

TAKE-HOME MESSAGE

Although newer rapid influenza tests have improved our ability to rule out disease, they are still better at ruling in influenza. Change in management should be considered before testing.

METHODS**DATA SOURCES**

The authors searched PubMed, EMBASE, BIOSIS Previews, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials through May 21, 2017. In addition, they searched citations, recent guidelines, and narrative reviews. Language was restricted to English, Spanish, and French.

STUDY SELECTION

The systematic review included peer-reviewed studies of adult and pediatric patients with suspected influenza that compared the diagnostic accuracy of 1 or more of 3 commercially available types of rapid influenza tests (digital immunoassay, rapid nucleic acid amplification test, and rapid influenza diagnostic test) against the reference standard (reverse transcriptase polymerase chain reaction). To be included in the meta-analysis, studies were required to report the results for influenza A and B separately.

DATA EXTRACTION AND SYNTHESIS

Two authors independently screened studies for inclusion and extracted data. Discrepancies were resolved by consensus or a third party. Study quality was assessed with Quality Assessment of Diagnostic Accuracy Studies criteria.¹ To report the diagnostic accuracy of the 3 rapid influenza

Update: Can Newer Rapid Influenza Tests Rule Out Disease?**EBEM Commentators**

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Results

Pooled diagnostic accuracy for 3 types of commercially available rapid influenza tests.

Test	No. of Studies	Sensitivity, %* (95% CrI)		Specificity, %* (95% CrI)		Positive LR,* Influenza A; B	Negative LR,* Influenza A; B
		Influenza A	Influenza B	Influenza A	Influenza B		
RIDT	130	54.4 (48.9–59.8)	53.2 (41.7–64.4)	99.4 (99.1–99.7)	99.8 (99.7–99.9)	96.1; 319.4	0.5; 0.5
DIA	19	80.0 (73.4–85.6)	76.8 (65.4–85.4)	98.3 (97.4–98.9)	98.7 (97.5–99.4)	47.1; 59.7	0.2; 0.2
Rapid NAAT	13	91.6 (84.9–95.9)	95.4 (87.3–98.7)	99.2 (98.6–99.7)	99.4 (98.9–99.8)	116.0; 166.4	0.1; 0.05

CrI, Credibility intervals; RIDT, rapid influenza diagnostic test; DIA, digital immunoassay; NAAT, nucleic acid amplification test.

*Pooled estimates.

Of the 162 studies included for full-text review, 38 were excluded for not reporting influenza A and B results separately, leaving 124 articles for quantitative analysis. Overall, the new rapid influenza tests, digital immunoassays, and rapid nucleic acid amplification tests demonstrated strikingly higher sensitivities for influenza A and B compared with the more traditional rapid influenza diagnostic tests. The pooled sensitivities varied widely between test types (ranging from 53% to 95%), whereas the pooled specificities were consistently greater than 98.3%.

In assessment of risk of bias according to the Quality Assessment

of Diagnostic Accuracy Studies,¹ more than half of studies involving rapid influenza diagnostic tests and rapid nucleic acid amplification tests had selection bias or were at high risk of bias. Analysis suggests that bias could have been introduced through lack of blinding to the reference test (with the highest risk of bias in the non automated rapid influenza diagnostic tests, and differences in other covariates (ie, industry sponsorship, point-of-care testing, and commercial brand). Although the heterogeneity identified in rapid test sensitivity could not be fully explained by underreporting of clinical

tests, authors calculated sensitivity, specificity, and positive and negative likelihood ratios (LRs) with 95% confidence intervals. Influenza A and B were considered separately. For meta-analysis, Bayesian bivariate random-effects models were used to generate pooled sensitivity, specificity, and LR estimates with 95% credible intervals. Forest plots and hierarchic summary receiver operating characteristic curves were created, and stratified analyses (eg, age, symptom duration, commercial brand, virus subtype) were done to further examine heterogeneity.

covariates, subgroup analysis revealed that pooled sensitivities favored children over adults by 12.1% to 31.8% and favored industry sponsorship by 6.2% to 34.0%. Sensitivity analysis did not change the main findings.

Commentary

For the 2015 to 2016 season, the Centers for Disease Control and Prevention estimated that influenza resulted in 25 million illnesses, 310,000 hospitalizations, and 12,000 deaths and predict that the 2017 to 2018 season will be more severe.^{2,3} Although influenza affects all populations, those at highest risk for serious outcomes include patients at extremes of age, those with chronic medical conditions, immunosuppression, and pregnant patients.⁴ Influenza symptoms are nonspecific; therefore, having a more accurate diagnostic test could improve patient outcomes by facilitating timely antiviral initiation to high-risk populations while potentially decreasing antibiotic overuse. In addition, early identification or ruling out of

influenza could facilitate throughput and admission processes while also using isolation space appropriately.

A previous 2012 systematic review examined only traditional rapid influenza diagnostic tests and reported excellent specificity of 98.2%, but poor sensitivity of only 62.3%, indicating these tests could be used to rule in influenza but not exclude the diagnosis.⁵ This updated review examines the diagnostic accuracy of 2 newer types of rapid influenza tests (digital immunoassays and rapid nucleic acid amplification tests) in addition to the traditional rapid influenza diagnostic tests. Similar to the rapid influenza diagnostic tests, the newer tests can be performed rapidly at the point of care, and do not require laboratory personnel to operate. The key finding was that digital immunoassays and rapid nucleic acid amplification tests offer markedly higher sensitivities (ranging from 76.8% to 95.4%), with similarly high specificities (>98%). The rapid nucleic acid amplification tests had an overall negative LR less than 0.1, making them the only test that could usefully rule out influenza; however, performance varied widely among different commercial assays, making this finding inconclusive. The authors of this systematic review reported that the rapid nucleic acid amplification tests cost 2 to 5 times more than the rapid influenza diagnostic tests or digital immunoassays.

Current guidelines from the Centers for Disease Control and Prevention recommend testing patients for influenza only if test results would change clinical

management or if patients are being admitted to the hospital.⁶ Therefore, clinicians should use the newer rapid influenza diagnostic tests in the context of each patient encounter, understanding that although the newer tests have improved the ability to rule out disease, they are still better at ruling in disease. Before a local influenza epidemic has been identified, given the extremely high positive LR, rapid diagnostic testing would rule in disease when results were positive. Once the local health department has announced the onset of an epidemic, routine diagnostic testing for influenza may not be required and empiric treatment could be considered for high-risk populations.

The findings should be interpreted with caution because of the risk of bias introduced by industry sponsorship. The majority of the digital immunoassay (68%) and rapid nucleic acid amplification test (62%) studies were sponsored by industry, and a sensitivity analysis found that industry sponsorship was associated with higher sensitivities. Of note, the systematic review itself was funded in part by a rapid influenza test company. The medical literature is clear that industry-sponsored research tends to favor the industry's product and affects how physicians practice medicine; therefore, further research on rapid tests is warranted.^{7,8}

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshots (SRS) series. The source for this systematic review snapshot is: **Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared**

with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis. *Ann Intern Med.* 2017;167:394-409.

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Michael Brown, MD, MSc, Justin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.