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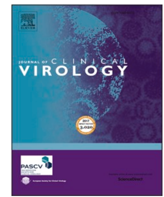

Clinical evaluation of the molecular-based BD SARS-CoV-2/Flu for the BD MAX™ system

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ABSTRACT

Background: COVID-19 and influenza (flu) share similar clinical symptoms. Therefore, differential detection of these viruses during the respiratory virus season will be an important component for proper patient triage, management, and treatment.
Objectives: Establish the diagnostic performance related to SARS-CoV-2 and Flu A/B detection for the BD SARS-CoV-2/Flu for BD MAX™ System ("MAX SARS-CoV-2/Flu") multiplex assay.
Materials and methods: Two hundred and thirty-five (235) retrospective nasopharyngeal specimens were obtained from external vendors. The BD BioGx SARS-CoV-2 Reagents for BD MAX™ System ("BioGx SARS-CoV-2″) and the Cepheid Xpert® Xpress Flu/RSV ("Xpert Flu/RSV") were utilized as reference methods.
Results: By reference methods, 52 specimens were SARS-CoV-2-positive, 59 were Flu A-positive, and 60 were Flu B-positive. MAX SARS-CoV-2/Flu had positive percent agreement (PPA) and negative percent agreement (NPA) values for SARS-CoV-2 detection of 96.2% ([95%CI]:87.0–98.9) and 100% [95%CI:88.7–100], respectively; PPA values for Flu A and Flu B of 100% [95%CI:93.9–100] and 98.3% [95%CI:91.1–99.7], respectively, and NPA values for Flu A and Flu B of 98.9% [95%CI:94.0–99.8] and 100% [95%CI:95.9–100], respectively.
Conclusions: The MAX SARS-CoV-2/Flu assay met FDA-EUA performance criteria for SARS-CoV-2 (≥95% for PPA and NPA) and FDA clearance criteria for Flu A/B (PPA ≥90%; lower bound of the 95%CI ≥80% and NPA ≥95%; lower bound of the 95%CI ≥90%).

1. Introduction

Since the report of the first cluster of COVID-19 cases in December 2019, over 196 million COVID-19 cases and 4.19 million COVID-19-related deaths worldwide have been reported by the end of July 2021, and the numbers continue to rise [1,2]. In the U.S., more than 34.8 million COVID-19 cases and over 612,000 COVID-19 deaths have been recorded [1]. Although it seems that the 2020–2021 influenza season did not impact health care systems, the 2019–2020 flu season resulted in over 38 million cases involving symptomatic illness and approximately 22,000 deaths in the U.S. [3] Each year, there are an estimated 1 billion cases of influenza globally, of which, 3–5 million are severe cases and 29,000–655,000 lead to influenza-related respiratory deaths [4]. Although as of now influenza activity is low in the U.S. [5], this virus has the potential of increasing the workload of healthcare workers already overwhelmed by COVID-19.

As society gradually reopens and social interactions increase, the potential coincidence of both COVID-19 and influenza cases in high numbers during respiratory virus season is a significant concern. Therefore, differential detection of COVID-19 and influenza will be an important component for proper patient triage, management, and treatment.

Molecular diagnostics for the detection of SARS-CoV-2, including real-time polymerase chain reaction (RT-PCR) assays, have played an important role in the detection of SARS-CoV-2 and diagnosis of COVID-19 due to their high sensitivity [6]. Similarly, RT-PCR-based detection of Influenza A/B ("Flu A/B") virus nucleic acid has been established for a number of years and is commonly employed to establish an influenza diagnosis [7]. Due to the expected co-circulation with the potential co-infection of SARS-CoV-2 and Flu A/B, a multiplex RT-PCR assay, for detection all three targets, could help provide faster results and improve patient management and treatment [8].

This report describes the performance of the new BD SARS-CoV-2/Flu assay reagents for BD MAX™ System multiplex assay for detection

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of SARS-CoV-2 and Flu A/B. The comparator reference methods were the BD BioGx SARS-CoV-2 Reagents for BD MAX™ System and Cepheid Xpert® Xpress Flu/RSV. The objective here was to determine the performance characteristics of the new multiplex BD SARS-CoV-2/Flu assay.

2. Materials and methods

2.1. Specimens

Two hundred and thirty-five (235) nasopharyngeal specimens, either in Copan Universal Transport Medium (UTM®) or in BD Universal Viral Transport (UVT) system, were collected between November 30, 2019 and September 3, 2020 as part of standard of care (SOC). The samples were obtained from individuals with ages ranging from 1 year to ≥90 years and the residual transport media was stored at −65 °C ~ −80 °C (Table 1). Only positive samples that met the age requirement of the U.S. Food and Drug Administration (FDA) were selected. The positive samples selected for the study sample set demonstrated an equitable distribution of Flu A and Flu B positive samples. The viral load was estimated using the cycle threshold (Ct) of each sample result. Retrospective specimens were reflective of the natural distribution of SARS-CoV-2, Flu A, and Flu B viral loads, and approximately 10–20% of the clinical specimens were positives with low viral loads (i.e., RT-PCR Ct counts >30), as has been observed in other, sequentially enrolled clinical studies [9,10].

Specimens for SARS-CoV-2 testing were obtained from New York Biologics, Inc. (Southampton, NY, USA) and Trans-Hit Bio (Laval, QC, Canada). Specimens for Flu A/B testing were obtained from New York Biologics, Inc. collected under protocols approved by Western Institutional Review Board (WIRB) and from Ethical & Independent Review Services (EIRS). These institutional review board approvals provide a waiver of informed consent on collection protocols for residual delinked and de-identified specimen collections. Samples obtained from Trans-Hit Bio were collected under their biobank umbrella protocol (approved by the Valleywise Health Institutional Review Board) that allows for the collection of various bio-specimens.

2.2. Assays

This study, which was conducted as part of a FDA-Emergency Use Authorization (EUA) submission, included data comparing the BD SARS-CoV-2/Flu for BD MAX™ System ("MAX SARS-CoV-2/Flu;" Becton, Dickinson and Company; BD Life Sciences—Integrated Diagnostic Solutions, Sparks, MD, USA) to two reference methods, BD BioGx SARS-CoV-2 Reagents for BD MAX™ System ("BioGx SARS-CoV-2;" Becton, Dickinson and Company; BD Life Sciences – Integrated Diagnostic Solutions, Sparks, MD, USA) and Cepheid Xpert® Xpress Flu/RSV ("Xpert Flu;" Cepheid®, Sunnyvale, CA, USA), for detection of SARS-CoV-2 and Flu A/B, respectively [11]. At the time this study was conducted there were no FDA cleared assays that detected all three targets. Therefore, two different assays, one EUA assay for testing SARS-CoV-2 and one cleared assay for testing Flu A/B and RSV, were chosen as references. The BD BioGx SARS-CoV-2 assay was selected because of performance, meeting the FDA requirement of being a high sensitivity EUA RT-PCR assay which uses a chemical lysis step followed by solid phase extraction of nucleic acid and the availability of testing kits.

The BioFire® Respiratory 2.1 Panel ("BioFire SARS-CoV-2;" BioFire Diagnostics, Salt Lake City, UT, USA) was used to test specimens for which MAX SARS-CoV-2/Flu and BioGx SARS-CoV-2 assay results were discordant; the cobas® Influenza A/B & RSV assay for use on the cobas® Liat® System ("Liat Flu A/B RSV;" Roche Diagnostics, Indianapolis, IN, USA) was used to test specimens for which MAX SARS-CoV-2/Flu and Xpert Flu assay results were discordant.

All assays were performed according to each manufacturer's instructions for use. MAX SARS-CoV-2/Flu, BioGx SARS-CoV-2, and BioFire SARS-CoV-2 assays were performed at BD Integrated Diagnostic Solutions; Xpert Flu A/B RSV and Liat Flu A/B RSV assays were performed at TriCore Reference Laboratories (Table S1).

Table 1
SARS-CoV-2 and influenza positivity distribution by reference method across age groups.

Age group	SARS-CoV-2	Influenza A	Influenza B
% (n)	n (%)	n (%)	n (%)
≤5 years 21.6% ($n = 50$)	0 (0.0)	19 (32.2)	13 (21.7)
6–21 years 19.8% ($n = 46$)	0 (0.0)	12 (20.3)	26 (43.3)
22–59 years 41.8% ($n = 97$)	39 (75.0)	16 (27.1)	16 (26.7)
≥60 years 16.8% ($n = 39$)	13 (25.0)	12 (20.3)	5 (8.3)
Overall ($N = 232$)[a]	52	59	60

[a]Reportable for MAX and comparator assays.

2.3. Data analysis

The primary outcome measures for this study were positive and negative percent agreement (PPA and NPA, respectively) point estimates (with 95% confidence interval [95% CI] calculated using the Wilson score method) for the MAX SARS-CoV-2/Flu assay, compared to each respective reference assay. The McNemar test was used for 2 × 2 classification to test the difference between paired proportions. The calculated difference is that of marginal proportions ([total proportion of SARS-CoV-2, Flu A, or Flu B positives] – [total proportion of positives (for each of the three causes) by clinical diagnosis]). A p-value <0.05 was utilized to distinguish significant differences (note here that a p-value >0.05 indicates only that disagreement between the two diagnostic methods is random). The Cohen's kappa coefficient was utilized to gauge the agreement between two raters (reference and test) to classify results into mutually exclusive categories: $K=(P_o{}^{-P}e)/1-P_e$ (<0, 0, and >0 indicating agreements worse than, no better or worse than, and better than that expected by chance).

Acceptance criteria for the MAX SARS-CoV-2/Flu assay for U.S. FDA-EUA authorization for SARS-CoV-2 was ≥95% for both PPA and NPA [12]. The PPA criteria for Flu A/B was ≥90% (lower bound of the 95%CI ≥80%) and the NPA criteria for Flu A/B was ≥95% (lower bound of the 95%CI ≥90%). Only compliant (no protocol deviations) and reportable results (no errors during specimen processing and a valid result obtained) for both MAX SARS-CoV-2/Flu and comparator assays were included in this analysis. This article was prepared according to standards for reporting diagnostic accuracy studies (STARD) guidelines [13].

2.4. Data availability

Data will be made publicly available upon publication.

3. Results

A total of 235 specimens were included in this study, from which three were excluded due to unreportable results from an instrumental failure. From the remaining 232 specimens, reference method testing for SARS-CoV-2 (BioGx SARS-CoV-2) and Flu A/B (Xpert Flu), resulted in 52 positive SARS-CoV-2 specimens, 59 positive Flu A specimens, and 60 positive Flu B specimens (Table 1). By reference methods, 30, 91, and 90 specimens were negative, respectively, for SARS-CoV-2, Flu A, and Flu B. Among all positive samples, data were stratified in age groups based on FDA guidance [14]. The 22–59 years age group had the highest SARS-CoV-2 positivity, the ≤5 years age group had the highest Flu A positivity, and the 6–21 years age group had the highest Flu B positivity.

MAX SARS-CoV-2/Flu results were compared to results from each respective reference method to determine PPA and NPA values. MAX SARS-CoV-2/Flu had PPA and NPA values of 96.2% [95%CI: 87.0, 98.9] and 100% [95%CI: 88.7, 100], respectively, for detection of SARS-CoV-

2. For Flu A, MAX SARS-CoV-2/Flu had PPA and NPA values of 100% [95%CI: 93.9, 100] and 98.9% [95%CI: 94.0, 99.8], respectively. For Flu B, MAX SARS-CoV-2/Flu had PPA and NPA values of 98.3% [95%CI: 91.1, 99.7] and 100% [95%CI: 95.9, 100], respectively (Table 2).

During discordant testing, the MAX SARS-CoV-2/Flu assay was in agreement with the third assays (i.e. BioFire SARS-CoV-2 assay and Liat Flu assay) for both SARS-CoV-2 negative results and for the Flu A positive result by the MAX SARS-CoV-2/Flu assay. For Flu B, the Liat Flu assay agreed with the Xpert Flu assay negative result. However, all discordant results were associated with high Ct values (ranging from 37.8 to 39.5). The MAX SARS-CoV-2 showed 100% PPA in specimens with reference method results associated with Ct values ≤30 (Table 3).

4. Discussion

The PPA for the MAX SARS-CoV-2/Flu assay when compared to reference assays meets FDA-EUA acceptance criteria for detection of SARS-CoV-2 (96.2%), Flu A (100%; with a lower bound 95%CI of 93.9%), and Flu B (98.3%; with a lower bound 95%CI of 91.1%). Similarly, compared to reference methods, the MAX SARS-CoV-2/Flu assay was associated with high NPA values for detection of SARS-CoV-2 (100%), Flu A (98.9%; with a lower bound 95%CI of 94.0%), and Flu B (100%; with a lower bound 95%CI of 95.9%), which met all of the FDA acceptance criteria. Discordant results were further tested with additional assays, BioFire SARS-CoV-2 assay for SARS-CoV-2 and Liat Flu assay for Flu A/B. All discordant results were associated with high Ct values. Because of the high PPA and NPA for SARS-CoV-2, Flu A, and Flu B, this multiplex assay should reduce specimen testing time and the amount of consumables and reagents necessary to test individually for both COVID-19 and influenza A/B.

Other approaches are currently available for the detection of SARS-CoV-2 and Flu A/B for the diagnosis of both COVID-19 and influenza, respectively [7,15]. Although culture-based assays were originally utilized to establish an influenza diagnosis, RT-PCR-based technology for detection of influenza currently represents the laboratory method of choice due to its relatively high analytic and clinical sensitivity, as well as short turn-around time [16]. Likewise, RT-PCR-based assays appear to have higher sensitivity for detection for SARS-CoV-2 compared to culture-based assays [17]. Rapid testing methods, such as immunochromatic techniques to detect viral antigen, have been developed for detection of both SARS-CoV-2 and Flu A/B [6,7]. Although rapid tests carry advantages, such as decreased time-to-result and ease of implementation in decentralized health care settings, RT-PCR-based assays have increased analytical sensitivity compared to rapid tests [7]. Ultimately, multiple factors should be considered before determining which strategy should be employed. For example, hospitals and their associated laboratory partners, which have established a streamlined workflow and a relatively fast turn-around time, can effectively employ RT-PCR-based assays—especially for patients admitted and managed according to their symptoms. This strategy carries the benefit of high sensitivity and the ability to rule out etiologic agents with a high degree of assurance.

The MAX SARS-CoV-2/Flu assay utilizes the same multiplexed primers and probes targeting RNA from the nucleocapsid phosphoprotein gene (N1 and N2 regions) of the SARS-CoV-2 virus as shown in the previous FDA-EUA approved MAX SARS-CoV-2 assay [18]. The MAX SARS-CoV-2/Flu assay also includes additional primers and probes recognizing a conserved region of the matrix protein M1 gene for influenza A and conserved regions of the matrix protein M1 gene and hemagglutinin (HA) gene for influenza B [19]. A positive result for either target with a low Ct value may be indicative of active infection, however, this result does not rule out bacterial infection or co-infection with other viruses [18]. This is important in the case of SARS-CoV-2, as asymptomatic infections occur and the positive results require clinical judgement. While the MAX SARS-CoV-2/Flu assay can detect SARS-CoV-2 and influenza A and B virus, it is not intended to detect influenza C virus [19]. The clinical presentation and contact history of an individual, along with other diagnostic information, are necessary to determine the actual infection status. Additionally, the differences of the limit of detection (LOD) of different assays may account for the discordant results. With BioGX showing the lowest LOD (according to the manufacturer's instructions for use) for detecting SARS-CoV-2, it is possible that the discordant results were positive even though BioFire testing agreed with the MAX negative results [19-22]. However, the lack of a gold standard for detecting SARS-CoV-2 precludes a firm conclusion according to discordant testing.

If the coincidence of high rates of both COVID-19 and influenza cases

Table 2
Performance of the MAX SARS-CoV-2/Flu assay for detection of SARS-CoV-2, Flu A and Flu B compared to reference.

	SARS-CoV-2[a,c]	Flu A[b,c]	Flu B[b,c]
PPA	96.2% [87.0%, 98.9%]	100% [93.9%, 100%]	98.3% [91.1%, 99.7%]
NPA	100% [88.7%, 100%]	98.9% [94.0%, 99.8%]	100% [95.9%, 100%]
MAX (+) / Ref (+)	50	59	59
MAX (+) / Ref (-)	0	1	0
MAX (-) / Ref (+)	2	0	1
MAX (-) / Ref (-)	30	90	90
kappa	0.948	0.986	0.986

Abbreviations: PPA, positive percent agreement; NPA, negative percent agreement.
[a] Reference method was the BioGx SARS-CoV-2 RT-PCR assay.
[b] Reference method was the Xpert Flu RT-PCR assay.
[c] A statistically significant difference (via McNemar's test on paired proportions was not observed for MAX SARS-CoV-2/Flu for detection of SARS-CoV-2 (-2.4 [95% CI: -5.8, 0.0]; $p = 0.500$), Flu A (0.67 [95% CI: -0.64, 1.97]; $p = 1.000$), or Flu B (-0.67 [95% CI: -1.97, 0.64]; $p = 1.000$).

Table 3
Comparison of MAX SARS-CoV-2/Flu assay results with those from the BioGx SARS-CoV-2 and Xpert Flu assays, stratified by cycle threshold (Ct) category.

	BioGx SARS-CoV-2	
MAX SARS-CoV-2	**Positive (Ct ≤ 30)**	**Positive (Ct > 30)**
Positive	41	9
Negative	0	2[a]
Total	41	11
PPA (95% CI)	100% (91.4% - 100%)	81.8% (52.3% - 94.9%)
	Xpert Flu A[b]	
MAX Flu A	**Positive (Ct ≤ 30)**	**Positive (Ct > 30)**
Positive	48	11
Negative	0	0
Total	48	11
PPA (95% CI)	100% (92.6% - 100%)	100% (74.1% - 100%)
	Xpert Flu B	
MAX Flu A	**Positive (Ct ≤ 30)**	**Positive (Ct > 30)**
Positive	48	11
Negative	0	1[c]
Total	48	12
PPA (95% CI)	100% (92.6% - 100%)	91.7% (64.6% - 98.5%)

Abbreviations: Ct, PCR cycle threshold; PPA, positive percent agreement
[a] One specimen corresponded to a Ct value for the N1 result = 39.5 and an N2 result = negative. One specimen corresponded to a N1 result = negative and a Ct value for the N2 result = 38.8. Discrepancy testing with the BioFire SARS-CoV-2 assay was negative (agreement with MAX) for both specimens.
[b] One specimen (not shown here) was positive by MAX (Ct value = 38.8) and negative by Xpert Flu. Discrepancy testing with the Liat Flu assay was positive (agreement with MAX SARS-CoV-2/Flu).
[c] Ct value for the Xpert Flu result = 37.8. Discrepancy testing with the Liat Flu assay was positive (agreement with Xpert Flu).

occurs during a respiratory virus season, differential diagnosis for the appropriate therapeutic approach could be challenging. Although COVID-19 and influenza spread through a similar transmission mechanism and have overlapping symptomology, the isolation length and the therapeutic approach for COVID-19 patients and influenza patients are not uniform [23]. For example, COVID-19 seems to involve a longer time to symptom onset than influenza, and may cause more severe illness in vulnerable populations once symptoms develop [24]. The recommended isolation period after symptoms onset is a minimum of 4–5 days for influenza [25], whereas it is a minimum of 10 days for COVID-19 [26], impacting absenteeism and contact tracing. Also, the therapeutic approach for COVID-19 patients and influenza patients is not similar. Anti-viral drug therapies, such as Tamiflu® or Xoflusa®, which have been used for influenza patients [27], are not approved nor is their efficacy well-understood for patients with COVID-19. Therefore, safety concerns may preclude any potential efficacy. A similar concern exists for drugs such as remdesivir and corticosteroids, which have been used to treat COVID-19 patients, but are not approved for use in influenza patients, and may (for example, in the case of corticosteroids) have negative side effects in influenza patients [23]. Distinguishing the diagnosis of COVID-19 and influenza, therefore, will be an important component for proper patient triage, management, and treatment.

4.1. Limitations

This research was conducted by using materials obtained from preselected frozen remnants, received after routine care. A study involving prospective collection could result in better estimations of the positive and negative predictive values of the assay.

5. Conclusions

The MAX SARS-CoV-2/Flu assay met U.S. FDA-EUA acceptance criteria for SARS-CoV-2 and Flu A/B detection. Dual detection of the etiologic agents causing COVID-19 and influenza will allow differentiation for those exhibiting common symptomology. This assay should help optimize patient management by decreasing the time and resources required for dual testing. Ultimately, the dual detection method should facilitate an informed decision by physicians on the appropriate treatment for patients exhibiting similar symptoms between the two diseases.

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Author contributions

Sonia Paradis: Conceptualization, Resources, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration. **Elizabeth Lockamy:** Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – Review & Editing. **Charles K. Cooper:** Conceptualization, Supervision, Writing – Review & Editing. **Stephen Young:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors disclose the following conflicts of interest: SP, EL, and CKC are employees of Becton, Dickinson and Company; SY, None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2021.104946.

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