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Multi-center evaluation of Cepheid Xpert® Xpress SARS-CoV-2/Flu/RSV molecular point-of-care test

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\textbf{A B S T R A C T}

\textit{Background:} SARS-CoV-2 is taking a huge toll on society while influenza and RSV detection are also becoming more important. These viruses pose a high burden on health care. Rapid and accurate diagnostics for these pathogens are important for swift triage in the hospital. Fast molecular point of care test (mPOCT) assays for these pathogens can prove an alternative. Here a multi-center evaluation of the Xpert® Xpress SARS-CoV-2/Flu/RSV assay is reported.

\textit{Study design:} The Xpert® Xpress SARS-CoV-2/Flu/RSV assay was compared to three reference assays at three Dutch medical microbiology laboratories. An external quality assessment panel consisting of 16 specimens containing SARS-CoV-2, influenza viruses, RSV or human seasonal coronaviruses, or a combination thereof were used. Clinical specimens containing SARS-CoV-2 (n = 57), influenza viruses (n = 21) or RSV (n = 12), at a wide range of relevant concentrations were used. One laboratory also tested zoonotic avian and swine influenza viruses, and eight relevant SARS-CoV-2 variants.

\textit{Results:} The Xpert® Xpress SARS-CoV-2/Flu/RSV assay showed equal performance compared to the reference assays. All SARS-CoV-2 variants of interest and variants of concern were accurately detected. Human seasonal coronaviruses were not detected. All four circulating seasonal influenza virus subtypes/lineages and both RSV types were accurately detected as well as a set of recent zoonotic avian and swine influenza viruses. The clinical specimens showed 98.2% concordance using this assay.

\textit{Conclusion:} The Xpert® Xpress SARS-CoV-2/Flu/RSV assay is a good alternative for accurate detection for SARS-CoV-2, influenza type A virus, influenza type B virus and RSV types A and B detection in a short timeframe.

1. Background

In December 2019 the first patient suffering from SARS-CoV-2 was reported in Wuhan, China and on the 11th of March 2020 SARS-CoV-2 was declared a pandemic.\textsuperscript{[1,2]} Since then over 182 million confirmed cases and over 3.9 million deaths worldwide have been attributed to the virus which continues to circulate and cause morbidity and mortality across the globe.\textsuperscript{[3]} The symptoms induced by a SARS-CoV-2 infection can vary a great amount from causing an asymptomatic infection to severe respiratory failure.\textsuperscript{[4]} Traditionally, specimens derived from patients with suspected SARS-CoV-2 infection are tested using RT-PCR, however the process of testing can be time consuming.

To provide a quick platform for SARS-CoV-2 diagnostics, Cepheid developed the Xpert® Xpress SARS-CoV-2 point-of-care test in April 2020 which has a hands on time limited to 2 – 3 min and a run-time of 45–50 min.\textsuperscript{[5]} Although the convenience of this test has been shown, one of the downsides of this assay is that it can only test for the presence of SARS-CoV-2. In the more temperate regions of the Northern Hemisphere, influenza virus A/B and RSV A/B infection levels normally peak each year from December – March. Infections with SARS-CoV-2 and RSV can show similar symptoms.\textsuperscript{[6,7]} In order to allow diagnostic laboratories to be able to test patient derived specimens on a multitude of respiratory diseases, Cepheid has developed the Xpert® Xpress SARS-CoV-2/Flu/RSV cartridges which allows for testing of patient material for the presence of SARS-CoV-2, Influenza A/B and RSV A/B virus using a single cartridge. The aim of this study is to evaluate the performance.
of the Xpert® Xpress SARS-CoV-2/Flu/RSV test and determine if it is a useful addition to the respiratory viral diagnostic repertoire.

2. Materials and methods

2.1. Panel preparation

The external quality assessment (EQA) panel used for this evaluation was prepared at the Dutch National Institute for Public Health and the Environment (RIVM). The SARS-CoV-2 virus (hCoV-19/Netherlands/NoordBrabant_10003/2020) was isolated from a nasopharynx swab obtained from a Dutch patient testing positive for SARS-CoV-2 by RT-PCR. The virus stock was grown by inoculating 100 µl of the isolate onto a monolayer of VERO-E6 (ATCC CRL-1586) cells in MEM with Hank’s salts with 10% Fetal Calf Serum (FCS) and 100 units of penicillin and streptomycin/mL at 37 °C for 7 days. After 7 days the cytopathic effect (CPE) was >90% and after a freeze/thaw cycle, another passage on a VERO-E6 monolayer took place. This second passage was incubated at 35 °C for 4 days until >90% CPE was reached, and a viral stock volume was made for further use. SARS-CoV-2 was heat inactivated before preparing the panel. Laboratory strains of human coronaviruses (for hCoV-OC43 and hCoV-229E from ATCC and for hCoV-NL63 kindly provided by Dr. L. van der Hoek, Amsterdam University Medical Center) and RSV-A and RSV-B (kindly provided by Dr. J. van Kampen, Erasmus Medical Center) were used for panel preparation.

The influenza viruses used were primary isolates obtained from national general practitioner-based influenza surveillance at RIVM (type, subtype, lineage and clades relevant for current circulating strains in Table 1). The panel comprised a total of 16 specimens containing either one or a combination of two viruses mentioned above. SARS-CoV-2 was also included as dilution series to determine sensitivity. All specimens were made in MEM with Hanks’ salts and to each specimen 10,000 HEp2 cells (ATCC® CCL-23) were added per milliliter to simulate a human specimen in virus transport medium. Details of the EQA panel with expected positivity indicated by Ct values are listed in Table 1.

As an extra evaluation of the Xpert® Xpress SARS-CoV-2/Flu/RSV assay laboratory 3 also tested specimens containing isolates of SARS-CoV-1, avian influenza viruses H5N8 (A/Chicken/Netherlands/EMC/3/2014 and A/Netherlands/14015531/2014), H7N7 (A/Netherlands/33/03) and H1N1 swine influenza virus (A/Netherlands/10370–1b/2020). Also several SARS-CoV-2 variants, namely Alpha, Beta, Gamma, Epsilon, Zeta and three other variants (pangolinelage B.1.177, B.1.258.21 and C.2.1) were tested using the assay.

2.2. Selection of clinical specimens

From each of the three participating laboratories a subset of specimens obtained from patients tested for SARS-CoV-2 in November 2020 were included in the evaluation. A total of 20 specimens were selected: 10 highly positive clinical specimens (original Ct values 20–30) and 10 weakly positive clinical specimens (original Ct value > 30). A total of twelve clinical specimens containing the following viruses were included: influenza virus A(H1N1)pdm09, A(H3N2), B/Victoria and B/Yamagata, RSV-A and RSV-B. For each virus, a specimen with a high and a low viral load was selected. If typing/subtyping was not available, two specimens with a high and two specimens with a low virus load were selected. The clinical specimens were obtained mainly by using a nasopharyngeal and oropharyngeal swab collected in Glucose-Lactalbumin-Yeast Virus Transportation Medium (GLY) or Universal Transport Medium (UTM) medium. Specimens were stored at −80 °C before testing. Laboratory 2 only had one specimen containing influenza virus B available. No lineage determination was performed for this sample. Influenza subtyping and lineage determination of the clinical samples of laboratory 1 was performed by laboratory 3. Table 2 provides an overview of the specifications of the selected clinical specimens.

2.3. Testing

The EQA panel was shipped frozen on dry ice ensuring the same amount of freeze-thaw cycles for all locations. Both panel specimens and clinical specimens were processed according to the routine diagnostic protocol as performed in each lab (see Table 3 and Table 4). Laboratory 1 did not perform RSV typing. Laboratory 2 did not perform influenza virus type A subtyping, no influenza virus type B lineage determination

![Table 1 composition of validation panel.](image-url)

| Panel coding | Specimen contents | dPCR RdRP-gene copies/mL for SARS-CoV-2 containing specimens | RT-qPCR Ct for RdRP-gene for SARS-CoV-2 containing specimens | Target specific Ct value for viruses other than SARS-CoV-2\(^a\) |
|--------------|-------------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| EQA-01       | SARS-CoV-2        | 1.73±05                                                    | 25.69                                                      | —                                                           |
| EQA-02       | SARS-CoV-2        | 1.73±04                                                    | 29.32                                                      | —                                                           |
| EQA-03       | SARS-CoV-2        | 8.65±02                                                    | 33.78                                                      | 28.62                                                      |
| EQA-04       | SARS-CoV-2        | 1.73±02                                                    | 36.10                                                      | —                                                           |
| EQA-05      | SARS-CoV-2        | 1.73±01                                                    | 37.31                                                      | —                                                           |
| EQA-06      | SARS-CoV-2        | 8.65±03                                                    | 31.25                                                      | 28.75                                                      |
| EQA-07      | SARS-CoV-2        | 8.65±02                                                    | 33.6                                                       | 23.66                                                      |
| EQA-08      | SARS-CoV-2        | 8.65±02                                                    | 35.05                                                      | 27.73                                                      |
| EQA-09      | (H1N1)pdm09 clade 6B1A5A |                                 | —                                                          | 28.69                                                      |
| EQA-10      | (H1N2) clade 3C.2A1B + 3I1K | 8.65±02                                                    | 33.6                                                       | 26.15                                                      |
| EQA-11      | (H3N2) clade 3C.3a | 8.65±01                                                    | 35.6                                                       | 26.45                                                      |
| EQA-12      | SARS-CoV-2        | 8.65±02                                                    | 33.9                                                       | 23.75                                                      |
| EQA-13      | hCoV-NL63        | 8.65±02                                                    | 34.32                                                      | 18.95                                                      |
| EQA-14      | hCoV-229E        | 8.65±02                                                    | 33.9                                                       | 23.75                                                      |
| EQA-15      | hCoV-OC43        | 8.65±02                                                    | 33.9                                                       | 23.75                                                      |
| EQA-16      | —                 | —                                                          | —                                                          | —                                                           |

\(^a\) Ct values for influenza viruses A(H1N1)pdm09, A(H3N2), B/Victoria and B/Yamagata, hCoV-229E, hCoV-NL63, hCoV-OC43, RSV-A and RSV-B.

\(^b\) Educational specimen. If the specimen is tested multiple times the RT-PCR assays can show a negative result for some of the replicates.
Table 2
RT-PCR Ct range of clinical specimens.

| Clinical specimens                        | N   | E-gene average Ct (range) | RdRP-gene average Ct (range) | N-gene average Ct (range) | Target specific average Ct (range) |
|------------------------------------------|-----|---------------------------|-----------------------------|---------------------------|-----------------------------------|
| High load SARS-CoV-2                    | 30  | 23.1 (17.2 – 30.7)        | 24.1 (19.8 – 29.5)          | 23.4 (18.8 – 28.1)        | NA                                |
| Low load SARS-CoV-2                     | 30  | 34.1 (31.5 – 37.0)        | NA                          | NA                        | NA                                |
| SARS-CoV-2                               |     |                           |                             |                           |                                   |
| High load influenza A(H1N1)pdm09 (n = 2), A(H3N2) (n = 2) and influenza A (n = 2) | 6   | NA                        | NA                          | NA                        | 23.1 (20.4 – 26.7)                |
| Low load influenza A(H1N1)pdm09 (n = 2), A(H3N2) (n = 2) and influenza A (n = 2) | 6   | NA                        | NA                          | NA                        | 33.8 (32.5 – 36.7)                |
| High load influenza B/Victoria (n = 1), B/Yamagata (n = 2) and influenza B (n = 1) | 4   | NA                        | NA                          | NA                        | 27.1 (24.6 – 29.1)                |
| Low load influenza B/Victoria (n = 2), B/Yamagata (n = 3) and influenza B (n = 0) | 5   | NA                        | NA                          | NA                        | 33.8 (31.4 – 37.3)                |
| High load RSV-A (n = 1) and RSV-B (n = 1) and RSV (n = 5) | 7   | NA                        | NA                          | NA                        | 25.2 (20.0 – 28.0)                |
| Low load RSV-A (n = 1) and RSV-B (n = 1) and RSV (n = 3) | 5   | NA                        | NA                          | NA                        | 35.5 (33.4 – 37.8)                |

a One out of three laboratories used RdRP-gene in addition to E-gene in the routine test used for SARS-CoV-2 diagnostics.
b Two out of three laboratories used N-gene in addition to E-gene in the routine test used for SARS-CoV-2 diagnostics.
c Twenty-seven could be confirmed by repeat testing of which the Ct values are shown.

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Table 4

| Laboratory | RT-PCR platforms | RNA extraction kit | Primers and probes used | RT-PCR enzymes |
|------------|------------------|--------------------|-------------------------|----------------|
| Laboratory 1 | Cepheid GeneXpert® | Xpert® Xpress Flu/RSV cartridges | M, PB2-gene, PA-gene, N2-gene (Influenza A) M, PB2-gene, NS-gene (Influenza B) | NA |
| Laboratory 2 | Cepheid GeneXpert® | Xpert® Xpress Flu/RSV cartridges | M, PB2-gene, PA-gene, N2-gene (Influenza A) M, PB2-gene, NS-gene (Influenza B) | A/B, RSV |
| Laboratory 3 | Cepheid GeneXpert® | Xpert® Xpress Flu/RSV cartridges | M, PB2-gene, PA-gene, N2-gene (Influenza A) M, PB2-gene, NS-gene (Influenza B) | NA |

Note: The table represents the routine diagnostic assay of each laboratory for influenza virus and RSV detection.

3. Results

3.1. EQA panel

Laboratory 1 did not test the EQA panel with the routine workflow (the Xpert® Xpress SARS-CoV-2 assay). This was deemed unnecessary as their routine SARS-CoV-2 diagnostics assay was already validated by Wolters et al. in a similar validation. [5] None of the assays used by the laboratories (neither routine assays nor the Xpert® Xpress SARS-CoV-2/Flu/RSV assay) gave positive results for the included seasonal coronaviruses (hCoV-NL63, hCoV-229E and hCoV-OC43). At laboratory 2 the routine assay did not detect SARS-CoV-2 in specimen 5 (17.3 copies RdRP/ml). Using the routine assay, laboratory 2 detected SARS-CoV-2 in specimens 4 and 11 (173 and 85.6 copies RdRP/ml, respectively), but only using the N2 target gene whilst the N1 target gene was reported as negative. None of the routine assays misdiagnosed any of the influenza virus or RSV containing specimens included in the panel. Using the Xpert® Xpress SARS-CoV-2/Flu/RSV assay laboratory 1 did not detect SARS-CoV-2 in specimen 5 (17.3 copies RdRP/ml) although the other two laboratories did detect SARS-CoV-2 in this specimen. Specimen 9 containing both influenza virus A(H1N1)pd09 and RSV-B tested positive for influenza virus A only in the Xpert® Xpress SARS-CoV-2/Flu/RSV assay at laboratory 3. The other two laboratories tested this specimen positive for both influenza virus A and RSV in this assay. Using the Xpert® Xpress SARS-CoV-2/Flu/RSV assay specimen 11 containing both SARS-CoV-2 (86.5 copies RdRP/ml) and influenza A(H3N2) tested positive for influenza A virus only in laboratory 2 and 3. In laboratory 1 this specimen tested positive for both influenza A virus and SARS-CoV-2. The data are summarized in Table 5. Taking into account false negatives for the 17.3 and 86.5 copies SARS-CoV-2 RdRP-gene/ml specimens and no false negatives with 10-fold higher concentration specimens, the SARS-CoV-2 LOD for the Xpert® Xpress SARS-CoV-2/Flu/RSV assay is estimated roughly between 86.5 and 173 copies RdRP-gen/ml specimen. All specimens containing avian and swine influenza viruses tested positive for influenza virus type A using the Xpert® Xpress SARS-CoV-2/Flu/RSV assay. The SARS-CoV-1 containing specimen as well as all SARS-CoV-2 variants were reported positive for SARS-CoV-2 by the Xpert® Xpress SARS-CoV-2/Flu/RSV assay. All SARS-CoV-2 variants tested by laboratory 3 were accurately detected in a high and low concentration at 1.14E06–6.59E06 and 1.14E04–6.59E04 dPCR RdRP-gene copies/ml, respectively.

3.2. Clinical specimens

At all three laboratories the clinical specimens containing influenza virus or RSV, tested negative for SARS-CoV-2. All specimens tested positive for influenza and RSV with the Xpert® Xpress SARS-CoV-2/Flu/RSV assay, except for one specimen from laboratory 3 that tested negative for RSV. This specimen contained a low concentration of RSV-A confirmed by re-testing. All high titer SARS-CoV-2 containing clinical specimens were confirmed SARS-CoV-2 positive upon testing with the Xpert® Xpress SARS-CoV-2/Flu/RSV assay. Of the low titer clinical SARS-CoV-2 specimens laboratory 1 showed an N-gene only positive result for two specimens using their regular diagnostic workflow. The E-gene result was negative for these specimens. One of these two specimens also was negative upon retesting with the Xpert® Xpress SARS-CoV-2/Flu/RSV
In this study we have shown that Cepheid’s Xpert® Xpress SARS-CoV-2/Flu/RSV assay is a highly sensitive SARS-CoV-2, influenza A/B and RSV-A/B specific mPOCT. The performance of this assay using a variety of EQA and clinical specimens of high and low viral load was highly similar to that of the SARS-CoV-2, influenza A/B and RSV-A/B assays routinely performed by the participating laboratories. In another multicenter European validation this same conclusion was reached with 95% concordance of all tested clinical specimens. [8]

An advantage of the Xpert® Xpress SARS-CoV-2/Flu/RSV assay is the runtime of only 45–50 min as well as the option for random access. Decreased runtime of diagnostics can decrease length of stay on an emergency ward, expedite intake of antiviral drugs and lessen the number of tests ordered. The latter is especially true for multiplex assays as they test for multiple pathogens per run. [9,10]

As an extra control several SARS-CoV-2 variants, namely Alpha, Beta, Gamma, Epsilon, Zeta and three other variants (pangolins B.1.177, B.1.258.21 and C.2.1) were tested using the assay. All variants were accurately detected in a high and low concentration. The capacity of the assay to detect (novel) variants of SARS-CoV-2 makes it a robust assay.

The Cepheid’s Xpert® Xpress SARS-CoV-2/Flu/RSV assay uses two target genes for both SARS-CoV-2 and influenza detection. An advantage of this is that it decreases the chance of false negative test results when testing (novel) genetic variants of those pathogens. For example mutations in SARS-CoV-2 variant B.1.1.7/20B/501Y.V1 can cause an S-gene dropout in certain assays. [11] If an assay uses only one target gene for detection of a pathogen, there is a higher chance of false-negative results when confronted with novel variants than in assays with multiple target genes. There is a limited chance that a novel variant avoids detection of two or more target genes at the same time.

In addition, recent zoonotic avian and swine influenza viruses were accurately detected by the assay. Swine and avian influenza variants are known to infect the human population. [12] The ability of the Xpert® Xpress SARS-CoV-2/Flu/RSV assay to detect these strains increases its usability in potential outbreaks.

Currently there is an RSV epidemic in the Netherlands which does not fit in the regular yearly (winter) cycle in which the disease normally is present. [13] This finding is similar to the delayed increase in RSV infections found in France, Australia, Argentina, Chile and South-Africa. [14–20] As SARS-CoV-2, (zoonotic) influenza and RSV diseases show similar symptoms it is very convenient to triage patients quickly into the correct hospital ward. [4,6,7] This decreases the chance on cross-contamination between different patient groups. Considering the high throughput of suspected SARS-CoV-2/influenza/RSV patients in certain hospital wards, it is highly practical to have a multiplex assay capable of testing for all three diseases in the same run.

The LOD of Cepheid’s Xpert® Xpress SARS-CoV-2/Flu/RSV assay is estimated roughly between 86.5–173 digital copies of positive strand genomic SARS-CoV-2 RNA/ml. This is similar to the LOD of 131 copies/ml reported by the manufacturer. [21] The only false positive result with the Gene Xpert® SARS-CoV-2/Flu/RSV assay when testing any of the specimens was obtained with SARS-CoV-1. It is known that the E-gene component of the Xpert® Xpress SARS-CoV-2/Flu/RSV assay is specific for the SARS-like betacoronavirus group to which SARS-CoV-1 belongs. Considering the fact that SARS-CoV-1 currently does not circulate in

### Table 5

| Panel | Specimen | Content | Incorrect |
|-------|----------|---------|-----------|
| EQA-01 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-02 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-03 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-04 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-05 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-06 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-07 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-08 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-09 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-10 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-11 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-12 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-13 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-14 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-15 | SARS-CoV-2 | influenza A/Viruses | None |
| EQA-16 | SARS-CoV-2 | influenza A/Viruses | None |

Data is combined from all laboratories. Laboratory 1 did not test the EQA panel with the routine workflow.
the human population, there is no reason to question whether a clinical specimen might be SARS-CoV-1 positive when the assay reports it as SARS-CoV-2 positive.

All in all the Gene Xpert® SARS-CoV-2/Flu/RSV assay is a reliable method for rapid detection of SARS-CoV-2, influenza type A virus, influenza type B virus and RSV types A and B.

**CRediT author statement**

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**Declaration of Competing Interest**

None.

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