

**Using Prospective Illness Surveillance Data to Quantify,
Characterize, and Mitigate the Risk of Childcare-Associated
Respiratory Disease**

by

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List of Abbreviations and Acronyms

AdV	Adenovirus
ARI	Acute Respiratory Illness
hBoV	Bocavirus
CDC	Centers for Disease Control and Prevention
Flu A	Influenza A
Flu B	Influenza B
HAIVEN study	Hospitalized Adult Influenza Vaccine Effectiveness Network
CoV	Coronavirus
HIVE study	Household Influenza Vaccine Effectiveness study
hMPV	Human metapneumovirus
RV	Rhinovirus
IRR	Incidence rate ratio
MFIVE study	Michigan Henry Ford Influenza Vaccine Effectiveness study
OR	Odds ratio
PIV	Parainfluenza virus
RSV	Respiratory Syncytial Virus
RT-PCR	Real-time Reverse Transcriptase Polymerase Chain Reaction
UM-SPH	University of Michigan School of Public Health
95% CI	95% confidence interval

Note: Throughout this dissertation the terms *childcare* and *daycare* are used interchangeably to describe the programs and settings that provide out-of-home, non-parental group care for children. We note that a variety of programs exist to serve this purpose, which can be better distinguished with different labels; for the sake of simplicity in this dissertation, they are all referred using the same two terms. *Homecare*, on the other hand, is used to describe children who are cared for at their home by a parent or guardian and not in group settings.

Abstract

Young children experience high rates of morbidity and mortality associated with acute respiratory illness (ARI) and are noted contributors of ARI risk to their households as well. It is also well established that ARI risk is higher in children who attend out-of-home childcare, compared to children cared for at home. Using prospective illness surveillance data collected regionally in southeast Michigan, the four Aims of this Dissertation add pertinent information to better quantify, characterize, and mitigate childcare-associated ARIs in both children and their families.

Aim 1 investigates the association between household childcare use and illness risk for family members. Adjusted mixed-effects Poisson regression models reveal no association between whether or not a young child concurrently attends childcare and the incidence rate of reported ARI in family members. Likewise, we find no evidence for any relevant effect modification of the association by household or individual characteristics. Contrary to our original hypothesis, out-of-home childcare does not appear to be linked to higher illness incidence in associated families; several reasons are offered to explain these null findings.

In Aim 2, we shift our focus to the children themselves. Previous research has shown that childcare attendees are ill more often than their counterparts cared for at home—we were interested in whether childcare-associated ARI was also characteristically different in terms of illness etiology and severity. In this analysis, we compare molecular test results from ARI episodes of children who do and do not attend childcare. Adjusted mixed-effects logistic regression models

reveal higher odds of both adenovirus and human metapneumovirus infection in childcare attendees, yet lower odds of rhinovirus infection; we found no evidence for a difference in illness severity. Furthermore, we statistically show that the pool of viruses causing childcare illness is significantly more diverse than that of homecare illnesses. Our results support the idea that childcare children are sick more than homecare children because they are exposed to a wider array of viruses early in life.

Aim 3 steps back to assess surveillance data in the context of the larger community. Three prospective illness surveillance networks of southeast Michigan operate in distinct population subgroups; we wanted to determine how different surveillance settings influenced observed epidemic patterns. Using influenza as our outcome of interest, we find that a household, ambulatory clinic, and hospital network all capture similar epidemic trends across six surveillance seasons. Annually, all three systems report comparable distributions of influenza A and B and record similar timing in epidemic activity start and peak activity. Broad agreement between network epidemic curves should be reassuring for local public health departments that may only rely on one system of active influenza surveillance.

Aim 4 focuses on the role of illness surveillance in childcare programs. Epidemiologic data serve as an important tool in timely outbreak intervention; we wanted to understand how illness surveillance in childcare could be more effectively leveraged to mitigate childcare disease outbreaks. Using results from a series of semi-structured focus groups among childcare providers, we find that providers are eager to use epidemiologic data in their programs to corroborate their subjective experiences and policy decisions. Our findings offer a framework by which surveillance data could be collected and packaged in a more beneficial way for providers and parents, and—ideally—help to prevent childcare associated illness outbreaks.

Chapter 1: Background and Rationale

The overarching goal of this Dissertation is to better understand childcare-associated acute respiratory illness (ARI) using prospective illness surveillance methods. The four research Aims investigate specific questions to better quantify, characterize, and mitigate childcare ARI. In this chapter, I present an overview of existing research as it relates to the development of each Aim.

Below, I first discuss background information on childhood respiratory disease, the role of children in propagating outbreaks, and the excess illness risk associated with childcare attendance that has been reported in earlier literature. These concepts underscore the rationale for Aims 1 and 2. I then provide a more detailed look at the prospective surveillance dataset that I use to complete this Dissertation. In turn, I introduce the final two aims, which are centered on the topic of illness surveillance. Aim 3 investigates how particular illness surveillance data influence the interpretation of a regional epidemic, and Aim 4 qualitatively assesses how illness surveillance data can be best leveraged in childcare programs to mitigate disease outbreaks. A summary of this Dissertation's Aims and corresponding hypotheses concludes the chapter.

1.1 – Childhood Respiratory Disease

Children have long been recognized as a population at particular risk for respiratory illness. ARIs are the most common cause of illness and mortality in children in the US under 5 years of age, irrespective of geographic location or family socioeconomic status, and this population bears

the disproportionate burden of seasonal respiratory infection in a community.¹⁻⁵ Household studies of respiratory illness report decreasing ARI incidence with age, with some reporting upwards of 12 ARI episodes per year in children <5y, compared to approximately 7 in older children and 3 in adults.⁶⁻⁸ The well-studied epidemiology of seasonal influenza is testament to this age-specific risk, where year after year children bear the brunt of the influenza epidemic and experience rates of morbidity and mortality comparable to those of society's most elderly groups.⁹⁻¹³ While much literature exists regarding influenza burden, we know that children are also more at risk than adults for a wide swath of respiratory pathogens including rhinovirus, parainfluenza virus, and adenovirus.^{8,14-17}

Children are also recognized as important sources of respiratory illness within households.¹⁸⁻²¹ Molecular test results from prospective surveillance studies as well as simulation model analyses note that respiratory viruses like rhinovirus^{22,23} and influenza^{11,24} are frequently transmitted from children to older family members in a household. ARI overall in children is associated with secondary cases among parents approximately one-third of the time.²⁵ Retrospective analyses of both vaccination campaigns and outbreak dynamics similarly attest to the importance of children in disease transmission. In the past, targeted influenza vaccination campaigns among young children have revealed household and community-wide reductions in illness incidence²⁶⁻²⁸ and a comparison of relative risk throughout a seasonal epidemic indicated that children experience more risk prior to the peak of a community influenza outbreak than older age groups, suggesting that they play a role in driving transmission early on.²⁹

There is also evidence that the age of the child modifies this role, with most studies suggesting that young children (i.e., <5y of age) pose a higher illness risk to their households than older children.^{6,20,30,31} Household index cases are more often a young child and when young

children bring in an illness into a household it is more likely to spread.³² A four-month long prospective cohort in Germany found that transmission events between age groups were twice as likely when the initial household case was a young child (1.7 events per household, 95% CI: 1.4 - 2.0) compared to when they were not (0.73 per household, 95% CI: 0.55 - 0.95).³³ Similarly, another study from Nepal estimates a secondary infection incidence rate 2.4 times higher when the index case is 0-4y compared to other age groups.³¹

1.2 – Childcare Attendance is a Risk Factor for Childhood Respiratory Illness

The initial increase in use of nonparental childcare[†] in the US—which now plays a role in lives of the majority of children nationwide—is attributed to societal changes following World War II, when more and more women in the US began seeking employment outside of the house.^{34,35} Today, the most recent US Bureau of Labor Statistics estimates indicate that both parents are employed in some capacity in 64.2% of families with children; this number has remained largely unchanged since the mid-1990s.³⁶ This proportion of families with multiple parents employed largely correlates with national prevalence of childcare usage. In 2005, the US Census Bureau estimated that nearly two-thirds of all US children <5 years attended childcare at some point in their lives and that nearly 30% of these children required at least 10 hours of non-parental childcare each week.³⁷

Given the high burden of respiratory disease in children, it is unsurprising that ARIs—including sinusitis, bronchitis, pneumonia, and associated otitis media—account for the most common types of illness reported in childcare settings as well.^{17,38-41} Alone, a young child has increased immunologic susceptibility to viral disease, and children in groups display habits which

[†] In this dissertation, the terms childcare and daycare are used interchangeably

heighten disease transmission (i.e., mouthing toys, microbe sharing interactions).^{42,43} Preventing illness outbreaks in childcare is also more difficult given that viruses isolated from childcare programs (including: rhinovirus, coronavirus, bocavirus, parainfluenza virus, respiratory syncytial virus, and influenza virus) often persist as asymptomatic infections.^{39,44,45} In a Norwegian study, among 343 nasopharyngeal samples taken from childcare attendees, 43% tested positive for at least one respiratory virus; of these cases, the majority of viruses were isolated from children with mild or no signs of respiratory tract infection.⁴⁰

One of the earliest papers to specifically investigate the respiratory disease risk associated with childcare attendance was performed by University of North Carolina physicians Loda, Glezen, and Clyde.³⁴ Following a 40-month prospective study on the incidence of ARI in a single group childcare setting (with a maximum enrollment of 39 children, ranging from 1 month to 5 years in age), the authors calculated approximately 8.4 ARI episodes per child-year.³⁴ This rate was similar to contemporary household or clinic-based studies of illness in children. The authors concluded, therefore, that, “group day care is safe medically for infants and that exclusion of sick children is unnecessary in a day care program with adequate space and staffing”. A few years later, a review of similar research noted only “moderate evidence” for increased rates of illness in childcare programs.⁴⁶

Since then, the consensus in childhood health research has shifted to recognize non-parental childcare as a significant, independent risk factor for excess respiratory tract infections in children.^{39,47-50} Cross-sectional studies have calculated statistically significant increased odds of pneumonia, common cold, croup, and >6 ARI episodes reported in the past year among children in childcare.⁵¹⁻⁵⁴ Similarly, prospective cohorts tracking parental reports of childhood illnesses have reported both higher rates of ARI and risk of hospitalization for ARI among childcare

children—particularly when an ARI episode was recently reported in a child’s daycare program.^{14,55–58} Despite the increased risk during early childhood years, there also seems to be a protective effect of childcare attendance on early elementary school illness.^{55,56,59} Research indicates that during early elementary school years, children who previously attended childcare experience a lower ARI risk than children who did not. Authors explain this protective effect using the idea of acquired immunity, whereby an increased risk of ARI during a child’s time in childcare leads to a strengthened immune system and relatively lower risk of ARI for a short time after.

There are some other interesting aspects of the overall childcare-illness association worth noting.⁶⁰ For one, child age seems to be an important effect modifier. Dales et al, for instance, reported that while childcare attendance doubled the risk of illness in children over 18 months, very young children (i.e., <3 months) experienced no significant increase in the number of illness episodes.⁶¹ This positive association between age and risk has been observed elsewhere.⁶² Family composition also appears to play a role. In the same Dales et al study, childcare attendance nearly tripled the risk of illness among children without siblings compared to children with siblings, where risk only increased by around 30%. Other studies also attest to this protective effect of older household siblings.^{53,63}

Effect modification by presence of siblings and participant age is reasonable. In contrast to a firstborn child or “only-child,” children with older siblings are likely being immunologically primed from birth and so their enrollment in childcare has less of an impact on their health. Similarly, children < 6 months may maintain sufficient levels of maternal antibodies and interact less with the other children due to their infancy, both of which help protect them from childcare-associated illness.

1.3 – Rationale for Aims 1 and 2

Two primary, unanswered questions emerged from our review of the literature; these now form the basis for Aims 1 and 2.

Aim 1 investigates the effect of childcare use on household illness risk. Given the importance of children in household disease transmission and the fact that childcare attendance puts children at an increased risk of illness, we were interested in the how childcare attendance may affect the illness risk of family members of childcare attendees. In other words, we wanted to know whether individuals living in households that relied on childcare—for one or more family children—experienced higher illness rates than individuals living in households that did not. To date, epidemiologic research has not thoroughly investigated this idea. The small number of papers which have looked into this idea do suggest a positive association between household childcare use and household illness risk. These studies, however, relied heavily on retrospective outcome ascertainment and the authors were right to point out the possibilities of recall bias, which may have affected their exposure groups differentially.^{18,53,64}

Our second question relates more to the nature of childcare illnesses. While illness rates are higher in childcare children compared to homecare children, Aim 2 assesses whether these illnesses are characteristically different from each other, with regards to viral etiology and severity. This has not been investigated previously within a single, underlying source population.

To complete both Aims 1 and 2, we use data from a longstanding community household study operated by the University of Michigan School of Public Health (UM-SPH).

1.4 – The *Household Influenza Vaccine Evaluation (HIVE)* Study

One of the longest contemporary studies of community respiratory disease in the United States is coordinated by UM-SPH. Based on renowned household studies of the mid-twentieth century, such as the Houston Family Study, Seattle Virus Watch, Cleveland Families study, and Tecumseh Study, the HIVE study is an ongoing, prospective cohort of community households in and around Ann Arbor, Michigan and has been operational since the fall of 2010.^{6,32,65,66} While the fundamental purpose remains estimation of seasonal influenza vaccine effectiveness in community settings, HIVE monitors community ARI year-round using molecular testing for a panel of non-influenza respiratory viruses. The study focuses on young families with children, boasts a large enrolled population (approximately 1200 participants per year, Table 1-1), and retains hundreds of the same households from year-to-year. As such, the HIVE study provides us with a robust source of illness data that can be used to investigate childcare-associated illness risk; further, the prospective methods of the study allow us to circumvent limitations of previous research in the field. Below, we summarize details of the study; the full data resource profile is available as reference number 67.⁶⁷

Starting in October of 2010, community households were eligible to enroll in the HIVE study if they (i) received care from the Michigan Medicine healthcare system, (ii) had a child <10y old at enrollment, and (iii) had at least 4 household members. In the 2014-15 season the household member restriction was relaxed to at least 3 individuals and in the 2016-17 season recruitment began to particularly focus on families with young children (i.e., <3y old) though this was not made an eligibility requirement.

At enrollment, households are asked to complete questionnaires regarding individual and household-level demographic characteristics. This information is updated annually for households that remain in the study. An example of data collected is provided in Table 1-2.

During participation, households are instructed to report all ARI episodes—defined by the presence of 2 or more age-dependent, predefined ARI symptoms. For participants 3y and older, these consist of cough, fever/feverishness, nasal congestion, sore throat, body aches, chills, and headache. For those <3y, these consist of more objective measures: cough, fever/feverishness, nasal congestion or runny nose, trouble breathing, fussiness or irritability, and decreased appetite. To avoid missed cases and encourage active participation, households are reminded each week via email to report any recent illness episodes. From the 2010-11 to 2013-14 season, ARI surveillance was constrained to the traditional influenza season—roughly considered the time between October 1 and April 30 of the following year. Starting in October 2014, HIVE began year-round surveillance. While participants can report multiple illnesses during any given season, new illness reported are not recorded if reported within 14 days of a previous illness report (unless new illness symptoms include fever/feverishness).

Following an ARI report, the participant is asked to schedule an illness visit within 7 days of their reported illness onset at either the UM-SPH clinic or—more recently—at the participant's home address. During the illness visit, nasal and throat swabs are collected from the sick individual (only nasal swabs are collected if the sample is taken from a participant <3y old or taken at the participant's home). Illness swabs collected are then tested by real-time reverse transcriptase polymerase chain reaction (RT-PCR) for influenza A and B (along with subtype and lineage, respectively), using primers and probes developed by the Centers for Disease Control and Prevention. Samples are also tested by RT-PCR against a panel of respiratory viruses, including

adenovirus (AdV); bocavirus (BoV); seasonal coronavirus (CoV) types HKU1, NL63, OC43, and 229E; human metapneumovirus (hMPV); parainfluenza virus (PIV) types 1 through 4; rhinovirus (RV); and respiratory syncytial virus (RSV).

Finally, participants are contacted approximately 1 week after their reported illness onset to complete a follow-up survey which collects information on experienced severity, including illness duration, contact with a healthcare provider (either over the phone or in person), medications used and/or prescribed, and hospitalization.

From year-to-year, the HIVE study boasts high levels of community participation. Across the study seasons of interest in this Dissertation, 85.3% to 100% of HIVE illness cases provided an illness sample while 57.2% to 94.8% provided answers to the follow-up survey (Table 1-1).

The HIVE Study is supported by the Centers for Disease Control and Prevention (U01 IP000170, U01 IP000474, U01 P001034) and the National Institute of Allergy and Infectious Diseases (R01 AI097150, R56 AI097150).

1.5 – Prospective Illness Surveillance

Infectious disease surveillance is a foundational component of public health, the ultimate goal of which is to quantify morbidity and mortality, identify potential risk factors associated with disease, and document epidemic spread.^{68,69} As Thacker, Berkelman, and Stroup write, surveillance is a “dynamic process” in that disease data is used in real-time to inform public health policy decisions and resource allocation. It is essential, therefore, that the surveillance data collected are both valid and timely. It is not feasible (nor desirable, given the ethical implications) to monitor disease in all parts of the population at all times. Thus, the goal of surveillance systems is to present an accurate-as-possible representation of community disease. A variety of methods

have been devised to accomplish this goal, involving an array of population subgroups, outcomes of interest, and outcome reporting methods or surveillance strategies.⁷⁰⁻⁷⁵

The HIVE study is not the only prospective illness surveillance system coordinated by UM-SPH. Two other longstanding networks operate in the same southeast Michigan region monitoring the same underlying community respiratory disease outbreaks. They are all distinguished by the particular populations in which they operate. In contrast to the community households of HIVE, the *Hospitalized Adult Influenza Vaccine Effectiveness Network* (HAIVEN) monitors ARI in hospitalized populations while the *Michigan-Henry Ford Influenza Vaccine Effectiveness* study (MFIVE) records ARI in ambulatory clinics. The fundamental intention of each of these networks is to monitor seasonal influenza and determine vaccine effectiveness each year; they each are in operation because analyses of their data offer unique insights into their respective subpopulations (i.e., household, clinic, or hospital). These three networks have been used extensively in research to investigate influenza topics ranging from vaccine effectiveness to risk factors associated with disease severity.^{65,66,76-78} As such, they are critically important data sources for these retrospective analyses.

We also note that prospective, community illness surveillance serves as an important tool for real-time intervention and public health preparedness. These types of networks often rely on syndromic surveillance or other proxies of illness to optimize the timeliness of the data, which public health experts and other community stakeholders can monitor for concerning trends. Frequently, such networks operate in congregate group settings where rapid outbreak response is essential.^{70,71,79,80} Certainly, the ongoing COVID-19 pandemic has familiarized the public with this type of real-time surveillance data via online dashboards, which are being used to gauge the risk of transmission in specific regions. However, illness surveillance networks continue to

generally follow a traditional unidirectional paradigm, whereby information flows from public reports to expert analysis, with little information returning to the public outside of academic publications or press releases.

1.6 – Rationale for Aims 3 and 4

HAIVEN and MFIVE lack sufficient data on childcare use and childhood illness necessary to answer Aims 1 and 2. We used HIVE data, therefore, but during our analyses of household data we became interested in whether the hospital and ambulatory networks (which operate in the same region and during the same seasons) differentially captured past ARI epidemics. Comparison of epidemic curves captured by these three networks would offer important public health considerations regarding resource allocation and preparedness, and be novel in the field. We are unaware of anywhere else with multiple, established surveillance programs monitoring seasonal respiratory disease in a single region in real time; these networks provide a unique opportunity to investigate the consistency of surveillance networks. Aim 3, therefore, compares and contrasts the surveillance patterns from the three UM-SPH surveillance network across multiple seasons. As each system is designed to study influenza vaccine effectiveness, RT-PCR confirmed influenza is the shared outcome between the three networks and so, influenza case counts were used as our outcome in this analysis (not all respiratory pathogens tested for in the HIVE study are assessed in MFIVE or HAIVEN networks). We wanted to understand (i) how knowledge of surveillance data from all three networks improved our overall understanding of the regional influenza epidemics and also (ii) whether past influenza epidemics were captured in characteristic ways by a particular surveillance network.

Aim 4 remains in the topic of prospective illness surveillance, but refocuses to a childcare-specific population. In the childcare field, illness surveillance data are particularly relevant to the community, where the staff's ability to quickly react to emerging outbreaks is crucial. Real-time illness surveillance data are essential for prompt recognition of disease outbreaks and timely intervention to prevent further illness spread.⁸¹ Recently, an online childcare illness surveillance network called MCRISP was established in 2013 to monitor infectious disease outbreaks in Washtenaw County, Michigan. To date, however, MCRISP data have mostly been used for public health and academic research and has not been returned to the childcare providers. We were interested in how a system like MCRISP might be better leveraged by the childcare centers as a tool to prevent illness in childcare programs. Aim 4, a qualitative analysis, investigates how surveillance data collected by a regional childcare illness surveillance system might be tailored to further benefit childcare providers and help to reduce childhood illness transmission.

Specific Aims and Hypotheses

Collectively, this dissertation uses four primary research Aims to better quantify, characterize, and ideally mitigate respiratory illness in childcare. These Aims and their primary hypotheses are outlined below:

Aim 1: Quantify the reported acute respiratory illness (ARI) incidence associated with living in the same house as a child who attends childcare.

Hypothesis 1: Due to increased disease risk associated with childcare attendance in children, we will see higher incidence rates of reported ARI among household members that live with at least one family member who attends out-of-home childcare, compared to those that do not.

Aim 2: Characterize respiratory illnesses of children who attend childcare, comparing and contrasting with children who are cared for at home, with regards to particular viruses detected, the risk of viral codetection, and illness severity.

Hypothesis 2: Due to the crowded nature of childcare programs and germ-sharing behavior of children (which puts children at risk of infection, but strengthens their immune systems over time), childcare attendees will experience illnesses that are caused by a different distribution of viruses, have higher risk of viral codetection, and be associated with less severe illness than homecare children.

Aim 3: Compare and contrast seasonal influenza epidemics detected by three active, prospective influenza surveillance networks that operate within the same geographic region, but cover distinct household, ambulatory, and hospital populations.

Hypothesis 3: Due to differential case ascertainment methods, cases detected by each network are associated with differing levels of illness severity (and underlying population), therefore epidemic curves produced by each network will have distinguishing characteristics in timing and magnitude.

Aim 4: Using ground-up qualitative research, determine the ways in which epidemiologic data from a local childcare-based illness surveillance network can be leveraged by childcare providers to better understand (and ideally mitigate) childhood illness in their programs.

Hypothesis 4: Childcare providers will be receptive to summarized illness data and have ideas on how to best use this information to bolster illness prevention strategies in their own programs.

Table 1-1: Overview of HIVE population throughout six relevant seasons

	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18
Surveillance start	October 1	October 1	October 1	July 1	July 1	July 1
Surveillance stop	April 30	April 30	June 30	June 30	June 30	June 30
Number of individuals	1426	1049	1431	996	896	1192
Number of children ≤ 18 years	838	620	865	605	529	692
Number of childcare-aged children (approximately ≤ 5y)	201	115	183	89	112	214
Number of households	321	232	340	227	209	294
ARI episodes reported from all participants	1227	706	1566	1119	894	1374
ARI episodes with sample collected, N (%)	1133 (92.3)	676 (95.8)	1566 (100)	1119 (100)	851 (95.2)	1172 (85.3)
ARI episodes with follow-up completed, N (%)	702 (57.2)	664 (94.1)	1484 (94.8)	1022 (91.3)	779 (87.1)	1050 (76.4)

ARI = acute respiratory illness

HIVE = Household Influenza Vaccine Evaluation study

Table 1-2: Example data collected by HIVE study

Data	Variable/Question	Possible Answer	Variable Format
Annually-updated demographics	Date of birth	09/08/1978	Date
	Race	Asian, Black, White, Other	Character
	During the upcoming year, will _____ work or attend school or daycare?	Daycare	Character
	High risk health conditions	Yes/No	Binary
	Overall health	60	Scale from 0-100 (100=best)
	Number of children in household	2	Integer
	Number of adults in household	2	Integer
	Social subjective position	6	Scale from 1-9 (9=best off)
	...		
Illness report	Illness onset date	03/18/2017	Date
	Symptoms experienced at illness onset	Cough, fever, chills, sore throat, etc.	Binary (present or absent)
	Health on worst day of illness so far	70	Scale from 0-100 (100=best health)
	...		
RT-PCR result	Influenza virus	A, B, A(H1N1), A(H3N2), B(Victoria), B(Yamagata)	Binary (detected or not)
	Non-influenza virus	Adenovirus, rhinovirus, parainfluenza virus, coronavirus, etc.	Binary (detected or not)
	...		
Illness severity follow-up survey	Contact with healthcare provider (in-person/phone)	Yes	Binary (yes or no)
	Admitted as an outpatient for illness	No	Binary (yes or no)
	Admitted to hospital for illness	No	Binary (yes or no)
	Date that illness resolved	03/28/2017	Date
	...		

The above table is not exhaustive and does not represent all variables collected by HIVE study.

Chapter 2: Seasonality and Incidence of Respiratory Illness in Household Members Living with Children Who Do and Do Not Attend Childcare

2.1 – Introduction

Compared to other family members, children are not only more at risk for illness but also more often the index case in household transmission chains. This means that households with children are more at risk for respiratory illness than households without.^{21,82,83} For instance, in a year-long household study with weekly active sampling of family members, not only did ARI risk decrease with age (including cases of rhinovirus, coronavirus, bocavirus, and influenza infection), but the index cases responsible for both inter- and intra-household transmission were always children.²³ Research also indicates that out-of-home childcare is an established risk factor for respiratory disease in young children.^{14,39,41,49,84,85} Recent prospective cohorts and cross-sectional studies have indicated that childcare attendance is associated with increased risk of ARI, including significantly increased odds of pneumonia (OR=1.79), common cold (OR=1.98), croup (OR=1.38), and >6 colds reported in the past year (OR=2.57) compared to children who did not attend childcare.^{51,52,55,56}

We were interested in the extent to which these two established concepts in childhood ARI research interact with each other. Given that children put a household at higher risk for ARI and the fact that children who attend childcare are at higher illness risk themselves, we hypothesized that among families with young children, households that use childcare experience a higher illness

risk compared to households that do not. A few past studies have investigated this idea and suggested that household members do indeed experience a higher illness risk when they live alongside a child who attends childcare.^{18,53,86} Just as the authors of these past papers do, we note that methodologies used in past research were susceptible to issues of outcome ascertainment and recall bias; data available at UM-SPH provided us with an opportunity to circumvent these past limitations.

Using six seasons worth of data from a prospective household surveillance study that focuses on families with young children, we compared the incidence rate of respiratory illness reports between households that report childcare use and those that do not. We also investigated whether particular household and individual characteristics acted as effect modifiers on the association of interest.

2.2 – Methods

Study Population: The *Household Influenza Vaccine Evaluation* (HIVE) study is an ongoing, prospective study used to estimate seasonal influenza vaccine effectiveness in community households. HIVE methodology has been described in detail in Chapter 1 and in a published data resource profile.⁶⁷

Eligible participants for this study were those that (i) lived in a household with at least one child of childcare age and (ii) were older than childcare age themselves. Being of childcare age was determined each year based on a statewide date cut-off for kindergarten eligibility. Michigan law states that children must be at least 5 years of age by the predetermined date to enroll in kindergarten; between the 2012-13 and 2015-16 school year, the Michigan cut-off date for kindergarten enrollment was progressively moved back by one month from December 1 to

September 1. Each study year, children too young to be enrolled in kindergarten based on that season's date cut-off were considered to be of "childcare age".

Between the 2012-13 and 2017-18 HIVE seasons, 637 unique households were enrolled in the study, representing 2688 unique individuals. Of this, 362 households contained at least one child of childcare age. Childcare-aged children were then subsequently removed from the analysis population (N=479), leaving 1068 HIVE participants. Data from this final group included over 1600 person-years of surveillance, with a total of 1936 ARI episodes reported (Table 2-1).

Study variables: The study's primary exposure, household childcare use, was defined based on annual data for whether or not a childcare-aged family member was expected to attend childcare during the upcoming year. The exact wording of the question asked to HIVE participants was, "During the upcoming year, will [*participant name*] work or attend school or daycare?" If anyone in the household was reported to be attending daycare during the upcoming year, the household was categorized as a childcare household. The exposure was operationalized as both binary (daycare use, yes/no) and ordinal (0/1/2+ children attending daycare).

The study's primary outcome was the count of symptom-defined ARI episodes aggregated by season at the individual level. Surveillance for ARI was conducted between October 1 and April 30 through the 2013-14 season; in October of 2014, the HIVE study transitioned to year-round surveillance. During each period of surveillance, participants were instructed to report all episodes of from anyone in the household. To avoid missed cases and encourage active participation, households were reminded each week via email to report any recent illness episodes.

Study covariates were adopted from household adult answers to family and participant demographic forms, which were collected at enrollment and updated annually during each year of continued participation thereafter. These forms included questions about underlying health

conditions, education, and employment. HIVE also recorded a household value for subjective social position (SSP), which asks the family to “place their household on a rung of a 9-step ladder” where 1 represents *worst-off* and 9 *best-off*, in terms of household wealth, employment, and respect. This variable served as a proxy for household socioeconomic status in our study; validation work notes that the ladder question displays adequate test-retest reliability in a large, multiethnic nationally representative sample of the US.⁸⁷

Participant age was also categorized into four distinct age groups (4-5y, 6-11y, 12-17y, and ≥ 18 y) based on traditional age groups—preschool, elementary school, teenage, adult. We note that the 4-5y age group reflects all HIVE children enrolled in the study that year who had turned the eligible age of 5y by the date cut-off for kindergarten in Michigan. During this study period, the HIVE study enrolled very few community members over the age of 50y.

Statistical methods: HIVE demographic variables were updated annually, and so we compared characteristics of both households and individuals based on answers provided at the initial enrollment. Chi-square tests were used to compare categorical variables. Non-parametric Kruskal-Wallis tests were used to assess continuous variables because these variables each deviated from a normal distribution based on QQ plots and the Shapiro-Wilk test for normality.

We first assessed seasonality of illness in childcare homes compared to non-childcare homes. A multilevel logistic regression model was used to assess the association between household childcare use and the likelihood of an illness being reported during one month compared to all others. In other words, twelve models were run, which varied the outcome of interest—binary month of onset (i.e., September, yes/no). This model was adjusted for surveillance year, categorical age of individual, number of household children, and average age of household children; a random

effect term for household was also included to account for any potentially unexplained correlation or dependency in ARI reports from the same family over time.

A multilevel Poisson regression model was used to calculate the adjusted association between ARI incidence rate and household childcare use (Model A). This model accounted for the fact that not everyone was under surveillance for the same amount of time by including an offset term for surveillance time at risk. Time at risk was calculated for each individual based on official start and stop dates for study observation each year (Table 2-1); no risk time was contributed for 7 days following every ARI episode reported. This model was adjusted for categorical age of individual, average age of children in household, and total number of children in household. Similar to the logistic model, a random effect term for household was included to account for unexplained correlation in ARI reports from the same family over time. We additionally operationalized the exposure as ordinal instead of binary (i.e., 0, 1, or 2+ childcare children; Model B) to assess a potential dose-response relationship.

To investigate potential effect modification, interaction terms were added to Model A; these related to household SSP, number of household children, whether or not all household adults worked, and age of the individual. Effect modification was also assessed using Model A stratified to data subsets based on levels of those potential effect modifiers. Finally, a model was designed to account for differential illness risk during the school year by consolidating days at risk to either summer or school periods of surveillance (June 1 to August 31 or September 1 to May 30, respectively; Model C).

R (R Foundation for Statistical Computing; Vienna, Austria; version 3.6) was used to execute all statistical analyses and figures.

2.3 – Results

Eligible population: Across study years, overall incidence of ARI reports fluctuated between 2.7 to 4.0 cases per 1000 person-days (approximately 1.0 to 1.5 reports per person-year; Table 2-1). Nearly three-quarters of households each season reported childcare use, on average. Rhinovirus (N=455 total detections), coronaviruses (N=265), influenza A (N=127), parainfluenza viruses (N=92), and respiratory syncytial viruses (N=62) were the pathogens most commonly detected in ARI reports. In all seasons, rhinovirus and coronavirus were the first and second most commonly detected viruses, respectively.

Demographic comparison: Households reporting childcare use were no different with regard to average number of adults or children, average age of children, or SSP (Table 2-2). Neither was there a statistically significant difference in the distribution of race, sex, or age group in these categories and all participants reported to be generally healthy and free of high-risk medical conditions. In childcare households, children were slightly older on average and both household adults were statistically significantly more often employed than in non-childcare households.

ARI seasonality: Epidemic curves reflected the traditional shape of respiratory illness seasons, with notable peaks in winter months and persistent, low-level activity throughout the rest of the year (Figure 2-1A). Visually, seasonality of ARI did not differ markedly between childcare and non-childcare households. Mixed-effects adjusted logistic regression models revealed no evidence of a clear pattern across calendar time either (Figure 2-1B). Household childcare use was only associated with illness onset during one month. Participants living in childcare households were associated with a slightly increased likelihood of illness during the month of May, to a statistically significant degree, compared to non-childcare households.

ARI incidence rate comparisons: Approximately 70% of all ARI cases in the study analysis originated from childcare households, which was in line with the prevalence of childcare use each season (Table 2-3). The crude ARI incidence rate was slightly lower in participants from childcare households compared to non-childcare households (1.2 vs 1.4 cases per person-year, respectively; $p=0.026$). ARI episodes were not significantly different with regards to specific viruses detected, codetection proportion, illness symptoms, or traditional markers of severity (Table 2-3).

Using adjusted multilevel Poisson regression models, we detected no association between household childcare use and reported ARI incidence rates (IRR = 0.99, 95% CI=0.83 to 1.17, Figure 2-2A). When our exposure was operationalized as ordinal rather than binary, exposure to one or multiple children in childcare was not associated with increased ARI incidence (Figure 2-2B). Adjusting for differential baseline rates of ARI during school or summer months in Model C, made no impact on the estimates of Models A or B (results not shown).

Variables of interest like household SSP, number of household children, and number of adults were assessed as effect modifiers. Model stratification did not suggest that any of the variables played a discernable role in modifying the effect of the association (Figure 2-2C through F). Similarly, we found no evidence for effect modification when variables were analyzed with regression model interaction terms (included below facets in Figure 2). When the model was stratified by participant age group, there was a suggestion of significant effect modification by young age (Fig 2-2F). Compared to children in homecare households, rates of ARI in children of childcare households were 40.3% lower in those under 4 to 5y and approximately 27% lower in those aged 6 to 11y (95% CIs = 0.39 to 0.91 and 0.54 to 0.98, respectively). Rate ratios reverted to null in older age groups; the IRR calculated for those aged 12-17y was 0.85 (95%CI = 0.33 to 2.21) and for those ≥ 18 y, IRR= 1.05 (95%CI 0.86 to 1.3).

2.4 – Discussion

Given the outsized role children play in household infection transmission and the ARI risk associated with childcare attendance, our hypothesis was that individuals living alongside a childcare attendee would be associated with higher ARI incidence, compared to those that did not. Our results suggest that this is not the case. Overall, across 6 study years and over 1600 person-years of surveillance, our analysis revealed no statistically significant difference in characteristics, seasonality, or incidence rate of reported ARI episodes between households that used childcare compared to those that did not. Furthermore, incidence rate ratio estimates did not markedly change when we considered effect modification by household or individual level characteristics other than individual age.

These results differ from conclusions of existing literature which largely suggest a positive association between ARI risk and household childcare use. In one study based on a random digit dialing survey, families who had reported a respiratory disease within the past two weeks were associated with a non-statistically significant 1.18 times higher odds of a child in childcare compared to families who did not report an illness (95% CI, 0.93 to 1.5).⁵³ Similarly, a separate study determined that mothers who used outside childcare for their children had more than two times the odds of being ill in the past two weeks, compared to mothers who did not (OR: 2.26, 95% CI: 1.12—4.54).⁸⁶ This increased burden of illness remained even after common allergy symptoms were accounted for, though the effect of potential confounders—including family size, household SES, or number of siblings—was not considered. Another cross-sectional study from 2016 sent an illness survey to randomly-selected parents every month.¹⁸ Regression models revealed that odds of a parent experiencing an ARI episode in the past month were 2.4 times higher

(95%CI: 1.7–3.6) if their child was attending childcare; indeed, the exposure seemed to follow a dose-response relationship whereby multiple childcare children was associated with even higher odds of parental ARI.

One explanation for our null findings may be that limitations of previous work led to positive findings, which were not corroborated when we evaluated the same question with data from a longitudinal, prospective study. As the authors of the original work note, these previous study results should be interpreted with caveats. The majority of research in this topic relied on retrospective outcome ascertainment. Any event recalled during a past time window is always subject to the effects of recall bias as well as “telescoping,” where participants remember episodes as more recent than actually occurred. The implications of potential recall bias are more concerning if recall bias was differentially associated with levels of exposure. For instance, if childcare households more frequently misremembered ARI episodes as more recent than non-childcare households, this would positively bias the overall result. HIVE data, on the other hand, is prospectively collected and therefore has less risk of exposure and outcome ascertainment biases. Other differences in participant eligibility may impact the comparability between past results and our study. The Mughini-Gras paper, for instance, only considered families where all children were <4y old (capturing much younger families than in HIVE).

We also explored whether potential measurement errors in the HIVE study impacted our results. Specifically, we speculated that households where all adults were employed (fully-employed households) were possibly under-reporting illnesses compared to households where at least one adult remained at home (partially-employed households).^{88,89} Because the HIVE study requests that sick participants travel to the study clinic for sample collection, we thought that perhaps this acted as an impediment to ARI reporting in fully-working households—and

particularly for those employed without paid sick leave. Because fully-working households in HIVE are more often childcare homes (Table 2-2), this may have diminished any potential increase in illness rates associated with childcare use. We note however that although HIVE illness visits are requested for sample collection, illnesses can also simply be reported over the phone or via email, which hopefully reduces the burden on parents. Indeed, fully- and partially-working households reported a roughly equal proportion of illnesses without visiting the clinic (approximately 6.5%). Neither does the data suggest that a differential reporting rate was occurring. We re-ran Model A including a binary variable for fully-working households as an additional covariate. This did not change the ARI incidence rate ratio estimate associated with childcare attendance nor was the covariate itself calculated to be a significant predictor of the outcome (IRR = 0.97, 95%CI: 0.82 – 1.15).

Biases associated with exposure ascertainment could also contribute to the null findings. This analysis does assume that childcare use reported at the beginning of the season is static throughout the upcoming year. Although HIVE families are re-interviewed at the beginning of each study year, there is a possibility that families either start or cease childcare usage at some point during surveillance without updating the HIVE study. We do not expect this to be common though, given the necessity of childcare for many families.

Another explanation may be that children are already so infectious and important to household illness risk, that an increased risk associated with their own childcare attendance does not notably impact the role they play. Considerable research indicates that young children <5y put families at illness risk and often act as the index case.^{31,90} This association has been found in analysis of exclusively childcare populations as well, which focus on transmission from childcare attendees to other household members.^{25,30,33} Our study compared ARI risk between households

differing in their exposure to childcare, and so was restricted to families with at least one child <5y. In the end, the truth may be that whether or not a child attends childcare makes no difference on high illness rates associated with the presence of any child in the household. Other household studies like HIVE should also consider investigate this question to better understand our results in the context of prospectively collected information. The Utah Better Identification of Germs – Longitudinal Viral Epidemiology study (BIG-LoVE)⁹¹ and the Mobile Surveillance for Acute Respiratory Infections and Influenza-Like Illness in the Community (MoSAIC) are two good examples.⁹² To date, neither of these studies have published results related to childcare-associated illness.

A final explanation for our null findings may be that assessing the relationship between childcare use and household ARI risk requires a more complex analysis than our data allowed. Most significantly, the HIVE demographic form fails to capture the heterogeneity of childcare attendance and this lack of exposure detail might have obscured the association of interest. For one, literature has pointed to duration of childcare attendance as a modifier of illness risk.⁵⁶ Ball et al, assessing data from a prospective birth cohort, showed that childcare attendees experienced more frequent illness at the age of 2y than homecare children, but less frequent illness as they aged into early elementary school.⁵⁵ Their results underscore the benefits of protective, acquired immunity to be gained in childcare environments.

Indeed, our results offer some evidence of this acquired immunity. Compared to homecare households, we found significantly lower incidence rate of ARI in younger individuals living in childcare households (Figure 2-2F). Rates were lowest for the 4-5y age group, which represents children who had just turned 5y by that season's date cut-off for kindergarten. In childcare households, these children just aged-out of childcare and experienced a statistically significant

40% lower incidence rate of ARI compared to similarly aged children in non-childcare households (IRR=0.6, 95%CI = 0.39-0.91). In line with previous research, the effect estimate in this age group supports the idea of the protective immunity gained through early life childcare attendance.^{55,56,59} Also corroborating previous research, our results suggest that this effect modification wanes in elementary school; the effect estimate was slightly smaller, though still significantly significant, in the 6-11y age group (IRR=0.73, 95% CI = 0.54-0.98).

Our data are also unable to distinguish the weekly hours children spent in childcare nor the age at which children first started attending childcare—other established modifiers of the childcare-illness association. In our study, we have no information on childcare attendance prior to initial enrollment in the HIVE study. Without being able to adjust for the duration of childcare use at the household or individual level, we cannot account for any possibility of acquired protection in young children. As an example, if the population of childcare children in HIVE during these six seasons was approximately split between long-term attendees and those new to childcare—who, compared to homecare children, experience negative and positive illness associations, respectively—then the pooled association would be biased to the null.

There are also a variety of childcare program types, which can range from large enrollments of 200-plus to smaller, residential-based programs or care by family relatives. HIVE data collected, however, does not distinguish between the type of childcare attended. This is potentially significant as there is reason to believe that different childcare arrangements are themselves associated with differential illness risk, though past research is not definitive as to which direction this association may trend.^{62,63,93–95} Compared to smaller childcare groups (around 30 children), estimates from independent studies have calculated 40% lower to 64% higher odds of upper respiratory infection (URI) in children who attend large group care facilities.

Finally, the relationship between childcare use and household ARI risk may be modified by other household and individual-level factors that we collected data on but did not have the ability to assess robustly. While our study was powered to detect a change in ARI incidence rate across the whole study population, statistical power was lost when we subset the data to assess effect modification. In these model results, wide confidence intervals may mask an underlying association. Of note, the association between childcare use and household ARI incidence was markedly higher in families with one child compared to two or more (Figure 2-2D). The same hygiene hypothesis that supports the residual protective effect of childcare attendance in early elementary school may be acting in a similar manner here. In other words, the family's first child confers a higher disease risk than subsequent children because parents have not yet been exposed to common childhood illnesses. Literature regarding this idea is sparse, but there is crude support for this theory in the data—we found that, irrespective of childcare use, families with one child had the highest number of mean ARI reports each year (1.2), followed by families with two and then 3+ children (1.1 and 0.9, respectively); an ANOVA test indicated these mean values were not equivalent ($p=0.009$). Childcare may exacerbate the risk posed by one child but lose its impact as more children are introduced. Similar analyses in the future should work to more appropriately investigate these potential associations.

This analysis is unique in our comparison of ARI incidence between childcare and homecare households from the same underlying population. Our work contributed information towards better understanding the indirect ARI risk associated with out-of-home childcare which is pertinent information as more and more US children continue to spend at least some of their childhood in out-of-home care settings. Families should be made aware of this risk, particularly if they live with already at-risk members (like grandparents or the immunocompromised). This

knowledge would also support public health preparedness efforts and adequate responses to seasonal influenza outbreaks or the next pandemic.

Table 2-1: Seasonal breakdown of eligible participants and illnesses assessed in the HIVE study

Eligible Participants	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	Average
Start date	1-Oct	1-Oct	1-Oct	1-Jul	1-Jul	1-Jul	--
Stop date	30-Apr	30-Apr	30-Jun	30-Jun	30-Jun	30-Jun	--
Enrolled households	141	85	137	66	78	152	109.8
Enrolled participants	451	287	404	222	213	388	327.5
<i>Children under 6y*</i>	53	28	37	33	16	23	31.7
<i>Children 6 to 11y</i>	118	85	119	59	47	86	85.7
<i>Children 12 to 17y</i>	27	21	30	16	16	21	21.8
<i>Adults 18 and older</i>	253	153	218	114	134	258	188.3
Households using childcare, N (%)**	99 (70.2)	65 (76.5)	106 (77.4)	52 (78.8)	56 (71.8)	109 (71.7)	74.4%
ARI illnesses							Total
Total illnesses reported	436	226	406	213	211	444	1936
Total days at risk	108,056	58,951	142,474	79,809	71,328	135,273	595,891
Overall ARI incidence per 1000 person-days	4.0	3.8	2.8	2.7	3.0	3.3	
Top five viruses detected							
<i>Rhinovirus</i>	82	41	89	77	59	107	455
<i>Coronavirus†</i>	80	35	33	28	24	65	265
<i>Influenza A</i>	19	21	50	10	11	16	127
<i>Parainfluenza virus‡</i>	29	6	14	12	11	20	92
<i>Respiratory syncytial virus</i>	31	9	6	10	4	2	62

* under 6y individuals were at least 5y old at time of kindergarten age cutoff that season
 ** p value for significance test of all proportions equivalent = 0.64 (chi-square = 3.3)
 † aggregate of coronavirus types - NL63, OC43, HKU1, 229E
 ‡ aggregate of parainfluenza virus types 1 through 4

Table 2-2: Comparison of households and individuals by household childcare use status during first season enrolled

	Household childcare use		p
	No	Yes	
Households (N=362)	99	264	
Total adults in household, mean (SD)	2.1 (0.4)	2.0 (0.5)	0.11
Total children in household, mean (SD)	2.6 (1.3)	2.4 (0.9)	0.19
All household adults employed, N (%)	21 (20.8)	118 (45.0)	<0.001
Average age of children in household, mean (SD)	3.8 (2.5)	4.3 (2.2)	0.07
Subjective social position, mean (SD)*	6.6 (1.2)	6.5 (1.4)	0.31
Participants (N=1068)	320	748	
Female, N (%)	181 (56.6)	410 (54.8)	0.63
Race, N (%)			0.4
<i>Asian</i>	26 (8.1)	71 (9.5)	
<i>Black</i>	38 (11.9)	77 (10.3)	
<i>Other</i>	42 (13.1)	77 (10.3)	
<i>White</i>	214 (66.9)	523 (69.9)	
Age group in years, N (%)			0.39
4 to 5	51 (15.9)	94 (12.6)	
6 to 11	77 (24.1)	165 (22.1)	
12 to 17	19 (5.9)	38 (5.1)	
18 to 49	168 (52.5)	437 (58.4)	
50 and older	5 (1.6)	14 (1.9)	
At least one, high-risk medical condition, N (%)	59 (18.7)	135 (18.1)	0.86
Baseline Health**	88.3 (12.3)	87.7 (10.4)	0.04

P-values indicate chi-square tests for categorical data and Kruskal-Wallis for continuous

* Reflects the household's subjective opinion on their social position compared to everyone else (with regards to employment, income, material goods, etc.) on a scale of 1-9, where 9 represents those households "best-off"

** Reported on a scale from 0-100, where 100 represents best possible health

Person-time and reported ARI episodes values represent aggregate totals during full course of participation.

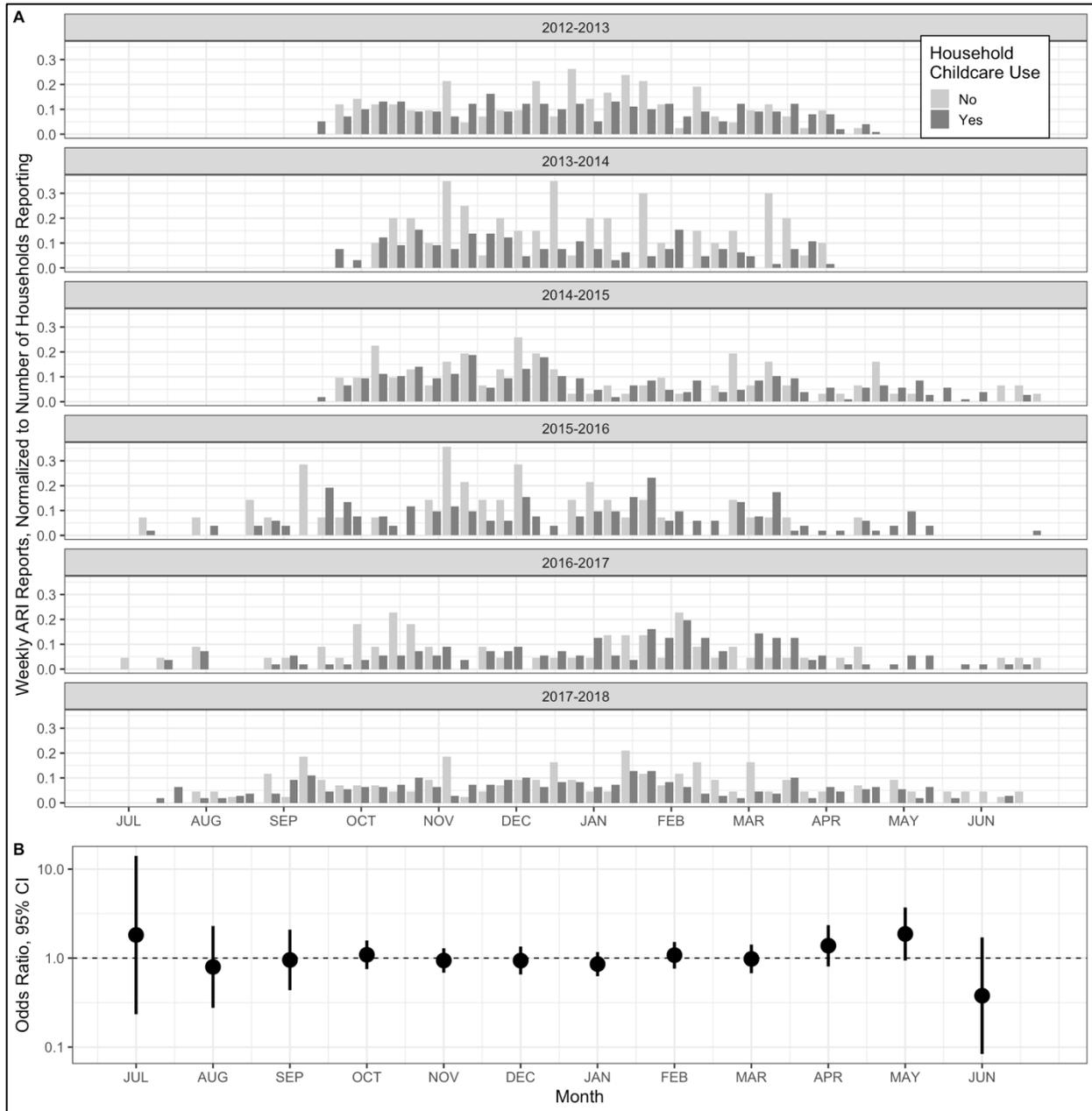
Table 2-3: Comparison of ARI episodes (N=1936) stratified by household childcare use at time of illness onset

	Annual household childcare use		p
	No	Yes	
Overall ARI episodes reported, N	582	1354	
Overall person-days under surveillance, mean (SD)	161,664	434,226	
Participant ARI incidence rate per person-year, mean (SD)	1.39 (1.8)	1.22 (1.7)	0.03
Viral infection, N (%)	326 (56.1)	720 (53.1)	0.23
Virus isolated, N (%)			
<i>Adenovirus</i>	8 (2)	30 (3.8)	0.12
<i>Coronavirus</i>	76 (13.9)	189 (15.2)	0.52
<i>Influenza</i>	50 (9.2)	116 (9.3)	1
<i>Respiratory Syncytial Virus</i>	29 (5.3)	45 (3.6)	0.12
<i>Rhinovirus</i>	146 (26.7)	309 (24.8)	0.41
Viral coinfection, N (%)	41 (7.1)	86 (6.3)	0.55
Experienced at onset, N (%)			
<i>Cough</i>	343 (59.4)	751 (56.2)	0.19
<i>Fever</i>	172 (29.9)	406 (30.4)	0.83
<i>Sore throat</i>	349 (60.6)	845 (63.2)	0.28
<i>Congestion</i>	403 (70.1)	998 (74.8)	0.04
<i>Body aches</i>	157 (27.3)	366 (27.4)	1
<i>Headache</i>	252 (43.7)	532 (39.9)	0.13
Contact with healthcare provider, N (%)	65 (14.3)	165 (15.3)	0.7
Hospitalized, N (%)	5 (1.0)	3 (0.3)	0.06
Missed at least one day of work or school, N (%)	158 (37.6)	356 (34.7)	0.31
Subjective rating of the worst day of the illness, mean (SD)	60 (19.3)	60 (20.1)	0.31

P-values indicate chi-square tests for categorical data and Kruskal-Wallis for continuous.

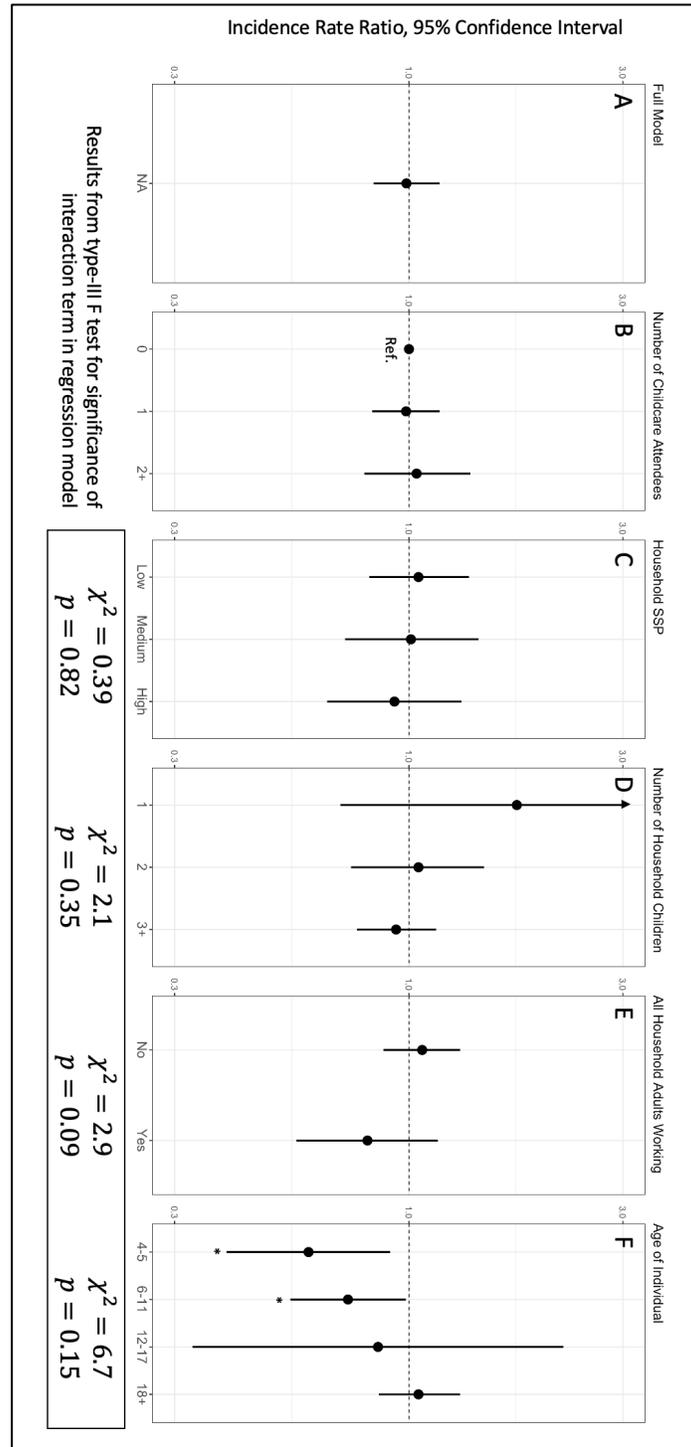
A fraction of illness cases were never molecularly tested for viruses and/or never linked to a follow-up survey, thus the denominator of the percentage values reflects the total number of cases with corresponding information.

Figure 2-1: Seasonality of ARI reports associated with household childcare use



(A) Weekly ARI cases reported by households using childcare—dark grey—and household that do not—light grey. ARI case reports are normalized to the number of childcare vs non-childcare households reporting ARI cases that year. Surveillance period in 2012/13 and 2013/14 seasons lasted between October and April and became year-round starting in October of 2014. (B) Forest plot representing odds ratios (and corresponding 95% confidence intervals) of childcare use from illnesses reported during specific months of surveillance. Values can be interpreted as the multiplicative change in odds of illness onset during month X (vs not) in childcare households compared to non-childcare households.

Figure 2-2: Results of adjusted mixed-effects Poisson regression models, comparing ARI incidence in childcare and non-childcare households



Results for: (A) Full model; (B) outcome operationalized as number of household children enrolled in childcare rather than binary childcare use; (C-F) results of baseline model A run stratified by level of effect modifier, type-III F test results for interaction term in base model—run with full dataset—are included below each panel. Asterisk denotes statistical significance at $\alpha=0.05$.

Chapter 3: Comparing Viral Respiratory Infections Between Children Who Do and Do Not Attend Childcare

3.1 – Introduction

Acute respiratory illness (ARI) is the most common cause of disease and mortality in US children under 5 years of age and is significantly associated with out-of-home childcare attendance.¹ Compared to their counterparts cared for at home, children who attend childcare experience a significantly higher risk of respiratory illness early in life.^{51,53,55,96} This excess illness risk is likely due to the wide range of viral respiratory pathogens circulating in childcare centers, the group care environment, and the behaviors and developing immune system of children which enhance viral transmission.^{40,50} Yet while childcare attendees have been shown to experience ARI more often, literature has yet to offer any definitive conclusions as to whether these ARI episodes are characteristically different than those experienced by homecare children. Epidemiologic research has not directly compared the etiology or severity of ARI in childcare and homecare children.

This type of knowledge would be essential for both childcare stakeholders and pediatric health professionals. Considerable effort is expended to mitigate disease transmission in childcare environments—including targeted immunization, environmental cleaning and disinfection, and child exclusion.⁹⁷ A better understanding of infection characteristics specific to childcare would help to further tailor these transmission mitigation efforts in these settings.

In this Aim, we assess six years of ARI episodes collected from a longitudinal study of community households, which contains a sizeable cohort of children differing in their exposure to out-of-home childcare. Among ARI cases of childcare and homecare children, we compare the risk of viral detection, viral codetection, and infection with particular respiratory viruses, as well as assess the underlying viral species richness in childcare and homecare.

3.2 – Methods

Six years' worth of HIVE data reported between the study years of 2012-13 and 2017-18 were used to complete this research aim; detailed methods of the HIVE study have been described previously in Chapter 1 and in a published data resource profile.⁶⁷

The study's primary exposure, childcare attendance, was based on each HIVE participant's demographic form which was updated on an annual basis. This analysis was restricted to only samples from children of childcare age. As mentioned in Aim 1, childcare age was determined each year based on a statewide date cut-off for kindergarten eligibility. Michigan law states that children must be at least 5 years of age by a predetermined date to enroll in kindergarten during any given year; between the 2012-13 and 2015-16 school year, the Michigan cut-off date for kindergarten enrollment was progressively moved back by one month from December 1 to September 1. Each study year, children too young to be enrolled in kindergarten based on that season's date cut-off were considered to be of "childcare age". Outcome variables were derived from RT-PCR testing of HIVE illness samples. Nine specific pathogens were included in our analysis: adenovirus (AdV); bocavirus (hBoV); coronavirus (CoV), including 229E, HKU1, NL63, and OC43; human metapneumovirus (hMPV), influenza A (flu A), influenza B (flu B),

parainfluenza virus (PIV), including types 1 through 4; rhinovirus (RV); and respiratory syncytial virus (RSV).

HIVE demographic variables were updated annually, and so we compared characteristics of childcare attendees and homecare children based on characteristics reported at the initial enrollment. Chi-square tests were used to compare categorical variables. Non-parametric Kruskal-Wallis tests were used to assess continuous variables because these variables each deviated from a normal distribution based on QQ plots and the Shapiro-Wilk test for normality.

Multivariable generalized linear models (GLM) with a log-link were used to calculate the odds of two outcomes associated with childcare attendance: (a) infection with particular viruses and (b) viral codetection. Models were adjusted for age at illness onset (using a spline term to capture nonlinear relationships), categorical month of illness onset, participant sex, and number of children in the participant's household. Regression models also included a random effect term to account for dependency or correlation in reports from the same child over time (e.g., individual susceptibility to certain pathogens).⁹⁸ In pathogen-specific outcome models, we assessed all swab samples regardless of whether viruses were detected or not; however, in codetection-outcome models, we only considered samples which had been infected with at least one virus (as a codetection event is not possible without at least one virus detected). Additionally, we assessed the potential for age modifying the association between childcare attendance and codetection. We used both age group stratified regression models as well as a Type III Wald test to assess the statistical significance of an interaction term between child's age group and childcare attendance.

Finally, we also calculated a Shannon's Diversity Index to compare the richness and abundance of viruses (i.e., the range and relative proportion of species present) detected among childcare and homecare illnesses. First, results of all illness samples were assigned a binary value

indicating presence or absence of each particular virus (a coinfecting sample would display an indicator value of 1 for each virus present). Then, because implementation of Shannon's H requires that the sampling frame for the groups be equivalent, we randomly subsampled 200 infection cases from both childcare and homecare populations to calculate H values.

Counts of viruses isolated were summed in each subsample, from which a Shannon H value was calculated. This subsampling process was repeated 1000 times, thereby generating 1000 H results for each group and effectively bootstrapping H estimates. All H values calculated were plotted in a distribution curve, and a t-test was then used to statistically compare the difference in overall mean estimates. As a check on the method's robustness, the same method was run with 50 and 300 randomly-selected samples.

All statistical analyses and images were produced using R (R Foundation for Statistical Computing; Vienna, Austria; version 3.6) including estimates for Shannon's H (*vegan* library).⁹⁹

3.3 – Results

Participant characteristics: Across six surveillance seasons, a total of 1520 ARI cases were reported from 382 childcare-aged children living in 265 distinct households (Table 3-1). Illnesses were reported from a pool of participants slightly more male than female, the vast majority of whom were non-Hispanic white (N=254, 71%); no demographic characteristics were significantly associated with childcare attendance.

Crude infection comparisons: Of all illnesses reported, 1418 (93%) submitted midturbinate swab samples that were then molecularly tested against the panel of respiratory viruses (Table 3-2). The proportion of non-tested illnesses was not dramatically different between homecare and childcare groups (4.5% and 7.6%, respectively). More than three-quarters of homecare and

childcare illnesses were positive for at least one respiratory virus (80.0% and 75.5%, respectively). Changes in testing protocol throughout surveillance years meant that the 1418 samples were not tested for all viruses. Most notably, no testing was completed for BoV in years 2012/13 through 2013/14 which explains why only two-thirds of samples have non-missing BoV results. The tested proportion for each virus individual did not differ markedly between childcare and homecare illnesses, however.

The distribution of detected viruses appeared similar between exposure groups (Table 3-2, Figure 3-1), where RV was found in over a third of all samples in both homecare and childcare illnesses, followed by CoV, RSV, and PIV (present in around 15%, 9%, and 9% of samples, respectively). In both childcare and homecare illnesses, AdV, hMPV, and CoV were the three viruses most commonly detected in codetections.

Unadjusted statistical comparisons suggested that childcare illnesses were less associated with RV, BoV, and any viral detection overall than homecare illnesses (Table 3-2). There was also a slight indication that childcare illnesses were reported as less severe than homecare illnesses, with both a better subjective experience on the worst day of the illness as well as a faster time to recovery. No severity differences were discernable when ARI cases were stratified by detected virus within exposure group (Table 3-3). Only 9 ARI episodes were hospitalized across all 6 seasons—4 with CoV, 3 with RV, and 1 with PIV (no virus was isolated in 1 of the hospitalized ARI cases).

Mixed-effects regression model results: Though not statistically significant, odds of viral detection given illness were lower for children attending childcare than their homecare counterparts (OR = 0.89, 95% CI: 0.64–1.24; Figure 3-2). Three particular viruses were statistically significantly associated with childcare attendance. Odds of AdV and hMPV detection

were 86% and 76% higher among childcare attendees than homecare children, respectively (95% CIs: 1.05–3.28 and 1.03–3.0). On the other hand, odds of RV detection were 33% lower among childcare attendees than homecare children (95% CI: 0.51–0.89).

Despite lower odds of any viral infection, odds of viral codetection were found to be slightly higher in childcare versus homecare illnesses with virus present (OR=1.05, 95%CI: 0.71–1.6; Figure 3-3), though this was not statistically significant. When the analysis was stratified by child's age at onset into 1y age groups, there was indication of a parabolic relationship between odds of codetection across age groups; where lowest odds were calculated in the <1y and >5y age groups (OR=0.38 and 0.15, respectively) and highest odds in the 2y and 3y old age groups (OR=1.21 and 1.47, respectively). None of these ORs from stratified regression models were individually significant nor were they significantly different from each other based on the statistical significance of the age group-childcare interaction term in our initial regression model.

The ecologic concept of Shannon's Diversity Index (H) was also used to compare the distribution of pathogens between illness groups. Bootstrapped H estimates for homecare and childcare virus pools were calculated to be 1.66 and 1.78, respectively, indicating a higher species richness and abundance in the childcare group. A subsequent two sample t-test for difference in means indicated that this difference was highly significant ($t = 46.5$, $p < 0.0001$). Results were robust to methods whether 50 or 300 samples were randomly selected from both exposure groups.

3.4 – Discussion

Our study—which assessed a single underlying source population using the same, sensitive RT-PCR methods—detected at least one virus (of nine total viruses tested for) in over 75% of all swabs from childcare and homecare children experiencing symptomatic ARI. This high percent

positivity is not unusual for childhood ARI. In recent studies, which used PCR methods to test for similar respiratory pathogens as we did, viruses were detected in 61% - 85% of pediatric ARI samples.^{16,44,45,100-103} We found multiple viruses in 15.5% of all cases positive for at least one virus; this number also falls in the range of previous work which cites codetection proportions ranging from 13% to 45% in young children.^{90,101,102,104,105} Regardless of childcare exposure, the three most commonly isolated viruses in our study were RV, CoV, and RSV. These predominant pathogens are also cited by previous epidemiologic literature in childhood ARI and suggests that the bulk of childhood ARI in both childcare and homecare environments is caused by the same viruses.^{16,101,102,106}

AdV and hMPV were found to be more strongly associated with childcare than homecare. The association between these viruses and childcare is supported by their biologic and epidemiologic characteristics. hMPV infection is strongly associated with young age and has been linked to daycare attendance in past studies.^{103,107} While AdV has not been specifically linked to childcare attendance previously, AdV is an unusually stable pathogen outside of the host and particularly resistant to physical and chemical agents.¹⁰⁸ Furthermore, AdV infection is associated with both long latency periods and prolonged illness duration; asymptomatic individuals can carry the virus for weeks to months and AdV epidemics are known to spread rapidly within crowded environments, with attack rates as high as 67%.^{44,109-111}

We found significantly lower adjusted odds of RV detection in childcare illnesses compared to homecare illnesses. This was more surprising to us, especially considering the well-documented circulation of RV in childcare, with a multitude of genotypes detected from a single childcare setting during eight months of surveillance.¹¹²

One reason for this result may be related to differential reporting. Children in childcare are frequently sick, which may lead to parents of childcare attendees who are less inclined to report mild illnesses, like those of a common cold. Furthermore, childcare is more frequently used in households where all household adults are employed—in these HIVE seasons studied, demographic questionnaires indicated that all resident adults were employed in 41% of childcare households but only 19% of homecare households. Only the most notable illnesses may be reported in childcare attendees because a reported illness corresponds to absence from childcare and also a day of missed work for employed parents. Altogether, given that RV infection is generally associated with minor illness symptoms and there may be a tendency to only report more severe illnesses in childcare children, this could underestimate the true infection prevalence of RV in childcare attendees.^{91,113}

We were interested in comparing the severity of illness associated with childcare attendance. While, nonparametric tests indicated statistically significant differences in reported illness severity (Table 3-2, Table 3-3), these differences were negligible. In addition to the small difference in mean values, the overall distribution of values was compared visually with histograms (Supplementary Figure 3-S1) which revealed no marked difference between responses of the two groups. Moreover, subjective markers of severity are difficult to interpret, particularly when parents/guardians are answering on behalf of their children. Regardless of statistical significance, differences of 3 points on a severity scale of 100 and 0.4 days in recovery are not clinically relevant. Thus, our study findings suggest no contrast in the severity of illnesses reported by the two groups.

Our study quantified a significantly richer and more diverse pool of viruses isolated from childcare illnesses compared to homecare illnesses (Shannon's H difference = 0.11, 95% CI: 0.105

– 0.115). A more interpretable comparison of H values can be produced by considering the difference in the “effective species” numbers, or the exponentiated H values.¹¹⁴ This value reflects the number of species expected to be present in an environment where all species are present equally. In this sense, our results suggest 5.9 equally distributed viruses in the childcare pool compared to 5.3 in the homecare pool—a difference of 0.60 viruses ($e^{1.77} - e^{1.66}$).

While the Shannon’s Diversity calculation has not been performed previously in this capacity, this finding was not unanticipated. Childcare environments have persistently been associated with a diverse swath of respiratory viruses and provide an ideal setting for disease transmission—due to closely gathered children with poor hygiene practices and asymptomatic carriage.^{34,40,42,115} It makes sense that illnesses collected from children who attend childcare would be associated with a greater diversity of respiratory pathogens than illnesses from children cared for in households.

The slightly increased odds of codetection among childcare attendees, while statistically insignificant, also speaks to the diversity of childcare viruses present and has been noted in the past.¹¹⁶ The observed parabolic nature of the relationship among childcare-aged children is also corroborated by previous studies, which suggest that among children <5y the 1-3y age group experiences codetection most often.^{83,117,118} This effect modification by age likely reflects changes in behavior throughout early childhood. As infants mature into toddlers (defined as approximately 2y of age), their maternal-derived immunity starts to wane while they become more adventurous and mobile—expanding their play area and becoming increasingly social with other children.¹¹⁹

Implications of any increased codetection risk in childcare remain unclear. Research offers no general consensus regarding the clinical impact of multiple virus infections. A number of papers, including several from childcare-specific populations, have found no association between

codetection and illness severity.^{17,120,121} Others have found an increased risk of codetection-associated severity, though most of these conclusions are based on hospitalized populations (which skew towards severe compared to the more benign illness of community-based surveillance).^{16,104,122,123} Our results suggest no association between codetection and illness severity; there was no statistically significant difference between single virus and codetection illnesses in terms of subjective worst day of illness, duration of illness, contact with healthcare providers, or hospitalization.

Future work should seek to remedy the primary limitation of this investigation, namely the lack of detail regarding the primary exposure. In other words, demographic questions should be designed to better capture the heterogeneity of the childcare exposure. For example, HIVE data collected did not distinguish between the many alternatives of childcare arrangements in the US (e.g., relative care, large commercial programs, family daycare houses, etc.). While still unclear, evidence suggests that varying childcare arrangements are associated with differential illness risk; their consolidation into a single exposure group may be masking underlying associations. Similarly, past literature has recognized important modifiers of the childcare-illness association, including the age at childcare enrollment and hours of attendance per week, neither of which we were able to account for in our models.

Our analysis has several notable strengths which build upon previous research. While previous studies have specifically focused on childcare illness they lacked a non-childcare comparison group.^{17,44,45,117} Analysis in this Aim provides a direct comparison of children who do and do not attend childcare. Moreover, the systematic case detection strategy of HIVE helped to identify many cases of mild respiratory disease that would have remained undetected in more common hospital-based studies, which skew towards more severe ARI cases. This is an especially

important consideration in populations of young children who experience a high number of mild respiratory illnesses each year; less than a quarter of all illnesses in our study sought any form of contact with a healthcare provider.⁹⁰

Overall, findings in this Aim helped to better characterize childhood ARI, especially as it relates to childcare-associated illness and contributed further information to the understanding of respiratory disease epidemiology in childcare facilities. Ultimately, children may be getting sick more in childcare simply because there is more to get sick with. This has important implications for childcare stakeholders. While we found that RV and CoV were the most common pathogens isolated from both childcare and homecare illnesses, our results demonstrate that the viral landscape in childcare settings is significantly richer and more diverse compared to homecare. Furthermore, we found AdV and hMPV to be significantly associated with childcare attendance. These results underscore the importance of vigilant and multifaceted environmental cleaning protocol in childcare; childcare directors should be aware that preventing ARI in their programs might require more than simply preventing RV transmission. Our findings also highlight the need for further epidemiologic research and molecular testing in group childcare settings—especially pertinent as the proportion of children attending childcare increases.

Table 3-1: Characteristics of 382 childcare-aged children from 265 distinct households who reported at least one illness to the HIVE study: 2012-2018

<i>Based on annual childcare status</i>	Homecare	Childcare	p
Children enrolled each season, N (% of season)			0.75
2012-2013	47 (35.8)	84 (64.1)	
2013-2014	25 (34.7)	47 (65.3)	
2014-2015	44 (36.4)	77 (63.6)	
2015-2016	21 (42.0)	29 (58.0)	
2016-2017	35 (44.9)	43 (55.1)	
2017-2018	53 (39.6)	81 (60.4)	
<i>Based on initial childcare status at enrollment</i>			
Female, N (%)	62 (42.2)	97 (45.8)	0.57
Non-hispanic white race/ethnicity, N (%)	103 (70.1)	151 (71.2)	0.88
Older siblings present - Yes, N (%)	126 (85.7)	149 (70.3)	0.001
Household number of adults, mean (SD)	2 (0.3)	2 (0.4)	0.97
Household number of children, mean (SD)	3 (1.3)	2 (0.9)	0.002

p-values indicate chi-square tests for categorical data and Kruskal-Wallis for continuous data

Table 3-2: Illness characteristics of childhood acute respiratory illness episodes reported and molecularly tested (N=1418), stratified by childcare attendance at time of illness

	Homecare	Childcare	<i>p</i>
N	609	809	
Female, N (%)	254 (41.7)	446 (55.1)	<0.001
Any virus detected, N (%)	488 (80.1)	611 (75.5)	0.04
Pathogen detected, N (%)			
Adenovirus	33 (5.8)	56 (7.2)	0.37
Bocavirus	18 (4.7)	5 (1.0)	<0.001
Coronavirus	92 (15.1)	113 (14.0)	0.59
Human Metapneumovirus	32 (5.3)	53 (6.6)	0.37
Influenza A	25 (4.2)	45 (5.6)	0.26
Influenza B	11 (1.8)	16 (2.0)	1
Parainfluenza	56 (9.2)	69 (8.6)	0.71
Rhinovirus	298 (49.0)	298 (36.9)	<0.001
Respiratory Syncytial Virus	54 (8.9)	81 (10.0)	0.52
Coinfection (2+ viruses isolated), N (%)	104 (17.1)	117 (14.5)	0.18
Number of coinfecting viruses, mean (SD)	2.15 (0.38)	2.15 (0.35)	0.99
Contact with healthcare provider, N (%)	117 (21.8)	153 (21.4)	0.89
Hospitalized, N (%)	5 (0.9)	4 (0.5)	0.51
Subjective health rating on worst day of illness (0-100, 0=worst), mean (SD)	55.4 (18.3)	58.2 (19.1)	0.005
Illness duration in days, mean (SD)	8.2 (3.6)	7.8 (3.9)	0.044

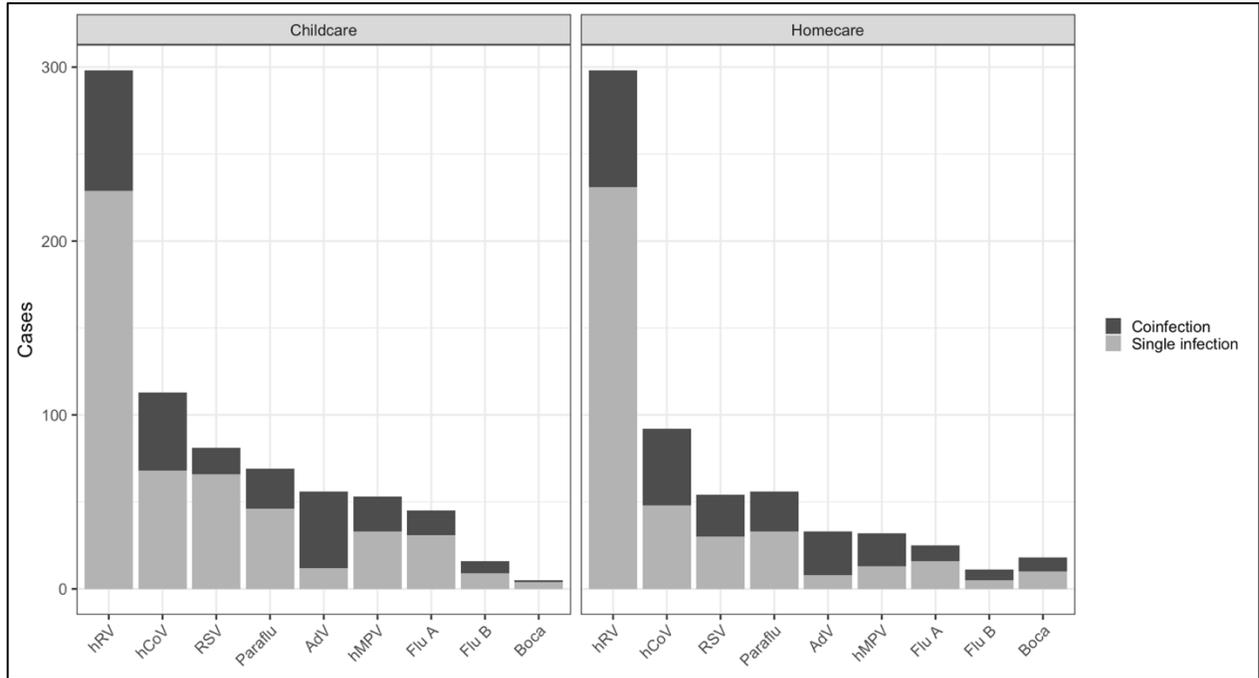
p-values indicate chi-square tests for categorical data and Wilcoxon rank sum tests for continuous

Table 3-3: Illness severity indicators, stratified by isolated virus and childcare attendance

		Homecare	Childcare	p
Detected with other viruses	<i>AdV</i>	25 (75.8)	44 (78.6)	0.79
	<i>CoV</i>	44 (47.8)	45 (39.8)	0.26
	<i>hMPV</i>	19 (59.4)	20 (37.7)	0.07
	<i>hRV</i>	67 (22.5)	69 (23.2)	0.92
	<i>Influenza</i>	15 (41.7)	21 (34.4)	0.52
	<i>Paraflu</i>	23 (41.1)	23 (33.3)	0.46
	<i>RSV</i>	24 (44.4)	15 (18.5)	0.002
Contact with healthcare provider, N (%)	<i>AdV</i>	8 (29.6)	10 (23.3)	0.58
	<i>CoV</i>	20 (26.3)	17 (16.8)	0.14
	<i>hMPV</i>	10 (34.5)	15 (34.9)	1
	<i>hRV</i>	50 (19.3)	40 (15.5)	0.3
	<i>Influenza</i>	4 (12.5)	15 (27.3)	0.18
	<i>Paraflu</i>	18 (34.6)	16 (29.6)	0.68
	<i>RSV</i>	13 (28.9)	28 (38.9)	0.32
<i>Coinfection</i>	28 (32.2)	18 (19.6)	0.06	
Hospitalized, N (%)	<i>AdV</i>	0	0	--
	<i>CoV</i>	3 (3.4)	1 (0.9)	0.32
	<i>hMPV</i>	0	0	--
	<i>hRV</i>	2 (0.7)	1 (0.4)	0.62
	<i>Influenza</i>	0	0	--
	<i>Paraflu</i>	0	1 (1.7)	1
	<i>RSV</i>	0	0	--
<i>Coinfection</i>	0	0	--	
Worst day of illness (0-100), mean (SD)	<i>AdV</i>	54 (21)	60 (19)	0.35
	<i>CoV</i>	54 (19)	60 (18)	0.02
	<i>hMPV</i>	52 (22)	54 (22)	0.63
	<i>hRV</i>	58 (16)	62 (17)	0.001
	<i>Influenza</i>	49 (18)	47 (7)	0.59
	<i>Paraflu</i>	53 (13)	52 (16)	0.55
	<i>RSV</i>	52 (17)	50 (18)	0.34
<i>Coinfection</i>	55 (18)	58 (20)	0.17	
Illness duration in days, mean (SD)	<i>AdV</i>	8 (3)	8 (4)	0.96
	<i>CoV</i>	9 (4)	8 (4)	0.57
	<i>hMPV</i>	8 (4)	8 (3)	0.53
	<i>hRV</i>	8 (4)	8 (3)	0.06
	<i>Influenza</i>	8 (3)	7 (4)	0.21
	<i>Paraflu</i>	9 (4)	9 (4)	0.35
	<i>RSV</i>	9 (3)	9 (4)	0.3
<i>Coinfection</i>	8 (4)	8 (4)	0.71	

* For worst day of illness, 0 = "worst health imaginable", bocavirus not presented due to small numbers

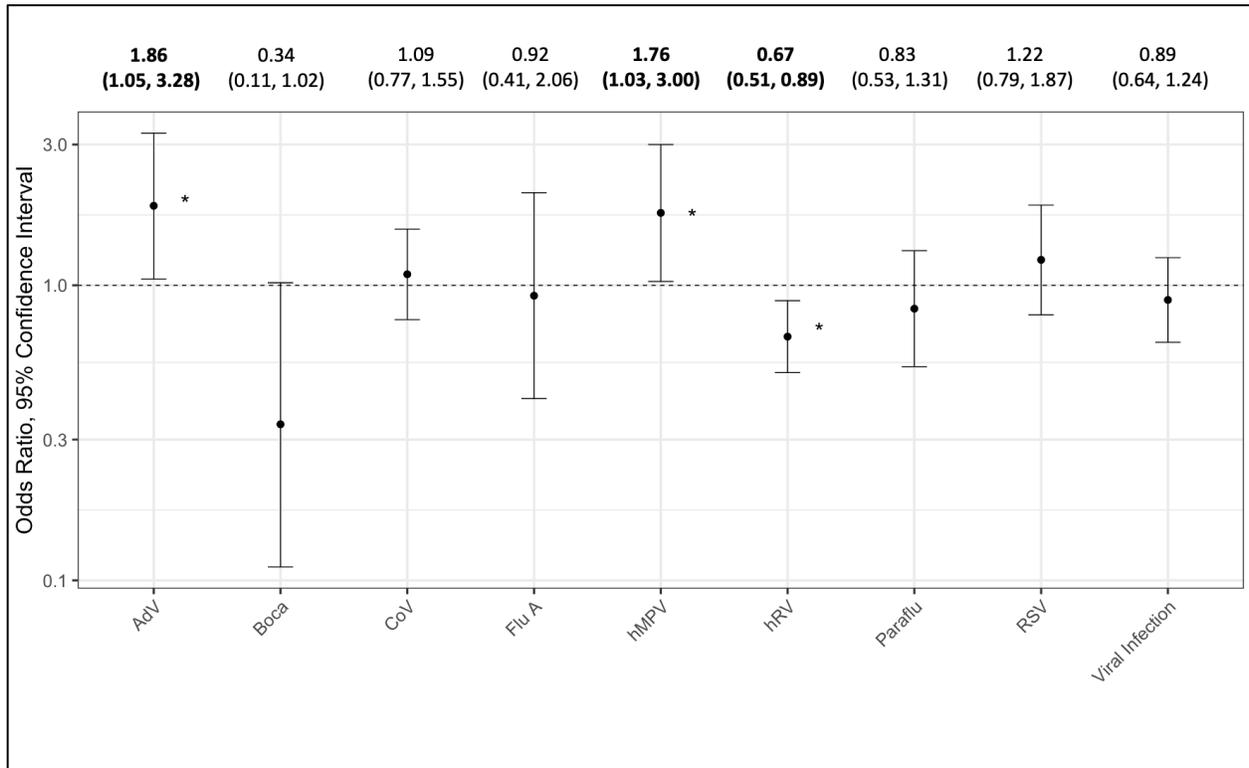
Figure 3-1: Distribution of viruses detected in all childhood ARI episodes reported to the HIVE study 2012-2018 (N=1520), stratified by childcare attendance



ARI = acute respiratory illness
HIVE = Household Influenza Vaccine Evaluation Study,

AdV = Adenovirus,
CoV = Coronavirus
hMPV = Human Metapneumovirus
Flu A = Influenza A
Flu B = Influenza B
Parafllu = Parainfluenza virus
hRV = Rhinovirus
RSV = Respiratory Syncytial Virus
Boca = Bocavirus

Figure 3-2: Odds of pathogen detection in molecularly tested ARI episodes (N=1418), comparing children who attend childcare to those who do not



ARI = acute respiratory illness
HIVE = Household Influenza Vaccine Evaluation Study,

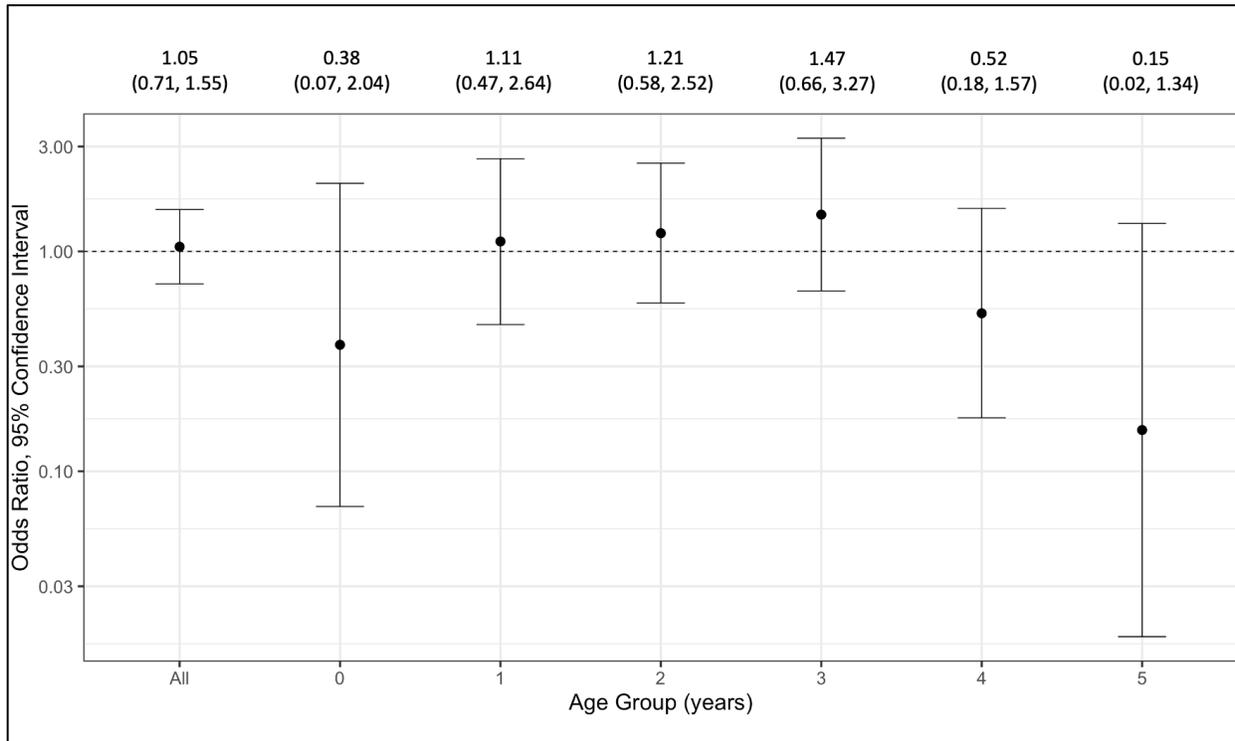
AdV = Adenovirus,
CoV = Coronavirus
hMPV = Human Metapneumovirus
Flu A = Influenza A
Paraflu = Parainfluenza virus
hRV = Rhinovirus
RSV = Respiratory Syncytial Virus
Boca = Bocavirus

Viral infection reflects infection with at least one of the pathogens tested for.

Due to small numbers, the regression model did not converge for influenza B and therefore a result is not presented for influenza B.

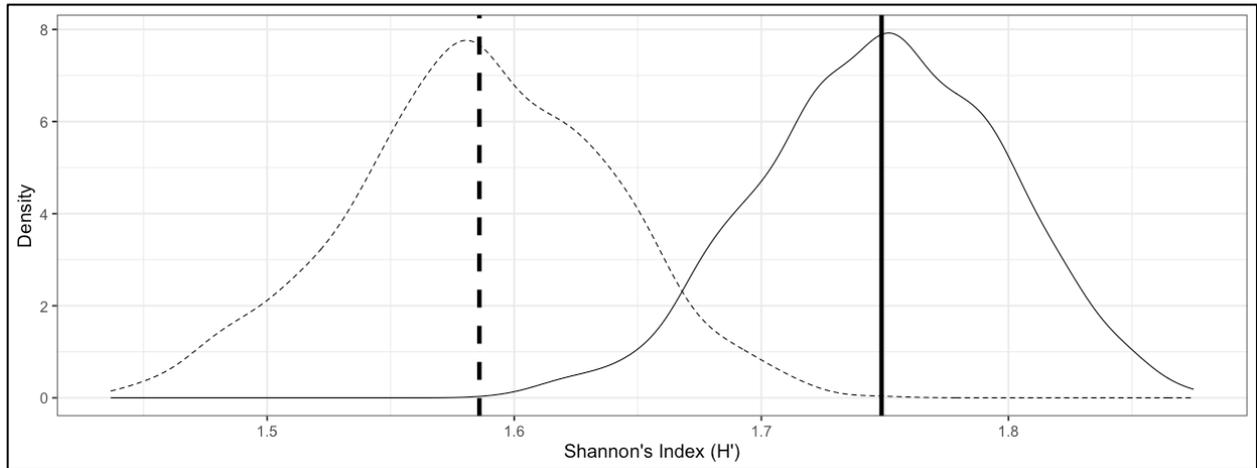
Mixed-effects logistic regression models, with random intercept for individual ID, include spline term for age at illness onset, categorical month at illness onset, categorical sex, and total number of children living in house

Figure 3-3: Odds of viral codetection in ARI episodes of children who attend childcare compared to those who do not



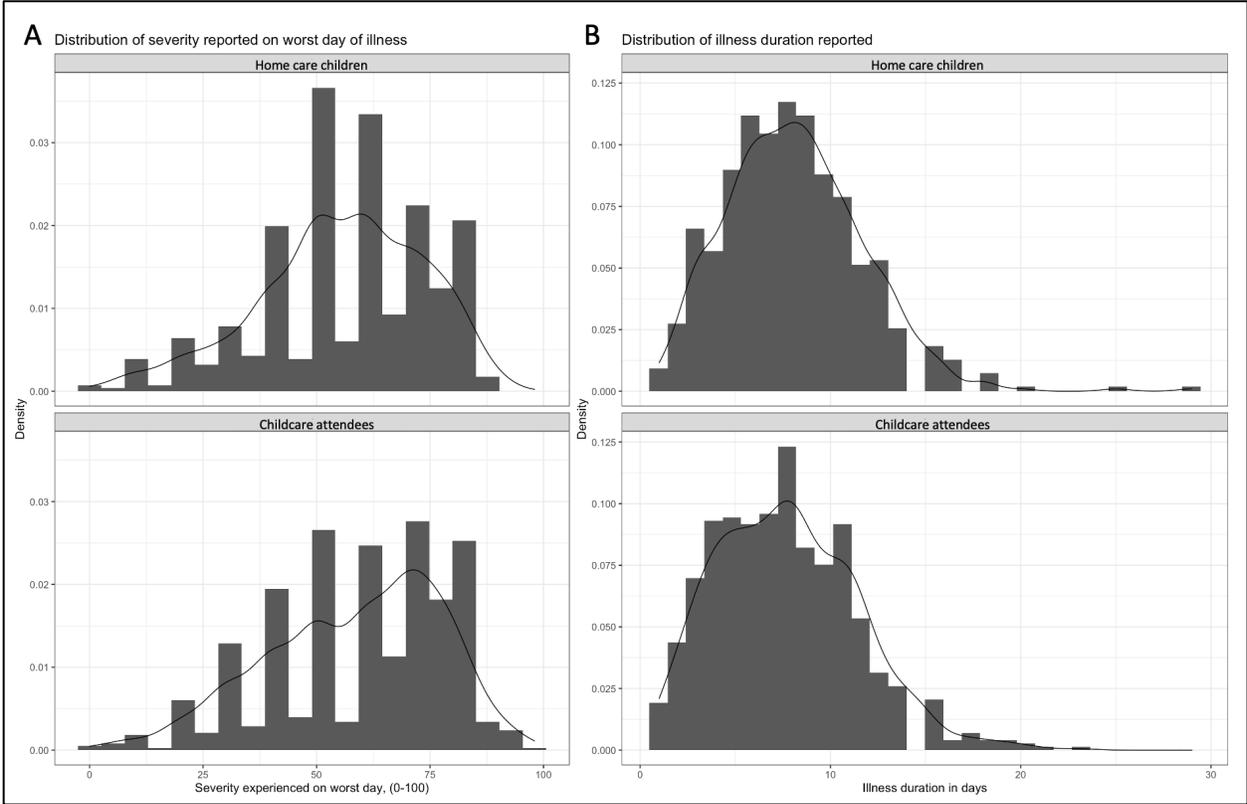
ARI = acute respiratory illness
 HIVE = Household Influenza Vaccine Evaluation Study

Figure 3-4: Density plot of Shannon's Diversity Index calculations



Density curves reflect the bootstrapped estimates of Shannon's Diversity Index calculations from the pool of childcare illnesses and homecare illnesses (N=809 and 609, respectively). The solid black curved line represents calculations from the childcare pool and the dashed line represents the homecare pool. Vertical lines correspond to mean values for each density curve. Estimates were calculated based on 300 illnesses sampled without replacement. The selection process was repeated 1000 times.

Supplementary Figure 3-S1: Distribution of severity indicator variables as reported by childcare attendees and homecare children



Histograms for both variables include overlaid Kernel density curves.

Chapter 4: Comparing Past Influenza Epidemics Detected by Prospective Surveillance Data of Household, Ambulatory, and Hospital Settings in Southeast Michigan

Of the three active, prospective illness surveillance networks operated by UM-SPH, the HIVE network was our only choice to answer questions related to childcare, due to its focus on young families and collection of appropriate exposure information. During research for Aims 1 and 2, we became interested in how respiratory disease outbreaks captured by HIVE differed from that of the other two networks. Because the purpose of each is to estimate the effectiveness of vaccines against seasonal influenza, this Aim compares the three distinct surveillance networks with regards to influenza epidemics.

4.1 – Introduction

Influenza is a vaccine-preventable, communicable disease that is associated with upwards of 30 million illnesses in the US each year. Surveillance of seasonal influenza is a vital component of effective public health practice and preparedness. The challenge is that seasonal influenza epidemics are neither consistent nor predictable events. From year-to-year, for a multitude of reasons, there is wide variation in epidemic incidence rate by calendar week as well as the predominant subtypes and lineages of circulating influenza.

Knowledge of epidemic timing and intensity is also helpful for public health modeling purposes and handling surges of health care demands—via both practitioner education and resource allocation. Data resulting from influenza surveillance can also provide valuable insight

into topics ranging from vaccine effectiveness and uptake, immunization policy, disparities in influenza disease outcomes, and genetic variation in circulating virus types. Consequently, a wide range of surveillance systems have been developed to monitor seasonal influenza epidemics, based on everything from over-the-counter medication purchases, to school and workplace absenteeism, and even internet search results. The most traditional and representative data come from active surveillance for confirmed influenza cases, though there are many methods for this as well.

The University of Michigan School of Public Health operates three large active surveillance networks that capture both influenza A and B cases from hospitals, ambulatory clinics, and community households in southeast Michigan. Each network is designed to estimate vaccine effectiveness against a specific outcome (influenza hospitalization, medically attended influenza, and household influenza of any severity, respectively). As a result, data captured by each of the three networks reflect the epidemic experience of three distinct population groups—varying in characteristics like age, underlying health status, and experienced illness severity. Analogues of each of these networks exist in other US locations, but it is entirely unique to have these three distinct surveillance networks operating simultaneously within the same, small geographic region using identical molecular detection techniques.

In this Aim, we assess two ideas. For one, we wanted to determine whether a regional influenza epidemic is recorded differentially based on surveillance network setting. Effectively, we were interested in whether epidemic curves of the three networks displayed specific temporal patterns or characteristics (e.g., the timing of an epidemic peak or initial detection of epidemic spread). A better understanding of the relationship between surveillance setting and epidemic patterns detected (activity in one network foreshadowing activity in the other two, for example) would be vital for public health preparedness and response. We also were interested in how our

understanding of past influenza seasons can be bolstered by data from the three distinct regional illness surveillance networks. In other words, we were interested in whether our understanding of seasonal influenza epidemics in southeast Michigan was improved by knowledge of activity in three population subgroups.

4.2 – Methods

The University of Michigan School of Public Health (UM-SPH) coordinates three distinct influenza surveillance networks used to estimate annual vaccine effectiveness in various segments of the population. Methodology details of each network, which have been described previously in published literature, are briefly noted in the following three paragraphs and summarized in Table 4-1. Enrollment and sampling procedures for all three studies were approved by the UM Medical School IRB.

Household: Participants are recruited from the University of Michigan Medical System and the majority live in Washtenaw County in southeast Michigan (Figure 4-1). Please refer to Chapter 1 for further HIVE study details as well as the published data resource profile.⁶⁷

Ambulatory: UM-SPH operates as a site within the US Flu Vaccine Effectiveness Network, which is coordinated by the Centers for Disease Control and Prevention and monitors vaccine effectiveness in the ambulatory care setting.^{124,125} The branch of the study coordinated by UM-SPH is referred to as the *Michigan - Henry Ford Influenza Vaccine Effectiveness* study (MFIVE) because of participant enrollment at both the University of Michigan health system and the Henry Ford health system in the metro-Detroit area.

Ambulatory cases were identified from patient intake forms noting ARI symptoms and cough, with illness onset ≤ 7 days ago, and ≥ 6 months of age. If patients (or their legal guardians)

agreed to participate in the study, midturbinate nasal swabs were collected by study staff and participants (or their legal guardians) were asked to complete a demographic questionnaire. In this paper, we restricted to participants from University of Michigan sites (N=8) in order to match the underlying population of the household and hospital studies (Figure 4-1). The majority of clinics were located in Washtenaw County, while 3 clinics were located in neighboring Livingston and Wayne counties.

Hospital: UM-SPH also contributes data to the CDC's *Hospitalized Adult Influenza Vaccine Effectiveness Network* (HAIVEN), which monitors vaccine effectiveness against influenza-associated hospitalization.⁷⁶⁻⁷⁸ In this study, staff used hospital intake logs and admission notes to find eligible participants, defined as: in-patients ≥ 18 y who recently presented to the hospital (≤ 72 hrs) with ARI symptoms and cough and a reported illness onset ≤ 10 days ago. Similar to the ambulatory study, after enrollment and consent procedures, study staff collected a midturbinate nasal respiratory sample and completed a demographic questionnaire with the participant. Study recruitment occurred at the UM Hospital in Ann Arbor, Michigan (Figure 4-1).

Laboratory methods: Midturbinate 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 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 UM-SPH.

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 HIVE has operated year-round starting October 1 of 2014, MFIVE and HAIVEN studies commence at confirmation of regional influenza circulation each season, recruit for at least 12 weeks, and may

potentially end before complete termination of the epidemic in the community. Season week 1 in all figures corresponds to the calendar week containing October 1.

Epidemic comparisons: We created influenza epidemic curves for each network in each season to compare their epidemic characteristics. Because of the large difference in the number of cases reported to each network and to fit curves to the same scale, curves were proportionally standardized as influenza cases reported each week divided by the network's total cases recorded that season. Curves were created for both influenza A (aggregated H1N1, H3N2, and undetermined subtype) and influenza B (aggregated Yamagata, Victoria, and undetermined lineage). Cases of influenza A and B co-infection contributed to both influenza A and B epidemic curves.

Epidemic patterns were compared in various other ways. For one, we determined the time period each season during which each network recorded the middle 50% of all 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 total 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.

4.3 – Results

Altogether, a total of 13,028 ARI cases were recorded between 2014-15 and 2018-19 (Table 4-2). Of all ARI episodes captured by the three networks over the five seasons, 2,371 samples were positive for either influenza A or B (18.2%). Only two cases of influenza A and influenza B codetection were recorded—both were captured in the hospital network, one in the

2016-17 season and the other in the 2017-18 season. Across all seasons, samples were positive for influenza in 28.7% of ambulatory cases, 17.2% of hospitalized cases, and 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.

In general, surveillance seasons were characterized by a single dominant influenza A subtype and B lineage. Figure 4-2 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). For influenza B, B(Yamagata) was the dominant lineage in most 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.

Most ARI in the region generally occurred between January and April (Supplementary Figure 4-S1). Given the year-round surveillance protocol in the household cohort, there is less of a notable uptick in ARI reports in this population during the traditional influenza season, compared to the hospital and ambulatory studies. Seasonality of influenza was much more pronounced and captured similarly from year-to-year by each of the three networks (Figure 4-3). Epidemics in all five seasons began with influenza A circulation, which tended to reach its midpoint generally 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 notably 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, networks reported the middle 50% of all total influenza cases (i.e., 25% to 75% of that season's cases, represented by the colored horizontal line in Figure 4-3) over roughly the same interval—approximately 6 weeks in duration, which occurred about 6 weeks after initial epidemic circulation (Figure 4-3). In all but the notably early season of 2014-15, the bulk of this 6 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.

Figure 4-4 displays 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). Epidemic activity recorded by all three networks appeared broadly similar. In general, the beginning of influenza activity was noted about 8 to 10 weeks in advance of the community midpoint; the exception being the 2014-15 season, when all three networks displayed nearly identical rates of sharp growth about 5 weeks in advance of the community midpoint (Figure 4-4A). The 2014-15 season also displayed the longest epidemic decline, particularly in the household study, with influenza persistence noted for nearly 5 months after the calculated community midpoint. Additionally, just as the epidemic timing of the three networks was broadly similar each season, we saw no obvious differences in the epidemic timing of the four distinct age groups across seasons (Figure 4-4B). No curve from any one age group displayed a persistent, earlier epidemic rise than any of the other age groups.

4.4 – Discussion

Our study is the first to assess epidemic influenza data from three distinct, non-overlapping surveillance networks operating within a single geographic region in the US. We considered five seasonal influenza epidemics of a single community, consisting of cases reported by severely affected hospitalized patients to household members with only mild symptoms.

Prior to this work, we suspected that influenza epidemic curves detected by each network would have distinguishing characteristics because of their distinct surveillance populations. 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 similar 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.

This does not mean that knowledge of influenza surveillance data from the three systems is superfluous; indeed, data from the three systems provided us with a more wholistic view of regional influenza epidemics and help to better understand particular features of past influenza seasons. Below, we highlight three seasons in which data from all three networks helped to retrospectively explain particular characteristics of seasonal influenza, including vaccine effectiveness, 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. 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.^{126,127} 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. We do note that in the HIVE study around 70% of the study population reported vaccination in 2014-15, which was markedly higher than the 49.2% of the US population ≥ 6 mos vaccinated.¹²⁸ Our results underscore the fact that influenza can still transmit rapidly in a population well-immunized with a poorly matched vaccine.

The 2014-15 season also underscores 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.¹²⁶ Because surveillance is stopped at the designated end of the influenza epidemic for both ambulatory and hospital networks (determined during each season), they failed to capture the community outbreak of influenza B which lasted through early June. To best understand the season's complete influenza epidemic, a less stringent "end-of-season" definition or an extended surveillance period was needed.

Second, we want to address the 2017-18 season in our results, 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 4-3). More than in any other season, the hospital system's epidemic was more distinct than those of the household or ambulatory systems. In particular, the middle 50% of all hospital cases was recorded over a period of 11 wks (compared to the 5 wks and

8wks 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 4-2). Both of these observations support the idea of a severe flu season. Despite a well-matched vaccine and moderate effectiveness of 39% against all influenza, this season was indeed nationally notable for its dramatic illness severity.¹²⁹ 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.¹³⁰

Finally, we highlight the persistence of the 2018-19 season. In our study, and similar to previously published results, across most seasons cases in all three networks began to rise around 10 weeks in advance of the seasonal midpoint and then declined over a period of months.¹³¹ 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 around three months, which is corroborated by the CDC’s annual summary reporting that the 2018-19 season was the longest epidemic of the past 10 years.¹³² 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 4-S2). Figure 4-1 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.⁸⁰ This was part of the rationale for this study. For one, 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.^{11,18–20,23,24,113} This was not the case. While households reported ARI throughout the year, 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 were noted to higher experience influenza risk before the community epidemic midpoint, compared to other age groups.²⁹ 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 4-4B). 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.¹³³

Overall, epidemic peaks, troughs, viruses detected, and epidemic duration appeared largely similar across all three networks in each season, regardless of seasonally circulating influenza types. Leveraging data from all three systems provided us with a more comprehensive view of the overall, regional influenza epidemic. The 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. As the adage states, “if you’ve seen one influenza season, you’ve seen one influenza season” and so it is encouraging

that all three surveillance systems—clinical, hospital, or household-based—appeared to broadly agree on major patterns and dynamics of the influenza epidemic each year. Furthermore, while differences between networks were suggestive of unique epidemic features of the influenza season, these were largely useful only in retrospect. For real-time responsiveness, our results show that any level of influenza surveillance in a community can provide local public health and medical experts with reliable information and can be used to guide meaningful public health response and preparedness efforts in a timely fashion.

Table 4-1: Description of three prospective influenza surveillance studies in southeast Michigan

	<u>Hospital</u>	<u>Ambulatory</u>	<u>Household</u>
Study Name	HAIVEN (<i>Hospitalized Adult Influenza Vaccine Effectiveness Network</i>)	MFIVE (<i>Michigan - Henry Ford Influenza Vaccine Effectiveness study</i>)	HIVE (<i>Household Influenza Vaccine Evaluation study</i>)
Age eligibility	Participants ≥ 18 years old	Participants ≥ 6 months old	Households who use the University of Michigan health system with at least 3 members and one child <10y old at enrollment
Illness eligibility	Patients who were recently hospitalized (≤72hrs) for ARI ≤10 days' duration, broadly defined by admission diagnosis, with new onset cough	Clinical admission with a recent ARI, defined as the presence of new cough ≤ 7 days' duration	Participants are instructed to report illness cases from anyone in the household, defined as the presence of two or more symptoms of ARI
Laboratory methods	Multiplex RT-PCR	Multiplex RT-PCR	Multiplex RT-PCR
Geographic restrictions for this paper	Only patients seen at the University of Michigan hospital	Only patients seen at University of Michigan affiliated clinics	None
Period of surveillance each season			
2014-2015	17wks (Nov 5 to Mar 6)	16wks (Nov 10 to Mar 5)	Year-round, starting Oct 1
2015-2016	20wks (Nov 23 to Apr 15)	14wks (Jan 4 to Apr 14)	Year-round
2016-2017	27wks (Oct 16 to Apr 28)	14wks (Jan 3 to Apr 14)	Year-round
2017-2018	29wks (Oct 6 to Apr 28)	19wks (Nov 13 to Mar 30)	Year-round
2018-2019	31wks (Oct 19 to May 24)	20wks (Dec 10 to May 3)	Year-round
Enrollment sites assessed in study (or households/participants enrolled for HIVE)			
2014-2015	1 hospital	16 clinics	343 households / 1435 individuals
2015-2016	1 hospital	11 clinics	226 households / 992 individuals
2016-2017	1 hospital	11 clinics	297 households / 890 individuals
2017-2018	1 hospital	11 clinics	291 households / 1187 individuals
2018-2019	1 hospital	15 clinics	351 households / 1115 individuals

ARI: acute respiratory illness

RT-PCR: reverse transcriptase polymerase chain reaction

Table 4-2: Case counts of influenza and acute respiratory illness (ARI) in each surveillance network across seasons

Network	Season	A	B	A(H1N1)	A(H3N2)	B(Victoria)	B(Yamagata)	Total influenza	Seasonal ARI	Seasonal ARI -	
										influenza positive	Overall ARI - influenza positive
Ambulatory (M/F/V/E)	2014-15	254	12	1	251	1	12	266	1057	25.2%	
	2015-16	134	40	123	10	18	20	174	738	23.6%	
	2016-17	158	87	1	151	24	59	245	833	29.4%	28.7%
	2017-18	260	85	31	208	2	81	345	975	35.4%	
	2018-19	373	31	166	198	16	11	404	1386	29.1%	
Hospital (H/A/V/E/N)	2014-15	119	11	0	114	0	11	130	754	17.2%	
	2015-16	47	3	0	4	1	1	50	313	16.0%	
	2016-17	47	21	0	45	1	20	68	462	14.7%	17.3%
	2017-18	71	23	4	57	0	21	94	371	25.3%	
	2018-19	51	0	19	28	0	0	51	376	13.6%	
Household (H/V/E)	2014-15	166	46	0	166	11	34	212	1558	13.6%	
	2015-16	33	10	27	1	5	5	43	851	5.1%	
	2016-17	54	33	2	50	4	27	87	878	9.9%	9.4%
	2017-18	83	28	1	66	4	22	111	946	11.7%	
	2018-19	86	5	51	27	5	0	91	1530	5.9%	
All		1936	435	426	1376	92	324	2371	13028	N/A	18.2%

Figure 4-1: Location of unique HIVE households, MFIVE ambulatory clinics, and HAIVEN hospital across southeast Michigan census tracts, 2014/15 through 2017/18

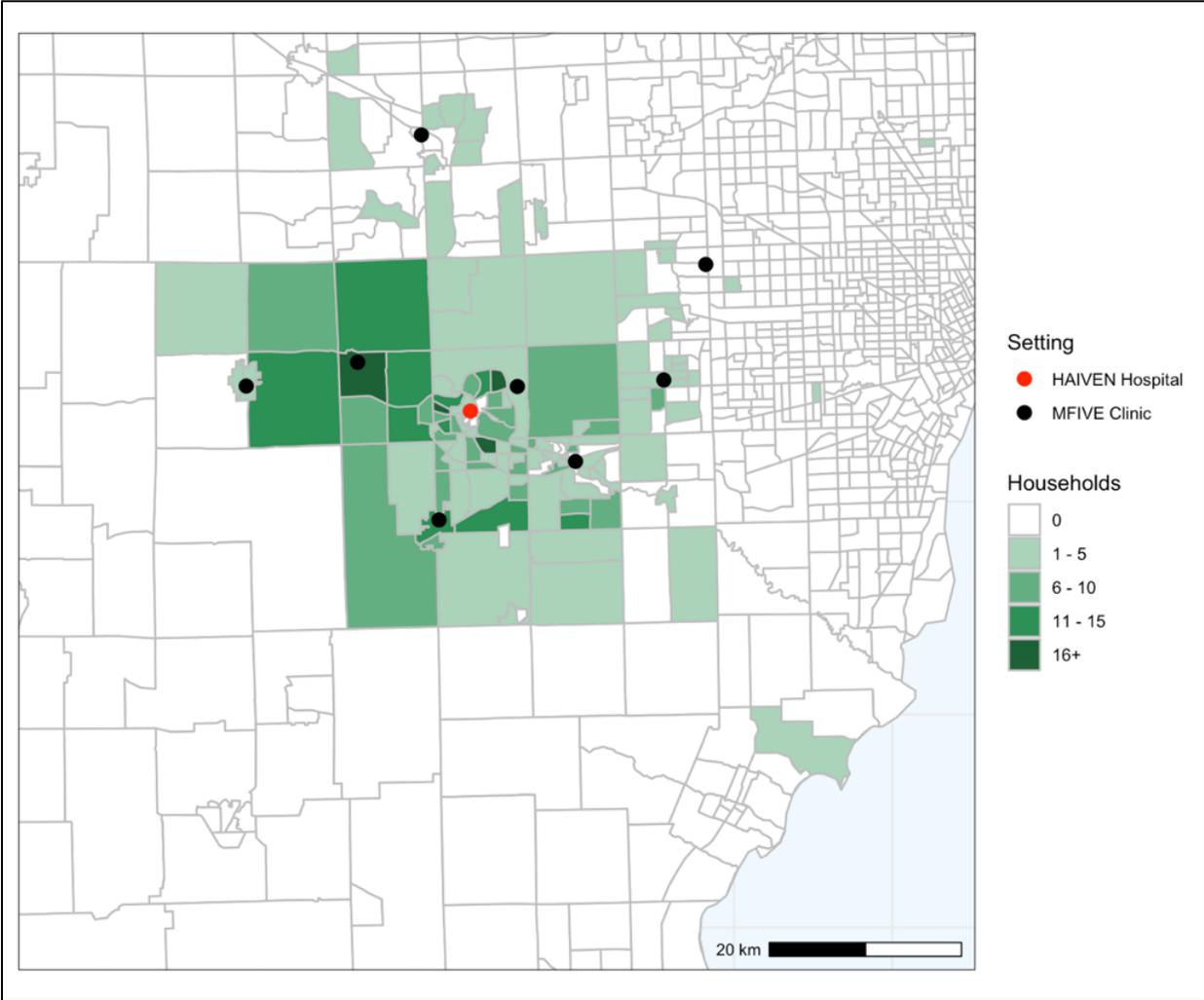


Figure 4-2: Detection of influenza A and B and their respective strains as a proportion of all cases, across five surveillance seasons (2014-15 through 2018-19)

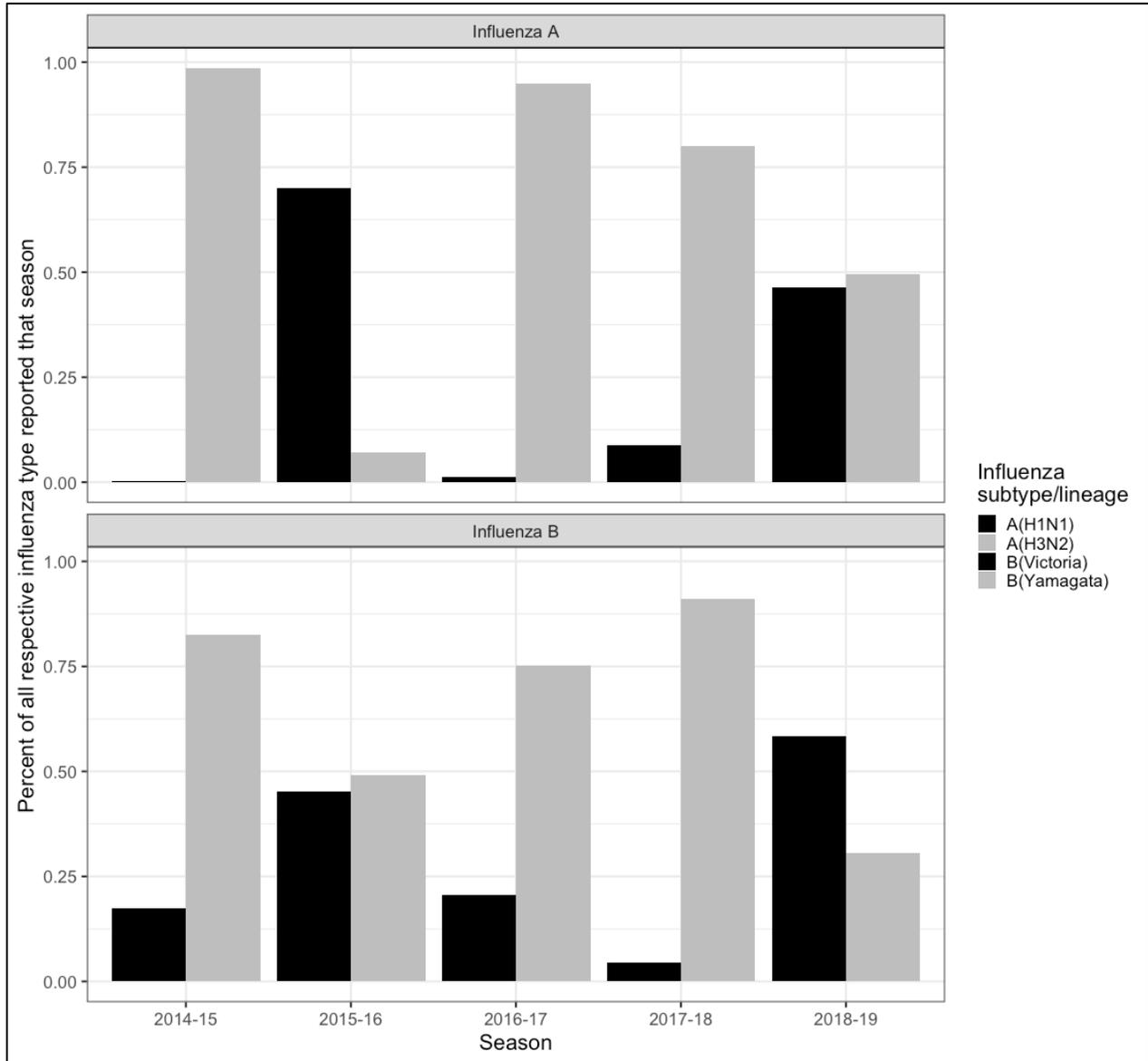
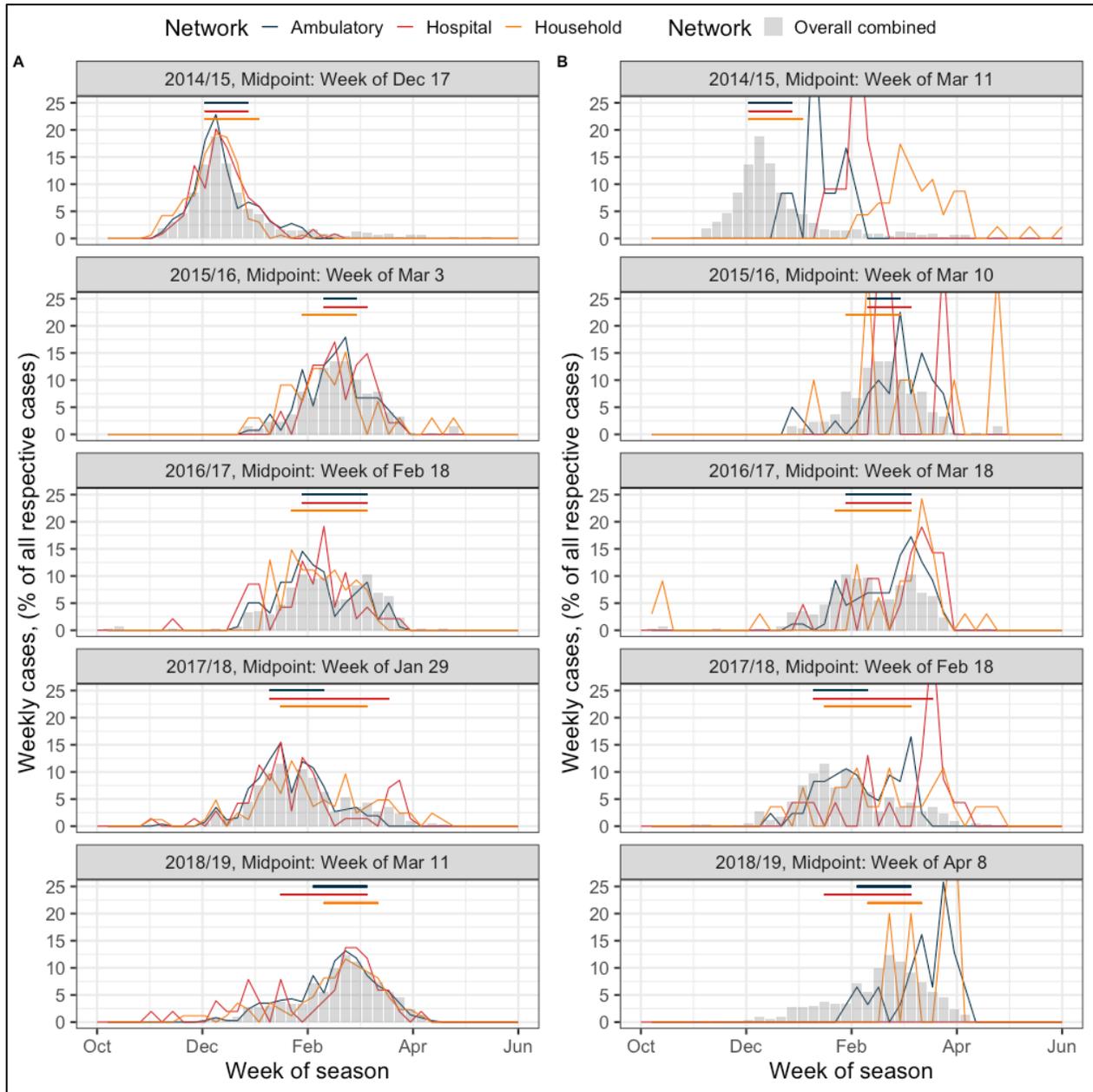


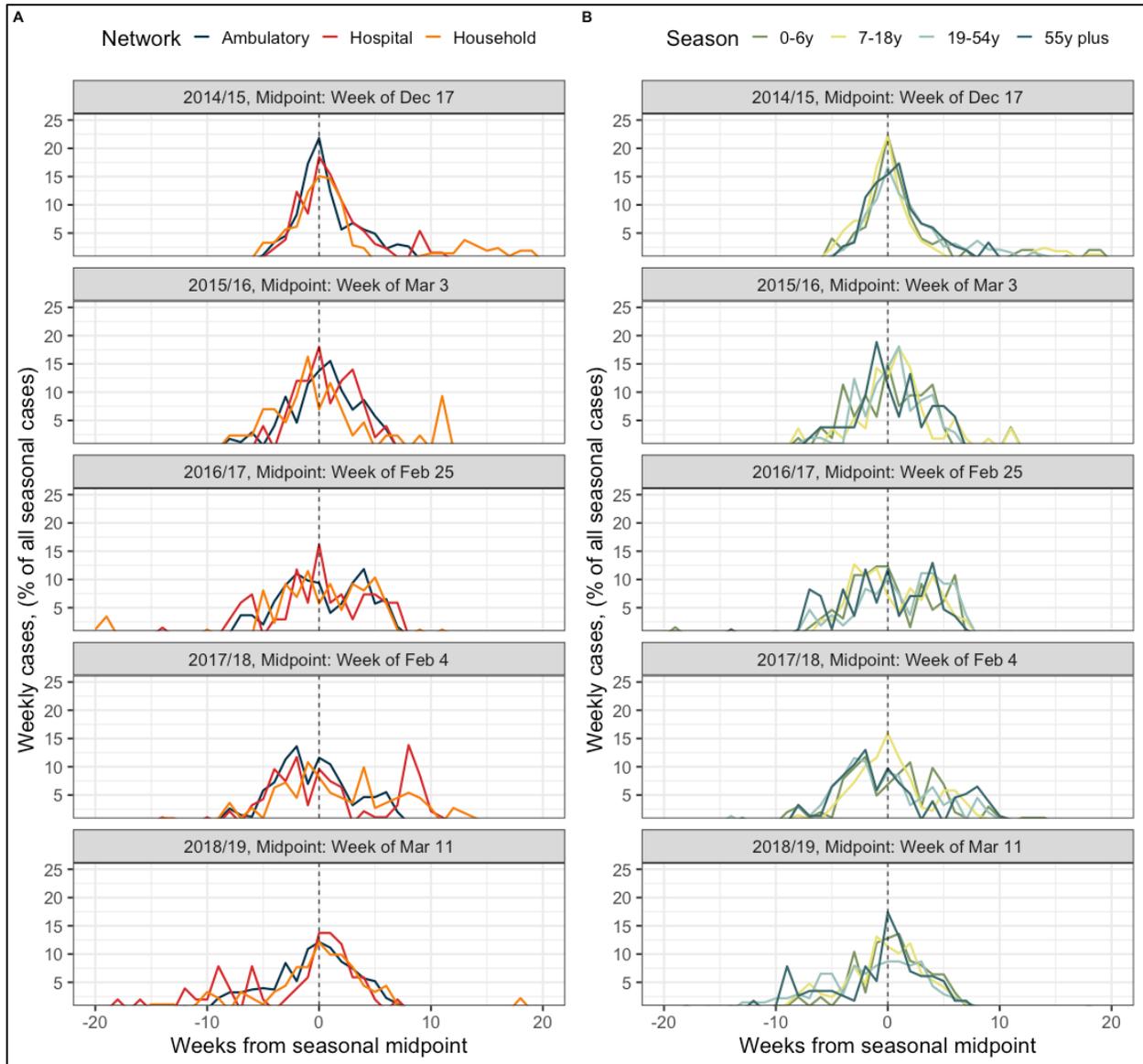
Figure 4-3: Overall epidemic curves for influenza A and B recorded by three surveillance networks of southeast Michigan (2014-15 through 2018-19)



The left column (A) represents influenza A cases (aggregate of H1N1, H3N2, undetermined subtypes) and the right column (B) represents influenza B cases (aggregate of Victoria, Yamagata, undetermined lineages). The colored lines reflect influenza A and B epidemics of each of the three networks. Y-axis units represent the network-standardized weekly number of cases reported, as a proportion of all cases reported in the network that season.

The grey bars reflect the epidemic curve of all influenza cases from all networks reported that season. Horizontal, colored lines are equivalent within rows and represent the period during which the middle 50% of all influenza cases (influenza A and B combined) were reported to a given network that season.

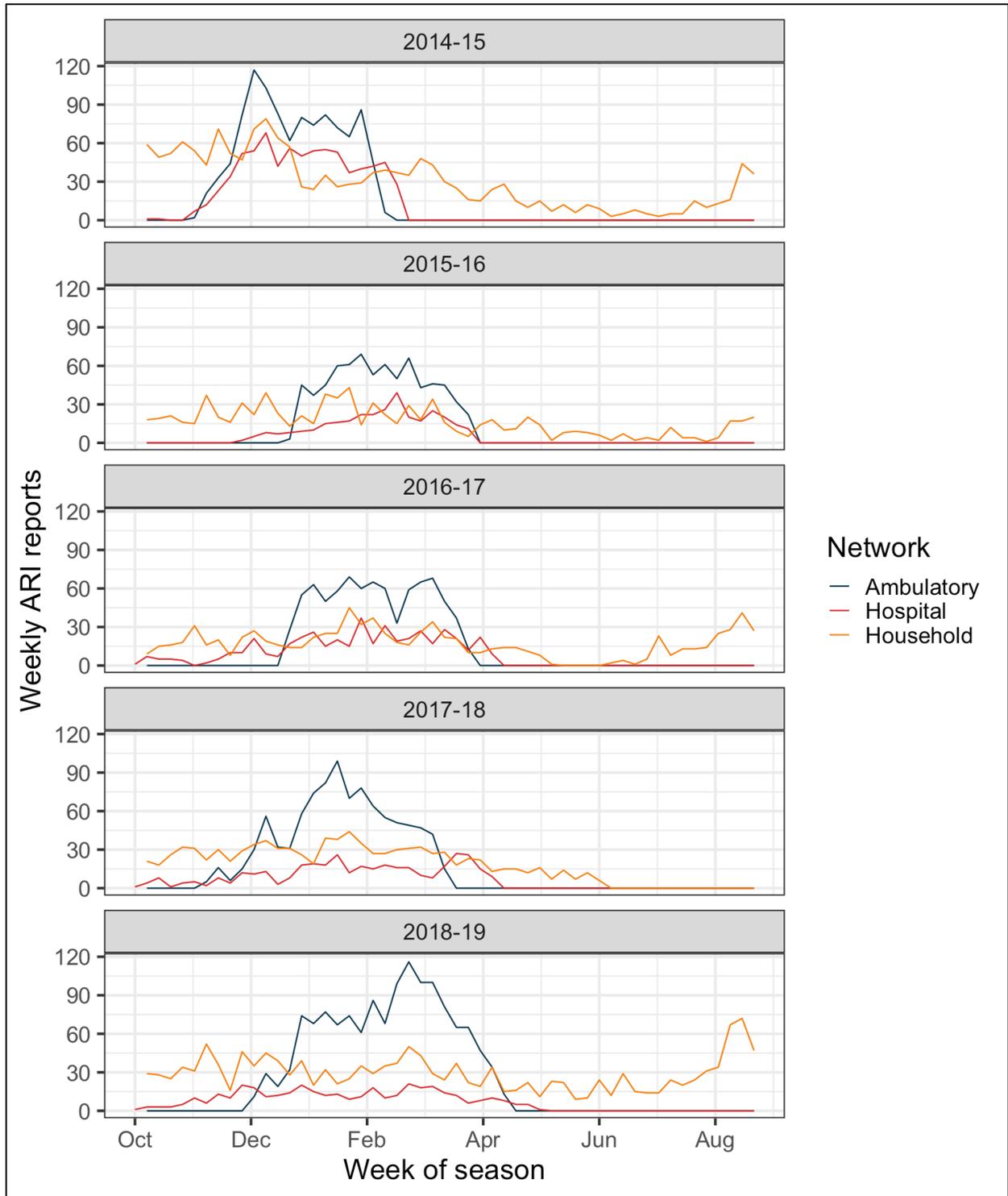
Figure 4-4: Epidemic curves centered at overall community midpoint in southeast Michigan, stratified by surveillance network and age group



The left column (A) represents epidemic curves of all influenza A and B, stratified by network. The right column (B) represents epidemic curves of all influenza A and B, stratified by age group of individual. Y-axis units represent the network (or age group) standardized weekly number of cases reported, as a proportion of all cases reported in the network (or age group) that season.

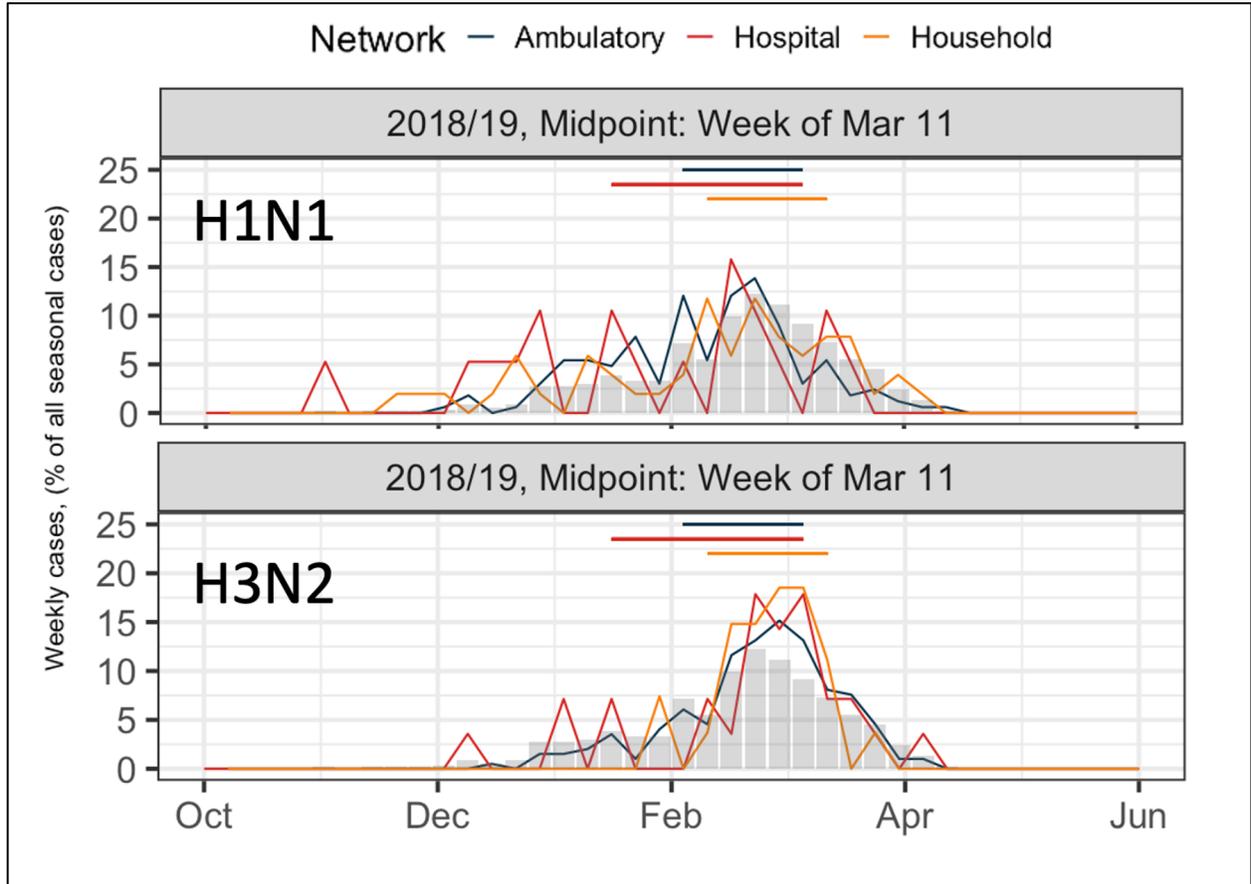
The seasonal midpoint is defined as the calendar week at which 50% of a season’s total influenza cases (A and B, across all three networks) had been reported. The week is noted in the facet title for each row.

Supplementary Figure 4-S1: Seasonal reports of acute respiratory illness (ARI) across three surveillance networks in southeast Michigan



Lines represent weekly sums of ARI reported to each network

Supplementary Figure 4-S2: Epidemic curves for influenza A subtypes during the 2018-19 season



The colored lines reflect influenza A and B epidemics of each of the three networks. Y-axis units represent the network-standardized weekly number of cases reported, as a proportion of all cases reported in the network that season.

Chapter 5: Leveraging Infectious Disease Surveillance Data to Prevent Illness Outbreaks in Childcare Programs[‡]

5.1 – Introduction

Childcare attendance is an established, independent risk factor for infectious diseases in childhood because of the pathogen-sharing behaviors of young children, their naïve immune systems, and the crowded environments of childcare programs compared to individual households.^{39,40,42,43} As a result, epidemic surveillance is a necessary component of early childcare practices.¹³⁴ Illness surveillance data provide valuable information on communicable disease occurrence in childcare centers, offering local public health departments the opportunity to quickly intervene on illness spread.^{68,84,135}

The web-based *Michigan Childcare Related Infections Surveillance Program* (MCRISP) was established in 2013 in southeast Michigan. In contrast to the traditional paper-based illness reporting in Michigan childcare programs, MCRISP allows participating childcare programs to submit childhood illness reports online in real time; these reports include information on symptoms, informal diagnoses, and actions taken. Reports are then summarized and sent to the local public health department and have been shown to be a valid representation of real-time

[‡] Chapter 5 is adapted from our manuscript *Expanding the Paradigm of Biosurveillance towards Data Sharing with the Community – Qualitative Insights from a Childcare Center Illness Surveillance Network* which was accepted for publication in the journal *Health Security*. This chapter includes edits as appropriate for the purposes of the dissertation. The full author list of the original published work is as follows: DeJonge P, Gribbin W, Gaughan A, Chedid K, Martin ET, Miller AL, Hashikawa AN.

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outbreaks.^{136,137} Healthcare experts use this type of information to evaluate disease incidence, transmission, and risk in these facilities. Subsequent program outreach and outbreak interventions based on this data are generally at the discretion of local officials.

In the most recent edition of *Caring for our Children*—a nationally published best-practice reference book of childcare recommendations—the authors stress the importance of using surveillance data in childcare programs to characterize daily illness patterns, identify outbreaks, and recognize effective interventions.¹³⁸ MCRISP disease surveillance data, however, are not regularly returned to childcare programs.

Our goal in this Aim, therefore, was to understand how MCRISP data could be further tailored to the priorities of childcare stakeholders and better serve as a tool in daily illness prevention efforts.^{136,137} To this end, and to avoid *a priori* assumptions from MCRISP researchers, we recruited a group of directors from MCRISP-affiliated childcare centers to participate in a series of focus group discussions. Qualitative data was collected using a ground-up, open-ended design, and was analyzed with multistage thematic assessment to identify consensus themes. We wanted to determine how MCRISP data could be more appropriately designed around user needs—thereby improving data collection and validity— and ultimately translated into illness outbreak prevention at the center level.

5.2 – Methods

Participants: We recruited childcare directors from the thirty licensed childcare programs participating in MCRISP during the fall of 2019. MCRISP operates within a single southeast Michigan county and captures childcare-related illness reports from over 4,000 young children across a blend of private facilities (70% of participating programs), university-affiliated programs

(20%), and federally-supported programs (10%, e.g., Head Start).¹³⁷ All MCRISP directors or primary MCRISP reporters from each program were eligible to participate in the study, all of whom were fluent in English. Our sampling goal was to recruit 20 directors (from the 30 centers overall) to capture perspectives from the majority of MCRISP-affiliated centers. Participants were contacted via email during early August 2019 and given the option to attend one of four focus group dates, which were scheduled throughout August and September 2019.

Setting: We worked in close partnership with the Childcare Network of Southeast Michigan (CCN), a non-profit organization established in 1971 to improve the quality and access of childcare in southeast Michigan.¹³⁹ CCN also serves as the regional resource center for *Great Start to Quality*, a program that assesses the quality of early childhood programs and providers in Michigan. In this role, CCN provides on-site consultants for quality improvement in local childcare programs. The CCN headquarters was familiar to MCRISP users and provided a conference room for each of our focus groups.

Data collection: Focus group conversations were semi-structured; study moderators worked from an interview protocol but the group was free to bring up new topics and ask questions (Table 5-1). The first and second author served as group moderator and co-moderator (PD and WG, respectively); the final author (AH), founder of MCRISP and most familiar to the participants, was not present at any of the focus groups so as not to influence potential responses. The first two focus groups were attended by both a moderator and co-moderator, while only the moderator attended the final two groups. Introductory “ice-breaker” questions were used at the outset of each group before transitioning to key study questions, which concerned how the illness surveillance data could better benefit childcare providers. Prior to the focus groups, we also

suspected that real-time, summarized MCRISP illness data would be valued by users; questions 7 and 8 were asked to better understand user familiarity with these types of data summaries.

Group sessions ranged from 60 to 90 minutes in length and were audio recorded. For study credibility purposes, at the end of each session the moderator summarized the group's main points from personal notes and recollection and confirmed that participants agreed with the summary.¹⁴⁰

Human participant compliance: Though the University of Michigan Medical School IRB deemed this study exempt, participants were asked to read and sign a formal informed consent noting the use of audio recording and that anonymous quotes may be published. Participants were provided food and also compensated with a \$50 gift card as a token of appreciation. Finally, all participants were asked to complete a short demographic questionnaire following the discussion. All participants spoke English as their native language.

Data analysis and thematic assessment: All four groups were audio-recorded. Group recordings were then independently transcribed verbatim by PD and AG, who cross-checked their results with each other. Corroborated, final transcripts were stored on a secure cloud-based server contracted with the University of Michigan. Participants were each assigned an alphanumeric identifier based on group number (i.e., A2 corresponds to participant 2 in Group A). Quotes were assigned to these identifiers throughout the transcripts.

Ideas and concepts from each of the four transcripts were coded and collated by the first author (PD). The main goal of the research—how childcare epidemiologic data can be a more beneficial illness prevention tool—was used to determine hierarchical themes using code piles and structural maps.^{140,141} Thematic results were shared and corroborated with both the third and the final author (AG and AH); themes were then re-structured based on collaboration of PD, AG, and AH. Consensus themes and subthemes were defined, named, and shared with the second author

(WG) who verified thematic assessment of after reading through all the focus group transcripts independently.

5.3 – Results

A total of 12 representatives from community childcare programs participated in our focus groups—3 individuals per group (Table 5-2). Participants were all women, almost all of whom were directors of their respective programs (in cases where directors were unable to attend, the primary MCRISP reporter was sent in their stead). Participants had an average of 24 years of experience working in childcare. The distribution of participants from private, university-affiliated, and government-affiliated programs (75%, 17%, and 8% respectively) was skewed towards private centers, though not unexpected given the distribution of Washtenaw County childcare programs at large (81%, 2.7%, and 17% respectively).¹³⁹ Notably, relatively more University-affiliated and fewer government-sponsored programs were represented in focus groups. Participants represented a mix of both urban and rural childcare programs (Figure 5-1).

We identified four major themes from our group audio recordings. Participants wanted an epidemiologic surveillance system that would: (1) support subjective experiences with objective data; (2) assist in program decision making; (3) provide educational resources; and (4) prioritize the reporter’s experience. Themes, subthemes, and supporting quotes are detailed below.

Theme 1: Objective Surveillance Data Can Support Subjective Illness Experiences

It was clear that illness data were not required to convince childcare providers that illness outbreaks were common challenges in their programs. Directors sympathized with each other about the frequency of child sickness, yet ironically there was a shared feeling that their program experienced more than the average number of illnesses. A major consensus theme was that

objective MCRISP data, especially aggregated and summarized at the community level, would help to ameliorate this sentiment and provide childcare providers with vital knowledge.

1.1) Knowledge of Community Illness Can Validate Experiences in Childcare Programs:

All four groups supported the idea that knowledge of aggregate illness data collected by MCRISP would lead to a better understanding of the current state of community childcare illnesses. In fact, childcare directors supported the idea because illness data would validate what they were experiencing and provide a sense of solidarity among centers.

“This is a community problem. Sometimes I feel like, ‘Oh gosh, we’ve caught everything.’ I’ve washed and Cloroxed everything. Everyone’s washing their hands—and obviously kids wash their hands very differently than I do—but it would be nice to know that this is not just something that’s happening in our school, that we’re doing enough” (D1)

“Those [illnesses] are kind of just going around—just to get an idea that, like, we are not the only ones in the boat, you know? Sometimes it feels like that, for sure” (D2)

Participants stated they had no issues with sharing illness information among all MCRISP centers as long as data were anonymized.

1.2) Knowledge of Community Illness Can Improve Relationships with Parents:

Experience validation seemed also be useful in conversations with parents. Participants shared a sentiment that childcare center practices or policies were often faulted for the illness of children.

“I feel like we do kind of get blamed. Like, ‘Oh, my kid got [sick] from childcare” (A3)

To reduce parental concerns, participants wanted to be able to share MCRISP illness data with parents. MCRISP data would not only corroborate the illness incidence experienced in a single center, but also assist parents in their own decision-making. For instance, a user’s knowledge of

outbreak data could help them advise parents on whether or not to keep home a younger, immunocompromised child.

“It’d be nice if the system [said] ‘hey, you know, this [illness] is running around in your area.’ That would be very helpful for a lot of our families.” (A1)

Theme 2: Surveillance Data Can Assist with Program Decision Making

Outside of using surveillance information for quantitative objective reassurance, we found that childcare providers were eager to use MCRISP data for reactive and proactive purposes. In the same way the local public health department uses community illness surveillance data, MCRISP directors proposed using the data for decision making related to preventing illness transmission.

2.1) Decision Making for the Present: Participants noted that MCRISP data would be a considerable aid during emergent community outbreaks. Aggregate MCRISP illness reports would bolster their understanding of the ongoing situation. Additionally, participants felt that MCRISP could help childcare programs best convert this surveillance data to action by being pairing the data with pertinent best-practice guidelines.

“We...send [outbreak information] to our custodial staff, so we can say, ‘Hey we’re getting notices that it’s peak flu season. Can you do, what they call, a hospital clean?’ So they do a deeper clean of the classrooms.” (B1)

“In cases of outbreaks, [we wonder] is there like a clear protocol or set of steps? ‘Okay, this is what you need to do.’ Whatever it may be.” (C1)

As an example of when enhanced MCRISP data would have been useful, participants often referred to the early fall of 2019, when southeast Michigan experienced a dramatic measles outbreak.¹⁴² Participants greatly appreciated the information they received from the health

department, but still felt as though more educational materials specific to childcare would have helped for both providers and parents.

“People were talking about, ‘*Well, anybody that enters an infant room will have to put on masks*’ but then, well, how effective is that? ... If there’d been a resource that you could’ve gone to and determine what’s a reasonable step to take to not have an exposure, versus this won’t make any difference at all ... that would’ve been something I used” (A2)

2.2) Decision Making for the Future: There was also some discussion of retrospectively using MCRISP data from their center to gauge the impact of their past interventions on historical incidence of disease.

“Is there a seasonal pattern here ... and did these extra steps we decided to add for sanitation, did they make a difference? And if [they] didn’t, then let’s stop doing that.” (A2)

Participants felt that their ability to understand past patterns in illness would help them to better prepare for program outbreaks. Furthermore, there was a shared sentiment that changes to policy or practice should be associated with decreases in illness incidence.

Theme 3: Bolster the Strength of Data with Paired Educational Materials

To convert knowledge of illness data into actionable illness prevention efforts at both the childcare and household level, participants noted that a more effective surveillance system would package summarized epidemiologic data alongside educational materials.

3.1) Materials for Providers: Participants were interested in access to a sort of repository for advisory materials from expert organizations, like the American Academy of Pediatrics (AAP) or the Centers for Disease Control and Prevention (CDC). Providers noted that collated

information would be helpful in clearing up wider confusion regarding childhood illnesses and expert recommendations related to illness prevention.

“We will invariably hear multiple things from different pediatricians coming through families ... this one will say, *‘Oh it’s conjunctivitis, [but] it’s not contagious’* but then the next doctor’s like, *‘This is highly contagious’* ... I’ve been doing this for 20 some years and ... I mean none of [the opinions] ever aligned” (D1)

Here again, participants brought up the importance of relationships with parents as this type of information would serve to endorse their decisions as explained to parents. This was especially true for decisions related to child exclusion policies. Child exclusion is an important tactic in childcare outbreak prevention but can be associated with difficult conversations—especially because employed parents often have to miss work if their child is removed from care.

“[Parents] appreciate that our guidelines for exclusion are based on the American Academy of Pediatrics guidelines ... they like that it’s [an] official health source ... it gives credibility then to our policies because they’re based on [official sources].” (A2)

We also note here that childcare illnesses reported to MCRISP frequently originate from parents who let the childcare center staff know that the child was sick at home; parents, however, do not always offer the level of illness detail requested by the illness surveillance system. Details of these home illnesses are important to record, however, and participants stated that more official MCRISP materials would help them inquire further about the illness without feeling that they were being overly intrusive. Regarding questions to parents about details of their child’s illness, one director noted:

“It feels like we’re prying. We’ll say *‘oh, we just are part of a pilot project with this system and we just need to enter it in’* ... it would be helpful to just have something to send out saying we’re participating in this research.” (B1)

3.2) Materials for Families: Providers also thought that educational materials designed to send home to households would also be useful. To communicate with parents, directors agreed that scientifically vetted materials should take many forms (e.g., articles, videos, or pamphlets). Another participant stated that they have had success in combatting disease outbreaks using materials specifically catered to children.

“A curriculum about germs that’s geared towards kids. We’ve had good success with [a specific lesson plan] and [teaching kids] how to wash their hands ... that’s something I think would be helpful” (D2)

Theme 4: Prioritize the Illness Reporter’s Experience

Lastly, a successful childcare illness surveillance network must accommodate the needs of childcare providers. Because the validity and representativeness of data collected is directly related to the investment of childcare providers a system like MCRISP must work to address the following subthemes addressed by participants.

4.1) Operate Simply: Childcare providers repeatedly mentioned the frenetic nature of their jobs; MCRISP needs to be seamlessly integrated into the daily operations of childcare centers, otherwise the quality of data will decline.

“It’s just an issue [in childcare] that directors are so busy and are handling so many different things in a day that finding time and ways for them to communicate ... is always a challenge.” (B1)

“I feel like if I don’t try to report [illnesses] every day, it kind of falls off my radar.” (A3)

This idea also speaks to the need for simplicity in MCRISP data summaries. Participants were eager to use this information, but noted that data summaries and statistics should be catered to non-epidemiologist audiences (Figure 5-2). Descriptive summaries like bar graphs, pie charts, and time series plots to a lesser extent, were most appealing to providers.

4.2) Offer Feedback: Especially in light of their busy workdays, participants were frustrated that despite reporting illnesses on a daily basis, they received very little feedback from either MCRISP or local public health. Participants noted that they would appreciate some form of indication that their reports were being seen and used.

“If we’re taking the time to enter [illness reports] in, we’re getting something out of it too, you know? Like just getting updates or some kind of pop-up about an outbreak.” (B1)

Indeed, on the occasions they had received feedback from the health department, they felt it to be reassuring. It justified their decision to continue reporting illness data to the surveillance system.

“I mean, it was probably after using MCRISP for a while ... but I remember them reaching out and I was like, ‘*Somebody’s reading my stuff!*’ I just hit send and, yeah, I don’t know if anybody’s reading [the illness reports], so I found that very helpful.” (B2)

4.3) Use Language and Themes Familiar to Childcare Providers: We note also that focus groups allowed participants to comment on strengths and challenges of the current MCRISP illness reporting form. Overall, participants were generally satisfied with MCRISP’s improvement over previous reporting methods.

“One thing that I’ve appreciated about this system is that it’s an as-needed basis. I can go in every day. I can go in a couple of times today. If I go a whole week and nobody’s sick, I don’t have to do anything versus when we were recording to the health department before every Friday, I had to fill out a form and send it to them regardless of what was happening” (B2)

Still, the format of MCRISP reports fail to match a provider’s experience on the ground.

“I don’t feel like there are enough [symptom] options for what I need” (A3)

“It’s not an exhaustive list [of symptoms] nor has the ability to add things that are more appropriate to what is going on.” (C3)

Participant comments highlighted the fact that reporting forms should mirror the language and experience of childcare reporters and reinforce the idea that user input is necessary at all points in creating a surveillance network.

5.4 – Discussion

Online illness surveillance networks like MCRISP have the potential to significantly improve upon paper-based reporting methods, by reducing workload for community reporters and offering real-time information regarding local disease outbreaks.¹⁴³ Results from this study further contribute to this knowledge but also underscore the idea that surveillance data can and should be used in childcare programs as a tool to mitigate illness outbreaks. Our focus groups revealed that childcare providers were eager to optimize illness surveillance data for their own uses and recognized the potential it has to help mitigate disease outbreaks in their centers.

We found four themes related to the use of MCRISP data as a tool to prevent illness outbreaks in childcare centers. Participants indicated the importance of surveillance data in providing objective support for both their (1) subjective experiences as well as (2) present and future decision making. Furthermore, participants agreed that an effective surveillance system should also (3) incorporate corresponding educational resources and (4) pay attention to the user's priorities in order to serve as a more actionable tool for illness mitigation.

The most exciting aspect of a revamped MCRISP system for directors appeared to be the availability of aggregate illness data. For one, real-time data availability would provide users with a meaningful feedback mechanism—allowing them to directly observe that their reports were being collated as well as justifying their time spent entering data. Our results also suggest that sharing community data would improve program decision making, validate the subjective

experiences of providers, and provide a sense of solidarity between centers. Participants agreed that leveraging MCRISP data in conversations and decision making would help to support the relationship between directors and community parents. This all seemed to stem from the fact that the directors shared a sentiment of being blamed for community illness—a notable point considering that the directors all had an average of over 20 years of experience in dealing with common childhood disease. Unfortunately, this feeling has been noted previously in the childcare field by providers.¹⁴⁴ In addition to the valuable epidemiologic knowledge contained within the surveillance data, prioritizing the rapid sharing of aggregate MCRISP data can support childcare directors in conversations with parents, who are often who following appropriate outbreak policy (e.g., childcare exclusion guidelines).

Our findings also offer a framework by which epidemiologic surveillance systems can enhance their data collection to a serve as a more applicable tool to mitigate illness transmission. Childcare directors suggested that educational materials, with relevant information for caretakers and parents, should be provided alongside surveillance data. In addition to a repository of consolidated recommendations and guidance from national organization, focus group participants were interested in receiving pertinent information regarding particular disease outbreaks as they were happening. Participants also note the need for readily interpretable data summaries, which can be used to make real-time decisions. Our focus group participants agreed that while epidemiologic outbreak data would be useful, an illness surveillance system would be markedly more useful as a tool if data were accompanied with a summary of its importance and corresponding action items to further mitigate transmission.

The essential role of community childcare programs has been made clear during the ongoing COVID-19 pandemic. The childcare industry was already struggling with financial

difficulties prior to the pandemic; now, in the process of trying to re-open (or modify practices appropriately), programs are experiencing COVID-19 transmission events in the absence of appropriate public health resources and guidelines.^{134,145–147} Providing childcare experts with objective data and educational resources in an efficient manner is indispensable to further protecting the health and safety of young children and families throughout the remainder of this pandemic.

Our findings also underscore the idea that as technology advances, community surveillance has the opportunity to deviate from the traditional paradigm of one-way information flow—data from public reporters to research experts. In addition to data validity, disease surveillance systems should also strive for transparency and rapid data summarization. Indeed, this idea has previously been raised in medical genomics, where the importance of enhancing citizen participation in surveillance research is stressed, specifically via meaningful access to data apps and visualizations.¹⁴⁸ Furthermore, shifting this paradigm will only serve to be mutually beneficial. Our focus group results highlighted a group of users excited to provide data to a revamped system; user engagement would lead to improved user participation and, in turn, more reporters. As a result, public health departments would receive more data regarding real-time disease circulation in childcare—a significant fact considering that children serve as major propagators of localized transmission.^{7,20,30} Improved surveillance data allow public health to respond faster to emerging outbreaks, including mitigation strategies, triggered alerts, and resource allocation.

We do note three shortcomings of our study. For one, fewer childcare providers than the goal recruitment number of 20 agreed to participate. Likely, the busy back-to-school and return-to-care activities of late fall negatively affected participation rates. Fortunately, group moderators found that the childcare providers who did attend were highly engaged, which resulted in rich

conversation for focus group analysis and notable theme saturation across the four groups. Second, while the proportion of private centers represented was not overly different than that of Washtenaw County (75% vs 81%, respectively), this may not be representative of other counties in Michigan or the US where government-funded programs are more common.¹³⁹ Additionally, because no home care programs—or programs that care for a smaller number of children in a residential setting—currently participate in MCRISP, no study participants were from home-based childcare programs. Finally, we also note that a system like MCRISP, which is based on reliable internet-access, may prove challenging to implement in a more rural community.

Despite these limitations, however, we feel our findings are still largely generalizable across variability in program type, enrollment size, or even method of illness reporting. In other words, we believe these four broad themes—centered on education, communication, and support—would resonate with all types and sizes of childcare programs and that they are not necessarily specific to an online paradigm.

Table 5-1: Semi-structured question guide for focus groups

1. What is the process of reporting illnesses to MCRISP like in your childcare center?
2. What are some challenges your center has experienced in collecting this information?
3. Where do you currently get information about community illness outbreaks?
4. If you had regular access to community illness information, how would you use it (or how are you currently using it)?
5. Are there any potential concerns you have about sharing disease information from your facility?
6. On the piece of paper in front of you, I'd like you to jot down what you would like to know about disease in the surrounding childcare community. This can be a collection of words, sentences, images, questions—anything that you are interested in.
7. In what form would this information be most helpful to you?
8. We had some ideas about what childcare providers might be interested in. Which of these do you particularly like or dislike?
9. Let's say we design a website to share this surveillance data with you. Are there features that we could include to help you as childcare providers?
10. Summary and closing

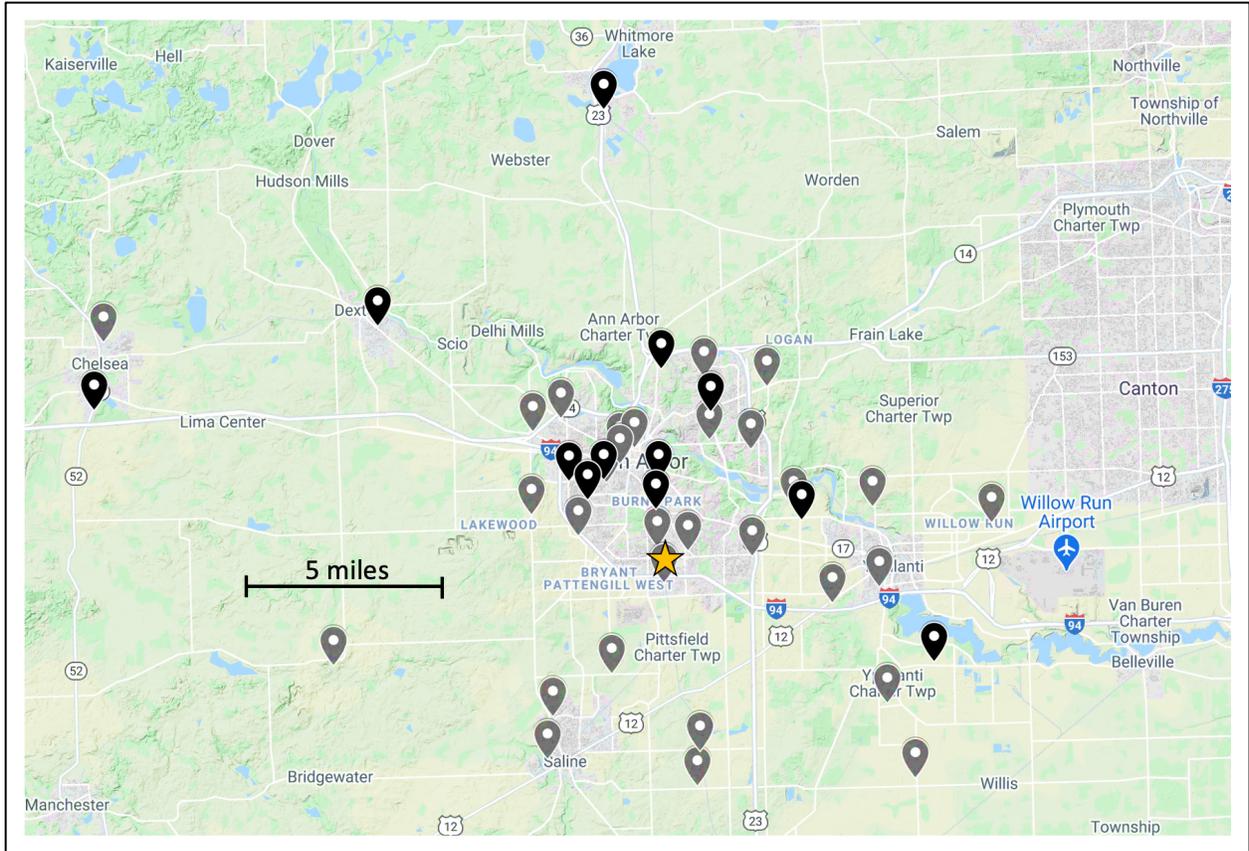
MCRISP = *Michigan Childcare Related Infections Surveillance Program*

Table 5-2: Characteristics of all childcare programs in Washtenaw County, Michigan and those represented in the study’s four focus groups, including individual participant characteristics

Characteristic	Focus group participants (N=12)	All Washtenaw Childcare Programs (N=187)*
N (%), Average (SD)		
Female	12 (100%)	
Position in childcare program		
<i>Director</i>	10 (83.3%)	
<i>Administrator</i>	1 (8.3%)	
<i>Family Service Worker</i>	1 (8.3%)	
Average number of years working in childcare	24 (6.7)	
Average number of children enrolled in program	91.4 (45.7)	
Average percent of children enrolled full-time	65.4 (19.5)	
Facility type		
<i>University-affiliated</i>	2 (16.7%)	5 (2.7%)
<i>Government-sponsored</i>	1 (8.3%)	30 (16%)
<i>Private</i>	9 (75%)	150 (80.9%)

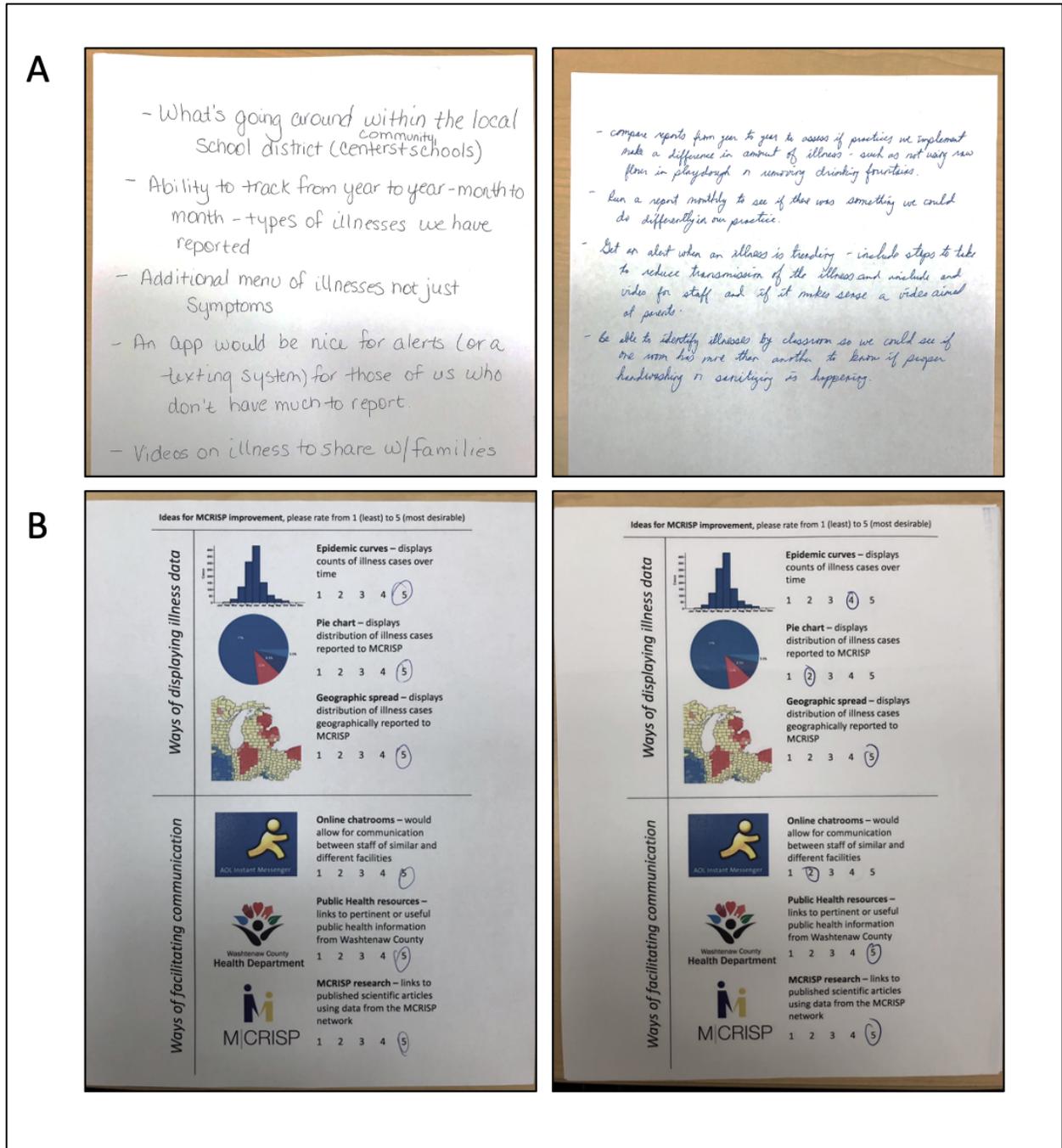
* Facility categories are approximate and not mutually exclusive as they are based on non-mandatory, self-assigned categories of licensed childcare programs in Washtenaw County, Michigan. Based on numbers from Michigan’s Great Start to Quality childcare website, greatstarttoquality.com.

Figure 5-1: Map of MCRISP childcare programs ever enrolled since October 2013



Starred point indicates location of Childcare Network of Southeast Michigan Headquarters. Darker points indicate the 12 centers involved in the focus group.

Figure 5-2: Examples of thoughts and opinions recorded during MCRISP focus groups.



Row (A) corresponds to participant free-response answers prompted by Question 6, Table 5-1, and row (B) reflects ratings of pre-conceived researcher notions prompted by Question 8, Table 5-1.

Chapter 6: Discussion and Future Directions

The central purpose guiding this dissertation was to better understand the risk of childcare-associated respiratory disease. With our access to strong prospective illness surveillance data, we designed research Aims to quantify, characterize, and offer insight on how to mitigate this risk. The first two Aims of this dissertation centered on aspects of the childcare-associated illness risk—to both children and their households. Aim 1 compared ARI incidence between individuals living in households that did and did not use childcare. Aim 2 contrasted the viral etiology and severity of respiratory disease detected in childcare and homecare children. The Dissertation's second two Aims analyzed the broader surveillance data underlying these studies. Aim 3 considered the information gained by knowledge of influenza surveillance data from three similar networks in different population settings, and also contrasted differences in their detection of the same underlying influenza epidemic. Aim 4 qualitatively investigated whether a local illness surveillance network in childcare programs could function as better tool for outbreak prevention.

This chapter concludes my dissertation. First, I restate the main findings of each Aim along with their respective strengths, limitations, and relevant public health implications. I then shift to a discussion of the pertinence this dissertation altogether along its strengths as a whole. I also remark on noteworthy directions for continued research in this field. The chapter concludes with a brief comment of the relevance of this work and significance of its findings.

6.1 – Summary of Findings

6.1.1 – Individual ARI Risk Associated with Household Childcare Use

Young children are important for both the introduction and transmission of illness in households.^{21,82,83} Knowing that children are also more at risk for respiratory disease when enrolled in childcare, we were interested in the childcare-associated illness risk in household members. Past studies have indicated a positive association, but methodological limitations undercut their findings.^{18,53,86} We had the opportunity to more appropriately investigate this question using data collected from an established prospective household study in southeast Michigan. Illness surveillance was restricted to individuals >5y old from households with at least one child of childcare age.

Analysis of 1936 illness episodes from over 1600 person-years of surveillance revealed no marked difference in the severity, seasonality, or reported incidence rate of ARI between participants in households that did and did not use childcare. Furthermore—based on analyses of both stratified regression models and full model interaction terms—we found no evidence for effect modification by variables of interest (including household number of children, household number of working adults, household SSP, and participant age). Our null findings did not agree with results of past literature, and so we interpreted this discrepancy with two primary explanations. For one, positive findings in previous work may have been impacted by outcome ascertainment biases inherent to past methodologies used. This Aim used alternative, prospective methods and a different study population. At the same time, we also noted the possibility for methodological limitations in our own work, including potentially differential reporting rates in childcare households—where the a much larger proportion of both adults were working—as well

as a sample size underpowered for the types of regression used. In other words, different studies led to different results.

A complementary explanation is that the association between childcare use and household illness risk is more complex than can be inferred with the HIVE data at hand. For instance, while the HIVE study provided us with a large dataset, the demographic form did not record variables related to the heterogeneity of childcare attendance—with regards to age at enrollment, duration of childcare attendance in the past and during the week, and the type of childcare program attended. Each of these factors has been noted to modify the relationship between childcare attendance and children.^{53,55,62,94,149} This lack of detail may have impacted our ability approximate the true relationship between ARI incidence and household childcare use.

Similarly, we know that childcare attendance is associated with acquired immunity as the child ages and a short-term reduced illness risk. This is evidenced by the influence of childcare attendance as well as the presence of older siblings, which both decrease a childcare attendee's illness risk (presumably through increased exposure to pathogens early in life).^{51,56,61} The effect of childcare use may be more pronounced when considering households with a single child, where protective effects of immunity have not yet solidified. Insufficient numbers of these single-child households were enrolled in study population, however, to appropriately assess this thought.

Findings in this Aim underscore the need to better understand the household risk associated with childcare attendance, especially as the prevalence of childcare use in the US continues to rise. Our initial study question remains unanswered by existing epidemiologic research, and our work—while the first to compare longitudinal data from the same underlying population—offers a null finding with caveats. Still, this is pertinent information for both community families and public health officials and must be continued to be investigated. Particularly during community

epidemics, households with elderly and immunocompromised members should be aware of any potential increase in disease risk and public health experts could use this information to design targeted intervention and vaccination efforts.

6.1.2 – Comparing Viral Infections of Children Who Do and Do Not Attend Childcare

Due to the naïve immune systems of young children, their unhygienic behaviors, the group-care nature of the childcare environment, and the wide range of viral respiratory pathogens that have been isolated from childcare facilities, out-of-home childcare attendance is significantly associated with ARI risk in young children.^{1,40,50} Past research had yet to offer any conclusions as to whether or not these childcare illnesses are characteristically different than those experienced by homecare children.

We collected information on over 1500 ARI cases in childcare-aged children reported to the HIVE study over the course of six years. Among all samples, 74.4% were positive for at least one respiratory virus. We found similar distributions of common childhood viruses in illnesses of both childcare and homecare children—RV was most common (in over one third of samples in both groups), followed by hCoV, RSV, and PIV. In adjusted mixed-effects logistic regression models, childcare illnesses were linked to significantly higher odds of AdV and hMPV but significantly lower odds of RV. There was some suggestion of higher risk for viral codetection in childcare children as an age-dependent association, which corroborated our finding that the pool of childcare viruses detected was significantly richer and more diverse than that of homecare illnesses.

Similar to Aim 1, this analysis would have benefited from more granular detail regarding childcare exposure. Certainly duration of past enrollment in childcare was likely to have an impact

in this analysis, especially as children who had attended childcare for multiple years prior to our seasons of interest would have gained a protective, acquired immunity to common viruses. It is also reasonable to believe that the lack of information type of childcare program may have obscured associations in our data. Family daycare programs smaller in facility size and enrollment may not share the same viral diversity as larger, commercial group-care facilities.

While previous work has investigated molecular epidemiology of childhood illnesses, including those reported in childcare populations, our study is the first to directly compare childcare and homecare illnesses from the same underlying source population. Other strengths of our study included its prospective illness reporting, implementation of sensitive RT-PCR techniques, and innovative use of a statistical analysis method from the field of ecology. We attributed the lower odds of RV to the relatively mild illnesses associated with RV and the likelihood that diversity of childcare viruses reported dilutes the prevalence of RV in childcare populations. The positive association of AdV and hMPV with childcare attendance agreed with previous research findings and is supported by the epidemiologic and virologic characteristics of the viruses. Childcare stakeholders should be aware of the outsized role of these viruses in their facilities—particularly because both demand highly potent decontamination methods. Moreover, the viral richness and diversity of childcare programs evidenced in this Aim highlight the importance of thorough environmental decontamination and hygiene practices in these settings.

6.1.3 – Epidemics captured by three illness surveillance networks of a single region

Prospectively collected illness surveillance data can be a vital tool for community level public health preparedness and timely interventions during epidemics. Using HIVE data in Aims 1 and 2, we became interested in how patterns in respiratory illness epidemics captured by HIVE

household data compared to that of two other regional surveillance networks—MFIVE and HAIVEN—which are collected in ambulatory clinics and hospital settings, respectively. Because each network is designed to study influenza, Aim 3 compared epidemic curves of seasonal influenza from each network across five years of surveillance. To date, no research has compared multiple prospective surveillance networks of the same region (which are thereby capturing epidemics of a single underlying community).

Overall, influenza epidemics patterns detected by all three networks in each season were broadly similar. The five years studied represented three A(H3N2) seasons, a single A(H1N1) season, and a blend of A(H3N2) and A(H1N1) in 2018-19. Influenza B outbreaks followed influenza A temporally in each of the five seasons, with the B(Yamagata) lineage as most common. Ambulatory clinic samples had the highest percent positivity for influenza (28.7%), followed by hospital and household samples (17.2% and 9.4%, respectively); this pattern was consistent across study years.

Influenza activity was generally detected between January and April in all three networks, outside of a notably early and prolonged 2014-15 season. Furthermore, the middle 50% of each network's total influenza cases occurred during roughly same period each year and approximately 6 weeks following initial epidemic activity. We saw no evidence of a consistent sequence in the order of network activity nor any indication of “foreshadowing” activity in a single network. Similarly, there was no evidence that influenza activity was regularly early or delayed in any given age group. The only notable discrepancies in network epidemic curves occurred during seasons with pronounced high severity or low vaccine efficacy.

This Aim offers the first direct comparison of three surveillance networks using similar methods for active, prospective illness detection and sensitive molecular testing. Future work here

might consider more advanced computational methods to explore and quantify the potential for dynamic, time-dependent relationships. Methods for time series analyses are common to the fields of economics and time-series forecasting and help to explain whether temporal patterns in one data source predictably lead or lag another; these methods have not yet been used extensively in epidemiologic literature.

Broad agreement between networks should be a point of encouragement. Because the only certainty of seasonal influenza epidemics is that they are neither constant nor predictable, the similarity between all three networks in terms of influenza epidemic start, peak timing, and bulk of cases is notable. For public health purposes, this means that any level of surveillance might provide local officials and medical practitioners with reliable and sufficient information to understand and intervene on local influenza epidemics from year-to-year. That being said, data from all three networks were useful in providing a more comprehensive assessment of particular characteristics of past influenza seasons.

6.1.4 – Tailoring Childcare Illness Surveillance Data to Mitigate Illness Outbreaks

Illness surveillance in childcare is vital, given the high rates of communicable disease incidence in both children and staff.^{39,42,44} Just as aggregate community surveillance data assists community public health officials, childcare illness surveillance provides an important source of information for childcare programs which can be used to characterize daily illness patterns, identify outbreaks, and recognize effective interventions.⁸¹ In this way, surveillance data should also function as a vital tool that childcare facilities can use (alongside environmental decontamination and child exclusion) to effectively mitigate disease transmission.

A childcare-specific illness surveillance network, MCRISP, has been operational in southeast Michigan since 2013. Our goal in Aim 4 was to determine how the MCRISP network could be leveraged to better assist childcare programs in their illness prevention efforts. Working in close partnership with a local non-profit dedicated to improving the quality of childcare in southeast Michigan, we moderated a series of semi-structured focus groups. Groups were audio-recorded, transcribed, and thematically assessed for consensus themes. Participants had an average of more than two decades of experience working in childcare. Thematic assessment revealed four themes related to topics of data utilization and packaging.

Objective surveillance data information is important to childcare providers because it supports both (1) their subjective experiences and (2) reactive and proactive decision making related to illness mitigation. This data should be provided as summarized aggregate illness data from both their respective centers and the MCRISP community of childcare providers at large. According to participants, summarized illness data would also act as a significant positive feedback mechanism. They noted that illness reporting felt more important and time well-spent if there was a way to directly observe that reports were being collated and assessed. In this way, real-time availability of illness data would help to keep users invested in reporting illnesses and subsequently leading to a more representative and valid surveillance system altogether.

Furthermore, surveillance data can be made into a more actionable tool if a surveillance system provides (3) corresponding educational resources and (4) is designed around the user's priorities. Childcare providers are overworked and reported little time dedicated to reporting daily illnesses in their centers. Illness reporting therefore should be structured as efficiently as possible, with minimal time required and the fewest necessary variables requested. Similarly, summarized illness data should be returned to childcare providers packaged with pertinent educational

resources. To better respond to emerging outbreaks detected in the data, providers noted that consolidated information about common childhood diseases (e.g., telltale symptoms, treatment, etc.) and recommended childcare protocols would be useful. There appeared to be a sense of confusion regarding expert guidance around child exclusion policies and other illness prevention efforts.

The study's main limitation was related to sample size. MCRISP is a relatively small collection of childcare programs already and fewer childcare directors agreed to participate than we had hoped. This resulted in an overrepresentation of private childcare programs (which often serve families of higher socioeconomic status and therefore have more financial resources) and no participation of any small, residential-based programs. Still, we believe the themes captured by our groups—related to education, communication, and support—would resonate with all types and sizes of childcare programs. This Aim offered important considerations as to how illness surveillance data should be tailored for community users, and specifically for childcare directors. For illness surveillance to be an effective tool in the prevention of childcare illness outbreaks, data collection and reporting needs to be centered around childcare stakeholder priorities.

6.2 – Significance of Findings

6.2.1 – Strengths of Dissertation

Using several strengths inherent to the HIVE study, this Dissertation builds upon limitations of prior epidemiologic research of childcare illnesses. For one, the prospective methods of the HIVE study avoid recall bias pitfalls and temporal challenges in previous research. Longitudinal data collection during year-round surveillance, with hundreds of households enrolled for multiple surveillance years, allowed for powerful calculations of disease incidence over time.

Active surveillance in a household setting also allowed for recognition of more mild illnesses that would not be captured by clinical- or hospital-based studies. This is particularly important in studies of childhood disease where a high proportion of illnesses are mild and never require medical attention. Though studies investigating childhood illness which rely on healthcare provider appointments are common, they fail to capture a large segment of childhood illnesses. The HIVE study encourages reports of all ARI cases, whether medically attended or not, and therefore represents a more commonly experienced type of illness. Outcome ascertainment in this Dissertation is also improved by the fact that illnesses reported to HIVE are molecularly tested against a panel of respiratory viruses using sensitive RT-PCR methods.

Furthermore, given the cohort's focus on young families and its annual demographic updates, we had sufficient numbers of individuals exposed and unexposed to children in childcare. This allowed direct comparison between exposure groups from the same underlying study population during the same time period; no external comparison group was needed. This is a major contribution to the understanding of childcare-specific risks. Comparing ARI risk in these two populations using past studies meant relying on results from entirely childcare-specific populations and comparing these to other studies of pediatric illness, which often were based on different geographies, timeframes, and outcome ascertainment.

HIVE also boasts a high level of community buy-in and participation. The vast majority of ARI cases reported during any given season are sampled for molecular testing and linked to a severity follow-up form. All of this supplementary information requires participant action and though participants are compensated for their time, we recognize that there is a fair amount of burden placed on individuals with every ARI report. Fortunately, over the past decade, study staff

have established strong relationships with community households. These high levels of engagement are vital for valid surveillance data.

We also point out there that this high level of community participation is true for the data collection in Aim 4 as well. Childcare users were directly involved in determining how surveillance data could be best used towards the goal of preventing illness, but three regional expert organizations were also involved in the study's fruition. The Washtenaw County Public Health Department, the Early Childhood Directors Association, and Child Care Network of Southeast Michigan all completely supported the project throughout and served as liaisons between the study team and local childcare centers. Conclusions in Aim 4 regarding the use of illness data to mitigate disease in childcare originated directly from the childcare community itself.

6.2.2 – Relevance to Community Public Health

The use of childcare continues to grow in the United States; at this point, nearly two-thirds of all children <5y experience out-of-home childcare at some point in their lives.¹⁵⁰ Accordingly, childcare programs have become an integral part of the fabric of US communities and so their associated disease risk is crucial for public health to better understand.

We knew that kids who attend childcare get sick more often—this Dissertation builds upon that existing knowledge and provides evidence that these illnesses are characteristically different. Childcare attendance is associated with particular pathogens hMPV and AdV, a more rich and diverse pool of respiratory viruses, and slightly increased odds of viral codetection—especially during the ages of 2-3y. These results are important for two reasons. For one, they highlight the need for continued childcare-specific studies of molecularly epidemiology and specifically those types of studies that compare childcare to homecare illnesses. If more research continues to suggest

that particular pathogens are linked to childcare attendance, this has ramifications for targeted prevention of childhood illness, for instance via vaccination campaigns.

Our results also underscore the necessity for vigilant surface cleaning and hygiene procedures in childcare. For one, we provide evidence that childcare is rife with viral pathogens—Aim 2 noted that children experience a significantly richer and more diverse viral environment in childcare than at home. Secondly, while rhinovirus, coronavirus, and respiratory syncytial virus were the most common pathogens identified in each group, we found that adenovirus infection was significantly associated with childcare attendance—notably, AdV is known for its extended survival outside of the host and on environmental surfaces.^{16,108,109} Extensive environmental decontamination guidelines for childcare exist at both state and federal levels, but unfortunately, actual implementation of these guidelines at childcare centers remains an uphill battle. Compliance and knowledge of these policies in childcare centers has been shown to be lacking.^{151,152} Childcare staff and children also display suboptimal rates of less intensive handwashing procedures, especially without continued monitoring post-training interventions.^{153–155}

Instead of unrealistically expecting 100% compliance in hygiene or sanitation procedures, public health should focus on expanding the variety of methods available in childcare programs to combat disease transmission. This Dissertation offers evidence that user-centric illness surveillance in childcare programs may serve as one option. Our focus group findings showcased a group of childcare providers that were eager and interested in access to summarized epidemiologic information. Our focus groups revealed that aggregate data would serve an important purpose in helping them to objectively support their center policies as well as monitor their own center's disease transmission. Directors were even excited by the idea of assessing program interventions using epidemiologic data.

As a public health tool for the wider community, our work also highlighted the relevance of prospective surveillance for understanding regional influenza epidemics. Regardless of whether a community monitors influenza cases in households, clinics, or hospitals, we found that data from each group adequately captures the timing of the epidemic's start, peak, and bulk of cases.

This Dissertation also speaks to the importance of engaging the public in surveillance systems which rely on community reports. In childcare specifically, there is a considerable public health benefit to providing these stakeholders with a more active role in disease surveillance within their own centers. For childcare providers, summarized data can be used to help them better communicate with parents, support rationale for child exclusion, make timely decisions, and gauge the success of their own illness mitigation efforts. Furthermore, for the purposes of academic research, bolstering active prospective illness surveillance in childcare could help to illuminate some of the granularity in childcare as an exposure. Illness reports from childcare centers, for instance, could be submitted with information related to hours per week attending, age group of child, age at first enrollment, and a marker for a child's first year in childcare. The validity of community-based illness surveillance data will always be tied to the community's investment in reporting.

As a brief aside, lessons learned in Aim 4 of this Dissertation have already been implemented locally. In response to focus group findings, the MCRISP infrastructure has been updated with two entirely new online components. The first addition was to provide users with a real-time, data visualization dashboard composed of aggregate illness data from both their respective centers and the MCRISP community as a whole (Figure 6-1). We have also uploaded a repository of informational resources and best-practice guidelines, in response to the participants' desire for accessible educational materials. These materials were tailored to a more informal

audience and will be regularly updated to reflect current knowledge. Certainly, the ongoing COVID-19 pandemic has provided a striking use-case scenario for these materials. Future qualitative and quantitative assessments of the new illness reporting paradigm should be planned to determine when and how childcare users are leveraging available data to prevent illness in their programs.

6.3 – Future Directions

6.3.1 – Investigate Effect Modifiers of Childcare-Illness Association

As discussed in previous chapters, this dissertation was unable to sufficiently examine potential effect modifiers of the association between childcare and ARI. Future work in this area should make a point of collecting data on variables like age of initial childcare enrollment as well as the duration of both past and current of childcare attendance. Previous research shows that childcare attendees experience higher rates of respiratory infection early in life; during early elementary school, however, their relative risk of illness compared to non-childcare counterparts is reduced. Exposure to childcare illnesses appears to effectively prime a child’s immune system prior to grade school attendance.^{53,55,56,59} This phenomenon may explain null findings in our own work and comparable rates of illness between childcare and homecare households; older siblings in childcare households likely attended childcare themselves, yet they may be experiencing residual protective effects from that attendance early in life. These modifiers appear to be crucial to better understanding the childcare ARI risk and should be therefore be prioritized in future cohort studies of both childcare attendees and their associated households.

Similarly, the association between childcare and ARI risk may be modified by childcare facility type.^{53,55,62,94,149} Several established forms of childcare exist. *Family home care* is a type of program that provides care for no more than 10 children in a residential setting; often the

caretaker's children are attendees. A *school-age facility* offers activities for school-aged children before and after school hours as well as during non-school weekends/holidays. *Childcare centers* are independent facilities that operate on a regular basis and provides care to at least 10 children in a nonresidential setting. In 2011, childcare centers provided care to 25% of all US children under 5 years-old, compared to family home care programs which cared for around 4% of that age group.³⁷ The direction of effect modification by facility type remains unclear.

Moving forward, household studies like HIVE should focus on details associated with childcare attendance and family use, given the importance of modifying factors. For instance, in upcoming years all families re-engaging or enrolling in the HIVE study should be asked specific questions related about their children's childcare (e.g., duration of childcare attendance and the particular childcare center attended - Figure 6-2). Provided enough families are retained from year to year, these additional details collected could be appended to data from past seasons as appropriate. Analyses could be constructed using this information if response is sufficient, though more valid data would be based on prospective collection as with the rest of HIVE data.

6.3.2 – Account for the Disproportionate Impact Across Levels of Socioeconomic Status

Childhood illness is costly. Accounting for the direct costs (medication and physician visits) and indirect costs (missed work) linked to childhood ARI episodes, past research has estimated totals ranging from \$43 to \$220 USD per ARI episode.^{156–158} Childhood illness is associated with more than just financial repercussions. Qualitative data from personal interviews reveal that childhood cases of severe ARI have a considerable negative impact on the parents' quality of life.¹⁵⁹ Parents reported feelings of social isolation, relationship challenges, stress from work, feelings of guilt, and constant worry associated with childhood cases of severe ARI. These

repercussions are magnified when children are enrolled in childcare. ARI episodes in this group are more costly because of its impact on parental employment, both financially and emotionally.¹⁵⁷ A national poll reported that 75% of parents missed work for a sick childcare child in the past year and half of them (47%) noted a negative impact on employment.¹⁶⁰

These are important considerations in the context of health equity. The indirect financial and emotional consequences of childhood ARI are likely to disproportionately impact families of low socioeconomic status (SES). This is because families of lower SES are more likely to have children enrolled in daycare programs (or have minimal options for childcare) and children of low SES families are more likely to experience ARI.^{61,160–162} Only few HIVE demographic variables collected relate to this topic, including educational attainment of parents and subjective social position (SSP) and there is little variation in the socioeconomic status of participating HIVE households. Moving forward, household studies should focus on regional populations with varied SES and collect related, relevant information.

6.3.2 – Investigate the role of childcare centers in outbreak propagation

In considering the association between childcare use and reported ARI incidence in HIVE households, we deliberately refrained from discussions of disease transmission. Though we approximated risk, the research methods in this Dissertation were not intended to analyze the dynamics of viral transmission from daycare children to their families. Household studies like HIVE however, can provide sufficient data and parameters for analysis via compartmental or agent-based transmission models. Indeed, transmission hazard modeling techniques have already been applied in the HIVE study to estimate direct and indirect vaccine effectiveness.¹⁶³

These types of analyses should consider the importance of childcare in transmission pathways. Schools have been recognized as important propagators of disease within a community; school closures—or targeted vaccination campaigns aimed at schools—help to mitigate community transmission of influenza.^{28,164–166} Only limited research has investigated the role of childcare programs in seeding community outbreaks.¹⁶⁷ A future analysis should consider household data like that of HIVE where an appropriate transmission model could be used to assess secondary cases resulting from children who do and do not attend childcare.

An interesting supplementary study could involve linking MCRISP data to HIVE data. The first step would be to find out whether any HIVE households reporting childcare use send their children to any MCRISP-affiliated programs. If a sufficient proportion do so, there is an opportunity to quantify the association between outbreaks at an MCRISP childcare center (determined by surveillance data) and outbreaks in affiliated childcare households. It would be interesting to determine whether individuals living in MCRISP-affiliated households experience higher illness risk than non-childcare households during an MCRISP center outbreak. While not based on a formal transmission model, this study would provide evidence for communicable disease risk transferred from childcare center to household and be a novel study of two linked surveillance networks. This information would be useful for public health preparedness, resource mobilization during seasonal outbreaks, and even future pandemic scenarios.

6.4 – Final Remarks

Out-of-home childcare is crucial for working parents and significantly benefits the educational and social development of children. At the same time, we know that childcare attendance is associated with an increased risk of disease in young children. Because childcare has

become such an integral part of the daily lives of most people living in the US, it is important that we better understand the disease risk associated with childcare to both children and their families. Altogether, this dissertation offers some of the first direct comparisons of respiratory risk in families and children differing in their exposure to childcare and highlights the strengths of using prospective illness surveillance to make these comparisons.

Figure 6-1: Data visualization dashboard images reflecting concept and post-development



(A) the consolidated opinions of twelve childcare providers involved in the MCRISP focus groups
 (B) the working product available to childcare providers after logging-in to their respective program's home page on mcrisp.org.

Figure 6-2: Possible supplemental questions for the HIVE study

1	Since enrollment into the HIVE study has [participant] ever attended a daycare or childcare program? <input type="checkbox"/> <i>Yes</i> <input type="checkbox"/> <i>No</i>
2	What month and year did [participant] start attending a daycare program? <i>MM/YYYY</i>
3	What month and year did [participant] stop attending a daycare program (if applicable)? <i>MM/YYYY</i> <input type="checkbox"/> <i>Still attending</i>
4	Approximately how many hours per week does/did [participant] attend a daycare program? <i>Number</i>
5	Approximately how many children attend (or attended) [participant]'s daycare program each day? <i>Number</i>
	Child's age at initial childcare enrollment can be deduced using date of birth Siblings in childcare can be deduced with other HIVE family information

HIVE = Household Influenza Vaccine Evaluation study

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