Using a novel rapid viral test to improve triage of emergency department patients with acute respiratory illness during flu season

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ABSTRACT

Background: Acute respiratory illnesses (ARI) are mostly viral in etiology and cause significant morbidity and mortality. Point of care PCR (POC-PCR) is a promising new technology for rapid virus identification but utility in the Emergency Department (ED) is not yet defined.

Objectives: Primarily, to investigate the value of POC-PCR in rapidly identifying RSV and influenza in the setting of ED triage. Additionally, to assess whether rapid knowledge of accurate test results would improve patient management by preventing nosocomial transmission and optimizing the prescription of antimicrobials for ARIs.

Study Design: A prospective cohort study of consecutive ED patients with ARI symptoms during peak flu season was conducted. Patient nasopharyngeal swabs were collected and tested using a POC-PCR device; physicians and patients were blinded to results. Virus positive and negative groups were compared by ED patient room placement and antimicrobial therapy ordered. Specificity and sensitivity were calculated using laboratory-PCR as the gold standard.

Results: Of 119 participants, 52.9% were POC-PCR positive - Influenza A (42.9%), RSV (41.3%), influenza B (15.9%). Nearly 70% of virus positive patients were placed rooms shared with non-ARI patients. Antibiotics were prescribed for 27.3% of virus positive patients, and 77.8% of oseltamivir-eligible patients did not receive therapy. POC-PCR was 100% sensitive (95% CI, 80.5–100.0%) and 95.2% specific (95% CI, 76.2–99.9%).

Conclusions: Rapid POC-PCR for influenza and RSV in ED triage has excellent sensitivity and specificity and the potential to improve social distancing practices through better triage and increase appropriate prescription of antimicrobials.

1. Background

Acute respiratory illnesses (ARI) cause significant morbidity and mortality in both adult and pediatric patients, especially during winter months. The most common ARI etiology is viral with influenza and respiratory syncytial virus (RSV) accounting for 40% of cases [1,2]. Every year, influenza is estimated to cause 200,000 hospitalizations and 20,000 deaths in the United States, and 250,000–500,000 deaths globally [3–5]. In addition to immunization, early treatment, social distancing, and good hygiene reduce the incidence and severity of disease [6–8].

During peak ARI seasons, Emergency Departments (ED) experience increased demand. One study found that 25% of ED visits during peak periods are for fever and respiratory infection symptoms [9]. Peak influenza circulation is associated with reduced ED throughput efficiency, increased ED length of stay (LOS), and a greater proportion of patients who depart before seeing a physician [10]. Additionally, influenza patients' median LOS is five times greater than other ambulatory ED patients [11]. Most EDs lack space to accommodate such increases and standard operating procedures require patients to remain in crowded waiting rooms until patient rooms become available. Such space limitations and overcrowding facilitate nosocomial infections [12,13].

Rapid identification of respiratory viruses is crucial for prevention of nosocomial transmission especially given the immune compromised and inherently vulnerable nature of ED patients, including very young and elderly patients, and those with chronic health conditions. Despite

numerous attempts, syndromic formulas for distinguishing influenza from other respiratory illnesses lack the sensitivity required to inform clinical decisions regarding patient care and isolation [14–17]. The gold standard for viral testing is laboratory polymerase chain reaction (PCR). Despite high sensitivities and specificities, test turnaround times (TAT) are too long to facilitate clinical decision-making. Recent technological advancements in point-of-care (POC) testing, such as rapid antigen testing, have provided test results in less than 20 min yet exhibit low sensitivity [18–21].

More recently, POC-PCR has proved promising [22,23]. This technology exhibits high sensitivity and specificity compared to laboratory-PCR and can be performed at bedside without complex machinery or laboratory-trained personnel [24,25]. Physicians report higher satisfaction with the TAT of POC testing versus laboratory analyses [24]. Rapid POC-PCR also reduces hospital admissions and improves the appropriate use of antimicrobials in clinic and hospitalized patients [26]. In pediatric settings, POC-PCR decreases ancillary testing such as chest X-rays and urine analyses [27,28] and saves costs, especially when multiple viruses are tested simultaneously [27–30].

POC-PCR utility for ARIs in the ED is not yet defined. The primary study aim was to investigate the validity of POC-PCR in identifying RSV and influenza compared to laboratory-PCR, and explore whether POC-PCR can potentially improve ED triage through social distancing to prevent nosocomial transmission and reduce LOS. Secondarily, this study examined the potential of POC-PCR to improve appropriate antimicrobial treatment of ARIs.

2. Study design

We conducted a prospective observational cohort study in a university-affiliated tertiary care hospital ED between December 2016 and March 2017. During the study, a previously described real-time electronic alert identified potential participants based on the following triggers: 1) complaint of fever, cough, rhinorrhea, or sore throat or 2) PCR swab ordered and 3) chart recorded temperature > 38 °C. [31]. Trained research coordinators received these notifications and also screened the ED track board for eligible patients 7 days a week from 7am to 10 pm. Potential participants were eligible if they had ARI symptoms - measured fever at home or in ED > 38 °C and a cough, sore throat, or rhinorrhea with a duration of symptoms > 12 h and < 1 week; all ages were eligible. Those arriving by ambulance or who had already received oseltamivir for their current illness were excluded. After verifying eligibility, coordinators gained approval from the triage physician to approach the patient for consent; patients requiring urgent management were thus excluded.

After obtaining consent, the triage physician collected a nasopharyngeal swab sample which the coordinator tested immediately for influenza A, influenza B, and RSV using the Roche **cobas**® Influenza A/B Nucleic Acid test for use on the **cobas**® Liat system, a CLIA waived PCR assay. Our team used one system, located in the ED, according to the manufacturer's instructions for the duration of the study. Results were available in approximately 20 min. Coordinators also collected patient information including demographics, clinical history of current illness, and relevant past medical history using a standardized REDCap data form hosted at the Stanford Center for Clinical Informatics [32]. Physicians were blinded to POC-PCR results. After triage, patients were placed in one of three room types - private, cohort, or shared – a decision based on current room availability and attending physician's discretion. A cohort room, defined as a room in which all patients have respiratory symptoms, is recommended by the World Health Organization (WHO) as a method of limiting respiratory disease transmission [33]. A shared room is one in which patient placement occurs regardless of symptoms or diagnosis. A convenience subset of 38 patients also had a nasopharyngeal sample sent for laboratory-PCR analysis during the course of their ED treatment, ordered by their treating physician outside of this study. The procedures followed by this laboratory are

described by Rogan et al (2017) [34]. Briefly, ED nasopharyngeal swabs for viral testing are sent to an off-site facility where they are batch-processed then analyzed with the Respiratory Virus Panel XT8 (GenMark) for 9 viruses – influenza A and B, RSV, parainfluenza 1–4, metapneumovirus, rhinovirus, adenovirus, and coronavirus; TAT is 8–24 hrs.

Analyses were performed in SAS 9.3 (SAS Institute, Cary, NC). Basic descriptive statistics were used to characterize the population by demographic and clinical variables. Physician orders for oseltamivir and antibiotics were compared between POC-PCR positive and negative patients using parametric tests. Sensitivity and specificity of the POC-PCR were calculated using standard formulas assuming that laboratory-PCR is the gold standard.

Local Institutional Review Board approval was obtained prior to the beginning of the study and verbal consent was obtained from each participant or parental consent and minor assent if the participant was under 18 years of age. During the consent process, patients were informed that the POC-PCR device, while FDA-cleared, was not approved by the hospital for use in medical decision-making; therefore, the rapid test results would neither be shared with their physician nor impact their care.

3. Results

During the study period, 220 consecutive patients screened as eligible. After further screening 213 were eligible for enrollment and 119 consented to enrollment and nasopharyngeal swab for POC-PCR testing. Fig. 1, illustrates patient enrollment.

Among 119 participants, gender proportion was fair (50.4% female) and median age was 7.6 years (range 0.3–91). Most were Hispanic (55.5%), White (18.5%), or Asian/Pacific Islander (13.5%). More than half (56.3%) had received the seasonal flu vaccine. Approximately 10% of participants had a history of smoking. Additional sample characteristics are detailed in Table 1.

Of 119 participants, 52.9% (n = 63) had positive POC-PCR. Influenza (58.8%, n = 37) was more prevalent than RSV (41.3%, n = 26) with influenza A (42.9%, n = 27) more prevalent than influenza B (15.9%, n = 10). The median age of participants infected with influenza A (15.4 years, range 0.6–79.4) and influenza B (14.7 years, range 6.5–71.4) was similar (p = 0.972) while RSV infected a younger population (3.0 years, range 0.5–78.1, p = 0.008). One-quarter (25.4%, n = 17) of patients who received the seasonal flu vaccine were POC-PCR influenza positive. Of the 38 patients who also received the laboratory-PCR panel, 28.9% (n = 11) were positive for viruses other than influenza or RSV including two who were co-infected with one of these additional viruses and influenza A or RSV.

Table 2 displays room placement type and TAT for laboratory-PCR test results. Less than half of all participants were placed in a private room (32.8%) with the majority of POC-PCR positive patients (69.8%) placed in a shared room. Time to room placement varied widely for
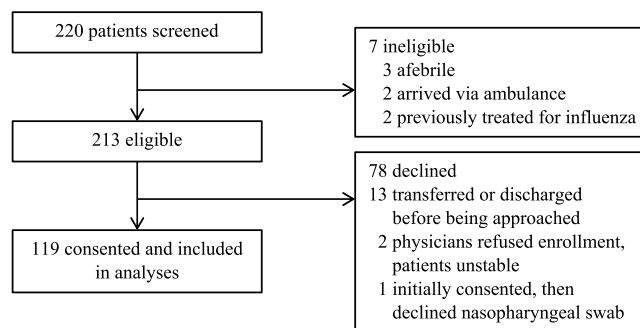

Fig. 1. Flow chart of the patient cohort presenting with ARI symptoms during the study period.

Table 1
Patient Characteristics.

Variable		N = 119 (%)[a]
Age	median (range), years	7.6 (0.3–91)
	0 to < 12mo	17 (14.3)
	12mo to < 6yrs	35 (29.4)
	6 yrs to < 18 yrs	24 (20.2)
	18 yrs to < 65 yrs	35 (29.4)
	65+ yrs	8 (6.7)
Sex	Male	59 (49.6)
	Female	60 (50.4)
Race	White	22 (18.5)
	Asian/Pacific Islander	16 (13.5)
	Hispanic	66 (55.5)
	Black	6 (5.0)
	Other	9 (7.6)
Flu vaccination status	Received	67 (56.3)
History of smoking	Never	106 (89.1)
	Yes, Past	11 (9.2)
	Yes, Present	2 (1.7)
POC-PCR results	Negative rapid test	56 (47.1)
	Positive rapid test	63 (52.9)
	Type:	27 (42.9)
	Influenza A	10 (15.9)
	Influenza B	26 (41.3)
	RSV	

[a] Percentages may not sum to 100% due to rounding.

Table 2
Social distancing and time to test result.

Room type	All patients (N = 119)	Positive POC-PCR (N = 63)
Private room, n (%)	39 (32.8)	19 (30.2)
Shared room, n (%)	80 (67.2)	44 (69.8)
Cohort room, n (%)	0 (0.0)	0 (0.0)
Time to test result	**Median (range)**	
ED arrival to room placement, mins	26 (1–200)	
Sample collection to laboratory-PCR result, mins	324 (138–1,332)	

patients in the triage area, with a median wait time of 18 min (range 1–200). The median duration from nasopharyngeal sample collection to laboratory-PCR result was 324 min (range 138–1,332) compared to the 20 min for POC-PCR. As shown in Table 3, in the 38 samples that were incidentally tested with both laboratory-PCR and POC-PCR, POC-PCR was highly sensitive (100.0%, 95% CI 80.5–100.0%) and specific (95.2%, 95% CI 76.2–99.9%) when compared to the laboratory-PCR panel.

Table 4 details oseltamivir and antibiotics ordered by physicians. Antibiotics were ordered for 18.5% (n = 22) of patients. Six (9.5%) patients were POC-PCR positive and received antibiotics; four were

Table 3
Comparison of POC-PCR to laboratory-PCR for detection of Influenza A/B and RSV.

POC-PCR	PCR[a]		Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
	No. Positive[b]	No. Negative[c]		
Positive	17	1	100.0% (80.5–100.0%)	95.2% (76.2–99.9%)
Negative	0	20		

[a] Laboratory-PCR was considered gold standard for comparison.
[b] 9 positive for influenza A, 3 for influenza B, and 5 for RSV.
[c] 1 false positive for laboratory-confirmed metapneumovirus – a virus for which the POC-PCR does not test, 4 other samples of laboratory-confirmed metapneumovirus were appropriately POC-PCR negative.

immunocompromised or had a chest x-ray suggestive of community-acquired pneumonia. Oseltamivir was ordered for 11 patients, all but one were POC-PCR positive for influenza A or B. Of the 27 influenza positive cases, 77.8% (n = 21) who were eligible to receive oseltamivir – those < 2 and > 65 years old, with history of pulmonary or cardio-vascular disease, or with an illness duration < 48 h – did not receive therapy. Eligibility was determined using criteria from the Centers for Disease Control and Prevention (CDC). [35]. A POC-PCR test could potentially modify treatment decisions and improve proper utilization of antimicrobial therapies in up to 19.3% of cases (n = 23 of 119).

4. Discussion

This is the first study evaluating the utility of rapid POC-PCR in ED triage during peak ARI season. In addition to excellent sensitivity and specificity compared to hospital-based laboratory testing, our results suggest that POC-PCR could drastically improve social distancing practices and curb nosocomial infections. Measures like cohorting patients by pathogen or symptoms can reduce the risk of nosocomial infections and is recommended by the WHO [36,33]. Over half of patients tested were virus positive, 84% of these with Influenza A or RSV. Nearly 70% of virus positive patients were placed in shared rooms with patients who did not have ARI symptoms. The ED has 57 beds, including 15 isolation rooms; the remaining rooms are shared between 2–6 pa-

tients (median 4). The bed selection process was not recorded per patient and is at the discretion of the triage physician, per level of acuity and room availability. Sharing rooms increases the likelihood of nosocomial infections, which can cause severe complications and increase morbidity among ED populations. EDs nationwide are overburdened and crowded especially during peak ARI seasons. Rapid virus detection could improve triage decisions and allow more efficient investigation, treatment, and disposition of patients.

In concordance with previous studies, our results indicate potentially suboptimal prescription of antimicrobials among respiratory illness patients [37]. Oseltamivir reduces complications, decreases symptom duration, and is recommended by the CDC, WHO, and Infectious Disease Society of America (IDSA) [38,35,39,40]. However, over three-fourths of eligible cases did not receive this therapy; similar under-utilization has been previously reported [14]. Appropriate delivery of oseltamivir is especially important in outbreak situations to limit virus transmission. Antiviral medications should be administered within 48 h of symptom onset [35] yet delays in patient presentation, lack of a reliable clinical diagnosis, and diagnostics with low sensitivity or long TATs make timely antiviral delivery difficult. Similarly, our study suggests that rapid test results could improve patient management by preventing unnecessary antibiotic administration. In 9% of cases, antibiotics were prescribed because no clear etiology was determined. These are likely patients for whom a viral source may have caused reconsideration of antibiotic therapy. Antibiotic resistance is a looming threat to public health. Taken together, POC-PCR could be another clinical intervention employed to improve antimicrobial

Table 4
Oseltamivir and Antibiotics Ordered by Physicians.

Antibiotic ordered		Virus Positive n = 63 (%)	Virus Negative n = 56 (%)	Oseltamivir ordered		Influenza Positive n = 37 (%)	Influenza Negative n = 82 (%)
No	97 (81.5)	57 (90.5)	40 (71.4)	No	108 (90.8)	27 (73.0)	81 (98.8)
Yes	22 (18.5)	6 (9.5)	16 (28.6)	Yes	11 (9.2)	10 (27.0)	1 (1.2)

stewardship.

POC testing utility is measured by both speed and reliability. For example, despite its speed, rapid antigen technology has not become clinically relevant due to its low sensitivity. In addition to providing rapid results, previous studies have shown POC-PCR to have high sensitivity (97.5%–100%) and specificity (100%) as compared to laboratory-PCR [25,41]. Although the subset of patients who received both POC-PCR and laboratory-PCR was small (N = 38 with 18 positive samples), the POC-PCR sensitivity and specificity reported here is consistent with previous studies. The false positive recorded in this study was laboratory-PCR positive for metapneumovirus – a virus for which the POC-PCR does not test. Importantly, three other cases also laboratory-PCR positive for metapneumovirus and one case PCR positive for both metapneumovirus and coronavirus were appropriately POC-PCR negative. In all, the POC-PCR detected over two-thirds of virus-positive patients as influenza and RSV prevalence far outweighed that of the 9 other viruses in the laboratory-PCR panel.

Given concerns about pandemic influenza and ED overcrowding especially during peak respiratory season, our study highlights the need for better risk recognition and infection control measures upon patient arrival to mitigate infection transmission. This aligns with WHO Guidelines which strongly recommend rapidly identify patients with ARIs at triage, the use of face masks, and spatial separation of ARI patients and non-ARI patients and moderately recommend cohorting patients to reduce ARI transmission to both health care workers and other patients [33].

ED LOS is affected by proximal factors, such as room availability, and distal factors, such as number of ancillary diagnostic tests and test results TAT. During peak influenza season, both the hospital and laboratory are burdened. Decreasing outlier TAT for laboratory tests decreases ED LOS [42]. Although our current study was not designed to evaluate rapid POC-PCR impact on ED LOS, our prior study suggests ED LOS reduction by 33 min if POC-PCR is performed during post-rooming ED evaluation, with potential for further reduction if POC-PCR is performed at triage [34]. Additional clinical impact includes reduced ancillary diagnostic testing and costs [30,27–29]. Future studies are needed to ascertain if decreasing ED LOS may reduce disease transmission by limiting contact time and to assess POC-PCR cost-effectiveness at triage during both peak and non-peak ARI season.

This was a prospective cohort study of CDC-defined ARI criteria. Our study enrollment hours were purposefully chosen during peak ED hours to examine POC-PCR utility in an efficient manner. It is possible that patients in off-study hours or those who declined enrollment were different than participants. A large number of patients refused to participate because the test results were not used to guide care. However, we found no difference in demographic and screening clinical characteristics among participants and non-participants. Additionally, our sample's median age was 7.6 years. Given that children shed higher virus titers than adults, the reported POC-PCR sensitivity could be falsely inflated.

POC-PCR utility and cost-effectiveness should also be examined during times when EDs are not burdened by viral respiratory illness, when utility may be reduced. Our study's generalizability is potentially handicapped by conduction in a single academic medical center - operating protocols and disease burden vary geographically and by hospital type. However, given the ARI burden during winter months, we propose that our results are likely generalizable during peak ARI season.

ARIs cause significant morbidity and mortality globally and the need for improved diagnostic methods is clear. Our data suggest that during peak ARI season, a rapid and accurate POC-PCR in ED triage could improve social distancing measures for patients who present with ARI symptoms, optimize antiviral and antibiotic prescription practices, and shorten patient dispositions. Further investigation of ED triage POC-PCR and its utility during non-peak ARI season should be conducted.

Authors' contributions

Courtney J. Pedersen: Formal analysis, Writing - Original draft preparation, Writing – Reviewing & Editing. **Daniel T. Rogan**: Methodology, Writing – Reviewing & Editing. **Samuel Yang**: Conceptualization, Methodology, Resources, Writing – Reviewing & Editing. **James V. Quinn**: Conceptualization, Methodology, Resources, Writing – Reviewing & Editing.

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Competing interests

Roche Molecular Systems had no contribution to data collection, data analysis, or writing of this manuscript.

Ethical approval

Stanford University Institutional Review Board approval was obtained prior to the beginning of the study and informed consent and assent (for those under 18) documents (English and Spanish) were approved for the study with a waiver of documentation (no signature or documentation of consent required). Participants were provided the appropriate consent documents and consent was obtained from every participant in the study prior to enrollment. For participants under the age of 18, parental consent and when possible, child assent was obtained.

Acknowledgements

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