RPS

Right Diagnosis, Right Treatment, Right Now®

FebriDx®

AN RPS DIAGNOSTIC SOLUTION

FebriDx: Rapid POC test

- Rapid POC test that uses a fingerstick blood sample to aid in the diagnosis and management of patients with Acute Respiratory Infection (ARI)
  1. Diagnose a clinically significant acute respiratory infection
  2. Differentiates viral or bacterial acute respiratory infection

- Detects an elevation of specific blood proteins
  - Myxovirus resistance protein A (MxA) and C-reactive protein (CRP)
- Results in 10 minutes with hands-on procedure in 30 seconds
- FebriDx has the ability to identify a clinically significant immune response with a 99% NPV for bacterial infection
- Differentiates colonization from true systemic infection

Acute Respiratory Infection (ARI)

- More than 20% of the global population seek care annually for acute respiratory infection (ARI)[1]
- The clinical diagnosis of ARI is challenging
- Diagnostic uncertainty combined with patient pressures influences physicians to prescribe antibiotics for more than **50%** of ARIs,[2-3] despite a common viral etiology
- ***Unnecessary antibiotic prescriptions lead to antibiotic resistance, antibiotic allergies and toxicities, resulting in adverse events and higher costs***
- Lack of early detection and spread of disease
- Rising health care costs

[1] Gonzales R, Malone DC, Maselli JH, Sande MA. Clin Infect Dis 2001;33:757-62. [2] Rattinger GB, Mullins CD, Zuckerman IH, et al. A sustainable strategy to prevent misuse of antibiotics for acute respiratory infections. PLoS One 2012;7(12):e51147. [3] Ewig, S., and A. Torres. Curr. Opin. Crit. Care. 2002; 8:453-460

Implications of Antibiotic Overuse

- In the EU, antibiotic resistance is responsible for 25,000 deaths per year and 2.5 million extra hospital days[2]
- Adverse drug events (ADEs) caused by antibiotics are responsible for 20% of emergency department visits[1]
- Antibiotic resistance in the EU is estimated to cause an economic loss of €1.5 billion per year[2]
  - ADEs, including anaphylaxis, are estimated to increase hospital costs by €1,521 per patient[3]
  - *C. difficile* infections generate costs of €5-15K per case in the UK and up to €3Billion in Europe per year. Costs expected to double over the next 40 years.[4]

[1] Shehab N, Patel PR, Srinivasan A, Budnitz DS. Clin Infect Dis. 2008;47(6):735-43. [2] Estimates of Burden of Antibacterial Resistance. World Health Organization (WHO) Antimicrobial Resistance – Global Report on Surveillance 2014. [3] http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/data-and-statistics. [4] http://anaphylacticreactions.com/ReviewArt1.asp. [5] http://www.ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/clostridium_difficile_infection/pages/index.aspx.

Lord O'Neill's Assessment…

- Doctors still **prescribe antibiotics based only on their immediate assessment** of a patient's symptoms, just like they used when antibiotics entered common use in the 1950s
- When a test is used to confirm the diagnosis, it is often **based on a slow technology** that hasn't changed significantly since the 1860's
- There **aren't enough good and rapid tests** to confirm the professional judgement of the doctor
- …and **the tests** that are available today **are often more expensive than prescribing drugs 'just in case'**

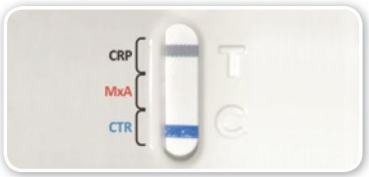
We need a STEP CHANGE
in the diagnostic technology available

FebriDx

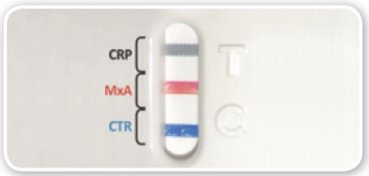
FEBRIDX TEST PROCEDURE

Lance finger	Collect blood sample	Deliver blood sample	Deliver blood solution
			

Viral infection



Bacterial infection



Viral infection

Negative results

Technology Utilizing Both MxA and CRP

MxA[1-4]

- Intracellular blood protein found in lymphocytes which is stimulated by type I interferon
- MxA levels remain low with bacterial infection
- Sensitive and specific marker for viral infection
  - Healthy people have a low concentration [less than 15 ng/ml][2,3]
  - Fast induction after infection [1-2 hours][2]
  - Peaks at 16 hours and remains elevated in the presence of elevated interferon[4]
  - Long half-life [2.3 days][2]

CRP[5-9]

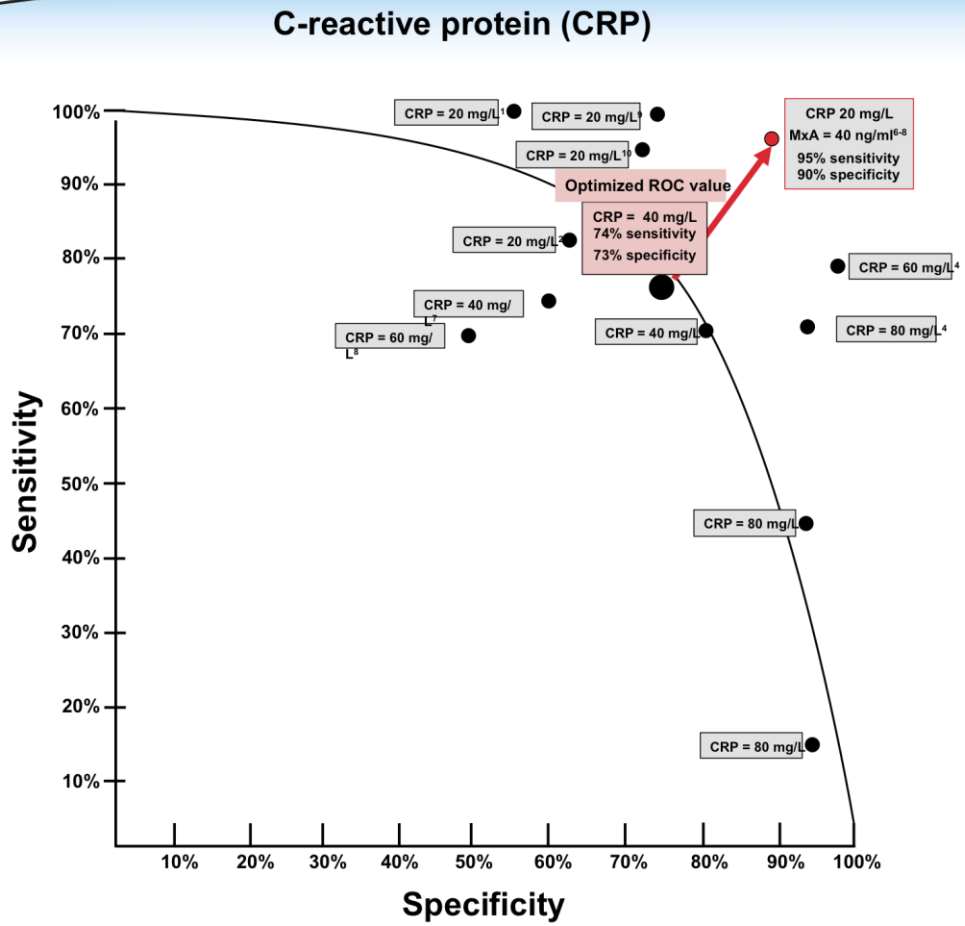
- Acute-phase protein synthesized by the liver
- Nonspecific marker for acute inflammation
- At low levels, CRP is very sensitive but nonspecific at confirming a bacterial infection
- At high levels, CRP becomes very specific for bacterial infection, but has low sensitivity
  - Bacterial infection is a potent stimulus
  - Elevates within 4-6 hours of infection and peaks after 26 hours[6-7]
  - Half-life is 18 hours[6-7]

FebriDx®

Together, MxA and CRP provide an accurate way to differentiate clinically significant viral from bacterial ARI

[1] [1] Haller O, Freese M, Kpchs G. Rev Sci Tech 1998;17(1):220-30. [2] Nakabayashi M, Adachi Y, Itazawa T, et al. Pediatr Res 2006;60:770-774. [3] Kawamura M, Kusano A, Furuya A, et al. J Clin Lab Anal 2012;26:174-183. [4] Goetschy JF, Zeller H, Content J. J Virol 1989;63:2616-2622 [5]] Falk G, Fahey T. Fam Prac 2009;26(1):10-21. [6] Andreola B, Bressan S, Callegaro S, et al. Ped Infect Dis J 2007;26(8):672-77. [7] Simon L, Gauvin F, Amre DK, et al. Clin Infec Dis 2004;39:206-17. [8] Salonen EM, Vaheri A. J Med Virol 1981;8(3):161-7. [9] Halminen M, Ilonen J, Julkunen I, et al. Pediatr Res 1997;41:647-50.

CRP + MxA Receiver Operator Curve



[1] Hatherill M, Tibby SM, Sykes K, et al. Arch Dis Child 1999;81:417-21. [2] Berger RM, Berger MY, van Steensel-Moll HA. Eur J Pediatr 1996;155:468-73. [3] Andreola G, Bressan S, Callegaro S. Pediatr Infect Dis J 2007;(8):672-7. [4] Liu A, Bui T, Van Nguyen H. Age Ageing 2010;559-65. [5] Korppi M, Kroger L. Scand J Infect Dis 1992;207-213. [6] Nakabayashi M, Adachi Y, Itazawa T, et al. Pediatr Res 2006;60:770-74. [7] Kawamura M, Kusano A, Furuya A, et al. J Clin Lab Anal 2012;26:174-183. [8] Engelmann I, Dubos F, Lobert PE, et al. Pediatrics 2015;135:e985-93.[7] Lala S, Madhi S, Pettifor J. The discriminative value of C-reactive protein levels in distinguishing between community-acquired bacteraemic and respiratory virus-associated lower respiratory tract infections in HIV-1-infected and -uninfected children. Ann Trop Pediatr. 2002;22:271–279. [8] Moulin F, Raymond J, Lorrot M, et al. Procalcitonin in children admitted to hospital with community acquired pneumonia. Arch Dis Child. 2001;84:332–336.[9] Putto A, Ruuskanen O, Meurman O, C reactive protein in the evaluation of febrile illness. Arch Dis Child. 1986 Jan;61(1):24-9. [10] Stolz D1, Christ-Crain M, Gencay MM, et al. Diagnostic value of signs, symptoms and laboratory values in lower respiratory tract infection. Swiss Med Wkly. 2006 Jul 8;136(27-28):434-40.

- In isolation, neither MxA nor CRP **independently** is sensitive or specific enough to differentiate viral from bacterial infection
  - At low levels, CRP is very sensitive but nonspecific at confirming a bacterial infection
  - At high levels, CRP becomes very specific for a bacterial infection but has low sensitivity
  - MxA is specific to identify viral infection only and is insensitive for the presence of bacterial infection

A MULTIPLEXED PATTERN OF RESULTS

Combining an MxA value with CRP provides an accurate way to differentiate **clinically significant** viral from bacterial acute respiratory infection.

Clinical Performance in Febrile Patients

A PROSPECTIVE, MULTICENTER CLINICAL EVALUATION OF A RAPID DIAGNOSTIC TEST TO DETECT CLINICALLY SIGNIFICANT IMMUNE RESPONSES TO VIRAL AND BACTERIAL ACUTE RESPIRATORY INFECTIONS

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- Two prospective, multi-center clinical trials
- Major inclusion criteria: age > 1 year, new fever ≥ 100.5ºF reported or exhibited within the past 3 days, and new onset of cough or sore throat within the past 7 days
- Major exclusion criteria included use of antibiotics, antiviral agents, interferon therapy, immunosuppressive therapy or a live viral immunization within the past 30 days

Sample size (n)	Fever (hyperthermia)	Clinical diagnosis	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]
121 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 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 Self et al.[3]	*Reported* within l ast 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

Reference Tests

Viral testing

- BioFire respiratory PCR panel
  - *Influenza A/B, Adenovirus, RSV, Parainfluenza, Metapneumovirus*
  - *Rhinovirus and Coronavirus associated with elevated MxA ELISA*
- *Additional PCR testing for HSV and CMV*
- *Serum Epstein-Barr IgM/IgG*

Bacterial testing

- BioFire respiratory PCR panel
  - *Chlamydia pneumoniae, mycoplasma pneumoniae, Bordetella pertussis*
- PCR for Fusobacterium and Neisseria
- Throat culture

Laboratory testing

- Procalcitonin
- White blood cell count (WBC)

Source: Self WH, Rosen J, Sharp SC, Filbin MR, Hou PC et al. Diagnostic Accuracy of FebriDx: A Rapid Test to Detect Immune Responses to Viral and Bacterial Upper Respiratory Infections J. Clin. Med. 2017;6: 94. Shapiro N, Self WH, Rosen J, Sharp SC, Filbin MR, Hou PC et al. A Prospective, Multi-Center US Clinical Trial to Determine Accuracy of FebriDx Point-of-Care Testing for Acute Upper Respiratory Infections With and Without a Confirmed Fever 2018. Submitted

UK Outcome Study 2017 Results

Introduction

- 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

Results

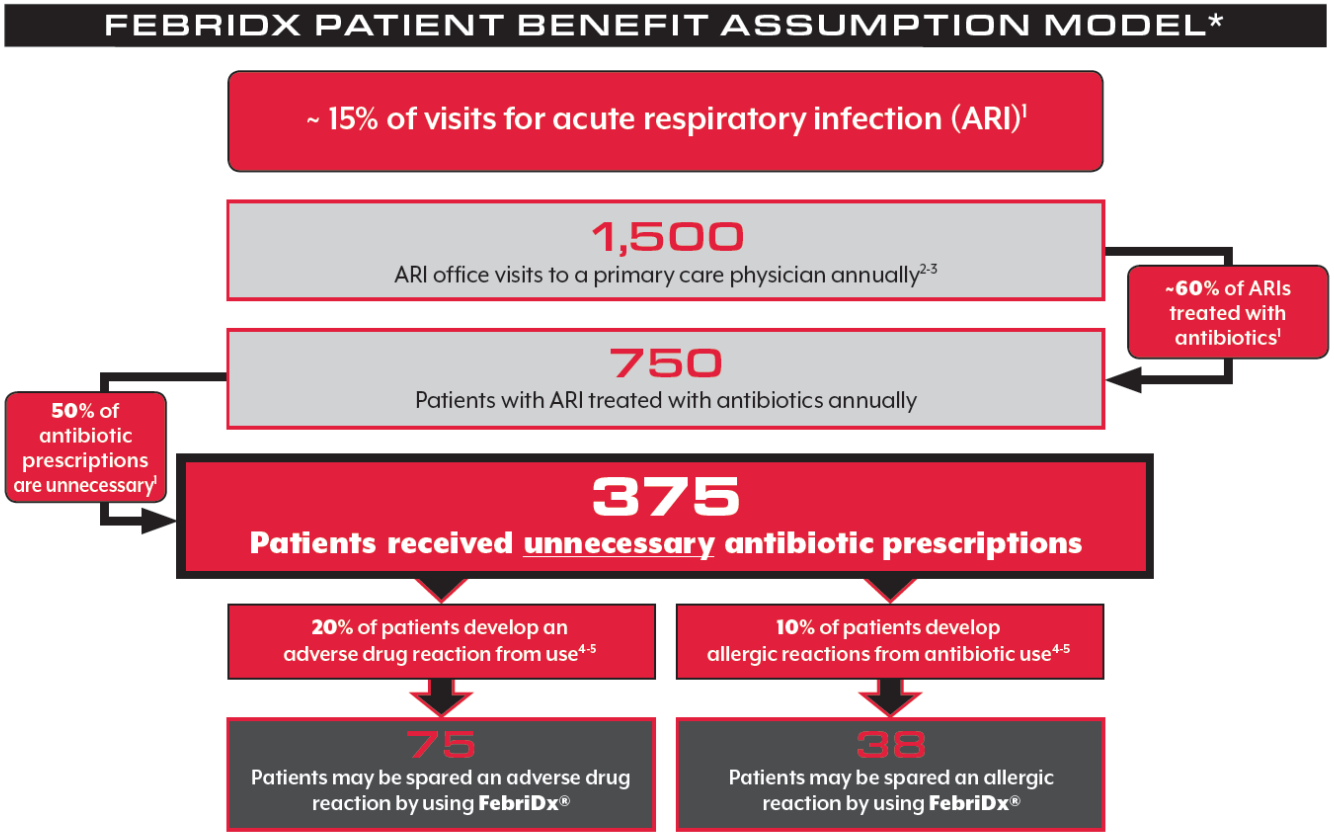
- Mean age of 46.3 years, ranging in age from 3 years to 84 years old
- Clinical diagnoses of nonspecific upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI)
- One patient discharged from a hospital with a presumed viral infection but confirmed bacterial sepsis with FebriDx
- **FebriDx altered clinical management in 48% (10/21) and reduced unnecessary antibiotic prescriptions in 80% (8/10)**
- **All of the patients demonstrated full clinical recovery without additional unscheduled medical consultations or subsequent newly initiated antibiotic prescriptions**

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

Davidson M (2017) FebriDx Point-of-Care Testing to Guide Antibiotic Therapy for Acute Respiratory Tract Infection in UK Primary Care: A Retrospective Outcome Analysis. J Infect Dis Preve Med 5: 165.

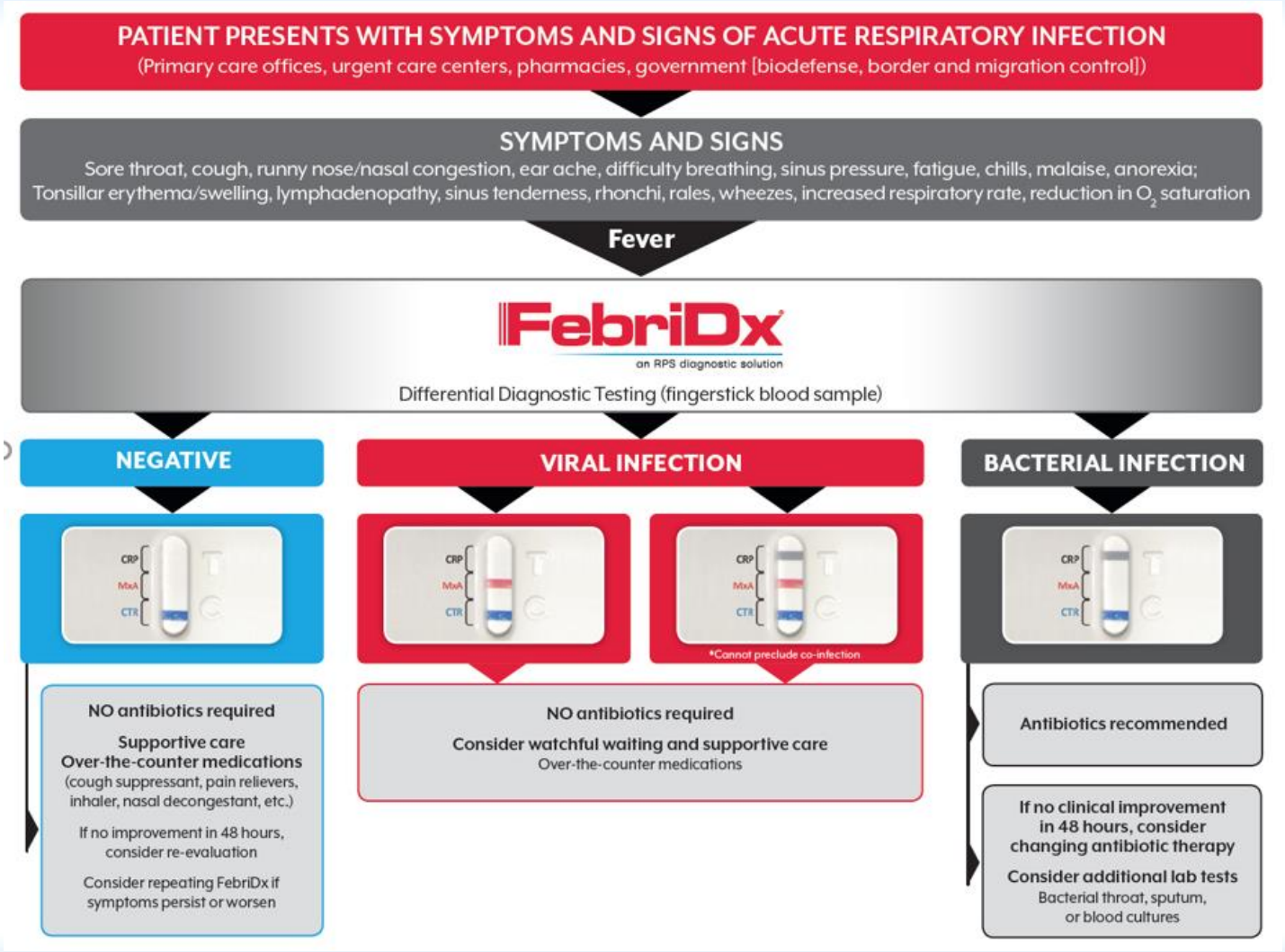
Patient Benefit Model



*Numbers are estimates and refer to annual prevalence.

1] Harris AM, Hicks LA, Qaseem A, for the High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164:425–434. [2] BMA. org.UK - General practice in the UK – Briefing 2017. [3] European Forum for Pimary care. http://www.euprimarycare.org/column/primary-care-Germany. [4] Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008;47:735-43. [5] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372:825-34.

Out Patient management of ARI



Rapid Point-of-Care Triage Solution

FebriDx
an RPS diagnostic solution

① **Identify clinically significant acute respiratory infection in 10 minutes**

② **Differentiate viral from bacterial etiology**

- ✓ ***99% NPV for bacterial infection****

③ **Differentiate systemic infection from colonization/carrier state**

Improving antibiotic stewardship in the healthcare setting

*NPV – negative predictive value is the probability that subjects with a negative screening test truly don't have the disease