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Identification of pathogens from the upper respiratory tract of adult emergency department patients at high risk for influenza complications in a pre-Sars-CoV-2 environment

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ABSTRACT

The emergence of SARS-CoV-2 and subsequent COVID-19 pandemic highlights the morbidity and potential disease severity caused by respiratory viruses. To elucidate pathogen prevalence, etiology of coinfections and URIs from symptomatic adult Emergency department patients in a pre-SARS-CoV-2 environment, we evaluated specimens from four geographically diverse Emergency departments in the United States from 2013-2014 utilizing ePlex RP RUO cartridges (Genmark Diagnostics). The overall positivity was 30.1% (241/799), with 6.6% (16/241) coinfections. Noninfluenza pathogens from most to least common were rhinovirus/enterovirus, coronavirus, human metapneumovirus and RSV, respectively. Broad differences in disease prevalence and pathogen distributions were observed across geographic regions; the site with the highest detection rate (for both mono and coinfections) demonstrated the greatest pathogen diversity. A variety of respiratory pathogens and geographic variations in disease prevalence and copathogen type were observed. Further research is required to evaluate the clinical relevance of these findings, especially considering the SARS-CoV-2 pandemic and related questions regarding SARS-CoV-2 disease severity and the presence of coinfections.

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1. Introduction

Acute upper respiratory tract infections (URIs) that are caused by a diverse range of viral and bacterial pathogens are one of the most common illnesses observed in humans (Berry et al., 2015). The morbidity, mortality, and economic burden associated with all types of URIs have been demonstrated significant, with influenza virus being the focus of identification as a causative pathogen for URIs in ambulatory clinical settings (Berry et al., 2015, Fendrick et al., 2003). The emergence of SARS-CoV-2, and the subsequent COVID-19 pandemic further highlights the impact and clinical consequences of respiratory virus infections (Lotfi and Rezaei, 2020). Traditional diagnostic testing methods for URIs including antigenic methods, cell culture, and serology have limitations with regard to sensitivity, specificity, and/or turn-around-times, rendering them relatively limited for routine use in ambulatory care settings (van Elden et al., 2002, Mahony, 2010, Mahony et al., 2011).

Recent technological advances have led to the development of multiplexed molecular amplification assays that are capable of detecting multiple common causes of URI pathogens from a single nasopharyngeal swab (NP). These methods have been shown to be rapid, highly sensitive, and specific (Zimmerman et al., 2015, Green et al., 2016, Chan et al., 2018, Babady et al., 2018), although uptake for routine practice has been relatively limited to research studies, due in part to lack of available treatment options for noninfluenza respiratory viruses and the added expense of employing multiplex molecular methods (Zimmerman et al., 2015). More recently several of these methods including the BioFire RP panels (BioFire Diagnostics, Salt Lake City; UT), ePlex RP panels (Genmark Diagnostics; Carlsbad, CA) and Verigene panels (Luminex; Austin, TX) have been FDA approved and are commonly used, permitting early rapid
identification of respiratory infections, and in some instances impacting the use of antivirals (Huang et al., 2018). These assays also afford new opportunities to better understand the etiologic distribution, prevalence of co-infections associated with URIs. Several recent studies employing multiplex technologies have been conducted with specific select populations, including patients with community-associated pneumonia (Zhou et al., 2019, Lim et al., 2019, Quah et al., 2018), hospitalized patients, (Zhou et al., 2019, Lim et al., 2019, Quah et al., 2018, Çağlayan Serin et al., 2014, Vissieux et al., 2017) military personnel (Ho et al., 2015, Lau et al., 2018, Tavakoli et al., 2019), relatively healthy outpatients (Green et al., 2016, Galanti et al., 2019, Kaku et al., 2018, Busson et al., 2019), and selected pediatrics cohorts (Assane et al., 2018, Kenmoe et al., 2016, Finiano et al., 2016).

To date, there is limited data regarding the etiology of noninfluenza, non-RSV, URI viral and bacterial pathogens in unselected ambulatory populations considered at high risk for respiratory and influenza virus related complications. Such research could be helpful not only for understanding the epidemiology and etiology of acute URIs, but also could help inform future research to address antibiotic stewardship. (Green et al., 2016, Kenmoe et al., 2016, Finiano et al., 2016)

Our aim was to contribute to the existing knowledge regarding the epidemiology and etiology of acute URIs in a pre-SARS-CoV-2 ED environment. We collected residual samples from a broad population of patients presenting to 4 geographically disparate EDs, who were considered to be at high-risk for influenza complications (Dugas et al., 2020, Kumar et al., 2009). These patients were tested for influenza (Dugas et al., 2020), and the residual specimens were subsequently tested for other pathogens utilizing the multiplex Genmark ePlex respiratory panel (RP) research use only (RUO) platform.

2. Methods

2.1. Study design

Adults at high risk for influenza complications according to the Centers for Disease Control and Prevention (CDC) definition (Dugas et al., 2020) reporting to 4 U.S. EDs (Johns Hopkins Hospital, Baltimore, MD (JHH), Truman Medical Center, Kansas City, MO (TMC), Maricopa Medical Center, Phoenix, AZ (MMC), and Olive View-UCLA Medical Center, Sylmar, CA (OMC)) were systematically screened by trained research coordinators, who assessed consecutive ED patients. All adult patients (age ≥18 years) were assessed for the presence of fever and/or respiratory symptoms, including documented fever (defined as >100.4 °F) measured in the ED and any of the following, self-reported symptoms beginning within the previous 7 days: subjective fever, cough, nasal congestion, sinus congestion, rhinorrhea, sore throat, or shortness of breath. A patient who reported 1 or more of the above complaints was further evaluated to determine whether he or she met at least 1 of the 2011 CDC high-risk for influenza complication criteria for antiviral medication (Dugas et al., 2020, Kumar et al., 2009). Those patients, who met the CDC criteria for influenza antiviral treatment, spoke English, had not had a diagnosis of influenza within the last 2 weeks, had not been previously enrolled, and had the ability for follow-up were offered participation in the study and signed written consent forms. The Institutional Review Boards at each site approved the study protocol.

2.2. Clinical specimen and data collection

NPs were collected by trained clinical coordinators. Specimens were transported immediately to the laboratory in viral transport media, aliquoted, and stored at –80 °C. Clinical data was collected as previously described (Dugas et al., 2020), and included the following variables: age, sex, ethnicity, race (African American vs White vs Other), body mass index, influenza vaccination status, private residence, current symptoms, medical history, ED physical exam, temperature, pulse, respiratory rate, systolic blood pressure, oxygen saturation, pharyngeal erythema, cervical lymphadenopathy, altered mental state or confusion, oxygen supplementation, hospital admission, hospital length of stay (days), ICU admission, ICU length of stay, diagnosis of pneumonia, and death.

2.3. Molecular detection of respiratory pathogens

NPs underwent testing for influenza virus utilizing Prodesse ProFlu + (Hologic, Bedford, MA) according to manufacturer instructions. A total of 41% (799/1941) had sufficient residual volumes to permit further testing with the ePlex RP RUO cartridge (Genmark Diagnostics; Carlsbad, CA). This multiplex assay detects: adenovirus (AdV); coronavirus HKU1, NL63, OC43, 229E, MERS (CoV); human metapneumovirus (hMPV); influenza A, A/H1N1, A/H1N1pdm 2009, A/H3N2 (IAV); influenza B (IBV), parainfluenza 1–4 (PIV), rhinovirus/enterovirus (RhV/EV), RSV A/B (RSV), Bordetella pertussis, Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae (M. pneumonia). Testing was performed per manufacturer's instructions. Briefly, 200 μL of NP was added to the specimen delivery device, vortexed for 10 seconds and added to the RP RUO cartridge. RP RUO cartridges were run on the ePlex platform. The complete assay time was 1 hour and 40 minutes.

2.4. Statistical analysis

Categorical variables were analyzed by Fisher’s exact using R software and GraphPad Prism v 8.0.1. and a P value of <0.05 was considered significant.

3. Results

3.1. Molecular detection of respiratory pathogens

The original cohort had influenza prevalence 9.4% (183/1941), with no subtype reported (Dugas et al., 2020). The ePlex results in this study, demonstrated that 30.1% (241/799) of patients tested positive for any respiratory pathogen, with 2% of the total specimens having co-infections (16/799) (Fig. 1A). The composition of different pathogens detected is summarized in Fig. 1B. RhV/EV was the most common pathogen detected (32.7% of the total detections: mono- or co-infections), followed by IAV (26.1%), CoV and hMPV (both 10.9%), and RSV (9.3%). Overall, 28.4% (69/241) of positives were infected with influenza (IAV or IBV). Less common pathogens were AdV (3.5%), PIV (3.1%), IBV (2.3%), and M. pneumonia (1.2%).

Sixteen patients had co-infections (32 detections total), the composition of which is shown in Fig. 1B and C. IAV (7/16, 43.8%), RhV/EV (7/16, 43.8%), and AdV (6/16, 37.5%) were the most frequently detected pathogens in individuals with coinfections. For individuals infected with AdV, co-infections (N = 6, 66.6%) were more common than monoinfections (N = 3, 33.3%), ratio of 2.0 (Fig. 1B).

3.2. Geographical analysis

The prevalence of pathogens at the 4 sites was compared (Fig. 2). The lowest rate of any pathogen detection was seen at JHH; 22.9% (60/262) of specimens positive (Fig. 2A). This was significantly different than those seen at MMC, 39.3% (59/150, P = 0.007, Fig. 2B), TMC 31.5% (53/168, P = 0.003, Fig. 2C), and OVM 31.5% (69/219, P = 0.04, Fig 2D). Co-infections were most commonly found at MMC: 5.3% of specimens compared to approximately 1% at other sites.

All respiratory pathogens detected were observed at each site, with the exception of M. pneumoniae (N = 2), which was only detected at MMC (Fig. 2G). While not statistically significant, other differences were observed in the composition of pathogens between sites (Fig. 2E-H). MMC had the greatest number of unique pathogens
3.3. Temporal analysis

Specimens were collected from November 2013 to April 2014, the traditional time period for influenza/respiratory virus season. Graphing pathogens with >20 total detections (CoV, hMPV, IAV, and RhV/EV) across the 4 sites, temporal differences at the sites were observed (Fig. 3). Trends in RhV/EV detection at all 4 sites were consistent over time. CoV, hMPV, and IAV showed similar trends at JHH, MMC, and OVM, but were distinct at TMC. TMC had an early IAV peak and later peaks of CoV and hMPV than the other sites.

3.4. Patient characteristics

Patient characteristics are described in Table 1. Briefly, a total of 799 specimens from 799 unique patients were analyzed. The range of ages was 18 to 93 years of age, median was 50 years and 60.6% (484/799) were females. 67.3% (538/799) had more than one condition of high-risk for influenza complication criteria, with the median being 2 conditions. Comparisons of patient demographics and outcomes with no detection, influenza detection, or other respiratory pathogen detections are shown in Table 1. While results were not statistically significant, there was a trend for a greater number of influenza-positive patients being admitted to the ICU and having radiographic diagnosis of pneumonia, compared to those with no pathogen or other pathogen.

4. Discussion

The recent emergence of SARS-CoV-2 (COVID-19) has demonstrated the importance of surveillance for noninfluenza respiratory viruses. Here we present descriptive findings from noninfluenza surveillance and how it can provide meaningful information regarding their composition and prevalence. Our goal was to add to the knowledge generated by other studies (Green et al., 2016, Zhou et al., 2019, Lim et al., 2019, Quah et al., 2018, Çağlayan Serin et al., 2014, Vissieux et al., 2017, Ho et al., 2015, Lau et al., 2018, Tavakoli et al., 2019, Galanti et al., 2019, Kaku et al., 2018, Busson et al., 2019, Assane et al., 2018, Kenmoe et al., 2016, Finianos et al., 2016) regarding viral etiologies associated with URIs aside from influenza viruses in a population of adults characterized as high-risk for influenza complications.

A few studies focusing on high-risk populations have employed multiplex molecular methods. For example, one study illustrated that there was a high incidence of complications related to noninfluenza respiratory viruses, and that disease severity was similar to influenza, indicating that surveillance of these viruses is important (Zhou et al., 2019). A large longitudinal retrospective study highlighted that picornaviruses, specifically RhV/EV, are potentially neglected as a
significant contributor to the development of disease severity and can lead to lower respiratory infections (Quah et al., 2018). Lastly, other studies utilizing multiplex molecular methods have highlighted the importance of coinfections (Ho et al., 2015), and diversity of non-influenza respiratory viruses. (Tavakoli et al., 2019).

Ho et al. (2015) found a substantially higher proportion of coinfections at 20.2% than our study did, but Ho et al., included surveillance of additional bacterial pathogens, including *S. pneumoniae* and *H. influenza* that likely contributed to the difference between studies. In this population of adults at high-risk for influenza complications, we identified a viral or bacterial respiratory pathogen etiology in 30.1% (241/799) of the total specimens with a coinfection detection rate of 6.6% (16/241). Overall, the pathogens identified, AdV, CoV, hMPV, IV, PIV, RhV/EV, RSV, and *M. pneumoniae*, are consistent with known causes of URIs, regardless of the specific population (Grief, 2013). We found that RhV/EV was the most common single pathogen detected in high-risk adult ED patients, and other studies have presented similar findings, albeit in military personnel (Lau et al., 2018, Tavakoli et al., 2019).

We found that AdV was more commonly associated with coinfections and this finding is supported by previous studies in military recruits (Ho et al., 2015) and a study in hospitalized children that suggested that AdV may play a larger role than previously thought in the development of more severe disease, such as bronchitis and pneumonia (Kenmoe et al., 2016). The pathogen detection rate and time of year for varied across the sites. The lowest detection rate was observed at JHH, while the highest detection (both mono- and coinfections) observed at MMC. MMC also had the greatest pathogen detection rate.

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**Table 1**

| Total | No detection | Influenza only | Other pathogens | Coinfections |
|-------|--------------|----------------|-----------------|--------------|
| N     | 799          | 558            | 66              | 159          | 16           |

**Demographics**

| Age   | 50 (18–93) | 51 (18–93) | 47 (19–80) | 50 (18–88) | 46 (28–62) |
| Gender | 484 (60.6%) | 332 (59.5%) | 38 (57.6%) | 104 (65.4%) | 10 (62.5%) |

**Ethnicity**

| Hispanic or Latino | 259 (32.7%) | 166 (29.7%) | 25 (37.9%) | 64 (40.3%) | 4 (25%) |
| Race | 348 (43.6%) | 254 (45.5%) | 27 (40.9%) | 59 (37.1%) | 8 (50.0%) |
| White | 199 (24.9%) | 144 (25.8%) | 11 (16.7%) | 39 (24.5%) | 5 (31.3%) |
| Asian | 10 (1.3%) | 7 (1.3%) | 0 (0%) | 2 (1.3%) | 1 (6.3%) |
| American Indian | 12 (1.3%) | 11 (2.0%) | 1 (1.5%) | 0 (0%) | 0 (0%) |
| Other | 224 (28.0%) | 137 (24.6%) | 27 (40.9%) | 58 (36.5%) | 2 (12.5%) |

**CDC high risk**

| Greater than 1 | 538 (67.3%) | 387 (69.4%) | 46 (69.7%) | 96 (60.4%) | 9 (56.3%) |

**Disease severity**

| Oxygen supplementation | 214 (26.8%) | 148 (26.5%) | 21 (31.8%) | 41 (25.8%) | 4 (25.0%) |
| Admitted | 348 (43.6%) | 269 (48.2%) | 27 (40.9%) | 48 (30.2%) | 4 (25.0%) |
| Hospital length of stay (d) | 3 (5–29) | 3 (3–17) | 2 (1–21) | 2.5 (5–29) | 1 (1–5) |
| ICU | 45 (13%) | 34 (12.6%) | 6 (22.2%) | 5 (10.4%) | 0 (0%) |
| ICU length of stay (d) | 3 (1–21) | 3.5 (1–13) | 6 (1–21) | 2 (2–3) | 0 (0–0) |
| Pneumonia | 158 (19.8%) | 107 (19.2%) | 15 (22.7%) | 31 (19.5%) | 5 (31.3%) |
| Death | 1 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) | 0 (0%) |

Values shown as N (%).
For length of stay = median (range).
diversity and was the only site where atypical bacteria were found. While the Rh/DEV proportion of pathogens was fairly consistent across the sites, the peak detections for pathogens varied based on time of year. TMC had an early peak of influenza activity, with shifted peak detections of CoV and hMPV observed as compared to the other three sites. Similar results, in terms of temporal variation have been observed in other studies and each of these studies (Ho et al., 2015, Busson et al., 2019, Kenmoe et al., 2016) illustrated the temporal nature of respiratory virus infections. Situational awareness from broad surveillance may impact patient management.

This study had several limitations. First, it was only conducted over a single season and the numbers of positive tests was too low to make major comparisons. Additionally, because the population had many underlying conditions, there were not many differences found in the clinical outcomes and many confounders exist. Larger scale studies would be needed to make major conclusions on the impact of multiplex methods. However, this study does provide a description of the variety of pathogens found in adults at high-risk of influenza infections who report with influenza symptoms to the ED.

The value and meaningfulness of applying multiplex molecular methods for respiratory viruses aside from influenza virus has been under debate, although there is a growing rationale for broader employment and new strategies have been suggested to mitigate potential barriers (Diaz-Decaro et al., 2018). Some studies utilizing point-of-care diagnostic tests for these specific organisms have shown value in terms of patient management, patient cohorting, droplet precautions, and appropriate antiviral therapy (Pedersen et al., 2018, Benirschke et al., 2019, Rahamat-Langendoen et al., 2019). Additionally, 2 relatively recent studies indicate the clinical impact of employing these methods, and illustrate they can be applied to antimicrobial stewardship, (Echavarría et al., 2018, Yang et al., 2020), while other studies have illustrated the value in differentiating the cause of illness (Green et al., 2016, Çağlayan Serin et al., 2014, Galanti et al., 2019, Kaku et al., 2018, Busson et al., 2019, Echavarría et al., 2018, Yang et al., 2020, Lai et al., in press). The importance of detecting coinfections has also been highlighted in a recent study from China, and the importance of detecting coinfections and differentiating respiratory virus etiologies beyond influenza is further emphasized by the emergence of SARS-CoV-2 (Echavarría et al., 2018, Yang et al., 2020, Lai et al., in press). A recent pilot analysis of NP samples (N = 320) collected at The Johns Hopkins Hospital from April 2020 to November 2020 found that 1.8% (6/320) of sample tested were coinfected (unpublished data). It should be noted that these coinfections were observed during a period where mask wearing and social distancing practices were state mandated. The SARS-CoV-2 pandemic has illustrated that broad surveillance of respiratory viruses should be considered critical for identifying changes in respiratory virus epidemiology and etiology, as well as mitigating the spread of emerging viruses.

Overall, the applicability, clinical value and value to surveillance efforts of employing multiplex molecular methods may be specific to certain populations, such adults at high-risk for influenza complications, or may be of more benefit when applied locally, to identify small outbreaks of specific viruses not routinely surveyed for, in specific locations.

Author contributions

Justin Hardick-manuscript preparation, sample analysis, data summarization; Kathryn Shaw-Saliba-manuscript preparation, data analysis, statistical analysis, table and figure preparation; Breana McBryde-clinical recruitment, inventory management, data analysis; Charlotte A Gaydos-co-investigator, manuscript preparation, consultation; Yu-Hsiang Hsieh-co-investigator, project conceptualization, statistical analysis; Richard Rothman-primary investigator, project conceptualization, manuscript preparation.

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