Evaluation of the Xpert Xpress SARS-CoV-2/Flu/RSV Assay for Simultaneous Detection of SARS-CoV-2, Influenza A and B Viruses, and Respiratory Syncytial Virus in Nasopharyngeal Specimens

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ABSTRACT Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A (flu A), influenza B (flu B), and respiratory syncytial virus (RSV) have overlapping clinical presentations, but the approaches to treatment and management of infections caused by these viruses are different. Therefore, rapid diagnosis in conjunction with infection prevention measures is important to prevent transmission of the diseases. Recently, a new Xpert Xpress SARS-CoV-2/Flu/RSV (Xpert 4-in-1) assay enables the detection and differentiation of SARS-CoV-2, flu A, flu B, and RSV in upper respiratory tract specimens. In this study, we evaluated the performance of the Xpert 4-in-1 assay by comparing it with that of the Xpert Xpress SARS-CoV-2 and Xpert Xpress Flu/RSV assays for the detection of the four viruses in nasopharyngeal (NP) specimens. A total of 279 NP specimens, including 66, 56, 64, and 53 specimens positive for SARS-CoV-2, flu A, flu B, and RSV, respectively, were included. The Xpert 4-in-1 assay demonstrated high concordance with the comparator assays, with overall agreement for SARS-CoV-2, flu A, flu B, and RSV at 99.64%, 100%, 99.64%, and 100%, respectively, and a high Cohen’s kappa (κ) value ranging from 0.99 to 1.00, indicating an almost perfect correlation between assays. The cycle threshold value association between positive samples also showed a good correlation between assays. In conclusion, the overall performance of the Xpert 4-in-1 assay was highly comparable to that of the Xpert SARS-CoV-2 and Xpert Flu/RSV assays for the detection and differentiation of SARS CoV-2, flu A, flu B, and RSV in NP specimens.

KEYWORDS Xpert 4-in-1

Coronavirus disease (COVID-19) refers to viral pneumonia cases occurring in Wuhan, Hubei Province, China, since December 2019 (1). A novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was found to be the causative agent. Subsequently, the COVID-19 pandemic has caused over 37 million COVID-19 cases of pneumonia and upper respiratory illness and 1 million deaths worldwide (2). The pandemic is rapidly evolving and has become a major public health concern worldwide. With the ongoing COVID-19 pandemic, many countries face a threat of influenza virus-associated infection in the coming influenza season (3). Influenza viruses and respiratory syncytial virus (RSV) have contributed to serious respiratory infections, which are a significant cause of morbidity, mortality, hospital admissions, and burden of health care during the global epidemics each year (4). Influenza viruses are a major cause of lower respiratory tract infections in adults and the elderly (5, 6), while RSV is a common pathogen in young children (7). However, the situation is expected to be worse in this COVID-19 pandemic era; coinfection of influenza and COVID-19 epidemics is now a major concern for public health authorities. Patients
infected with SARS-CoV-2, influenza A (flu A), influenza B (flu B), and RSV have overlapping clinical presentations, but the approaches to treatment and management of these viruses are different. Unlike common cold viruses, infection with these four viruses is often associated with fever and other systemic manifestations that may be coupled with severe outcomes, especially in the elderly. Therefore, rapid diagnosis in conjunction with infection prevention measures is important to prevent the transmission of SARS-CoV-2, influenza, and RSV.

To assist global efforts in the fight against the spread of COVID-19 and influenza during the upcoming influenza season, a number of manufacturers are modifying existing assays to allow simultaneous multiplex testing for SARS-CoV-2 and flu A, flu B, and RSV. Recently, a new Xpert Xpress SARS-CoV-2/Flu/RSV (Xpert 4-in-1) assay (Cepheid, Sunnyvale, CA) for the qualitative detection and differentiation of SARS-CoV-2, flu A, flu B, and RSV in upper respiratory tract specimens in one cartridge for a single patient sample with results available in 36 min has been released with in vitro diagnostic emergency use authorization (EUA) by the U.S. Food and Drug Administration (FDA) in September 2020. The Xpert 4-in-1 assay aids in the combination of two individual rapid and random-access molecular assays, the Xpert Xpress SARS-CoV-2 (Xpert SARS-CoV-2) assay (Cepheid, Sunnyvale, CA) and the Xpert Xpress Flu/RSV (Xpert Flu/RSV) assay (Cepheid, Sunnyvale, CA). The Xpert Flu/RSV assay has been widely used for the detection and differentiation of flu A, flu B, and RSV from upper respiratory tract specimens worldwide, especially during the influenza seasons (8, 9). To effectively manage the spread of COVID-19, the Xpert SARS-CoV-2 assay received FDA EUA in March 2020 for the rapid detection of SARS-CoV-2. Currently, we are using these two Xpert assays in our laboratory for the rapid diagnosis of SARS-CoV-2, flu A, flu B, and RSV. We have previously reported the high sensitivity and specificity of the Xpert SARS-CoV-2 assay for the detection of SARS-CoV-2 and those of the Xpert Flu/RSV assays for the detection of flu A, flu B, and RSV (8, 10). In this study, we evaluated the performance of the Xpert 4-in-1 assay by comparing it with those of the Xpert SARS-CoV-2 and Xpert Flu/RSV assays for the detection of SARS-CoV-2, flu A, flu B, and RSV in nasopharyngeal (NP) specimens.

MATERIALS AND METHODS

Specimen collection. NP specimens, including nasopharyngeal aspirates and nasopharyngeal swabs, were collected from patients with suspected influenza during the 2017 to 2019 influenza seasons and from suspected COVID-19 patients in 2020. Specimens were collected in viral transport medium (VTM) and sent to a regional hospital in Hong Kong for routine respiratory virus detection. After routine testing, aliquots of samples were collected and stored at −80°C. In this study, the archived sample aliquots were retrieved and thawed for testing immediately on the Xpert 4-in-1, Xpert SARS-CoV-2, and Xpert Flu/RSV assays. In total, 279 retrospective NP specimens, including 66 positive for SARS-CoV-2, 56 positive for flu A, 64 positive for flu B, 53 positive for RSV, and 40 negative for all four viruses, were included in this study.

Xpert 4-in-1 assay. The Xpert 4-in-1 assay is a multiplex real-time PCR assay for the simultaneous detection and differentiation of SARS-CoV-2, flu A, flu B, and RSV. The assay targets (i) two unique regions of the nucleocapsid gene (N2 gene) and the envelope protein gene (E gene) of SARS-CoV-2, (ii) genes encoding matrix protein, PB2, and PA of influenza A, (iii) genes encoding the matrix protein and nonstructural protein of influenza B, and (iv) genes encoding the nucleocapsids of RSV A and RSV B. This assay was performed on the GeneXpert instrument systems according to the manufacturer’s instructions. Briefly, after opening the cartridge lid, 300 µl of the sample in the VTM was transferred with a disposable pipette supplied to the sample chamber. The cartridge lid was closed, and the cartridge was loaded into the instrument following the instructions displayed in the GeneXpert system window.

Comparison studies. The Xpert SARS-CoV-2 and Xpert Flu/RSV assays were used as comparator assays (11, 12). The two assays were performed following the instructions by the manufacturer. Specimens with discordant results between the Xpert 4-in-1 and comparator assays were further resolved with two individual in-house laboratory-developed real-time PCR (LD-PCR) assays for SARS-CoV-2 and flu A, flu B, and RSV. The protocols of the two LD-PCR assays have been described previously (8, 13).

Data analysis. Contingency tables were constructed to assess the agreement between the Xpert 4-in-1, Xpert SARS-CoV-2, and Xpert Flu/RSV assays. The level of agreement between the assays was determined by Cohen’s kappa (κ), the overall percent agreement, positive percent agreement, and negative percent agreement with two-sided 95% confidence interval (CI). In addition, the cycle threshold (Ct) values of positive samples between assays by simple linear regression were assessed using the Pearson correlation coefficient for comparative analysis. Correlation analyses were performed using MedCalc
RESULTS

Agreement between the Xpert 4-in-1 and comparator assays. A total of 239 positive NP specimens were included in this study. The general demographic details of the study population are listed in Table 1. All of the NP specimens were tested using the Xpert 4-in-1 and comparator assays side by side. Of the 279 samples tested, 65, 56, 63, and 53 samples were concordantly positive by the Xpert 4-in-1 and comparator assays for the detection of SARS-CoV-2, flu A, flu B, and RSV, respectively (Table 2), while 213, 223, 215, and 226 results, respectively, were concordantly negative for the four viruses. Only two samples yielded discordant results between the Xpert 4-in-1 and comparator assays for SARS-CoV-2 and flu B. One sample was SARS-CoV-2 negative by the Xpert 4-in-1 assay but positive by the Xpert SARS-CoV-2 assay, for which the positive result was based on the detection of the N2 gene with CT values of >40 only, without detection of the E gene target. The sample was further tested using an in-house LD-PCR, and the result was negative. Another discordant sample tested positive for flu B by the Xpert 4-

### TABLE 1 General demographic details of the study population

| Patient characteristic | No. (%) positive results for: |
|------------------------|--------------------------------|
|                        | SARS-CoV-2 (n = 66) | Flu A (n = 56) | Flu B (n = 64) | RSV (n = 53) |
| Gender                 |                          |                |                |              |
| Male                   | 28 (42.4)               | 30 (53.6)      | 36 (56.3)      | 20 (37.7)    |
| Female                 | 38 (57.6)               | 26 (46.4)      | 28 (43.8)      | 33 (62.3)    |
| Age group (yrs)        |                          |                |                |              |
| ≥10                    | 10 (15.2)               | 29 (51.8)      | 17 (26.6)      | 51 (96.2)    |
| 11–30                  | 9 (13.6)                | 9 (16.1)       | 8 (12.5)       | 0 (0)        |
| 31–50                  | 16 (24.2)               | 3 (5.4)        | 6 (9.4)        | 0 (0)        |
| 51–70                  | 22 (33.3)               | 10 (17.9)      | 14 (21.9)      | 0 (0)        |
| 71–90                  | 6 (9.1)                 | 5 (8.9)        | 13 (20.3)      | 2 (3.8)      |
| >90                    | 3 (4.5)                 | 0 (0)          | 6 (9.4)        | 0 (0)        |
| Placement              |                          |                |                |              |
| Inpatient              | 63 (95.5)               | 50 (89.3)      | 54 (84.4)      | 50 (94.3)    |
| Outpatient             | 1 (1.5)                 | 0 (0)          | 0 (0)          | 0 (0)        |
| Emergency department   | 2 (3.0)                 | 6 (10.7)       | 10 (15.6)      | 3 (5.7)      |

### TABLE 2 Comparison of the clinical performance of the Xpert 4-in-1 assay to comparator assays

| Xpert 4-in-1 result | Xpert SARS-CoV-2 or Xpert Flu/RSV assay result | χ² (95% CI)* | Overall percent agreement (95% CI) | Positive percent agreement (95% CI) | Negative percent agreement (95% CI) |
|---------------------|-----------------------------------------------|--------------|-----------------------------------|------------------------------------|-----------------------------------|
| SARS-CoV-2          |                                               |              |                                   |                                    |                                   |
| Positive            | 65                                             | 0            | 65                                | 0.99 (0.97–1)                      | 98.71% (95% CI)                    |
| Negative            | 1                                              | 213          | 214                               |                                    |                                   |
| Flu A               |                                               |              |                                   |                                    |                                   |
| Positive            | 56                                             | 0            | 56                                | 0.99 (0.97–1)                      | 98.31% (95% CI)                    |
| Negative            | 0                                              | 223          | 223                               |                                    | 98.36% (95% CI)                    |
| Flu B               |                                               |              |                                   |                                    |                                   |
| Positive            | 63                                             | 1            | 64                                | 0.99 (0.97–1)                      | 97.71% (95% CI)                    |
| Negative            | 0                                              | 215          | 215                               |                                    | 97.45% (95% CI)                    |
| RSV                 |                                               |              |                                   |                                    |                                   |
| Positive            | 53                                             | 0            | 53                                | 1 (98.31–100)                      | 98.38% (95% CI)                    |
| Negative            | 0                                              | 226          | 226                               |                                    |                                   |

*95% CI, two-sided 95% confidence interval.
TABLE 3 Details of two discordant samples

| Sample no. | Individual test result | Comparator assay (CT value) | LD-PCR (CT value) |
|------------|------------------------|-----------------------------|------------------|
| 7406       | SARS-CoV-2 negative (0) | Xpert SARS-CoV-2 positive (E gene, 0; N2 gene, 41.6) | SARS-CoV-2 negative (0) |
| 5733       | Flu B positive (35.5)  | Xpert Flu/RSV Flu B negative (0) | Flu B positive (34.19) |

In summary, the Xpert 4-in-1 assay demonstrated high concordance with the currently used Xpert SARS-CoV-2 and Flu/RSV assays, with overall agreements for SARS-CoV-2, flu A, flu B, and RSV at 99.64%, 100%, 99.64%, and 100%, respectively, and high kappa values ranging from 0.94 to 1.00, indicating an almost perfect correlation between assays.

Association of CT values between the Xpert 4-in-1, Xpert SARS-CoV-2, and Xpert Flu/RSV assays. The Xpert 4-in-1 assay reported positive results with CT values for SARS-CoV-2 (E or N2 gene targets), flu A, flu B, and RSV. The correlation between CT values of samples positive for the four viruses obtained by both the Xpert 4-in-1 and the comparator assays is shown in Fig. 1 to 4. There was remarkably good correlation between CT values of positive samples by the two assays for

![Graph showing correlation between cycle threshold (CT) values of SARS-CoV-2 samples by the Xpert 4-in-1 and Xpert SARS-CoV-2 assays (n=65).](jcm.asm.org)
SARS-CoV-2 \((R^2 = 0.956)\), flu A \((R^2 = 0.949)\), while flu B and RSV showed moderate correlation with \(R^2\) values of 0.8074 and 0.8736, respectively.

**DISCUSSION**

We are witnessing the unprecedented health and economic impact of the COVID-19 pandemic. With the ongoing COVID-19 pandemic, caution should be exercised in the upcoming influenza seasons because the rates of testing for non-SARS-CoV-2 respiratory viruses are greatly curtailed during the COVID-19 pandemic. Patients infected by SARS-CoV-2, flu A, flu B, and RSV have overlapping clinical presentation but fundamentally different treatment and management approaches. Diagnostic testing providing rapid results to identify patients infected with these viruses can be an important factor for effective control, proper choice of treatment, and prevention of widespread outbreaks (14).

Currently, multiple reverse transcription-PCR (RT-PCR) assays for SARS-CoV-2 detection assays from rapid turnaround time to fully automated testing have been developed (15, 16), but further improvement of diagnostic testing can be accomplished by simultaneous detecting SARS-CoV-2, flu A, flu B, and RSV in one tube, thereby accelerating the workflows and scaling up the testing capacity. Recently, a rapid respiratory virus molecular detection assay, the Xpert 4-in-1 assay, was launched with FDA EUA in September 2020. The assay is a rapid and user-friendly real-time RT-PCR test for the qualitative detection and differentiation of SARS-CoV-2, flu A, flu B, and RSV in upper

**FIG 2** Correlation between cycle threshold \((C_T)\) values of positive flu A samples by the Xpert 4-in-1 and Xpert Flu/RSV assays \((n = 56)\).
respiratory tract specimens using a single cartridge. In this study, we assessed the performance of this assay by comparing it to the currently available Xpert individual assays for SARS-CoV-2 and Flu/RSV.

In this comparative analysis, the Xpert 4-in-1 assay demonstrated a very high level of agreement and a high kappa value with comparator assays for SARS-CoV-2, flu A, flu B, and RSV across a wide range of tested CT values of the four viruses (Table 2). There are only two discordant samples for SARS-CoV-2 and flu B, and these were resolved by LD-PCR assay. The discrepant sample tested positive high CT value (41.6) of the Xpert-SARS-CoV-2 assay but negative results by the Xpert 4-in-1 and LD-PCR tests suggest that the sample had a very low SARS-CoV-2 viral load for detection or the negative testing result could be due to multiple freeze-thaw steps of sample processing, which has a significant impact on molecular detection (17). Another discordant sample tested positive for flu B by the Xpert 4-in-1 assay with a CT value of 35.5, while it was negative by the Xpert Flu/RSV assay. The LD-PCR result was positive for flu B, with a CT value of 34.19. As both assays are positive at CT values of >34, the target of flu B might potentially be present at a very low level. Referring to the package inserts, the claimed limit of detection (LoD) of Xpert 4-in-1 for flu B is 0.04 50% tissue culture infective dose (TCID$_{50}$/ml, whereas, the LoD of the Xpert Flu/RSV assay is 0.4 TCID$_{50}$/ml, the sample might be at the detection limit of the Xpert Flu/RSV assay. Another possible reason for the discrepancy is the sample adequacy, especially for the samples with low viral load. Therefore, negative sample results cannot exclude the inadequate sampling or

**FIG 3** Correlation between cycle threshold (CT) values of positive flu B samples by the Xpert 4-in-1 and Xpert Flu/RSV assays (n=63).
inadequate sample integrity of targets, where sample adequacy might not be identical in 2 repetitions (18). For this reason, the future introduction of sample adequacy control (SAC) in the assay design is recommended; SAC is present in some other Cepheid assays, namely the Xpert Ebola and Xpert CT/NG assays, for monitoring the false-negative results by confirming adequate patient sample and appropriate testing conditions. Maximizing confidence in a negative result is an important issue of public health, especially in the cases where false-negative results are reported for pathogens having a high potential of infection spread.

The correlation values ($R^2$) for $C_T$ value association for positive samples of the four viruses by the Xpert 4-in-1 and comparator assays showed a good correlation between them. As shown in Fig. 1 and 2, a remarkably good correlation for SARS-CoV-2 and flu A, with $R^2$ values of 0.956 and 0.949, respectively, was observed. The slightly lower $C_T$ value association for RSV ($R^2 = 0.8736$) may be related to the predominance of high-viral-load samples from pediatric specimens in this study (Table 1). For flu B, the lower correlation of $C_T$ values ($R^2 = 0.8074$) could be due to the small number of positive samples. Although lesser correlation values for $C_T$ were obtained with RSV and flu B, the assays were noncalibrated, and their performance was excellent considering only the qualitative results.

The Xpert 4-in-1 assay has one limitation, in that the assay utilizes the E and N2 genes as targets for the detection of SARS-CoV-2 but does not differentiate between the two targets. Thus, the presence of other coronaviruses in the B lineage,

![Fig 4](image.png)

**Fig 4** Correlation between cycle threshold ($C_T$) values of positive RSV samples by the Xpert 4-in-1 and Xpert Flu/RSV assays ($n=53$).

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