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Attribution Of Febrile Illness To Circulating Respiratory Viruses In The United States, July 2016 - March 2023

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Abstract

Background: SARS-CoV-2, an emerging epidemic respiratory virus, has circulated in the United States since early 2020. The dynamics of Influenza (flu) and Respiratory Syncytial Virus (RSV) have shifted, causing atypical timing and levels of illness across the country and in particular age groups. Fever, recorded on at-home bluetooth-enabled thermometers, is a promising new tool with which to monitor respiratory disease. Quantifying the proportion of fever attributable to these three viruses, at a particular time or within a particular age group, would strengthen the collective understanding of viral circulation in the U.S., and enable the use of fever data in the prediction and prevention of respiratory disease.

Methods: The study period, July 2016-March 2023, encompassed the first years of the COVID-19 pandemic. A negative binomial Bayesian hierarchical model was fit to fever with different measures of viral covariates, accounting for temporal changes in diagnostic testing behavior. MCMC simulations informed estimation of the proportion of fever attributable to respiratory viral causes. Attributable proportions were compared across groups and across a Pre- and Post-COVID temporal stratification.

Results: Prior to the COVID-19 pandemic, both flu and RSV were strongly correlated with fever. Post-COVID, the timing, magnitude, and fever correlation of both viruses shifted. The model attributed more Pre-COVID fever to flu than RSV. In the Post-COVID period, fever was less attributable to viral causes than before. SARS-CoV-2 contributed to fever incidence more than flu or RSV with the models that used viral covariates adjusted for testing behavior. Pre-COVID, viruses were most responsible for fever in children 5-17 and least responsible for fever among elders 65-100. SARS-CoV-2 only minimally impacted fever incidence of pediatric populations.

Conclusions: This study emphasizes the utility of fever for capturing and understanding respiratory disease in the U.S. and across age groups. As new variants emerge, or SARS-CoV-2 stabilizes and develops endemic seasonality, it will be necessary to continue monitoring the age distribution of viral disease, and nonclinical fever surveillance is a strong supplement to traditional methods.

Acknowledgements

I extend the deepest gratitude to my primary advisor, Dan Weinberger, for instilling in me an appreciation for the wild world of modeling and the courage to wade through it. Further, I wouldn't have found my way through it without the code, insight, and generosity of Dan's team on the Israel Pneumo study.

Many thanks to Ginny Pitzer, my second reader, for her vast knowledge of quantitative methods and for saying "that's way too complicated for a thesis" when I had an even more ridiculous and less feasible research question at the start of the year.

I'd like to thank Danielle Bloch and the team at Kinsa Inc. for access to the fever data, for introducing me to applied surveillance, and for expressing much enthusiasm – the fever fever, if you will.

Lastly, a million Monte Carlo simulations of appreciation to my support system – the friends who were tackling their own theses or academic programs, the relatives who let me show them pretty graphs even though they don't quite get what's going on, and my partner Jacob who has been patient and curious all while conducting his own field-defining research (on a less…finite timescale).

To Nolan and Andrew, my parents, I am grateful for the way in which they have cared for me while balancing their own hard work and passionate engagement in their community. To my brother Sam who has always been my closest friend and partner in mischief, thank you for inspiring me to think big and critically, to take risks, and to enjoy my surroundings. And many, many thanks to my six grandparents–Grandpaw Steve, Granny, Grammy, Grampy, Nano, and Paps–all of whom have played a major role in who I am today as a scholar, thinker, and human.

Specific Aims & Hypotheses

Aims:

1. Quantify the proportion of fever at a given time that is attributable to each study virus across age groups
    a. Study viruses: SARS-CoV-2, seasonal influenza virus, RSV
    b. Identify shifts in attribution of fever to study viruses over the time period of interest, as different viruses came in and out of circulation
2. Visualize the impact of SARS-CoV-2 on the incidence of other respiratory viruses in the U.S.
3. Investigate the reliability of self-reported fever data as a novel form of surveillance for viral respiratory diseases

Hypotheses:

1. SARS-CoV-2 drove fever incidence more in the first year of the COVID-19 pandemic, shrinking in proportion as other respiratory viruses came back into circulation.
2. The proportion of fever attributable to the study viruses varies across age groups.
3. Fever is correlated with and indicative of respiratory viral disease in the U.S.

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Table 1. Descriptive Comparison of Active Thermometer Users and the United States Population, July 2016 – Feb 2020 and March 2020 – March 2023

	U. S. Census, 2018	Users, Pre-COVID	p	Users, Post-COVID	p
Total Population, N					
	322903030	1414721		799298	
Age Cohort, n(%)					
0-4	19836850 (6.14)	311208 (22.00)	<0.05	160737 (20.11)	<0.05
5-17	53716390 (16.64)	407457 (28.8)		234891 (29.39)	
18-24	30903719 (9.57)	78097 (5.52)		47404 (5.93)	
25-44	85331186 (26.43)	385256 (27.23)		213202 (26.67)	
45-64	83876304 (25.98)	166359 (11.76)		97373 (12.18)	
65-100	49238581 (15.25)	66344 (4.69)		45691 (5.72)	
Sex, n(%)					
Female	163918840 (50.76)	786018 (56.38)	0.43	786018 (56.38)	0.43
Male	158984190 (49.24)	608240 (43.62)		608240 (43.62)	
Urbanization, n(%)					
1	99489188 (30.81)	434766 (30.73)	0.98	253571 (31.72)	0.99
2	80416423 (24.91)	399533 (28.24)		212923 (26.64)	
3	67446921 (20.89)	304120 (21.50)		176472 (22.08)	
4	29467933 (9.13)	125761 (8.89)		67560 (8.45)	
5	27236785 (8.44)	94399 (6.67)		57429 (7.19)	
6	18823247 (5.83)	56124 (3.97)		31326 (3.92)	
SVI, weighted mean*					
Socioeconomic Status	0.48	0.53	<0.05	0.53	<0.05
Household Characteristics	0.48	0.56	<0.05	0.54	<0.05
Racial & Ethnic Minority Status	0.52	0.59	<0.05	0.58	<0.05
Housing Type & Transportation	0.50	0.61	<0.05	0.58	<0.05

Notes: The COVID-19 pandemic reached the U.S. on March 1, 2020; this date is used to split the analysis, looking at the user population both Pre- and Post-COVID. P-values are significant at the 0.05 level. The first p-value compares the Pre-COVID users to the U.S. population, and the second p-value (the final column in the table) compares the Post-COVID users to the U.S. population. The p-values for the continuous data, the SVI themes, were obtained by comparing weighted scores for each theme in each census region. The scores were weighted by calculating the proportion of the total populations (U.S. or thermometer user) living in each census tract and multiplying by that tract's score for each of the four SVI themes. Those updated proportion-times-score values for each tract were then summed to obtain a weighted average based on the distribution of each population.

Table 2. Correlation between Fever and Study Viruses, United States,
July 2016 – Feb 2020 and March 2020 – March 2023

	Correlation with Fever		
	Unadjusted	**Yearly Adjustment**	**Weekly Adjustment**
Pre-COVID			
Influenza	0.8987	0.9102	0.9281
RSV	0.8320	0.8426	0.7433
Post-COVID			
Influenza	0.7372	0.7957	0.7308
RSV	0.6363	0.4390	0.3948
SARS-CoV-2	-0.1421	0.3935	0.3959

Note: Pearson correlation coefficients > 0.7 represent strongly correlated relationships.

Table 3. Percentage of Fever Attributable to Study Viruses, United States, July 2016 – Feb 2020 and March 2020 – March 2023

	Attributable Percent (95% CI)		
	Unadjusted	**Yearly Adjustment**	**Weekly Adjustment**
Pre-COVID			
Influenza	24.51 (23.60, 25.38)	27.42 (26.30, 28.52)	35.03 (34.00, 36.10)
RSV	9.14 (8.44, 9.86)	10.36 (9.39, 11.33)	11.46 (10.57, 12.34)
Study Viruses	33.65 (32.89, 34.37)	37.78 (36.91, 38.62)	46.48 (45.58, 47.35)
Post-COVID			
Influenza	13.99 (13.38, 14.60)	5.57 (5.31, 5.83)	8.70 (8.41, 9.01)
RSV	11.35 (10.53, 12.21)	6.32 (5.74, 6.91)	6.89 (6.34, 7.43)
SARS-CoV-2	5.21 (4.78, 5.61)	10.53 (9.79, 11.28)	17.00 (16.17, 17.88)
Study Viruses	30.54 (29.74, 31.31)	22.42 (21.61, 23.22)	32.59 (31.67, 33.55)

Notes: The COVID-19 pandemic reached the U.S. on March 1, 2020; this date is used to split the aggregation of estimates from the model into two periods: Pre-COVID and Post-COVID. The effect of "Study Viruses" is the overall percent of fever attributable to any one of the study viruses; Influenza + RSV in the Pre-COVID period, and Influenza + RSV + SARS-CoV-2 in the Post-COVID period.

Table 4. Percentage of Fever Attributable to Study Viruses by Age Group, United States, July 2016 – Feb 2020 and March 2020 – March 2023

	Attributable Percent (95% CI)		
	Unadjusted	**Yearly Adjustment**	**Weekly Adjustment**
Pre-COVID			
Ages 0-4			
Influenza	12.69 (11.20, 14.26)	14.29 (12.46, 16.23)	21.34 (19.29, 23.36)
RSV	8.88 (7.59, 10.12)	11.65 (9.88, 13.33)	12.32 (10.72, 13.87)
Study Viruses	21.58 (20.27, 22.87)	25.93 (24.46, 27.50)	33.68 (32.01, 35.31)
Ages 5-17			
Influenza	35.06 (33.52, 36.67)	38.88 (36.82, 40.85)	46.06 (44.33, 47.82)
RSV	12.12 (10.91, 13.40)	13.47 (11.71, 15.16)	15.28 (13.74, 16.86)
Study Viruses	47.18 (45.92, 48.47)	52.33 (50.99, 53.75)	61.35 (60.03, 62.61)
Ages 18-24			
Influenza	23.87 (21.97, 25.78)	27.00 (24.57, 29.06)	36.91 (34.78, 38.92)
RSV	5.99 (4.28, 7.69)	4.07 (2.31, 6.11)	3.37 (1.85, 5.13)
Study Viruses	29.84 (28.28, 31.49)	31.10 (29.41, 32.60)	40.33 (38.51, 42.03)
Ages 25-44			
Influenza	27.76 (26.02, 29.64)	31.23 (29.32, 33.04)	40.65 (38.76, 42.42)
RSV	4.57 (3.04, 6.14)	2.76 (1.51, 4.43)	3.40 (2.05, 5.01)
Study Viruses	32.34 (30.94, 33.85)	34.03 (32.59, 35.53)	44.06 (42.32, 45.67)
Ages 45-64			
Influenza	28.50 (26.51, 30.48)	30.88 (28.85, 32.61)	42.18 (40.24, 43.93)
RSV	4.32 (2.71, 5.99)	2.25 (1.17, 3.91)	1.80 (0.65, 3.34)
Study Viruses	32.86 (31.25, 34.39)	33.16 (31.70, 34.63)	44.03 (42.42, 45.70)
Ages 65-100			
Influenza	14.52 (12.33, 16.45)	14.21 (12.34, 16.10)	23.19 (21.11, 25.26)
RSV	4.16 (2.49, 6.01)	2.26 (1.07, 3.75)	2.19 (1.01, 3.63)
Study Viruses	18.68 (17.09, 20.30)	16.48 (15.04, 18.05)	25.40 (23.55, 27.22)
Post-COVID			
Ages 0-4			
Influenza	9.36 (8.12, 10.74)	3.55 (3.10, 4.06)	6.61 (5.98, 7.26)
RSV	13.98 (12.09, 15.82)	8.72 (7.40, 9.93)	9.54 (8.29, 10.75)
SARS-CoV-2	0.12 (0.04, 0.31)	7.87 (6.45, 9.30)	5.66 (4.15, 7.32)
Study Viruses	23.51 (21.94, 24.99)	20.13 (18.51, 21.74)	21.80 (20.06, 23.78)
Ages 5-17			
Influenza	23.98 (22.67, 25.37)	10.44 (9.76, 11.11)	15.69 (14.96, 16.45)
RSV	18.26 (16.52, 20.08)	10.74 (9.34, 12.10)	12.28 (11.03, 13.60)
SARS-CoV-2	0.11 (0.03, 0.25)	11.13 (9.57, 12.69)	8.45 (6.79, 10.25)
Study Viruses	42.34 (40.89, 43.81)	32.31 (30.63, 34.00)	36.42 (34.51, 38.37)
Ages 18-24			
Influenza	8.02 (7.25, 8.79)	2.88 (2.60, 3.14)	4.66 (4.34, 4.97)
RSV	4.29 (3.09, 5.59)	1.41 (0.78, 2.13)	1.06 (0.56, 1.65)
SARS-CoV-2	13.14 (11.15, 15.23)	12.49 (11.13, 13.78)	25.80 (23.84, 27.74)
Study Viruses	25.46 (23.17, 27.79)	16.79 (15.46, 18.16)	31.52 (29.50, 33.59)
Ages 25-44			
Influenza	11.94 (11.04, 12.96)	4.52 (4.18, 4.86)	6.73 (6.34, 7.11)
RSV	4.13 (2.80, 5.55)	1.29 (0.71, 2.05)	1.36 (0.79, 2.02)
SARS-CoV-2	11.58 (9.92, 13.23)	13.79 (12.36, 15.17)	32.30 (30.35, 34.31)
Study Viruses	27.66 (25.69, 29.64)	19.62 (18.16, 21.02)	40.38 (38.38, 42.46)
Ages 45-64			
Influenza	8.46 (7.72, 9.21)	3.04 (2.82, 3.26)	4.70 (4.45, 4.96)
RSV	2.72 (1.72, 3.77)	0.66 (0.32, 1.23)	0.51 (0.18, 0.92)
SARS-CoV-2	17.13 (15.11, 19.09)	12.53 (11.26, 13.84)	34.84 (33.00, 36.74)
Study Viruses	28.35 (26.08, 30.43)	16.27 (14.93, 17.64)	40.06 (38.16, 41.97)
Ages 65-100			
Influenza	2.11 (1.74, 2.45)	0.63 (0.55, 0.72)	1.18 (1.07, 1.29)
RSV	1.33 (0.81, 1.92)	0.35 (0.16, 0.60)	0.32 (0.14, 0.53)
SARS-CoV-2	15.24 (13.09, 17.40)	5.07 (3.93, 6.32)	29.23 (27.07, 31.41)
Study Viruses	18.70 (16.41, 20.96)	6.07 (4.93, 7.33)	30.75 (28.53, 32.91)

Notes: The COVID-19 pandemic reached the U.S. on March 1, 2020; this date is used to split the aggregation of estimates from the model into two periods: Pre-COVID and Post-COVID. The effect of "Study Viruses" is the overall percent of fever attributable to any one of the study viruses; Influenza + RSV in the Pre-COVID period, and Influenza + RSV + SARS-CoV-2 in the Post-COVID period.

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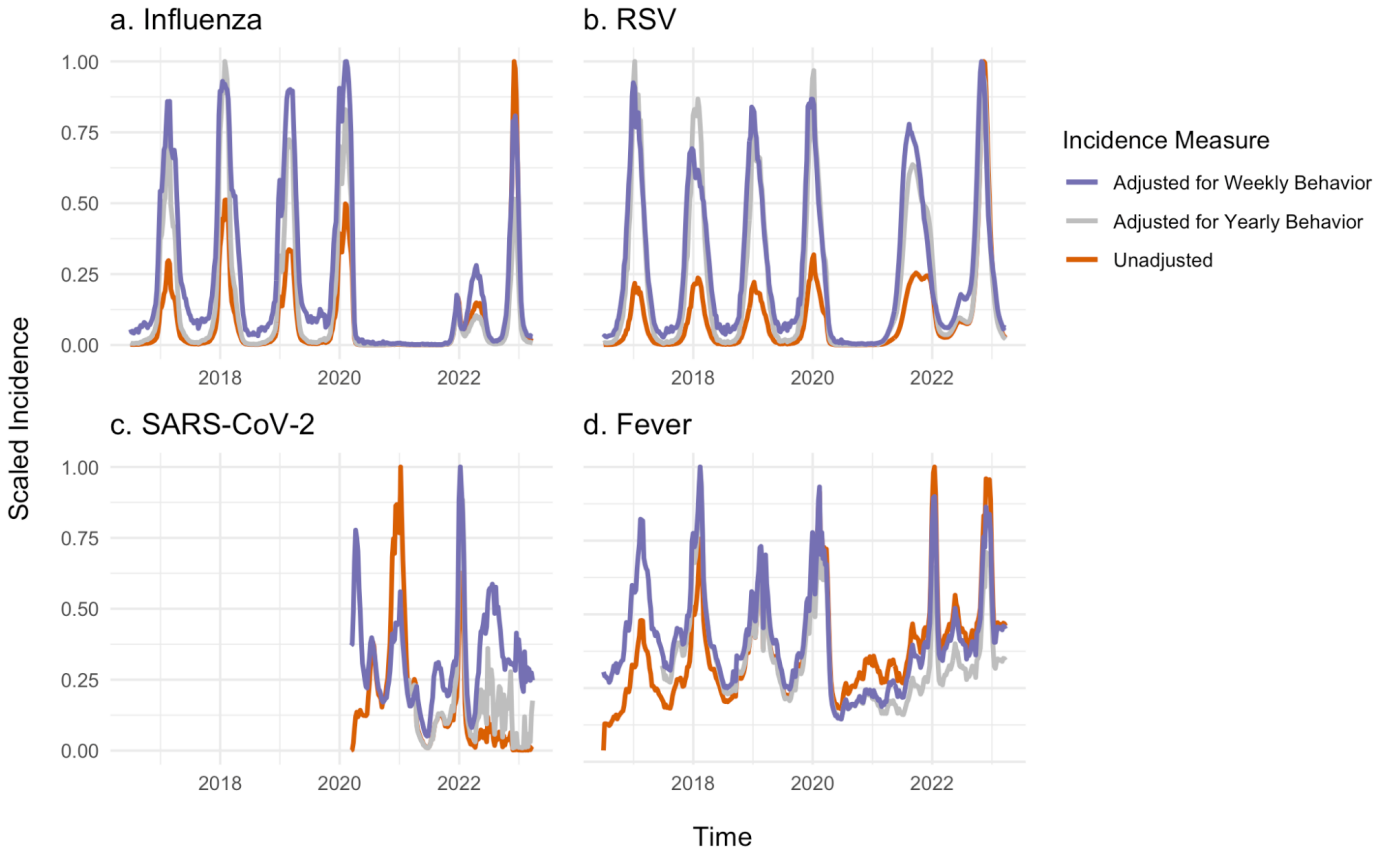

Fig 2. Time Series of Fever and Study Viruses, Incidence Adjusted for Weekly Behavior, United States HHS Regions, July 2016 – March 2023

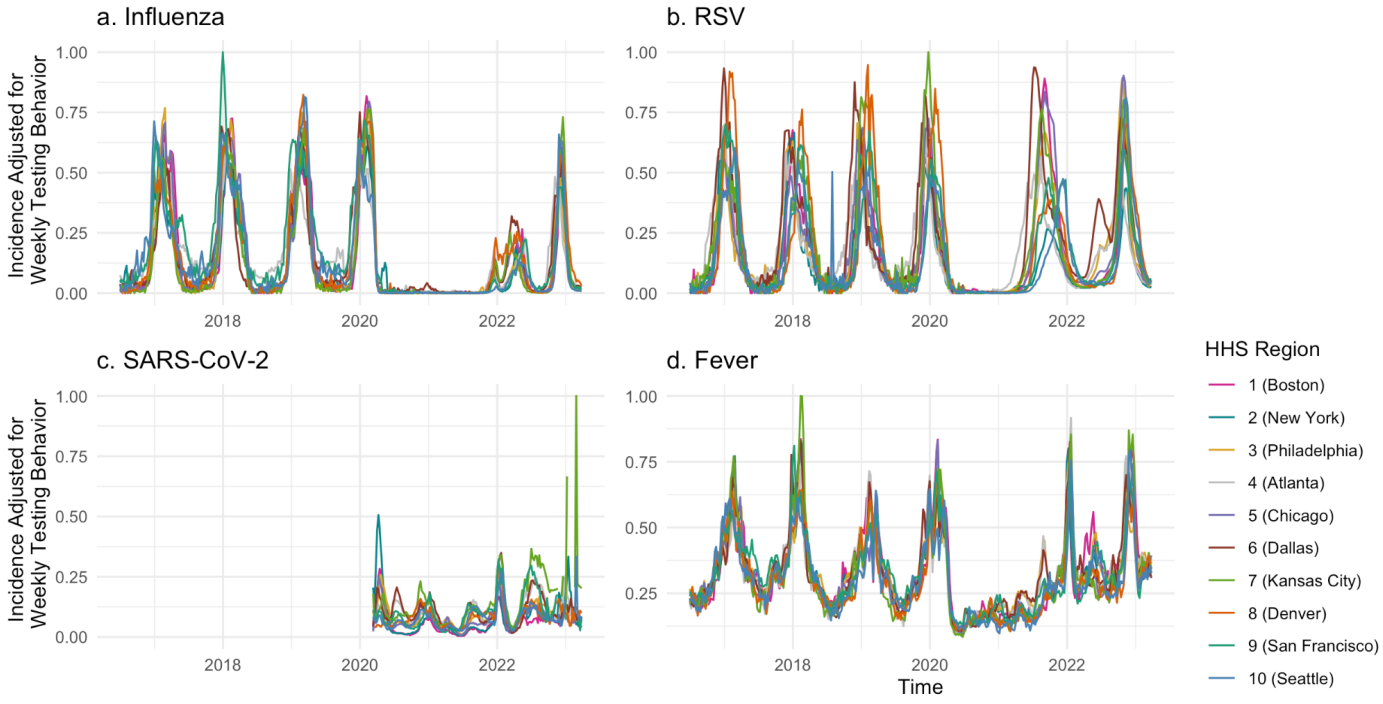

Fig. 3 Time Series of Age-Stratified Fever, United States, July 2016 – March 2023

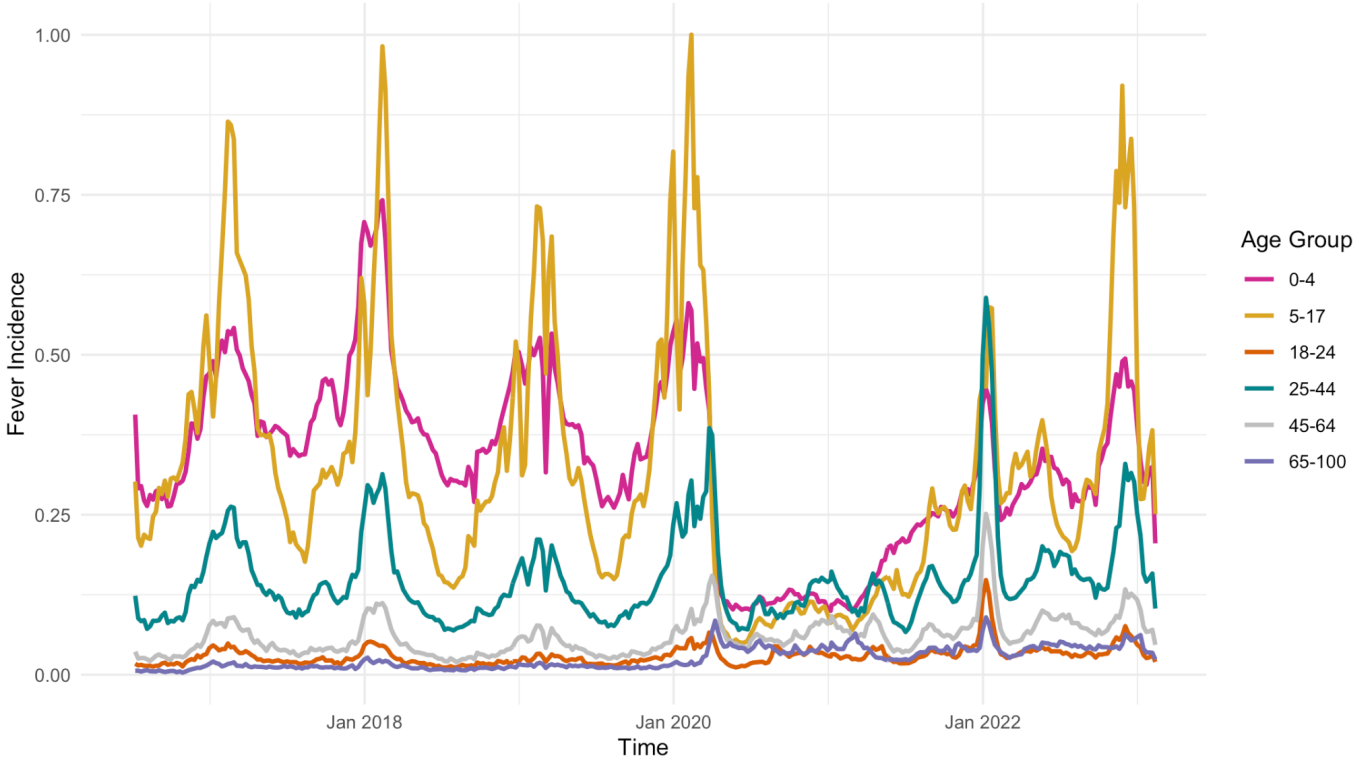

Fig. 4 Proportion of Fever Attributable to Study Viruses, Three Models, United States, July 2016 – March 2023

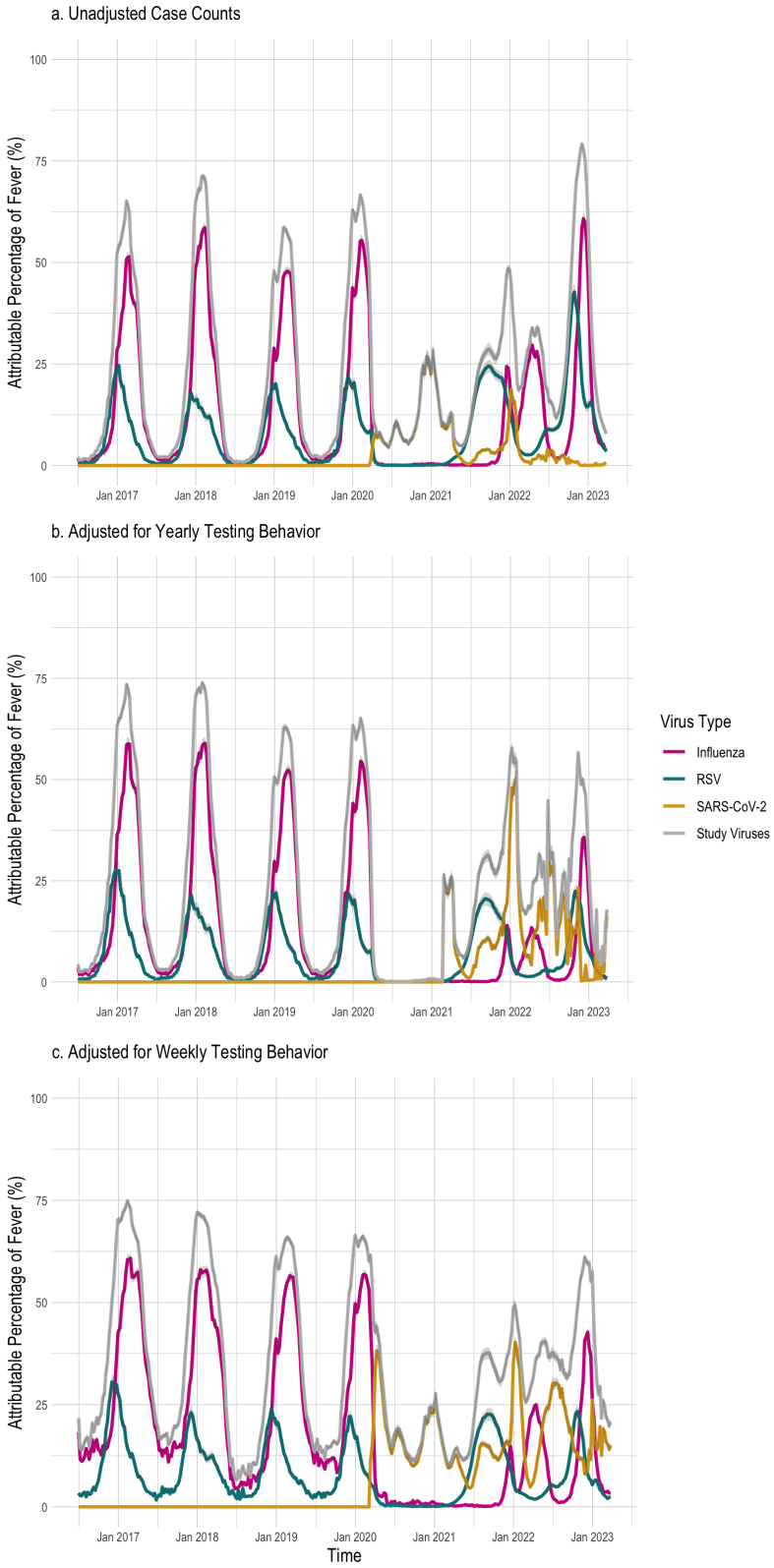

Fig. 5 Proportion of Fever Attributable to Study Viruses, Stratified by Age Group, Three Models, United States, July 2016 – March 2023

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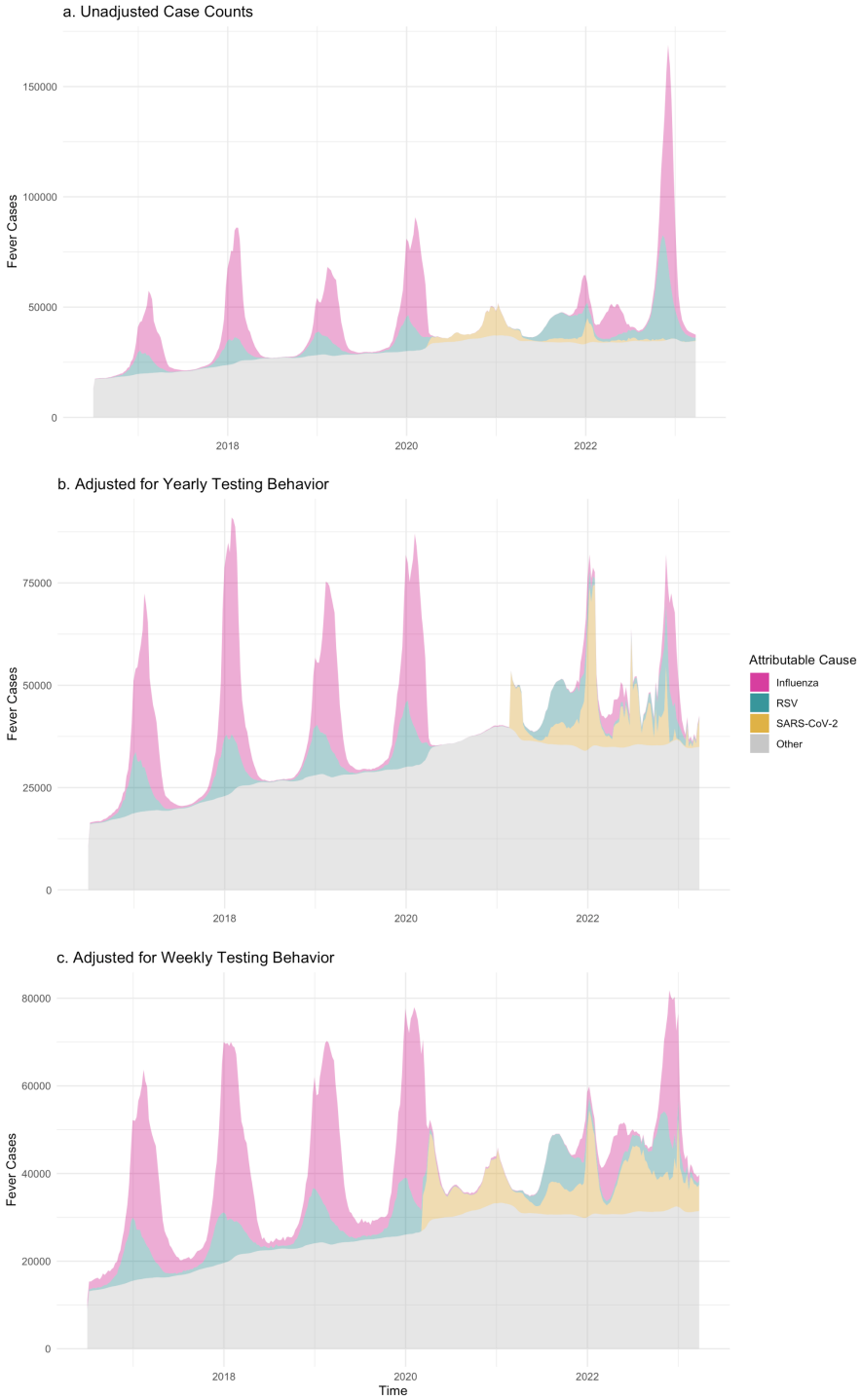
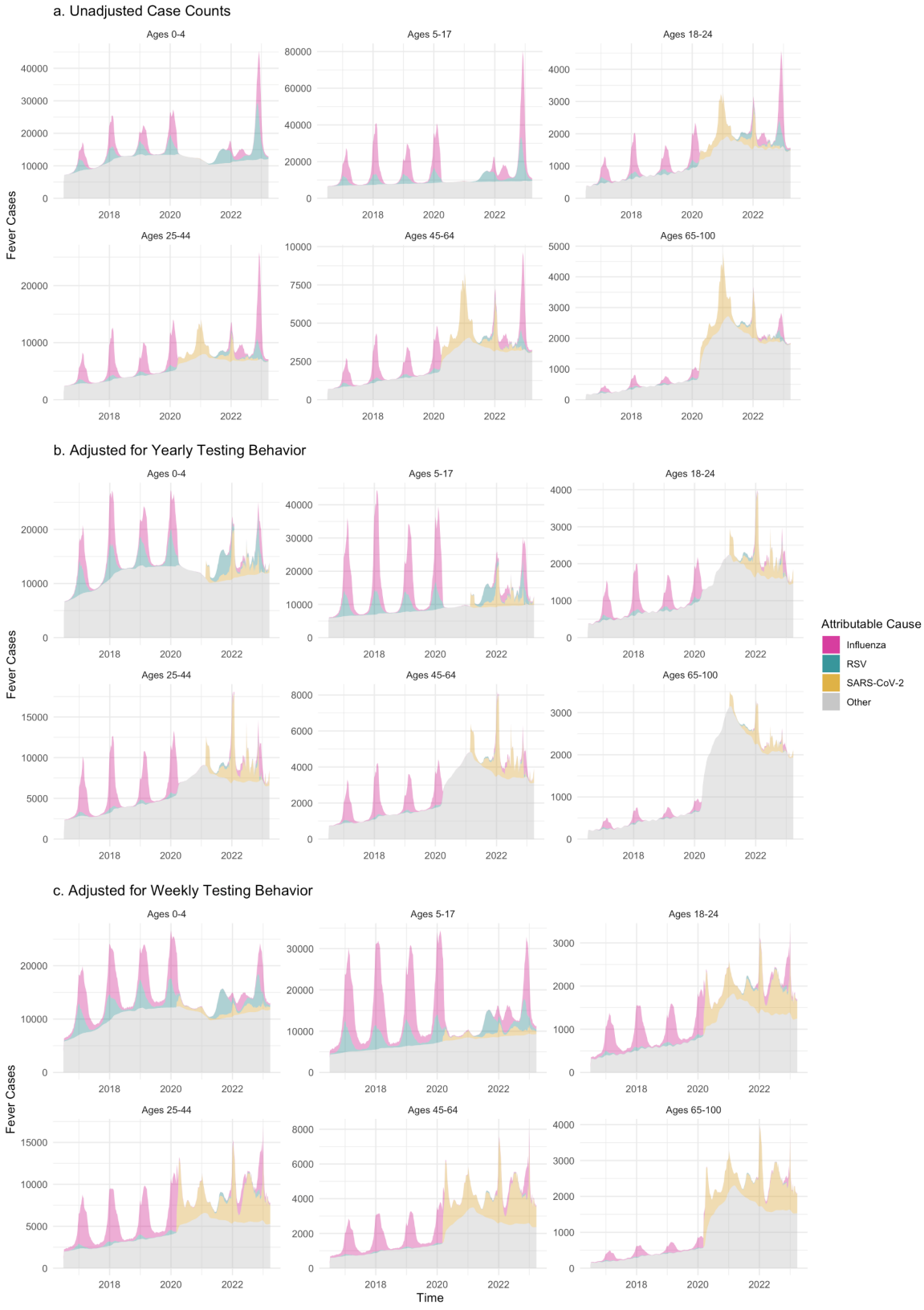


Fig. 7 Cases of Fever Attributable to Study Viruses or Other Causes, Stratified by Age Group, Three Models, United States, July 2016 – March 2023



Introduction

Background

Since the first known human-to-human transmission of the virus SARS-CoV-2 in late 2019, the United States has seen more than 100 million cases of the resulting disease, COVID-19. (1) Over a million U.S. residents have died of COVID-19 or related complications, and the U.S. hospital system has been overburdened by multiple waves of the declared pandemic. Mitigation measures such as school closures, mass screening, and vaccination helped to reduce the risk of COVID-19 infection for much of the population. Vaccination can reduce disease severity, keeping many sick people out of the hospital, but in order to anticipate total burden, the illness incidence in a population needs to be accurate, encompassing more cases than the subset that officially enter the healthcare system.

Novel surveillance methods can successfully supplement our preexisting systems for monitoring levels of disease. (2) As exemplified during the COVID-19 pandemic, reliance on diagnostic testing results for national surveillance is only beneficial when those tests are actively being reported; the expanded access to and familiarity with at-home rapid antigen testing for SARS-CoV-2 drove a major decrease in the number of test results being reported, skewing the incidence rates calculated from those tests alone. (3) Wastewater surveillance earned a lot of attention and trust within the public health community and general public for its broad catchment and the sensitivity of sampling and detection tools. (4) However, not all U.S. residents are connected to wastewater management systems, and factors such as social vulnerability and age may not be accurately represented by the wastewater being sampled. (5) Additionally, wastewater tracks the presence of pathogens, not the severity of illness. On the other hand, people seeking diagnostic tests tend to have symptoms, so surveillance that relies on lab results only catches symptomatic cases. It is essential to explore alternative methods of disease monitoring and outbreak detection to optimize awareness of and response to levels of infectious disease.

Fever is a common, nonspecific symptom of respiratory illness. When people don't feel well, they often reach first for a thermometer to test whether or not they are feverish. A bluetooth-enabled thermometer, kept in the home and connected to a smartphone application with profiles for each member of the household, catches both feverish and non-feverish temperature readings whether or not an individual seeks medical care. (6) Sometimes, people with mild or moderate fevers stay home and rest, limiting the number of individuals who receive medical care and diagnostic testing, and thus limiting the number of disease episodes that get confirmed by a clinician or in a lab. In the midst of infectious disease epidemics, people are even more likely to avoid seeking healthcare in person. (7,8) Additionally, temperature-taking behavior can be used as a proxy for illness levels, representing coherence with public health mandates or anxiety about being at high risk for illness in a particular area at a particular time. (9)

At the start of the COVID-19 pandemic, Non-Pharmaceutical Interventions (NPIs) such as lockdowns and masking pulled other respiratory illnesses out of circulation. (10,11) For a while, most reports of fever could be reasonably attributed to SARS-CoV-2, since that virus was dominating the illness distribution. However, NPIs aren't associated with specific pathogens; they affect behaviors. The revocation of NPIs that were in place to limit SARS-CoV-2 transmission was also associated with an increase in incidence and severity of other diseases, due to lack of exposure and minimal development of natural immunity during the first part of the pandemic. (12) As people returned to schools, workplaces, and social environments, so did diseases like influenza and Respiratory Syncytial Virus (RSV), appearing again in illness reports. (13,14)

Fever incidence depends on the type and quantity of pathogens in circulation, as well as the level of protection of the population due to prior infection or vaccination. Incidence estimates also depend on the type of surveillance being conducted. The CDC's ILINet, a clinical syndromic surveillance system, changed their definition of influenza-like illness to no longer include "without a known cause other than influenza" as a criteria for reporting. (15) This move, due to the overlap between symptoms of flu and

COVID-19, diminishes the accuracy of syndromic surveillance systems. Parsing out what proportion of fever is attributable to some of the most common circulating viruses can help to enhance surveillance accuracy, direct policy, allocate resources, and inform communities of their specific risks when they prepare to enter public spaces.

Study Value

Viral co-circulation may worsen susceptibility and disease severity during the ongoing COVID-19 pandemic, even among vaccinated individuals. This unprecedented illness could place a large burden on a hospital system, lead to educational delays, and hinder economic growth at levels both local and broad. It is essential to have a sense of what pathogens are causing symptoms such as fever that influence illness severity, care-seeking behaviors, and recognition of potential infectiousness.

This study aims to quantify the proportion of fever attributable to certain respiratory viruses–influenza, RSV, and SARS-CoV-2, referred to collectively as the "study viruses"–during the study period within each of six age groups. Secondarily, this study will identify shifts in the attributable proportion of fever over the time period of interest as different viruses came in and out of circulation. In preparation for the attribution analysis, we will investigate the reliability of self-reported fever data as a novel form of surveillance for respiratory diseases. This will enhance our understanding of co-circulation, identify major drivers of febrile illness among different age groups, and inform public health mitigation measures and hospital preparedness.

Methods

Study Setting

This observational study examined viral and fever incidence in the United States from July 1, 2016 to March 31, 2023, a time period encompassing the first years of the COVID-19 pandemic, which is widely recognized to have started in the U.S. in March 2020. (16) The national emergency response officially ended on April 10, 2023, while the public health emergency is expected to end in May 2023. (17) Due to the effects that the COVID-19 pandemic may have had on fever, respiratory viruses, and behavior, much of the analysis was stratified into two time periods: Pre-COVID from July 2016 through February 2020, and Post-COVID from March 2020 through March 2023.

Data Sources

The study viruses, based on prominence of fever and regional incidence, were SARS-CoV-2, seasonal influenza virus (referred to throughout as flu; includes all subtypes), and RSV. (18,19) Given the inconsistencies in disease reporting across geographies and time, data on total tests and positive results were drawn from a variety of sources, as outlined here. Flu data were from the CDC's FluView program, a collaborative of clinical and public health laboratories across the U.S. RSV data were from the CDC's National Respiratory and Enteric Virus Surveillance System (NREVSS). SARS-CoV-2 data were aggregated by the New York Times, which receives case counts from state and local health departments and adjusts for testing and reporting delays. Daily SARS-CoV-2 data were then further aggregated into weekly data so as to align with flu and RSV. All viral data sources were stratified by Health and Human Services region (HHS; Appendix Fig. 1), and not by age group. (20)

Data on fever and temperature-taking behavior were from Kinsa, Inc., a health tech company that manufactures and distributes thermometers that are connected via bluetooth to a smartphone application. Users can create a demographic profile, report symptoms, receive healthcare guidance, and record their

body temperatures. These temperatures and the associated demographic information, as well as GPS location of the device used to access the app, were deidentified and aggregated to monitor levels of febrile disease across the U.S. Temperature readings of 37.7 degrees Celsius or above were considered febrile. To focus on incident fever, follow-up fever readings within seven days of a user's first fever were excluded. Only users who logged a temperature more than once in the last year were included in the active user population for the analysis, and only their temperature readings are included in the data. In this study, fever and temperature-taking data were stratified by HHS region and age group. Six age groups were compared: 0-4 years, 5-17 years, 18-24 years, 25-44 years, 45-64 years, and 65-100 years. Daily temperature data were aggregated by week so as to match the viral time series.

This national network of smart thermometers records an average of over 36 thousand temperature readings per day. Throughout the period of interest, there were over 90 million temperature readings, including over 16 million fever readings. The thermometers were used to track temperature and/or symptoms during the study period by over 3 million users nationally, with active user counts ranging from 28 thousand to 148 thousand within individual HHS regions in a year. The viral datasets contain thousands of data points for daily or weekly reports throughout the period of interest.

Adjusted Incidence of Viral Covariates

Testing behavior throughout the study period may vary across time and virus type, misrepresenting levels of illness in the population. For this reason, three measures of incidence were used for time series visualizations, correlation assessment, and model covariates in this study: unadjusted incident cases, incident cases divided by a right-aligned 12-month rolling average of total tests, and incident cases divided by a weekly sum of total tests–also known as weekly percent positivity. Temperature-taking behavior may have varied during the study as well, but rather than using adjusted fever data as the model outcome, the number of active users across HHS regions and age groups was included as a covariate.

When plotting fever or virus incidence, the data were scaled so as to appear on the same axis, with each variable at a specific time point divided by its overall maximum.

Statistical Analysis

Population Comparison

In order to gauge the reliability of each data source, the population of thermometer users was compared to the U.S. census data from 2018. Categorical data were compared using Pearson's Chi-Squared test, and nonparametric continuous data were compared using the Kruskal-Wallis test. P-values under 0.05 were considered to be statistically significant.

Due to a shift in thermometer user quantity and behavior that occurred in response to the COVID-19 pandemic, the demographic characteristics were calculated for the population of thermometer users that activated their devices prior to March 1, 2020 and then again for the population that activated their devices after the emergence of COVID-19. The p-values shown in the table compare each group of active thermometer users on either side of the COVID-19 pandemic onset to the U.S. population from the 2018 census, highlighting whether or not the thermometer-using population is representative of the larger U.S., and revealing potential shifts in that representation as a result of the COVID-19 pandemic.

Time Series Correlation of Variables

The correlation between viral incidence and the fever time series was examined for each virus. Pearson correlation coefficients were calculated for each virus and fever during both the Pre- and Post-COVID periods, assessing the relationship between the curves to determine whether or not it makes sense to attribute fever to each virus at all. Correlation coefficients were calculated for all three measures of virus incidence: unadjusted case counts, cases adjusted for annual testing behaviors, and cases adjusted for weekly testing behaviors. Fever counts were similarly left raw or adjusted based on yearly or weekly behavior, and compared to the appropriate measure of incidence for each virus. Time series pairs with a

Pearson Correlation Coefficient greater than or equal to 0.7 were considered to be strongly correlated. All analyses were conducted in R version 4.2.0 and RStudio version 2023.03.0.

In addition to the statistical assessment of correlation, time series of the three viruses and fever were plotted, first at the national level to compare the three incidence measures, and then at the regional level with the weekly-adjusted incidence which was deemed to be most regular and accurate.

Statistical Modeling

This study used hierarchical Bayesian modeling, an approach that forces the viral covariate effect estimates to be nonnegative in a simpler way than with maximum likelihood estimation. Additionally, Bayesian models allow for more flexibility and training information than Null Hypothesis Statistical Testing in the context of epidemiological data, and account for diagnostic error and high variability at the individual level. (21,22) Negative binomial regression models pertain to disease counts and rates, and work well with large datasets and high disease rates like those of seasonal respiratory viruses across the U.S.

Three negative binomial regression models were fit to the data, with fever as the outcome and seasonal influenza, RSV, and SARS-CoV-2 as the predictors in all three models. This model used an identity link so as to ensure that estimated effects of each virus on fever were additive; the sum of the proportions attributable to flu, RSV, and SARS-CoV-2 was equal to the proportion of fever attributable to any one of those viral causes. (23) For the model fitting, the Bayesian modeling approach and minimally-informative prior probabilities were applied using the rjags package in R. (24) This study drew heavily on a model by Dagan et. al, with the major difference being the inclusion of various adjustments for diagnostic testing and temperature-taking behaviors. (25)

Model Parameters & Structure

All three models used unadjusted counts of incident fever as an outcome, stratified by HHS region and age group. Each model used a different incidence measure of the viral covariates: unadjusted incident cases, incident cases adjusted for annual testing behavior, and incident cases adjusted for weekly testing behavior.

For each time point *t,* HHS region *i,* and age group *j*, the number of fevers *Y* was modeled with the following structure:

$$Y_{t,i,j} \sim NegBin(p_{t,i,j}, r)$$

$$p_{t,i,j} = \frac{r}{r + \lambda_{t,i,j}}$$

$$\lambda_{t,i,j} = b_{1_{i,j}} + b_{2_{i,j}} * sin(\frac{2\pi t}{12}) + b_{3_{i,j}} * cos(\frac{2\pi t}{12}) + b_{4_{i,j}} * t + b_{5_i} * flu_t + b_{6_i} * rsv_t + b_{5_i} * cov_t + b_{8_{i,j}} * u_t$$

where *r* is the overdispersion parameter, and $\lambda_{t,i,j}$ is the expected number of fever cases at a particular time point *t* within each regional and age subgroup. The first term, $b_{1_{i,j}}$, is the regression intercept for each group; the second and third term, $b_{2_{i,j}} * sin(\frac{2\pi t}{12}) + b_{3_{i,j}} * cos(\frac{2\pi t}{12})$, are 12-month harmonic variables that account for seasonal variation in fever; the fourth term, $b_{4_{i,j}} * t$, adjusts for a linear time trend during the study period. Terms five through seven incorporate the viral incidence data, with different measures depending on the particular model version. The coefficients b_{5_i}, b_{6_i}, and b_{7_i} allow for variation across HHS regions but not age group, since the viral data aren't stratified by age. The eighth and final term, $b_{8_{i,j}} * u$, adjusts for shifts in the number of active thermometer users across time and subgroup.

The underlying assumptions of the model included the notion that fever is primarily attributable to infectious diseases, and further, the three study viruses. However, it is widely known that humans experience fever from other sources: foodborne pathogens, vaccination, local dermatological infection, and more.

MCMC Simulations

To obtain the most accurate estimates and to control for outliers and erratic time series behavior, three thousand Markov Chain Monte Carlo (MCMC) model simulations were run, with the medians of all resulting posterior probabilities aggregated at various levels to provide the proportions of fever attributable to each viral source. The convergence of the estimates was checked visually and the estimates were aggregated across simulations.

Attributable Proportions

These models informed the estimation of the proportion of fever that is attributable to each virus of interest, any of the study viruses at all, or other factors such as seasonality, and thus none of the study viruses. The attributable proportions were estimated for each virus over the entire study period and population, and then by age group over time (in weeks) and then overall Pre- and Post-COVID. Once the model was fit, we set each coefficient equal to zero, one at a time, to remove the effect of a particular covariate and estimate the number of fevers *not* caused by that predictor. We then took the model outputs, subtracted them from the total fitted number of fevers, and obtained the estimated number of fevers attributed to each covariate in turn.

Model Validation

Each of the three models were trained on historical data through June 2022, and their predictions of fever trends from July 2022 through March 2023 were tested against observed data for those eight months. The attributable proportions were used to estimate the number of incident fevers caused by each source. The

accuracy of the model to predict the number of fever cases nationally and across the six age groups was checked visually.

Results

Descriptive Statistics (Table 1)

The population of thermometer users has a distribution comparable to that of the U.S. population in terms of gender and urbanization. The user population skews younger with about 50% of users under 25 years old, relative to the older U.S. population. Thermometer users tend to live in census tracts with slightly lower SVI rankings, indicating lower levels of social vulnerability (and thus higher levels of social stability).

National Disease Incidence (Fig. 1)

Before the circulation of SARS-CoV-2, the study viruses and fever showed similar seasonality, surging each winter and dipping during the summer months. Immediately after the 2019-2020 illness season, both flu and RSV cases disappeared. Eventually, in the 2021-2022 illness season, flu and RSV returned with levels lower than before the pandemic. Interestingly, there was more flu and RSV in the summer of 2022 than any year in the dataset, leading into a period of high incidence during the 2022-2023 winter illness season.

Unadjusted counts for flu and RSV seemed to increase steadily with each winter illness season, but once the data were adjusted for weekly or annual testing behaviors, the magnitude stayed relatively constant over the years.

Fever incidence didn’t change much when adjusted for weekly or annual temperature-taking behavior, after an initial adjustment period from 2016 to 2017. Overall, fever adjusted for weekly user behavior remained relatively stable across illness seasons, with a notably small uptick during the winter of 2021.

Once it had reached the U.S., unadjusted SARS-CoV-2 incidence climbed quickly and mellowed out after the highest spike during winter 2021. With adjustments, the incidence demonstrated more typical peaks and valleys reminiscent of respiratory viruses, though this emerging disease has yet to settle into routine endemic patterns. SARS-CoV-2 is the variable for which the consideration of testing behavior had the greatest impact on the incidence rate; the adjusted time series' diverged often, different than the mostly parallel activity of the different measures' for flu, RSV, and fever over time.

Regional Disease Incidence (Fig. 2)

Flu didn't vary much across HHS regions, demonstrating relatively consistent timing and magnitude of disease rates across the U.S. As was true at the national level, the 2020-2021 flu season didn't exist in any regions with the exception of a very small blip in Dallas (HHS Region 6), and flu re-entered circulation in early 2022, drawing the season later into the spring and summer than is typical.

RSV incidence was similarly steady in terms of magnitude, but showed more staggered starts and peaks to illness seasons across regions. Notably, the regional RSV peaks developed even more of an offset in timing after a lull that coincides with the start of the COVID-19 pandemic in 2020, occurring at varying times of the year in 2021 and synching back up in late 2022.

SARS-CoV-2 incidence and epidemic timing varied greatly across HHS regions. All regions experienced a surge in 2021-2022, with the width and magnitude of each curve varying by region. The timing of that surge was uniform across HHS regions, whereas other peaks are staggered or only experienced in some parts of the country.

Fever demonstrated seasonal regularity during the study period across all HHS regions as well. It follows similar patterns to flu and RSV in that it lay low during the 2021-2022 illness season and extended uncharacteristically into the summer of 2022.

Age-Stratified Fever (Fig. 3)

Fever demonstrated seasonal regularity in the pediatric age groups, 0-4 and 5-17, during the study period, and surged much higher in the post-COVID period than prior to 2020 for adult age groups. The pediatric age groups demonstrated strong seasonal patterns of fever. Fever in these groups didn't rise substantially with the onset of the COVID pandemic but rather stayed low until increasing during the 2021-2022 illness season. Fever among 5-17 year-olds in particular dipped very low as SARS-CoV-2 began to spread in the U.S., but climbed faster than other groups in the fall of 2021. The 65-100 age group consistently had the lowest levels of fever, with a sharp increase as SARS-CoV-2 emerged in spring of 2020. Prior to the pandemic, this older age group held a very steady baseline with little seasonality, but they have experienced a few distinct surges in the post-COVID timeframe. The 25-44 cohort experienced higher levels of fever in 2021-2022 than in the pre-COVID study period, and they had the most tumultuous few years after the onset of the COVID pandemic, experiencing wave after wave rather than seeing a plateau like the two oldest age groups.

Correlation between Fever and Study Viruses (Table 2)

Before the COVID-pandemic began in the U.S. in March 2020, both influenza cases and RSV cases were highly correlated with fever incidence, for all three measures of incidence. After the onset of the COVID-19 pandemic, all correlation between fever and both influenza and RSV weakened, with all measures of RSV dropping below the strength threshold of 0.7. SARS-CoV-2, only measured in the Post-COVID period by nature, demonstrated very little correlation with fever data.

Attribution Analysis (Tables 3 & 4; Figs. 4 - 7)

Attributable proportions of fever vary across the viral covariates, the timing relative to the onset of the COVID-19 pandemic, and the specific measure of incidence to which the model was fit. (Table 3) Using unadjusted, raw case counts of flu, RSV, and SARS-CoV-2 returned a more conservative estimate for

overall viral contributions to fever incidence in the Pre-COVID period (33.65%), whereas the model using data adjusted for weekly testing behaviors attributed almost 50% of all fever in the U.S. during that first period to the three study viruses. With all measures, flu is considered the primary Pre-COVID viral cause of fever, with RSV contributing roughly a third as much. After SARS-CoV-2 began to spread, the contributions of flu went down substantially, especially for the adjusted data. RSV didn't change its contributions much once the COVID-19 pandemic hit. The attribution of SARS-CoV-2 was higher than flu or RSV for both models that used adjusted viral covariates.

Stratifying by age provides more information about potential causes of fever. (Table 4) With the unadjusted model in the Pre-COVID period, viruses were least responsible for fevers among infants and toddlers (21.58%) and among the oldest cohort (18.68%), compared to groups in the middle. About half of fevers among 5-17 year-olds were attributed to any virus of interest, according to all three models (ranging from 47.18% to 61.35%), the largest proportion of any cohort. Adjusting viral incidence to weekly testing behavior increased the attributable proportion of fever due to any virus of interest across all age groups.

Notably, in the Post-COVID period, attributable proportions for flu and RSV among elders were very low, while the percentages for SARS-CoV-2 were highest among those 65-100 relative to other age groups across models. RSV contributed more to fever among kids than adults, while SARS-CoV-2 contributed very little to fever within the pediatric population. Flu was responsible for fairly consistent proportions of fever across age groups younger than 65, with the contribution of flu slightly higher among those in the 5-17 age range than other groups across models.

The proportion of fever attributable to each virus over time (Fig. 4 & 6) mimicked the pre-COVID seasonality and post-COVID chaos of the observed viral incidence (Fig. 1). Both the age-stratified attributable proportions of fever across the entire time period (Table 4) and the age-stratified

time series of attributable proportions (Fig. 5 & 7) demonstrated the prominence of SARS-CoV-2 contribution among adult age groups and the lesser impact on pediatric groups, with all models for those ages 25-100 showing relatively high and fluctuating levels of SARS-CoV-2 towards the final years of the study period.

Model Validation

The distribution of twelve different parameter estimates for each model demonstrated the sufficiency of the number of MCMC simulations. (Appendix Fig. 2) Generally, the variance of each parameters' estimates appeared to be constant with increasing iteration index, indicating that the parameters were being estimated at or around their true value. There were a few exceptions, where the estimates surged or dipped for a certain number of iterations in a row, as was seen with the plotted estimates for mu[247, 3, 4]--the estimated number of fevers in the 247th week, HHS region 3, among 25-34 year-olds. However, the overall consensus of iteration estimates was sufficient to claim model robustness.

When fever outcome data from July 2022 to March 2023 were excluded from the model fitting, the model failed to capture the three primary surges of fever that had happened during that subset of weeks. (Appendix Fig. 3) Especially severe is the overestimate of the most recent surge, which was only half the magnitude of the estimation.

The age-stratified prediction periods experienced the same overestimation, with the exception of those 18-24 and 65-100, groups which saw a very close fit and a slight underestimation (respectively) of the March 2023 fever surge. (Appendix Fig. 4) The two pediatric age cohorts also saw a slight overestimation of the plateau period occurring during the first year of the pandemic, with the model never quite catching up with the Post-COVID action.

Discussion

Summary of Findings

This study observed that the study viruses are strong drivers of population-level fever in the U.S., and that the emergence and circulation of one respiratory virus may be strongly associated with the dynamics of other viruses. Fever has historically had strong correlation with flu and RSV incidence, but with the emergence of the COVID-19 pandemic and the resulting NPIs, other viruses stopped circulating. While this may have shifted the primary febrile cause to SARS-CoV-2 for a bit, the pandemic interfered with the typical patterns of flu and RSV, shifting the timing, magnitude, and attributable proportion of fever associated with each virus. Across age groups, there are distinct differences in the proportion of fever attributable to the study viruses both before and after the onset of the COVID-19 pandemic. We quantified and visualized the relationship between the study viruses and fever, as well as the consequences of the COVID-19 pandemic on said relationships. Once that was established, we demonstrated in the primary analysis that the attributable proportion of fever varies drastically by age group.

Febrile-Viral Correlation Heterogeneity

The demonstrated strength of the temporal association between fever and Pre-COVID respiratory viruses is intuitive in that flu and RSV sometimes cause fever, and those pathogens are circulating most intensely during the winter, potentially causing the most fever out of the year. (26) Other pathogens can cause fever, such as rotavirus, but aren't nearly as widespread, so the bulk of the fevers that occur and get picked up by smart thermometers are likely due to the common fever-causing respiratory viruses. (19)

Post-COVID, it also makes sense that those strong correlations would weaken, since another fever-causing virus came into the mix and dominated for over one illness season before flu and RSV returned, staggering viral incidence peaks and muddling the fever curve. The correlation between flu and fever remained strong Post-COVID, whereas that of RSV and fever was substantially diminished. This

may be due to the age distribution of both viruses in the wake of SARS-CoV-2 circulation. RSV hit certain age groups harder than usual in the Post-COVID period, such as elders, whose waning immune capacities make them less likely to develop fever; as RSV cases go up among older folks, the proportion of RSV cases resulting in fever goes down. (27,28) Flu didn't necessarily impact age groups differently than it usually does, though the 2022-2023 flu season was particularly severe across the board. (29)

The case with SARS-CoV-2 is interesting. As was previously mentioned, this virus has yet to develop seasonal regularity or provide a convincing baseline for the offseason. Additionally, different ages, immune statuses, and viral variants determine the likelihood that an infected individual will develop fever, so certain periods Post-COVID may have seen a large proportion of feverless COVID-19 cases. In a different vein, testing and reporting for SARS-CoV-2 are still delayed, and people often take their temperature well in advance of seeking medical care and receiving diagnostic testing, so it is possible that at a lag of a week or more, the fever and SARS-CoV-2 cases would be better aligned. This absence of association between SARS-CoV-2 and fever is also evident in the model results: the percent of fever attributable to SARS-CoV-2 remained quite small, and since those values were calculated from the model equation, this indicates that the coefficients for SARS-CoV-2 were relatively small. The closer a regression coefficient is to zero, the stronger the suggestion that the covariate has no effect. In this case, the models find that SARS-CoV-2 had a minimal impact on fever, which may shift as time continues, for there aren't enough data available or established patterns pertaining to SARS-CoV-2 to fully understand its dynamics.

Age Heterogeneity

The differences in attribution of fever across age groups can be explained by a number of factors. The original strains of SARS-CoV-2 were known to infect older adults at higher rates than kids, and when kids were infected, they often weren't symptomatic. (30) Many kids were also removed from school and social settings due to strict NPIs, reducing viral circulation among pediatric groups while adults with more

agency, mobility, or obligation still got sick and spread illness around. When children did return to school and activities, dates which staggered around the U.S. but generally hovered around the fall of 2021, their proportion of fever attributable to SARS-CoV-2 soared, perhaps because a new strain was circulating that was more likely to cause illness in the pediatric population, or because they didn't have antibodies from the previous illness season so they were more vulnerable to symptomatic infection from all respiratory viruses. (31–33) Additionally, most children have typically been exposed to and infected by RSV by the time they are two years old, making RSV one of the primary sources of disease in infants and toddlers. (34) The cohort who missed the 2020-2021 RSV season were susceptible the following year when RSV returned, causing RSV to surpass flu in estimated contribution while the proportion attributable to SARS-CoV-2 for the 0-4 age group was minimal.

On the other end of the age spectrum, those 65 and older have a higher risk of SARS-CoV-2 infection, but based on the historical data, tend to experience less seasonality of fever, aren't as likely to develop fever, and aren't as likely to have flu or RSV as children. (35) Consequently, when the elder population was hit by SARS-CoV-2 and many cases were feverish and symptomatic, their attributable proportion of fever skewed heavily towards SARS-CoV-2 relative to the minimal viral causality that existed Pre-COVID.

In terms of other age groups, the proportion of fever attributable to viral causes for 18-24 year-olds was also low. This cohort doesn't spend as much time around children or elders, spending lots of time among peers, and minimizing their illness risks for respiratory viruses common among both age extremes. (36) They also tend to be healthier, experiencing more asymptomatic disease that wouldn't result in fever. This differs from the slightly higher attributable proportions among adults 25-64 who tend to interact more with other generations, both younger and older. This changed during 2021-2022, when young adults 18-44 were all hit relatively hard by the Omicron BA.1 variant of SARS-CoV-2 which was known to cause mild but symptomatic illness in a wider swath of the infected population. (37)

Model Heterogeneity

Unsurprisingly, the different incidence measures used to fit the models shifted the resulting attribution of fever. When visualizing the time series, the raw viral cases demonstrated the expected seasonality but indicate massive spikes in the last year, which may not be a reflection of the viral circulation itself but more so a result of increased testing awareness and access. Both yearly and weekly adjustments brought the magnitude of each surge to a more consistent place, but the yearly adjustment had a 52-week lag on SARS-CoV-2 data due to the recency of diagnostic test development for that virus. (Fig. 4b) The yearly adjustment accounted for major changes in testing behavior or availability from one year to the next, but the weekly adjustment accounted for more acute shifts, as we saw in 2021-2022 with the encouragement and distribution of rapid antigen tests for SARS-CoV-2. (38) This weekly adjustment is the most robust and impactful, adjusting each week for major changes in testing behavior in an attempt to more accurately capture the levels of illness in the population.

The weekly model shifts the attributable proportion of fever higher for adults across all viral causes while the same model shifts pediatric proportions lower or keeps them about the same. (Table 4) This might be because adults get tested more often, allowing their behaviors to change more substantially and resulting in a larger impact post-adjustment. It could also be due to the high rates at which children have their temperature taken, either because of parental worry or school guidelines that mandate certain protocols for feverish students. With a larger number of total and feverish temperature readings coming consistently from kids, it is possible that major changes accounted for in the weekly adjustment would already be diluted by nature of the temperature-taking population and their behaviors, lessening the impact of adjusting viral case counts.

Strengths

This study has numerous strengths. The historical data span four years prior to the Post-COVID period, four years during which the study viruses and fever had relatively stable seasonality. This provides insight

into annual pandemic dynamics and sets the stage for the tumultuous shifts in seasonality that occurred in early 2020. The network of thermometer users is vast and dense, providing strong sample sizes for analysis at the regional and age-stratified levels. Additionally, the user population is representative of the U.S. population in terms of regional dispersion, urbanization, and gender, all characteristics which shape transmission of infectious disease.

Limitations

These findings are subject to certain limitations. The user population skews younger and less socially vulnerable than the general U.S. population, which may leave out large swaths of people who get ill and don't access clinical care, and thus aren't counted by any of the surveillance systems utilized in this study. The continuation of the COVID-19 pandemic and the recency of its origins provide opportunities for research, but the literature is currently limited and the data are full of gaps. Moving forward, data on SARS-CoV-2 and other diseases may be less available and timely, given the non standardized reporting requirements and ever-shifting testing access and patterns. Additionally, while the binary time variable, Pre-COVID or Post-COVID, was useful for much of the descriptive analysis, it could have enhanced the model as an additional covariate to account for changes brought about by the COVID-19 pandemic.

Conclusion

Implications for Public Health Practice

This study begins to leverage novel surveillance approaches to understand the burden of illness in the population beyond just the cases that present to the healthcare system. If we could strengthen our understanding of circulating illness–both mild and severe–and make informed inferences about its causes, we could better respond to and prepare for seasonal and epidemic illness periods. Using fever or other symptoms is one way to supplement surveillance systems that are heavily reliant on lab results, official diagnostic codes, or clinical visits and follow-up reporting. There will be more room and support for these methods moving forward; they have the capacity to broaden our catchment and enhance our data.

Future Pathways for Research

While this study examined the differences in models with varying levels of covariate adjustment, it would be interesting to train the model without SARS-CoV-2 data, generating counterfactuals with which to compare observed incidence, quantifying the impact of the COVID-19 pandemic on flu and RSV. Additionally, the Post-COVID time period could be broken down further, perhaps into waves of variant dominance so as to explore the age-stratified attributable proportion of fever when different SARS-CoV-2 strains were circulating heterogeneously across age groups and causing different combinations of common symptoms. Finally, a more technical study might explore the probability that an individual's incident fever is attributable to one particular viral cause, based on demographic and behavioral risk factors as well as regional incidence. There is much to be learned about fever and its relationship to the study viruses, and with each new discovery comes a wealth of opportunities to be implemented by the essential public health workforce to keep populations as healthy as can be.

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Appendix

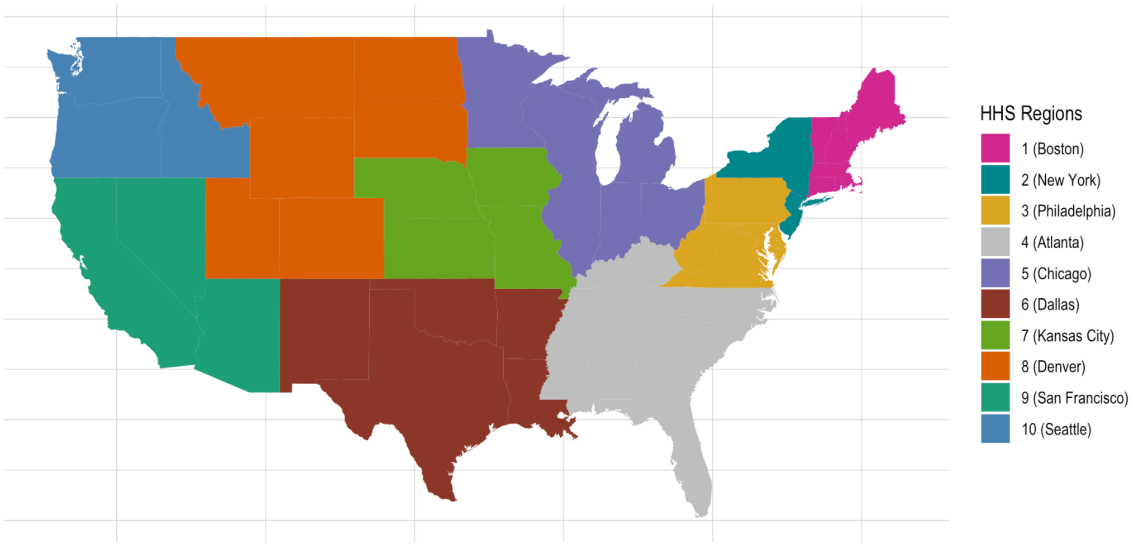
Appendix Fig. 1 HHS Regions of the United States

Appendix Fig. 2 Visual Checks for Model Convergence

Appendix Fig. 3 Model Prediction vs. Observed Fever Incidence, Model fit to Fever Data from July 2016 – June 2022 using Unadjusted Viral Covariates, with July 2022 – March 2023 as Prediction Period

Appendix Fig. 4 Model Prediction vs. Observed Fever Incidence, Model fit to Fever Data from July 2016 – June 2022 using Unadjusted Viral Covariates, with July 2022 – March 2023 as Prediction Period, Stratified by Age Groups

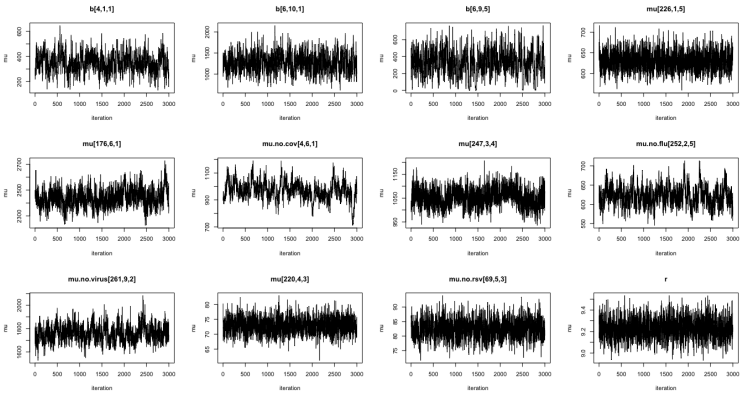
Appendix Fig. 1 HHS Regions of the United States



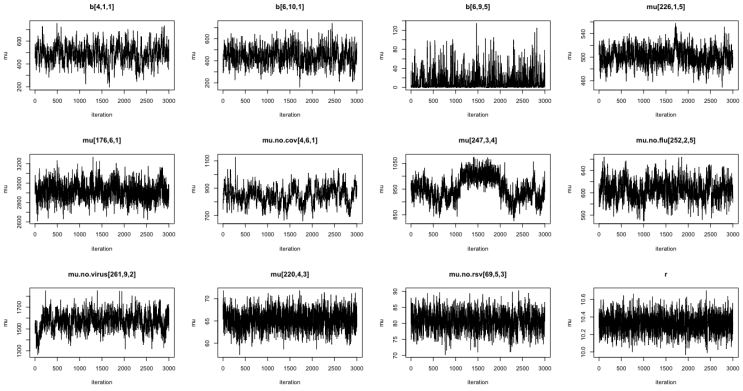
Note: the code for this plot was adapted from a CDC Github Repository. (39)

Appendix Fig. 2 Visual Checks for Model Convergence

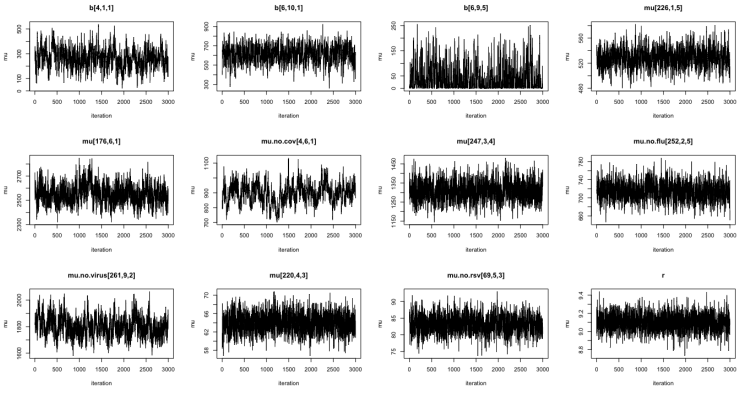
Unadjusted Viral Covariates



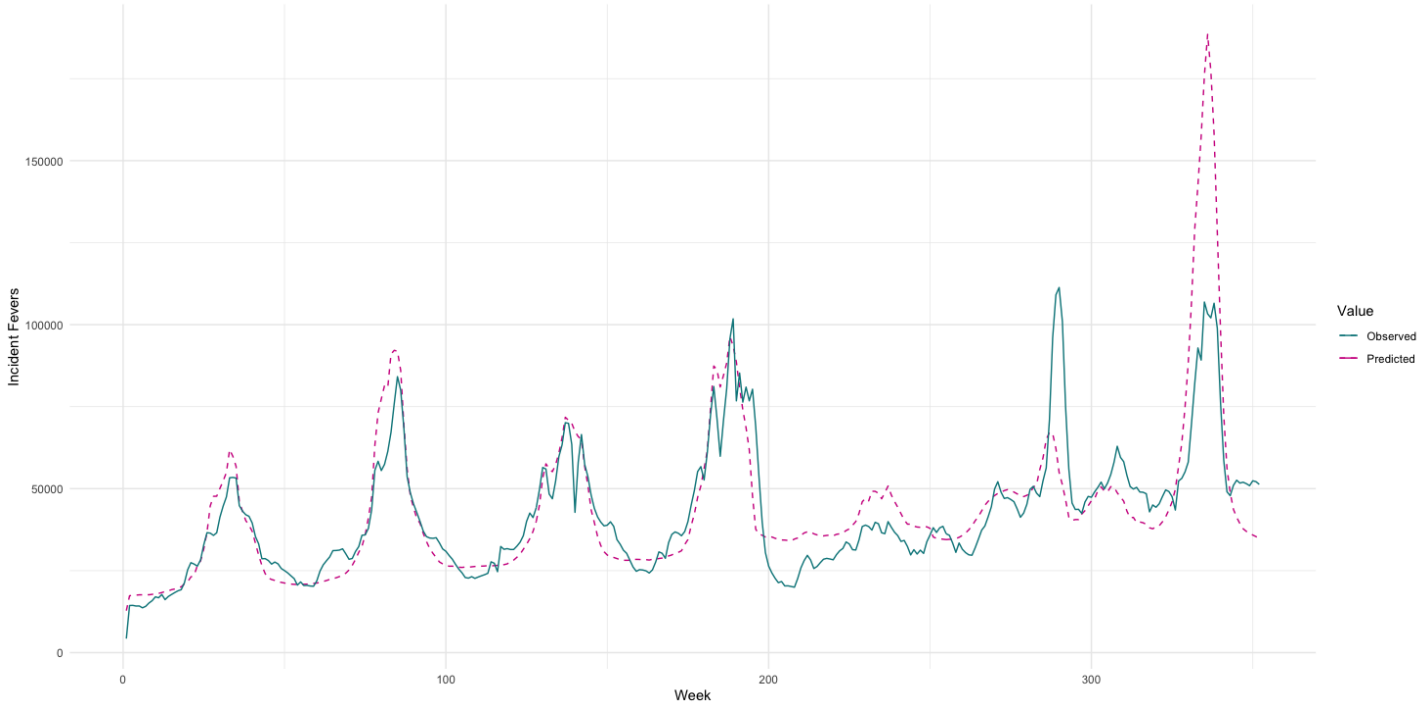
Viral Covariates with Yearly Adjustment



Viral Covariates with Weekly Adjustment



Appendix Fig. 3 Model Prediction vs. Observed Fever Incidence, Model fit to Fever Data from July 2016 – June 2022 using Unadjusted Viral Covariates, with July 2022 – March 2023 as Prediction Period



Appendix Fig. 4 Model Prediction vs. Observed Fever Incidence, Model fit to Fever Data from July 2016 – June 2022 using Unadjusted Viral Covariates, with July 2022 – March 2023 as Prediction Period, Stratified by Age Groups