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FebriDx Point-of-Care Testing to Guide Antibiotic Therapy for Acute Respiratory Tract Infection in UK Primary Care: A Retrospective Outcome Analysis

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Abstract

Introduction: Acute respiratory tract infection (ARTI) is a common illness presenting to general practice in the United Kingdom. Viral and bacterial infections clinically present similarly and are frequently misdiagnosed. Diagnostic uncertainty leads to inappropriate use of antibiotic prescriptions.

Objective: All patients tested with FebriDx, a new rapid diagnostic test for identifying clinically significant viral or bacterial infections, were examined to determine if test results safely impacted antibiotic prescription behaviour that would have been otherwise determined based solely on clinical signs and symptoms.

Method: A retrospective chart review was performed on 21 patients that presented to an outpatient general practice with symptoms of an acute respiratory tract infection and were administered the FebriDx test. In each case, a clinical diagnosis was identified, the FebriDx test recorded, antibiotic prescriptions analysed, and the response to therapy evaluated.

Results: FebriDx testing was performed on 21 patients with a mean age of 46.3 years, ranging in age from 3 years to 84 years old, including 12 males and 9 females. Patients had clinical diagnoses of both nonspecific upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI). FebriDx altered clinical management in 48% (10/21) and reduced unnecessary antibiotic prescriptions in 80% (8/10). All of the patients, inclusive of those patients given antibiotics or withheld antibiotics, demonstrated full clinical recovery without additional unscheduled medical consultations or subsequent newly initiated antibiotic prescriptions. One patient was diagnosed with bacterial sepsis and admitted to the hospital.

Conclusion: Point-of-Care (POC) diagnostic testing may help primary care general practitioners cost-effectively manage patients presenting with clinical evidence of an acute febrile respiratory tract infection. FebriDx test results improved clinical management decisions and resulted in a reduction in antibiotic therapy without any subsequent adverse events.

Keywords:
FebriDx; MxA; CRP; Point-of-care; Diagnostic; Respiratory infection

Introduction

Acute respiratory tract infection (ARTI) is a common illness presenting to general practice in the United Kingdom. General practitioners (GPs) regularly assess patients presenting with symptoms suggestive of ARTI, which can include otitis media, sinusitis, pharyngitis, acute bronchitis and pneumonia [1]. Viral and bacterial infections clinically present similarly and are frequently misdiagnosed.

The decision to prescribe antibiotics for ARTI is challenging [2,3] and is frequently based solely on clinical symptoms and signs, which is known to be of limited value [4-6] because of their inherent low sensitivity and specificity [7,8]. Diagnostic uncertainty and patient-related factors, such as patient expectations and pressure, often lead GP's to unnecessarily prescribe empiric antibiotic treatments.

The use of antibiotics in a population is the primary driver of the development of resistant bacteria and it is estimated that more than 25,000 patients die annually in the European Union due to multidrug-resistance (MDR) in bacterial infections [9]. A reduction in the excess antibiotic use is critical for combating the growing number of resistant infections [10]. Moreover, antibiotics are the second most common cause of adverse drug events in the elderly and account for 20% of all drug-related emergency department visits in the United States of which 80% are for allergic reactions [11]. Furthermore, antibiotics lead to diarrhoea in 2-25% and *C. difficile* infection is the major identifiable cause of antibiotic-associated diarrhoea and is responsible for 15–25% of all cases of diarrhoea [12]. Unnecessary antibiotic use for ARTI is an important public health problem [13] that not only contributes to the selection of resistant microorganisms [14] but also increases the frequency of adverse events and subsequently results in higher medical expenditures [15].

Improving diagnostic certainty may help identify those patients that will benefit from antibiotic treatment [16-18]. A meta-analysis that looked at 13 studies of upper respiratory tract infection (URI) and lower respiratory tract infection (LRTI) on the association between point-of-care (POC) C-reactive protein (CRP) testing and antibiotic prescribing for ARTIs in general practice found that CRP testing significantly decreased antibiotic prescribing at the initial consultation [19]. Any reduction in antibiotic consumption will have a relatively higher impact when done in a primary care setting [20,21]. Excessive use of antibiotics drives the development of antimicrobial resistance, medicalisation of patients and increases health care costs [22,23].

A five-year United Kingdom national antimicrobial resistance strategy, comprising seven areas for action aimed at controlling and ideally reducing the burden of resistance was initiated [24]. Two key parameters of the national antimicrobial resistance strategy, improved diagnostics and improved antibiotic stewardship both may be positively impacted with FebriDx, a new rapid POC test that can identify clinically significant infections and aid in the differentiation of viral from bacterial ARTIs. An outcome analysis was performed to confirm the clinical impact of FebriDx testing.

Method

A retrospective chart review was performed on 21 patients that presented to an outpatient general practice and were administered the FebriDx test. The objective was to determine if the FebriDx test results impacted therapeutic decisions that would have been otherwise determined based solely on clinical exam findings. In each case, a suspected clinical diagnosis was identified, the FebriDx test recorded, antibiotic prescriptions analysed, and the response to therapy evaluated. The patient's history and medical chart was reviewed to confirm any medical consultations or hospital admissions in the month period following the use of the FebriDx test. This was a retrospective analysis based on a chart review, and does not involve any new studies of human or animal subjects performed by the author, and deemed exempt from IRB approval.

Each patient underwent testing with FebriDx® (RPS Diagnostics; Sarasota, FL), which is a rapid, qualitative, single-use, disposable, whole blood immunoassay with a turn-around time of 15 min [25] Sambursky 2015. FebriDx requires 10 µL of whole blood obtained by capillary ("finger") stick. It provides a qualitative red test line result line for elevated levels of myxovirus resistance protein A (MxA) (≥ 40 ng/ml), and a black test line result for CRP with separate CRP thresholds of 20 mg/L ("low CRP" threshold) and 65 mg/L ("high CRP" threshold), and the presence of test lines in both control positions indicated a valid test result. FebriDx results indicating an elevated MxA, with or without an elevated CRP test line, was interpreted as a viral infection and the presence of any CRP test results without an associated elevated MxA, was interpreted as a bacterial infection.

Results

FebriDx testing was performed on 21 patients with a mean age of 46.3 years, ranging in age from 3 years to 84 years old, including 12 males and 9 females. Patients had clinical diagnoses of nonspecific URTI and LRTI (Table 1).

Patient	Age	Gender	Clinical Diagnosis	Clinical Aetiology	FebriDx Result	Management Alterations; Antibiotic impact	New Consultation for Clinical Worsening	Adverse Events
1	72	M	Neutropenic fever with possible subclinical RTI	Probable viral infection	Bacterial infection	Yes Antibiotic prescribed	No	Hospitalised for bacterial sepsis as a direct consequence of the test result
2	52	F	LRTI	Probable viral infection	Bacterial infection	Yes Antibiotic prescribed	No	Full recovery
3	36	M	Nonspecific URTI	Possible bacterial infection	Negative	Yes No antibiotic	No	Full recovery
4	14	M	LRTI	Possible bacterial infection	Viral infection	Yes No antibiotic	No	Full recovery
5	54	F	LRTI	Possible bacterial infection	Viral infection	Yes No antibiotic	No	Full recovery
6	84	M	Bronchitis	Possible bacterial infection	Viral infection	Yes No antibiotic	No	Full recovery
7	76	M	Bronchitis	Possible bacterial infection	Negative	Yes No antibiotic	No	Full recovery
8	39	F	Pharyngitis	Possible bacterial infection	Bacterial infection	No antibiotic prescribed	No	Full recovery *

9	72	F	Nonspecific URTI	Possible bacterial infection	Bacterial infection	No antibiotics prescribed	No	Full recovery
10	60	M	Nonspecific URTI	Possible bacterial infection	Negative	No antibiotics prescribed	No	Full recovery **
11	3	M	Otitis Media	Possible bacterial infection	Negative	No antibiotics prescribed	No	Full recovery
12	27	M	Nonspecific URTI	Possible bacterial infection	Viral infection	Yes No antibiotics	No	Full recovery
13	66	F	Bronchitis	Probable viral infection	Negative	No No antibiotics	No	Full Recovery
14	57	M	Nonspecific URTI	Possible bacterial infection	Viral infection	Yes No antibiotics	No	Full Recovery
15	44	F	Nonspecific URTI	Probable viral infection	Negative	No No antibiotics	No	Full Recovery
16	52	F	Nonspecific URTI	Probable viral infection	Negative	No No antibiotics	No	Full Recovery
17	43	F	Nonspecific URTI	Probable viral infection	Viral infection	No No antibiotics	No	Full Recovery
18	22	M	Nonspecific URTI	Probable viral infection	Negative	No No antibiotics	No	Full Recovery
19	17	F	Otitis Media	Probable viral infection	Negative	No No antibiotics	No	Full Recovery
20	66	M	Nonspecific URTI	Probable viral infection	Negative	No No antibiotics	No	Full Recovery
21	18	M	Nonspecific URTI	Possible bacterial infection	Viral infection	Yes No antibiotics	No	Full Recovery

URTI: Upper Respiratory Tract Infection; LRTI: Lower Respiratory Tract Infection; M: Male; F: Female;*Confirmed with positive bacterial culture. Required a 2nd course of antibiotics;** Slightly raised neutrophil count; a modest rise in erythrocyte sedimentation rate (41) and a modest elevation in c-reactive protein (38 mg/L).

Table 1: Patients tested with FebriDx.

FebriDx altered clinical management in 48% (10/21) and reduced antibiotics in 80% (8/10) clinical cases of possible bacterial infection. In two cases, the physician prescribed an antibiotic despite the test result including 1) a 3 year old patient that presented with sudden lethargy and respiratory signs tested negative within 4 h after symptoms began and was prescribed antibiotics despite the negative FebriDx test; 2) an immunocompromised patient with 10 days of persistent symptoms and was prescribed antibiotic despite the negative FebriDx test. All patients except one, inclusive of those patients given antibiotics or withheld antibiotics, demonstrated full clinical recovery at 1 month without additional unscheduled medical consultations or subsequent newly initiated antibiotic prescriptions. One FebriDx positive patient for bacterial infection was subsequently diagnosed with bacterial sepsis and admitted to the hospital (Table 2).

Total number of patients	**21**
Age range	3 years to 84 years
Mean age	46.3 years

Gender	
Males	57% (12/21)
Females	43% (9/21)
Change in antibiotic management	48% (10/21)
Reduction in antibiotic unnecessary antibiotic prescriptions	80% (8/10)
Complications	0% (0/21)
Repeat consultations	0% (0/21)
Full recovery	100% (21/21)

Table 2: Diagnostic demographic analysis and impact on clinical management.

Discussion

The current standard of care for the management of patients with acute respiratory tract symptoms in the United Kingdom outpatient setting is diagnosed by GPs clinically without the additional aid of ancillary laboratory testing such as rapid antigen testing, bacterial cell cultures, or molecular tests. In this retrospective chart review, use of the FebriDx test lowered the rate of antibiotic prescriptions without leading to increased morbidity, mortality, increased consultations, or increased complications. FebriDx results altered the clinical management plan in 48% (10/21) of the patients tested including two patients that were clinically presumed viral infection that FebriDx determined a bacterial infection and led to antibiotic therapy. Of note, one of these patients was admitted to the hospital with sepsis. Of the 21 patients tested with FebriDx, 81% (17/21) were determined to be nonbacterial, 29% viral (6/21) and 52% negative (11/21) with the FebriDx test. Two patients were tested within several hours of symptom onset while several others were tested up to 10 days later. The FebriDx negative patients were thought to possibly represent illness too early in the course of the infectious process, illness that already transitioned from the acute phase to the recovery phase of infection to stimulate a systemic response, or suggested a clinically insignificant illness. Symptomatic patients presenting more than a week after symptom onset may have a component of reactive airway disease contributing to their lingering symptoms. Antibiotics were withheld in 80% (8/10) patients that were clinically a possible bacterial infection but tested either as viral positive or negative with the FebriDx test. Clinically, these patients had a high enough clinical suspicion for a bacterial infection that an antibiotic prescription would have been prescribed without the FebriDx result.

A single case of a 3 year old patient that presented with sudden lethargy and respiratory signs tested negative within 4 h after symptoms despite the negative FebriDx test. This physician discretion was due to the age of the patient, his sudden physical deterioration, and the physician's lack of experience with the FebriDx test. Also, an immunocompromised patient with a 10 day history of symptoms was prescribed antibiotics despite the FebriDx negative result. Given that ancillary laboratory testing should be viewed in the context of the clinical condition, confronted with similar clinical circumstance in the future, antibiotics would likely be withheld and a watchful waiting strategy instituted.

Ninety-six percent (20/21) of the patients recovered completely without any clinical complications. One patient, confirmed positive for bacterial infection with FebriDx, was admitted with sepsis to the hospital. Two patients presented for routine scheduled follow up including a patient with a bacterial positive FebriDx result that was confirmed bacterial positive Group A *Streptococcus* with oropharyngeal cell culture that required an extended course of antibiotics and a patient with a viral diagnosis with FebriDx was seen with improvement obviating any need for prescribing antibiotics.

It is known that the patients' perceived expectations can influence the decision to prescribe antibiotics [26]. Further, patients seen on a Friday that might be developing a significant ARI when follow up access to the practice would not be possible for several days, typically would result in the temptation to prescribe an antibiotic. However, the availability of the FebriDx results at the office visit helped support the clinical decision to withhold antibiotics in 3 patients presenting on Friday and pursue a watchful waiting strategy.

POC CRP testing is a cost-effective part of the routine evaluation of patients with LRTI in general practice in Scandinavia [27-28]. A normal CRP in a patient with symptoms of respiratory infection usually indicates a self-limiting infection that does not require referral to hospital or antibiotic treatment, although it may also be observed early in the presentation of an illness [29]. A systematic review and meta-analysis of 13 studies in primary care demonstrated CRP testing led to significantly reduced antibiotic prescribing at the index consultation [19]. Patient recovery without antibiotics at the same speed and with comparable rates of complications (hospitalisation, mortality, and number of re-infections), suggest that the infection was of non-bacterial origin or so mild that the immune defense could clear the infection unassisted [30].

CRP testing may help to identify respiratory tract infections that have a higher likelihood for a complicated course and support a delayed prescribing strategy for low risk patients [31]. Delayed prescriptions based on CRP assistance resulted in an absolute 50% lower fill rate compared with delayed prescription in the control group [31]. As a single biomarker, CRP is less sensitive but more specific for confirming the presence of a bacterial infection at high concentrations but at lower concentrations of CRP is frequently observed during both viral and bacterial infections [32]. Certain viral infections, such as influenza, adenovirus, and others have been shown to cause substantial increases in CRP [33-36]. Using only CRP as a single biomarker at a cut off of 20 mg/L will reduce the risk of missing a clinically significant bacterial infection but simultaneously lead to overtreatment of viral infections that do not necessitate any antibiotic therapy.

MxA protein expression in peripheral whole blood is a specific biomarker for viral infection [25,37-42]. Higher levels of MxA level are seen in viral infections compared to bacterial infection and this can be explained by the fact that the MxA protein is induced exclusively by type I IFN and not by IFN-gamma, IL-1, TNF-alpha, or any of the other cytokines induced by bacterial infections [43].

Independently, neither MxA nor CRP alone is sensitive or specific enough to differentiate viral from bacterial infection. FebriDx testing results improved clinical management decisions and resulted in a reduction in antibiotic therapy without any adverse events. The simultaneous identification of both MxA and CRP, allows MxA to confer enhanced specificity onto the CRP biomarker [44]. FebriDx has high sensitivity and specificity for identifying a clinically significant infection and aiding in the differentiation of viral from bacterial infection. Since the test has a 97% NPV for bacterial infection, this

supports watchful waiting prior to initiating antibiotics and supports antibiotic stewardship [45].

POC testing should be viewed as an aid to the clinical exam that can increase the selectivity for determining the infectious etiology. This strategy may be demonstrated for patients with pharyngitis and acute bronchitis. Since group A or C beta-haemolytic *Streptococcus* is the most frequent, and arguably the only common cause for bacterial pharyngitis requiring initial antibiotic treatment, patients presenting with symptoms of pharyngitis without a significant cough or rhinitis that test positive for bacterial infection could be treated presumptively for *Streptococcus* with Penicillin. Patients presenting with cough consistent with bronchitis who test positive for a bacterial infection may have one of a range of common pathogens including *Haemophilus influenzae, Streptococcus pneumoniae, Mycoplasma or Chlamydophila*, for which a Macrolide or Tetracycline may be considered. Amidst influenza season, a viral positive test within the first 24 h of presentation would suggest an influenza infection and could justify antiviral therapy. Those patients negative for a clinically significant infection or confirmed viral positive, may be initially treated without antibiotics and only with supportive measures.

This study has three primary limitations including the small sample size, single centre and the lack of prospective, randomised controlled trial results, which can result in selection bias. The data supports pursuing larger outcome studies.

Conclusion

POC testing is not the current standard of care in the United Kingdom today and acute respiratory tract infections are routinely managed based only on clinical symptoms and signs. POC diagnostic testing with the FebriDx test may help primary care general practitioners cost-effectively manage patients presenting with clinical evidence of an ARTI. FebriDx test results improved clinical management decisions and resulted in a significant reduction in antibiotic therapy without any subsequent testing related adverse events. Larger antibiotic outcome studies should be performed to evaluate FebriDx's potential to mitigate against antibiotic resistance and save healthcare costs.

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Conflict of Interest

Author declares no financial interest or conflict of interest.

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References

1. Macfarlane J, Holmes W, Gard P (2001) Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. Thorax 56: 109–114.
2. Metlay JP, Fine MJ (2003) Testing strategies in the initial management of patients with community-acquired pneumonia. Ann Intern Med 138: 109–118.
3. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348: 1546–1554.
4. e Sutter A, Lemiengre M, Van Maele G (2006) Predicting prognosis and effect of antibiotic treatment in rhinosinusitis. Ann Fam Med 4: 486-493.
5. Hopstaken RM, Stobberingh EE, Knottnerus JA (2005) Clinical items not helpful in differentiating viral from bacterial lower respiratory tract infections in general practice. J Clin Epidemiol 58: 175-183.
6. Lindbaek M, Hjortdahl P, Johnsen UL (1996) Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ 313: 325-329.
7. Metlay JP, Kapoor WN, Fine MJ (1997) Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 278: 1440-1445.
8. Hoare Z, Lim WS (2006) Pneumonia: update on diagnosis and management. BMJ 332: 1077-1079.
9. ECDC/EMEA Joint Working Group (2016) The bacterial challenge: time to react. EMEA/576176. 13-42.
10. Guillemot D, Courvalin P (2001) Better control of antibiotic resistance. Clin Infect Dis 33: 542–547.
11. Grijalva CG, Nuorti JP, Griffin MR (2009) Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. JAMA 302: 758–766.
12. Bartlett JG, Gerding DN (2008) Clinical recognition and diagnosis of *Clostridium difficile* infection. Clin Infect Dis 46: S12-18.
13. Wenzel RP (2004) The antibiotic pipeline-challenges, costs, and values. N Engl J Med 351: 523–526.
14. Schito GC, Debbia EA, Marchese A (2000) The evolving threat of antibiotic resistance in Europe: new data from the Alexander Project. J Antimicrob Chemother 46: 3–9.
15. Hopstaken RM, Muris JWM, Knottnerus JA (2003) Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. Br J Gen Pract 53: 358-364.
16. Mainous AGIII, Hueston WJ (1998) The cost of antibiotics in treating upper respiratory tract infections in a medicaid population. Arch Fam Med 7: 45–49.
17. Flanders SA, Stein J, Shochat G (2004) Performance of a bedside C-reactive protein test in the diagnosis of community-acquired pneumonia in adults with acute cough. Am J Med 116: 529-535.
18. Van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ (2005) Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ 331: 26-29.
19. Huang Y, Chen R, Wu T (2013) Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract 63: e787-94.
20. Goossens H, Ferech M, Vander SR, Elseviers M (2005) Outpatient antibiotic use in Europe and association with resistance: a cross-national database study Lancet 365: 579-587.
21. Sande-Bruinsma N, Grundmann H, Verloo D (2008) Antimicrobial drug use and resistance in Europe. Emerg Infect Dis 14:1722-1730.
22. Hopstaken RM, Butler CC, Muris JW (2006) Do clinical findings in lower respiratory tract infection help general practitioners prescribe antibiotics appropriately? An observational cohort study in general practice. Fam Pract 23: 180-187.
23. Jakobsen KA, Melbye H, Kelly MJ (2010) Influence of CRP testing and clinical findings on antibiotic prescribing in adults presenting with acute cough in primary care. Scand J Prim Health Care 28: 229-236.
24. Department of Health (2015) UK Five Year Antimicrobial Resistance Strategy 2013 to 2018.
25. Sambursky R, Shapiro N (2015) 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 Resp J 10: 28245.

26. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N (1998) Understanding the culture of prescribing: qualitative study of general practitioners and patients' perceptions of antibiotics for sore throats. BMJ 317: 637–642.
27. Diederichsen HZ, Skamling M, Diederichsen A, Grinsted P, Antonsen S (2000) Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. Scand J Prim Health Care 18: 39-43.
28. Dahler Eriksen BS, Lauritzen T, Lassen JF, Lund ED, Brandslund I (1999) Near-patient test for C-reactive protein in general practice: assessment of clinical, organizational, and economic outcomes. Clin Chem 45: 478-485.
29. Putto A, Ruuskanen O, Meurman O (1986) C reactive protein in the evaluation of febrile illness. Arch Dis Child 61: 24–29.
30. Dinant GJ, Buntinx FF, Butler CC (2007) The necessary shift from diagnostic to prognostic research. BMC Fam Pract 8: 53.
31. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM (2010) Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med 8: 124-133.
32. Ten Oever J, Tromp M, Bleeker-Rovers CP (2012) Combination of biomarkers for the discrimination between bacterial and viral lower respiratory tract infections. J Infect 65: 490-495.
33. Salonen EM, Vaheri A (1981) C-Reactive protein in acute viral infections. J Med Virol 8: 161–167.
34. Sarov I, Shainkin-Kestenbaum R, Zimlichman R (1982) Serum amyloid A levels in patients with infections due to cytomegalovirus, varicella-zoster virus and Herpes simplex virus. J Infect Dis 146: 443.
35. Whicher JT, Chambers RE, Higginson J (1985) Acute phase response of serum amyloid A protein and C reactive protein to the common cold and influenza. J Clin Pathol 8: 312–316.
36. Melbye H, Hvidsten D, Holm A, Nordbø SA, Brox J (2004) The course of C-reactive protein response in untreated upper respiratory tract infection. Br J Gen Pract 54: 653-658.
37. Forster J, Schweizer M, Schumacher RF (1996) MxA protein in infants and children with respiratory tract infection. Acta Paediatr 85: 163–167.
38. Halminen M, Ilonen J, Julkunen I (1997) Expression of MxA protein in blood lymphocytes discriminates between viral and bacterial infections in febrile children. Pediatr Re. 41: 647–650.
39. Chieux V, Hober D, Harvey J (1998) The MxA protein levels in whole blood lysates of patients with various viral infections. J Virol Methods 70: 183–191.
40. Chieux V, Hober D, Chehadeh W (1999) MxA protein in capillary blood of children with viral infections. J Med Virol 59: 547–551.
41. Engelmann I, Dubos F, Lobert PE (2015) Diagnosis of viral infections using myxovirus resistance protein A (MxA). Pediatrics 135: e985-993.
42. Ivaska L, Niemelä J, Lempainen J (2017) Aetiology of febrile pharyngitis in children: Potential of myxovirus resistance protein A (MxA) as a biomarker of viral infection. J Infect 74: 385-392.
43. Simon A, Fah J, Haller O, Staeheli P (1991) Interferon-regulated Mx genes are not responsive to interleukin-1, tumor necrosis factor, and other cytokines. J Virol 65: 968–971.
44. Sambursky R, Shapiro N (2015) Diagnostic/laboratory methods other than molecular FebriDx: the ability of a 10-minute rapid point-of-care immunoassay to reduce antibiotic prescriptions for acute febrile respiratory infection.
45. Shapiro N, Drusano M, Rosen J (2015) A Prospective, Multicenter Clinical Evaluation of a Rapid Diagnostic Test to Detect Clinically Significant Immune Responses to Viral and Bacterial Acute Respiratory Infections. Open Forum Infect Dis 2: 882.