Diagnostic Accuracy of the Quidel Sofia Rapid Influenza Fluorescent Immunoassay in Patients with Influenza-like illness: A Systematic Review and Meta-analysis

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Research

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Abstract

Background: Although the Quidel Sofia rapid influenza fluorescent immunoassay (FIA) is widely used to identify influenza A and B, the diagnostic accuracy of this test remains unclear. We compared the diagnostic performances of this test with reverse transcriptase-polymerase chain reaction.

Methods: A systematic literature search was performed using MEDLINE, EMBASE, and the Cochrane Central Register. The sensitivity, specificity, diagnostic odds ratio (DOR), and a hierarchical summary receiver-operating characteristic curve (HSROC) of this test for identifying influenza A and B were pooled using meta-analysis. A sensitivity and subgroup analysis was used to identify potential sources of heterogeneity within the selected studies.

Results: We identified seventeen studies comprising 8,334 patients. The pooled sensitivity, specificity, and DOR of the Quidel Sofia rapid influenza FIA to identify influenza A were 0.78 (95% CI, 0.71–0.83), 0.99 (95% CI, 0.98–0.99), and 251.26 (95% CI, 139.39–452.89), respectively. The pooled sensitivity, specificity, and diagnostic odds ratio of this test to identify influenza B were 0.72 (95% CI, 0.60–0.82), 0.98 (95% CI, 0.96-0.99), and 140.20 (95% CI, 55.92-351.54), respectively. The area under the HSROC for this test was similar for identification of influenza A and influenza B. Age was considered a probable source of heterogeneity.

Conclusions: The pooled sensitivities of the Quidel Sofia rapid influenza FIA did not quite meet the target level (≥80%) for both influenza A and B. The interpretation of data should be carefully considered due to substantial between-study heterogeneity.

Background

Influenza, an acute respiratory viral infection caused by influenza A or B viruses, occurs mainly in the winter months throughout the world and causes significant morbidity and mortality worldwide [1, 2]. Adequate antiviral therapy can shorten the time of illness and reduce the duration of hospitalization and the risk of complications from influenza infection [3]. Clinical benefit of antiviral therapy is greatest when started soon after the onset of influenza illness [4]. Therefore, rapid and accurate diagnosis of influenza infection is necessary in clinical practice.

Although polymerase chain reaction (PCR) has been used as the reference standard for diagnosing viral infections, performing PCR is relatively expensive and requires technical expertise [5]. Alternatively, point-of-care rapid influenza diagnostic tests (RIDTs) detect viral antigens by immunoassay and provide quick results within 30 minutes. They can facilitate antiviral therapy, reduce additional diagnostic tests and hospitalization therapy, and induce appropriate infection control measures [6, 7]. A recent systematic review and meta-analysis for 162 diagnostic accuracy studies of RIDTs revealed that traditional RIDTs had high specificity greater than 98% but poor sensitivity (54.4% for influenza A and 53.2% for influenza B) [5]. Two classes of RIDTs, automated immunochromatographic antigen detection tests (digital immunoassays [DIAs]) and rapid nucleic acid amplification tests (NAATs), have been used since 2011 [5]. The pooled sensitivities for DIAs (80.0% for influenza A and 76.8% for influenza B) and rapid NAATs (91.6% for influenza A and 95.4% for influenza B) are significantly higher than those for traditional RIDTs [5].

As a type of DIA, the Quidel Sofia rapid influenza fluorescent immunoassay (FIA) (Quidel Corporation, CA, USA) is a point-of-care test to detect influenza A and B in less than 15 minutes using a compact instrument (Sofia Analyzer). Although the performance characteristics of this test to detect seasonal influenza virus strains have been established, the diagnostic accuracy of the Quidel Sofia rapid influenza FIA is not yet fully known.

Methods

Data Sources and Search Strategy

Based on a systematic review and meta-analysis of clinical trial data, we investigated the diagnostic properties of the Quidel Sofia rapid influenza FIA in patients with influenza like illness. This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses of Diagnostic Test Accuracy Studies statement [8]. We performed a comprehensive search of three electronic databases (MEDLINE, EMBASE, and the Cochrane Central Register) up to July, 2020. Search terms for influenza included: “Influenza, Human” [MeSh] OR “Influenza A virus” OR “Influenza B virus” OR “influenza” OR “flu”. Search terms for the tests included: “rapid test*” OR “rapid diagnos*” OR “point-of-care test*” OR “immunoassay*” OR “immunochromatographic test*” OR “influenza FIA” OR “Quidel Sofia Influenza” OR “Rapid Detection Flu”. As this study was a systematic review of published articles, neither informed consent nor ethics approval was required. We also conducted a manual search of the references listed in relevant review articles.

Study selection

We included studies that met the following inclusion criteria: (1) full-length reports published in peer-reviewed English language journals; (2) evaluated the performance of the Quidel Sofia rapid influenza FIA, compared to a reference standard; (3) included patients with influenza-like illness; and (4) provided sufficient data to calculate absolute numbers of true-positive, false-positive, false-negative, and true-negative results. Review articles, case reports, commentaries, and studies reporting outcomes without raw data or peer review were excluded. Participant demographics and underlying diseases were not restricted.

Influenza-like illness was defined as fever ≥ 38 °C and any signs/symptoms of respiratory tract infection (e.g., cough, sputum, sore throat, wheezing, etc.). We allowed the followings as specimens; nasopharyngeal aspirates, swabs, or washes; nasal aspirates, swabs, or washes; and throat swabs. A reference standard was either a commercial or laboratory-developed reverse transcriptase-polymerase chain reaction (RT-PCR).

Data Extraction and Quality Assessment

J-U.S. and J.L. independently performed extraction of potentially relevant studies and reviewed each study according to predefined eligibility criteria, after which data were extracted. Any disagreements that arose during the process of study selection or data extraction were resolved by discussion. A predefined form was used to extract data from each study. The following data from each study included in the meta-analysis were extracted: author, year of publication, study design, place of study, number of participants, age, gender, study period, type of reference standard, type of specimens, and type of population. As recommended by the Cochrane Collaboration, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool to assess the risk of bias in diagnostic test accuracy [9]. Discrepancies were resolved by consensus between the two authors (J-U.S. and J.L.).

Data Synthesis and Statistical Analysis

For diagnostic meta-analysis, we used random effects meta-analyses to generate pooled estimates with 95% confidence intervals (CIs). We extracted the numbers of patients with true-positive, false-positive, false-negative, and true negative test results either directly or through a recalculation based on the reported measures of accuracy in combination with the prevalence and sample size of the included study. We calculated the pooled sensitivity and specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the receiver-operating characteristic curve (AUC) as pooled estimates with a 95% confidence interval (CI) [10]. We also constructed hierarchical summary receiver-operating characteristic curves (HSROCs). To assess the effect of potential sources of heterogeneity, we added the following covariates to the model: study design (single vs. multicenter), number of participants (≥ 250 vs. <250), study period (influenza vs. non-specific season), reference standard (RT-PCR only vs. RT-PCR and virus culture), and study population (children vs. adult). We calculated pooled sensitivity and specificity estimates for each covariate. To investigate the effect of study quality, we performed sensitivity analyses. A P value < 0.05 was considered statistically significant. Statistical analyses were performed with Stata statistical software (Version 14.2, Stata Corp LP, College Station, TX, USA), and Review Manager (Version 5.3, Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Study search and characteristics and quality of included studies

The literature search process is shown in Fig. 1. We initially identified 432 articles from Pubmed, 1,310 articles from EMBASE, and 356 articles from the Cochrane library, and an additional article from hand-searching. After removing duplicate articles, we screened 1,664 potentially eligible articles. After reviewing the title and abstracts, 1,629 search records were removed, and the remaining 35 articles were eligible for reading the full text. Fifteen articles were excluded for the reasons shown in Fig. 1. With quantitative synthesis, seventeen studies were included in our final analysis [11–27].

Table 1 summarizes the features of the included studies. For influenza A, we identified seventeen studies comprising 8,334 participants. For influenza B, sixteen studies involving 7,909 subjects met the defined inclusion criteria. One study assessed influenza A infection only [21]. The number of patients in each trial ranged from 68 to 1,649. All studies were published between 2012 and 2018. Most of the studies evaluated combined populations of adults and children. Two studies included virus culture with RT-PCR as reference standards [18, 26]. From the QUADAS assessment, the quality of the included studies was deemed satisfactory as a whole.

Table 1
Characteristics of the studies included in the meta-analysis

Study, year	Design	Country	Number of participants	Age, years (mean or median)	Male (%)	Study period	Reference standard	Type of specimens	Population
Bruning, 2014 [11]	Single-center study	Netherlands	68	NA	NA	December 2013 to February 2014	RT-PCR	NP swabs or aspirates	Children (aged 0–16 years old) with symptoms of respiratory illness admitted to either pediatric ICU or infant ward
Busson, 2017 [12]	Multi-center study	Belgium	267	3.5	46.6	January 2015 to March 2015	RT-PCR	NP swabs, NP aspirates, broncho-alveolar lavages	Children and adult patients admitted with suspected influenza
Dunn, 2014 [13]	Single center study	USA	240	NA	NA	January 2013 to April 2013	RT-PCR	Nasal wash	Symptomatic patients under 18 years of age
Gomez, 2016 [14]	Single center study	Spain	1065	NA	NA	November 2013 to April 2014	RT-PCR	NP swabs, NP aspirates	Adult (80.6%) and pediatric (19.4%) patients with respiratory tract symptoms hospitalized
Hazelton, 2015 [15]	Single center study	Australia	202	56	NA	NA	RT-PCR	NP swabs	Patients ≥ 16 years old with an influenza-like illness
Hazelton, 2015 [16]	Single center study	Australia	209	56	NA	NA	RT-PCR	Throat swabs, NP swabs, or nose swabs	Patients with an influenza-like illness
Kammerer, 2016 [17]	Multi-center study	USA	871	NA	NA	2012 to 2014	RT-PCR	Nasal swabs	Patients with an influenza-like illness (> 70% of patients were under the age of 25 years)
Lee, 2012 [18]	Single center study	South Korea	169	27.7	56.4	December 2011 to February 2012	RT-PCR and virus culture	NP swabs	Patients with an influenza-like illness

ICU, intensive care unit; NA, not available; RT-PCR, reverse-transcription polymerase chain reaction

Study, year	Design	Country	Number of participants	Age, years (mean or median)	Male (%)	Study period	Reference standard	Type of specimens	Population
Leonardi, 2016 [19]	Single center study	USA	141	NA	NA	Influenza seasons from 2006 to 2011 and the 2011–2012	RT-PCR	NP swabs	Frozen original influenza-positive specimens and prospective specimens
Lewandrowski, 2013 [20]	Multi-center study	USA	2047	NA	52.9	NA	RT-PCR or virus culture	Nasal swabs and NP swabs or aspirates.	Patients with an influenza-like illness
Noh, 2015 [21]	Multi-center study	South Korea	391	40	37.6	December 2012 to April 2013	RT-PCR	NP swabs	Adult patients with influenza-like illness
Ryu, 2016 [22]	Single center study	South Korea	314	30.4	51.9	January 2014 to February 2015	RT-PCR	NP swabs	Patients showing influenza-like symptoms
Ryu, 2018 [23]	Single center study	South Korea	158	NA	NA	2016	RT-PCR	NP swabs	Patients with an influenza-like illness between neonates and 90 years old
Selove, 2016 [24]	Single center study	USA	1649	57	50	September 2014 to May 2015	RT-PCR	Nasal aspirates	Patients with an influenza-like illness
Tuttle, 2015 [25]	Single center study	Germany	686	3.5 for mean, 1.8 for median	55	December 2012 to April 2013	RT-PCR or virus culture	NP or nasal swabs	Patients aged 0–18 years with an influenza-like illness
Yang, 2018 [26]	Single center study	Taiwan	109	38.8	56.9	January 2012 to December 2013	RT-PCR and/or virus culture	NP or throat swabs	Patients who presented at out-patient clinics or the emergency department with influenza-like illness
Yoon, 2017 [27]	Single center study	South Korea	385	46	46.5	December 2014 to April 2015	RT-PCR	NP swabs or saliva	Patients with an influenza-like illness

ICU, intensive care unit; NA, not available; RT-PCR, reverse-transcription polymerase chain reaction

Diagnostic accuracy of the Quidel Sofia rapid influenza FIA to identify influenza A and B

Figures 2 and 3 show paired forest plots of sensitivity and specificity of the Quidel Sofia rapid influenza FIA for detection of influenza A and B. The pooled sensitivity across studies of the Quidel Sofia rapid influenza FIA to identify influenza A was 0.78 (95% CI, 0.71 to 0.83), and the pooled specificity was 0.99 (95% CI, 0.98 to 0.99). The pooled PLR and NLR were 56.99 (95% CI, 31.87 to 101.90) and 0.23 (95% CI, 0.18 to 0.29), respectively. The DOR for influenza A was 251.26 (95% CI, 139.39 to 452.89).

The pooled sensitivity across studies on influenza B was 0.72 (95% CI, 0.60 to 0.82), and the pooled specificity was 0.98 (95% CI, 0.96 to 0.99). The pooled PLR and NLR were 40.08 (95% CI, 17.26 to 93.07) and 0.29 (95% CI, 0.19 to 0.42), respectively. The DOR for influenza B was 140.20 (95% CI, 55.92 to 351.54). The pooled sensitivity and specificity of the Quidel Sofia rapid influenza FIA were similar for both influenza A and B ($p = 0.341$ for sensitivity and $p = 0.206$ for specificity). Figure 4 shows HSROCs for index test and indicates Fig. 4 shows HSROCs for index test and indicates that the AUCs of the Quidel Sofia rapid influenza FIA were similar between identifications of influenza A and influenza B (0.96; 95% CI, 0.94–0.98 for influenza A and 0.95; 95% CI, 0.92–0.96 for influenza B, respectively; $p = 0.166$).

Subgroup analyses and sensitivity analyses for the Quidel Sofia rapid influenza FIA to identify influenza A and B

Table 2 summarizes the results of subgroup analyses with respect to the diagnostic performance of this test. The sensitivity of the Quidel Sofia rapid influenza FIA was significantly increased when tests were performed in children (0.86; 95% CI, 0.78–0.92 for influenza A and 0.79; 95% CI, 0.71–0.85 for influenza B, respectively), compared with performance in adults (0.74; 95% CI, 0.67–0.79 for influenza A and 0.33; 95% CI, 0.10–0.65 for influenza B, respectively).

Table 2
Subgroup analysis for the diagnostic performance of the Quidel Sofia rapid influenza fluorescent immunoassay

			Sensitivity		Specificity	
Variable	**No. of studies**	**No. of patients**	**Adjusted (95% CI)**	***P* value**	**Adjusted (95% CI)**	***P* value**
Studies that evaluated influenza A						
Study design						
Single center	13	5,344	0.79 (0.72–0.85)	0.583	0.99 (0.98-1.00)	0.574
Multicenter	4	2,990	0.75 (0.63–0.87)		0.99 (0.97-1.00)	
Number of participants						
≥250	9	7,038	0.72 (0.65–0.79)	0.173	0.99 (0.98-1.00)	0.114
<250	8	1,296	0.84 (0.77–0.90)		0.97 (0.95–0.99)	
Study period						
Influenza season	11	3,784	0.79 (0.73–0.86)	0.440	0.99 (0.98-1.00)	0.610
Non-specific season	6	4,550	0.74 (0.64–0.85)		0.99 (0.97-1.00)	
Reference standard						
RT-PCR	15	8,056	0.77 (0.70–0.83)	0.801	0.99 (0.98–0.99)	0.071
RT-PCR and virus culture	2	278	0.82 (0.73–0.89)		0.96 (0.94–0.98)	
Population						
Children	3	951	0.86 (0.78–0.92)	0.019	0.97 (0.96–0.98)	0.332
Adults	2	593	0.74 (0.67–0.79)		0.97 (0.94–0.98)	
Studies that evaluated influenza B						
Study design						
Single center	13	5,310	0.72 (0.59–0.84)	0.937	0.98 (0.97-1.00)	0.228
Multicenter	3	2,599	0.73 (0.48–0.97)		0.97 (0.93-1.00)	
Number of participants						
≥250	8	6,690	0.69 (0.53–0.84)	0.730	0.99 (0.97-1.00)	0.432
<250	8	1,219	0.75 (0.60–0.90)		0.97 (0.94-1.00)	
Study period						
Influenza season	10	3,372	0.76 (0.63–0.89)	0.403	0.98 (0.96-1.00)	1.000
Non-specific season	6	4,537	0.65 (0.45–0.85)		0.98 (0.96-1.00)	
Reference standard						
RT-PCR	14	7,632	0.71 (0.59–0.83)	0.901	0.98 (0.97-1.00)	0.536
RT-PCR and virus culture	2	277	0.78 (0.50-1.00)		0.98 (0.92-1.00)	
Population						
Children	3	994	0.79 (0.71–0.85)	< 0.001	0.92 (0.90–0.94)	0.005
Adults	1	202	0.33 (0.10–0.65)		0.99 (0.97-1.00)	

In sensitivity analysis to investigate the influence of each individual study on the overall analysis estimate, one study had a significantly different sensitivity than the other studies on influenza A [24]. After exclusion of that study [24], the pooled sensitivity across studies on influenza A was similar to that of the overall studies (0.79, 95% CI, 0.75 to 0.82).

Discussion

According to a rule by the Food and Drug Administration (FDA), RIDTs for influenza A and B are required to have a sensitivity of at least 80% and a specificity of at least 95% compared to an FDA-cleared nucleic acid based-test or other currently appropriate and FDA accepted comparator methods other than a correctly performed viral culture method [28]. A recent systematic review and meta-analysis, which was searched to May 2017, compared accuracy of traditional RIDTs, rapid NAATs, and DIAs in patients with suspected influenza [5]. For diagnosis of influenza A and B, the pooled sensitivities of DIAs including the Quidel Sofia rapid influenza FIA were 80.0% and 76.8%, respectively [5].

In the present study, when compared to RT-PCR, the pooled sensitivity of the Quidel Sofia rapid influenza FIA to identify influenza A and B were 78% and 72%, respectively, which indicate that our findings did not quite reach the target level of sensitivity required by the FDA. Therefore, some patients with negative results on the Quidel Sofia rapid influenza FIA may still be confirmed to have an influenza infection by alternative and more sensitive diagnostic methods.

Influenza type could have an effect on the accuracy of RIDTs. A previous meta-analysis revealed that overall RIDTs had increased sensitivity for detection of influenza A compared with influenza B (64.6% vs. 52.2%; $p = 0.05$) [29]. Influenza A virus causes more severe disease, higher influenza-associated hospitalization, and death compared to influenza B virus [29]. More severe virulence of influenza A may cause higher viral burden, which can lead to relatively high sensitivity [19]. In the present study, although the pooled sensitivity of the Quidel Sofia rapid influenza FIA to identify influenza A tended to be higher than that for influenza B, there was no statistical difference.

The Quidel Sofia rapid influenza FIA has the advantages of providing a simple, fast, and easy method for viral testing. The pooled specificity of this tool in our study was approximately 98%, above the target level for both influenza A and B. From these findings, we believe that clinicians would be able to diagnose influenza with assurance on the basis of a positive result from the Quidel Sofia rapid influenza FIA.

Large heterogeneities are commonly reported in systematic reviews of studies on diagnostic test accuracy, and substantial between-study heterogeneity among the enrolled studies was also observed in the present study [30]. Age is a probable source of heterogeneity for between-studies in the pooled estimates. In the present study, the pooled sensitivities of the Quidel Sofia rapid influenza FIA were significantly higher by approximately 12 percentage points for influenza A and 46 percentage points for influenza B in children compared to adults. The duration of influenza virus shedding is commonly measured from symptom onset to shedding cessation time, and children have been reported to have a tendency to shed the virus for a longer duration compared to adults [31]. Longer duration of influenza virus shedding in children might be associated with a higher sensitivity of this test compared to adults. However, because the number of studies that distinguish children from adults is very small, our findings should be interpreted with caution.

The sensitivity observed in one study was significantly lower than that observed in most studies [24]. In this study, an older patient population (median age 57 years) and a study protocol that did not specify the need for particular symptoms and duration of illness may have contributed to the reduced sensitivity [24]. These factors may have been affected by low virus shedding [24]. In our sensitivity analysis conducted after excluding this study [24], the pooled sensitivity of the Quidel Sofia rapid influenza FIA across studies on influenza A was slightly increased.

To the best of our knowledge, this is the first meta-analysis to investigate the Quidel Sofia rapid influenza FIA for detection of influenza. However, potential limitations of the present study should be considered when interpreting our results. First, because this present study was based on a relatively small number of trials, our results should be carefully interpreted with limited statistical power. Second, we could not make an assessment for publication bias since no reliable methods exist to investigate this issue in diagnostic test accuracy studies [32]. Third, although we used RT-PCR as the control reference for influenza diagnosis, two included studies used both RT-PCR and virus culture as reference standards. This use of dual reference standards may elicit the introduced bias due to diagnostic differences between references standards. However, for the pooled sensitivities and specificities across studies on the Quidel Sofia rapid influenza FIA to identify influenza A and B, there were no significant differences between RT-PCR and virus culture and only RT-PCR as control references. Finally, as a sample for viral diagnosis, nasopharyngeal aspirates would present with higher quality than nasopharyngeal swabs. Although we tried to investigate the diagnostic accuracy of the Quidel Sofia rapid influenza FIA according to the type of sample, we were not able to perform this analysis because of data limitations.

Conclusion

We found that the pooled sensitivities of the Quidel Sofia rapid influenza FIA were slightly below the target level prescribed by the FDA for both influenza A and B. Therefore, especially for adults, physicians should consider the possibility of false-negative results by this test. While the pooled specificity of this test was very high for both influenza A and B, substantial between-study heterogeneity requires careful interpretation of the data.

Abbreviations

AUC, area under the receiver-operating characteristic curve; CI, confidence interval; DIA, digital immunoassay; DOR, diagnostic odds ratio; FIA, fluorescent immunoassay; HSROC, hierarchical summary receiver-operating characteristic curve; NAAT, nucleic acid amplification test; NLR, negative likelihood ratio; PCR, polymerase chain reaction; PLR, positive likelihood ratio; QUADAS, the quality assessment of diagnostic accuracy studies; RIDT, rapid influenza diagnostic test; RT-PCR, reverse transcriptase-polymerase chain reaction

Declarations

Acknowledgements

Not applicable

Authors' contributions

Jae-Uk Song contributed to data acquisition, data interpretation, statistical analysis, and drafted the manuscript. Jonghoo Lee contributed to the study design, data acquisition, data interpretation, statistical analysis, writing of the manuscript, and critical revision of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

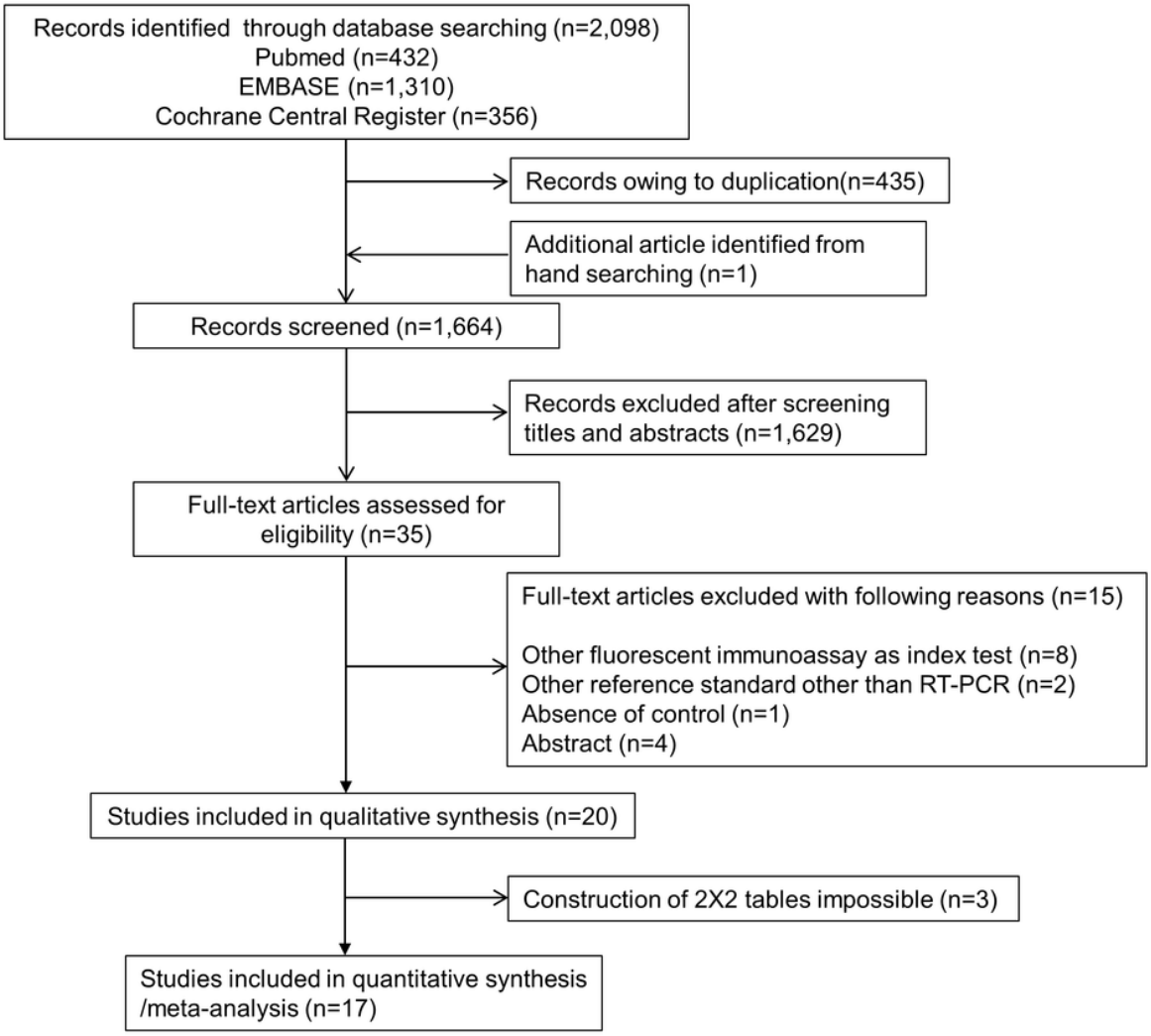

Figure 1

Flow diagram for identification of eligible studies

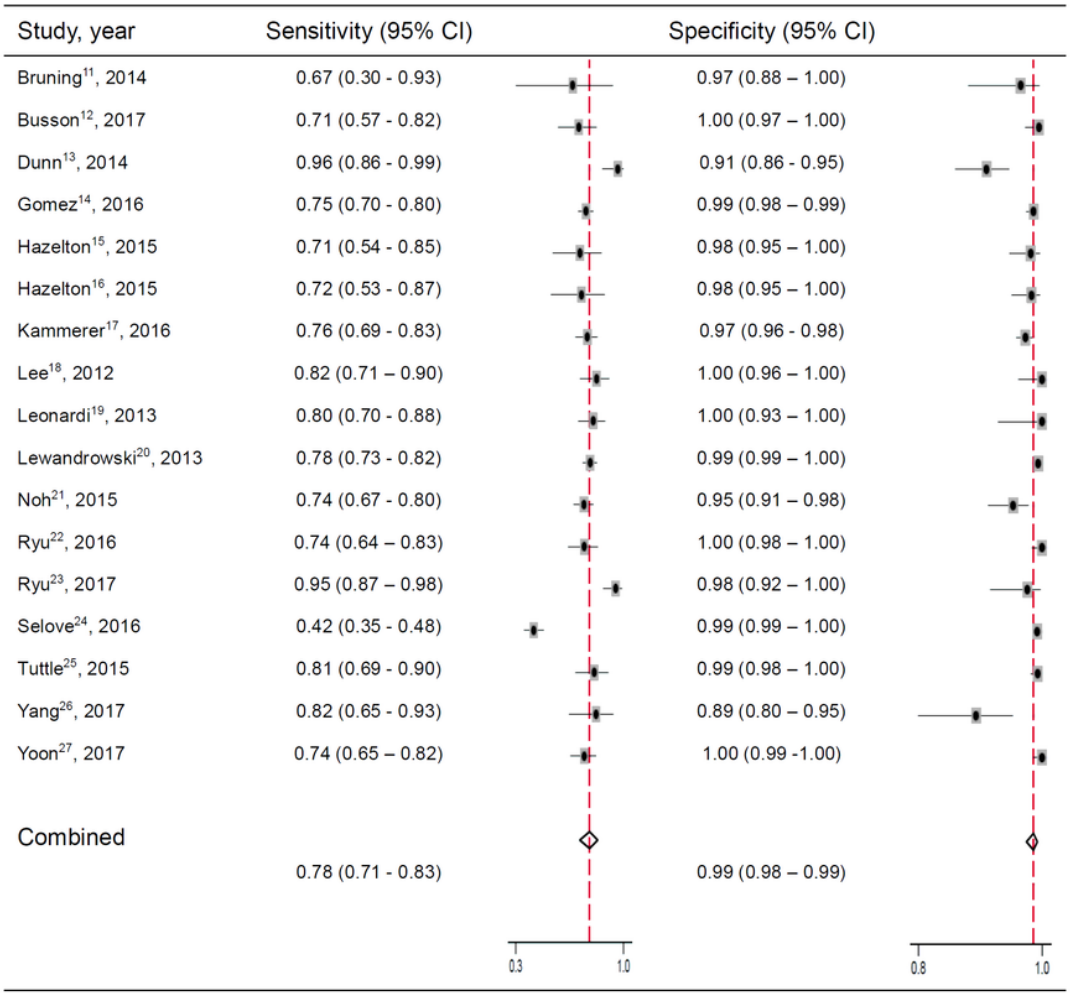

Figure 2

Paired forest plots of sensitivity and specificity of the Quidel Sofia rapid influenza FIA for detection of influenza A

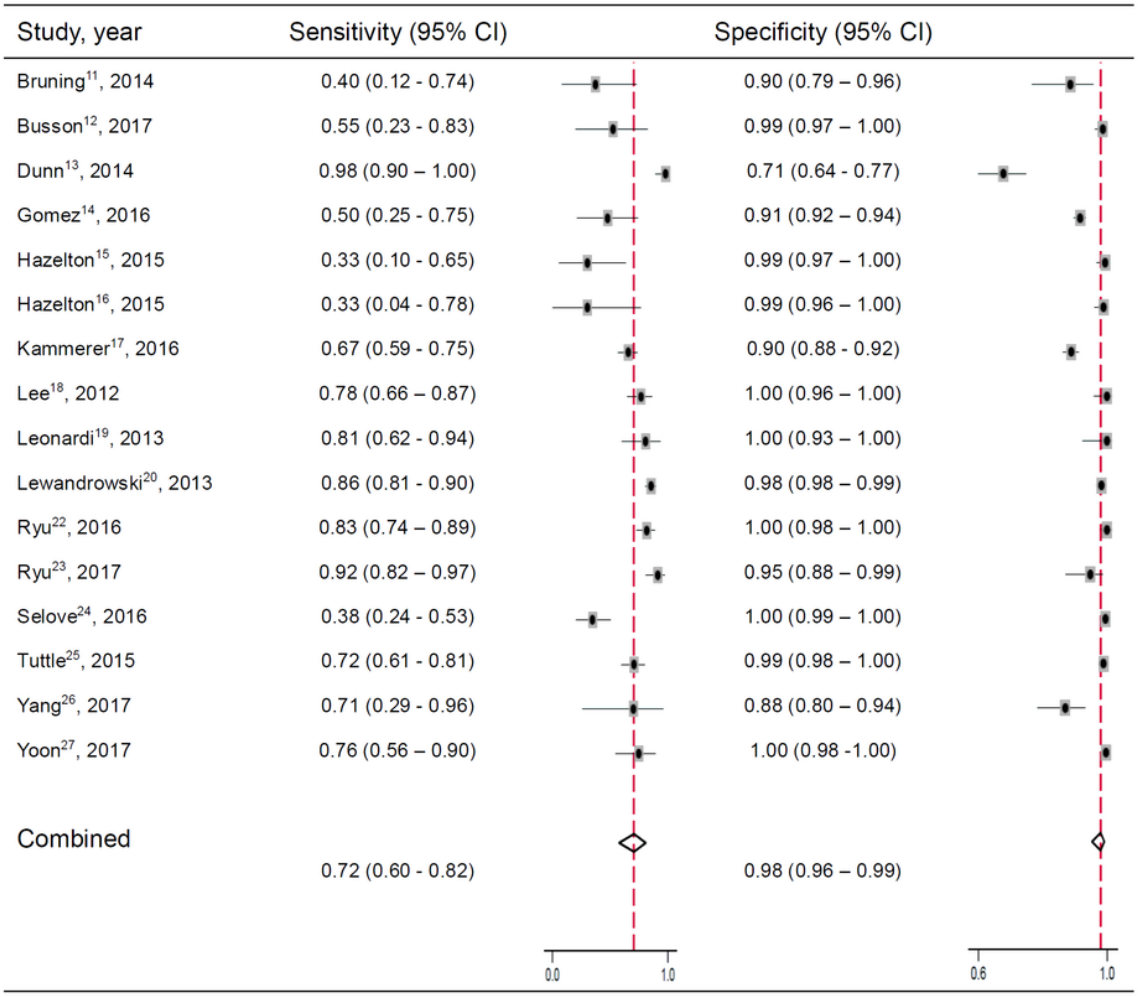

Figure 3

Paired forest plots of sensitivity and specificity of the Quidel Sofia rapid influenza FIA for detection of influenza B

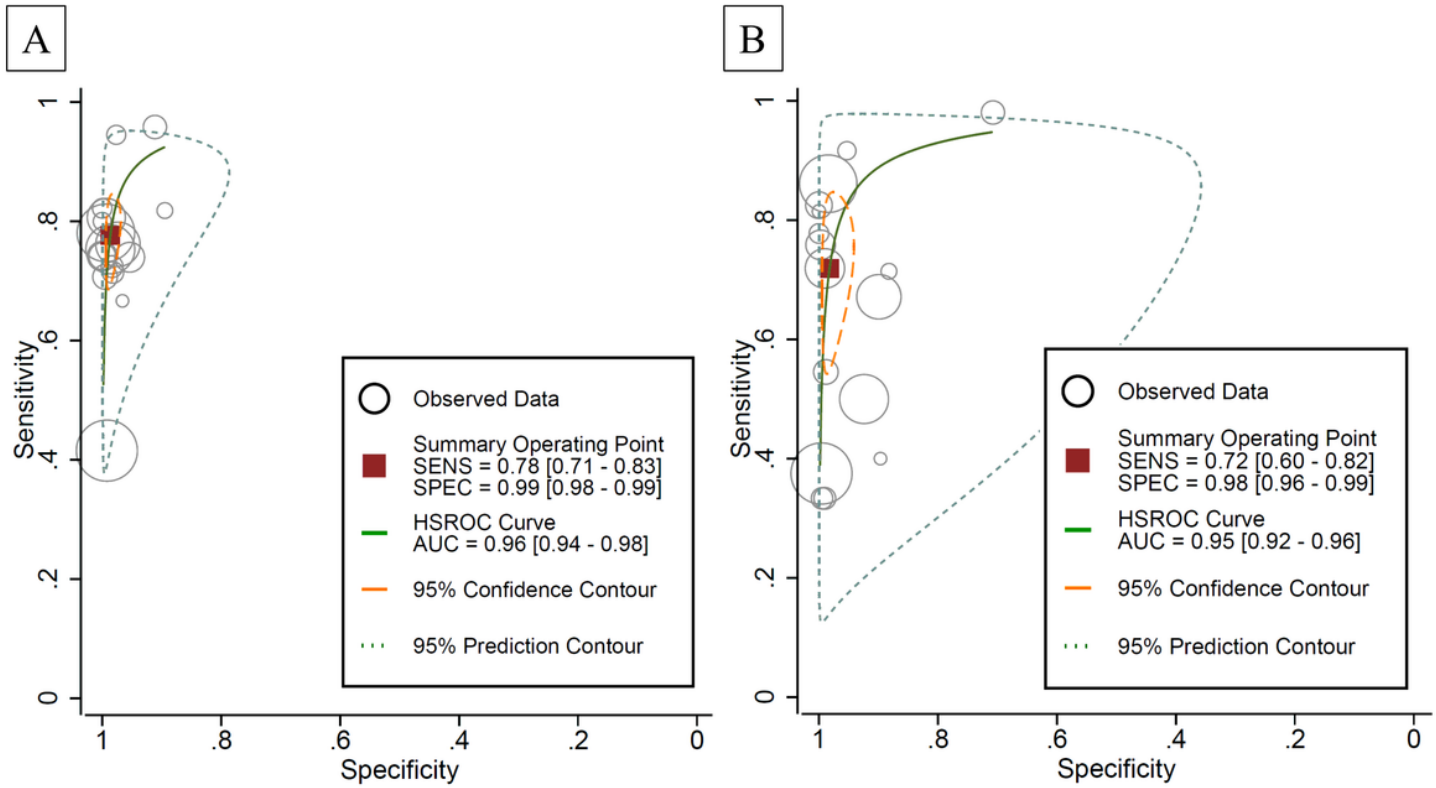

Figure 4

Hierarchical summary receiver operating characteristic curves for the Quidel Sofia rapid influenza FIA for detection of (A) influenza A and (B) influenza B