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Running title: Diagnostic accuracy of Xpert Xpress Flu/RSV

Keywords: Xpert Xpress Flu/RSV; influenza virus; respiratory syncytial virus; PCR

Summary: Xpert Xpress Flu/RSV is a fast and automated real-time nucleic acid amplification tool for detecting influenza virus and respiratory syncytial virus (RSV). The aim of this study was to verify the accuracy of Xpert Xpress Flu/RSV in detecting influenza virus and RSV. PubMed, EMBASE, Cochrane Library, and Web of Science were searched up to October 2020. The quality of original research was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 guidelines. Meta-DiSc 1.4 software was used to analyze the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and Summary
receiver operating characteristic curve. Deek’s funnel plot asymmetry test was used to evaluate the publication bias by Stata 12.0. Ten studies with 25 fourfold tables were included in this analysis. The sensitivity of Xpert Xpress Flu/RSV in detecting influenza A, influenza B, and RSV was 0.97, 0.98, 0.96, respectively, and the specificity was 0.97, 1.00, 1.00, respectively. Compared with other common clinical real-time reverse transcriptase PCR (RT-PCR), Xpert Xpress Flu/RSV is a valuable tool for diagnosing influenza virus and RSV with high sensitivity and specificity.

Introduction

Belonging to two different generations of Orthomyxoviridae, Influenza A and influenza B can cause the recurrence of respiratory diseases and seasonal epidemics annually, which has a significant impact on healthcare systems worldwide due to a great number of medical visits and hospitalizations(1, 2). These viruses can cause pneumonia with acute respiratory distress development syndrome (ARDS), respiratory failure, and even death in some extreme cases(2, 3). Also, it was estimated that 291 243–645 832 seasonal influenza-associated respiratory deaths occur every year(4).

Respiratory syncytial virus (RSV) is another type of single-strand RNA virus affecting all age groups(5). It is the main cause of lower respiratory tract infection and hospitalization that affects the population at the extremes of age, resulting in a high rate of emergency department visits and elderly and young children's
hospitalization(5-8). Rapid and accurate diagnosis of influenza virus and RSV may shorten the hospitalization time of infected persons, reduce the need for additional diagnostic tests, and guide the wise and appropriate use of antibiotics and antiviral drugs, thus improving treatment.

Over the last decade, rapid polymerase chain reaction (PCR) has been used to detect viruses affecting the respiratory tract(9-11). Nevertheless, this method is time-consuming and requires professional laboratories and specialized instruments. In addition, many intermediate steps of PCR experiments need to be performed by professionals, which may cause errors(9, 10, 12). Under ideal circumstances, there should be a method to diagnose influenza virus and RSV in a convenient and fast way without compromising the accuracy.

The Xpert Xpress Flu/RSV assay (Cepheid, Sunnyvale, CA) is a fast and automated real-time nucleic acid amplification test, which can be used for accurate and reliable detection of influenza A, influenza B, and RSV(13, 14). Compared to traditional PCR diagnosis assay, this method is straightforward and can be used by anyone without training(14). All the steps in this assay, including sample extraction, nucleic acid purification and concentration, quantitative PCR amplification detection and analysis, are completed automatically and do not require precision pipetting, which significantly decreases the possibility of errors and time for diagnosis(12, 14).

The Xpert Xpress Flu/RSV is an updated version of the previous Xpert Flu/RSV XC, which requires less time to be completed (from 63min to 32min), and has higher
sensitivity and specificity against RNA targets(15). In 2016, the use of Xpert Xpress Flu/RSV for in vitro diagnosis of influenza A, influenza B, and RSV infection was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), followed by National Medical Products Administration (NMPA) in China in 2019(12). Currently, there are still no systematic reviews and meta-analysis on the accuracy of identification of influenza virus and RSV using Xpert Xpress Flu/RSV assay in the field of evidence-based medicine. The aim of this study was to verify the accuracy of Xpert Xpress Flu/RSV in detecting the influenza virus and RSV. Our results provide new ideas and methods for the clinical diagnosis of influenza virus and RSV.

Materials and Methods

Search for strategy and sources of information

We respectively searched “Influenza” and “respiratory syncytial virus” in Medical Subject Headings terms (MeSH) and EMTREE terms. EMBASE, Cochrane Library, PubMed, Web of science were all searched from inception to October 2020, using the following keywords: (Xpert Xpress Flu/RSV AND (Influenza [all synonyms] OR RSV [all synonyms])). The reference sections of relevant articles were reviewed to find additional primary studies. The study was carried out in October 2020(16).

Inclusion and exclusion criteria
The inclusion criteria were the following: (I) analysis of human specimens; (II) comparison of Xpert Xpress Flu/RSV with another gold standard (PCR) to influenza virus/RSV; (III) data in the articles were sufficient to draw a fourfold table; (IV) articles published up to October 2020; (V) articles published in English; (VI) articles including RSV OR Influenza and Xpert.

The exclusion criteria were: (I) samples from animals or other species; (II) the gold standard was not revealed, or the Xpert Xpress Flu/RSV assay was not performed; (III) repeated publications; (IV) conferences, letters, editorials, and abstracts.

**Research Screening and Selection**

The search results were imported into Endnote X9. Two reviewers independently screened articles in accordance with inclusion and exclusion criteria. Duplicate references, conference abstracts, and unrelated articles were excluded. Subsequently, the full text of all selected studies was reviewed, the quality was assessed, and the data were extracted. If there were disagreements, both reviewers would seek the advice of a third reviewer.

**Data extraction and quality estimate**

Two reviewers extracted data independently from each study and resolved differences through consensus. Retrieved data included the year of publication, country, author, the number of samples, type of study (prospective or retrospective), the sample type
in the article, gold standard, type of specimens, the diagnostic fourfold table with its four cells: true positives, false negatives, true negatives, and false positives. Each study's methodological quality was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool of the diagnostic accuracy study(17). Quality assessment of the included studies was performed by Review Manager 5.3.

Statistical analysis

Two reviewers independently analyzed all the data, including the specificity, sensitivity, negative likelihood ratio (-LR), positive likelihood ratio (+LR), diagnostic odds ratio (DOR), through the Meta-DiSc 1.4 software. Summary of receiver operating characteristic (SROC) curve and the area under the curve (AUC) were used to summarize overall diagnostic performance. Deek’s funnel plots asymmetry test was used to evaluate the publication bias by Stata12.0.

Results

Studies characteristics

Fourteen articles in PubMed, 17 in EMBASE, 11 in Web of Science, and 3 in Cochrane Library were found. After manually eliminating searched and duplicated articles, the title and main points from 22 articles were included in the final analysis.
Three articles were excluded by screening titles and abstracts, and 19 articles were retained for full-text scanning. In addition, 9 studies, including two conference abstracts, six studies (not possible to extract a fourfold table), and one letter article were additionally excluded.

Finally, ten articles that analyzed 4798 Influenza A samples, 4586 Influenza B samples, and 3834 RSV samples were included in the meta-analysis (8, 10, 12-15, 18-21). The PRISMA flow diagram of this study is shown in Figure 1, while the study characteristics are shown in Table 1.

**QUADAS-2 quality evaluation results**

The risk of bias and applicability concerns summary is shown in Figure 2. In the patient selection domain and flow and timing, approximately 50% of the studies had an unclear risk of bias and an unclear concern of applicability. In terms of the reference standard, all studies demonstrated a low risk of bias and a low concern of applicability because the gold standard can correctly distinguish the target disease status, and blind method is used to interpret gold standard results. However, almost 40% of the studies were identified as high risk and a high concern in the index test.

**Influenza A**

Ten reports evaluated Influenza A (Figure 3)(8, 10, 12-15, 18-21). Figure 3A, 3B, 3C, 3D and 3E show the combined sensitivity, specificity, +LR, -LR and DOR of Xpert
Xpress Flu/RSV to detect influenza A were 0.97 (95% CI: 0.95, 0.98), 0.97 (95% CI: 0.96, 0.97), 88.25 (95% CI: 34.81, 223.73), 0.02 (95% CI: 0.01, 0.07) and 5491.13 (95% CI: 1100.83, 27390.76), respectively. The SROC curve in influenza A is shown in Figure 3F. AUC was 0.9985, and the Q index was 0.9874 (SE = 0.0043). We calculated the Spearman correlation coefficient of 0.079 (P=0.829) in the threshold analysis, suggesting no significant threshold effect in the meta-analysis of Xpert Xpress Flu/RSV in influenza A. No publication bias was found in Deek’s funnel plot of influenza A (Figure 3G). In addition, the Egger test indicated that the publication bias of these articles in influenza A were low (P = 0.499).

Influenza B

Nine reports evaluated Influenza B (Figure 4)(8, 10, 12-15, 18, 20, 21). Figure 4A, 4B, 4C, 4D and 4E show the combined sensitivity, specificity, +LR, -LR and DOR of Xpert Xpress Flu/RSV to detect influenza B were 0.98 (95% CI: 0.96, 0.99), 1.00 (95% CI: 0.99, 1.00), 165.63 (95% CI: 109.20, 251.23), 0.03 (95% CI: 0.01, 0.06) and 6602.46 (95% CI: 2839.93, 15349.84), respectively. The SROC curve in influenza B is shown in Figure 4F; AUC was 0.9990, and the Q index was 0.9914 (SE = 0.0029). We calculated the Spearman correlation coefficient of 0.300 (P=0.433) in the threshold analysis, suggesting no significant threshold effect in the meta-analysis of Xpert Xpress Flu/RSV in influenza B. No publication bias was found in Deek’s funnel plot of influenza B (Figure 4G). In addition, the Egger test indicated that the publication bias of these articles in influenza B were low (P = 0.400).
**Respiratory syncytial virus**

Six reports evaluated the RSV (Figure 5)(8, 12, 14, 15, 18, 21). Figure 5A, 5B, 5C, 5D and 5E show the combined sensitivity, specificity, +LR, -LR and DOR of Xpert Xpress Flu/RSV to detect RSV were 0.96 (95% CI: 0.94, 0.98), 1.00 (95% CI: 0.99, 1.00), 238.56 (95% CI: 139.92, 406.74), 0.05 (95% CI: 0.02, 0.12) and 5336.18 (95% CI: 2387.40, 11927.14), respectively. The SROC curve in RSV is shown in Figure 5F; AUC = 0.9993, and the Q index was 0.9947 (SE = 0.0028). In the threshold analysis, the Spearman correlation coefficient was 0.257 (P=0.623), suggesting no significant threshold effect in the meta-analysis of Xpert Xpress Flu/RSV in RSV. No publication bias was found in Deek’s funnel plot of RSV (Figure 5G). In addition, the Egger test indicated that the publication biases of these articles in RSV were low (P = 0.506).

**Discussion**

Influenza virus and RSV are two common pathogens that cause respiratory tract infections(22). Thus, developing new tools for the rapid diagnosis of this type of virus is of extreme importance.

. We analyzed the articles to verify the Xpert Xpress Flu/RSV's accuracy for detecting influenza A, influenza B, and RSV. The +LR of influenza A, influenza B, and RSV were all larger than 10, while -LR were both < 0.1. For influenza A, a pooled +LR of 88.25 and a pooled -LR of 0.02 showed that patients with positive or
negative Xpert were 88.25 times more likely to develop influenza A or 0.02 times less likely to develop influenza A. AUCs (all over 0.9) indicated that Xpert's overall diagnostic accuracy for influenza virus and RSV was relatively high. Also, the DORs of influenza A, influenza B, and RSV were very large, indicating that the correct diagnosis was far greater than the wrong diagnosis. To sum up, Xpert Xpress Flu/RSV is highly accurate for diagnosing influenza A, influenza B, and RSV. Moreover, the biases coefficients of influenza A, influenza B, and RSV were \( P = 0.499, 0.400, 0.506 \), respectively; since there were all greater than 0.05, it is possible to conclude that there is a subtle publishing bias.

The equipment based on nucleic acid amplification has shorter operation time and turnover time, which meets the requirements of speed and ease of use for the application of medical point. The Point-of-Care testing based on nucleic acid amplification test for detection of respiratory virus mainly includes Xpert Xpress Flu/RSV, Filmarray respiratory panel and Cobas® Liat® System etc.. In terms of operational performance, compared with Cobas, there is no invalid result in the analysis of Xpert in the research of Ling et al.. It has relatively short test around time (254.4min vs. 44.2min) and hands on time in random access single sample and batch format, and has more capacity (12 vs.16)(18). Filmarray can be used to detect 15 kinds of respiratory virus preparations. Compared with Xpert, the main disadvantage of Filmarray is single-sample throughput, and it has been pointed out that Filmarray is
less sensitive to RSV (23). In terms of diagnostic sensitivity, Merckx et al. showed that
the pooled sensitivity of Cobas modified RT-PCR was more than 97%. The sensitivity
and specificity of Cobas in detecting influenza A were 0.9683 and 0.9913 respectively,
and the detection rates of influenza B were 0.9878 and 1.00 respectively (24). The
meta-analysis of Huang et al. showed that the pooled sensitivity of FilmArray to
detect influenza A, B and RSV was 0.911, 0.822 and 0.911, respectively (25). In our
study, compared with other common clinical real-time RT-PCR, the sensitivity of
Xpert Xpress Flu/RSV in detecting influenza A, influenza B, and RSV was 0.97, 0.98,
0.96, respectively. Therefore, by comparing several diagnostic systems that have been
used in clinical diagnosis, Xpert Xpress flu / RSV still has advantages in test
turnaround time, sample size and the detection accuracy.

From the results of QUADAS-2 quality evaluation, the quality of the articles
included in the analysis affected the conclusions to a certain extent. Among them, 25%
of the analyzed articles were considered to take a high risk of bias and high
applicability concern in patient selection, mainly because of: 1. One article did not
include consecutive samples (8); 2. Two articles did not avoid inappropriate
exclusions (8, 20); 3. Four articles did not avoid case-control design, that is, in these
four articles, patients with definite diagnosis were included in the experimental group,
and suspected patients or normal people were included in the control group (8, 15, 18,
20). The inclusion of discontinuous samples will lead to selection bias. In the article
of Banerjee et al., an invalid sample was excluded; in the article of Valentin et al., 7
out of 312 samples were excluded from the analysis due to negative cell control.
Improper exclusion will cause selection bias, but due to the small sample size, the impact is small. Too many case-control trials will increase the accuracy of diagnostic methods, which is also the main reason for high bias. Moreover, 50% of the analyzed articles were considered to take a high risk of bias and high applicability concern in the index test, mainly because of: 1. Five articles are to interpret the index test results with knowledge of the results of the reference standard(8, 13, 14, 18, 20); 2. The threshold in nine articles was not clear(8, 10, 12-15, 18, 20, 21). If the results of the test to be evaluated do not follow the blind method, the known reference standard results may affect the interpretation of the index test to be evaluated, resulting in inaccurate results. Selecting the test threshold to optimize sensitivity and specificity may lead to the improvement of diagnostic efficiency, while in independent samples, the diagnostic efficiency of using the same threshold for patients may become worse. However, most of the articles did not mention whether the threshold was used or not, so the impact of threshold on this study could not be evaluated.

This study has several limitations. First, the influenza virus and RSV's sensitivity and specificity were calculated based on all the samples included in the articles. However, when applied in the clinic, they needed to be considered more carefully in combination with the clinical situation. Applications of Xpert for influenza virus and RSV cases have been reported in some studies; however, the data are very limited. More data are needed in the future to supplement the results of the diagnosis of influenza virus and RSV by Xpert Xpress Flu/RSV. Secondly, we did not conduct group evaluation because of the limited literature, small sample size, and
comparability.

Conflict of interest

None to declare.

Reference


molecular tests for seasonal influenza in patients presenting at an emergency unit.


Figure legends
Figure 1. Flow diagram of study identification and inclusion.

Figure 2. Risk of bias and applicability concerns graph: review authors’ judgments about each domain presented as percentages across the ten articles.

Figure 3. Forest plots of (A) combined sensitivity, (B) specificity, (C) positive LR, negative LR, (D) diagnostic OR, (F) summary receiver operating characteristic (SROC) curve, (G) Deeks’ funnel plot asymmetry test of Xpert Xpress Flu/RSV for the diagnosis of Influenza A.

Figure 4. Forest plots of (A) combined sensitivity, (B) specificity, (C) positive LR, negative LR, (D) diagnostic OR, (F) summary receiver operating characteristic (SROC) curve, (G) Deeks’ funnel plot asymmetry test of Xpert Xpress Flu/RSV for the diagnosis of Influenza B.

Figure 5. Forest plots of (A) combined sensitivity, (B) specificity, (C) positive LR, negative LR, (D) diagnostic OR, (F) summary receiver operating characteristic (SROC) curve, (G) Deeks’ funnel plot asymmetry test of Xpert Xpress Flu/RSV for the diagnosis of RSV.
<table>
<thead>
<tr>
<th>Type of specimens</th>
<th>Test used</th>
<th>Influenza A</th>
<th>Influenza B</th>
<th>RSV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TP</td>
<td>FP</td>
<td>TN</td>
</tr>
<tr>
<td>NPA and NPS</td>
<td>Prodesse ProFlu+ real-time RT-PCR assay</td>
<td>250</td>
<td>105</td>
<td>2000</td>
</tr>
<tr>
<td>NPS</td>
<td>FilmArray Respiratory Panel</td>
<td>50</td>
<td>0</td>
<td>144</td>
</tr>
<tr>
<td>NPS</td>
<td>The Centers for Disease Control and Prevention – developed real-time RT-PCR assay</td>
<td>74</td>
<td>1</td>
<td>149</td>
</tr>
<tr>
<td>NPS</td>
<td>Multiplex influenza real-time RT-PCRa</td>
<td>78</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>NPS</td>
<td>Laboratory-developed testsb</td>
<td>56</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>NPS</td>
<td>Cobas® Liat® system</td>
<td>61</td>
<td>2</td>
<td>249</td>
</tr>
<tr>
<td>NPA</td>
<td>Monopex RT-PCR</td>
<td>48</td>
<td>2</td>
<td>161</td>
</tr>
<tr>
<td>NPA and NPS</td>
<td>In-house Flu/RSV triplex real-time RT-PCR</td>
<td>54</td>
<td>0</td>
<td>118</td>
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<tr>
<td>NPS</td>
<td>Real-time RT-PCR</td>
<td>42</td>
<td>1</td>
<td>261</td>
</tr>
<tr>
<td>NPS</td>
<td>Real-time RT-PCR</td>
<td>132</td>
<td>13</td>
<td>491</td>
</tr>
</tbody>
</table>

Test used:
- Prodesse ProFlu+ real-time RT-PCR assay
- FilmArray Respiratory Panel
- The Centers for Disease Control and Prevention – developed real-time RT-PCR assay
- Multiplex influenza real-time RT-PCR
- Laboratory-developed tests
- Cobas® Liat® system
- Monopex RT-PCR
Multiplex RT-PCR was performed using the Path-ID Multiplex One-Step RT-PCR Kit (Thermo Fisher Scientific, Waltham, MA) and the Roche LightCycler96 real-time instrument (Roche Diagnostics, Mannheim, Germany).

200 μl of specimen was extracted using the Total Nucleic Acid Isolation Kit on the MagNAPure (Roche Applied Science, Indianapolis, IN) with amplification and detection performed on the ABI 7500 FAST (Life Technologies, Carlsbad, CA). The influenza A/B and RSV A/B LDTs used primer and probe sequences previously described for influenza A and influenza B viruses (5) and separately for RSV A and RSV B.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Country</th>
<th>Source of strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen (2017)</td>
<td>Retrospective and Prospective</td>
<td>America</td>
<td>2176 fresh clinical specimens and 259 pre-selected frozen specimens</td>
</tr>
<tr>
<td>Ling (2017)</td>
<td>Retrospective</td>
<td>America</td>
<td>194 clinical specimens</td>
</tr>
<tr>
<td>Banerjee (2018)</td>
<td>Retrospective</td>
<td>America</td>
<td>225 clinical specimens</td>
</tr>
<tr>
<td>Chen (2017)</td>
<td>Retrospective</td>
<td>China</td>
<td>134 clinical specimens</td>
</tr>
<tr>
<td>Popowtich (2018)</td>
<td>Retrospective</td>
<td>America</td>
<td>200 clinical specimens</td>
</tr>
<tr>
<td>Schmidt (2018)</td>
<td>Prospective</td>
<td>Vienna</td>
<td>313 clinical samples</td>
</tr>
<tr>
<td>To (2018)</td>
<td>Prospective</td>
<td>China</td>
<td>212 clinical samples</td>
</tr>
<tr>
<td>Ho (2018)</td>
<td>Prospective</td>
<td>China</td>
<td>20 external quality assurance samples and 172 clinical samples</td>
</tr>
<tr>
<td>Valentin (2019)</td>
<td>Prospective</td>
<td>Austria</td>
<td>305 clinical samples</td>
</tr>
<tr>
<td>Zou (2019)</td>
<td>Retrospective</td>
<td>China</td>
<td>658 clinical samples</td>
</tr>
</tbody>
</table>
Abbreviations: TP: true positive; FP: false positive; FN: false negative; TN: true negative; NPA: nasopharyngeal aspirate; NPS: nasopharyngeal flocked swab.
PRISMA 2009 Flow Diagram

Identification

PubMed (14), Embase (17), Cochrane Library (3), Web of Science (11) (n=45)

Records after duplicates removed (n=22)

Records screened (n=19)

Full-text articles assessed for eligibility

Studies included in qualitative synthesis (n=10)

Studies included in quantitative synthesis (meta-analysis) (n=10)

Additional records identified through other sources (n=0)

3 excluded by screening title/abstract

9 articles excluded after reading full text
   Reasons for exclusion:
   Conference abstract (2)
   Insufficient information (6)
   Letter (1)


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Figure 2
Figure 4