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Title: Distinct influenza surveillance networks and their agreement in recording regional influenza circulation: experience from Southeast Michigan

Short title: Comparing three flu networks of a single region

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Abstract:

Introduction: In southeast Michigan, active surveillance studies monitor influenza activity in hospital, ambulatory clinics, and community households. Across five respiratory seasons, we assessed the contribution of data from each of the three networks towards improving our overall understanding of influenza circulation.

Methods: All three networks used case definitions for acute respiratory illness (ARI) and molecularly tested for influenza from research-collected respiratory specimens. Age- and network-stratified epidemic curves were created for influenza A and B. We compared stratified epidemic curves by centering at seasonal midpoints.

Results: Across all seasons (2014/15 to 2018/19), epidemic curves from each of the three networks were comparable in terms of both timing and magnitude. Small discrepancies in epidemics recorded by each network support previous conclusions about broader characteristics of particular influenza seasons.

Conclusion: Influenza surveillance systems based in hospital, ambulatory clinic, and community household settings appear to provide largely similar information regarding regional epidemic activity. Together, multiple levels of influenza surveillance provide a detailed view of regional

influenza epidemics, but a single surveillance system—regardless of population subgroup monitored—appears to be sufficient in providing vital information regarding community influenza epidemics.

Introduction

Influenza surveillance is a vital component of effective public health practice during seasonal influenza epidemics, which can be associated with upwards of 35 million illnesses in the US each year.[1] During the "flu season," surveillance data are used to concurrently assess epidemic trajectory, determine the most at-risk populations, and provide interim guidance regarding intervention.[2–5] It is therefore indispensable that surveillance data are timely and valid reflections of the community's underlying influenza epidemic.

A wide range of surveillance systems are used to track seasonal influenza epidemics, based on everything from over-the-counter medication purchases, to school and workplace absenteeism, and even internet search results.[6–10] The most traditional and representative data are generated by active surveillance for confirmed influenza cases, though there are many methods for this as well.[11,12] In southeast Michigan, three prospective surveillance systems exist to actively capture influenza cases from regional households, ambulatory clinics, and tertiary care hospitals. While the primary purpose of each network is to assess seasonal vaccine effectiveness in these distinct populations, their data is also used to monitor epidemic trends in the region. To date, the surveillance data recorded by each of the three networks. A better understanding of how these systems agree or disagree epidemiologically has important implications regarding how the choice of surveillance population influences an overall interpretation of the regional influenza epidemic.

In this investigation, we consolidated surveillance data from each of these distinct networks across five different influenza seasons. For one, we were interested in whether epidemic curves of any of the three networks displayed unique temporal patterns or features (e.g., characteristic timing of an epidemic peak or initial detection of epidemic spread). Secondly, we assessed whether there were any consistent patterns or relationships between the three networks (e.g., activity in one network foreshadowing activity in the other two). Finally, we considered how seasonal patterns in network activity corroborated aligned with knowledge of past influenza season characteristics.

Methods

The Michigan Influenza Center at the University of Michigan operates three large studies which conduct prospective, active surveillance for influenza cases from hospitals, ambulatory clinics, and community-dwelling households in southeast Michigan (Table 1). Each network is designed to estimate vaccine effectiveness against a specific influenza outcome (community-acquired, medically-attended, and hospitalized disease). As a result, data captured by each of the three networks reflect the seasonal patterns of regional influenza circulation within three distinct source populations—each of which with unique characteristics like age, underlying health status, and experienced illness severity.

This work utilizes data from five respiratory seasons, during which all networks were active and operational in their current form, starting during the 2014/15 season and ending in 2018/19. Enrollment and sampling procedures for all three studies were approved by the University of Michigan Medical School IRB.

Household: The *Household Influenza Vaccine Evaluation* study (HIVE) is an ongoing, prospective cohort study of community households, the majority of which are in Washtenaw County in southeast Michigan (Figure 1).[13–16] While specific eligibility criteria changed over the course of the study, currently eligible households receive care from the Michigan Medicine healthcare system and have at least 3 members with at least one child <10 years old.[16] Participants are queried weekly about the occurrence of acute respiratory illness (ARI) in any household member. An ARI episode is defined as the presence of two or more age-specific symptoms of ARI, as described previously.[16] Following an illness, participants visit the study clinic where combined throat and nasal swabs (nasal swabs only for children <3 years) are collected by study staff.

Ambulatory: As part of the US Flu Vaccine Effectiveness Network, the *Michigan-Ford Influenza Vaccine Effectiveness* (MFIVE) study contributes data to annual estimates of influenza vaccine effectiveness in the ambulatory care setting.[17,18] Cases in ambulatory patients are identified from outpatient intake forms noting ARI symptoms and cough, with illness onset ≤7 days ago, and from individuals ≥6 months of age. If patients (or their legal guardians) agree to participate in the

study, combined throat and nasal swabs (nasal swabs only for children <3 years) are collected by study staff; participants (or their legal guardians) are asked to complete a demographic questionnaire. During study years considered in this analysis, a majority of clinics were located in Washtenaw County, while 3 clinics were located in neighboring Livingston and Wayne Counties (Figure 1).

Hospital: The *Hospitalized Adult Influenza Vaccine Effectiveness Network* (HAIVEN) monitors vaccine effectiveness against influenza-associated hospitalization in adults.[19–21] In this study, staff use hospital intake logs and admission notes to find eligible participants, defined as: adult inpatients (≥18 years old) who recently presented to the hospital (≤72 hours) with ARI symptoms, cough, and a reported illness onset ≤10 days ago. Similar to the ambulatory study, after enrollment and consent procedures, study staff collect a combined throat and nasal respiratory sample and complete a demographic questionnaire with the participant. Study recruitment occurs at the University of Michigan Hospital in Ann Arbor, Michigan (Figure 1).

Laboratory methods: Respiratory illness swabs collected from participants in all three surveillance networks were tested for influenza using reverse transcriptase polymerase chain reaction (RT-PCR). The Influenza Division of the US Centers for Disease Control and Prevention (CDC) provided all primers, probes, and lab protocol for each study; these were designed for detection of universal influenza A and B, as well as their respective subtypes and lineages. All tests were performed at the Michigan Influenza Center laboratory.

Seasonality: We included all influenza positive cases that had been prospectively collected in each of the three networks from the 2014/15 through 2018/19 season. Notably, while the household study has operated year-round starting October 1 of 2014, the ambulatory and hospital studies commence active surveillance at confirmation of regional influenza circulation each season, continue for at least 12 weeks, and may potentially end surveillance before complete termination of the epidemic in the community.

Epidemic comparisons: We created influenza epidemic curves for each network in each season. Curves were proportionally standardized as influenza cases reported each week divided by

the network's total cases recorded that season; these curves were created separately for influenza A (aggregated H1N1, H3N2, and undetermined subtype) and influenza B (aggregated Yamagata, Victoria, and undetermined lineage). Cases of influenza A and B codetection contributed to both influenzas A and B epidemic curves.

One method of comparison in this analysis was based on the time period each season during which each network recorded the middle 50% of its respective influenza cases that season (i.e., 25% to 75% of all influenza A and B cases). Secondly, we compared curves by centering each network's total influenza epidemic curve to the seasonal midpoint of the overall region. These seasonal epidemic midpoints were defined as the week at which 50% of all influenza cases that season had been detected across all three networks. Finally, we stratified epidemic curves by age of participant at illness onset. Ages were categorized into four groups—0 to 6 years, 7 to 18 years, 19 to 54 years, and 55 years plus.

Results

Case counts: Altogether, 13,028 ARI cases were recorded across the three networks between 2014/15 and 2018/19 in southeast Michigan (Table 2). Among these, 2,371 (18.2%) samples were RT-PCR-positive for either influenza A or B. Influenza A and influenza B codetection was recorded in 27 cases over this time period (1.1%)—25 in the ambulatory network and 2 in the hospital network. Across all seasons, samples were positive for influenza in 1,434 of 4,989 (28.7%) ambulatory cases, 393 of 2,276 (17.2%) of hospitalized cases, and 544 of 5,763 (9.4%) of household cases. This ranked order of percent positivity was consistent across seasons— the highest percent positivity was always recorded in the ambulatory setting, followed by the hospital, and then the household network (Table 2).

Circulating virus: In all but 2018/19, respiratory seasons were characterized by a single dominant influenza A subtype and B lineage. Figure 2 displays this phenomenon using aggregated data from all three networks, though the dominant strains remained consistent across study population when we stratified by network (data not shown). Three of five seasons were

characterized by a dominant A(H3N2) virus (2014/15, 2016/17, 2017/18), while in the 2015/16 season A(H1N1) predominated. The 2018/19 season displayed roughly equal proportions of A(H3N2) and A(H1N1) detections. For influenza B, B(Yamagata) was the dominant lineage in three surveillance seasons (2014/15, 2016/17, and 2017/18); there was a considerable mix of both influenza B lineages in 2015/16 and 2018/19.

Seasonality: Most ARI in the region generally occurred between January and April (Supplementary Figure 1). Seasonality of influenza was pronounced and captured similarly from year-to-year by each of the three networks (Figure 3). The influenza epidemic in all five seasons began with influenza A circulation, which tended to reach its midpoint in late February. Influenza B activity followed and generally reached its midpoint one to four weeks after the influenza A midpoint. The exception to this was in 2014/15, when influenza A activity was early and prolonged in all three networks, reaching its midpoint in mid-December—much earlier than the other seasons. We saw no evidence of any consistent sequence or patterning in the order of network activity; for example, no one network was persistently peaking prior to the others.

In each season, the middle 50% of each network's total influenza cases was detected over roughly the same interval, which generally occurred six weeks after initial epidemic circulation and lasted for around six weeks (represented by the colored horizontal lines in Figure 3). In all but the notably early season of 2014/15, the bulk of this six-week period happened during the month of February. In two seasons, 2017/18 and 2018/19, the hospital's middle 50% of all influenza cases lasted markedly longer than that of either the household or ambulatory networks.

Epidemic activity recorded by all three networks appeared broadly similar when evaluating curves centered at the community's epidemic midpoint for overall influenza each season (i.e., the week at which the combined total of household, ambulatory, and hospital cases reached 50% of all seasonal cases, Figure 4). In general, the beginning of each network's influenza activity was recorded about eight to 10 weeks in advance of the community midpoint. The exception to this was the 2014/15 season, when all three networks displayed nearly identical rates of sharp growth about five weeks in advance of the community midpoint (Figure 4A). The 2014/15 season also

displayed the longest epidemic decline, particularly in the household study, with influenza persistence noted for nearly five months after the calculated community midpoint. Regional epidemic patterns were also similar when stratified by age group across seasons (Figure 4B).

Discussion

Our study compared epidemic influenza data from three distinct surveillance networks operating within a single geographic region in the US. Analogues of HIVE, HAIVEN, and MFIVE exist in other parts of the US, but it is unusual to have three active surveillance platforms operating simultaneously within the same area.

Prior to this work, we suspected that influenza epidemic curves detected by each network would have distinguishing characteristics because of their unique surveillance populations. For instance, because more mild illnesses are detected in the household study, HIVE, compared with to the more severe cases in the HAIVEN hospital network, we anticipated differences in the timing and magnitude of when HIVE and HAIVEN detected regional influenza cases. Instead, we found that influenza epidemics in southeast Michigan were recorded similarly by each of the three networks across all five seasons. All three networks (i) captured comparable distributions of circulating influenza A subtypes and B lineages, (ii) reported both the peak and bulk of influenza activity at approximately the same week each season, and (iii) displayed a similar epidemic progression, represented by the shape of their epidemic curves.

Each of the three networks uses influenza surveillance as a means to an end; the primary purpose of each study is to gauge influenza vaccine effectiveness against different outcomes (community-acquired, medically-attended, and hospitalized disease).[16,20,22] Surveillance data from the household network has also been used to provide estimates and predictors of vaccine uptake, as well as influenza transmission parameters.[23,24] Therefore each individual network is necessary for a better understanding of influenza prevention in these three distinct settings.

Our results also attest to the unique information provided by each of the three surveillance systems. Despite the overall similarity of the regional epidemic curves produced by each of the three networks, our findings also highlight the idea that when data from the three systems is

considered as a whole, we are provided with a more holistic view of regional influenza epidemics. Below, we highlight three seasons in which data from all three networks helped to retrospectively explain characteristics of seasonal influenza, including vaccine effectiveness, disease severity, and circulating strains.

First, the 2014/15 season is notable in our results for its early activity and rapid escalation to peak. All three networks displayed markedly early activity and epidemic peaks. This matches national summaries of that season.[25] Our observed peak in southeast Michigan occurred about a week earlier than the reported national peak (week of December 27). The rapid escalation nationwide is likely due to the fact that the dominant A(H3N2) virus was antigenically distinct from its counterpart in the vaccine that year. Of all seasons assessed in our study, this season was associated with the lowest adjusted overall vaccine effectiveness. The CDC's final estimated vaccine effectiveness against influenza-associated ARI was 19% for all age groups and only 1% against the circulating A(H3N2) strain.[25,26] The considerable mismatch in vaccine strain and circulating strain may have been an important factor contributing to the rapid progression of the epidemic in southeast Michigan, much like the rest of the US. In the HIVE household network, around 70% of the study population reported vaccination in 2014/15, which was much higher than the 49.2% of the US population older than 6 months of age who were vaccinated.[27] Our results underscore the fact that influenza can still transmit rapidly in a population with high uptake of a poorly matched vaccine.

The 2014/15 season also attests to the importance of extending surveillance periods outside of pre-specified timeframes—a limitation of both the hospital and ambulatory networks. In 2014/15, the household network was the only system to capture the lingering influenza B transmission; this epidemic persistence was a notable feature of the CDC's seasonal summary that year.[25] Because surveillance is stopped at the designated end of the influenza epidemic for both ambulatory and hospital networks (determined during each season in collaboration with the CDC), they failed to capture the community outbreak of influenza B which lasted through early June. For

complete surveillance of the season's entire influenza epidemic, a less stringent "end-of-season" definition or an extended surveillance period would have been necessary.

Second, we point to the 2017/18 season, where influenza transmission was detected for a prolonged period of time in the hospital system and even accelerated to a secondary peak in late March (Figure 3). More than in any other season, the hospital system's epidemic in 2017/18 was more distinct than that of the household or ambulatory system. In particular, the middle 50% of all hospital cases was recorded over a period of 11 weeks (compared to the 5 weeks and 8 weeks of our household and ambulatory systems, respectively). Alongside this fact, 25% of all eligible ARI admissions in the hospital that season tested positive for influenza—considerably higher than any other season's percent positive value, which ranged from around 14% to 17% (Table 2). Both of these observations reflect the severity of the influenza season that year. Despite a well-matched vaccine and moderate effectiveness of 39% against all influenza, this season was indeed nationally notable for its dramatic illness severity.[28] Based on the CDC's standard method of categorizing the severity of seasonal influenza epidemics from 2003/04 onward, the 2017/18 season was the first season to classify as high severity across all age groups; influenza-associated hospitalization rates were the highest ever recorded through the national FluSurv-NET system.[29]

Finally, the 2018/19 season was notable for its recorded persistence of influenza circulation. Generally, in most seasons that we assessed, cases recorded in all three networks began to rise around 10 weeks in advance of the seasonal midpoint and then declined over a period of months. This influenza epidemic progression agrees with previous work.[4] The 2018/19 season does not follow this pattern, however. Instead, all three networks slowly grew to their peaks that year over the course of three months; CDC's annual summary corroborates this finding, which reported that the 2018/19 season was the longest epidemic of the past 10 years.[30] Nationally, outpatient visits for influenza-like illness were recorded above the national baseline for 21 consecutive weeks. As was observed in our southeast Michigan networks, this observation may have been due to a dual influenza A season, where a surge of influenza A(H1N1) in the early winter was followed by a subsequent wave of influenza A(H3N2). In this way, A(H3N2) replaced

a waning A(H1N1) season and maintained steady influenza transmission in a still-susceptible population (Supplementary Figure 2). Figure 1 reflects this dual-A season regionally, where 2018/19 was the only season with a non-dominant influenza A strain detected.

A reliable early warning sign of impending influenza epidemics would be indispensable for public health preparedness and resource allocation—particularly in the event of a novel pandemic strain.[31] Because research has established school as a driver of communicable disease spread and children as important introducers of virus to their households, we initially thought that a season's influenza activity would be first picked up by our household study.[32–38] This was not the case. While households reported ARI throughout the year (Supplementary Figure 1), there was no persistent early reporting of confirmed influenza in our household network (or the other two networks, for that matter). We were also interested in whether a particular age group would experience influenza activity before all others; in one past study, children experienced higher influenza risk before the community epidemic midpoint compared to older age groups.[39] After we stratified epidemic curves into four age groups, we found no evidence that influenza activity was occurring persistently earlier in children or any other age group (Figure 4B). This is not to say that children are not important purveyors of influenza transmission in a community. Instead, our regionally-focused data suggest that children did not serve as the proverbial "canaries in the coal mine" for community outbreaks during those five seasons.[40]

While considering data from all three systems together provided us with a more comprehensive view of the overall, regional epidemic our results show that epidemics detected by the three networks are largely comparable. Epidemic peaks, troughs, viruses detected, and epidemic duration appeared largely similar across all three networks in each season, regardless of seasonally circulating influenza types. This general agreement between networks should be considered a point of reassurance for local public health departments that generally do not have access to data from three distinct, prospective influenza surveillance networks. For real-time responsiveness, our results show that household-, clinic-, or hospital-based influenza surveillance

in a community can provide local public health experts with reliable information and could be used to guide meaningful response and preparedness efforts in a timely fashion.

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