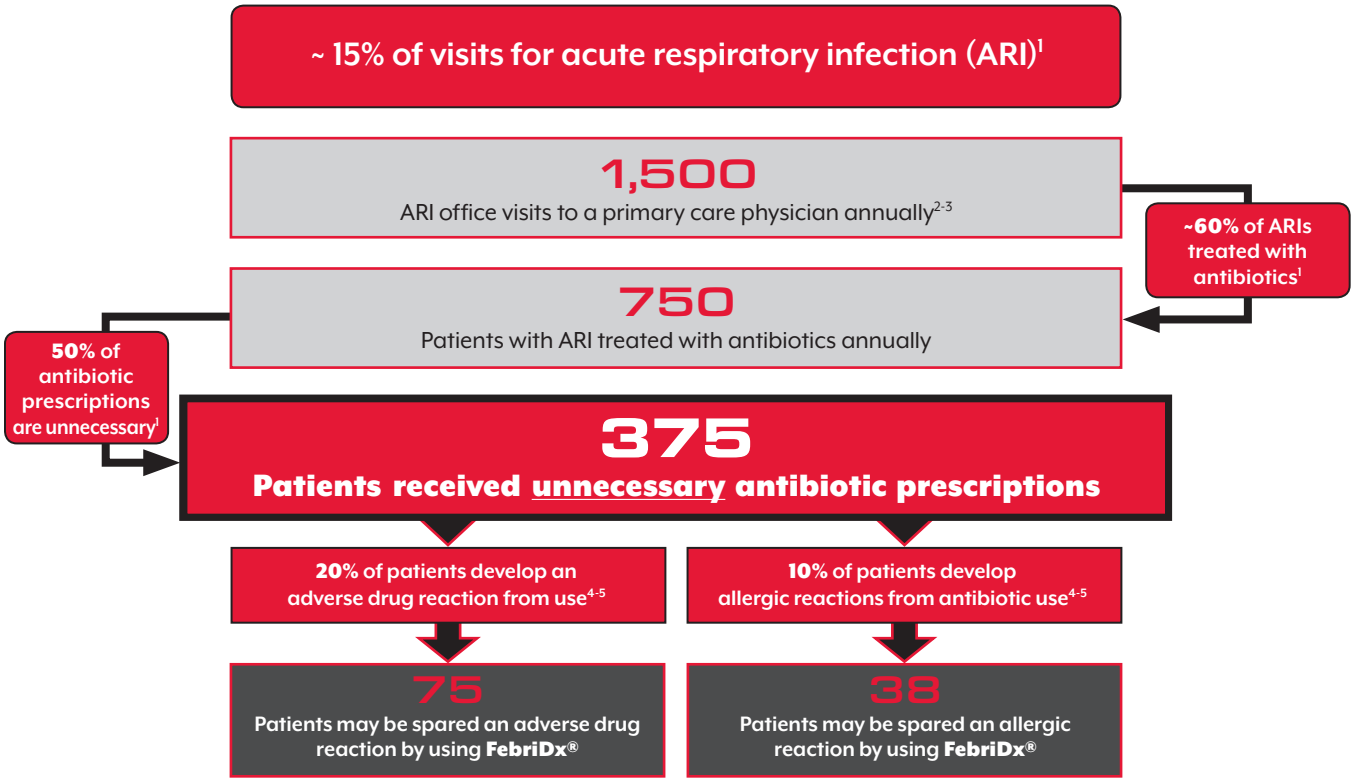
## Increase patient satisfaction and outcomes

- Results in 10 minutes at the initial office visit streamlines patient care
- Provides a tangible result that fosters patient acceptance of the treatment plan and leads to patient education on proper antibiotic use and harms of overprescribing
- Reduces time away from school, work, or daycare while seeking medical consultation

## Lower patient and healthcare costs

- Significant costs are incurred from the excessive use of antibiotics and the resulting adverse events, allergic reactions, and the development of resistant bacteria
- Reduce the need for, and costs associated with, additional laboratory testing

## FEBRIDX PATIENT BENEFIT ASSUMPTION MODEL*




*Numbers are estimates and refer to annual prevalence.

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FebriDx is regulatory cleared in Europe and Canada.
FebriDx is not FDA cleared and is not available in the United States.

RPS® diagnostics

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