

Accuracy of Rapid Influenza Diagnostic Tests

A Meta-analysis

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Background: Timely diagnosis of influenza can help clinical management.

Purpose: To examine the accuracy of rapid influenza diagnostic tests (RIDTs) in adults and children with influenza-like illness and evaluate factors associated with higher accuracy.

Data Sources: PubMed and EMBASE through December 2011; BIOSIS and Web of Science through March 2010; and citations of articles, guidelines, reviews, and manufacturers.

Study Selection: Studies that compared RIDTs with a reference standard of either reverse transcriptase polymerase chain reaction (first choice) or viral culture.

Data Extraction: Reviewers abstracted study data by using a standardized form and assessed quality by using Quality Assessment of Diagnostic Accuracy Studies criteria.

Data Synthesis: 159 studies evaluated 26 RIDTs, and 35% were conducted during the H1N1 pandemic. Failure to report whether results were assessed in a blinded manner and the basis for patient recruitment were important quality concerns. The pooled sensitivity

and specificity were 62.3% (95% CI, 57.9% to 66.6%) and 98.2% (CI, 97.5% to 98.7%), respectively. The positive and negative likelihood ratios were 34.5 (CI, 23.8 to 45.2) and 0.38 (CI, 0.34 to 0.43), respectively. Sensitivity estimates were highly heterogeneous, which was partially explained by lower sensitivity in adults (53.9% [CI, 47.9% to 59.8%]) than in children (66.6% [CI, 61.6% to 71.7%]) and a higher sensitivity for influenza A (64.6% [CI, 59.0% to 70.1%]) than for influenza B (52.2% [CI, 45.0% to 59.3%]).

Limitation: Incomplete reporting limited the ability to assess the effect of important factors, such as specimen type and duration of influenza symptoms, on diagnostic accuracy.

Conclusion: Influenza can be ruled in but not ruled out through the use of RIDTs. Sensitivity varies across populations, but it is higher in children than in adults and for influenza A than for influenza B.

Primary Funding Source: Canadian Institutes of Health Research.

Ann Intern Med. 2012;156:500–511.

www.annals.org

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This article was published at www.annals.org on 28 February 2012.

Worldwide, 3 to 5 million individuals develop severe influenza each year and 250 000 to 500 000 die of influenza-related causes (1). Even in developed countries, such as the United States, influenza is responsible for more than 200 000 hospitalizations annually and 3000 to 49 000 deaths (2, 3). Moreover, as illustrated by the 2009 H1N1 pandemic that affected 214 countries (4), influenza has the potential to rapidly spread globally.

Early identification of influenza is important for optimal patient management and infection control. However, the case definition of influenza-like illness, defined by the Centers for Disease Control and Prevention and the World Health Organization as fever (temperature $>37.8^{\circ}\text{C}$) and cough or sore throat (5, 6), has modest sensitivity (64% to

65%) and specificity (67%) (7, 8). For this reason, physicians sometimes use tests to diagnose influenza.

Viral culture was the time-honored gold standard for influenza diagnosis. However, 3- to 10-day turnaround times for results reduce its utility for patient management, although shell vial culture can produce results in 48 hours with similar accuracy (9, 10). More recently, reverse transcriptase polymerase chain reaction (RT-PCR) has replaced viral culture as the gold standard. It is considered the most sensitive and specific test for influenza, with a 2% to 13% higher detection rate than culture and results that can be obtained within hours (11). It is also the most expensive and least widely available test because of the specialized equipment and expertise required, and results may be delayed because samples are usually run in batches (9, 10, 12).

Rapid influenza diagnostic tests (RIDTs) attempt to overcome some of these problems. They are simple to use; give results in 15 to 30 minutes; and, in some cases, can be used at the point of care in a routine clinical setting, such as a physician's office or an emergency department. These tests are usually immunochromatographic assays that detect specific influenza viral antigens in respiratory specimens (11). Their costs (approximately \$15 to \$20 per test for kit and reagents [13]) are similar to those of laboratory-based influenza tests, such as RT-PCR.

Unfortunately, RIDTs may have inconsistent accuracy, with reported sensitivity ranging from 10% to 80%

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CME quiz (preview on page I-50)
Conversion of graphics into slides

(10–12, 14), whereas specificity usually exceeds 90%. Even so, the Infectious Diseases Society of America, the Centers for Disease Control and Prevention, and the World Health Organization still consider them part of their guidelines, recognizing their usefulness in patient and outbreak management—especially when other tests, such as RT-PCR or immunofluorescence, are not readily available—while cautioning against potential misdiagnosis associated with their use (10, 11, 14). In light of these recommendations and the availability of many RIDTs approved for point-of-care use, it is important for health care providers to better understand the accuracy of these tests. Previous systematic reviews have been limited to pediatric studies (15) or have addressed only 1 commercial RIDT (8) and were conducted before the emergence of the influenza A(H1N1) 2009 strain (8, 15).

METHODS

We developed and followed a protocol based on standard guidelines for the systematic review of diagnostic studies (16, 17) and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (18) as the template for reporting the review.

Data Sources and Searches

We searched 4 electronic databases: PubMed (January 1950 to December 2011), EMBASE (January 1980 to December 2011), BIOSIS (January 1969 to March 2010), and Web of Science (January 1980 to March 2010). The databases were searched in March 2010, and an updated search of PubMed and EMBASE was conducted in December 2011. Bibliographies of included studies, recent narrative reviews on RIDTs, and guidelines on influenza were hand-searched for additional relevant studies. Diagnostic manufacturers were also contacted to get additional or unpublished studies.

The search strategy was designed with the help of a medical librarian and contained search terms for the influenza disease or virus combined with search terms for rapid diagnostic immunoassays, including brand names for the most common commercial RIDTs. Search terms for influenza included: “Influenza, Human” [MeSh] OR “Influenza A virus” [MeSh] OR “Influenza B virus” [MeSh] OR “influenza” OR “flu” OR “grippe.” Search terms for the tests included: “rapid test*” OR “rapid diagnos*” OR “rapid diagnostic test*” OR “point-of-care test*” OR “antigen detection test*” OR “antigen detection” OR “rapid antigen test*” OR “immunoassay*” OR “immunochromatographic test*” OR “Binax NOW” OR “Directigen Flu” OR “Flu OIA” OR “QuickVue Influenza” OR “Rapid Detection Flu” OR “SAS Influenza” OR “TRU FLU” OR “XPECT flu” OR “Zstat flu.” Studies published in either English or French were considered.

Context

Rapid influenza diagnostic tests (RIDTs) are immunochromatographic assays that detect influenza viral antigens.

Contribution

This systematic review of 159 studies involving 26 RIDTs found that RIDTs have a high specificity and positive likelihood ratio and modest and highly variable sensitivity for detecting influenza.

Caution

Studies that assessed the effect of ordering RIDTs on clinical outcomes were not reviewed.

Implication

Positive RIDT results rule in but negative results do not rule out influenza. Whether routine use of these tests is warranted is unclear.

—The Editors

Study Selection

Studies were included if they assessed the accuracy of an RIDT against 1 of the 2 accepted reference standards. For this review, RIDTs were defined as any commercially available assay that identified influenza viral antigens or neuraminidase activity in respiratory specimens through simple immunochromatographic formats. In-house tests and precommercial versions were excluded. Acceptable reference standards included viral culture or RT-PCR. If both were available, data on RT-PCR were chosen because of the test’s superior sensitivity and specificity.

Studies were excluded if they compared RIDTs with immunofluorescence or enzyme-linked immunosorbent assay (because those are not widely acknowledged reference standards for influenza diagnosis), if they used the result of the RIDTs as part of a composite reference standard (incorporation bias), or if they performed the reference standard only on samples with negative RIDT results (partial verification bias). We also excluded conference abstracts and case-control studies (testing with the RIDT of known positive or negative samples), which, by creating spectrum bias, can overestimate the accuracy of a test (19). If a selected publication included more than 1 RIDT, each test comparison was included as a separate “study.”

One reviewer screened titles and abstracts for relevance and examined full-text articles of those judged to be potentially eligible. When there was uncertainty about eligibility, a second reviewer was involved and consensus was reached.

Data Extraction and Quality Assessment

A data extraction form was piloted on a subset of included articles by 2 reviewers before being finalized. One reviewer extracted data from all of the articles. A second reviewer extracted data from a randomly chosen sample of 22 articles (approximately 20% of all included articles). The numbers in the extracted 2×2 tables matched exactly

Table 1. Characteristics of the 159 Included Studies

Characteristic	Studies, n (%)
Population	
Children	54 (34)
Adults	22 (14)
Mixed/not reported	83 (52)
Clear definition of ILI*	
Yes	53 (33)
Study conducted during the H1N1 pandemic	
Yes	56 (35)
Commercial RIDT†	
BinaxNOW Flu A and Flu B	6 (4)
BinaxNOW Influenza A & B	22 (14)
Directigen Flu A	11 (7)
Directigen Flu A+B	30 (19)
FLU OIA	7 (4)
QuickVue Influenza	18 (11)
QuickVue Influenza A+B	23 (14)
SD Bioline Influenza	6 (4)
ZstatFlu	6 (4)
Mixed tests‡	3 (2)
Others§	27 (17)
Reference standard	
RT-PCR	86 (54)
Culture	69 (43)
Culture and RT-PCR inseparable	4 (3)
Type of specimen	
Throat swab	4 (3)
Nasal swab	10 (6)
Nasal aspirate	3 (2)
Nasal wash	4 (3)
Nasopharyngeal swab	26 (16)
Nasopharyngeal aspirate	21 (13)
Nasopharyngeal wash	3 (2)
Mixed/not reported	88 (55)
Duration of symptoms before testing	
Any information	21 (13)
Point-of-care testing	
Yes	31 (20)

ILI = influenza-like illness; RIDT = rapid influenza diagnostic test; RT-PCR = reverse transcriptase polymerase chain reaction.

* Article provided a clear definition of the clinical symptoms on the basis of which patients were recruited for the study.

† Manufacturers for each RIDT are as follows: 3M Rapid Detection Flu A+B, 3M, St. Paul, Minnesota; Actim Influenza A&B, Medix Biochemica, Kaunianen, Finland; BinaxNOW Flu A and Flu B and BinaxNOW Influenza A&B, Inverness Medical Innovations, Portland, Maine; BioTracer Influenza A&B, Bio Focus, Gunpo-si, Korea; Capilia Flu A + B, Alfresa Pharma, Osaka, Japan; Clearview Exact Influenza A&B, Inverness Medical Innovations, Portland, Maine; Directigen Flu A and Directigen Flu A+B, Becton, Dickinson and Company, Franklin Lakes, New Jersey; ESPLINE Influenza A&B-N, Fujirebio, Tokyo, Japan; FLU-A Dot-ELISA, Wantai Biological Pharmacy Enterprise Company, Beijing, China; FLU OIA, BioStar, Boulder, Colorado; ImmunoCard STAT! Flu A and B, Meridian Bioscience, Cincinnati, Ohio; INFLU A.B-Quick, Denka Seiken, Tokyo, Japan; Influenzatop, ALLDIAG, Strasbourg, France; NanoSign Influenza A/B, SICL CO LTD, Seoul, South Korea; QuickVue Influenza and QuickVue Influenza A+B, Quidel Corporation, San Diego, California; Rockybe Influenza A Antigen, Rockybe Biomed, Singapore; SD Bioline Influenza and SD Bioline Influenza Ag A/B/A(H1N1)Pandemic, Standard Diagnostics, Yonjin, Korea; OSOM Influenza A&B, Sekisui Medical, Tokyo, Japan; TRU FLU, Meridian Bioscience, Cincinnati, Ohio; Xpect Flu A&B, Remel, Lenexa, Kansas; ZstatFlu, ZymeTx, Oklahoma City, Oklahoma.

‡ More than 1 RIDT was used concomitantly without separate data on the results of each test.

§ Other tests: ESPLINE Influenza A&B-N (4 studies), Xpect Flu A&B (3 studies), ImmunoCard STAT! Flu A and B (2 studies), 3M Rapid Detection Flu A+B (1 study), INFLU A.B-Quick (2 studies), Actim Influenza A&B (2 studies), Rockybe Influenza A Antigen (2 studies), FLU-A Dot-ELISA (2 studies), SD Bioline Influenza Ag A/B/A(H1N1)Pandemic (2 studies), Clearview Exact Influenza A&B (1 study), TRU FLU (1 study), Capilia Flu A + B (1 study), Influenzatop (1 study), NanoSign Influenza A/B (1 study), BioTracer Influenza A&B (1 study), OSOM Influenza A&B (1 study).

in 20 of the 22 articles, with minor differences for the other 2 articles.

Attempts were made to contact the authors if information was lacking to construct the main 2×2 table or for 1 of the prespecified subgroups (see Data Synthesis and Analysis section). Of the 25 authors contacted by e-mail, 13 provided new data or information.

For the reference standards, both traditional viral culture and shell vial culture were considered together, regardless of the cell line used or variation in techniques. Similarly, RT-PCR was considered as a whole, independent of the specific assay protocol used.

Children were defined as individuals younger than 18 years. The study population was considered to be mostly pediatric or mostly adults if 85% of individuals were below or above that cutoff, respectively. In mixed-study populations with separate results for children and adults, we used the cutoff used by the authors.

Point-of-care testing was defined as a test conducted at the patient's bedside (or in a clinic or office setting), immediately after specimen acquisition. When studies failed to mention when and where the RIDT was done, it was presumed not to have been done at the point of care. Methodological quality of the included studies was assessed by using Quality Assessment of Diagnostic Accuracy Studies criteria (20).

Data Synthesis and Analysis

Data were extracted to construct 2×2 tables, which were used to calculate sensitivity and specificity. Some articles (26 of 119) tested samples from the same patient with different commercial RIDTs. To avoid double counting of results from the same patient, we included only one 2×2 table from each article, unless results clearly came from different patients (for example, adults and children or persons infected with influenza A or B). The sensitivity and specificity estimates were pooled by using bivariate random-effects regression models, as recommended by the Cochrane Diagnostic Test Accuracy Working Group (16). The bivariate model takes into consideration the potential tradeoff between sensitivity and specificity by explicitly incorporating this negative correlation in the analysis (21, 22). The model was also used to draw hierarchical summary receiver-operating characteristic (HSROC) curves (23). The closer the curve is to the upper left-hand corner of the HSROC curve plot, the better the overall accuracy of the test. Positive and negative likelihood ratios were directly computed from pooled sensitivity and specificity estimates.

We expected substantial heterogeneity in test accuracy and used random-effects models that also allow for the addition of covariates to account for that heterogeneity. The following variables were selected a priori as potential sources of heterogeneity: population age (children vs. adults), virus type (influenza A vs. influenza B and subtypes of influenza A), reference standard used (viral culture

or RT-PCR), commercial brand of RIDT, type of specimen, duration of symptoms before testing, point-of-care versus laboratory testing, and methodological quality (such as lack of blinding and clear definition of influenza-like illness). These variables were added to the bivariate model, provided that at least 5 studies were identified for each subgroup.

Summary sensitivity and specificity estimates for each covariate were generated, along with their 95% CIs. A *P* value below 0.050 for sensitivity or specificity was used to determine whether there was a statistically significant difference in sensitivity, specificity, or both among the levels of a particular covariate. Because the effects of some of these prespecified covariates may influence each other, multivariate meta-regression was also done to take into account the possible interrelations among the variables. All analyses were conducted by using PROC NLMIXED in SAS, version 9.2 (SAS Institute, Cary, North Carolina) (22).

Role of the Funding Source

This study was supported in part by the Canadian Institutes of Health Research. The funding source had no involvement in study design, conduct, analysis, or publication.

RESULTS

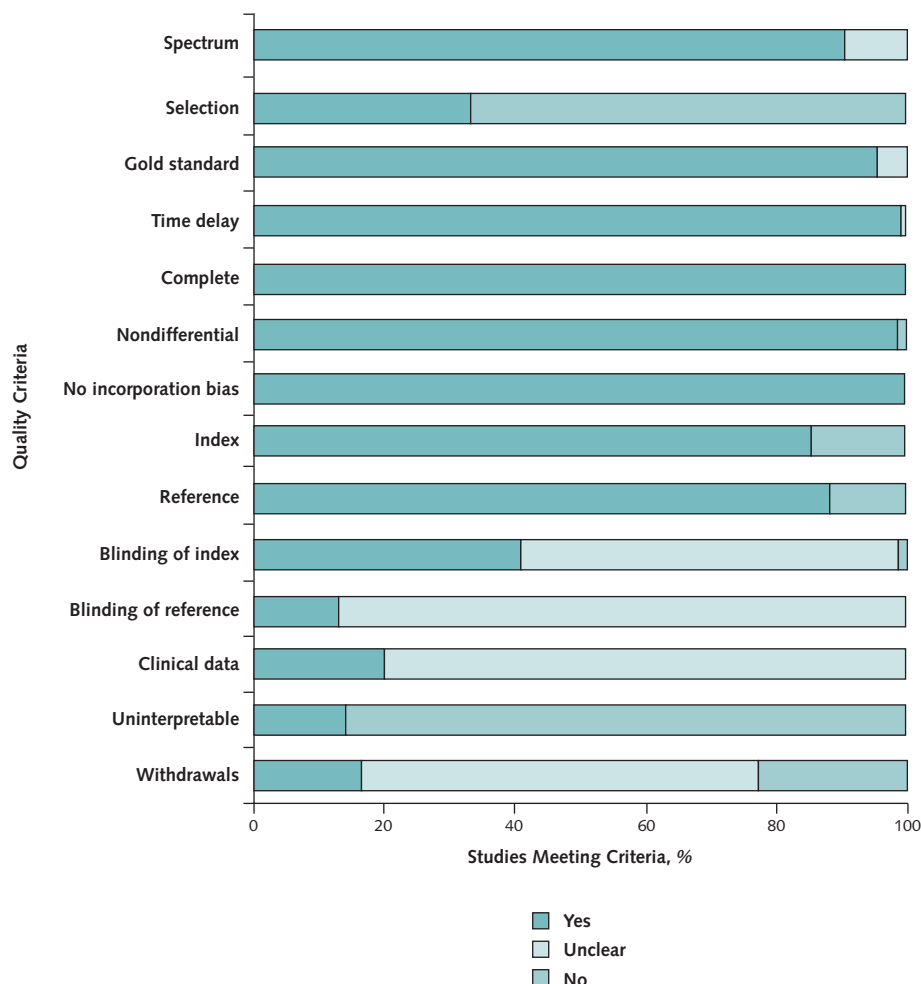
Study Selection

After the titles and abstracts were screened, 286 articles were eligible for full-text review. Of these, 119 were included (**Appendix Figure**, available at www.annals.org) (24–142). Because some articles evaluated more than 1 RIDT, the final analysis included 159 studies. A list of excluded studies with reasons for exclusions is available from the authors on request.

Characteristics of Included Studies

The **Appendix Table** (available at www.annals.org) describes the key characteristics and results of all 159 in-

Figure 1. Quality Assessment of Diagnostic Accuracy Studies assessments of the quality of included studies.



cluded studies, and **Table 1** summarizes their main study-level characteristics. Most studies (52%) included both adults and children, although 34% and 14% included only children and adults, respectively. Only 33% of the studies defined the basis on which patients or specimens were recruited, and even fewer (13%) gave any information on duration of patients' clinical symptoms before testing. Approximately 35% of the included studies were conducted during the H1N1 2009 pandemic.

The included studies evaluated 26 commercial RIDTs. Of these, the most frequently studied tests were the Binax tests (BinaxNOW Flu A and Flu B [6 studies] and BinaxNOW Influenza A & B [22 studies]; Inverness Medical Innovations, Portland, Maine), the Directigen tests (Directigen Flu A [11 studies] and Directigen Flu A+B [30 studies]; Becton, Dickinson and Company, Franklin Lakes, New Jersey), and the QuickVue tests (QuickVue Influenza [18 studies] and QuickVue Influenza A+B [23 studies]; Quidel Corporation, San Diego, California). Both reference standards were used with almost equal frequency.

Quality of Included Studies

Figure 1 presents an overview of the quality of included studies. Because of our inclusion criteria, most studies were free of partial verification, differential verification, and incorporation bias and used an appropriate reference

standard. However, only 33% of the included studies gave a clear rationale for patient or specimen inclusion (selection criteria), and only 41% reported blinding of the evaluation of the result of the RIDTs (mostly because they were evaluated at the point of care).

Overall Accuracy of RIDTs

As shown in **Figure 2**, specificity seemed to be more consistent across studies than sensitivity, with sensitivity estimates ranging from 4.4% to 100% and specificity estimates ranging from 50.5% to 100%. Overall, for all RIDTs (119 studies) compared with 1 of the 2 acceptable reference standards, the pooled sensitivity from bivariate random-effects regression was 62.3% (95% CI, 57.9% to 66.6%) and the pooled specificity was 98.2% (CI, 97.5% to 98.7%). This corresponds to a positive likelihood ratio of 34.5 (CI, 23.8 to 45.2) and a negative likelihood ratio of 0.38 (CI, 0.34 to 0.43). **Figure 2** shows the HSROC, which shows greater variation in sensitivity than in specificity, with only 17 studies (10.7%) reporting specificity estimates below 85%.

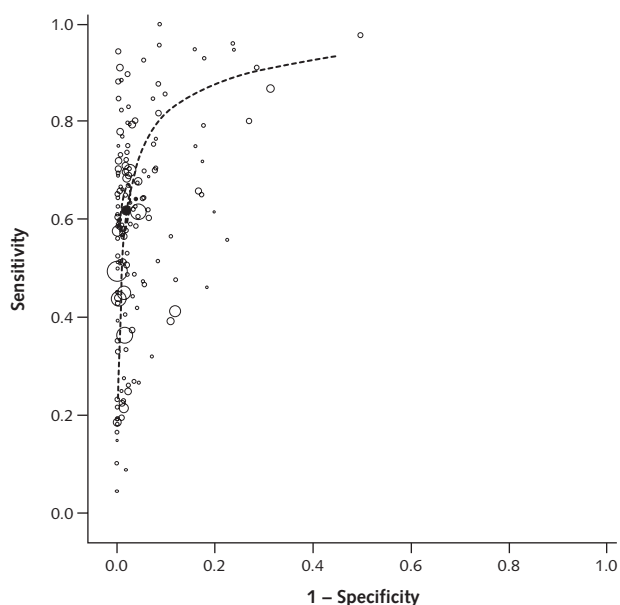
Investigation of Heterogeneity

Subgroup analyses were conducted to investigate heterogeneity in sensitivity, and to a lesser degree, in specificity (**Table 2**). Rapid influenza diagnostic tests showed a higher pooled sensitivity in children (66.6% [CI, 61.6% to 71.7%]) than in adults (53.9% [CI, 47.9% to 59.8%]) that was statistically significant ($P < 0.001$), whereas specificities in the 2 groups were similar. The difference in pooled sensitivity between children and adults remained statistically significant when adjusted for brand of RIDT, specimen type, or reference standard (results not shown).

Virus type also had an effect on the accuracy of RIDTs. Rapid influenza diagnostic tests had increased sensitivity for detecting influenza A (64.6% [CI, 59.0% to 70.1%]) compared with influenza B (52.2% [CI, 45.0% to 59.3%]; $P = 0.050$). They did not perform markedly worse in studies during the recent outbreak of pandemic influenza A(H1N1) 2009: There was no statistically significant difference in sensitivity estimates from studies conducted during the pandemic and those conducted before it ($P = 0.065$). The difference, which was not statistically significant, disappeared when adjusted for the reference standard used ($P = 0.54$ and 0.46 for sensitivity and specificity, respectively; results not shown).

There was considerable overlap among the accuracy estimates for the RIDTs (**Table 2**). Directigen Flu A had the highest pooled sensitivity (76.7% [CI, 63.8% to 86.0%]), followed by QuickVue Influenza test, although the difference from the overall estimate was not statistically significant. However, BinaxNOW, Directigen Flu A+B, and QuickVue Influenza A+B had a lower sensitivity compared with the overall estimate (57.0%, 57.2%, and 48.8%, respectively). Specificity was consistent among most RIDTs.

Figure 2. Hierarchical summary receiver-operating characteristic curve plot of rapid influenza diagnostic test studies.



Individual studies ($n = 159$) are shown as open circles whose size is proportionate to the size of the study. Summary point is shown as a closed circle, representing sensitivity estimates pooled by using bivariate random-effects regression model. The hierarchical summary receiver-operating characteristic curve is shown as a dashed line and is truncated outside the area for which data exist.

Table 2. Accuracy Estimates From Subgroup Analyses

Characteristic	Pooled Sensitivity (95% CI), %	P Value	Pooled Specificity (95% CI), %	P Value
Population				
Children (60 studies)	66.6 (61.6–71.7)	<0.001	98.2 (97.5–99.0)	0.135
Adults (33 studies)	53.9 (47.9–59.8)	Reference	98.6 (98.0–98.9)	Reference
Virus type				
Influenza A (72 studies)	64.6 (59.0–70.1)	0.62	99.1 (98.7–99.4)	<0.001
Influenza B (27 studies)	52.2 (45.0–59.3)	0.050	99.8 (99.7–99.9)	<0.001
Influenza A and B (47 studies)	62.3 (55.2–69.4)	Reference	96.1 (94.4–97.8)	Reference
Study conducted during the H1N1 pandemic				
Yes (41 studies)	56.3 (48.7–63.9)	0.065	98.9 (98.3–99.5)	0.022
No (74 studies)	65.0 (59.7–70.4)	Reference	97.5 (96.6–98.5)	Reference
Index test*				
BinaxNOW (17 studies)†	57.0 (45.9–67.5)	0.028‡	98.6 (96.9–99.3)	0.057‡
Directigen Flu A (10 studies)	76.7 (63.8–86.0)	0.49‡	97.2 (92.6–99.0)	0.62‡
Directigen Flu A+B (30 studies)	57.2 (48.8–65.2)	0.011‡	99.3 (98.8–99.6)	<0.001‡
QuickVue Influenza (16 studies)	69.0 (58.1–78.2)	0.66‡	95.8 (91.3–98.0)	0.82‡
QuickVue Influenza A+B (21 studies)	48.8 (39.0–58.8)	<0.001‡	98.4 (96.8–99.2)	0.064‡
Reference standard				
RT-PCR (67 studies)	53.9 (48.2–59.6)	<0.001	98.8 (98.3–99.3)	0.002
Culture (48 studies)	72.3 (66.8–77.9)	Reference	96.7 (95.2–98.3)	Reference
Type of specimen				
Nasopharyngeal aspirate (15 studies)	66.6 (56.2–77.0)	0.42§	97.8 (95.6–100)	0.34§
Nasopharyngeal swab (19 studies)	61.6 (52.0–71.3)	0.75§	99.1 (98.4–99.9)	0.133§
Nasopharyngeal wash (3 studies)	50.7 (25.1–76.3)	0.32§	98.1 (94.0–100)	0.82§
Nasal swab (10 studies)	65.9 (53.3–78.5)	0.61§	99.2 (98.2–100)	0.28§
Throat swab (4 studies)	54.9 (32.7–77.1)	0.45§	90.0 (74.7–100)	0.018§
Testing at the point of care				
Yes (28 studies)	58.0 (48.8–67.2)	0.28	97.6 (96.1–99.1)	0.30
No (91 studies)	63.6 (58.8–68.5)	Reference	98.4 (97.7–99.0)	Reference
Study quality				
Spectrum of disease				
During influenza season (105 studies)	60.6 (56.0–65.2)	0.032	98.2 (97.6–98.9)	0.62
Outside influenza season (14 studies)	74.2 (63.9–84.4)	Reference	97.8 (95.8–99.8)	Reference
Patient selection				
ILI defined (45 studies)	59.4 (52.2–66.6)	0.30	97.9 (96.9–99.0)	0.50
ILI not defined (74 studies)	64.1 (58.7–69.5)	Reference	98.3 (97.7–99.0)	Reference
Blinding				
Any blinding reported (54 studies)	61.7 (55.2–68.2)	0.78	97.8 (96.7–98.8)	0.20
No blinding reported (65 studies)	62.9 (57.0–68.7)	Reference	98.5 (97.8–99.2)	Reference
Handling of indeterminate results				
Reported (19 studies)	66.9 (56.5–77.3)	0.37	98.0 (96.5–99.6)	0.82
Not reported (100 studies)	61.5 (56.7–66.2)	Reference	98.2 (97.6–98.9)	Reference
Industry sponsoring				
Sponsored (23 studies)	73.3 (65.3–81.3)	0.007	97.4 (95.5–99.2)	0.24
Not sponsored (96 studies)	59.4 (54.6–64.2)	Reference	98.4 (97.8–99.0)	Reference

ILI = influenza-like illness; RT-PCR = reverse transcriptase, polymerase chain reaction.

* See footnote in Table 1 for names of manufacturers of rapid influenza diagnostic tests.

† BinaxNOW Flu A and B and BinaxNOW Influenza A&B were pooled together because statistical tests showed that they performed similarly (data not shown).

‡ Reference category is the combination of the other tests.

§ Reference category is the combination of the other specimens.

|| Article provided a clear definition of the clinical symptoms on the basis of which patients were recruited for the study.

Rapid influenza diagnostic tests performed better when assessed against viral culture rather than RT-PCR (pooled sensitivity, 72.3% [CI, 66.8% to 77.9%] for culture, 53.9% [CI, 48.2% to 59.6%] for RT-PCR; $P < 0.001$), because of the increased accuracy of the latter.

Neither the type of specimen collected from patients nor whether the RIDT was performed at the point of care

had a noticeable effect on their accuracy. Also, the quality criteria investigated (patient selection, blinding, and handling of uninterpretable results) did not have a statistically significant effect on pooled accuracy estimates, with the exception of a higher sensitivity for the few studies for which the timing (during or outside the influenza season) was unclear. Industry-sponsored studies showed a higher

Table 3. Studies That Provided Data on Effect of Duration of Symptoms on Test Accuracy

Study, Year (Reference)	Duration*	Sensitivity (95% CI), %	Specificity (95% CI), %
Gordon et al, 2009 (69)	Day 1	51.9 (40.3–63.3)	98.4 (95.3–99.7)
	Day 2	75.1 (68.3–81.1)	97.9 (96.0–99.1)
	Day 3	74.2 (62.0–84.2)	97.9 (94.1–99.6)
	Day 4	57.9 (33.5–79.7)	98.6 (94.2–100)
Gordon et al, 2010 (68)	<24 h	41.7 (22.1–63.4)	97.9 (88.9–99.9)
	≥24 h	72.1 (59.9–82.3)	98.4 (94.3–99.8)
Keitel et al, 2011 (83)†	≤12 h	35.0 (19.0–55.0)	100 (88.0–100)
	12–24 h	66.0 (54.0–76.0)	97.0 (86.0–100)
	24–48 h	92.0 (80.0–97.0)	96.0 (82.0–99.0)
	>48 h	59.0 (36.0–78.0)	100 (90.0–100)
Nilsson et al, 2008 (100)	1–3 d	71.4 (58.7–82.1)	100 (95.1–100)
	1–5 d	62.8 (51.7–73.0)	100 (96.7–100)
	>5 d	13.8 (3.9–31.7)	100 (90.0–100)
Poehling et al, 2002 (108)	<4 d	100 (63.1–100)	96.6 (90.4–99.3)
	≥4 d	54.5 (23.4–83.3)	98.4 (94.4–99.8)
Stein et al, 2005 (131)	<48 h	58.3 (27.7–84.8)	96.2 (80.4–99.9)
	>48 h	25.0 (12.1–42.2)	98.6 (95.0–99.8)
Stripeli et al, 2010 (132)	<48 h	75.0 (42.8–94.5)	100 (92.1–100)
	≥48 h	65.4 (44.3–84.8)	94.2 (88.4–97.6)

* Duration of clinical symptoms at the time of testing by the rapid influenza diagnostic test.

† Numbers taken directly from the study because there was not enough information to reconstruct the 2 × 2 table.

sensitivity (73.3% [CI, 65.3% to 81.3%]) than studies not sponsored by industry (59.4% [CI, 54.6% to 64.2%]). Although this difference was statistically significant, sensitivity analysis revealed that the overall estimates did not change when sponsored studies were removed from the analyses, which was probably due to the small number of sponsored studies ($n = 23$). Only 7 studies gave comparative information on duration of symptoms before testing. As shown in Table 3, there was a tendency toward lower accuracy on the first day of symptoms, with highest sensitivity on days 2 and 3 and a rapid decline thereafter.

DISCUSSION

Overall, RIDTs have high specificity, with modest and highly variable sensitivity. For the clinician, this means that a positive test result is unlikely to be false positive. In the presence of a positive RIDT result in a patient with influenza-like illness, a clinician can confidently diagnose influenza and begin appropriate infection-control measures and antiviral therapy, if indicated, while forgoing unnecessary additional diagnostic testing and antibiotic prescription. However, a negative RIDT result has a reasonable likelihood of being false negative and should be confirmed by other laboratory diagnostic tests if the result is likely to affect patient management.

An important finding is that RIDTs perform better in children than in adults, with approximately 13% higher sensitivity in children. This is plausible because young children have higher viral loads and longer viral shedding than adults (12). After adjustment for other factors, such as reference standard used, brand of RIDT, and type of specimen, RIDTs still show increased accuracy in children compared with adults.

Rapid influenza diagnostic tests have a higher sensitivity for detecting influenza A than influenza B. Studies have shown that infection with influenza A(H3N2) (the most common circulating subtype of influenza A in North America in past decades) leads to more severe disease and higher annual rates of influenza-associated hospitalization and death than infection with influenza B. Conversely, influenza A(H1N1) has been shown to have the lowest severity index and the lowest morbidity and mortality (2, 143, 144). More severe disease usually means higher viral load and, thus, better sensitivity. During the H1N1 2009 pandemic, there were reports of even lower sensitivity of RIDTs for this new strain, compared with published accuracy estimates (145). However, we found no important difference in the accuracy of the RIDTs between studies conducted during the influenza A(H1N1) 2009 pandemic and those conducted before, with any small difference disappearing after adjustment for the reference standard used.

Overall, no single commercial brand of RIDT seemed to perform markedly better or worse than others, but this finding should be interpreted cautiously because head-to-head comparisons were not done in most studies. No difference in accuracy was found among the respiratory specimens, although these analyses were limited by the absence of stratification by specimen type in most studies and the inconsistent reporting of many other factors known to affect specimen quality, such as the type of swab and the operator. Although common practice guidelines have held nasopharyngeal specimens as the best specimen type (10, 12), followed by nasal specimens and throat swabs, other studies have not shown a difference among them (146–148).

Point-of-care testing also showed no effect on the accuracy of RIDTs. Thus, in this analysis, administration of the RIDTs by personnel other than a trained laboratory technician does not seem to adversely influence the performance of these tests. This could be good news, because it is likely that they find their most useful application and have the most effect in the diagnostic work-up for influenza when they are used as first-line tests, outside of the laboratory setting. However, no study directly compared accuracy between RIDTs performed at the point of care versus in a laboratory setting or made a distinction between who collected and who processed the specimen.

The strengths of our systematic review are that we followed a standard protocol and used a comprehensive search strategy. By contacting several authors, we were able to gather information that was missing from the original publications. We used rigorous methods of data analysis, including bivariate random-effects regression models and HSROC curve analyses. We also added predefined covariates to the bivariate model to explain heterogeneity in accuracy estimates.

The evidence base for the review had several limitations. Over the years, RT-PCR has gradually replaced viral culture as the preferred reference standard for influenza diagnosis. Although we preferentially included results from RT-PCR when available, both are currently accepted reference standards, and choosing only RT-PCR would have biased our review to include only recent studies. Considerable heterogeneity was found in the pooled estimates, as expected. Despite our attempts to explain it through the regression model, substantial heterogeneity remained unexplained. Many factors, possibly contributing to this residual heterogeneity, could not be assessed because they were not reported in most studies. For example, duration of clinical symptoms before testing is likely to have an important effect on test performance (12). This information was mentioned in only 13% of the included studies. Many studies failed to stratify by specimen type. Also, some subgroups, such as children and adults, were by necessity broad and could encompass different age ranges. Finally, other variables, such as flu vaccination coverage of the population under study, inclusion or exclusion of persons with comorbid conditions, type of swab used, who collected the specimen, transport medium used, and time elapsed before specimen processing, were reported so infrequently that their effect was difficult to assess.

Studies also had methodological limitations. In particular, less than one half of the studies reported blinded assessment of the RIDTs. Although RIDTs give a dichotomous yes/no answer, faint lines seen during reading may be an important source of false-positive results (113). Unblinded assessment could lead to an overoptimistic estimate of the test performance, even though we did not find any difference in reported accuracy between studies that reported blinding versus no blinding.

Although we searched several sources and updated our searches, we may have missed some eligible studies. Further, we extracted data on studies only in English and French. We could not formally assess publication bias because there is no valid method to do so when dealing with diagnostic studies.

The most important advantage of RIDTs is their rapid turnaround time, providing clinicians with an answer within minutes. Although they undoubtedly have higher accuracy, RT-PCR and viral culture take hours or even days to give results, even discounting transportation time to the nearest laboratory. Thus, RIDTs fill a void at the point of care that no other test is likely to fill in the near future: as a first-line test to be confirmed (especially if negative) by more time-consuming, definitive testing. As long as clinicians understand the limitations of RIDTs, namely that a negative result is unreliable and should be confirmed by using culture or RT-PCR, RIDTs could enable clinicians to institute prompt infection-control measures, begin antiviral treatment in high-risk populations, and make informed decisions about further diagnostic investigations. Although additional studies that evaluate test accuracy of RIDTs are not likely to add new knowledge, studies that evaluate clinical effect of RIDTs on patient management are needed to confirm whether and when RIDTs may decrease use of ancillary tests and empirical antibiotic treatment and increase appropriate use of antiviral treatment (88, 109, 149–154). Finally, cost-effectiveness studies are essential to see whether potential benefits offset the added costs of routine use of RIDTs.

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Acknowledgment: The authors thank all of the study authors who provided additional information or clarifications.

Grant Support: The study was supported in part by the Canadian Institutes of Health Research. Dr. Pai is a recipient of a New Investigator Career Award from the Canadian Institutes of Health Research. He also receives research support from Grand Challenges Canada and European and Developing Countries Clinical Trials Partnership. Dr. Leeflang is supported by the Netherlands Organization for Scientific Research (NWO); project 916.10.034.

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-2863.

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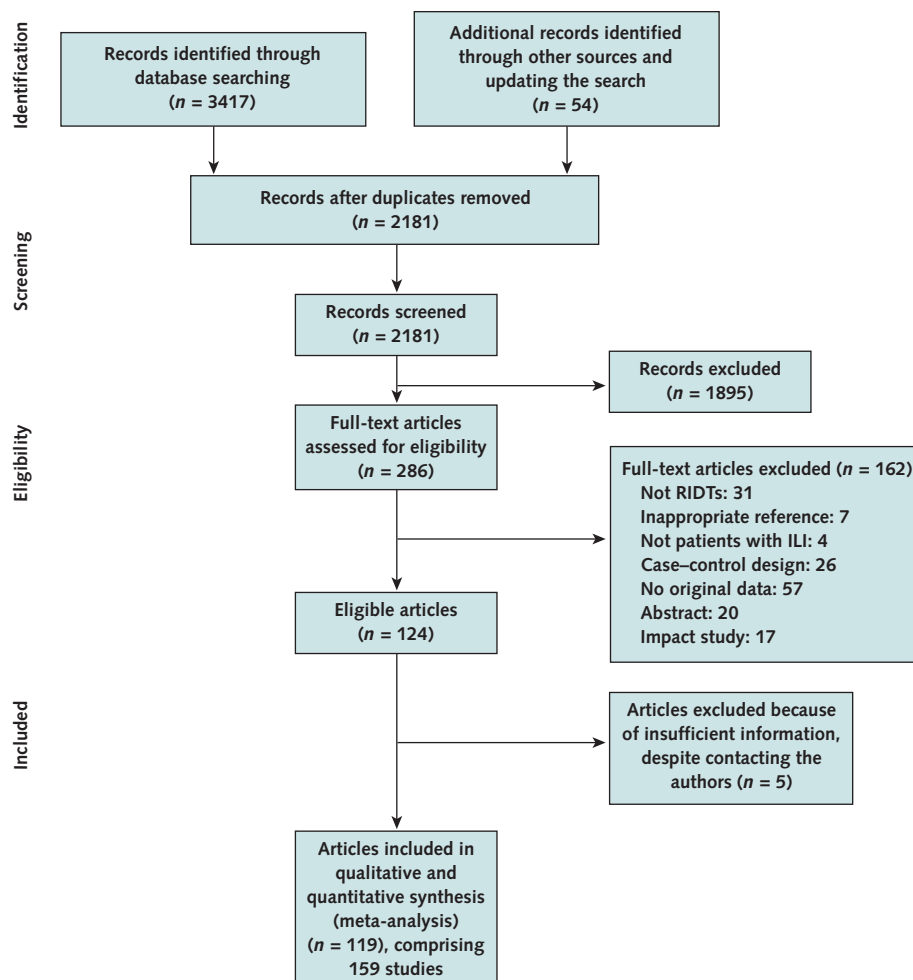
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Appendix Figure. Summary of evidence search and selection.



ILI = influenza-like illness; RIDT = rapid influenza diagnostic test.

Appendix Table. Study Characteristics

Study, Year (Reference)	Population	Specimen Type	RIDT*	Reference Test	Specimens, n	Sensitivity (95% CI), %	Specificity (95% CI), %
Agoritsas et al, 2006 (24)	Children	Nasopharyngeal wash	QuickVue Influenza	Culture and RT-PCR	Ref+: 59; Ref-: 63	69.5 (56.1–80.8)	98.4 (91.5–100)
Al Johani et al, 2011 (25)†	Mixed	Nasopharyngeal aspirate, nasopharyngeal swab, throat swab	Directigen Flu A+B	RT-PCR	Ref+: 34; Ref-: 109	8.8 (1.9–23.7)	98.2 (93.5–99.8)
Alexander et al, 2005 (26)	Children	Nasopharyngeal aspirate, nasal swab, throat swab, bronchoalveolar lavage	TRU FLU	RT-PCR	Ref+: 28; Ref-: 109	25.0 (10.7–44.9)	99.1 (95.0–100)
			Directigen Flu A+B	RT-PCR	Ref+: 94; Ref-: 97	83.0 (73.8–89.9)	97.9 (92.7–99.7)
Arsene et al, 2004 (27)	Children	Nasal swab, nasal aspirate†	QuickVue Influenza	RT-PCR	Ref+: 16; Ref-: 17	87.5 (61.7–98.4)	100 (80.5–100)
Bellei et al, 2003 (28)	Adults	Nasopharyngeal swab	QuickVue Influenza	Culture	Ref+: 28; Ref-: 4	85.7 (67.3–96.0)	75.0 (19.4–99.4)
Bellmann-Weiler et al, 2011 (29)†	Adults	Nasal swab, throat swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 29; Ref-: 78	27.6 (12.7–47.2)	98.7 (93.1–100)
Biggs et al, 2010 (30)	Mixed	Nasopharyngeal swab	Directigen Flu A+B	RT-PCR	Ref+: 25; Ref-: 71	32.0 (14.9–53.5)	93.0 (84.3–97.7)
			BinaxNOW Influenza A & B	RT-PCR	Ref+: 97; Ref-: 469	69.1 (58.9–78.1)	97.7 (95.8–98.8)
Boivin et al, 2001 (31)	Mixed	Throat swab	FLU OIA	RT-PCR	Ref+: 77; Ref-: 58	55.8 (44.1–67.2)	77.6 (64.7–87.5)
Boivin et al, 2004 (32)	Children	Nasopharyngeal aspirate	Directigen Flu A+B	RT-PCR	Ref+: 42; Ref-: 130	40.5 (25.6–56.7)	98.5 (94.6–99.8)
Boon et al, 2001 (33)	Children	Nasal swab, throat swab	Directigen Flu A	Culture	Ref+: 26; Ref-: 11	46.2 (26.6–66.6)	81.8 (48.2–97.7)
Booth et al, 2006 (34)	Mixed	Nasopharyngeal aspirate, nasal swab, throat swab	BinaxNOW Flu A and Flu B	Culture	Ref+: 93; Ref-: 131	69.9 (59.5–79.0)	94.7 (89.3–97.8)
			ImmunoCard STAT! Flu A and B	Culture	Ref+: 95; Ref-: 129	70.5 (60.3–79.4)	92.2 (86.2–96.2)
Cazacu et al, 2004 (35)	Children	Nasopharyngeal swab, nasal wash, tracheal specimen, bronchoalveolar lavage, sputum	Directigen Flu A+B	Culture	Ref+: 219; Ref-: 3873	43.8 (37.2–50.7)	99.7 (99.5–99.9)
Cazacu et al, 2004 (36)	Mixed	Nasopharyngeal swab, nasal wash, throat swab, tracheal specimen, bronchoalveolar lavage, sputum	Xpect Flu A&B	Culture	Ref+: 125; Ref-: 275	94.4 (88.8–97.7)	100 (98.7–100)
Cazacu et al, 2003 (37)	Children	Nasal wash	Directigen Flu A+B	Culture	Ref+: 54; Ref-: 302	72.2 (58.4–83.5)	98.3 (96.2–99.5)
Chan et al, 2002 (38)	Children	Nasopharyngeal aspirate	QuickVue Influenza	Culture	Ref+: 54; Ref-: 302	70.4 (56.4–82.0)	97.7 (95.3–99.1)
Chen et al, 2010 (39)	Not reported	Nasal swab, throat swab	Directigen Flu A+B	Culture	Ref+: 54; Ref-: 196	92.6 (82.1–97.9)	94.9 (90.8–97.5)
Cheng et al, 2009 (40)	Adults	Nasal swab, throat swab	FLU-A Dot-ELISA	Culture	Ref+: 78; Ref-: 147	88.5 (79.2–94.6)	99.3 (96.3–100)
Cheng et al, 2011 (41)†	Mixed	Nasopharyngeal swab	QuickVue Influenza A+B	Culture	Ref+: 186; Ref-: 812	67.7 (60.5–74.4)	95.8 (94.2–97.1)
			FLU-A Dot-ELISA	RT-PCR	Ref+: 235; Ref-: 572	91.1 (86.7–94.4)	99.7 (98.7–100)
Choi et al, 2011 (42)†	Adults	Nasopharyngeal swab, throat swab†	Directigen Flu A+B	RT-PCR	Ref+: 235; Ref-: 571	71.9 (65.7–77.6)	99.8 (99.0–100)
			SD Bioline Influenza	RT-PCR	Ref+: 266; Ref-: 672	44.0 (37.9–50.2)	99.9 (99.2–100)
Choi et al, 2010 (43)†	Mixed	Nasopharyngeal swab	SD Bioline Influenza Ag A/B/(H1N1)Pandemic	RT-PCR	Ref+: 313; Ref-: 446	78.0 (72.9–82.4)	99.6 (98.4–99.9)
Choi et al, 2010 (44)†	Mixed	Nasopharyngeal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 141; Ref-: 113	64.5 (56.0–72.4)	94.7 (88.8–98.0)
Covalciuc et al, 1999 (45)	Mixed	Nasopharyngeal swab, nasal aspirate, throat swab, sputum	SD Bioline Influenza	RT-PCR	Ref+: 141; Ref-: 113	69.5 (61.2–77.0)	100 (96.8–100)
			FLU OIA	Culture	Ref+: 151; Ref-: 253	80.1 (72.9–86.2)	73.1 (67.2–78.5)
Crum-Cianflone et al, 2009 (46)†	Mixed	Nasopharyngeal swab	QuickVue Influenza A+B	RT-PCR	Ref+: 79; Ref-: 492	50.6 (39.1–62.1)	98.2 (96.6–99.2)

Continued on following page

Appendix Table—Continued

Study, Year (Reference)	Population	Specimen Type	RIDT*	Reference Test	Specimens, n	Sensitivity (95% CI), %	Specificity (95% CI), %
Cruz et al, 2008 (47)	Children	Nasopharyngeal swab, nasal wash, tracheal specimen, bronchoalveolar lavage, sputum	Xpect Flu A&B	Culture	Ref+: 259; Ref-: 4112	36.3 (30.4–42.5)	98.4 (98.0–98.8)
Cruz et al, 2006 (48)	Children	Nasal wash, nasal swab, tracheal specimen, bronchoalveolar lavage, sputum	BinaxNOW Influenza A & B	Culture	Ref+: 283; Ref-: 4532	62.9 (57.0–68.5)	97.9 (97.4–98.3)
Cruz et al, 2010 (49)†	Children	Nasopharyngeal swab, nasal wash, nasal swab, tracheal specimen, bronchoalveolar lavage, sputum	BinaxNOW Flu A and Flu B	RT-PCR	Ref+: 437; Ref-: 3946	61.6 (56.8–66.1)	95.8 (95.1–96.4)
Dale et al, 2008 (50)	Adults	Nasopharyngeal swab, nasal swab	3M Rapid Detection Flu A+B	Culture	Ref+: 40; Ref-: 202	75.0 (58.8–87.3)	98.0 (95.0–99.5)
de la Tabla et al, 2010 (51)†	Adults	Nasopharyngeal swab, throat swab	BinaxNOW Influenza A & B	Culture	Ref+: 41; Ref-: 208	56.1 (39.7–71.5)	100 (98.2–100)
De Witte et al, 2011 (52)	Children	Nasopharyngeal aspirate	QuickVue Influenza A+B	Culture	Ref+: 41; Ref-: 208	73.2 (57.1–85.8)	99.5 (97.4–100)
Diederer et al, 2010 (53)†	Mixed	Nasopharyngeal aspirate	Cleanview Exact Influenza A&B	RT-PCR	Ref+: 297; Ref-: 698	18.5 (14.3–23.4)	100 (99.5–100)
Dominguez et al, 1993 (54)	Children	Nasal wash, nasal swab, throat swab	ESPLINE Influenza A&B-N	Culture	Ref+: 79; Ref-: 219	91.1 (82.6–96.4)	71.7 (65.2–77.6)
Drinka, 2006 (55)	Adults	Nasopharyngeal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 38; Ref-: 97	47.4 (31.0–64.2)	94.8 (88.4–98.3)
Dunn et al, 2003 (56)	Not reported	Nasopharyngeal swab, nasal wash, throat swab, tracheal specimen, bronchoalveolar lavage, sputum	Directigen Flu A	Culture	Ref+: 20; Ref-: 61	75.0 (50.9–91.3)	100 (94.1–100)
Effler et al, 2002 (57)	Not reported	Nasopharyngeal swab, throat swab	Directigen Flu A+B	Culture	Ref+: 53; Ref-: 274	64.2 (49.8–76.9)	99.3 (97.4–99.9)
Fader, 2005 (58)	Mixed	Nasal aspirate, nasal wash	INFLU A-B-Quick	Culture	Ref+: 55; Ref-: 200	60.0 (45.9–73.0)	99.5 (97.2–100)
Faix et al, 2009 (59)†	Not reported	Not reported	Directigen Flu A+B	Culture	Ref+: 55; Ref-: 200	58.2 (44.1–71.3)	99.5 (97.2–100)
Fernandez et al, 2010 (60)†	Mixed	Nasopharyngeal swab, nasal swab	FLU OIA	Culture	Ref+: 473; Ref-: 1596	41.2 (36.8–45.8)	88.2 (86.5–89.8)
Foo et al, 2009 (61)	Adults	Nasal swab, throat swab	BinaxNOW Flu A and Flu B	Culture	Ref+: 77; Ref-: 378	64.9 (53.2–75.5)	98.4 (96.6–99.4)
Fuenzalida et al, 2010 (62)†	Mixed	Nasopharyngeal aspirate	QuickVue Influenza A+B	RT-PCR	Ref+: 39; Ref-: 728	51.3 (34.8–67.6)	99.0 (98.0–99.6)
Genzenmueller et al, 2010 (63)†	Mixed	Nasopharyngeal swab, throat swab, bronchoalveolar lavage	QuickVue Influenza A+B	Culture	Ref+: 52; Ref-: 95	75.0 (61.1–86.0)	84.2 (75.3–90.9)
Gao et al, 2011 (64)†	Mixed	Nasopharyngeal swab	QuickVue Influenza A+B	Culture and RT-PCR	Ref+: 64; Ref-: 73	51.6 (38.7–64.2)	91.8 (83.0–96.9)
			BinaxNOW Influenza A & B	Culture and RT-PCR	Ref+: 16; Ref-: 32	68.8 (41.3–89.0)	93.8 (79.2–99.2)
			BinaxNOW Influenza A & B	RT-PCR	Ref+: 227; Ref-: 285	60.4 (53.7–66.8)	93.7 (90.2–96.2)
			QuickVue Influenza A+B	RT-PCR	Ref+: 44; Ref-: 128	18.2 (8.2–32.7)	100 (97.2–100)
			Directigen Flu A+B	RT-PCR	Ref+: 66; Ref-: 163	59.1 (46.3–71.0)	97.5 (93.8–99.3)
			Xpect Flu A&B	RT-PCR	Ref+: 43; Ref-: 150	48.8 (33.3–64.5)	98.0 (94.3–99.6)
			BinaxNOW Influenza A & B	RT-PCR	Ref+: 122; Ref-: 724	56.6 (47.3–65.5)	98.8 (97.7–99.4)

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Study, Year (Reference)	Population	Specimen Type	RIDT*	Reference Test	Specimens, n	Sensitivity (95% CI), %	Specificity (95% CI), %
Ghebremedhin et al, 2009 (65)	Children	Nasopharyngeal aspirate, nasopharyngeal swab, tracheal specimen, bronchoalveolar lavage	Actim Influenza A&B	RT-PCR	Ref+: 23; Ref-: 450	65.2 (42.7–83.6)	100 (99.2–100)
Gimeno et al, 2010 (66)†	Adults	Nasopharyngeal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 14; Ref-: 135	50.0 (23.0–77.0)	100 (97.3–100)
Gooskens et al, 2008 (67)	Adults	Nasopharyngeal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 76; Ref-: 278	32.9 (22.5–44.6)	100 (98.7–100)
Gordon et al, 2010 (68)†	Children	Nasopharyngeal swab, nasopharyngeal wash, throat swab	Directigen Flu A & B	RT-PCR	Ref+: 65; Ref-: 20	21.5 (12.3–33.5)	100 (83.2–100)
Gordon et al, 2009 (69)	Children	Nasal swab	QuickVue Influenza A+B	RT-PCR	Ref+: 92; Ref-: 173	64.1 (53.5–73.9)	98.3 (95.0–99.6)
Grijalva et al, 2007 (70)	Children	Nasal swab, throat swab	QuickVue Influenza A+B	RT-PCR	Ref+: 359; Ref-: 798	68.5 (63.4–73.3)	98.1 (96.9–98.9)
Gröndahl et al, 2005 (71)	Children	Nasopharyngeal aspirate	Mixed tests	Culture and RT-PCR	Ref+: 41; Ref-: 229	63.4 (46.9–77.9)	97.4 (94.4–99.0)
Hamilton et al, 2002 (72)	Children	Nasal aspirate	Directigen Flu A+B	RT-PCR	Ref+: 61; Ref-: 238	23.0 (13.2–35.5)	98.7 (96.4–99.7)
Hara et al, 2008 (73)	Children	Nasopharyngeal aspirate	ZstatFlu	Culture	Ref+: 65; Ref-: 235	87.7 (77.2–94.5)	91.9 (87.7–95.1)
			Directigen Flu A+B	Culture	Ref+: 65; Ref-: 235	75.4 (63.1–85.2)	92.8 (88.7–95.7)
			ESPLINE Influenza A&B-N	Culture	Ref+: 323; Ref-: 171	88.2 (84.2–91.5)	100 (97.9–100)
			Directigen Flu A+B	Culture	Ref+: 323; Ref-: 171	80.2 (75.4–84.4)	96.5 (92.5–98.7)
			BinaxNOW Influenza A & B	Culture	Ref+: 323; Ref-: 171	81.7 (77.1–85.8)	91.8 (86.6–95.5)
Harnden et al, 2003 (74)	Children	Nasopharyngeal aspirate, nasal swab†	QuickVue Influenza	RT-PCR	Ref+: 61; Ref-: 96	44.3 (31.5–57.6)	96.9 (91.1–99.4)
Hawkes et al, 2010 (75)†	Children	Nasopharyngeal swab, nasal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 107; Ref-: 71	61.7 (51.8–70.9)	98.6 (92.4–100)
Heinonen et al, 2011 (76)	Children	Nasal swab	Actim Influenza A&B	Culture and RT-PCR	Ref+: 39; Ref-: 119	76.9 (60.7–88.9)	99.2 (95.4–100)
Herrmann et al, 2001 (77)	Mixed	Nasopharyngeal aspirate, nasopharyngeal swab	FLU OIA	RT-PCR	Ref+: 92; Ref-: 92	56.5 (45.8–66.8)	89.1 (80.9–94.7)
Hindiyeh et al, 2000 (78)	Not reported	Nasopharyngeal swab, nasal wash, throat swab, bronchoalveolar lavage, sputum	FLU OIA	Culture	Ref+: 44; Ref-: 101	47.7 (32.5–63.3)	88.1 (80.2–93.7)
Hulson et al, 2001 (79)	Mixed	Throat swab	ZstatFlu	Culture	Ref+: 241; Ref-: 117	65.1 (58.8–71.1)	82.9 (74.8–89.2)
Hurt et al, 2007 (80)	Mixed	Nasopharyngeal aspirate, nasal swab, throat swab, bronchoalveolar lavage, sputum	BinaxNOW Influenza A & B	Culture	Ref+: 59; Ref-: 118	66.1 (52.6–77.9)	99.2 (95.4–100)
			Directigen Flu A+B	Culture	Ref+: 59; Ref-: 118	62.7 (49.1–75.0)	100 (96.9–100)
			INFLU A&B-Quick	Culture	Ref+: 59; Ref-: 118	64.4 (50.9–76.4)	100 (96.9–100)
			ESPLINE Influenza A&B-N	Culture	Ref+: 59; Ref-: 118	61.0 (47.4–73.5)	100 (96.9–100)
			Rockeby Influenza A Antigen	Culture	Ref+: 49; Ref-: 128	10.2 (3.4–22.2)	100 (97.2–100)
Johnston and Bloy, 1993 (81)	Not reported	Nasopharyngeal swab, throat swab	QuickVue Influenza A+B	Culture	Ref+: 59; Ref-: 118	61.0 (47.4–73.5)	100 (96.9–100)
Karre et al, 2010 (82)†	Not reported	Nasopharyngeal wash	Directigen Flu A	Culture	Ref+: 50; Ref-: 161	62.0 (47.2–75.3)	93.8 (88.9–97.0)
Keitel et al, 2011 (83)†	Children	Nasopharyngeal swab, nasal swab†	Directigen Flu A+B	RT-PCR	Ref+: 80; Ref-: 145	48.8 (37.4–60.2)	96.6 (92.1–98.9)
			Influenzatop	RT-PCR	Ref+: 164; Ref-: 137	64.0 (56.2–71.4)	98.5 (94.8–99.8)

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Study, Year (Reference)	Population	Specimen Type	RIDT*	Reference Test	Specimens, n	Sensitivity (95% CI), %	Specificity (95% CI), %
Kim et al, 2010 (84)†	Mixed	Nasopharyngeal swab	SD Bioline Influenza Ag A/B/(H1N1)Pandemic	RT-PCR	Ref+: 260; Ref-: 688	70.0 (64.0–75.5)	98.4 (97.2–99.2)
Kok et al, 2010 (85)	Not reported	Nasal swab, throat swab	SD Bioline Influenza	RT-PCR	Ref+: 260; Ref-: 688	58.8 (52.6–64.9)	99.6 (98.7–99.9)
Landry et al, 2008 (86)	Mixed	Nasopharyngeal swab	QuickVue Influenza A+B	RT-PCR	Ref+: 269; Ref-: 231	60.6 (54.5–66.5)	100 (98.4–100)
Lee et al, 2010 (87)†	Mixed	Nasopharyngeal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+: 132; Ref-: 105	53.0 (44.2–61.8)	98.1 (93.3–99.8)
Leonardi et al, 1994 (88)	Mixed	Nasal swab	NanoSign Influenza A/B	RT-PCR	Ref+: 199; Ref-: 824	79.4 (73.1–84.8)	97.2 (95.8–98.2)
Leonardi et al, 2010 (89)†	Mixed	Nasopharyngeal swab, throat swab	Directigen Flu A	Culture	Ref+: 46; Ref-: 114	84.8 (71.1–93.7)	93.0 (86.6–96.9)
Liao et al, 2009 (90)	Mixed	Nasopharyngeal swab	Directigen Flu A+B	Culture	Ref+: 145; Ref-: 468	70.3 (62.2–77.6)	100 (99.2–100)
Likitnukul et al, 2009 (91)†	Mixed	Nasopharyngeal aspirate, nasopharyngeal swab	Directigen Flu A+B	Culture and RT-PCR	Ref+: 51; Ref-: 129	58.8 (44.2–72.4)	99.2 (95.8–100)
Louie et al, 2010 (92)†	Mixed	Nasal swab	Mixed tests†	RT-PCR	Ref+: 569; Ref-: 272	86.8 (83.8–89.5)	68.8 (62.9–74.2)
Lucas et al, 2011 (93)†	Mixed	Nasopharyngeal swab, nasal swab, throat swab	QuickVue Influenza	RT-PCR	Ref+: 404; Ref-: 299	65.8 (61.0–70.5)	83.6 (78.9–87.6)
Marcante et al, 1996 (94)	Mixed	Nasal wash	QuickVue Influenza A+B	RT-PCR	Ref+: 56; Ref-: 1482	21.4 (11.6–34.4)	98.7 (97.9–99.2)
Mee Lee, 2010 (95)†	Mixed	Nasopharyngeal aspirate	Directigen Flu A	Culture	Ref+: 14; Ref-: 27	64.3 (35.1–87.2)	96.3 (81.0–99.9)
Ming et al, 2010 (96)†	Mixed	Nasopharyngeal swab	SD Bioline Influenza	RT-PCR	Ref+: 1225; Ref-: 929	70.0 (67.4–72.6)	97.5 (96.3–98.4)
Mizuike et al, 2011 (97)†	Children	Nasopharyngeal aspirate	BinaxNOW Influenza A&B	RT-PCR	Ref+: 176; Ref-: 76	21.6 (15.8–28.4)	100 (95.3–100)
Monto et al, 2004 (98)	Adults	Nasal wash	Directigen Flu A+B	RT-PCR	Ref+: 176; Ref-: 76	35.2 (28.2–42.8)	100 (95.3–100)
Newton et al, 2002 (99)	Mixed	Throat swab	ESPLINE Influenza A&B-N	RT-PCR	Ref+: 176; Ref-: 76	23.3 (17.3–30.2)	100 (95.3–100)
Nilsson et al, 2008 (100)	Adults	Nasal wash, nasal swab, throat swab, sputum	BioTracer Influenza A&B	RT-PCR	Ref+: 176; Ref-: 76	16.5 (11.3–22.8)	100 (95.3–100)
Noel et al, 2011 (101)†	Children	Nasal aspirate	Capilia Flu A + B	RT-PCR	Ref+: 83; Ref-: 43	79.5 (69.2–87.6)	97.7 (87.7–99.9)
Nogueira et al, 2011 (102)†	Adults	Nasal wash	Directigen Flu A+B	Culture	Ref+: 17; Ref-: 65	76.5 (50.1–93.2)	92.3 (83.0–97.5)
Nougairede et al, 2010 (103)†	Mixed	Nasal wash, nasal swab, throat swab, sputum	Directigen Flu A	Culture	Ref+: 71; Ref-: 219	60.6 (48.3–72.0)	95.6 (92.3–98.1)
Nougairede et al, 2010 (104)†	Children	Nasopharyngeal aspirate	BinaxNOW Influenza A & B	RT-PCR	Ref+: 120; Ref-: 155	52.5 (43.2–61.7)	100 (97.6–100)
Noyola et al, 2000 (105)	Children	Nasal aspirate, nasal wash	Directigen Flu A+B	RT-PCR	Ref+: 120; Ref-: 438	65.8 (56.6–74.2)	99.5 (98.4–99.9)
Noyola et al, 2000 (106)	Children	Nasal aspirate, nasal wash, throat swab	Directigen Flu A+B	RT-PCR	Ref+: 42; Ref-: 232	42.9 (27.7–59.0)	100 (98.4–100)
Pierron et al, 2008 (107)	Children	Nasopharyngeal aspirate	Directigen Flu A+B	RT-PCR	Ref+: 111; Ref-: 1863	57.7 (47.9–67.0)	100 (99.8–100)
Poehling et al, 2002 (108)	Children	Nasal swab	Directigen Flu A+B	RT-PCR	Ref+: 1615; Ref-: 5844	49.4 (46.9–51.9)	100 (99.9–100)
Poehling et al, 2006 (109)	Children	Nasal swab, throat swab	ZstatFlu	Culture	Ref+: 124; Ref-: 355	70.2 (61.3–78.0)	92.4 (89.1–94.9)
Pongthanasith et al, 2011 (110)†	Children	Nasal aspirate, nasal wash	Directigen Flu A	Culture	Ref+: 97; Ref-: 320	89.7 (81.9–94.9)	98.1 (96.0–99.3)
Pongthanasith et al, 2011 (111)†	Children	Nasal aspirate, nasal wash, throat swab	ZstatFlu	Culture	Ref+: 51; Ref-: 145	96.1 (86.5–99.5)	76.6 (68.8–83.2)
Pregliasco et al, 2004 (112)	Children	Nasopharyngeal aspirate	QuickVue Influenza	Culture	Ref+: 69; Ref-: 108	95.7 (87.8–99.1)	91.7 (84.8–96.1)
Quach et al, 2002 (113)	Children	Nasal swab	QuickVue Influenza	RT-PCR	Ref+: 19; Ref-: 214	73.7 (48.8–90.9)	98.1 (95.3–99.5)
Rahman et al, 2007 (114)	Mixed	Nasal swab, throat swab	QuickVue Influenza	Culture and RT-PCR	Ref+: 51; Ref-: 154	82.4 (69.1–91.6)	99.4 (96.4–100)
		Nasal swab, throat swab	QuickVue Influenza A+B	RT-PCR	Ref+: 119; Ref-: 90	26.1 (18.4–34.9)	97.8 (92.2–99.7)
		Nasopharyngeal swab	OSOM Influenza A&B	RT-PCR	Ref+: 164; Ref-: 46	69.5 (61.9–76.5)	100 (92.3–100)
		Nasal swab, throat swab	QuickVue Influenza A+B	RT-PCR	Ref+: 164; Ref-: 46	58.5 (50.6–66.2)	100 (92.3–100)
		Nasal swab, throat swab	SD Bioline Influenza	RT-PCR	Ref+: 164; Ref-: 46	45.1 (37.4–53.1)	100 (92.3–100)
		Nasal swab, throat swab	QuickVue Influenza	Culture	Ref+: 74; Ref-: 770	39.2 (28.0–51.2)	89.1 (86.7–91.2)
		Nasopharyngeal aspirate	QuickVue Influenza	Culture	Ref+: 53; Ref-: 247	79.2 (65.9–89.2)	82.6 (77.3–87.1)
		Nasopharyngeal swab	Directigen Flu A+B	Culture	Ref+: 43; Ref-: 75	41.9 (27.0–57.9)	96.0 (88.8–99.2)

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Study, Year (Reference)	Population	Specimen Type	RIDT*	Reference Test	Specimens, n	Sensitivity (95% CI), %	Specificity (95% CI), %
Rahman et al, 2008 (115)	Mixed	Nasopharyngeal swab	BinaxNOW Flu A and Flu B	RT-PCR	Ref+; 18; Ref-; 55	61.1 (35.7–82.7)	100 (93.5–100)
Rashid et al, 2007 (116)	Mixed	Nasal swab	QuickVue Influenza	RT-PCR	Ref+; 58; Ref-; 497	22.4 (12.5–35.3)	99.0 (97.7–99.7)
Rawlinson et al, 2004 (117)	Mixed	Nasopharyngeal aspirate, throat swab	ZstatFlu	Culture	Ref+; 91; Ref-; 495	37.4 (27.4–48.1)	97.0 (95.1–98.3)
Reina et al, 1996 (118)	Children	Nasopharyngeal aspirate	Directigen Flu A	Culture	Ref+; 59; Ref-; 318	84.7 (73.0–92.8)	100 (98.8–100)
Reina et al, 2002 (119)	Mixed	Nasopharyngeal aspirate, throat swab	Directigen Flu A+B	Culture	Ref+; 74; Ref-; 86	68.9 (57.1–79.2)	100 (95.8–100)
Rodriguez et al, 2002 (120)	Children	Nasal wash, nasal swab, throat swab	Directigen Flu A	Culture§	Ref+; 58; Ref-; 58	94.8 (85.6–98.9)	84.5 (72.6–92.7)
			ZstatFlu	Culture§	Ref+; 57; Ref-; 58	71.9 (58.5–83.0)	82.8 (70.6–91.4)
			QuickVue Influenza FLU OIA	Culture§	Ref+; 57; Ref-; 55	94.7 (85.4–98.9)	76.4 (63.0–86.8)
				Culture§	Ref+; 58; Ref-; 57	93.1 (83.3–98.1)	82.5 (70.1–91.3)
Rouleau et al, 2009 (121)	Mixed	Nasopharyngeal aspirate	QuickVue Influenza A+B	RT-PCR	Ref+; 267; Ref-; 221	19.5 (14.9–24.7)	99.1 (96.8–99.9)
Ruest et al, 2003 (122)	Mixed	Nasopharyngeal aspirate	Directigen Flu A+B	RT-PCR	Ref+; 79; Ref-; 105	79.7 (69.2–88.0)	98.1 (93.3–99.8)
			QuickVue Influenza	RT-PCR	Ref+; 84; Ref-; 115	85.7 (76.4–92.4)	90.4 (83.5–95.1)
Sambol et al, 2010 (123)†	Mixed	Nasopharyngeal swab, nasal wash, nasal swab	Mixed tests**	RT-PCR	Ref+; 130; Ref-; 206	97.7 (93.4–99.5)	50.5 (43.5–57.5)
Sandora et al, 2010 (124)†	Children	Nasopharyngeal swab	BinaxNOW Influenza A & B	RT-PCR	Ref+; 208; Ref-; 333	59.6 (52.6–66.3)	99.7 (98.3–100)
Scansen et al, 2010 (125)	Children	Nasopharyngeal swab, nasal swab†	QuickVue Influenza A+B	RT-PCR	Ref+; 56; Ref-; 44	71.4 (57.8–82.7)	97.7 (88.0–99.9)
Schultze et al, 2001 (126)	Mixed	Nasopharyngeal swab, nasal aspirate, throat swab, sputum	FLU OIA	Culture§	Ref+; 205; Ref-; 195	64.4 (57.4–70.9)	94.9 (90.8–97.5)
Simmerman et al, 2007 (127)	Mixed	Nasopharyngeal swab, nasal swab†	QuickVue Influenza	RT-PCR	Ref+; 252; Ref-; 840	71.0 (65.0–76.6)	98.5 (97.4–99.2)
Smit et al, 2007 (128)	Mixed	Nasopharyngeal swab, nasal wash, throat swab	BinaxNOW Influenza A & B	Culture	Ref+; 119; Ref-; 402	58.0 (48.6–67.0)	98.8 (97.1–99.6)
			BinaxNOW Flu A and Flu B	Culture	Ref+; 119; Ref-; 402	57.1 (47.7–66.2)	99.0 (97.5–99.7)
			Directigen Flu A+B	Culture	Ref+; 78; Ref-; 331	51.3 (39.7–62.8)	99.7 (98.3–100)
Stebbins et al, 2011 (129)	Children	Throat swab	QuickVue Influenza A+B	RT-PCR	Ref+; 104; Ref-; 174	26.9 (18.7–36.5)	96.6 (92.6–98.7)
Steed et al, 1994 (130)	Mixed	Nasopharyngeal aspirate, nasopharyngeal wash, nasopharyngeal swab, nasal aspirate, nasal wash, nasal swab, throat swab	Directigen Flu A	Culture	Ref+; 14; Ref-; 83	64.3 (35.1–87.2)	96.4 (89.8–99.2)
Stein et al, 2005 (131)	Adults	Nasopharyngeal wash	QuickVue Influenza	RT-PCR	Ref+; 48; Ref-; 169	33.3 (20.4–48.4)	98.2 (94.9–99.6)
Stripeli et al, 2010 (132)	Children	Nasopharyngeal aspirate, nasal swab†	QuickVue Influenza	RT-PCR	Ref+; 40; Ref-; 177	67.5 (50.9–81.4)	96.0 (92.0–98.4)
Suntaratwong et al, 2010 (133)†	Children	Nasal swab, throat swab	QuickVue Influenza A+B	RT-PCR	Ref+; 181; Ref-; 237	64.1 (56.6–71.1)	99.2 (97.0–99.9)
Talbot et al, 2010 (134)	Adults	Nasal swab, throat swab	QuickVue Influenza A+B	RT-PCR	Ref+; 26; Ref-; 201	19.2 (6.6–39.4)	100 (98.2–100)
			BinaxNOW Influenza A & B	RT-PCR	Ref+; 15; Ref-; 46	26.7 (7.8–55.1)	95.7 (85.2–99.5)
Uyeki et al, 2009 (135)	Mixed	Nasal swab, throat swab	QuickVue Influenza A+B	RT-PCR	Ref+; 210; Ref-; 447	24.8 (19.1–31.2)	97.8 (95.9–98.9)
Velasco et al, 2010 (136)†	Mixed	Nasal swab	QuickVue Influenza A+B	RT-PCR	Ref+; 226; Ref-; 114	62.8 (56.2–69.1)	96.5 (91.3–99.0)
Waner et al, 1991 (137)	Children	Nasopharyngeal wash, nasopharyngeal swab, throat swab, tracheal specimen, bronchoalveolar lavage, sputum	Directigen Flu A	Culture	Ref+; 23; Ref-; 167	100 (85.2–100)	91.6 (86.3–95.3)

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Appendix Table—Continued

Study, Year (Reference)	Population	Specimen Type	RIDT*	Reference Test	Specimens, n	Sensitivity (95% CI), %	Specificity (95% CI), %
Watcharanan et al, 2010 (138)†	Mixed	Nasopharyngeal swab	QuickVue Influenza A+B	RT-PCR	Ref+: 26; Ref-: 51	61.5 (40.6–79.8)	80.4 (66.9–90.2)
Weinberg et al, 2005 (139)	Not reported	Nasopharyngeal swab, nasal wash, throat swab, tracheal specimen, bronchoalveolar lavage, sputum	BinaxNOW Flu A and Flu B	Culture	Ref+: 9; Ref-: 12	44.4 (13.7–78.8)	91.7 (61.5–99.8)
Weitzel et al, 2007 (140)	Mixed	Nasal swab	ImmunoCard STAT! Flu A and B	Culture and RT-PCR	Ref+: 27; Ref-: 176	66.7 (46.0–83.5)	99.4 (96.9–100)
Yoo et al, 2007 (141)	Mixed	Nasopharyngeal aspirate, nasal swab, throat swab‡	SD Bioline Influenza	Culture	Ref+: 75; Ref-: 220	58.7 (46.7–69.9)	96.4 (93.0–98.4)
Zetti et al, 2010 (142)†	Mixed	Nasopharyngeal swab, nasal aspirate, nasal wash, nasal swab, throat swab	QuickVue Influenza A+B	Culture	Ref+: 75; Ref-: 220	46.7 (35.1–58.6)	94.5 (90.7–97.2)
			QuickVue Influenza A+B	RT-PCR	Ref+: 45; Ref-: 34	4.4 (0.5–15.1)	100 (89.7–100)
			BinaxNOW Influenza A & B	RT-PCR	Ref+: 45; Ref-: 29	4.4 (0.5–15.1)	100 (88.1–100)
			Rockeby Influenza A Antigen	RT-PCR	Ref+: 27; Ref-: 10	14.8 (4.2–33.7)	100 (69.2–100)
			Directigen Flu A+B	RT-PCR	Ref+: 28; Ref-: 51	39.3 (21.5–59.4)	100 (93.0–100)

Ref+ = number of specimens positive by the reference standard; Ref- = number of specimens negative by the reference standard; RIDT = rapid influenza diagnostic test; RT-PCR = reverse transcriptase polymerase chain reaction.

* See footnote in Table 1 for names of manufacturers of RIDTs.

† Studies conducted during the pandemic of influenza A(H1N1) 2009.

‡ Differences in the type of specimen used for the RIDT and for the reference standard.

§ Reference standard was culture- and/or immunofluorescence-positive.

|| Directigen Flu A+B, QuickVue Influenza A+B, Directigen Flu A, and BinaxNOW Flu A and Flu B.

¶ QuickVue Influenza A+B and SD Bioline Influenza.

** BinaxNOW Influenza A&B, TRU FLU, Xpect Flu A&B, and QuickVue Influenza A+B.