Missed opportunities for respiratory disease diagnosis in the United States during endemic spread of SARS-CoV-2

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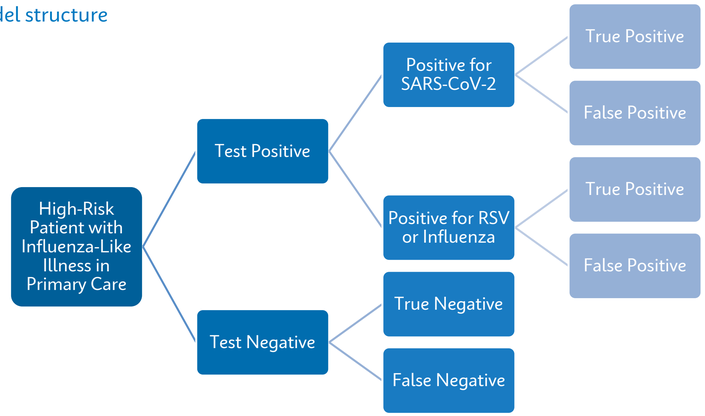
Introduction

Influenza-like illness (ILI) is an acute respiratory illness that results in a measured fever of ≥ 38.0° C and a cough, with onset within the last ten days.[1] Common causes of ILI include influenza, SARS-CoV-2, and respiratory syncytial virus (RSV). Various testing methods are available to detect and differentiate these causes of ILI, including both molecular and antigen-based methods. Such methods can be singleplex (single pathogen, e.g. SARS-CoV-2 alone), duplex (two pathogens, e.g. SARS-CoV-2 and influenza) or multiplex in nature (e.g., SARS-CoV-2, influenza, and RSV). Multi-pathogen testing is recommended to facilitate surveillance of pathogens of concern, such as RSV, and because clinical differentiation of the causative pathogen can be difficult.[2,3,4] Furthermore, the Infectious Disease Society of America recommends molecular testing for symptomatic patients suspected of having COVID-19, but antigen testing is still frequently used.[5] While antigen-based diagnostic methods tend to provide a more rapid answer, molecular methods are generally more sensitive.[6] As such, use of antigen testing may result in missed opportunities for appropriate diagnosis and treatment or management of common viruses, including SARS-CoV-2, influenza, and respiratory syncytial virus (RSV), compared to point-of-care (POC) multiplex molecular tests such as Xpert® Xpress CoV-2/Flu/RSV *plus* ("Xpert Xpress"). Xpert Xpress is a US-IVD multiplexed real-time PCR test intended for rapid, simultaneous detection and differentiation of SARS-CoV-2, influenza A, influenza B, and RSV.

Objective

The aim of this study was to assess potential missed opportunities for diagnosis of SARS-CoV-2, influenza, and RSV in the United States between October 2022 – November 2023 with antigen tests compared to Xpert Xpress.

Figure 1. Model structure



Methods

- A decision tree model was constructed in Microsoft Excel to compare testing with Xpert Xpress versus antigen testing for SARS-CoV-2 and/or influenza in terms of the number of true positive disease results detected (Figure 1)
- Weekly test positivity data was drawn from the National Respiratory and Enteric Virus Surveillance System. Monthly test positivity was calculated based on the weighted average of tests performed per week vs test positivity, and was based on Centers for Disease Control Morbidity and Mortality Weekly Report week start dates[7,8]
- Diagnostic tests included in the comparison were:
  - Xpert Xpress
  - Antigen testing for SARS-CoV-2 (single-plex antigen)
  - Simultaneous antigen testing for SARS-CoV-2 and influenza (duplex antigen)
- Test accuracy for detection of SARS-CoV-2 was drawn from a systematic review and meta-analysis of test accuracy; accuracy for flu and RSV was drawn from peer-reviewed literature (Table 1)[6,9,10]
- The model considers number of tests performed, pathogen positivity, and test accuracy to estimate the number needed to test with Xpert Xpress to detect one additional true positive result compared to single-plex or duplex antigen testing
- Number needed to test to identify an additional true positive detection (NNT) was used to quantify the diagnostic effectiveness of each strategy compared to Xpert Xpress

Table 1. Test specifications

Pathogen	SARS-CoV-2		Influenza		RSV	
Test	Xpert Xpress	Antigen	Xpert Xpress	Antigen	Xpert Xpress	Antigen
Sensitivity	98.0%[6]	74.8%[6]	100%[9]	69.0%[10]	100%[9]	N/A
Specificity	96.0%[6]	98.6%[6]	100%[9]	97%[10]	100%[9]	N/A

Results

- Disease positivity varied substantially throughout the study period across viral targets, from as low as 0.4% RSV positivity to a maximum of 26.3% influenza positivity on a weekly basis (Table 2)
- Compared to antigen testing for SARS-CoV2, the NNT with Xpert Xpress to yield one additional true positive detection of SARS-CoV-2, influenza, or RSV ranged from three to 39
- Compared to duplex antigen testing for SARS-CoV-2 and influenza, NNT with Xpert Xpress to yield one additional true positive detection of SARS-CoV2 or influenza ranged from five to 54 (Table 3)
- NNT was lowest during November 2022 and highest in July 2023. In general, NNT was lower during the respiratory virus season

Table 2. Minimum and Maximum Reported Weekly Test Positivity, By Disease

	SARS-CoV-2 positivity	Influenza positivity	RSV positivity
Minimum	4.1%	0.7%	0.4%
Maximum	14.5%	26.3%	19.5%

Table 3. Test Volumes and Disease Positivity By Month

	SARS-CoV-2 positivity	Influenza positivity	RSV positivity	NNT, Xpert Xpress vs SARS-CoV-2 Antigen	NNT, Xpert Xpress vs SARS-CoV-2 & Influenza Antigen
October-22	6.92%	4.40%	14.42%	5	6
November-22	6.90%	17.95%	17.18%	3	5
December-22	9.42%	22.42%	7.16%	4	7
January-23	8.98%	4.55%	3.68%	10	14
February-23	8.00%	1.30%	1.75%	21	25
March-23	6.98%	0.93%	1.00%	29	35
April-23	5.66%	0.98%	0.58%	35	46
May-23	4.75%	1.08%	0.48%	38	53
June-23	4.25%	1.10%	0.53%	39	54
July-23	6.66%	1.06%	0.66%	31	40
August-23	12.63%	0.93%	0.93%	21	25
September-23	12.68%	0.80%	1.68%	19	21
October-23	9.50%	1.43%	5.38%	12	13
November-23	9.48%	4.40%	11.13%	6	7

Limitations

- Test positivity rate reported in NREVSS may not represent geographic and time-specific considerations and trends on disease prevalence and positivity
- This analysis does not consider impact of correct diagnosis on treatment decision nor does it evaluate the potential for correct diagnosis with appropriate treatment to improve clinical outcomes
- This model does not consider co-infections, nor does it model potential for prevention of infections or transmissions. As a result, this model may underestimate the true value of point-of-care multiplex molecular testing for detection and differentiation of SARS-CoV-2, influenza, and RSV

Discussion

- During the peak of the 2022-2023 respiratory season, an additional true positive detection of SARS-CoV-2, influenza, or RSV could have been identified by testing as few as three patients with Xpert Xpress rather than by antigen for SARS-CoV-2 alone
- Failure to detect the underlying cause of ILI may result in inappropriate treatments or missed opportunities for treatments, which may increase the risk of complications or death
- Implementation of rapid, multiplex POC molecular testing for ILI may enhance disease surveillance and testing efficacy
- Considered through a public health lens, unattended diagnoses may contribute to increased disease transmission rates and amplify the burden on healthcare systems

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