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VIROLOGY

Novel Use of Rapid Antigen Influenza Testing in the Outpatient Setting To Provide an Early Warning Sign of Influenza Activity in the Emergency Departments of an Integrated Health System

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ABSTRACT Seasonal influenza virus is associated with high morbidity and mortality especially in vulnerable patient populations. Here, we demonstrate the novel use of Sofia influenza A+B fluorescent immunoassay (FIA), a rapid antigen-based influenza point-of-care test (POCT), combined with Virena software for automatic deidentified tracking of influenza activity across the Los Angeles area and for predicting surges of influenza cases in the emergency department (ED). We divided outpatient clinics into 6 geographic zones and compared weekly influenza activity. In the outpatient setting, there were 1,666 and 274 influenza A and influenza B positives, respectively, across the 2018 to 2019 influenza season and 1,857 and 1,449 influenza A and influenza B positives, respectively, during the 2019 to 2020 influenza season, with zone-specific differences observed. Moreover, we found that a rapid increase in outpatient influenza was followed by an influx in influenza-positive cases in the ED, offering a 1- to 3-week warning sign for ED influx of triple or quadruple the number of influenza cases compared to the prior week. Sofia influenza A+B FIA allows for surveillance of real-time deidentified influenza activity. Tracking of such data may serve as a valuable region-specific influenza indicator and predictor to guide infection prevention measures in both the outpatient and hospital settings. High-impact interventions include designating areas for waiting rooms for influenza-like illnesses, altering staff scheduling in anticipation of surges, and securing sufficient personal protective equipment and antivirals during the height of influenza season.

KEYWORDS antigen testing, flu season, influenza, rapid testing

Influenza viruses are negative-stranded RNA viruses (1) that are responsible for an estimated 291,000 to 646,000 global deaths annually (2). The elderly population has one of the highest risks (2), accounting for 54 to 70% of hospitalizations and 71 to 85% of deaths (3). Other risk factors include asthma, cardiac conditions, and pneumonia (4). In the United States, 11.3 to 25.6 million health care visits and $2.0 to 5.8 billion in health care costs are results of annual seasonal influenza (5), with numbers likely to be underestimated (3). The U.S. Veterans Affairs population alone makes up an estimated 10,674 and 2,522 emergency department (ED) visits and hospitalizations, respectively, each year (6).

Influenza has well-documented dramatic impacts on ED visits, with younger patients presenting to the ED at higher rates while elderly patients are admitted more frequently (7). The ability to rapidly and accurately diagnose influenza infection is prudent, not only from a treatment perspective but also for infection prevention as the virus is highly transmissible (2). Infection prevention methods include patient isolation, use of personal protective equipment (PPE), requiring annual influenza vaccinations for em-

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ployees, and screening employees and visitors for signs of respiratory illness (1). Even with these precautions, during the peak of influenza season, drastic workforce reductions due to illness and use of nearly all available ventilators are not uncommon (1). During these influenza surges, there have been profound shortages in space and supply availability, particularly at pediatric EDs, as well as increases in length of stay, wait time to see a clinician, and number of patients leaving prior to ever seeing a clinician (8). The ability to best estimate when an influenza surge will occur would allow for additional preparations that are too costly or elaborate to be implemented throughout the influenza season. These measures could include sectioning off a portion of the ED for respiratory illnesses and employing non-ED physicians in the ED to prepare for staffing shortages and to decrease patient wait times, stockpiling antiviral medication and PPE, early vaccination of health care workers, and enacting more stringent visitor policies, strategies that have been shown to be effective in mitigating the impact of influenza pandemics (9).

Previous studies have used sentinel surveillance of influenza-like illness to define local epidemics (10), but currently there is a lag in data collection and inability to track confirmed influenza positivity in real-time across specific geographic areas that can accurately inform hospital systems of local community spread. To address this, we describe the use of Virena software to automatically transmit deidentified Sofia influenza A+B fluorescent immunoassay (FIA) (Quidel, San Diego, CA) results for influenza surveillance in the Los Angeles area community. Sofia influenza A+B FIA is a second-generation rapid antigen immunofluorescence-based lateral flow assay that uses a reading device, improving sensitivity from initial rapid antigen assays (11). Because this assay is Clinical Laboratory Improvement Amendments (CLIA) waived, it can be performed in clinics by nonlaboratory trained individuals, with the advantage of having a result within minutes while the patient is still in clinic (11). This is critical for administering effective antiviral therapy, which is most effective within the first 48 h of symptom onset (2, 12). Moreover, the use of rapid influenza testing has been shown to result in an estimated avoidance of 10.7% of hospitalizations (13), a 46.4% reduction of unnecessary antibiotic prescriptions (13), a decreased length of stay (14), and a lower number of additional tests performed (14).

Here, we describe the use of Sofia influenza A+B FIA in an outpatient setting to discern differences in influenza positivity across the Los Angeles area as well to evaluate whether outpatient influenza data could be used to predict influenza activity in the ED. A total of 54 University of California Los Angeles (UCLA)-affiliated clinics, 2 ED, and 2 hospitals participated in this study during the 2018 to 2019 and 2019 to 2020 influenza seasons. Due to the large geographic area covered by UCLA-affiliated clinics, the outpatient clinics were divided into 6 zones to allow for interarea comparisons. All outpatient clinics utilized the Sofia influenza A+B FIA with data wirelessly transmitted using Virena, while the hospital systems used PCR-based methodologies. To the best of our knowledge, this is the first study examining regional community level influenza spread using a point-of-care test (POCT) as well as the community POCT data to predict surges in influenza activity in the ED.

MATERIALS AND METHODS

Test locations and subjects. A total of 54 UCLA-affiliated outpatient clinics were included in this study (Fig. 1). Prior to beginning the study, the outpatient clinics were divided into geographic zones based on standard grouping of neighborhoods and zip code as follows: zone 1 (Brentwood, Santa Monica, Malibu, Pacific Palisades), zone 2 (West Los Angeles, Westwood, Beverly Hills, Century City, Marina Del Rey, Studio City, other neighborhoods within the City of Los Angeles), zone 3 (South Bay area including Manhattan Beach, Redondo Beach, Torrance, Rolling Hills Estates), zone 4 (Burbank, Glendale, Pasadena), zone 5 (Woodland Hills, Porter Ranch, Simi Valley, Santa Clarita), and zone 6 (Thousand Oaks, Ventura, Westlake Village, Calabasas). All clinics in zones 1 to 4 were located in Los Angeles County. A total of three clinics located in zone 5 and zone 6 were located in the neighboring Ventura County. Sofia influenza A+B FIA was used for all outpatient testing. This assay utilizes an automated digital reader to increase sensitivity and reduce variability between readers and produces results within 15 min (15). Virena technology automatically deidentified and wirelessly transmitted the influenza results (number of tests performed, number of positive tests, clinic location, date) to an online application where results could be downloaded remotely. This did not require any additional time or action from the nursing staff

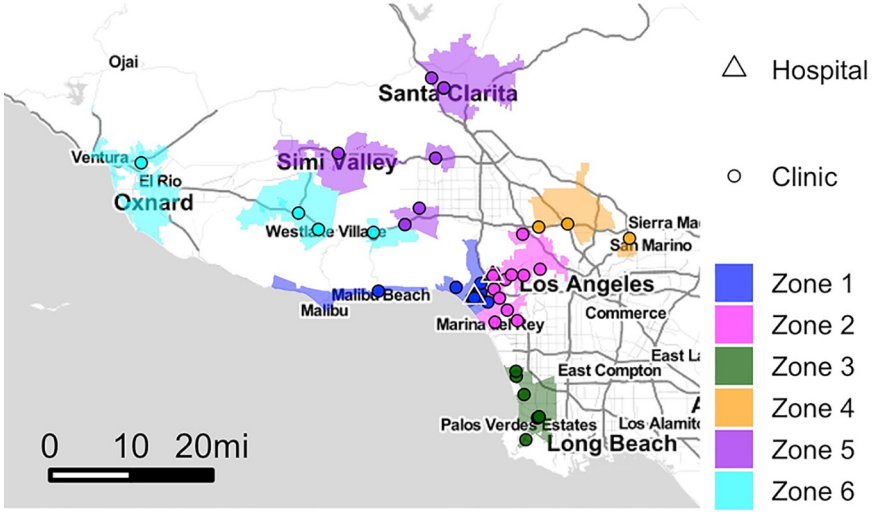

FIG 1 Map of participating UCLA-affiliated outpatient clinics and hospitals. Outpatient clinic locations are indicated by circles while the hospital locations are depicted using triangles. The neighborhoods where the clinics are located are shaded. The map was generated using R.

who were trained on the platform. For influenza testing in the ED, the following two UCLA hospitals participated: Ronald Reagan UCLA Medical Center (Los Angeles, CA) and UCLA Medical Center, Santa Monica (Santa Monica, CA). This study was exempt from UCLA institutional review board (IRB) review.

Influenza testing. Outpatient influenza testing was performed on nares swabs using the CLIA-waived Sofia influenza A+B FIA (Quidel, San Diego, CA, USA) assay following standard manufacturer protocols on the Sofia 2 platform in each clinic. Virena (Quidel, San Diego, CA, USA), a global wireless surveillance and remote data management device, then wirelessly transmitted the deidentified results from each clinic in real time to an online database that could be accessed by the research team. This allowed the data to be broken down by clinic location, date of test, and influenza result.

In the hospital setting, a choice of the following three PCR-based influenza assays was performed depending on the specific patient: cobas Liat influenza A/B assay (Roche Diagnostics, Indianapolis, IN, USA), ePlex respiratory pathogen panel (GenMark Diagnostics, Carlsbad, CA, USA), and Simplexa flu A/B & RSV direct assay (Focus Diagnostics, Cypress, CA, USA).

Influenza results were compiled weekly across the participating hospitals and outpatient clinics during the 2018 to 2019 (2 December 2018 to 20 April 2019; $n = 20$ weeks) and 2019 to 2020 (3 November 2019 to 14 March 2020; $n = 19$ weeks) influenza seasons. Influenza seasons were defined by the UCLA hospital system. To avoid the confounding effects of COVID-19 and implementation of school closures (16, 17), influenza data collection was terminated the week prior to the "shelter in place" order and subsequent reduction in outpatient clinic availability for the 2019 to 2020 influenza season.

Map generation and statistical analysis. The map of UCLA-affiliated clinics was generated using the ggmap package in R software. Prism 8 (GraphPad Software, San Diego, CA) was used for linear regression analysis.

RESULTS

Influenza in the outpatient setting. Influenza testing was tracked across the outpatient clinics (Fig. 1 and 2), with Table 1 showing the number of participating clinics in each zone and tests performed and the raw number and percentage positive for influenza A or B. Number and percentage of influenza-positive tests varied across outpatient clinic locations on a weekly basis (Fig. 2; see also Fig. S1 in the supplemental material). The average influenza A positivity across the 2018 to 2019 and 2019 to 2020 influenza seasons ranged from 16.95 to 25.83% and 12.63 to 18.40%. The 2018 to 2019 season exhibited a higher rate of positive influenza A than influenza B (Table 1; Fig. 2). With influenza B, the 2019 to 2020 season had a higher number of positive tests (range = 48 to 595) and overall percentage positivity (range = 8.19 to 18.52%) than the 2018 to 2019 season (range = 10 to 92 positive tests; 3.44 to 7.12% positivity) (Table 1; Fig. 2).

Outpatient influenza positivity predicts influxes of influenza cases in the emergency department. We sought to determine whether the early influenza strain in the outpatient setting could provide an early warning sign for ED influenza activity. While we compared each zone individually and together (see Table S1 in the supple-

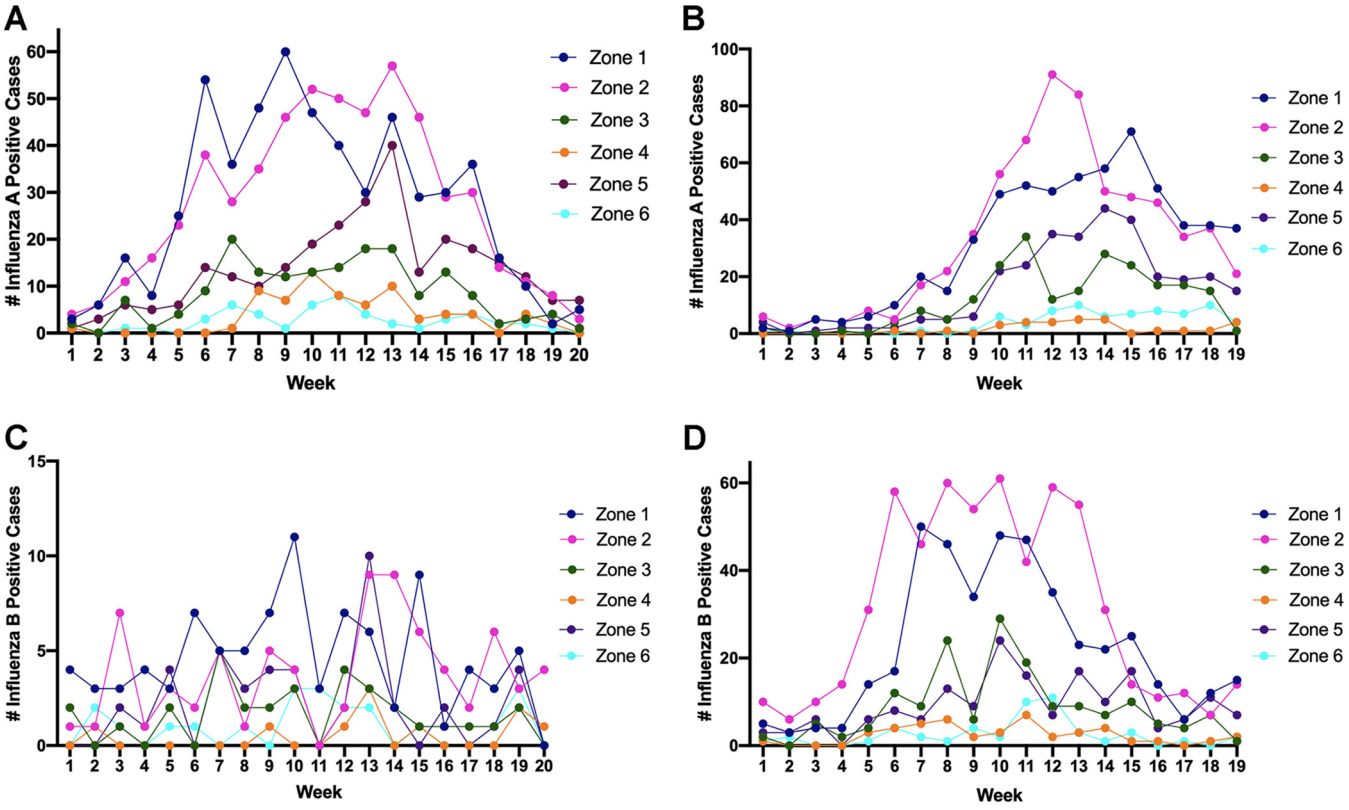

FIG 2 Rapid antigen influenza-positive tests across UCLA-affiliated outpatient clinics during the 2018 to 2019 and 2019 to 2020 influenza seasons. Influenza A-positive tests during the 2018 to 2019 (A) and 2019 to 2020 (B) influenza seasons. Influenza B-positive tests during 2018 to 2019 (C) and 2019 to 2020 (D) influenza seasons.

mental material), we specifically focused on zones 1 and 2. These zones had the highest overall number of influenza tests and were located in the same geographic zone as the hospitals. The number of positive influenza tests followed a similar trajectory as percentage positivity, with the early strain, influenza A for the 2018 to 2019 season and influenza B for the 2019 to 2020 season, increasing in both number of positive tests (Fig. 2) and percentage positivity (see Fig. S2 in the supplemental material). When focusing on the early influenza strain, there was a notable increase in the number of influenza cases in the outpatient setting prior to the increase in ED positive influenza cases (Fig. 3). To further investigate this, the slope of the best fit line (change in positive cases per week) was determined for the number of influenza cases in outpatient clinics

TABLE 1 Influenza testing across UCLA-affiliated outpatient clinics during the 2018 to 2019 and 2019 to 2020 influenza seasons

Location	Influenza season	No. of wks	No. of clinics	No. of tests performed	No. influenza A positive	Influenza A positivity (%)	No. influenza B positive	Influenza B positivity (%)	Overall positivity (%)
Zone 1	2018–2019	20	16	2,283	547	23.96	92	4.03	27.99
	2019–2020	19	15	3,570	595	16.67	424	11.88	28.54
Zone 2	2018–2019	20	12	2,145	554	25.83	75	3.50	29.32
	2019–2020	19	14	3,603	639	17.74	595	16.51	34.25
Zone 3	2018–2019	20	7	751	170	22.64	32	4.26	26.90
	2019–2020	19	7	1,190	219	18.40	164	13.78	32.18
Zone 4	2018–2019	20	3	291	72	24.74	10	3.44	28.18
	2019–2020	19	3	243	30	12.35	45	18.52	30.86
Zone 5	2018–2019	20	8	1,157	273	23.60	44	3.80	27.40
	2019–2020	19	8	1,669	300	17.97	173	10.37	28.34
Zone 6	2018–2019	20	3	295	50	16.95	21	7.12	24.07
	2019–2020	19	5	586	74	12.63	48	8.19	20.82
All zones	2018–2019	20	49	6,922	1,666	24.07	274	3.96	28.03
	2019–2020	19	52	10,861	1,857	17.10	1,449	13.34	30.44

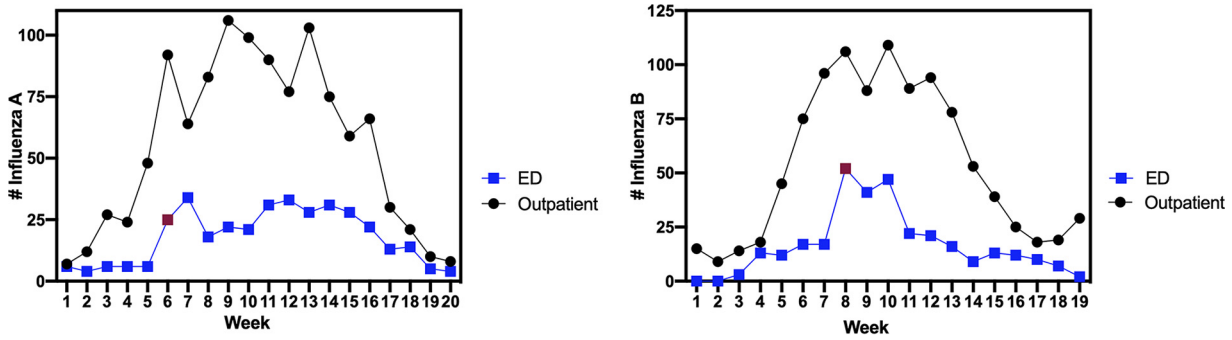

FIG 3 Influenza cases in the outpatient setting compared to influenza cases in the ED. Outpatient cases for zone 1 and zone 2 clinic locations were combined on a weekly basis. Positive influenza ED cases were combined for Santa Monica Hospital and Ronald Reagan Hospital. The number of cases of the early influenza strains are shown for influenza A from 2018 to 2019 (A) and influenza B from 2019 to 2020 (B). The red data point indicates the influx week in the ED.

the weeks leading up to the influx of influenza cases in the ED. ED influx was defined as a week with more than 20 cases and at least 2× the number of cases as that of the previous week in the ED. These higher parameters were selected to reduce noise from normal week-to-week variations that occur toward the beginning of influenza testing (Fig. 2). The following was calculated for both the outpatient setting and ED: (i) the slope for each week compared to that of the prior week, (ii) the overall slope from week 1 until the week prior to ED influx, and (iii) the slope of the ED influx week compared to that of the week just prior (Table 2). Compared to that of the week prior, the ED volume quadrupled and tripled in influenza cases during the influx week for the 2018 to 2019 (week 6) and 2019 to 2020 (week 8) influenza seasons, respectively (Table 2). When examining all weeks leading up to the ED influx, the early strain in the outpatient setting exhibited a steeper increase (overall slope of influenza A 2018 to 2019 = 9.40; overall slope of influenza B 2019 to 2020 = 14.50) compared to that of the ED (overall slope of influenza A 2018 to 2019 = 0.2; overall slope of influenza B 2019 to 2020 = 3.357) (Table 2). A slope of greater than 20 was considered to be a rapid increase in influenza positivity and indicated a warning while reducing effects of any random week to week fluctuations. On a week by week basis in the outpatient setting,

TABLE 2 Comparison of the slope of early influenza strain cases in the outpatient setting to corresponding influenza cases in the ED[a]

Influenza type (season) and wks	Slope	
	Outpatient	ED
Influenza A (2018 to 2019)		
1–2	5	−2
2–3	15	2
3–4	−3	0
4–5	**24**	0
5–6 (Influx wk)	44	19
Overall slope prior to influx	9.4	0.2
Influenza B (2019 to 2020)		
1–2	−6	0
2–3	5	3
3–4	4	10
4–5	**27**	−1
5–6	**30**	5
6–7	**21**	0
7–8 (Influx wk)	10	35
Overall slope prior to influx	14.5	3.357

[a]Linear regression analysis was performed on a weekly basis for the current and prior week, all weeks prior to influx, and the week prior to and week of ED influx. Weeks in the outpatient setting where slope was greater than 20 are bolded for influenza A during the 2018 to 2019 influenza season and influenza B during the 2019 to 2020 influenza season.

a slope of greater than 20 was observed 1 week prior to the ED influx for influenza A during the 2018 to 2019 season and 3 consecutive weeks prior to the ED influx for influenza B during the 2019 to 2020 season (Table 2), offering a 1- to 3-week warning sign for an upcoming ED influx.

DISCUSSION

Here, we describe the use of Virena software for tracking influenza cases in outpatient clinics across the Los Angeles area as well as serving as an early warning sign for ED influenza influxes during the 2018 to 2019 and 2019 to 2020 influenza seasons. The ability to predict influxes of influenza cases in the ED is critical for enacting effective infection prevention measures and ensuring adequate availability of supplies and staff. Increases in the number of positives of the early influenza strain in the outpatient setting in zone 1 and zone 2 preceded an influx of influenza cases in the ED. For the early strain, influenza A in 2018 to 2019 and influenza B in 2019 to 2020, the steep incline in the number of influenza cases in the outpatient setting preceded an influenza influx in the ED. The number of cases in the ED during the influx more than quadrupled (influenza A) or tripled (influenza B) the number of cases compared to that of the week prior for the 2018 to 2019 and 2019 to 2020 influenza seasons, respectively. Thus, the early influenza strain can be used to predict influx in the ED.

The UCLA Health System is uniquely positioned to track influenza cases across the expansive Los Angeles area. UCLA has two main hospitals, Ronald Reagan and Santa Monica Hospital, which are located in the heart of the city. However, the outpatient clinics are scattered around the Los Angeles area, and given the geographic breadth of the clinics, each area serves a different patient population, allowing for cross county comparisons. We noted differences in testing, percentage positive, and trends across the six geographic areas of the outpatient clinics, highlighting the unique trends in influenza activity in specific geographic areas. This area-specific information would likely be more beneficial for surge planning purposes at outpatient clinics rather than data based on the entirety of Los Angeles and Ventura County, where infection rates vary, as observed.

Sofia influenza A+B FIA, as demonstrated by our study, can be used as a method to track influenza activity throughout a large geographic area regardless of access to a hospital laboratory. The Sofia influenza A+B kit is user friendly and has a documented high specificity albeit a lower sensitivity, which varies with different influenza strains (18–20). This device can serve as an accessible device for stand-alone clinics, resource-limited areas, or those without high-complexity CLIA licensure to accurately and rapidly track influenza. This can translate into the ability to enact timely infection prevention methods, provide appropriate therapy, and ensure adequate supplies. In the case of clinics distributed across a large geographic area, influenza results could inform clinicians of influenza activity in neighboring areas, serving as a potential warning sign for an influx of patients and testing as demonstrated by our study.

Sofia influenza A+B FIA has previously been used as influenza surveillance in the primary care setting in Wisconsin (21). In that study, 19 clinics were enrolled across the state of Wisconsin, with 251 influenza A positives and 62 influenza B positives across the state (21). In contrast, our study saw 1,666 and 274 influenza A and influenza B positives, respectively, across the 2018 to 2019 influenza season and 1,857 and 1,449 influenza A and influenza B positives, respectively, during the 2019 to 2020 influenza season in the outpatient setting across 54 participating clinics. To the best of our knowledge, our study is the first to compare regional county-level outpatient rapid influenza cases to influenza-related ED visits and hospital admissions and use this as a metric for predicting ED influenza.

There are important limitations to consider. This study took place over two influenza seasons, two EDs, and one geographic area. The number of participating clinics in each zone varied, and there were gaps in geographic coverage as well as other hospital systems that serve the general Los Angeles patient population. As such, this study does not encompass all Los Angeles residents who may seek care at other outpatient clinics

due to insurance, location, availability, and other personal reasons. Thus, the algorithm should be evaluated and adjusted yearly as more clinics are added, but this study serves as a preliminary evaluation for the use of outpatient influenza data to serve as an early indicator for ED influenza. Because Virena automatically deidentifies the results, it is not possible to gather information regarding age, sex, gender, ethnicity, vaccination status, or symptoms, which could provide further valuable data for influenza prediction. Moreover, it is possible that a patient that tested positive in the outpatient clinic could present in the ED and be retested if symptoms worsened; in such a case, the outpatient data are still essential for predicting surges in the ED. Despite these limitations, the methodologies, specifically the use of Virena to allow real-time tracking of cases across the Los Angeles area and potential prediction capabilities, can be used virtually anywhere.

A future direction is to include additional respiratory viruses with available POCTs. Of particular interest is respiratory syncytial virus (RSV), which is a substantial cause of hospitalization and illness in the elderly and children less than 4 years of age (22). In fact, one study in England found that ED presentation of patients between the ages of 1 and 4 years served as a sensitive predictor for RSV seasonal activity (23). Therefore, using a POCT to determine distribution of RSV could also provide valuable information for hospital systems and clinics about the community spread and potential influx of pediatric RSV cases into the ED. Sofia offers a rapid antigen test for influenza A+B and RSV as one combined test, with studies demonstrating a sensitivity of 92.1 to 100% and a specificity of 91.8 to 98.6% for RSV (24, 25).

Taken together, we used Virena software to wirelessly transmit deidentified rapid influenza results from the outpatient setting to compare influenza activity across the Los Angeles area, where influenza activity varied across geographic zones. The relationship between the outpatient clinics, specifically zone 1 and zone 2, and the ED was particularly striking, with the number of influenza-positive cases in the outpatient setting offering a potential early warning sign for influenza cases in the ED. Thus, the use of outpatient influenza data may be useful in monitoring ED and inpatient influenza activity while providing an in-depth view of influenza in the community setting. With its ease of use, Sofia influenza A+B FIA and Virena are viable options for outpatient clinics to rapidly track influenza in their community while also reducing patient length of stay and unnecessary antibiotic use, using appropriate PPE, and administering antivirals promptly. We plan to use these data to guide decision-making processes at hospitals, such as to start restricting visitors when influenza activity in the outpatient setting has increased, implement temperature screenings, and schedule more staff in case of illness.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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