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Narrative review

Rapid diagnostic tests for infectious diseases in the emergency department

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ABSTRACT

Background: Rapid diagnostic tests (RDTs) for infectious diseases, with a turnaround time of less than 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, although 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 was 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 US Food and Drug Administration (FDA) or Conformité Européenne (CE) *in vitro* diagnostic devices with data on clinical samples, ability to run on fully automated systems and result delivery within 2 hours.
Content: A nonexhaustive 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 returning travellers and sexually transmitted infection, including HIV. The performance of tests was described on the basis of 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 work flow should be preplanned considering local constraints of given settings. Additional clinical studies are needed to further evaluate their clinical effectiveness and cost-effectiveness. **D. Bouzid, Clin Microbiol Infect 2021;27:182**

Introduction

Rapid diagnostic tests (RDTs) for infectious diseases have been implemented in many laboratories and emergency departments (EDs), with the goal of expediting the diagnosis of infectious

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diseases, infection prevention, appropriate initial management and facilitation of antimicrobial stewardship in the ED, where rapid clinical decisions must be undertaken in the context of overcrowding and time pressure [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 was 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.

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 terms and keywords: RDT, point of care, panel, turnaround time <2 hrs, 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, STI.

Inclusion criteria were commercial tests approved by the US Food and Drug Administration (FDA) or Conformité Européenne (CE) *in vitro* diagnostic with data published on clinical samples; ability to run on fully automated systems; and result delivery within 2 hours [3].

Assay performance characteristics, including sensitivity and specificity, were outlined on the basis of published clinical validation studies whenever available. In the absence of test comparison against a reference standard assay, the reported positive and negative percentage agreement in identified clinical studies or manufacturer performance data were not reported to avoid any misinterpretation.

Overview of available tests

A nonexhaustive 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 the impact of tests on clinical outcomes and anti-infective use in the ED (Table 2) [6,32,40–55].

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* pharyngitis, diagnosis and immunofluorescence-based assay demonstrated higher diagnostic performances compared to an immunochromatographic rapid antigen detection test in paediatric patients presenting with pharyngitis with a McIsaac score of $\geq$2; the negative predictive value of the immunofluorescence-based assay was also higher (92%) in this paediatric population, with a group A *Streptococcus* prevalence of 37% [4].

In patients with a high likelihood of streptococcal infection, guidelines recommend the use of RDTs because they are associated with decreased antibiotic use in paediatric ED populations [56]. However, the usefulness of clinical scores in children appears to be lower than for adults as a result of the different clinical presentation of sore throat in infants and young children. Point-of-care PCR assays demonstrated improved performance compared to culture or rapid antigen detection test as well as reduced unnecessary antibiotic use in paediatric studies [5–7].

In patients with influenzalike 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 meta-analysis evaluated the clinical impact of molecular RDTs for respiratory viruses by analysing 56 individual test accuracy studies, and it showed that compared to conventional molecular assays, RDTs did not reduce antibiotic use and duration, isolation measures or admission rates but increased receipt of oseltamivir in positive cases of influenza cases and reduced LOS [57].

Lower respiratory tract infections

The most frequent lower respiratory tract infections seen in the ED include acute bronchitis, community-acquired pneumonia, influenzalike illness and acute 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 community-acquired pneumonia 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.

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% compared to blood or sputum culture [8]. The performance of *L. pneumophila* urinary antigen detection tests varies according to several factors [9,58], including (a) assay type, with improved performance for immunofluorescence tests; (b) sample type (clinical vs. simulated urine samples prepared with strains of *L. pneumophila* serogroup 1 are best detected); (c) preanalytic sample processing; and (d) 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 community-acquired pneumonia diagnosis. Such treatment includes 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].

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 turnaround times of about an hour (Table 1). They allow the detection of all the most common respiratory viruses and some atypical bacteria, including *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 ten positive samples, and performance characteristics of bacterial PCR have

Table 1
Nonexhaustive list of commercially available US Food and Drug Administration– and Conformité Européenne–approved point-of-care tests in infectious diseases classified by syndrome or disease of interest

Syndrome or disease	Specific test, duplex or panel	Targeted pathogens	Technique	Clinical specimen types	Trade names of some available assays	Test performance characteristics[a]			Reference
						Sensitivity	Specificity	TAT (minutes)	
Upper respiratory tract infections	Specific	Group A *Streptococcus*	LFIA	Pharyngeal swabs	Sofia StrepA FIA	84.9%	96.8%	5	[4]
	Specific	Group A *Streptococcus*	LFIA	Pharyngeal swabs	TestPack Strep A	75.3%	98.1%	5	[4]
	Specific	Group A *Streptococcus*	rPCR	Pharyngeal swabs	AmpliVue GAS Assay	98.3%	93.2%	60	[5]
	Specific	Group A *Streptococcus*	rPCR	Pharyngeal swabs	cobas Liat Strep A Assay	95.5%	99.3%	15	[6]
	Specific	Group A *Streptococcus*	rPCR	Pharyngeal swabs	Xpert Xpress Strep A	100%	79.3%	25	[7]
Lower respiratory tract infections	Specific	*Streptococcus pneumoniae*	LFIA	Urine samples	Sofia *S. pneumoniae* FIA	66%	100%	10	[8]
	Specific	*S. pneumoniae*	LFIA	Urine samples	BinaxNow *Streptococcus pneumoniae* Antigen Card	62%	98%	15	[8]
	Specific	*Legionella pneumophila*	LFIA	Urine samples	BinaxNOW *Legionella* Urinary Antigen Card	79.7%	97.1%	15	[9]
	Specific	*Mycoplasma pneumoniae*	LAMP	Throat swabs	Illumigene *Mycoplasma* Direct DNA amplification assay	87%	97.9%	60	[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%	20	[11]
	Specific	Influenza A and B	rRT-PCR	NP swabs	ID NOW INFLUENZA A & B (formerly Alere i. Influenza A & B)	NA	NA	15	[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%	15	[13]
	Specific	RSV	rRT-PCR	NP swabs/aspirate	ID NOW RSV (formerly Alere I RSV)	100%	97%	15	[14]
	Panel	Influenza A/B, RSV	rRT-PCR	NP swabs	cobas Influenza A/B & RSV	NA	NA	20	[15]
	Panel	Influenza A/B, RSV	rRT-PCR	Nasal wash fluid samples/aspirates and NP swabs	Xpert Flu/RSV XC	NA	NA	40	[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	65	[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 Pane12 plus (RP2plus)	NA *M. pneumoniae:* 95.8%	NA *M. pneumoniae:* 99.7%	45	[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	90	[20]
Gastro-intestinal infections	Specific	*Clostridium difficile*	rPCR	Stool samples	Xpert *C. difficile* BT	21.5%	100%	47	[21,22]
	Specific	*C. difficile*	rPCR	Stool samples	cobas Cdiff test	92.9%	98.7%	20	[23]
	Specific	*C. difficile*	EIA	Stool samples	Xpect *C. difficile* Toxin A/B Test	48%	84%	20	[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%	50	[25]
	Panel	*Campylobacter* (*jejuni, coli* and *upsaliensis*), *Clostridium difficile* (toxin A/B), *Plesiomonas shigelloides, Salmonella, Yersinia enterocolitica* *Vibrio* (*parahaemolyticus, vulnificus, cholerae*), *Escherichia 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. 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*	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	60	[26]
Central nervous system infections	Duplex	*Cryptococcus neoformans, Cryptococcus gattii*	LFIA	Serum, CSF samples	CrAg LFA	100%	99.8%	20	[27]
	Specific	*S. pneumoniae*	LFIA	CSF samples	BinaxNow *Streptococcus pneumoniae* Antigen Card	95.4–100%	100%	15	[28]
	Specific	*Enterovirus*	rRT-PCR	CSF samples	NucliSENS EasyQ Enterovirus v1.1	NA	NA	120	[29]
	Panel	*E. coli* K1, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, S. pneumoniae, Streptococcus agalactiae,* enterovirus, HSV-1/2, VZV, CMV, HHV-6, human parechovirus, *C. neoformans*/ *C. gattii*	r(RT-)PCR	CSF samples	BioFire FilmArray Meningitis/ Encephalitis (ME) Panel	*E. coli* K1: 100% *Haemophilus influenzae:* 100% ($n = 1$) *L. monocytogenes:* NA *N. meningitidis:* NA *S. agalactiae:* 0% ($n = 1$) *S. pneumoniae:* 100%	*E. coli* K1: 99.9% *H. influenzae:* 99.9% *L. monocytogenes:* 100% *N. meningitidis:* 100% *S. agalactiae:* 99.9% *S. pneumoniae:* 99.2%	65	[30]
Fever in the returning traveller	Specific	*Plasmodium* spp.	LFIA	Whole blood samples	BinaxNOW Malaria	All patients 84.2% Patients without antimalarial therapy: 92.9%	99.8%	15	[31]
	Specific	*Plasmodium* spp.	LAMP	Whole blood samples	Illumigene Malaria DNA amplification assay	98.1%	97.6%	10	[32]
	Specific	Dengue virus	EIA	Plasma, serum samples	NS1 Ag detection[b]				[33]
					• Dengue NS2 Ag Strip	52%	77%	30	
					• OnSite Dengue Ag Rapid Test	40%	76%	30	
					• Dengue Early Rapid Test	60%	75%	20	
					• SD Bioline Dengue Duo IgM detection	59%	78%	20	
					• Dengue IgG/IgM Rapid Test Device	63%	91%	20	
					• OnSite Dengue IgG/IgM Combo	46%	86%	30	
					• SD Bioline Dengue Duo	89%	80%	20	

(*continued on next page*)

Table 1 (*continued*)

Syndrome or disease	Specific test, duplex or panel	Targeted pathogens	Technique	Clinical specimen types	Trade names of some available assays	Test performance characteristics[a]			Reference
						Sensitivity	Specificity	TAT (minutes)	
Sexually transmitted infections	Duplex	*Chlamydia trachomatis, Neisseria 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 female subjects in endocervical, vaginal, urine samples: 100%, 100%, 95.6% *N. gonorrhoeae* in male urine samples: 98%	*C. trachomatis* in female and male samples: ≥99.4% *N. gonorrhoeae* in female and male samples: ≥99.8%	90	[34]
	Duplex	*C. trachomatis, N. gonorrhoeae*	rPCR	Endocervical and ureteral samples	Gen-Probe PACE2C system for *Chlamydia trachomatis* and *Neisseria gonorrhea*	96.3%	98.8%	95	[35]
	Specific	*Treponema pallidum*	LFIA	Serum, plasma, whole blood samples	DETERMINE SYPHILIS TP	95.6–98.4%	97.3–95.7%	15	[36]
	Specific	*T. pallidum*	LFIA	Serum, plasma, whole blood samples	VisiTect Syphilis	57%	99%	30	[37]
	Specific	*T. pallidum*	LFIA	Serum, plasma, whole blood samples	Syphicheck-WB	67.4%	98.4%	15	[38]
	Specific	HIV		Blood samples	Antibody detection	(sensitivity for HIV-1 M Ab)			[39]
					• EXACTO TEST HIV Self-test	100%	98.5%	20	
					• INSTI HIV	100%	100%	30	
					• Stat-View HIV-1/2	100%	100%	Immediately	
					• Vikia HIV-1/2	100%	100%	20	
					Antibody/antigen detection	99.5%	99.5%	30	
					• Determine HIV-1/2 Ag/Ab Combo	100%	Antigen p24: 99.5% Antibodies: 100%	40	

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EIA, enzyme immunoassay; FIA, fluorescent immunoassay; HSV, herpes simplex virus; LAMP, loop-mediated isothermal amplification; LFIA, lateral flow immunoassay; NA, not applicable; NP, nasopharyngeal; r(RT-)PCR, real-time (reverse transcription-)polymerase chain reaction; RSV, respiratory syncytial virus; SSTI, skin and soft tissue infection; TAT, turnaround time; VZV, varicella zoster virus.

[a] 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 reference standard assay, the reported positive and negative percentage agreement in the clinical studies reviewed were not reported to avoid misinterpretation.

[b] Sensitivity has been extracted from the 'acute infection' population and specificity has been extracted from the 'naive individuals' population described in the corresponding reference.

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

Syndrome or disease	Approach and targeted pathogens	Test brand	Population (*n*)	Study design	Findings	Reference
Upper Respiratory tract infections	Group A *Streptococcus* RADT	QuickVue (Quidel)	Infants (223)	SSPS	After using RADT, antibiotic prescriptions decreased by 42.6%	[40]
	Group A *Streptococcus* PCR	cobas Liat Strep A (Roche)	Infants (275)	SSPS	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 ED vs. usual tests in central laboratory	FilmArray (BioFire, bioMérieux)	Infants (1136)	Single-centre retrospective	mPCR in 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 ED vs. usual tests in central laboratory	FilmArray (BioFire, bioMérieux)	Adults (720)	SSPS	mPCR in 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 ED vs. usual tests in central laboratory	FilmArray (BioFire, bioMérieux)	Adults (606)	SSPS	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 (620)	Multicentre retrospective	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 (337)	Single-centre retrospective	Diagnosis of influenza by FilmArray was associated with significantly lower 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 (170)	SSPS	Positive RADT 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 (827)	Multicentre prospective	For a cohort of 1000 participants, annual estimated nondiagnostic cost savings with Alere are £215040.	[47]
	Pneumococcus (SP) and legionella (LP) urinary antigen	Binax NOW (Alere)	Adults (1941)	Epic study multicentre prospective	IDSA/ATS indications had 61% sensitivity (95% 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 (1224)	Single-centre 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 € during a 3 year period, that is 8748 € per year.	[49]
Gastrointestinal infections	GI PCR panel	FilmArray (BioFire, bioMérieux)	Adults + infants (9402)	Cross sectional retrospective	Patients who received a GI panel were less likely to undergo any endoscopic procedure (8.4% GI panel vs. 9.6% stool culture, p 0.008) or any abdominal radiology (29.4% GI panel vs. 31.7%, p 0.002). Within 14 days after stool testing, patients who received a GI panel were less likely to be prescribed any antibiotic (36.2% GI panel vs. 40.9%, $p < 0.001$).	[50]
	GI PCR panel	FilmArray (BioFire, bioMérieux)	Adults + infants (241)	Single-centre retrospective	The GI panel helped decrease 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 (145)	Multicentre prospective	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 (298)	Multicentre retrospective and prospective	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 (706)	SSPS	The addition of Xpert HIV-1 Qual testing led to an increase in confirmed diagnoses by 25% (from 24 to 30 cases).	[53]
	Chlamydia trachomatis and *Neisseria gonorrhoeae* testing (PCR)	Xpert (Cepheid)	Adults (70)	Single-centre RCT	The use of Xpert CT/NG reduced overtreatment and improved adherence.	[54]
	C. trachomatis and *N. gonorrhoeae* testing (PCR)	Xpert (Cepheid)	Women (254)	Single-centre RCT	Xpert CT/NG reduced overtreatment and improved undertreatment of patients tested in ED.	[55]

CI, confidence interval; ED, emergency department; GI, gastrointestinal; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; LP, *Legionella pneumophila*; mPCR, multiplex PCR; OR, odds ratio; POC, point of care; RADT, rapid antigen detection test; RCT, randomized controlled trial; SP, *Streptococcus pneumoniae*; SSPS, single-centre prospective study.

sometimes been reported to be lower than those of viral PCR [19], thus highlighting the need for caution when interpreting cumulative performance results. Furthermore, the performance of some panels only consists of percentage agreement—a strong and perhaps underappreciated limitation (Table 1).

For the diagnosis of lower respiratory tract infections in the ED, short turnaround time is a key parameter for relevant therapeutic measures when targeted treatments and specific infection prevention measures exist, as for respiratory syncytial virus or influenza [62].

Gastrointestinal infections

The rapid diagnosis of *Clostridium difficile* infection is often based on a two- or three-stage diagnostic approach using specific glutamate dehydrogenase antigen with enzyme immunoassays, amplification of toxin A/B genes by PCR and detection of toxins A/B by enzyme immunoassay (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, like other syndromic panels, validation studies of some assays were performed among populations with low prevalence of certain targets, including *Vibrio* spp., *Entamoeba histolytica* and *Yersinia enterolitica* [26]—an important consideration for interpretation of negative results.

Few data have been published on the clinical impact of RDTs for the diagnosis of gastrointestinal infections in the ED. Additional research is needed to evaluate their impact and cost-effectiveness, especially for costly but point-of-care (POC)-friendly rapid multiplex PCR assays [50,51].

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 turnaround times [27].

To date, only one fully automatized rapid multiplex PCR system is available: the FilmArray ME panel (BioFire, bioMérieux), which provides results in about an hour. Common bacteria and viruses are detected, as well as the yeast *Cryptococcus 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 culture if there a high index of suspicion [30].

No data were available on the impact of RDTs on the management of patients with suspicion of meningitis/encephalitis in the ED. A retrospective analysis of 145 paediatric cases of meningitis showed that 20% of infants were discharged less than 24 hours after an enterovirus-positive result, thus highlighting some potential benefits of rapid syndromic testing [65]. Further investigation of this approach is needed, especially in adults.

Fever in the returning traveller

Malaria RDTs are critically needed for patients returning from malaria-endemic countries. Approximately 90% of cases occur in the World Health Organization African region, with *Plasmodium falciparum* being the most prevalent species, accounting for nearly all mortality. Malaria is diagnosed by three categories of tools: expert light microscopy, immunochromatographic tests (ICTs) and nucleic acid amplification tests [66]. Light microscopy is widely used, but it requires highly trained staff. ICTs are cheap and have a sensitivity of a minimum of 95% compared to microscopy, and a specificity of >90% for all *Plasmodium* species [67]. The BinaxNOW malaria test (Alere), which is 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 loop-mediated isothermal amplification–based molecular test (Malaria LAMP assay; Illumigene M; Meridian Biosciences) is commercially available [68]. In a prospective trial in returning travellers, this approach showed excellent analytical performance versus microscopy, with near 100% accuracy [32].

With 96 million dengue infections per year in over 100 tropical and subtropical countries in patients with nonspecific symptoms, rapid and accurate testing is important. Unfortunately, rapid ICTs detecting both NS1 antigen and immunoglobulin M have relatively low performance profiles. Their use should be limited to strong clinical suspicion, which is then confirmed by ELISA or PCR assays [33]. There is a need for multiplex testing for other arboviruses, such as Zika and chikungunya, which have resulted in large outbreaks.

Sexually transmitted infections and HIV infection

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

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

Several manufacturers have also developed rapid ICTs for HIV diagnosis. Performance evaluations are generally carried out on plasma or serum samples, but not fingerstick whole-blood samples. Their use should also be cautiously implemented in the context of patients with primary infection or wide HIV diversity (HIV-1, HIV-2, HIV-O). Indeed, one study demonstrated excellent performance (sensitivity 100%, 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 receiving antiretroviral therapy [71,72]. Although 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].

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 LOS. Various clinical studies have demonstrated a significant impact on reducing antimicrobial duration when RDTs are used in the ED [54,74–76]. Conversely, other studies have failed to report such a reduction, especially in complex healthcare environments [41,43]. In this context, multidisciplinary diagnostic stewardship is essential. This 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 are 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].

Work flow 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? And 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 influenza-like illness), quick administration of anti-infective drugs in critical patients (e.g. malaria in febrile returning traveller) or improved patient throughput testing might be performed by triage nurses on the basis of precise and simple clinical case definitions. Conversely, other tests require more complex interpretation or sampling, such as lower respiratory tract infection panels, and should thus be limited to confirmed pneumonia patients. Training for assay implementation is needed, and additional human resources may be required for timely integration into ED work flow. 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.

Conclusions

This review provides a nonexhaustive overview of currently commercially available FDA and CE RDTs for infectious diseases in the ED. Most of these assays have adequate analytical performance, but additional high-quality studies are needed to better assess their impact. These assays must be appropriately integrated into ED work flow, taking into account local constraints and priorities. Furthermore, RDTs cannot replace conventional methods because they are not exhaustive, they have performance limitations and they 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 and mortality, as well as their role in antimicrobial stewardship interventions.

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. The other authors report no conflicts of interest relevant to this article.

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