Rapid diagnostic tests for infectious diseases in the emergency department

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Running title: RDTs in the ED

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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*, *Chlamydophila 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 underappreicated – 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, Eumédica, 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.

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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	Tests performance characteristics†			Reference
						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% IB: 96.9%	IA: 97.9% IB: 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% IB: 77.8%	IA: 100% IB: 100%	15min	[13]
	Specific	RSV	rRT-PCR	NP swabs/aspirate	ID NOW™ RSV (formerly Alere™ I RSV)	100%	97%	15min	[14]
	Panel	Influenza A/B, RSV	rRT-PCR	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	Human adenovirus, human metapneumovirus, rhinovirus/enterovirus, influenza A, B, parainfluenza , RSV, *Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae*	r(RT-)PCR	NP swabs	BIOFIRE® FILMARRAY® Respiratory Panel	NA	NA	65min	[17, 18]
	Panel	Human adenovirus, Coronavirus, human metapneumovirus, rhinovirus/enterovirus, Influenza A, B, parainfluenza, RSV, Mers-Cov, *Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae, Bordetella parapertussis*	r(RT-)PCR	NP swabs	BIOFIRE® FILMARRAY® Respiratory Panel2 plus (RP2plus)	NA *M. pneumoniae:* 95.8%	NA *M. pneumoniae:* 99.7%	45min	[19]
	Panel	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]
Gastro-intestinal infections	Specific	*C. difficile*	rPCR	Stool samples	Xpert® C. difficile BT	21.5%	100%	47min	[21,22]
	Specific	*C. difficile*	rPCR	Stool samples	Cobas® Cdiff test	92.9%	98.7%	20min	[23]
	Specific	*C. difficile*	EIA	Stool samples	Xpect™ C. difficile Toxin A/B Test	48%	84%	20min	[24]
	Specific	*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]
	Panel	*Campylobacter (jejuni, coli & upsaliensis), Clostridium difficile (Toxin A/B), Plesiomonas shigelloides, Salmonella, Yersinia enterocolitica* *Vibrio (parahaemolyticus, vulnificus, cholerae), E. coli O157, Enteroaggregative E. coli (EAEC), Enteropathogenic E. coli (EPEC), Enterotoxigenic E. coli (ETEC) lt/st, Shiga-like toxin-producing E. coli (STEC) stx1/stx2 E. coli O157, Shigella/Enteroinvasive E.*	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]

		coli (EIEC), Adenovirus F 40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, Sapovirus (I,II, IV, and V), *Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia*							
Central nervous system infections	Duplex	*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	95.4%-100%	100%	15min	[28]
	Specific	*Enterovirus*	rRT-PCR	CSF samples	NucliSENS EasyQ® Enterovirus v1.1	NA	NA	120min	[29]
	Panel	*E. coli K1, H. influenzae, L. monocytogenes, N. meningitidis, S. pneumoniae, S. agalactiae,* enterovirus, HSV-1/2, VZV, 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% NA	*E.coli K1*: 99.9% *H.influenza*: 99.9% *L.monocytogenes*: 100% *N.meningitidis*: 100% *S.agalactiae*: 99.9% *S.pneumoniae*: 99.2% NA	65min	[30]
Fever in the returning traveler	Specific	*Plasmodium spp.*	LFIA	Whole blood samples	BinaxNOW ® Malaria	All patients 84.2% Patients without antimalarial therapy : 92.9%	99.8%	15min	[31]
	Specific	*Plasmodium spp.*	LAMP	Whole blood samples	illumigene Malaria DNA amplification assay	98.1%	97.6%	10min	[32]
	Specific	Dengue virus	EIA	Plasma, serum samples	NS1 Ag detection* - Denge NS2 Ag Strip® - OnSite Dengue Ag Rapid Test - Dengue Early Rapid Test - SD Bioline Dengue Duo® IgM detection - Dengue IgG/IgM Rapid Test Device - OnSite Dengue IgG/IgM Combo - SD Bioline Dengue Duo®	 52% 40% 60% 59% 63% 46% 89%	 77% 76% 75% 78% 91% 86% 80%	 30min 30min 20min 20min 20min 30min 20min	[33]
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]

					samples : 98%			
Duplex	*C. trachomatis, N. gonorrhoeae*	rPCR	Endocervical and uretral samples	Gen-probe PACE2C system for *Chlamydia trachomatis* and *Neisseria gonorrhea*	96.3%	98.8%	95min	[35]
Specific	*Treponema pallidum*	LFIA	Serum, plasma, whole blood samples	DETERMINE™ SYPHILIS TP	95.6-98.4%	97.3-95.7%	15min	[36]
Specific	*Treponema pallidum*	LFIA	Serum, plasma, whole blood samples	VisiTect® Syphilis	57%	99%	30min	[37]
Specific	*Treponema pallidum*	LFIA	Serum, plasma, whole blood samples	Syphicheck ®-WB	67.4%	98.4%	15min	[38]
Specific	HIV		Blood samples	Antibody detection	(sensitivity for HIV-1 M Ab)			[39]
				- EXACTO® TEST HIV Self-test	100%	98.5%	20 min	
				- Genie™ Fast HIV1/2				
				- INSTI® HIV	100%	100%	30 min	
				- Stat-View® HIV1/2	100%	100%	Immediatly	
				- Vikia® HIV1/2	100%	100%	20 min	
				Antibody/antigen detection	99.5%	99.5%	30 min	
				Determine™ HIV–1/2 Ag/Ab Combo	100%	Antigen p24: 99.5% Antibodies: 100%	40 min	

† 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.*

Table 2 : Clinical studies evaluating the clinical impact of RDT use in the ED

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 33-37%) 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 9 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%, $p < 0.001$).	[50]
	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.	[51]
Central nervous system infections	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.	[52]
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.	[32]
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).	[53]
	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.	[54]
	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.	[55]

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