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# Comparison of the Cepheid Xpert Xpress Flu/RSV assay and commercial real-time PCR for the detection of influenza A and influenza B in a prospective cohort from China

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ABSTRACT

*Background:* The Xpert Xpress Flu/RSV assay is released by FDA for rapid detection of influenza A (FluA), influenza B (FluB), and respiratory syncytial virus (RSV). This study aimed to evaluate its clinical performance in comparison to that of the RT-PCR assay cleared by China FDA (CFDA-PCR).
*Methods:* Nasopharyngeal specimens were collected from patients and tested by the two assays side by side. Discordant results were tested with a laboratory-developed real-time PCR for resolution. Viral load in the sample was quantified with a droplet digital PCR.
*Results:* A total of 658 specimens were involved and gave 94.7%–99.1% agreement between the two assays. The Xpert assay showed higher sensitivity for FluA (100% vs. 89.8%) and FluB detection (100% vs. 95.3%), and also higher accuracy (98.9% vs. 95.7%) for FluA than the CDFA-PCR. The positive and negative predictive values (NPV) for the three viruses ranged from 90.5% to 100% in the two assays, with higher NPV for FluA and FluB in Xpert assay. Moreover, the Xpert Ct values showed a linear correlation with virus titer in specimens tested.
*Conclusion:* Overall, the Xpert assay is a reliable and sensitive tool for the detection of FluA, FluB and RSV in our clinical settings.


## Introduction

Respiratory infections are a significant cause of morbidity, mortality, hospital admissions, and health care burden worldwide (Rao and Nyquist, 2014). Respiratory viruses such as influenza virus and respiratory syncytial virus (RSV) contributed most of these severe cases, especially in young children, pregnant women, older adults, and patients with comorbidities (Tregoning and Schwarze, 2010). Influenza virus caused 30.9 million infections and was responsible for 600,000 hospitalizations in the United States during the 2016–2017 influenza season (CDC, 2018). RSV also triggered over 2 million outpatient visits and 57,000 hospitalizations for children under the age of 5, and caused 11,000–17,000 adults death each year (Rose et al., 2018). Influenza virus and RSV were also the top frequently detected viruses in community-acquired pneumonia patients in China (Qu et al., 2015). Influenza viruses were the main cause of acute lower respiratory infections in adults and the elderly in China, while RSV was the most common pathogen (17.0%) in young children aged <2 years (Feng et al., 2014).

Rapid and accurate detection of causative viruses in respiratory illness enable timely and targeted antiviral therapy. Currently, PCR-based molecular tests are the most commonly used tools for virus infection diagnosis in clinical laboratories. A traditional PCR diagnosis assay usually involves nucleic acid purification, PCR reaction mixture preparation, real-time PCR signal acquisition, and results determination. All these steps require multiple manual operations and thus are prone to introduce artificial errors. The Xpert Flu/RSV Xpress assay (Cepheid, Sunnyvale, CA) is a rapid, random-access molecular test capable of detecting and

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differentiating influenza A (FluA), influenza B (FluB) and RSV virus from nasopharyngeal swabs. This real-time PCR assay uses a single disposable cartridge containing all required reagents, which automates nucleic acid preparation from a clinical sample, performs real-time PCR detection, and reports multiple test results in about 32 min.

The Xpert Flu/RSV assay demonstrated high sensitivity and specificity compared with other molecular methods or traditional diagnosis tests (Chen et al., 2018; Cohen et al., 2018; Ling et al., 2018). Therefore, this assay has been approved for *in vitro* diagnosis of FluA, FluB and RSV infection in the USA and Europe, but not in China currently. The objective of this prospective study was to establish performance characteristics of the Xpert Xpress Flu/RSV Assay compared to those of the commercially available real-time RT-PCR assay approved by China Food and Drug Administration (CFDA) for the detection of FluA, FluB, and RSV in Chinese patients.

## Methods

### *Specimen collection and testing*

This study involved both pediatric and adult patients suspected of having respiratory tract infection who presented to the China-Japan Friendship Hospital. Nasopharyngeal swab (NP) specimens in universal transport medium (UTM, Copan diagnostics) were collected from involved patients during the 2017–2018 respiratory virus season (November 13, 2017 to April 20, 2018). Patients of all ages were eligible to participate in the study. Fresh NP swabs in UTM were stored at 2 to 6 °C and sent to the clinical microbiology laboratory in 4 h for testing with the Xpert assay and CFDA-cleared RT-PCR test (CFDA-PCR). For the Xpert assay, 300 μl of UTM were transferred into the cartridge and the cartridge was inserted to the GeneXpert Dx instrument to start the run. For the CFDA-PCR assay, 200 μl of UTM were subjected to total nucleic acid extraction using the Viral Total Nucleic Acid Extraction kit (HEAS BioTech, Guangzhou, China) in the SMART32 system (Liferiver, Shanghai, China). The reaction solution was prepared by mixing 19 μl of buffer A (contain reaction buffer, primers, and probe) and 1 μl of enzyme mix in the Influenza Virus A Nucleic Acid Detection Kit (Liferiver, Shanghai, China). After 5 μl of extracted nucleic acid was added as template, the assay was run on a LightCycler 480 II real-time PCR system (Roche, Basel, Switzerland) and the result was reported by qualified faculty in the clinical laboratory. Influenza virus B and RSV were detected with the same method but using Influenza Virus B and Respiratory Syncytial Virus Nucleic Acid Detection kit (Liferiver, Shanghai, China), respectively. The remaining UTM was divided into two aliquots and stored in −80 °C for future validation testing. The study protocol was approved by the Medical Ethical Committee of China-Japan Friendship Hospital, and written informed consents were obtained from all subjects who participated in the study and/or their families.

### *Laboratory-developed real-time PCR validation and viral load quantification*

Specimens with discordant results between Xpert and CFDA-PCR were further evaluated with a laboratory-developed real-time PCR (LD-PCR) test. Viral RNA was extracted from 140 μl sample using the QIAamp Viral RNA Mini Kit (Qiagen, Hiden, Germany) and from which 5 μl was used as template for real-time amplification and detection using the SensiFAST™ Probe One-Step Kits (Bioline, London, UK) on the LightCycler 480 II system (Roche, Basel, Switzerland). The primers and probes targeting FluA and FluB were provided by Chinese National Influenza Center (WHO, 2018), also the WHO Collaborating Centre for Reference and Research on Influenza. The RSV primers and probe were synthesized by the Takara company (Takara, Dalian, China) according to the sequences described previously (Kamau et al., 2017). Viral loads in the selected samples were directly quantified using the QX200 Droplet Digital PCR system (BIO-RAD, Hercules, USA) with the primers and probes used in the LD-PCR (Yan et al., 2016). Briefly, 20 μl of reaction mixtures was prepared using Bio-Rad One-Step RT-ddPCR Kit for Probes containing 0.5 μM of primers, 0.25 μM of probes and 5 μl of viral RNA. The reaction solutions were then loaded into the Bio-Rad DG8 cartridge and covered with 70 μl Bio-Rad DG Oil for Probes in each well. Droplets were generated using the Bio-Rad QX200 Droplet Generator and transferred to a 96-well PCR plate for RT-PCR amplification using Bio-Rad C1000 Touch Thermal Cycler according to the following reaction conditions: 45 °C for 60 min, 95 °C for 10 min, 45 cycles of 95 °C for 30 s and 58 °C for 1 min, followed by 98 °C for 10 min for enzyme deactivation. Data were subsequently read and analyzed on Bio-Rad OX200 Droplet Reader with QuantaSoft version 1.7.4. The absolute quantification was determined for each sample in three replicates.

### *Data collection and analysis*

The performance of the Xpert assay and CFDA-PCR for detecting FluA, FluB, and RSV were evaluated based on the results from LD-PCR of the same sample. Accuracy for detection of each virus was determined on the fraction of positive (or negative) results consistent with the reference method among the total samples. The Xpert assay result or CFDA-PCR result was considered to be a true positive (TP) or a true-negative (TN) if it agreed with the LD-PCR. The exact (Clopper-person) method was used to calculate 95% confidence intervals. Test characteristics of sensitivity (or positive percent agreement [PPA]), specificity (or negative percent agreement [NPA]), accuracy, positive predictive value (PPV), and negative predictive value (NPV) for each pathogen were calculated based on two-by-two tables for the entire prospective specimens, and their differences between the two assays were compared using Chi squared analysis. Statistical analyses were performed using GraphPad 7 (La Jolla, CA), with which the Mann-Whitney test for non-parametric nonpaired data was performed to compare the Xpert cycle threshold (Ct) value between TP and false positive (FP) samples for each targeted virus, and linear regression analysis was used to explore the relationship between Xpert Ct values and viral loads. In samples with two Ct values reported for FluA in Xpert assay, the Ct value A1 was selected for statistical analysis.

## Results

### *Agreement between Xpert Xpress Flu/RSA assay and CFDA-PCR*

A total of 658 NP specimens from 621 patients were collected in our study, including 384 males and 274 females. Among them, 0.3% patients were ≤ 5 years old, 1.8% were 6–12 years old, 36.3% were 22–59 years old, 38.8% were 60–79 years old, and 22.8% were ≥ 80 years old (Table 1). Most samples were from inpatients (77.8%), followed by emergency departments (9.7%) and intensive care unit (ICU) (9.3%). Outpatients contributed the remaining 3.2% of samples.

All the specimens were tested by both Xpert assay and CFDA-approved monoplex RT-PCR (CFDA-PCR) side by side. Of the 658 samples tested, 132, 124, and 17 were concordantly positive by the two methods for the detection of FluA, FluB, and RSV, respectively (Table 2); meanwhile, 491, 522, and 635 were concordantly negative for the three viruses, respectively. Only 35, 12, and 6 samples yielded discordant results in the two methods for the detection of the three viruses, respectively. In aggregate, the Xpert

**Table 1**
General demographic details of the study population.

| Patient and sample characteristics | |
|---|---|
| Characteristic | Number (percentage) |
| Gender | |
| Male | 384 (58.4%) |
| Female | 274 (41.6%) |
| Age group (year) | |
| ≤5 | 2 (0.3%) |
| 6–21 | 12 (1.8%) |
| 22–59 | 239 (36.3%) |
| 60–79 | 255 (38.8%) |
| ≥80 | 150 (22.8%) |
| Subject status or placement | |
| Outpatient | 21 (3.2%) |
| Inpatient | 512 (77.8%) |
| Emergency department | 64 (9.7%) |
| Intensive Care unit (ICU) | 61 (9.3%) |
| Total | 658 |

**Table 2**
Concordance of the Xpert Xpress Flu/RSV with the CFDA -PCR.

| Xpert Xpress Flu/RSV | CFDA RT-PR | | | | | |
|---|---|---|---|---|---|---|
| | FluA | | FluB | | RSV | |
| | Positive | Negative | Positive | Negative | Positive | Negative |
| Positive | 132 | 22 | 124 | 10 | 17 | 4 |
| Negative | 13 | 491 | 2 | 522 | 2 | 635 |

assay demonstrated high concordance with the CFDA-PCR method for the detection of FluA (94.7%), FluB (98.2%), and RSV (99.1%).

*Clinical performance evaluation using reference method*

For the total group, there were 53 samples with discordant results between Xpert and CFDA-PCR. These samples were resolved with monoplex LD-PCR targeting at FluA, FluB, and RSV individually. The clinical sensitivity of the Xpert assay (or positive percent agreement [PPA]) was 100%, 100%, and 90.5% for FluA, FluB, and RSV, respectively; while for CFDA-PCR, the sensitivity was 89.8%, 95.3%, and 85.7% for the three targets, respectively (Table 3). Clinical specificity (negative percent agreement [NPA]) ranged from 98.6% to 99.7% and 97.5% to 99.8% for Xpert assay and CDFA-PCR, respectively. Chi squared analysis showed a significant difference in sensitivity ($P < 0.05$) between the Xpert and CFDA-PCR for the detection of FluA and FluB, but no significant differences in specificity between the two assays for all the three viruses. Total accuracy for detection of the three viruses ranged from 98.9% to 99.4% in Xpert assay, and 95.7% to 99.4% in CFDA-PCR (Table 3), with significant difference ($P < 0.05$) found in FluA detection between the two assays. The PPVs of the Xpert assay was 95.5% for FluA, 97.0% for FluB, and 90.5% for RSV, corresponding to 91.0%, 96.8%, and 94.7 in the CFDA-PCR, respectively. The NPVs of the Xpert assay and CFDA-PCR for all three respiratory pathogens ranged from 99.7% to 100% and 97.1% to 99.5, respectively. No significant differences were observed in PPV for all the three targets between the two assays but Xpert demonstrated higher ($P < 0.05$) NPV for FluA and FluB detection (Table 4).

*Association between Xpert Ct values and virus loads*

The Xpert assay also reported Ct values for each sample with a positive result, which could be used for semi-quantitative analysis of the viral load in the sample. The Ct value for true positive samples was $26.91 \pm 0.5681$ (n = 147), $27.21 \pm 0.5454$ (n = 130), and $28.57 \pm 1.23$ (n = 20) for detection of FluA, FluB, and RSV, respectively. The Ct values in samples with false positive results were significantly higher than those with true positive results ($P < 0.01$), which was $37.84 \pm 0.4017$ (n = 7), $37.88 \pm 1.096$ (n = 4), and $38.85 \pm 0.15$ (n = 2) for the three tested viruses, respectively (Figure 1A). However, the Xpert Ct values (FluA and FluB) showed no difference between ICU patients and general ward patients, outpatients and inpatients, and among patients in different age intervals (Figure 1B, S1).

Several Xpert-positive samples covering a wide range of Ct values were randomly selected for viral load quantitation using the droplet digital PCR (ddPCR). Finally, 19, 10, and 6 samples were used for linear regression analysis between the Xpert Ct value and viral load for FluA, FluB, and RSV, respectively. For all the three viruses, the Xpert Ct values showed good correlation with viral loads in the samples (Figure 2). The linear regression analysis generated equations between Ct value and the logarithm of viral load, with high R squared value of 0.8894, 0.9076, and 0.9931 for FluA, FluB, and RSV, respectively. In samples with quantitative results, the Xpert could detect virus with loads as low as 130, 290, and 1800 copies/ml for FluA, FluB, and RSV, respectively.

## Discussion

Early detection of respiratory virus infection provides clinicians a number of advantages in treatment and outbreaks management. In addition to reduction of unnecessary antibiotic prescription, accurate virus identification enables targeted antiviral treatment at the early stage of infection, which can significantly improve

**Table 3**
Xpert Xpress Flu/RSV performance versus CFDA-approved RT-PCR method.

| | | No. of results by type[a] | | | | Sensitivity | Specificity | Accuracy (% [95% CI]) |
|---|---|---|---|---|---|---|---|---|
| Assay | Target | TP | FP | TN | FN | PPA[b] (% [95% CI]) | NPA[c] (% [95% CI]) | |
| Xpert | Influenza A | 147 | 7 | 504 | 0 | 100.0 (97.5–100)* | 98.6 (97.2–99.4) | 98.9 (97.8–99.6)* |
| | Influenza B | 130 | 4 | 524 | 0 | 100.0 (97.2–100)* | 99.2 (98.1–99.8) | 99.4 (98.5–99.8) |
| | RSV | 19 | 2 | 635 | 2 | 90.5 (69.6–98.8) | 99.7 (98.9–100) | 99.4 (98.5–99.8) |
| CFDA-PCR | Influenza A | 132 | 13 | 498 | 15 | 89.8 (83.7–94.2)* | 97.5 (95.7–98.6) | 95.7 (93.9–97.2)* |
| | Influenza B | 124 | 2 | 526 | 6 | 95.3 (90.1–98.3)* | 99.3 (98.1–99.8) | 98.5 (97.2–99.3) |
| | RSV | 18 | 1 | 636 | 3 | 85.7 (63.7–97.0) | 99.8 (99.1–100) | 99.4 (98.5–99.8) |

[a] TP, true positive; FP, false positive; TN, true negative; FN, false negative.
[b] PPA, positive percent agreement; PPA = TP/(TP + FN).
[c] NPA, negative percent agreement; NPA = TN/(TN + FP).
* Significant difference was observed in this virus detection between the two assays by Chi squared analysis. $P \leq 0.05$ was accepted as significant.

**Table 4**
Positive and negative predictive values of Xpert and CDFA-PCR.[a]

| Assay | Target | Positive predictive value (PPV) (%) | | Negative predictive value (NPV)(%) | |
|---|---|---|---|---|---|
| | | TP/(TP + FP) | 95% CI | TN/(TN + FN) | 95% CI |
| Xpert | Influenza A | 95.5 (147/154) | 90.9–97.8 | 100.0 (504/504)* | 99.2–100 |
| | Influenza B | 97.0 (130/134) | 92.6–98.8 | 100.0 (524/524)* | 99.3–100 |
| | RSV | 90.5 (19/21) | 71.1–97.3 | 99.7 (635/637) | 98.9–99.9 |
| CFDA-PCR | Influenza A | 91.0 (132/145) | 85.3–94.7 | 97.1 (498/513)* | 95.2–98.2 |
| | Influenza B | 96.8 (122/126) | 91.1–98.8 | 98.9 (526/532)* | 97.6–99.5 |
| | RSV | 94.7 (18/19) | 75.4–99.1 | 99.5 (636/639) | 98.6–99.8 |

[a] TP, true positive; FP, false positive; TN, true negative; FN, false negative; with the the same value in Table 3.
* Significant difference was observed in this virus detection between the two assays by Chi squared analysis. $P \leq 0.05$ was accepted as significant.

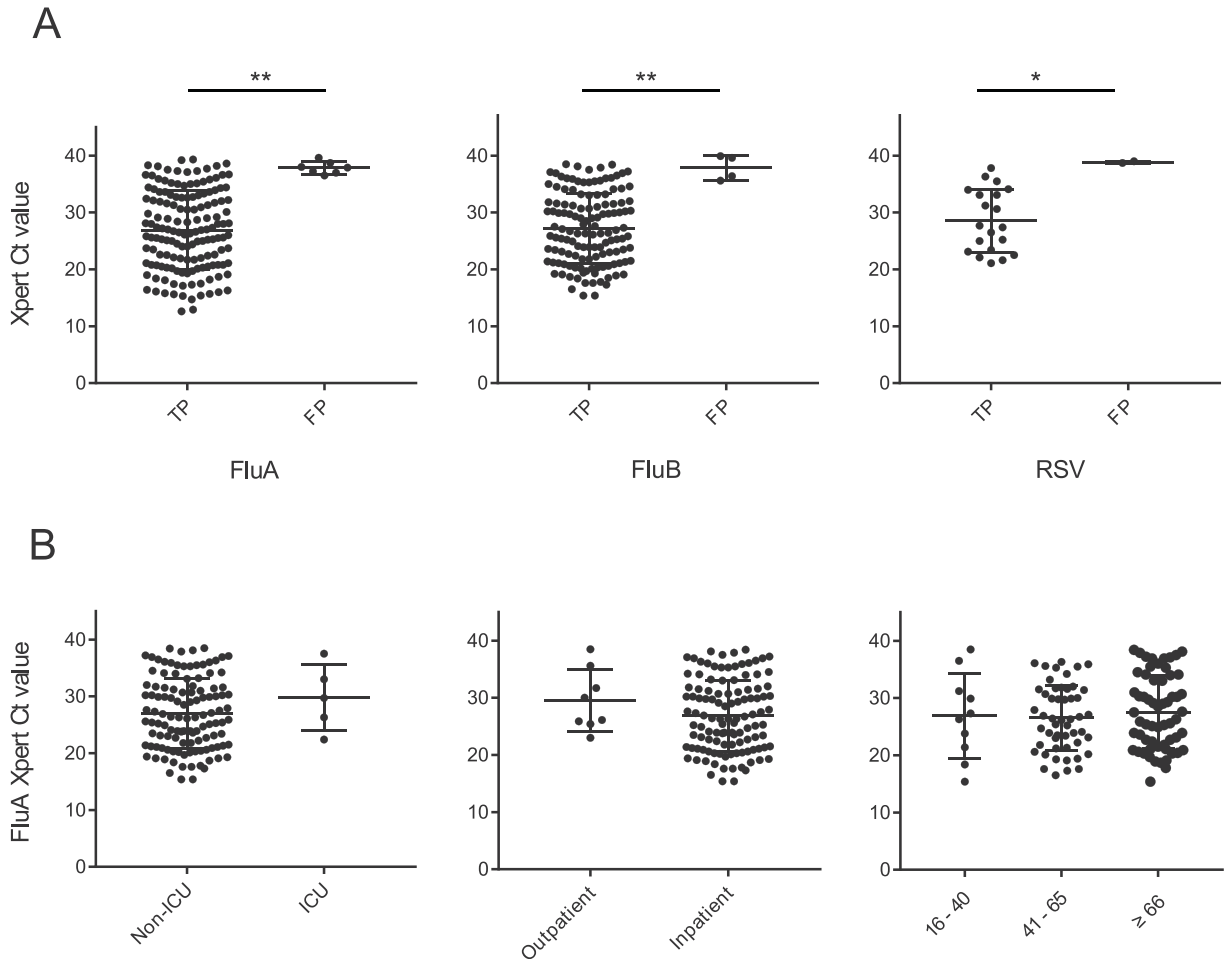


**Figure 1.** (A) Comparison of the Ct values between true positive and false positive samples in Xpert Xpress Flu/RSV assay for the detection of FluA, FluB, and RSV. (B) Comparison of the Ct values between FluA-positive patients in different clinical situations and ages (Years). Ages started with the youngest patients with positive FluA result reported by Xpert assay. The Mann-Whitney test for non-parametric non-paired data was applied to compare the difference of Ct values between different groups. $P < 0.05$ was accepted as significant difference ($^{**}P < 0.01$, $^{*}P < 0.05$).

clinical outcomes (Vallieres and Renaud, 2013; Xu et al., 2013). The Xpert Xpress Flu/RSV Assay is a fast, automated in vitro diagnostic test for detection and differentiation of FluA, FluB and RSV. This assay was cleared for in-vitro diagnosis in USA and Europe in 2016 but has not yet been cleared in China. The assay demonstrated high sensitivity and specificity in performance evaluation studies in the USA (Cohen et al., 2018; Ling et al., 2018), UK (Bennett et al., 2018), and Hong Kong of China (Chen et al., 2018). The data presented here also demonstrate that the Xpert assay is a suitable method for rapid and accurate identification of these causative pathogens in respiratory infections in mainland China.

Our study prospectively involved 658 samples for performance comparison of the Xpert assay and a CDFA-approved real-time PCR method. High concordance rate was observed between the Xpert assay and the CFDA-PCR method. Samples with discordant results were resolved with LD-PCR and we observed higher sensitivity of Xpert in the detection of FluA and FluB, compared with the in-use PCR method in Chinese hospital (Table 3). Both methods expressed high specificity (>97%) and accuracy (>95%), but Xpert demonstrated significantly higher accuracy in the detection of FluA virus (Table 3). The Xpress assays target multiple segments of the FluA genome and may contribute its better performance in FluA detection. The Xpert

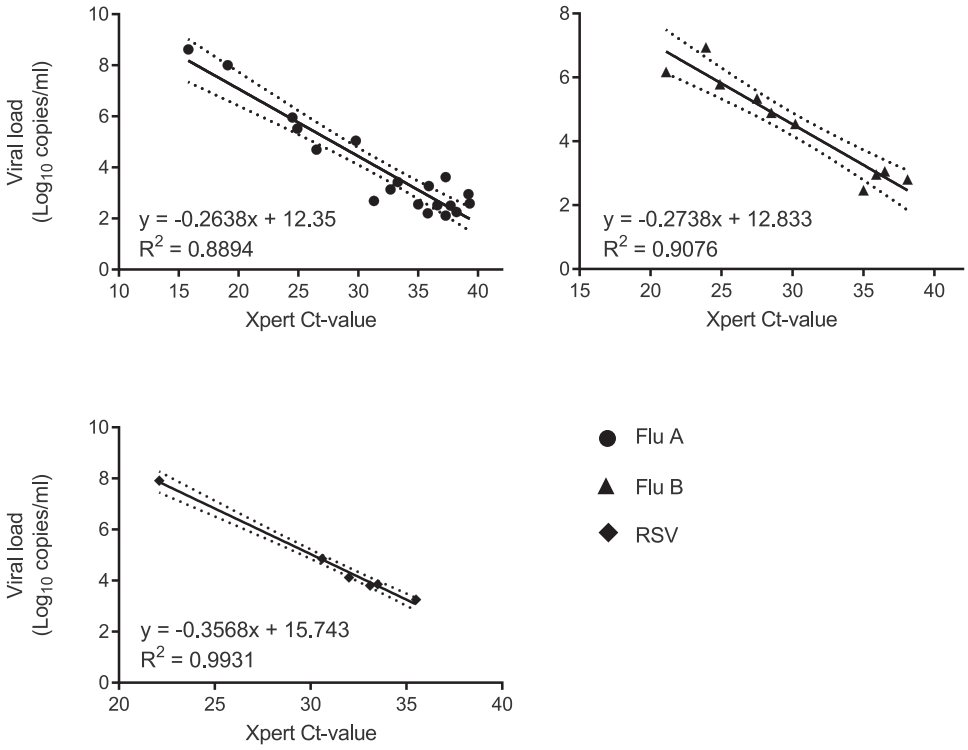


**Figure 2.** Relationship between Xpert Ct value and viral load in the samples. Linear regression showed a good correlation between the Ct value and the logarithm of viral load for the three viruses. $R^2$ values and equation were indicated in the figure. Dotted lines showed 95% confidence band.

showed 100% sensitivity for both FluA and FluB in our patients, which was close to the 100% sensitivity for FluA and 96.3% for FluB in the Hong Kong study (Chen et al., 2018). The specificity of Xpert for FluA and FluB in the two studies was also very similar.

The Xpert Xpress Flu/RSV is an updated version of previous Xpert Flu/RSV XC, which reduced the time to results (32 min vs. 63 min) and increased the number of RNA targets for both influenza viruses to increase test sensitivity and specificity (Popowitch and Miller, 2018). Moreover, the Xpert Xpress assay has only one manual pipetting step involved in adding samples into the cartridge, which requires <1 min. However, the current CFDA-PCR requires approximately 240 min of hands on time, which is about 6 times the time required by the Xpert Xpress assay. The rapidity and simple manual processing steps enable the Xpert Xpress to be used in point-of-care settings by non-laboratory staff (Cohen et al., 2018). On the other hand, the CFDA-PCR required substantial manual steps including sample lysis, PCR reaction solution preparation, running the test in the real-time PCR instrument, and results determination based on amplification curves. These manual steps increase the possibility of contamination and manual errors.

Among the 154, 134, and 21 samples with positive results reported by Xpert assay, 7, 4, and 2 were negative compared to the reference method (false positive, FP), for the detection of FluA, FluB, and RSV, respectively. These FP samples in Xpert typically showed significantly higher Ct values than the ones from true positive samples (Figure 1A). However, no significant difference was observed between patients in different clinical situations or ages (Figure 1B). The Xpert Ct values also correlated well with viral loads in the samples (Figure 2). We also used linear regression modelling to correlate the Xpert Ct values and the logarithm of viral loads determined by digital PCR. The equation provided in this study also could be used to infer the viral loads in other samples tested in the same platform.

Our study had several limitations. This study mainly involved patients coming from the north of China in the 2017–2018 influenza season. Thus, data from patients in other regions and other seasons is necessary to determine the overall performance of Xpert assay in Chinese clinical settings. Secondly, for the low frequency of RSV infection in adults, the number of RSV positive samples in our study was relatively small, which hindered an extensive performance evaluation of the detection of this virus. Future studies should include more RSV positive samples from children and adults to comprehensively assess the performance of the Xpert. Last, both the LD-PCR and ddPCR used the frozen samples stored at −80 °C and might impact their sensitivity.

This is, to our knowledge, the first prospective study assessing the Cepheid Xpert Xpress Flu/RSV assay in mainland China. Compared with the CFDA approved PCR method, the Xpert assay demonstrated high sensitivity, specificity and accuracy for detection of FluA, FluB and RSV. The Xpert reported Ct values correlated well with viral loads in the samples, which could be used for semi-quantitation of viral amounts in samples tested. The assay is easy to use and provide fast results to clinicians, which enables confident clinical decision-making and improve clinical outcomes.

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The authors declare that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.12.014.

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