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REVIEW

Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction

A Systematic Review and Meta-analysis

Joanna Merckx, MD, MSc; Rehab Wali, BSc, MBBS; Ian Schiller, MSc; Chelsea Caya, MScPH; Genevieve C. Gore, MLIS; Caroline Chartrand, MD, MSc; Nandini Dendukuri, PhD; and Jesse Papenburg, MD, MSc

Background: Rapid and accurate influenza diagnostics can improve patient care.

Purpose: To summarize and compare accuracy of traditional rapid influenza diagnostic tests (RIDTs), digital immunoassays (DIAs), and rapid nucleic acid amplification tests (NAATs) in children and adults with suspected influenza.

Data Sources: 6 databases from their inception through May 2017.

Study Selection: Studies in English, French, or Spanish comparing commercialized rapid tests (that is, providing results in <30 minutes) with reverse transcriptase polymerase chain reaction reference standard for influenza diagnosis.

Data Extraction: Data were extracted using a standardized form; quality was assessed using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) criteria.

Data Synthesis: 162 studies were included (130 of RIDTs, 19 of DIAs, and 13 of NAATs). Pooled sensitivities for detecting influenza A from Bayesian bivariate random-effects models were 54.4% (95% credible interval [CrI], 48.9% to 59.8%) for RIDTs, 80.0% (CrI, 73.4% to 85.6%) for DIAs, and 91.6% (CrI, 84.9% to 95.9%) for NAATs. Those for detecting influenza B were 53.2% (CrI, 41.7% to 64.4%) for RIDTs, 76.8% (CrI, 65.4% to 85.4%) for DIAs, and 95.4% (CrI, 87.3% to 98.7%) for NAATs. Pooled specificities were uniformly high (>98%). Forty-six influenza A and 24 influenza B studies presented pediatric-specific data; 35 influenza A and 16 influenza B studies presented adult-specific data. Pooled sensitivities were higher in children by 12.1 to 31.8 percentage points, except for influenza A by rapid NAATs (2.7 percentage points). Pooled sensitivities favored industry-sponsored studies by 6.2 to 34.0 percentage points. Incomplete reporting frequently led to unclear risk of bias.

Limitations: Underreporting of clinical variables limited exploration of heterogeneity. Few NAAT studies reported adult-specific data, and none evaluated point-of-care testing. Many studies had unclear risk of bias.

Conclusion: Novel DIAs and rapid NAATs had markedly higher sensitivities for influenza A and B in both children and adults than did traditional RIDTs, with equally high specificities.

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Influenza viruses cause yearly epidemics of acute respiratory illness affecting 5% to 30% of the population (1, 2). Diagnosing influenza on the basis of only clinical symptoms is difficult because manifestations vary and are nonspecific (3). Consequently, results of diagnostic tests are useful to guide clinical management. Potential benefits of rapid and accurate diagnosis of influenza infection include prompt initiation of antiviral therapy (4–6), fewer ancillary diagnostic tests (7, 8), fewer hospitalizations (4, 9), prompt institution of hospital infection control measures (10), and less unnecessary antibiotic use (7, 11).

Diagnostic tests for influenza identify the virus in a patient's respiratory secretions by isolation in cell culture, detection of viral RNA by nucleic acid amplification, or detection of viral antigens by immunoassay (10). Reverse transcriptase polymerase chain reaction (RT-PCR) has replaced viral culture as the gold standard for influenza diagnosis because of its superior analytic and clinical sensitivity (12, 13). However, specimens for RT-PCR are typically sent to specialized laboratories, and testing is done in batches, resulting in turnaround times that extend beyond the clinical encounter. Rapid influenza diagnostic tests (RIDTs) that detect viral antigens by immunoassay are widely used because they are simple enough to do at the point of care and provide results in less than 30 minutes. A 2012 systematic review and meta-analysis by Chartrand and colleagues evaluated 159 diagnostic accuracy studies of RIDTs published to December 2011 (14). They showed that commercially available RIDTs had high specificity (98.2% [95% CI, 97.5% to 98.7%]) but poor sensitivity (62.3% [CI, 57.9% to 66.6%]). In light of these findings, regulators and professional societies have questioned the utility of RIDTs (13, 15–17). Since 2011, the following 2 novel classes of rapid influenza diagnostic assays (that is, with results available in <30 minutes) have been

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commercialized, with claims of improved sensitivities based on technological improvements: automated immunochromatographic antigen detection tests (digital immunoassays [DIAs]) and rapid nucleic acid amplification tests (NAATs). Digital immunoassays use an instrument-based digital scan of the test strip to enhance antigen detection accuracy by eliminating the need for an operator to visualize and subjectively interpret test results (16). Rapid NAATs use a modified RT-PCR (18) or isothermal amplification technology (19) to greatly reduce analytic times.

In February 2017, the U.S. Food and Drug Administration (FDA) reclassified and instituted minimum performance standards for rapid influenza tests (17). Therefore, an updated and comprehensive synthesis of the evidence on their accuracy is warranted. The primary objective of this systematic review and meta-analysis was to estimate and compare the diagnostic accuracy of commercialized RIDTs, DIAs, and rapid NAATs for detecting influenza A and B infection in patients with suspected influenza, compared with an RT-PCR reference standard. We also aimed to evaluate patient, test, and methodological factors associated with test accuracy within each of the 3 classes of rapid tests.

METHODS

We used methods recommended by the Cochrane Diagnostic Test Accuracy Working Group (20, 21), including the preparation of a prespecified protocol and analysis plan developed according to the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-analyses Protocols) statement (22). The PRISMA guidelines were used for preparing this report (23).

Data Sources and Searches

On the basis of the PubMed search strategy in Chartrand and colleagues' systematic review (14) and in collaboration with a medical librarian (G.G.), we searched PubMed, Embase, BIOSIS Previews, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials on 18 August 2015, with an update on 21 May 2017 (**Supplement Table 1**, available at Annals.org). We used EndNote (Clarivate Analytics) libraries from Chartrand and colleagues' systematic review (14) to exclude records they had screened and excluded while keeping studies they had included, provided the reference standard used was RT-PCR. In addition, we hand-searched recent guidelines, narrative reviews, and citations of included articles.

Study Selection

We included peer-reviewed studies in English, French, or Spanish providing original data on the diagnostic accuracy of rapid influenza tests against an RT-PCR reference standard. Eligible participants were children and adults with clinically suspected influenza during periods of influenza activity. Editorials, letters to the editor, and conference abstracts were excluded because they contain insufficient information on important data items for investigating sources of heterogeneity and ascertaining methodological quality. Studies using a case–control design (spectrum bias) and those performing the reference standard depending on index test results (partial verification bias) were also excluded. We attempted to contact authors if studies provided insufficient information to construct a 2 × 2 table.

Rapid influenza tests were defined as commercially developed assays that detect influenza A, B, or A/B within 30 minutes by identifying influenza viral antigen or RNA directly from an unprocessed specimen. Acceptable specimens included nasopharyngeal aspirates, swabs, or washes; nasal aspirates, swabs, or washes; and throat swabs. For a study to be eligible, the index test and comparator needed to test the same clinical specimen or 2 specimens taken concurrently from the same anatomical site. Commercial and laboratory-developed RT-PCR assays were acceptable reference tests. When more than 1 RT-PCR assay was used as a reference standard, preference was given to the commercial assay with the best reported analytic sensitivity for influenza A. We excluded studies if the rapid test itself was part of a composite reference standard (incorporation bias).

Two reviewers (R.W. and J.M.) independently screened citations (titles and abstracts) identified by our search strategy and not already screened by Chartrand and colleagues. Potentially relevant articles were retrieved in full and screened for eligibility by the 2 reviewers. Disagreements were resolved by consensus or by involvement of a third reviewer (J.P.).

Data Extraction and Quality Assessment

A data extraction sheet (**Supplement Table 2**, available at Annals.org) based on the form used by Chartrand and colleagues was created in Google Forms to minimize the risk for transcriptional errors (24). It was then pilot-tested on a subset of included articles by 2 reviewers (J.M. and R.W.) before being finalized. Two reviewers independently extracted data. Disagreements were resolved by consensus or by a third reviewer (J.P.). Articles that assessed several index tests against a reference standard were counted as several studies; a separate extraction form was completed for each index test.

The study population was considered pediatric or adult if 85% of persons were below or above, respectively, an age cutoff of 18 to 21 years (as defined by the study). In studies that provided separate results for children and adults, we used the age cutoff applied by the investigators. Point-of-care testing was defined as index testing done outside the traditional laboratory setting by persons other than trained laboratory personnel. We considered a study to have been industry-sponsored if a commercial entity funded it or provided index tests.

Two reviewers independently assessed the quality of individual studies using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) criteria (25).

Data Synthesis and Analysis

For each study, we calculated sensitivity, specificity, and positive and negative likelihood ratios (LRs) along with 95% CIs. Results are presented separately for influenza A and B and for each of the 3 index test types (RIDTs, DIAs, and rapid NAATs). We considered influenza A and B to be separate diagnostic targets; studies that reported only combined influenza A/B data were not included in the quantitative synthesis. We calculated the pooled accuracy estimates (sensitivity, specificity, and LRs) across studies with 95% credible intervals (CrIs) using Bayesian bivariate random-effects meta-analysis models (details in the Supplement, available at Annals.org). The bivariate random-effects approach deals with potential sources of variation caused by imprecision of sensitivity and specificity estimates within individual studies, correlation between sensitivity and specificity across studies, and variation in sensitivity and specificity between studies (26). Because heterogeneity is expected in meta-analysis of diagnostic accuracy studies, a random-effects model is preferred (21). Analyses were done using noninformative priors. We also used the model to create a plot depicting the pooled estimates with the credible and prediction regions and a hierarchical summary receiver-operating characteristic (HSROC) curve (20, 27, 28).

We first assessed heterogeneity by visual inspection of the HSROC curves and the credible and prediction regions (20). Subgroup analyses were planned to further investigate heterogeneity for covariates that provided at least 3 studies per stratum by index test type. Variables selected a priori as potential sources of heterogeneity were population age (children vs. adults), duration of symptoms before testing, type of respiratory specimen, point-of-care testing, commercial brand, infecting virus subtype, study quality, and industry sponsorship. Summary sensitivity and specificity estimates were calculated for each level of a covariate, along with their 95% CrIs. Differences in accuracy were then compared across levels of a covariate. Analyses were done using STATA, version 13 (StataCorp); R, version 3.2.1 (R Foundation; www.r-project.org); and WinBUGS, version 1.4.3 (29).

Researchers usually assume that RT-PCR is a perfect reference standard (that is, 100% sensitivity and 100% specificity) when doing a meta-analysis of the diagnostic accuracy of comparator tests for respiratory viruses (14, 30, 31). However, acknowledging that accuracy varies across commercial and laboratory-developed RT-PCR assays for influenza (32, 33), we did a sensitivity analysis to assess whether our study conclusions would remain unchanged if we allowed RT-PCR to be considered imperfect. We thus repeated our pooled accuracy calculations without forcing a sensitivity and specificity of 100% for the reference standard in the random-effects models (34, 35).

Role of the Funding Source

This study was supported in part by the Québec Health Research Fund and by an investigator-initiated study grant from BD Diagnostic Systems. Funding sources had no involvement in study design, conduct, analysis, or publication.

RESULTS

Search Results

After screening titles and abstracts and doing full-text assessments (Figure 1), we included 61 articles (18, 19, 36–67-68–94). Another 55 articles from Chartrand and colleagues' review (14) that used RT-PCR as the reference standard (95–126-127–149) were also included. Of the 162 studies, 38 did not report 2 × 2 tables separately for influenza A and B. Thus, we included 124 studies in our meta-analysis of accuracy estimates.

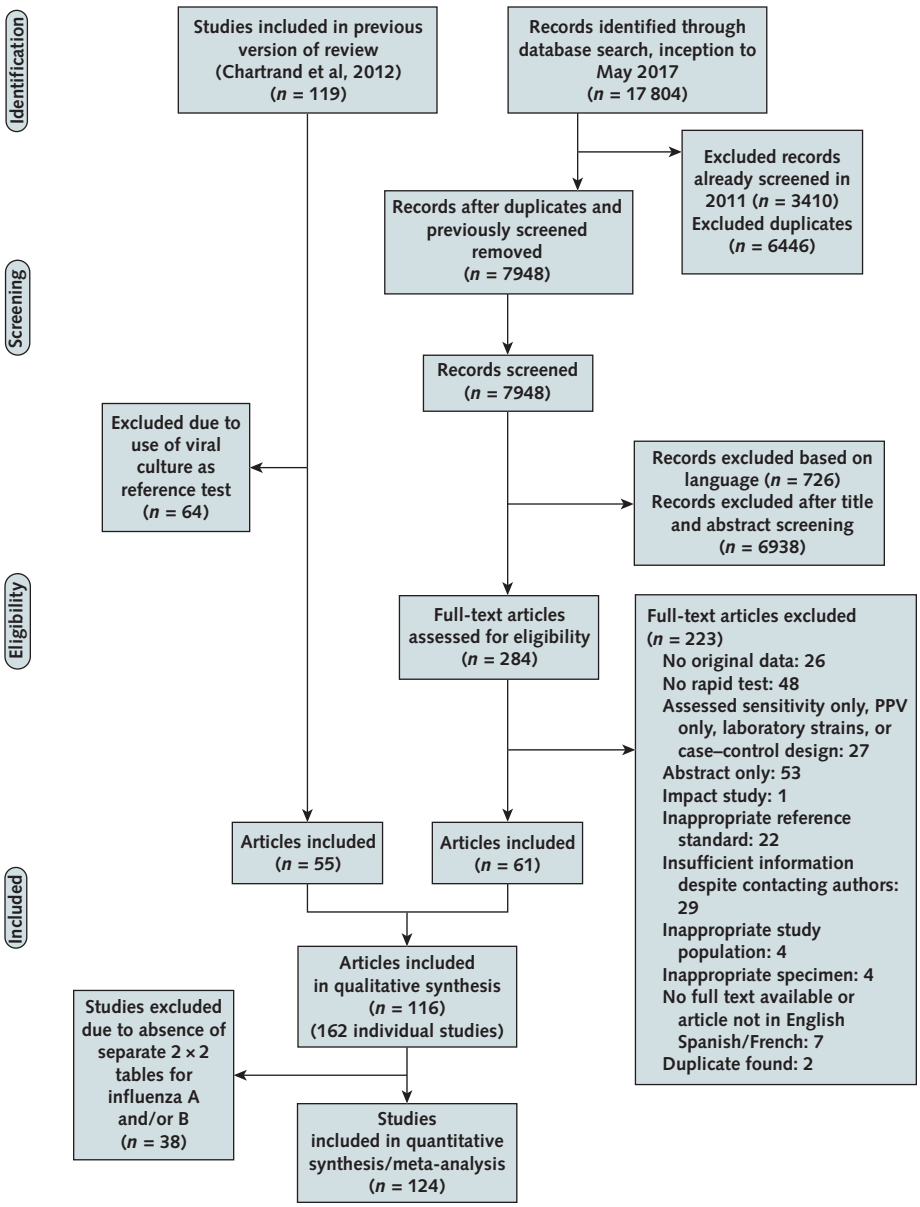
Study Characteristics

Table 1 describes the 162 included studies. Supplement Table 3 (available at Annals.org) provides more details of their characteristics and accuracy estimates. Of the studies, 130 (80.2%) investigated the accuracy of traditional RIDTs, 19 (11.7%) of DIAs, and 13 (8.0%) of rapid NAATs. Among RIDTs, 35 commercial tests were evaluated (Supplement Table 4, available at Annals.org). We also evaluated 2 DIAs, the BD Veritor System for Flu A+B (6 studies; 31.6%) (BD Diagnostic Systems) and the Sofia Influenza A+B Fluorescent Immunoassay (13 studies; 68.4%) (Quidel), and 2 rapid NAATs, the Alere i Influenza A & B (8 studies; 61.5%) (Alere) and the cobas Liat Influenza A/B assay (5 studies; 38.5%) (Roche Diagnostics). Most studies assessed mixed populations of adults and children. The population was considered pediatric in 22.3% (29 of 130), 31.6% (6 of 19), and 7.7% (1 of 13) of RIDT, DIA, and rapid NAAT studies, respectively. Point-of-care testing was done in 23.1% of RIDT studies versus 36.8% of DIA and 0% of rapid NAAT studies. Most studies combined patients in hospital and outpatient settings without separating data or did not report the study setting. Nasopharyngeal swabs were the most commonly used specimens (range, 28.5% to 53.8%). Industry sponsorship was more frequent in DIA (68.4%) and rapid NAAT (61.5%) studies than RIDT studies (20.0%). An insufficient number of studies reported on the duration of symptoms before presentation and testing (2 of 15 DIA studies [68, 75] and 1 of 11 NAAT studies [18]).

Quality Assessment

Quality assessments using QUADAS-2 criteria are summarized in Supplement Figure 1 (available at Annals.org). Most RIDT (53.8%) and rapid NAAT (69.2%) studies did not present clear patient or specimen selection criteria and processes or were at high risk of bias; risk of selection bias was less common in DIA studies (42.1%). Limited reporting of blinding to reference standard results during interpretation of the index test resulted in a risk of bias in 15.8% to 63.2% of studies across index test types. Because DIAs and rapid NAATs have machine-based, objective readers, a

Figure 1. Study search and selection flow chart.



Flow chart summarizing evidence search and study selection. PPV = positive predictive value.

lack of blinding when evaluating these test results represents a smaller risk of bias than for nonautomated colorimetric assays, such as RIDTs.

Synthesis of Results

Primary Analysis: Overall Accuracy

All index test types showed large variability in sensitivity for both influenza A and B across studies (see forest plots in Figures 2 and 3 and HSROC plots in Supplement Figure 2 [available at Annals.org]), whereas specificity was consistently above 95% (Supplement Figure 3, available at Annals.org). Pooled sensitivities and specificities for influenza A and B are presented in Table 2 (see Supplement Table 5, available at Annals.org, for 95% prediction intervals). Forest plots of individual and pooled LRs are presented in Supplement Figure 4 (available at Annals.org). Because pooled specificity was at least 98.3% across classes, we deemed that any differences between groups would not be clinically relevant. Therefore, we calculated differences in pooled accuracy only for sensitivity. Digital immunoassays had sensitivities that were 25.5 percentage points (95% CrI, 17.0 to 33.4 percentage points) and 23.5 percentage points (CrI, 7.7 to 37.9 percentage points) higher than those for traditional RIDTs for diagnosing influenza A and B, respectively. Rapid NAAT sensitivity was superior to that of RIDTs by 37.1 percentage points (CrI, 28.6 to 44.2 percentage points) and 41.7 percentage points (CrI, 28.5 to 54.0

percentage points) for influenza A and B, respectively, and to that of DIAs by 11.5 percentage points (CrI, 2.9 to 19.5 percentage points) and 18.2 percentage points (CrI, 6.9 to 30.6 percentage points).

Subgroup Analyses and Sensitivity Analysis: Investigation of Heterogeneity

We did subgroup analyses to explain the heterogeneity in test accuracy (in terms of sensitivity) seen on visual inspection of the forest and HSROC plots (Table 2). Pooled rapid test sensitivity was consistently higher in children than adults (range of differences in sensitivity, 12.1% [CrI, 3.1% to 22.1%] to 31.8% [CrI, 6.1% to 52.6%]), except with rapid NAATs for influenza A (difference, 2.7% [CrI, −10.7% to 19.7%). For NAATs, adult-specific pooled estimates were generated from 4 studies, 3 of which were on the Alere assay. We therefore did a post hoc sensitivity analysis removing the Liat study (76). The sensitivities for Alere among adults were 80.3% (CrI, 63.7% to 90.8%) and 68.5% (CrI, 40.2% to 87.2%) for influenza A and B, respectively (Supplement Table 6, available at Annals.org).

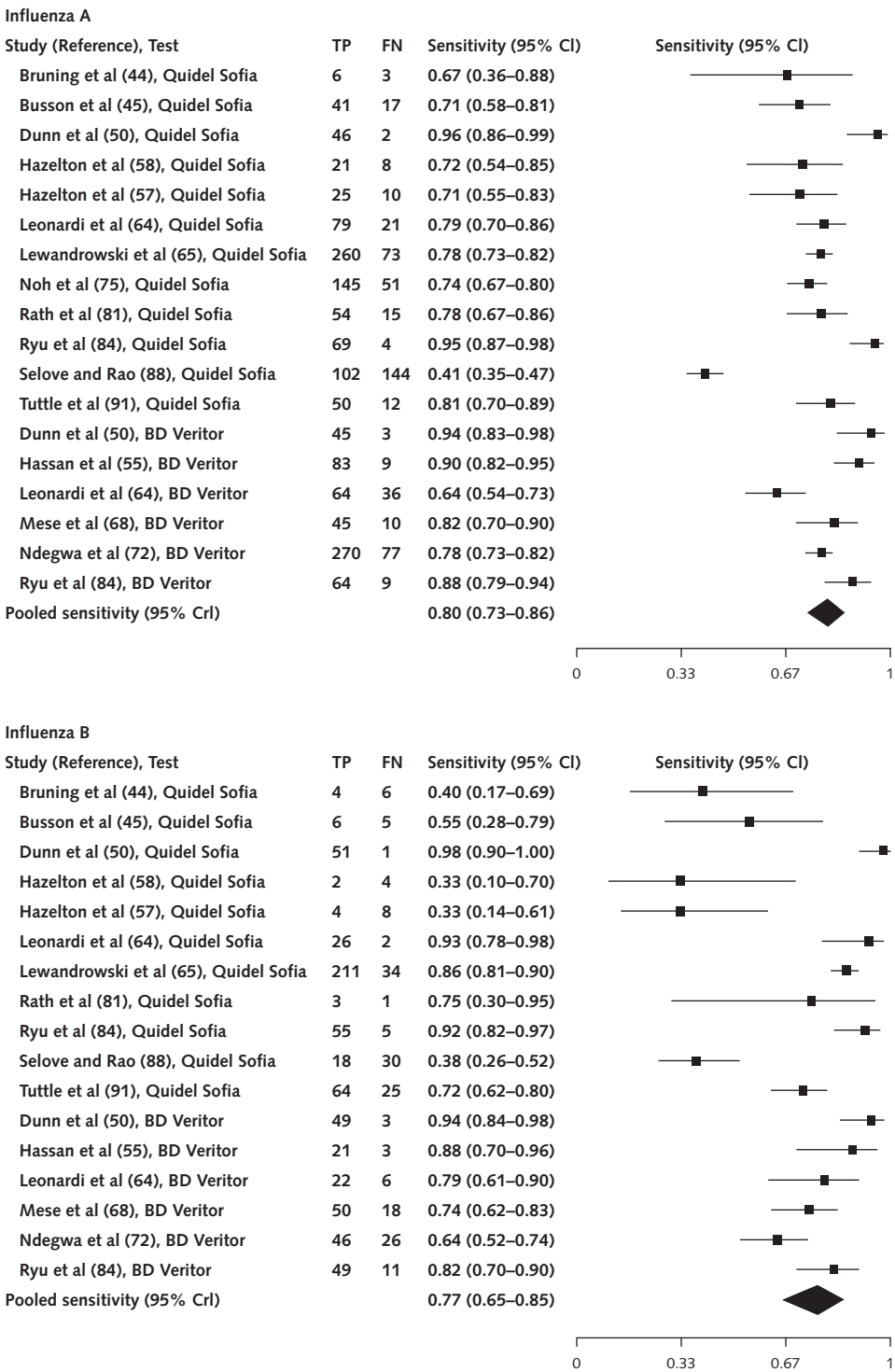
Doing the index test at the point of care did not affect test accuracy for RIDTs and DIAs. No studies evaluated rapid NAATs at the point of care. Pooled sensitivity estimates favored industry-sponsored studies by 6.2 to 34.0 percentage points. Studies evaluating the BD Veritor showed higher pooled sensitivities than

Table 1. Characteristics of the 162 Included Studies

Study Characteristic	Studies of Traditional RIDTs (*n* = 130), *n (%)*	Studies of DIAs (*n* = 19), *n (%)*	Studies of Rapid NAATs (*n* = 13), *n (%)*
Population			
Children	29 (22.3)	6 (31.6)	1 (7.7)
Adults	17 (13.1)	4 (21.1)	1 (7.7)
Mixed/not reported	84 (64.6)	9 (47.4)	11 (84.6)
Commercial brand*			
Directigen Flu A+B	29 (22.3)	–	–
BinaxNOW Influenza A&B	21 (16.2)	–	–
QuickVue Influenza A+B	21 (16.2)	–	–
QuickVue Influenza Test	9 (6.9)	–	–
BD Veritor Flu A+B	–	6 (31.6)	–
Sofia Influenza A+B	–	13 (68.4)	–
Alere i Influenza A & B	–	–	8 (61.5)
Cobas Liat Influenza A/B	–	–	5 (38.5)
Industry sponsorship			
Yes	26 (20.0)	13 (68.4)	8 (61.5)
Majority specimen type			
Nasopharyngeal aspirate or wash	20 (15.4)	0 (0)	0 (0)
Nasopharyngeal swab	37 (28.5)	10 (52.6)	7 (53.8)
Nasal aspirate or wash	7 (5.4)	3 (15.8)	0 (0)
Nasal swab	19 (14.6)	1 (5.3)	1 (7.7)
Throat swab	4 (3.1)	0 (0)	0 (0)
Mixed	7 (5.4)	2 (10.5)	3 (23.1)
Not reported	36 (27.7)	3 (15.8)	2 (15.4)
Setting in which the test was performed			
Outpatient only	31 (23.8)	1 (5.3)	1 (7.7)
Hospital only	15 (11.5)	1 (5.3)	0 (0)
Emergency department only	7 (5.4)	2 (10.5)	0 (0)
Mixed	32 (24.6)	6 (31.6)	6 (46.2)
Other†	3 (2.3)	0 (0)	0 (0)
Not reported	43 (33.1)	9 (47.4)	6 (46.2)
Point-of-care testing			
Yes	30 (23.1)	7 (36.8)	0 (0)
Studies conducted during 2009 H1N1 pandemic period			
Yes	77 (59.2)	0 (0)	2 (15.4)
Not reported	1 (0.8)	1 (5.3)	0 (0)
Influenza strains detected			
Influenza A/B combined	54 (41.5)	5 (26.3)	4 (30.8)
Influenza A	94 (72.3)	18 (94.7)	12 (92.3)
Influenza B	30 (23.1)	17 (89.5)	12 (92.3)

DIA = digital immunoassay; NAAT = nucleic acid amplification test; RIDT = rapid influenza diagnostic test.
* Among traditional RIDTs, 35 commercially available tests were used (see Supplement Table 4 for list). The 4 most common brands are presented. Note: Directigen Flu A+B includes both Directigen EZ Flu A+B and Directigen Flu A+B.
† Includes nursing homes, Haj pilgrims, and H1N1 school outbreak.

Figure 2. Forest plots of the sensitivities of digital immunoassays for influenza A and B.



CrI = credible interval; FN = false negative; TP = true positive.

those evaluating the Quidel Sofia for influenza A (83.0% vs. 77.8%) and B (80.0% vs. 73.5%); however, the 95% CrIs of both differences crossed the null. Test sensitivity was higher for the Liat than the Alere assay for influenza A (97.1% vs. 84.4%; difference, 12.4 percentage points [CrI, 4.9 to 21.9 percentage points]) and influenza B (98.7% vs. 86.6%; difference, 11.8 percentage points [CrI, 2.8 to 29.5 percentage points]). An insufficient number of studies provided data about the duration of symptoms, type of respiratory specimens used, circulat-

ing subtype, or clinical setting (hospitalized vs. outpatient) to allow for these subgroup analyses.

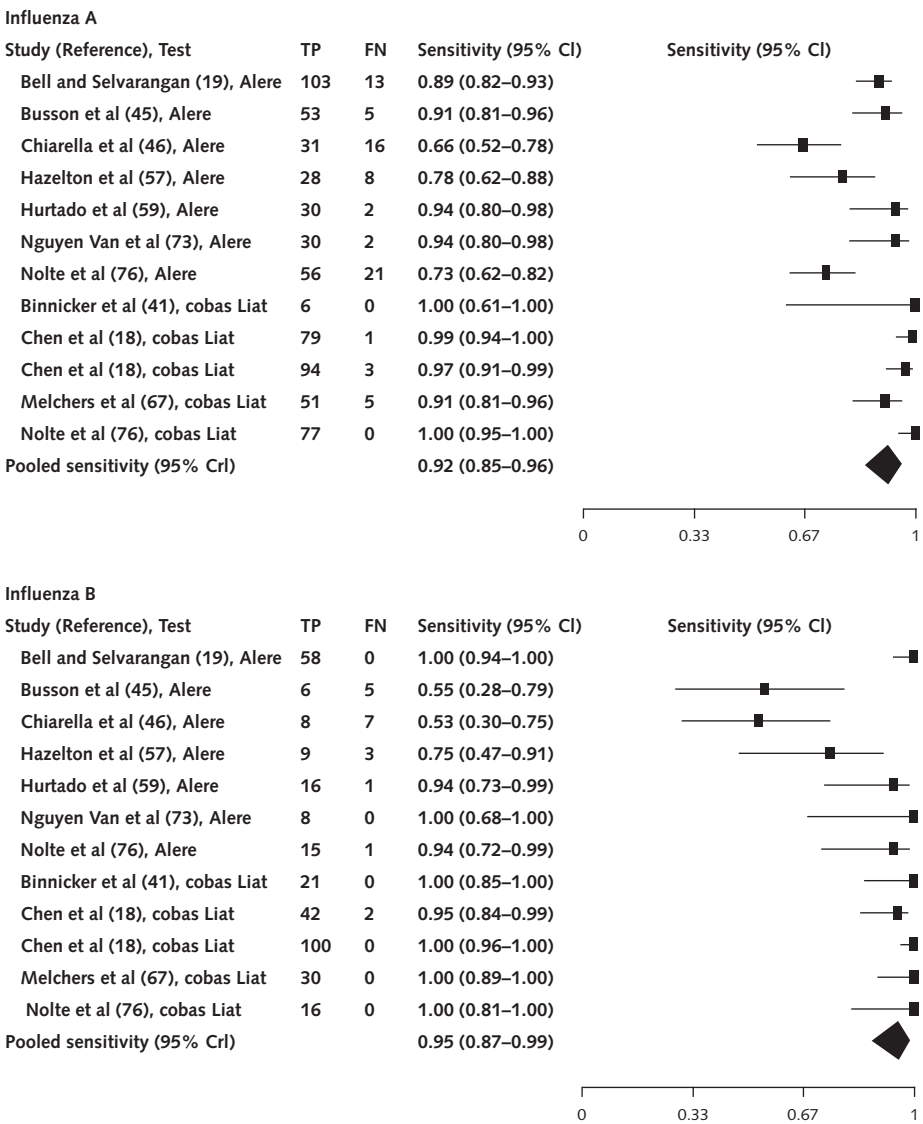
We did a sensitivity analysis for our overall pooled estimates that relaxed the assumption that RT-PCR is a perfect reference standard (**Supplement Table 6**). As expected, we observed higher accuracy estimates than in our primary analysis for all index test types. Nevertheless, our main finding that DIAs and rapid NAATs demonstrated markedly higher sensitivities for influenza A and B than did traditional RIDTs did not change.

DISCUSSION

Through an update and expansion of Chartrand and colleagues' 2012 systematic review and meta-analysis on traditional RIDTs, this study synthesizes the available evidence and compares the diagnostic accuracy of commercially available rapid tests for the detection of influenza A and B infection. Like RIDTs, the newer DIAs and rapid NAATs are simple, fast, and approved for use at the point of care by nonlaboratory personnel. Overall, the rapid tests displayed very high specificities (≥98.3%) and positive LRs (>48). Physicians can therefore diagnose influenza with confidence on the basis of a positive RIDT, DIA, or rapid NAAT result. This should lead to improved patient outcomes and decreased health care costs through prompt implementation of infection control measures and initiation of antiviral treatment when indicated, while decreasing unnecessary ancillary investigations and antibiotic overuse (5, 7, 9).

A key finding of our study is that the pooled sensitivities for DIAs (80.0% for influenza A and 76.8% for

Figure 3. Forest plots of the sensitivities of rapid nucleic acid amplification tests for influenza A and B.



CrI = credible interval; FN = false negative; TP = true positive.

Table 2. Overall and Subgroup Analyses of Pooled Rapid Test Accuracy Estimates for Influenza A and B, by Index Test Type*

Index Test Type	Influenza A		Influenza B	
	Pooled Sensitivity (95% CrI), %	Pooled Specificity (95% CrI), %	Pooled Sensitivity (95% CrI), %	Pooled Specificity (95% CrI), %
Overall				
Traditional RIDTs (94 influenza A studies; 30 influenza B studies)	54.4 (48.9 to 59.8)	99.4 (99.1 to 99.7)	53.2 (41.7 to 64.4)	99.8 (99.7 to 99.9)
DIAs (18 influenza A studies; 17 influenza B studies)	80.0 (73.4 to 85.6)	98.3 (97.4 to 98.9)	76.8 (65.4 to 85.4)	98.7 (97.5 to 99.4)
Rapid NAATs (12 influenza A studies; 12 influenza B studies)	91.6 (84.9 to 95.9)	99.2 (98.6 to 99.7)	95.4 (87.3 to 98.7)	99.4 (98.9 to 99.8)
Difference in sensitivities, overall				
Traditional RIDTs vs. DIAs	**−25.5 (−33.4 to −17.0)**	–	**−23.5 (−37.9 to −7.7)**	–
Traditional RIDTs vs. rapid NAATs	**−37.1 (−44.2 to −28.6)**	–	**−41.7 (−54.0 to −28.5)**	–
DIAs vs. rapid NAATs	**−11.5 (−19.5 to −2.9)**	–	**−18.2 (−30.6 to −6.9)**	–
Subgroup analyses†				
Study population (age)‡				
Traditional RIDTs				
Children (31 influenza A studies; 9 influenza B studies)	61.2 (55.0 to 67.2)	99.2 (98.5 to 99.7)	65.7 (45.3 to 80.5)	99.6 (99.2 to 99.8)
Adults (23 influenza A studies; 5 influenza B studies)	42.6 (34.8 to 50.9)	99.5 (98.6 to 99.8)	33.2 (19.9 to 50.7)	99.9 (99.4 to 100)
Difference in RIDT sensitivity: children vs. adults	**18.5 (8.4 to 28.3)**	–	**31.8 (6.1 to 52.6)**	–
DIAs				
Children (11 influenza A studies; 11 influenza B studies)	87.6 (81.8 to 92.2)	98.1 (96.4 to 99.1)	82.5 (71.2 to 90.2)	98.8 (95.6 to 99.7)
Adults (8 influenza A studies; 7 influenza B studies)	75.4 (66.6 to 82.6)	96.7 (94.7 to 98.0)	57.0 (39.5 to 71.6)	98.8 (97.5 to 99.5)
Difference in DIA sensitivity: children vs. adults	**12.1 (3.1 to 22.1)**	–	**25.3 (6.9 to 44.7)**	–
Rapid NAATs				
Children (4 influenza A studies; 4 influenza B studies)	90.2 (79.2 to 95.8)	99.0 (96.8 to 99.8)	95.9 (82.9 to 99.2)	99.5 (98.2 to 99.9)
Adults (4 influenza A studies; 4 influenza B studies)	87.4 (71.1 to 95.6)	98.0 (93.2 to 99.5)	75.7 (51.8 to 90.7)	99.3 (97.8 to 99.8)
Difference in NAAT sensitivity: children vs. adults	2.7 (−10.7 to 19.7)	–	**19.5 (1.0 to 43.7)**	–
Location of testing				
Traditional RIDTs				
POC (17 influenza A studies; 4 influenza B studies)	61.2 (48.4 to 72.7)	98.0 (96.2 to 99.0)	44.8 (17.5 to 76.2)	99.5 (98.9 to 99.8)
Not POC (77 influenza A studies; 26 influenza B studies)	52.9 (46.9 to 58.8)	99.6 (99.3 to 99.8)	54.4 (43.1 to 65.7)	99.9 (99.8 to 99.9)
Difference in RIDT sensitivity: POC vs. not POC	8.2 (−5.9 to 21.3)	–	−9.5 (−39.1 to 23.5)	–
DIAs				
POC (7 influenza A studies; 6 influenza B studies)	77.6 (70.4 to 83.4)	98.1 (95.7 to 99.1)	72.0 (57.4 to 82.0)	98.7 (95.9 to 99.5)
Not POC (11 influenza A studies; 11 influenza B studies)	82.3 (72.1 to 89.7)	98.2 (97.1 to 98.9)	80.4 (64.5 to 90.3)	98.4 (96.5 to 99.4)
Difference in DIA sensitivity: POC vs. not POC	−4.7 (−14.9 to 7.0)	–	−8.4 (−25.9 to 10.0)	–
Industry sponsorship				
Traditional RIDTs				
Sponsored (20 influenza A studies; 8 influenza B studies)	70.8 (60.0 to 79.6)	99.1 (98.2 to 99.6)	77.8 (60.0 to 90.1)	99.7 (99.4 to 99.9)
Not sponsored (74 influenza A studies; 22 influenza B studies)	50.0 (43.9 to 55.2)	99.5 (99.1 to 99.7)	43.5 (33.3 to 54.3)	99.8 (99.7 to 99.9)
Difference in RIDT sensitivity: sponsored vs. not sponsored	**21.1 (9.1 to 31.7)**	–	**34.0 (13.7 to 50.5)**	–
DIAs				
Sponsored (13 influenza A studies; 12 influenza B studies)	84.1 (78.3 to 88.8)	98.1 (96.7 to 98.9)	79.7 (66.1 to 88.4)	98.6 (96.0 to 99.5)
Not sponsored (5 influenza A studies; 5 influenza B studies)	67.5 (52.9 to 79.4)	98.6 (97.0 to 99.4)	69.4 (51.1 to 84.2)	99.0 (97.9 to 99.5)
Difference in DIA sensitivity: sponsored vs. not sponsored	**16.5 (3.5 to 31.9)**	–	10.0 (−9.6 to 30.4)	–

Continued on following page

Table 2–Continued

Index Test Type	Influenza A		Influenza B	
	Pooled Sensitivity (95% CrI), %	Pooled Specificity (95% CrI), %	Pooled Sensitivity (95% CrI), %	Pooled Specificity (95% CrI), %
Rapid NAATs				
Sponsored (8 influenza A studies; 8 influenza B studies)	92.6 (84.5 to 96.8)	99.4 (98.6 to 99.8)	97.2 (92.7 to 99.0)	99.6 (99.1 to 99.8)
Not sponsored (4 influenza A studies; 4 influenza B studies)	86.2 (71.3 to 94.7)	98.5 (96.2 to 99.5)	80.0 (53.0 to 94.7)	98.6 (96.3 to 99.5)
Difference in NAAT sensitivity: sponsored vs. not sponsored	6.2 (−5.1 to 21.7)	–	**16.9 (1.7 to 44.1)**	–
Commercial brand				
DIAs				
Sofia (12 influenza A studies; 11 influenza B studies)	77.8 (68.8 to 85.4)	98.5 (97.4 to 99.2)	73.5 (55.8 to 86.1)	98.0 (95.4 to 99.1)
Veritor (6 influenza A studies; 6 influenza B studies)	83.0 (73.4 to 90.1)	97.5 (95.5 to 98.7)	80.0 (68.8 to 88.2)	99.5 (98.8 to 99.8)
Difference in DIA sensitivity: Sofia vs. Veritor	−5.1 (−16.4 to 6.9)	–	−6.4 (−25.8 to 10.4)	–
Rapid NAATs				
Alere (7 influenza A studies; 7 influenza B studies)	84.4 (75.3 to 90.9)	98.9 (97.7 to 99.6)	86.6 (69.0 to 95.3)	99.1 (98.1 to 99.7)
Liat (5 influenza A studies; 5 influenza B studies)	97.1 (92.9 to 98.9)	99.4 (98.4 to 99.8)	98.7 (95.6 to 99.7)	99.5 (98.7 to 99.9)
Difference in NAAT sensitivity: Alere vs. Liat	**−12.4 (−21.9 to −4.9)**	–	**−11.8 (−29.5 to −2.8)**	–

CrI = credible interval; DIA = digital immunoassay; NAAT = nucleic acid amplification test; POC = point of care; RIDT = rapid influenza diagnostic test.
* Differences in pooled sensitivity estimates between groups that did not include the null (0%) in its 95% CrI are in boldface.
† For subgroups that contained ≥3 studies per stratum by index test type.
‡ Data from studies performed in ≥85% adult or ≥85% pediatric populations or from studies of mixed-age populations that provided data for the adult and pediatric subgroups.

influenza B) and rapid NAATs (91.6% for influenza A and 95.4% for influenza B) are markedly higher than those for RIDTs. The use of DIAs and rapid NAATs improves detection of true cases of influenza by 25 and 40 percentage points, respectively, compared with RIDTs.

Similar to Chartrand and colleagues, we found that traditional RIDTs have summary sensitivities (54.4% for influenza A and 53.2% for influenza B) well below new FDA minimum performance requirements. Effective December 2018, tests detecting influenza antigens will need to show a sensitivity of at least 80%, with a 95% CI lower bound of 70%, against an RT-PCR comparator (17).

Our literature searches to May 2017 identified 1 meta-analysis of rapid influenza test accuracy based on a literature search done in the past 5 years (150). Bruning and colleagues reviewed the accuracy of rapid tests for respiratory viruses against RT-PCR. They included 134 influenza studies (122 RIDTs, 9 Sofia, 1 BD Veritor, and 2 Alere) published to January 2016 and reported pooled sensitivity and specificity estimates of 61.1% and 98.9% for any influenza. They did not evaluate DIAs as a class but saw a pooled sensitivity for the Sofia of 75.3%. Of importance, the literature on novel tests has evolved rapidly since January 2016. Our review included an additional 8 DIA and 10 NAAT studies. We could thus compare results across classes of tests and perform clinically relevant subgroup analyses within each class. Moreover, we presented all data separately for influenza A and B, in keeping with FDA guidance.

The improved sensitivity of DIAs is likely due to proprietary chemistry innovations and to automated readers that eliminate the subjectivity of an operator visualizing and interpreting test results (16). Molecular techniques, such as NAATs, are expected to have low analytic detection limits and thus higher clinical sensitivity (151). We found that rapid NAATs were the only class of rapid tests with overall negative LRs below 0.1, thereby making a negative result useful to rule out influenza (152). However, the cost of DIAs ($15 to $20 per test) is similar to that of RIDTs, whereas rapid NAATs may cost 2 to 5 times that amount. Whether the incremental gains in sensitivity of rapid NAATs versus DIAs are worth their added costs will likely depend on the patient populations and clinical contexts in which they are used. Moreover, different commercial rapid NAATs might not perform equally. Pooled sensitivities were above 97% for the Liat modified RT-PCR assay. In contrast, the Alere isothermal assay had sensitivities for influenza A and B of 84.4% and 86.6%, respectively, similar to those of the Veritor DIA (83.0% and 80.0%).

By updating Chartrand and colleagues' review on RIDTs, we could make direct statistical comparisons of the performance of RIDTs versus newer rapid tests. However, we note that no new information has been gained from studying traditional RIDTs since 2012. Despite the addition of 39 evaluations of RIDTs published after Chartrand and colleagues' review, summary estimates for this class are nearly identical. Thus, additional diagnostic accuracy research on RIDTs seems to be of

no value; it will not change future pooled estimates or the interpretation of the test's clinical utility (153).

In children, the pooled sensitivities for influenza A and B of DIAs (87.6% and 82.5%) and rapid NAATs (90.2% and 95.9%) make these newer-generation tests acceptable for use in the pediatric population. We saw that RIDT and DIA sensitivity was higher by approximately 15 percentage points for influenza A and 30 percentage points for influenza B in children than adults, likely related to more prolonged and abundant viral shedding in the former (154, 155). Studies of DIAs in adult populations exhibited pooled sensitivities of at most 75% and negative LRs of 0.25 or more. Therefore, clinicians should be aware of the possibility of false-negative results in adults tested by DIA and consider retesting by RT-PCR if the result could influence patient management. In contrast, rapid NAAT pooled sensitivities of 87.4% and 75.7% for influenza A and B in adults suggest that they may be the preferred rapid test in this population. However, we caution that our adult rapid NAAT results should not be overinterpreted because they are based on only 4 studies (442 participants; 155 influenza infections). Moreover, 3 of the 4 adult studies evaluated the Alere assay.

The DIA and rapid NAAT assays evaluated in our review have received Clinical Laboratory Improvement Amendments waivers as low-complexity tests that can be done outside the laboratory. On the basis of 7 studies, we found that using DIAs at the point of care did not affect performance. Unfortunately, no studies evaluating NAATs at the point of care were identified. Given their high sensitivity, NAATs may be prone to false-positive results if protocol breaches cause environmental contamination. Moreover, the Alere NAAT is approved for point-of-care testing only if done directly on a swab. Some included studies evaluated the Alere on swabs eluted in transport medium, for which it is considered a moderately complex assay. Further investigation of the performance, feasibility, and effect of near-patient testing with DIAs and NAATs is therefore warranted; this is the setting in which they are expected to most improve patient outcomes (156, 157).

Studies that declared industry sponsorship produced higher sensitivity estimates by 6.2 to 34.0 percentage points than nonsponsored studies. These differences were statistically significant for RIDTs, DIAs for influenza A, and NAATs for influenza B. This is a consideration when interpreting our results, because a large proportion of DIA (68.4%) and rapid NAAT (61.5%) studies received industry sponsorship in the form of funding or in-kind provision of study materials. This underscores the importance of conducting and publishing independent diagnostic accuracy evaluations of commercial assays, preferably done within the flow of the usual diagnostic pathway, either in the clinical laboratory or at the point of care.

This review has potential limitations. First, we could not assess publication bias because no reliable methods exist to investigate this in diagnostic accuracy studies (20). Second, we saw differences in the distribution of covariates that could affect test sensitivity, such as point-of-care testing and industry sponsorship, across the 3 index test types. Unfortunately, because of the limited number of studies on DIAs and rapid NAATs, we could not adjust simultaneously for all covariates using metaregression. Moreover, no NAAT studies evaluated point-of-care testing and very few reported adult-specific data. Third, our pooled estimates do not account for the conditional dependence of several index tests done on a single sample. This may lead to underestimation of between-study variance and narrower CrIs but would not affect point estimates. Fourth, this study was partly funded by BD Diagnostic Systems, the manufacturers of a DIA. However, we used publicly available data and transparent methods to draw our inferences, and sponsors were not involved in study design, conduct, analysis, or interpretation. Finally, we also highlight a lack of important contextual information in the evidence base. Data not readily available in the diagnostic laboratory, such as study setting, clinical manifestations, presence of comorbid conditions, and duration of symptoms, could affect test accuracy but are frequently missing from reports.

Because of their simplicity and speed, rapid influenza tests are potentially valuable diagnostic tools, especially if deployed at the point of care. Understanding the performance characteristics of different test methods across different patient populations is important for laboratory directors who must decide on their implementation and clinicians who must interpret their results for patient management. The results of our systematic review and meta-analysis, using RT-PCR as a reference standard, suggest that traditional RIDTs are likely to be phased out by regulatory agencies like the FDA because of their poor sensitivity, especially in adults. Digital immunoassays and rapid NAATs showed markedly higher sensitivities for influenza A and B than did RIDTs, with equally high specificities. Performance of the newer-generation rapid influenza tests was also better in pediatric than adult populations, although the difference was less pronounced for rapid NAATs. Additional clinical impact and cost-effectiveness analyses of DIAs and NAATs should help guide decisions about applying rapid testing for influenza in clinical practice.

From McGill University, McGill University Health Centre, and Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montreal, Quebec, Canada, and Royal College of Surgeons in Ireland, Dublin, Ireland.

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Reproducible Research Statement: *Study protocol:* See Supplement. *Statistical code:* See Supplement. *Data set:* Full data set and codebook available on www.nandinidendukuri.com.

Requests for Single Reprints: Jesse Papenburg, MD, MSc, McGill University Health Centre, E05.1905, 1001 Décarie Boulevard, Montreal, Québec H4A 3J1, Canada; e-mail, jesse.papenburg@mail.mcgill.ca.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Merckx: Department of Epidemiology, Biostatistics and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, Quebec H3A 1A2, Canada.
Dr. Wali: 3 Tullyhall Way, Lucan, Dublin K78 TH73, Ireland.
Mr. Schiller: Centre for Outcomes Research and Evaluation (CORE), 5252 Boulevard de Maisonneuve, Bureau 3C.07, Montreal, Quebec H4A 3S5, Canada.
Ms. Caya: McGill University Health Centre–Research Institute, EM3.3509, 1001 Décarie Boulevard, Montreal, Quebec H4A 3J1, Canada.
Ms. Gore: Schulich Library of Physical Sciences, Life Sciences, and Engineering, Macdonald-Stewart Library Building, 809 Sherbrooke Street West, Montreal, Quebec H3A 0C1, Canada.
Dr. Chartrand: CHU Sainte-Justine, Département de Pédiatrie, 3175 Chemin de la Côte Sainte-Catherine, Montreal, Quebec H3T 1C5, Canada.
Dr. Dendukuri: Centre for Outcomes Research and Evaluation (CORE), 5252 Boulevard de Maisonneuve, Bureau 3F.50, Montreal, Quebec H4A 3S5, Canada.
Dr. Papenburg: McGill University Health Centre, E05.1905, 1001 Décarie Boulevard, Montreal, Quebec H4A 3J1, Canada.

Author Contributions: Conception and design: J. Merckx, R. Wali, C. Chartrand, N. Dendukuri, J. Papenburg.
Analysis and interpretation of the data: J. Merckx, R. Wali, I. Schiller, C. Caya, C. Chartrand, N. Dendukuri, J. Papenburg.
Drafting of the article: J. Merckx, R. Wali, C. Caya, N. Dendukuri, J. Papenburg.
Critical revision of the article for important intellectual content: J. Merckx, C. Caya, N. Dendukuri, J. Papenburg.
Final approval of the article: J. Merckx, R. Wali, I. Schiller, C. Caya, G.C. Gore, C. Chartrand, N. Dendukuri, J. Papenburg.
Provision of study materials or patients: G.C. Gore, J. Papenburg.
Statistical expertise: J. Merckx, I. Schiller, C. Chartrand, N. Dendukuri, J. Papenburg.
Obtaining of funding: J. Papenburg.
Administrative, technical, or logistic support: J. Merckx, R. Wali, G.C. Gore.
Collection and assembly of data: J. Merckx, R. Wali, C. Caya, G.C. Gore, C. Chartrand, J. Papenburg.