Rapid diagnostic tests for infectious diseases in the emergency department

Donia Bouzid, Marie-Céline Zanella, Solen Kerneis, Benoit Visseaux, Larissa May, Jacques Schrenzel, Vincent Cattoir

To cite this version:

Donia Bouzid, Marie-Céline Zanella, Solen Kerneis, Benoit Visseaux, Larissa May, et al.. Rapid diagnostic tests for infectious diseases in the emergency department. Clinical Microbiology and Infection, Elsevier for the European Society of Clinical Microbiology and Infectious Diseases, In press, 10.1016/j.cmi.2020.02.024 . hal-02499280

HAL Id: hal-02499280
https://hal-univ-rennes1.archives-ouvertes.fr/hal-02499280
Submitted on 27 Apr 2020
Rapid diagnostic tests for infectious diseases in the emergency department

Running title: RDTs in the ED

Donia BOUZID\textsuperscript{1,2\#}, Marie-Céline ZANELLA\textsuperscript{3,4 \#}, Solen KERNEIS\textsuperscript{2,5,6}, Benoît VISSEAUX\textsuperscript{2,7}, Larissa MAY\textsuperscript{8}, Jacques SCHRENZEL\textsuperscript{3,4,9}, Vincent CATTOIR\textsuperscript{10,11,12\*}

\# These authors contributed equally to this work

\textsuperscript{1} AP-HP, Bichat Claude Bernard Hospital, Emergency Department, Paris, France

\textsuperscript{2} University of Paris, IAME, INSERM, Paris, France

\textsuperscript{3} Laboratory of Bacteriology, Division of Laboratory Medicine and Division of Infectious Diseases, University of Geneva Hospitals, Geneva, Switzerland

\textsuperscript{4} University of Geneva Medical School, Geneva, Switzerland

\textsuperscript{5} AP-HP, Antimicrobial Stewardship Team, Hôpitaux Universitaires Paris Centre-Cochin, Paris, France

\textsuperscript{6} Pharmacoépidémiology and infectious diseases (Phemi), Pasteur Institute, Paris, France

\textsuperscript{7} AP-HP, Bichat Claude Bernard Hospital, Virology, 75018, Paris, France

\textsuperscript{8} Department of Emergency Medicine, University of California-Davis, Sacramento, CA, USA

\textsuperscript{9} Genomic Research Laboratory, Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland

\textsuperscript{10} Service de Bactériologie-Hygiène hospitalière, CHU de Rennes, Rennes, France
24  CNR de la Résistance aux Antibiotiques (laboratoire associé 'Entérocoques), Rennes, France

26  Unité Inserm U1230, Université de Rennes 1, Rennes, France

28  *Correspondance: Prof. Vincent Cattoir, CHU de Rennes, Service de Bactériologie-Hygiène hospitalière, 2 rue Henri Le Guilloux, 35033 Rennes Cedex, France. +33-2-99-28-98-28, Fax: +33-2-99-28-41-59, E-mail: vincent.cattoir@chu-rennes.fr.

32  Keywords: Rapid diagnosis; Infections; RDT; POC test; ED; Clinical impact.

34  Word count: Abstract: 242 words; Text = 2,509 words; 2 Tables; 80 References.
Abstract

Background: Rapid diagnostic tests (RDTs) for infectious diseases, with a turn-around time <2 hours, are promising tools that could improve patient care, antimicrobial stewardship and infection prevention in the emergency department (ED) setting. Numerous RDTs have been developed but not necessarily for the ED environment. Their successful implementation in the ED relies on their performance and impact on patient management.

Objectives: The aim of this narrative review is to provide an overview of currently available RDTs for infectious diseases in the ED.

Sources: PubMed was searched through August 2019 for available studies on RDTs for infectious diseases. Inclusion criteria included: commercial tests approved by the FDA or CE-IVD with data on clinical samples, ability to run on fully-automated systems and result delivery within 2 hours.

Content: A non-exhaustive list of representative commercially available FDA or CE approved assays was categorized by clinical syndrome: pharyngitis and upper respiratory tract infection, lower respiratory tract infection, gastrointestinal infection, meningitis and encephalitis, fever in the returning traveler and sexually-transmitted infection including HIV. The performance of tests was described based on clinical validation studies. Further, their impact on clinical outcomes and anti-infective use was discussed with a focus on ED-based studies.

Implications: Clinicians should be familiar with the distinctive features of each RDT and individual performance characteristics for each target. Their integration into ED workflow should be pre-planned considering local constraints of given settings. Additional clinical studies are needed to further evaluate their clinical and cost effectiveness.
I. Introduction

Rapid diagnostic tests (RDTs) for infectious diseases have recently been implemented in many laboratories and emergency departments (EDs) with the goal of expediting the diagnosis of infectious diseases, infection prevention, appropriate initial management, and to facilitate antimicrobial stewardship in the ED where rapid clinical decisions must be undertaken in the context of overcrowding and time pressures [1]. Even though multiple RDTs are currently available, their successful implementation in the ED requires careful assessment of performance characteristics, potential benefits to patient care and cost considerations, as well as a well-organized implementation plan to optimize their impact [2]. The goal of this narrative review is to provide an overview of currently available RDTs for infectious diseases in the ED with a detailed description of their performance and to discuss their impact on patient care.

II. Methods

A comprehensive PubMed search was conducted through August 2019 to identify studies on RDTs for infectious diseases in ED department using the following MeSH and keywords: “RDT”, “Point of care”, “Panel”, “Turnaround time <2hrs”, “ED”, “Emergency service”, “Pharyngitis”, “Respiratory tract infection”, “URTI”, “LRTI”, “Influenza”, “RSV”, “Urinary antigen”, “Pneumococcal urinary antigen”, “Legionella urinary antigen”, “Gastrointestinal infection”, “Central nervous system infection”, “Meningitis”, “encephalitis”, “Fever returning traveller”, “Sexually transmitted infection” and “STI”.

Inclusion criteria were: commercial tests approved by the FDA or CE-IVD with data published on clinical samples, ability to run on fully-automated systems and result delivery within 2 hours, as supported by Drancourt et al. [3]. Assay performance characteristics including sensitivity and specificity are outlined based on published clinical validation studies, whenever available. In the absence of test comparison against a gold standard assay, the reported positive and negative percent agreement in identified clinical studies or manufacturer performance data were not reported to avoid any misinterpretation.

III. Overview of available tests

A non-exhaustive list of representative commercially available FDA or CE approved RDTs is provided in Table 1 [4-39]. Of note, all assays discussed in this review are qualitative assays. When available, we describe the evidence for impact of tests on clinical outcomes and anti-infective use in the ED (Table 2) [6, 32, 40-55].

II.1. Pharyngitis and upper respiratory tract infections

Upper respiratory tract infection is the leading infectious cause of visits in the ED. In patients with pharyngitis, clinical scoring systems and rapid tests are recommended to target antibiotic use. For group A streptococcus (GAS) pharyngitis diagnosis an immunofluorescence-based assay recently demonstrated higher diagnostic performances compared to an immunochromatographic rapid antigen detection test (RADT) in pediatric patients presenting with pharyngitis with a McIsaac score ≥2; the negative predictive value (NPV) of
the immunofluorescence-based assay was also higher (92%) in this pediatric population with a GAS prevalence of 37% [4]. In patients with a high likelihood of streptococcal infection, guidelines recommend the use of RDTs as they are associated with decreased antibiotic use in pediatric ED populations [56]. However, the utility of clinical scores in children appears to be lower than for adults due to the different clinical presentation of sore throat in infants and young children. Point-of-care PCR assays demonstrated improved performance compared to culture or RADT as well reduced unnecessary antibiotic use in a pediatric study [5-7]. In patients with ILI (influenza-like illness), implementation of the FILMARRAY® multiplex PCR respiratory panel in the ED was associated with shorter times to diagnosis for all respiratory viruses, shorter duration of antibiotic use, decreased hospitalization rates, shortened length of stay (LOS), and reduced costs [41, 45]. A recent meta-analysis evaluated the clinical impact of molecular RDTs for respiratory viruses by analyzing 56 individual test accuracy studies and showed that, in comparison to conventional molecular assays, RDTs did not reduce antibiotic use and duration, isolation measures or admission rates, but increased use of oseltamivir in influenza positive cases and reduced LOS [57].

II.2. Lower respiratory tract infections

The most frequent LRTIs seen in the ED include: acute bronchitis, community-acquired pneumonia (CAP), ILI and acute COPD (chronic obstructive pulmonary disease) exacerbation. Current guidelines recommend that urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 antigens should be performed for CAP patients with severe illness and for legionellosis when clinically or epidemiologically suspected. Rapid
multiplex PCR tests from nasopharyngeal swabs for atypical bacteria and respiratory viruses should also be considered.

II.2.1. RDTs performed on urine specimens

Rapid urine antigen tests are widely used for the diagnosis of *S. pneumoniae* and *L. pneumophila* respiratory infections. Rapid tests for *S. pneumoniae* detection present sensitivities ranging from 62 to 66% as compared to blood or sputum culture [8]. The performance of *L. pneumophila* urinary antigen detection tests varies according to several factors [9, 58]: (i) assay type, with improved performance for immunofluorescence tests; (ii) sample type, clinical vs. simulated urine samples prepared with strains of *L. pneumophila* serogroup 1 are best detected; (iii) pre-analytic sample processing; (iv) serogroup, with higher sensitivities for *L. pneumophila* serogroup 1. False-positive results can be due to recent *L. pneumophila* or *S. pneumoniae* past infection or pneumococcal vaccination, respectively, warranting cautious interpretation in the absence of concomitant cultures. According to guidelines, antibiotic treatment should be initiated immediately after CAP diagnosis and include empiric therapy of *S. pneumoniae*. Rapid microbiologic confirmation theoretically offers the opportunity for antibiotic de-escalation. However, in practice, the poor sensitivity and specificity of urinary antigen testing for *S. pneumoniae* [48,59] do not allow such de-escalation, and a large proportion of patients remain treated with broader-spectrum antibiotics [49,60,61].

II.2.2 RDTs performed on respiratory specimens

Among panels developed for broad respiratory virus detection from nasopharyngeal samples, several are now available on a fully automatized system with turn-around times (TAT) around 1 hour (Table 1). They allow the detection of all the most common respiratory
viruses and some atypical bacteria: *Bordetella pertussis*, *Bordetella parapertussis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Analytical performance characteristics, compared to reference PCR assays, are good to excellent (sensitivity and specificity from 80 to 100% for all targets). Of note, some bacterial targets have been validated with fewer than 10 positive samples, and performance characteristics of bacterial PCR have sometimes been reported to be lower than those of viral PCR [19], highlighting the need for caution when interpreting cumulative performance results. Furthermore, the performance of some panels (Table 1) only consist of percent agreement, which represents a strong- and maybe underappreciated – limitation.

For the diagnosis of LRTIs in the ED, a short TAT is a key parameter for relevant therapeutic measures, when targeted treatments and specific infection-prevention measures exist, such as for RSV or influenza [62].

II.3. **Gastrointestinal (GI) infections**

The rapid diagnosis of *Clostridium difficile* infection (CDI) is often based on a 2- or 3-stage diagnostic approach using specific GDH antigen with enzyme immunoassays (EIA), amplification of toxin A/B genes by PCR and detection of toxins A/B by EIA (Table 1). No other enteric bacteria or virus dispose of sensitive rapid diagnostic method except for gastrointestinal multiplex PCR panels. Their performances should be considered separately for each target, and as other syndromic panels, validation studies of some assays were performed among populations with low prevalence of certain targets including *Vibrio* spp., *Entamoeba histolytica*, *Yersinia enterolitica* [26]; an important consideration for interpretation of negative results.
Very few data have been published on the clinical impact of RDTs for the diagnosis of GI infections in the ED. Additional research is needed to evaluate their impact and cost effectiveness, especially for costly, but POC-friendly, rapid multiplex PCR assays [50,51].

II.4. Meningitis and encephalitis

Pneumococcal antigen and cryptococcal antigen detection through immunochromatographic technology are marketed to be used in cerebrospinal fluid samples, with excellent performance and short TAT [27].

To date, only one fully-automatized rapid multiplex PCR system is available, the FilmArray ME panel (BioFire, bioMérieux), which provides results in about one hour. Common bacteria and viruses are detected, as well as the yeast C. neoformans/gattii (Table 1). Performances have been evaluated retrospectively [30,63]. Both false positive and false negative results are possible, and thus all biological and clinical parameters should be taken into account for result interpretation, especially for uncommon targets such as Cryptococcus [64]. These panels are also not intended to be fully exhaustive of all possible pathogens. Finally Listeria monocytogenes was not tested during the clinical validation study, necessitating specific PCR or cultures if there a high index of suspicion [30].

No data are available today on the impact of RDTs on the management of patients with suspicion of meningitis/encephalitis in the ED. A retrospective analysis of 145 pediatric cases of meningitis showed that 20% of infants were discharged in <24 h after an enterovirus-positive result, highlighting some potential benefits of rapid syndromic testing [65]. Further investigation of this approach is needed, especially in adults.
II.5. Fever in the returning traveler

Malaria RDTs are critically needed for patients returning from endemic countries. Around 90% of cases occur in the WHO African region with *Plasmodium falciparum* being the most prevalent species and accounting for nearly all the mortality. Malaria is diagnosed by three categories of tools: expert light microscopy; immunochromatographic tests (ICTs); and nucleic acid amplification tests (NAATs) [66]. Light microscopy is widely used but requires highly-trained staff. ICTs are cheap and have a sensitivity of minimum 95% compared to microscopy and a specificity of >90% for all *Plasmodium* species [67]. Note that the BinaxNOW malaria test (Alere), able to detect the four *Plasmodium* species, is the only ICT approved by the FDA. Currently, no PCR-based RDT is commercially available. Nonetheless, a LAMP-based molecular test (Malaria LAMP assay; illumigene M; Meridian Biosciences) is commercially available [68]. In a recent prospective trial in returning travelers, this approach showed excellent analytical performance vs microscopy with near 100% accuracy [32].

With 96 million dengue infections per year in over 100 tropical and sub-tropical countries with nonspecific symptoms, rapid and accurate testing is important. Unfortunately, rapid ICTs detecting both NS1 antigen and IgM have relatively low performance profiles. Their use should be limited to strong clinical suspicion and confirmed by ELISA or PCR assays [33]. There is a need for “multiplex testing” for other arboviruses, e.g. Zika and Chickungunya, that have resulted in large outbreaks.

II.6. Sexually-transmitted infections and HIV infection

Many patients seek to EDs for initial care of sexually transmitted infections (STIs). POC testing of STIs could allow treating cases during the initial clinical visit and thus improving adherence to treatment and further transmissions. For syphilis, available RDTs consist of
lateral flow immunoassays (LFIAs) detecting treponemal antibodies but unable to distinguish treated from active infection, leading to the risk of overtreatment. However, they may be useful in resource limited settings to avoid congenital syphilis, to reduce neonatal mortality and decrease disease transmissions [69].

Some RDT assays allow the individual or simultaneous detection of *C. trachomatis* and *N. gonorrhoeae*, with varying performance depending on clinical specimen type (Table 1) [34, 35]. Only simultaneous detection will be discussed in this review since dual testing is most clinically relevant. In the ED context, POC testing significantly decreases overtreatment of gonorrhea and trichomoniasis compared to NAAT testing [70]. Implementation of rapid testing for chlamydia and gonorrhea directly from triage using self-collected specimens can dramatically reduce overtreatment [34, 54]. In the future, to significantly reduce the STI burden, particularly for *N. gonorrhoeae* and *M. genitalium* infections, a combination of rapid POC diagnostic and antimicrobial resistance testing will likely be needed.

Multiple manufacturers have also developed rapid ICTs for HIV diagnosis. Performance evaluations are generally carried out on plasma or serum but not finger-stick whole blood. Their use should also be cautious in the context of patients with primary infection or wide HIV diversity (HIV-1, HIV-2, HIV-O). Indeed, a recent study demonstrated excellent performance (sensitivity of 100% and specificity >98.5%) for chronically infected patients but with inconsistent results for primary infected patients, even for tests detecting both HIV specific antibodies and p24 antigen [39]. These tests may rarely be falsely negative among HIV positive patients already on antiretroviral therapy [71,72]. While HIV POC testing in the ED has no immediate impact on stewardship, it increases screening rates, general disease awareness and prompt referral to an HIV specialist [73].
III. Antimicrobial stewardship and health economics

Most EDs face overcrowding, and POC tests may facilitate discharging or admitting patients more quickly and improving ED throughput while decreasing length of stay (LOS). Various clinical studies have demonstrated a significant impact on reducing antimicrobial duration when rapid diagnostic tests are employed in the ED [54, 74-76]. Conversely, others have failed to obtain such reduction, especially in complex healthcare environments [41, 43]. In this context, multidisciplinary diagnostic stewardship is essential, which refers to the appropriate use of laboratory testing to guide patient management, including treatment, in order to optimize patient outcomes and antibiotic use [77]. Indeed, implementation of new RDTs should rely on multidisciplinary approaches and high-quality evidence supporting their clinical validation and impact.

Currently, there is limited data on health economic outcomes related to use of POC tests in the ED, and several of the published studies are based on simulation only [78]. Reductions in ED LOS, wait time and the number of clinic visits required to receive results were reported [79].

IV. Workflow and implementation

Appropriate integration of RDTs into the clinical environment is often an overlooked component. Pragmatically, successful implementation depends on three key questions: Who will perform the test? What is the optimal time point of specimen collection? Where should the sample be processed? Questions on appropriate timing and who should be in charge are directly related to the ultimate goal of testing. If the primary objectives are prompt isolation (e.g., POC tests for detection of influenza in patients with ILI), quick administration of anti-
infective drugs in critical patients (e.g., malaria in febrile returning traveler) or improved patient throughput, testing might be performed by triage nurses, based on precise and simple clinical case definitions. Conversely, other tests require more complex interpretation or sampling such as LRTI panels and should thus be limited to confirmed pneumonia patients. Training for assay implementation is strongly required, and additional human resources may be needed for timely integration into ED workflow. Clinicians also need to receive regular training on indications and interpretation of RDT results in collaboration with clinical microbiologists [80]. Finally, with the rapid expansion of RDTs in the ED for both infectious and noninfectious syndromes, space and time constraints for instruments should also be anticipated.

V. Conclusions

This review provides a non-exhaustive overview of currently commercially available FDA and CE RDTs for infectious diseases in the ED. Most of these assays display adequate analytical performance yet additional high-quality studies are needed to better assess their impact. These assays must be appropriately integrated into ED workflow, taking into account local constraints and priorities. Furthermore, RDTs cannot yet replace conventional methods since they are not exhaustive, have performance limitations, and provide limited data on antimicrobial susceptibility profiles. Finally and most importantly, their clinical and economic impact remains uncertain: there is a need to conduct rigorous studies such as randomized controlled clinical trials, to determine their actual impact on clinical management and outcomes such as time to optimal therapy, length of ED or hospital stay, cost effectiveness, mortality, as well as their role in antimicrobial stewardship interventions.
Author’s contribution

MCZ, JS and VC conceived the study. DB and MCZ wrote the first draft. All authors commented on, or edited drafts and approved the final version of the manuscript.

Transparency declaration

VC reports personal fees from Accelerate Diagnostics, Astellas, bioMérieux, Correvio, Curetis, Eumedica, Menarini, Mylan, Pfizer and Sanofi. SK reports personal fees from Accelerate Diagnostics, bioMérieux and MSD. BV reports personal fees from bioMérieux and Qiagen, and grant from Stat-Dx. LM reports personal fees from Cepheid, Roche, Bio-Rad and Qvella, and research grants from BioFire Diagnostics and Roche. DB, MCZ and JS report no conflicts of interest.

Funding information

No external funding was received for this work.
References

1. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PLoS One 2018;13:e0203316.
2. Clerc O, Greub G. Routine use of point-of-care tests: usefulness and application in clinical microbiology. Clin Microbiol Infect 2010;16:1054-61.
3. Drancourt M, Michel-Lepage A, Boyer S, Raoult D. The point-of-care laboratory in clinical microbiology. Clin Microbiol Rev 2016;29:429-47.
4. Lacroix L, Cherkaoui A, Schaller D, Manzano S, Galetto-Lacour A, Pfeifer U, et al. Improved Diagnostic Performance of an Immunofluorescence-based Rapid Antigen Detection Test for Group A Streptococci in Children With Pharyngitis. Pediatr Infect Dis J 2018;37:206-11.
5. Faron ML, Ledeboer NA, Granato P, Daly JA, Pierce K, Pancholi P, et al. Detection of Group A Streptococcus in Pharyngeal Swab Specimens by Use of the AmpliVue GAS Isothermal Helicase-Dependent Amplification Assay. J Clin Microbiol 2015;53:2365-7.
6. Rao A, Berg B, Quezada T, Fader R, Walker K, Tang S, et al. Diagnosis and antibiotic treatment of group a streptococcal pharyngitis in children in a primary care setting: impact of point-of-care polymerase chain reaction. BMC Pediatr 2019;19:24.
7. Ralph AP, Holt DC, Islam S, Osowicki J, Carroll DE, Tong SYC, et al. Potential for Molecular Testing for Group A Streptococci to Improve Diagnosis and Management in a High-Risk Population: A Prospective Study. Open Forum Infect Dis 2019;6:ofz097.
8. Euser SM, Badoux P, Kracht-Kosten L, Yzerman EPF. Evaluation of the Sofia Streptococcus pneumoniae FIA test for the detection of S. pneumoniae antigen in urine. J Med Microbiol 2018;67:1743-6.
9. Helbig JH, Uldum SA, Luck PC, Harrison TG. Detection of Legionella pneumophila antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax Legionella Urinary Enzyme Immunoassay (EIA) and Biotest Legionella Urin Antigen EIA. J Med Microbiol 2001;50:509-16.
10. Ratliff AE, Duffy LB, Waites KB. Comparison of the illumigene Mycoplasma DNA amplification assay and culture for detection of Mycoplasma pneumoniae. J Clin Microbiol 2014;52:1060-3.
11. Chen L, Tian Y, Chen S, Liesenfeld O. Performance of the Cobas((R)) Influenza A/B Assay for Rapid PCR-Based Detection of Influenza Compared to Prodesse ProFlu+ and Viral Culture. Eur J Microbiol Immunol (Bp) 2015;5:236-45.
12. Valentin T, Kieslinger P, Stelzl E, Santner BI, Groselj-Strele A, Kessler HH, et al. Prospective evaluation of three rapid molecular tests for seasonal influenza in patients presenting at an emergency unit. J Clin Virol 2019;111:29-32.
13. Lee CK, Cho CH, Woo MK, Nyeck AE, Lim CS, Kim WJ. Evaluation of Sofia fluorescent immunoassay analyzer for influenza A/B virus. J Clin Virol 2012;55:239-43.
14. Peters RM, Schnee SV, Tabatabai J, Schnitzler P, Pfeil J. Evaluation of Alere i RSV for Rapid Detection of Respiratory Syncytial Virus in Children Hospitalized with Acute Respiratory Tract Infection. J Clin Microbiol 2017;55:1032-6.
15. Gibson J, Schechter-Perkins EM, Mitchell P, Mace S, Tian Y, Williams K, et al. Multi-center evaluation of the cobas((R)) Liat((R)) Influenza A/B & RSV assay for rapid point of care diagnosis. J Clin Virol 2017;95:5-9.
16. Popowitch EB, Miller MB. Performance Characteristics of Xpert Flu/RSV XC Assay. J Clin Microbiol 2015;53:2720-1.
17. Pierce VM, Elkan M, Leet M, McGowan KL, Hodinka RL. Comparison of the Idaho Technology FilmArray system to real-time PCR for detection of respiratory pathogens in children. J Clin Microbiol 2012;50:364-71.
18. Loeffelholz MJ, Pong DL, Pyles RB, Xiong Y, Miller AL, Bufton KK, et al. Comparison of the FilmArray Respiratory Panel and Prodesse real-time PCR assays for detection of respiratory pathogens. J Clin Microbiol 2011;49:4083-8.
19. Leber AL, Everhart K, Daly JA, Hopper A, Harrington A, Schreckenberger P, et al. Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples. J Clin Microbiol 2018;56.
20. Babady NE, England MR, Juric Smith KL, He T, Wijetunge DS, Tang YW, et al. Multicenter Evaluation of the ePlex Respiratory Pathogen Panel for the Detection of Viral and Bacterial Respiratory Tract Pathogens in Nasopharyngeal Swabs. J Clin Microbiol 2018;56.
21. Pancholi P, Kelly C, Raczkowski M, Balada-Llasat JM. Detection of toxigenic Clostridium difficile: comparison of the cell culture neutralization, Xpert C. difficile, Xpert C. difficile/Epi, and Illumigene C. difficile assays. J Clin Microbiol 2012;50:1331-5.
22. Dalpke AH, Hofko M, Zorn M, Zimmermann S. Evaluation of the fully automated BD MAX Cdiff and Xpert C. difficile assays for direct detection of Clostridium difficile in stool specimens. J Clin Microbiol 2013;51:1906-8.

23. Peterson LR, Young SA, Davis TE, Jr., Wang ZX, Duncan J, Noutsios C, et al. Evaluation of the cobas Cdiff Test for Detection of Toxigenic Clostridium difficile in Stool Samples. J Clin Microbiol 2017;55:3426-36.

24. Sloan LM, Duresko BJ, Gustafson DR, Rosenblatt JE. Comparison of real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in diagnosis of Clostridium difficile infection. J Clin Microbiol 2008;46:1996-2001.

25. Eastwood K, Else P, Charleott A, Wilcox M. Comparison of nine commercially available Clostridium difficile toxin detection assays, a real-time PCR assay for C. difficile tcdB, and a glutamate dehydrogenase detection assay to cytotoxin testing and cytotoxigenic culture methods. J Clin Microbiol 2009;47:3211-7.

26. Buss SN, Leber A, Chapin K, Fey PD, Bankowski MJ, Jones MK, et al. Multicenter evaluation of the BioFire FilmArray gastrointestinal panel for etiologic diagnosis of infectious gastroenteritis. J Clin Microbiol 2015;53:915-25.

27. Binnicker MJ, Jespersen DJ, Bestrom JE, Rollins LO. Comparison of four assays for the detection of cryptococcal antigen. Clin Vaccine Immunol 2012;19:1988-90.

28. Marcos MA, Martinez E, Almela M, Mensa J, Jiménez de Anta MT. New rapid antigen test for diagnosis of pneumococcal meningitis. Lancet 2001;357:1499-500.

29. Capaul SE, Gorgievski-Hrisoho M. Detection of enterovirus RNA in cerebrospinal fluid (CSF) using NucliSens EasyQ Enterovirus assay. J Clin Virol 2005;32:236-40.

30. Leber AL, Everhart K, Balada-Llasat JM, Cullison J, Daly J, Holt S, et al. Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens. J Clin Microbiol 2016;54:2251-61.

31. Dimaio MA, Pereira IT, George TI, Banaei N. Performance of BinaxNOW for diagnosis of malaria in a U.S. hospital. J Clin Microbiol 2012;50:2877-80.

32. Cheaveau J, Nguyen H, Chow B, Marasinghe D, Mohon AN, Yuan H, et al. Clinical Validation of a Commercial LAMP Test for Ruling out Malaria in Returning Travelers: A Prospective Diagnostic Trial. Open Forum Infect Dis 2018;5:ofy260.

33. Hunsperger EA, Yoksan S, Buchy P, Nguyen VC, Sekaran SD, Enria DA, et al. Evaluation of commercially available diagnostic tests for the detection of dengue virus NS1 antigen and anti-dengue virus IgM antibody. PLoS Negl Trop Dis 2014;8:e3171.

34. Gaydros CA, Van Der Pol B, Jett-Gooheen M, Barnes M, Quinn N, Clark C, et al. Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. J Clin Microbiol 2013;51:1666-72.

35. Iwen PC, Walker RA, Warren KL, Kelly DM, Hinrichs SH, Linder J. Evaluation of nucleic acid-based test (PACE 2C) for simultaneous detection of Chlamydia trachomatis and Neisseria gonorrhoeae in endocervical specimens. J Clin Microbiol 1995;33:2587-91.

36. Diaz T, Almeida MG, Georg I, Maia SC, De Souza RV, Markowitz LE. Evaluation of the Determine Rapid Syphilis TP assay using sera. Clin Diag Lab Immunol 2004;11:98-101.

37. Benzaken AS, Sabido M, Galban EG, Pedroza V, Vasquez F, Araujo A, et al. Field evaluation of the performance and testing costs of a rapid point-of-care test for syphilis in a red-light district of Manaus, Brazil. Sex Transm Infect 2008;84:297-302.

38. Li J, Zheng HY, Wang LN, Liu YX, Wang XF, Liu XR. Clinical evaluation of four recombinant Treponema pallidum antigen-based rapid diagnostic tests for syphilis. J Eur Acad Dermatol Venereol 2009;23:648-50.

39. Mourez T, Lemee V, Delbos V, Delaugerre C, Alessandri-Gradet E, Etienne M, et al. HIV rapid screening tests and self-tests: Be aware of differences in performance and cautious of vendors. EBioMedicine 2018;37:382-91.

40. Kose E, Sirin Kose S, Akca D, Yildiz K, Elmas C, Baris M, et al. The Effect of Rapid Antigen Detection Test on Antibiotic Prescription Decision of Clinicians and Reducing Antibiotic Costs in Children with Acute Pharyngitis. J Trop Pediatr 2016;62:308-15.

41. Rogers BB, Shankar P, Jerris RC, Kotzbauer D, Anderson EJ, Watson JR, et al. Impact of a rapid respiratory panel test on patient outcomes. Arch Pathol Lab Med 2015;139:636-41.

42. Brendish NJ, Malachira AK, Armstrong L, Houghton R, Aitken S, Nyimbili E, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med 2017;5:401-11.

43. Andrews D, Chetty Y, Cooper BS, Virk M, Glass SK, Letters A, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a...
47. Davis S, Allen AJ, O’Leary R, Power M, Price DA, Simpson AJ, et al. Diagnostic accuracy and cost analysis of the Alere i Influenza A&B near-patient test using throat swabs. J Hosp Infect 2017;97:301-9.

48. Bellew S, Grijalva CG, Williams DJ, Anderson EJ, Wunderink RG, Zhu Y, et al. Pneumococcal and Legionella Urinary Antigen Tests in Community-acquired Pneumonia: Prospective Evaluation of Indications for Testing. Clin Infect Dis 2018;66:2026-33.

49. Dinh A, Duran C, Davido B, Lagrange A, Sivadon-Tardy V, Bouchand F, et al. Cost effectiveness of pneumococcal urinary antigen in Emergency Department: a pragmatic real-life study. Intern Emerg Med 2018;13:69-73.

50. Axelrad JE, Freedberg DE, Whittier S, Greendyke W, Lebwohl B, Green DA. Impact of Gastrointestinal Panel Implementation on Health Care Utilization and Outcomes. J Clin Microbiol 2019;57.

51. Beal SG, Tremblay EE, Toffel S, Velez L, Rand KH. A Gastrointestinal PCR Panel Improves Clinical Management and Lowers Health Care Costs. J Clin Microbiol 2018;56.

52. Blaschke AJ, Shapiro DJ, Pavia AT, Bystington CL, Ampofo K, Stockmann C, et al. A National study of the impact of rapid influenza testing on clinical care in the emergency department. J Pediatric Infect Dis Soc 2014;3:112-8.

53. Sanders EJ, Chirro O, Oduor C, Mangi J, Wahome E, Price MA, et al. Point-of-care HIV RNA testing and immediate antiretroviral therapy initiation in young adults seeking out-patient care in Kenya. AIDS 2019;33:923-6.

54. May L, Ware CE, Jordan JA, Zocchi M, Zatorski C, Ajabnoor Y, et al. A Randomized Controlled Trial Comparing the treatment of patients tested for chlamydia and gonorrhea after a rapid polymerase chain reaction test versus standard of care testing. Sex Transm Dis 2016;43:290-5.

55. Gaydos CA, Ako MC, Lewis M, Hsieh YH, Rothman RE, Dugas AF. Use of a rapid diagnostic for Chlamydia trachomatis and Neisseria gonorrhoeae for women in the emergency department can improve clinical management: Report of a randomized clinical trial. Ann Emerg Med 2019;74:36-44.

56. Bird C, Winzor G, Lemon K, Moffatt A, Newton T, Gray J. A Pragmatic Study to Evaluate the Use of a Rapid Diagnostic Test to Detect Group A Streptococcal Pharyngitis in Children With the Aim of Reducing Antibiotic Use in a UK Emergency Department. Pediatr Emerg Care 2018.

57. Vos LM, Bruning AHL, Reitsma JB, Schuurman R, Riezebos-Brilman A, Hoepelman AIM, et al. Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies. Clin Infect Dis 2019;69:1243-53.

58. Beraud L, Gervasoni K, Freydiere AM, Descours G, Ranc AG, Vandenesch F, et al. Comparison of Sofia Legionella FIA and BinaxNOW(R) Legionella urinary antigen card in two national reference centers. Eur J Clin Microbiol Infect Dis 2019;38:1803-7.

59. Sinclair A, Xie X, Teltoscher M, Dendukuri N. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae. J Clin Microbiol 2013;51:2303-10.

60. Matta M, Kernéis S, Day N, Lescat M, Hoi AB, Varon E, Gutmann L, Mainardi JL. Do clinicians consider the results of the BinaxNOW Streptococcus pneumoniae urinary antigen test when adapting antibiotic regimens for pneumonia patients? Clin Microbiol Infect 2010;16:1389-93.

61. Schimmel JJ, Haessler S, Imrey P, Lindenauner PK, Richter SS, Yu PC, Rothenberg MB. Pneumococcal urinary antigen testing in US hospitals: A missed opportunity for antimicrobial stewardship. Clin Infect Dis 2019;69 pii: ci983.

62. Rogan DT, Kochar MS, Yang S, Quinn JV. Impact of Rapid Molecular Respiratory Virus Testing on Real-Time Decision Making in a Pediatric Emergency Department. J Mol Diagn 2017;19:460-7.

63. Liesman RM, Strasburg AP, Heitman AK, Theel ES, Patel R, Binnicker MJ. Evaluation of a Commercial Multiplex Molecular Panel for Diagnosis of Infectious Meningitis and Encephalitis. J Clin Microbiol 2018;56.
64. Lewis PO, Lanier CG, Patel PD, Krolikowski WD, Krolikowski MA. False negative diagnostic errors with polymerase chain reaction for the detection of cryptococcal meningoencephalitis. Med Mycol 2019.

65. Blaschke AJ, Holmberg KM, Daly JA, Leber AL, Dien Bard J, Korgenski EK, et al. Retrospective Evaluation of Infants Aged 1 to 60 Days with Residual Cerebrospinal Fluid (CSF) Tested Using the FilmArray Meningitis/Encephalitis (ME) Panel. J Clin Microbiol 2018;56.

66. Mukkala AN, Kwan J, Lau R, Harris D, Kain D, Boggild AK. An Update on Malaria Rapid Diagnostic Tests. Curr Infect Dis Rep 2018;20:49.

67. Tedla M. A focus on improving molecular diagnostic approaches to malaria control and elimination in low transmission settings: Review. Parasite Epidemiol Control 2019;6:e00107.

68. Ponce C, Kaczorowski F, Perpoint T, Mialhes P, Sigal A, Javouhey E, et al. Diagnostic accuracy of loop-mediated isothermal amplification (LAMP) for screening patients with imported malaria in a non-endemic setting. Parasite 2017;24:53.

69. Tucker JD, Bien CH, Peeling RW. Point-of-care testing for sexually transmitted infections: recent advances and implications for disease control. Curr Opin Infect Dis 2013;26:73-9.

70. Huppert JS, Taylor RG, St Cyr S, Hesse EA, Reed JL. Point-of-care testing improves accuracy of STI care in an emergency department. Sex Transm Infect 2013;89:489-94.

71. Sayre N, Poupard M, Nivose PL, Khuong MA. Risk of falsely negative results with rapid HIV tests in HIV-infected patients. Med Mal Infect 2018;48:491-2.

72. Tan WS, Chow EP, Fairley CK, Chen MY, Bradshaw CS, Read TR. Sensitivity of HIV rapid tests compared with fourth-generation enzyme immunoassays or HIV RNA tests. AIDS 2016;30:1951-60.

73. Brown J, Shesser R, Simon G, Bahn M, Czarnogorski M, Kuo I, et al. Routine HIV screening in the emergency department using the new US Centers for Disease Control and Prevention Guidelines: results from a high-prevalence area. J Acquir Immune Defic Syndr 2007;46:395-401.

74. Green DA, Hitoaliaj L, Kotansky B, Campbell SM, Peaper DR. Clinical Utility of On-Demand Multiplex Respiratory Pathogen Testing among Adult Outpatients. J Clin Microbiol 2016;54:2950-5.

75. Gelfer G, Leggett J, Myers J, Wang L, Gilbert DN. The clinical impact of the detection of potential etiologic pathogens of community-acquired pneumonia. Diagn Microbiol Infect Dis 2015;83:400-6.

76. Keske S, Ergonul O, Tutucu F, Karaaslan D, Palaoglu E, Can F. The rapid diagnosis of viral respiratory tract infections and its impact on antimicrobial stewardship programs. Eur J Clin Microbiol Infect Dis 2018;37:779-83.

77. Patel R, Fang FC. Diagnostic Stewardship: Opportunity for a Laboratory-Infectious Diseases Partnership. Clin Infect Dis 2018;67:799-801.

78. Weigl BH, Gaydos CA, Kost G, Beyette FR, Jr., Sabourin S, Rompalo A, et al. The Value of Clinical Needs Assessments for Point-of-Care Diagnostics. Point Care 2012;11:108-13.

79. Loubiere S, Moatti JP. Economic evaluation of point-of-care diagnostic technologies for infectious diseases. Clin Microbiol Infect 2010;16:1070-6.

80. Le Maréchal M, Agrinier N, Cattoir V, Pulcini C; ABS-CM working group. A nationwide survey on involvement of clinical microbiologists in antibiotic stewardship programmes in large French hospitals. Eur J Clin Microbiol Infect Dis 2019;38:2235-2241.
Table 1: Non exhaustive list of commercially available FDA and CE approved point-of-care tests in infectious diseases, classified according to syndrome (or disease) of interest.

| Syndrome or disease               | Specific test, duplex or panel | Targeted pathogen(s)          | Technique | Clinical specimen types | Trade names of some available assays | Sensitivity | Specificity | TAT |
|-----------------------------------|--------------------------------|-------------------------------|-----------|-------------------------|-------------------------------------|-------------|-------------|-----|
| **Upper respiratory tract infections** |                                |                                |           |                         |                                     |             |             |     |
| Specific                          | Group A Streptococcus          | LFIA                           | Pharyngeal swabs     | Sofia® StrepA FIA         | 84.9%                               | 96.8%       | 5min        | [4] |
| Specific                          | Group A Streptococcus          | LFIA                           | Pharyngeal swab      | TestPack Strep A          | 75.3%                               | 98.1%       | 5min        | [4] |
| Specific                          | Group A Streptococcus          | rPCR                           | Pharyngeal swabs     | AmpliVue® GAS Assay       | 98.3%                               | 93.2%       | 60min       | [5] |
| Specific                          | Group A Streptococcus          | rPCR                           | Pharyngeal swabs     | cobas® Liat Strep A Assay | 95.5%                               | 99.3%       | 15min       | [6] |
| Specific                          | Group A Streptococcus          | rPCR                           | Pharyngeal swabs     | Xpert® Xpress Strep A     | 100%                                | 79.3%       | 25min       | [7] |
| **Lower respiratory tract infections** |                                |                                |           |                         |                                     |             |             |     |
| Specific                          | Streptococcus pneumoniae       | LFIA                           | Urine samples       | Sofia® S. pneumoniae FIA  | 66%                                 | 100%        | 10min       | [8] |
| Specific                          | Streptococcus pneumoniae       | LFIA                           | Urine samples       | BinaxNow™ Streptococcus pneumoniae Antigen Card | 62%                               | 98%         | 15min       | [8] |
| Specific                          | Legionella pneumophila          | LFIA                           | Urine samples       | BinaxNOW™ Legionella Urinary Antigen Card | 79.7%                               | 97.1%       | 15min       | [9] |
| Specific                          | Mycoplasma pneumoniae          | LAMP                           | Throat swabs        | Illumigene Mycoplasma Direct DNA amplification assay | 87%                               | 97.9%       | 60min       | [10]|  |
| Specific                          | Influenza A and B              | rRT-PCR                        | NP swabs            | Cobas® Influenza A/B assay | IA: 97.5%                           | IA: 97.9%   | 20min       | [11]|
| Specific                          | Influenza A and B              | rRT-PCR                        | NP swabs            | ID NOW™ INFLUENZA A & B (formerly Alere™ i. Influenza A & B) | NA                               | NA          | 15min       | [12]|
| Specific                          | Influenza A and B              | LFIA                           | Nasal swabs, NP swabs, NP aspirate/wash | Sofia® influenza A+B FIA | IA: 82.2%                           | IA: 100%    | 15min       | [13]|
| Specific                          | RSV                            | rRT-PCR                        | NP swabs/aspirate/ NP swabs | ID NOW™ RSV (formerly Alere™ i RSV) | 100%                               | 97%         | 15min       | [14]|
| **Panel**                         | Influenza A/B, RSV             | rRT-PCR                        | NP swabs/ aspirate NP swabs | Cobas® Influenza A/B & RSV | NA                               | NA          | 20min       | [15]|
| **Panel**                         | Influenza A/B, RSV             | rRT-PCR                        | nasal wash fluid samples/aspirates and NP swabs | Xpert® Flu/RSV XC | NA                               | NA          | 40min       | [16]|
| Panel                                                                 | Test Type | Specimen | Platform | Sensitivity | Specificity | Time | Reference |
|----------------------------------------------------------------------|-----------|----------|----------|-------------|-------------|------|-----------|
| Human adenovirus, human metapneumovirus, rhinovirus/enterovirus, influenza A, B, parainfluenza , RSV, Bordetella pertussis, Chlamydiophila pneumoniae, Mycoplasma pneumoniae | r(RT-)PCR | NP swabs | BIOFIRE® FILMARRAY® Respiratory Panel | NA | NA | 65min | [17, 18] |
| Human adenovirus, Coronavirus, human metapneumovirus, rhinovirus/enterovirus, influenza A, B, parainfluenza, RSV, Mers-Cov, Bordetella pertussis, Chlamydiophila pneumoniae, Mycoplasma pneumoniae, Bordetella parapertussis | r(RT-)PCR | NP swabs | BIOFIRE® FILMARRAY® Respiratory Panel2 plus (RP2plus) | M. pneumoniae: 95.8% | M. pneumoniae: 99.7% | 45min | [19] |
| Human adenovirus, Coronavirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A, B, parainfluenza, RSV-A/-B, Chlamydia pneumoniae, Mycoplasma pneumoniae | r(RT-)PCR | NP swabs | ePlex® Respiratory Pathogen (RP) Panel | NA | NA | 90min | [20] |
| C. difficile                                                          | rPCR      | Stool samples | Xpert® C. difficile BT | 21.5% | 100% | 47min | [21,22] |
| C. difficile                                                         | rPCR      | Stool samples | Cobas® Cdiff test | 92.9% | 98.7% | 20min | [23] |
| C. difficile                                                        | EIA       | Stool samples | Xpect™ C. difficile Toxin A/B Test | 48% | 84% | 20min | [24] |
| C. difficile                                                        | EIA       | Stool samples | VIDAS® C. difficile GDH and VIDAS® C. difficile Toxin A & B | 80-89.8% | 96.7-97.3% | 50min | [25] |
| Campylobacter (jejuni, coli & upsaliensis), Clostridium difficile (Toxin A/B), Plesiomonas shigeloides, Salmonella, Yersinia enterocolitica Vibrio (parahaemolyticus, vulgaris, cholerae), E. coli O157, Enterohaemagglutative E. coli (EAEC), Enteropathogenic E. coli (EPEC), Enterotoxigenic E. coli (ETEC) R/t/st, Shiga-like toxin-producing E. coli (STEC) stx1/stx2 E. coli O157, Shigella/Enteroinvasive E. coli | rPCR      | Stool samples | Biofire® FILMARRAY® GI Panel | 100% for 12/22 targets ≥94.5% for an additional 7/22 targets | ≥97.1% for all panel targets | 60min | [26] |
| Central nervous system infections | Specific | Cryptococcus neoformans, Cryptococcus gattii | LFIA | Serum, CSF samples | CrAg® LFA | 100% | 99.8% | 20min | [27] |
|----------------------------------|----------|---------------------------------------------|------|------------------|-----------|-------|-------|--------|------|
|                                  | Specific | S. pneumoniae                                | LFIA | CSF samples      | BinaxNow™ Streptococcus pneumoniae Antigen Card | NA    | 100% | 15min | [28] |
|                                  | Specific | Enterovirus                                  | rRT-PCR | CSF samples | NucliSENS EasyQ® Enterovirus v.1 | NA    | NA | 120min | [29] |
| Panel                            | E. coli K1, H. influenzae, L. monocytogenes, N. meningitidis, S. pneumoniae, S. agalactiae, enterovirus, HSV-1/2, ZV2, CMV, HHV-6, human parechovirus, Cryptococcus neoformans/C. gattii | r(RT)-PCR | CSF samples | BIOFIRE® FILMARRAY® Meningitis/Encephalitis (ME) Panel | E. coli K1: 100% | H.influenza: 100% (n=1) | L.monocytogenes: NA | N.meningitidis: NA | S.agalactiae: 0% (n=1) | S.pneumoniae: 100% | E. coli K1: 99.9% | H.Influenza: 99.9% | L.monocytogenes: 100% | N.meningitidis: 100% | S.agalactiae: 99.9% | S.pneumoniae: 99.2% | 65min | [30] |
| Fever in the returning traveler  | Specific | Plasmodium spp.                              | LFIA | Whole blood samples | BinaxNOW ® Malaria | All patients 84.2% | 99.8% | 15min | [31] |
|                                  | Specific | Plasmodium spp.                              | LAMP | Whole blood samples | illumigene Malaria DNA amplification assay | NS1 Ag detection*: 98.1% | 97.6% | 10min | [32] |
|                                  | Specific | Dengue virus                                 | EIA | Plasma, serum samples | OnSite Dengue Ag Rapid Test | Dengue Early Rapid Test | SD Bioline Dengue Duo*: | IgM detection | Dengue IgM Rapid Test Device | OnSite Dengue IgM/IgG Combo | SD Bioline Dengue Duo*: | C. trachomatis in female endocervical, vaginal, urine samples: 97.4%, 98.7%, 97.6% | C. trachomatis in male urine samples: 97.5% | N. gonorrhoeae in females in endocervical, vaginal, urine samples: 100%, 100%, 95.6% | N. gonorrhoeae in males urine: | C. trachomatis in female and male samples : ≥99.4% | N. gonorrhoeae in female and male samples : ≥99.8% | 90min | [34] |
| Sexually transmitted infections  | Duplex   | C. trachomatis, N. gonorrhoeae              | rPCR | Vaginal/endocervical and urine samples | Xpert® CT/NG | C. trachomatis in female endocervical, vaginal, urine samples: 97.4%, 98.7%, 97.6% | C. trachomatis in male urine samples: 97.5% | N. gonorrhoeae in females in endocervical, vaginal, urine samples: 100%, 100%, 95.6% | N. gonorrhoeae in males urine: | C. trachomatis in female and male samples : ≥99.4% | N. gonorrhoeae in female and male samples : ≥99.8% | 90min | [34] |
| Type        | Assay                  | Samples | Specificity | Sensitivity | Time (min) | Ref. |
|-------------|------------------------|---------|-------------|-------------|------------|------|
| **Duplex**  | **C. trachomatis, N. gonorrhoeae** | Endocervical and urethral samples | Gen-probe PACE2C system for *Chlamydia trachomatis* and *Neisseria gonorrhoea* | 96.3% | 98.8% | 95 | [35] |
| **Specific** | **Treponema pallidum**  | Serum, plasma, whole blood samples | DETERMINE™ SYPHILIS TP | 95.6-98.4% | 97.3-95.7% | 15 | [36] |
| **Specific** | **Treponema pallidum**  | Serum, plasma, whole blood samples | VisiTect® Syphilis | 57% | 99% | 30 | [37] |
| **Specific** | **Treponema pallidum**  | Serum, plasma, whole blood samples | Sydneycheck®-WB | 67.4% | 98.4% | 15 | [38] |
| **Specific** | **HIV**                | Blood samples | Antibody detection (sensitivity for HIV-1 M Ab) | 100% | 98.5% | 20 | [39] |
|             |                        |         | - EXACTO® TEST HIV Self-test | 100% | 100% | 30 | |
|             |                        |         | - Genie™ Fast HIV1/2 | 100% | 100% | Immediatly | |
|             |                        |         | - INSTI® HIV | 100% | 99.5% | 20 | |
|             |                        |         | - Stat-View® HIV1/2 | 100% | 99.5% | 30 | |
|             |                        |         | - Vikia® HIV1/2 | 100% | 99.5% | 40 | |
|             |                        |         | Antibody/antigen detection | 99.5% | 99.5% | | |
|             |                        |         | Determine™ HIV–1/2 Ag/Ab Combo | 100% | Antibodies: 100% | | |

† The performance characteristics of the assays are described as sensitivity and specificity according to published clinical validation studies when available. In the absence of test comparison against a gold standard assay, the reported positive and negative percent agreement in the clinical studies reviewed were not reported to avoid any misinterpretation by the reader.

* Sensitivity has been extracted from the "acute infection" population and specificity has been extracted from the "naïve individuals" population described in the corresponding reference.

Abbreviations: TAT: turn around time; r(RT-)PCR: real-time reverse transcription-polymerase chain reaction; EIA: enzyme immunoassay; LFIA: lateral flow immunoassay; LAMP: loop-mediated isothermal amplification; CSF: cerebrospinal fluid; NP: nasopharyngeal; SSTI: skin/soft tissue infection; min: minutes; NA: non available; HSV: herpes simplex virus; VZV: varicella zoster virus; CMV: cytomegalovirus; RSV: respiratory syncytial virus; E. coli: Escherichia coli; H. influenza: Haemophilus influenzae; L. monocytogenes: Listeria monocytogenes; N. meningitides: Neisseria meningitides; S. pneumoniae: Streptococcus pneumoniae.
| Syndrom or disease                          | Approach and targeted pathogens | Test brand          | Population | Study design     | Findings                                                                                   | Reference |
|--------------------------------------------|---------------------------------|---------------------|------------|------------------|--------------------------------------------------------------------------------------------|-----------|
| **Upper Respiratory tract infections**     |                                  |                     |            |                  |                                                                                             |           |
| Group A Streptococcus (GAS) RADT           |                                 | QuickVue (Quidel)   | Infants (n=223) | Single center Prospective study       | After using RADT, antibiotic prescriptions decreased by 42.6%                              | [40]      |
| Group A Streptococcus (GAS) PCR            |                                 | Coba Liat Strep A (Roche) | Infants (n=275) | Single center Prospective study       | Compared with RADT, POC PCR resulted in significantly greater appropriate antibiotic use (97.1% vs 87.5%; ) p =0.0065 | [6]       |
| **Lower Respiratory tract infections**     | mPCR in the ED vs usual tests in central laboratory | FilmArray (Biofire, bioMérieux) | Infants (n=1,136) | Single center Retrospective study | mPCR in the ED decreases the duration of antibiotic use (from 3.2 to 2.8 days p=0.003), the length of inpatient stay (from 3.4 to 3.2 days p=0.03) | [41]      |
|                                            | mPCR in the ED vs usual tests in central laboratory | FilmArray (Biofire, bioMérieux) | Adults (n=720) | Single center prospective study | mPCR in the ED decreases the duration of antibiotic use (from 6.5 to 2.9 days, p=0.0009), the hospital length of stay (from 6.8 to 5.7 days, p=0.004) | [42]      |
|                                            | mPCR in the ED vs usual tests in central laboratory | FilmArray (Biofire, bioMérieux) | Adults (n=606) | Single center Prospective study | No association between respiratory PCR POC testing and length of stay but a reduction in the median time to the first dose of antiviral (from 60.4 to 24h) and appropriate treatment of mycoplasma infection | [43]      |
|                                            | Influenza PCR                    | Cobas Liat (Roche)  | Adults (n=620) | Multicenter Retrospective study | Antivirals were prescribed more often in patients that tested positive by LIAT PCR (82.4%) than in those testing positive by either RIDT or reflex PCR (69.9%; P < 0.05) | [44]      |
|                                            | Influenza PCR                    | FilmArray (Biofire, bioMérieux) | Adults (n=337) | Single center Retrospective study | Diagnosis of influenza by FilmArray was associated with significantly lower odds ratios (ORs) for admission (P = 0.046), length of stay (P = 0.040), duration of antimicrobial use (P = 0.032), and number of chest radiographs (P = 0.005). | [45]      |
|                                            | Influenza RADT                    | QuickVue (InGen)     | Infants (n=170) | Single center Prospective study | Positive RIDT enabled a significant decrease in orders for chest X-rays (64.4% vs. 45.8%, p<0.05) and laboratory tests (71.1% vs. 41.1%, p<0.05). | [46]      |
|                                            | Influenza immunoassay             | Binax NOW (Alere)    | Adults + Infants (n=827) | Multicenter Prospective study | For a cohort of 1000 participants, annual estimated non-diagnostic cost savings with Alere® are £215,040 | [47]      |
|                                            | Pneumococcus (SP) and legionella (LP) urinary antigen | Binax NOW (Alere)    | Adults (n=1,941) | EPIC study Multicenter Prospective study | IDSA/ATS indications had 61% sensitivity (95% confidence interval CI) 49-71% and 39% specificity (95% CI 37-41%) for SP, and 63% sensitivity (95% CI 44-79%) and 35% specificity (95% CI 33-53%) for LP. | [48]      |
|                                            | Pneumococcus (SP) and legionella (LP) urinary antigen | Binax NOW (Alere)    | Adults (n=1,224) | Single center Retrospective | Only 7 tests led to appropriate antimicrobial modification, and since 972 tests had no impact, we estimate that potential cost savings, if the test had not been used, would have been 26,244 € (972 x 27) during a 3 year period, that is 8748 € per year. | [49]      |
| **Gastrointestinal infections** | **GI PCR panel** | FilmArray (Biofire, bioMérieux) | Adults + infants (n=9,402) | Cross sectional Retrospective study | Patients who received a GI panel were less likely to undergo any endoscopic procedure (8.4% GI panel versus 9.6% stool culture, \( P = 0.008 \)) or any abdominal radiology (29.4% GI panel versus 31.7%, \( P = 0.002 \)). Within 14 days following stool testing, patients who received a GI panel were less likely to be prescribed any antibiotic (36.2% GI panel versus 40.9%, \( p < 0.001 \)). |
|-------------------------------|-----------------|-------------------------------|--------------------------|-----------------------------------|-----------------------------------------------------------------------------------|
| **Central nervous system infections** | **GI PCR panel** | FilmArray (Biofire, bioMérieux) | Adults + infants (n=241) | Single center Retrospective study | The GI panel helped reduce the need for other diagnostic tests, reducing unnecessary use of antibiotics, and leading to a reduction in hospital length of stay. |
| **Meningitis and encephalitis** | **Meningitis and encephalitis** | FilmArray (Biofire, bioMérieux) | Infants (n=145) | Multicenter Prospective study | FilmArray ME panel results may conduct in a decreased length of stay and in less antimicrobial exposure for infants with low-risk viral infection detected. |
| **Malaria** | **Malaria testing** | Illumigene Malaria (Meridian Bioscience) | Adults (n=298) | Multicenter Retrospective and prospective study | A cost-benefit analysis suggests savings of up to USD$13 per specimen using a novel algorithm with this test. |
| **Genital and sexually transmitted infections** | **HIV RNA testing (PCR)** | Xpert (Cepheid) | Adults (n=706) | Single center Prospective study | The addition of Xpert HIV-1 Qual testing led to an increase in confirmed diagnoses by 25% (from 24 to 30 cases). |
| **C. trachomatis and N. gonorrhoeae testing (PCR)** | **C. trachomatis and N. gonorrhoeae testing (PCR)** | Xpert (Cepheid) | Adults (n=70) | Single center RCT | The use of Xpert CT/NG reduced overtreatment and improved adherence. |
| **C. trachomatis and N. gonorrhoeae testing (PCR)** | **C. trachomatis and N. gonorrhoeae testing (PCR)** | Xpert (Cepheid) | Adult women (n=254) | Single center RCT | Xpert CT/NG reduced overtreatment and improved undertreatment of patients tested in the ED. |

GI, Gastrointestinal; mPCR, Multiplex PCR; RADT, Rapid antigen detection test