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Evaluating a multiplier model approach to burden estimation by estimating COVID-19 disease burden in Maryland, USA from April 2020-March 2021 and discussing international feasibility

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Evaluating a multiplier model approach to burden estimation by estimating COVID-19 disease burden in Maryland, USA from April 2020-March 2021 and discussing international feasibility

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An abstract of
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Abstract

Evaluating a multiplier model approach to burden estimation by estimating COVID-19 disease burden in Maryland, USA from April 2020-March 2021 and discussing international feasibility

By Dallas M. Rohraff

Background: COVID-19 disease burden estimation is valuable to understand the true impact of the disease considering that reported COVID-19 case counts are likely to be an underreport of the true number of infections. There remains a need for a straightforward approach to COVID-19 disease burden estimation which can be utilized in a variety of settings.

Methods: We developed a multiplier model approach to estimate COVID-19 burden, which can be modified for use in local or international settings. Using data from the state of Maryland as an example, we evaluated the use of the COVID-19 disease burden multiplier model to estimate COVID-19 associated symptomatic cases, medically attended illnesses, hospitalizations, and deaths from April 2020-March 2021. As a comparison, we estimated excess deaths due to COVID-19 during this time frame using age-specific time-series regression models.

Results: The multiplier approach estimated a total of 615,495 symptomatic illnesses, 234,853 medically attended illnesses, 33,567 hospitalizations, and 9,662 deaths across all age groups in the state of Maryland from April 2020 to March 2021. Those aged <50 years contributed to a majority of the estimated symptomatic and medically attended illnesses, but most hospitalizations and deaths estimated were among those aged ≥50 years. The regression model estimated 8,173 COVID-19 attributable deaths in the same time frame in Maryland.

Discussion: The multiplier model estimated COVID-19 burden in the state of Maryland reasonably well with estimates that were greater than reported case counts and deaths, but less than CDC seroprevalence estimates. This method may prove valuable in local areas if a straightforward approach is desired and the available data sources are well understood. The multiplier model seems feasible to use in Albania and South Africa, but further studies will be needed to evaluate its efficacy in international settings.

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Introduction

Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) infections are nationally notifiable in the United States (US) and reported by state and local health departments to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System (NNDSS).[1,2] These reported COVID-19 cases do not fully capture the totality of SARS-CoV-2 infections. COVID-19 disease burden estimation methods consistently suggest that the number of confirmed cases and deaths that are reported are likely much lower than the truth.[3-6] Seroprevalence studies conducted in the US have reported infection estimates that range from 6 to 56 times the number of reported cases.[7-10] This is not a new phenomenon as many diseases, such as those which cause respiratory illnesses, are underreported. Influenza burden, for example, is routinely estimated to better understand total cases, hospitalizations, deaths, and the burden on the population and healthcare system.[11-15]

There are numerous reasons why reported cases, hospitalizations, and deaths may underreport the true burden of COVID-19. Asymptomatic and mildly ill cases may be less likely to seek medical care or testing, reducing their likelihood of being detected. Symptomatic persons might avoid seeking medical care or seek it after the virus is no longer detectable. Presentation of non-specific symptoms may not prompt clinical testing by healthcare providers. Telemedicine appointments, which significantly increased during the pandemic, may affect the rate of testing.[16] Timing of specimen collection, specimen quality, and assay sensitivity affect the ability to confirm SARS-CoV-2 infection accurately and efficiently, leading to under-detection of infections.[17] Death from a COVID-19 illness can occur days to weeks after symptom onset or testing and may be incorrectly attributed to a cause of death other than COVID-19 because of this time delay or inability to detect virus upon death. Additionally, non-respiratory clinical complications and exacerbation of chronic conditions caused by SARS-CoV-2 infection may lead to COVID-19 being incorrectly omitted as a contributing cause of death on individual death certificates. Furthermore, factors involved in detecting and reporting cases and deaths due to COVID-19 can vary by

geographical region, over time, and across healthcare settings. Smaller regions, such as the state or county level, may find local COVID-19 burden estimation approaches useful to estimate the true burden of COVID-19 in their communities and inform their unique public health needs and efforts. Similarly, COVID-19 burden estimation may also prove useful in international settings where data availability and quality vary.

We have developed a method for estimating COVID-19 disease burden that can be easily modified to fit the data available at local or international regions of interest. The method utilizes a multiplier modeling approach and displays the COVID-19 disease burden estimates in a burden pyramid created by an excel template. The disease burden pyramid is a tool used to display the impact of disease at various levels of illness severity. Pyramids are used to describe burden for many diseases and are a useful visualization tool for diseases where all levels of severity are not directly monitored or reported. The levels of our burden pyramid include: COVID-19 associated symptomatic cases, persons seeking medical care, hospitalizations, and deaths. Each level of COVID-19 disease burden estimated with our method contributes to the understanding of the true incidence of COVID-19 disease in a population and its impact on the public health and healthcare systems in their jurisdiction. This knowledge can help evaluate the effectiveness of previous public health measures and inform future interventions needed in specific communities. The objectives of this study were to evaluate the use of the multiplier modeling method at the state level and explore its feasibility in international settings. To understand its use at the state level, we used the multiplier modeling approach to estimate illnesses, medically attended, hospitalizations, and deaths for the state of Maryland, USA. We aimed to evaluate our multiplier model by using an excess mortality modeling approach to compare with deaths estimated from the multiplier model. Lastly, we discussed the feasibility of using this method in international settings by exploring how it could be implemented in South Africa and Albania, as two examples.

Methods

Data Sources

Data sources utilized in the COVID-19 disease burden estimation are summarized in Table 1. COVID-19 symptomatic and medically attended illnesses were estimated using the COVID Near You (CNY) surveillance platform (now renamed Outbreaks Near Me to allow for more broad illness capture).[18] CNY is a digital participatory syndromic passive surveillance platform that collects crowdsourced data to understand current outbreaks and identify potential hotspots of COVID-19 disease. Though there has been some advertisement through social media and news outlets, participants likely seek out the surveillance opportunity themselves and are primarily motivated by the importance of disease tracking and the desire to be a part of a citizen science project.[19] Anyone aged 13 years or older in the US, Canada, or Mexico can voluntarily enroll themselves into the text message version of CNY or participate without enrollment by visiting the CNY website to self-report health status, symptoms, healthcare-seeking behavior, and vaccination status as often as they choose to report.[18,20,21] Most participants report via text message and are prompted to report every three days but can also report daily by visiting the CNY webpage. A single reporting session begins by users being asked if they are healthy or ill. If they respond that they are healthy, the session is completed, they are thanked for their time and will be reminded to report again in three days. If they report feeling ill, they are asked which symptoms they have experienced in the past week from a list of respiratory, whole body, digestive, and other symptoms; to provide the date which illness began; and to report if any medical care was sought due to symptoms. All participants are asked to provide their age, gender, and zip code upon registration into the text-message system or at the end of each reporting session that is completed on the website. Reporters are also asked about their Flu and COVID-19 vaccination status if they respond via text that they are ill or if they report through the website.[18] Since participants may report to

CNY more than once a week, we combined individuals' responses into a weekly summary which identified all symptoms and any healthcare seeking behaviors reported during each epidemiologic week.

Self-reported symptom data from CNY are utilized to understand the trends in COVID-like illness (CLI) in a specific region by week. For this study, we used two case definitions to identify persons with CLI from those reporting symptoms into CNY; a sensitive CLI case definition which is more likely to capture all possible COVID-19 cases is used in estimates of symptomatic illnesses, and a specific CLI case definition which is more likely to capture the illnesses that seek medical care. The specific case definition we used mirrors the COVID-19 interim case definition from August 5, 2020, used by the Council of State and Territorial Epidemiologists (CSTE).[1,2] Our specific CLI case definition included reporting any 2 of the following during a given epidemiologic week: fever, chills, sore throat, body ache, headache, nausea, diarrhea, running nose, fatigue; OR any 1 of the following: cough, shortness of breath, or loss of taste/smell. We calculated the percentage of people who sought medical care by dividing the number of respondents who reported seeking medical care (defined as visitation to a doctor office/HMO, urgent care center, in-store clinic, emergency room, hospital overnight, virtual care, or a COVID-19 testing center) by the number of respondents who met the specific CLI case definition each week. Calculations were performed across all age groups and separately for the following age groups: 0-17 years, 18-49 years, 50-64 years, and ≥65 years. Our sensitive CLI case definition included participants reporting any 1 of the symptoms listed in the specific CLI case definition above. The weekly percentage of age-specific symptomatic illness was calculated by dividing the number who report any CLI symptom by the total number of reporters that week for each age group and across all ages.

Commercial SARS-CoV-2 testing data were obtained from the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE) and include data from six major commercial laboratories participating in the National Syndromic Surveillance Platform (NSSP).[22,23] Viral data include real-time reverse transcriptase polymerase chain reaction (rt-PCR) SARS-CoV-2 testing and

results, as well as accompanying demographic information. Commercial viral data were obtained by age group and week for the state of Maryland and were combined with Maryland's age-specific weekly public health laboratory SARS-CoV-2 testing data from the Public Health Laboratory Interoperability project (PHLIP)[24] and Public Health Laboratory Information System2 (PHLIS2). Using the combined data from both the commercial and public health laboratory systems, the age-specific weekly proportion of SARS-CoV-2 positive tests were calculated as the number of positive SARS-CoV-2 test results divided by the total number of SARS-CoV-2 tests with a known result by age and week. For our excess mortality model comparison, SARS-CoV-2 testing data were used as a proxy for viral circulation patterns during the study timeframe. Influenza surveillance data from public health and clinical labs, utilized in the regression model, were obtained from CDC's FluView Interactive by epidemiologic week for the state of Maryland.[25]

COVID-19 hospitalization data were obtained from Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET), a population-based active surveillance system that captures data on laboratory-confirmed COVID-19-associated hospitalizations within its coverage areas.[26,27] Because the populations served by these hospitals are known, hospitalization rates can be estimated for specific states and regions.[22] COVID-NET sites cover 99 counties in 14 states which equates to around 10% of the US population and covers all 10 of the Health and Human Services (HHS) regions. COVID-NET was initiated in April of 2020 with retrospective testing beginning March 1, 2020. COVID-NET surveillance sites in Maryland report from all counties in the state and represent 100% of the state's population.[28] Maryland's COVID-19 hospitalization rates were obtained by age group and reported weekly as the cumulative rate since March 1, 2020.

Death data were obtained from the National Center of Health Statistics' (NCHS) National Vital Statistics System (NVSS), which collects, cleans, and systematically codes death certificate data. Maryland's COVID-19, pneumonia, influenza, and all-cause mortality data by sex and age from March 28,

2020 through April 3, 2021 were used in the multiplier model burden estimations.[29] All-cause mortality data from July 5, 2015 to April 3, 2021, used in the regression analysis, were obtained for Maryland and categorized by age and epidemiologic week.[30]

Population counts used in the multiplier model to estimate COVID-19 disease in Maryland were July 1, 2019 (midyear) estimates produced by the US Census Bureau's Population Estimates Program in collaboration with the National Center for Health Statistics based on the 2010 census counts. Population data were collected by state, county, and age.[31] Yearly vintage bridged-race postcensal population estimates for the state of Maryland from 2015 through 2019 used in the time-series regression model were also obtained from the US Census Bureau.[32]

Analytic Methods

Multiplier Approach to COVID-19 Burden Estimation

Burden estimates for symptomatic illness, medically attended illness, hospitalizations, and deaths were calculated for a full year, from the first epidemiologic week in April 2020 (beginning March 28, 2020) through the final epidemiologic week in March 2021 (ending on April 3, 2021). Despite the pandemic officially emerging in the US at the end of February 2020, burden estimation began in April once all necessary data to build out our estimates were available. Specifically, CNY was introduced in mid-March, but age-specific data were not available until April 2020. All calculations were conducted across all ages and using the following age groups: 0-17 years, 18-49 years, 50-64 years, and ≥65 years.

Dynamic Susceptible Population

Age-specific dynamic populations in Maryland were calculated each week throughout the study timeframe. These calculations were performed under the assumption that everyone in Maryland was susceptible to SARS-CoV-2 infection at the start of analysis, and that immunity to reinfection begins to decline approximately 2 months post infection.[33-35] The dynamic susceptible populations were calculated by setting the age-specific population for the first epidemiologic week in April equal to the 2019

population estimates by age group. Each subsequent week's age-specific susceptible populations were then calculated by subtracting the number of calculated age-specific COVID-19 symptomatic cases (defined as the age-specific CLI rate times the age-specific population and age-specific SARS-CoV-2 percent positive for each week) for the previous week from the population of the previous week. For the first two months of analysis, previous infections were assumed to have immunity to reinfection. Beginning the first epidemiologic week in June (two calendar months after the start of our analysis), the number of calculated age-specific COVID-19 symptomatic cases from two months (9 weeks) prior was added back into the susceptible population as a crude adjustment for potential loss of natural immunity to the virus. The goal of using dynamic populations in the analysis was to account for potential overestimation caused by applying illness and care-seeking rates to persons who were already considered infected or recovered over time.

Symptomatic Illnesses

Illness rates and health care seeking behaviors from CNY were analyzed using SAS Statistical Software Version 9.4 (SAS Institute, Inc., Cary, NC, USA) and summarized to calculate the burden pyramid levels in Microsoft Excel. CNY reported illness and health care seeking percentages were obtained for HHS region 3 as a proxy for Maryland to account for lower response rates in November and December across all age groups and across all weeks among those aged 0-17 years (Supplemental Figure 3). HHS region 3 proportions were used under the assumption that the proportions observed in the region, which contains Maryland, Delaware, Pennsylvania, Virginia, West Virginia, and the District of Columbia, were exchangeable for those of Maryland during the time frame. Indeed, weekly rates of reported CLI are similar among all states within HHS region 3 (Supplemental Figure 3). Age-specific weekly rates of CLI were defined as the number of respondents in HHS region 3 reporting symptoms meeting the sensitive CLI case definition among all respondents in each age group each week. The number of weekly CLIs were estimated by applying the age-specific weekly rate of CLI to the dynamic

population by age group and week. Symptomatic illnesses were then estimated by applying the age-specific weekly proportion of SARS-CoV-2 positive tests in the state of Maryland to the number of age-specific COVID-like illnesses each week.

Uncertainty intervals (UI) for estimates of symptomatic illnesses were calculated through reestimation using a stricter and broader CLI case definition for the lower and upper bounds, respectively. We will refer to these as the broader or stricter UI case definitions as opposed to the specific or sensitive CLI case definitions used in calculating our point estimates. The lower bound of the UI for symptomatic illnesses was calculated using response data of participants that reported any symptoms meeting the stricter UI case definition: fever, cough, shortness of breath, or loss of taste/smell, as these symptoms are more specific to COVID-19 infections and should capture fewer non-COVID-19 cases. The case definition for the upper bound includes reporting any of the following symptoms: sneezing, loss of appetite, rash, or any symptoms in our CLI definition: fever, chills, sore throat, body ache, headache, nausea, diarrhea, running nose, fatigue, shortness of breath, or loss of taste/smell. This broader UI case definition includes reporting any symptom into CNY to capture any possible reported symptoms which may not have been considered CLI based on our specific or sensitive case definitions. UIs for symptomatic illness estimates were calculated by applying the age-specific percentage of CNY respondents reporting symptoms that meet either the stricter or broader UI case definition to the age-specific proportion of SARS-CoV-2 tests and the dynamic weekly population by age group and week.

Medically Attended Illnesses

The age-specific weekly proportion of respondents seeking medical care was determined by the proportion of CNY respondents in HHS region 3 who reported seeking medical care among those meeting the specific CLI case definition for each age group and week. The age-specific proportion of respondents seeking medical care was then applied to the age-specific weekly number of COVID-like

illnesses to obtain the estimates for total number of medically attended illnesses in each age group and each week in Maryland. Medical care-seeking response data for the last 3 epidemiologic weeks in March was unavailable and thus the average proportion of individuals seeking medical care from the first two epidemiologic weeks in March was carried forward into the last three weeks of the month with missing data.

Similar to the uncertainty intervals calculated for symptomatic illnesses, uncertainty intervals (UIs) for estimates of symptomatic and medically attended illnesses were calculated through reestimation. For medically attended illness, however, the UI is calculated using the proportion of respondents who report seeking medical care among those meeting the broader or stricter UI case definitions (as described above for symptomatic illness uncertainty intervals). The proportion of respondents who report seeking medical care among those meeting the broader UI case definition provide the lower bound while the proportion of respondents who report seeking medical care among those who meet the stricter UI case definition provide the upper bound. The UI case definitions provided denominators that were used in this manner because those who report more general symptoms (broad UI case definition) are less likely to seek medical care and those reporting more severe symptoms (such as those meeting the stricter UI case definition) are more likely. The age-specific proportion of respondents that reported seeking medical care among those meeting the broader or stricter UI case definition was applied to the age-specific number of covid-like illnesses by age group and week to obtain UIs for medically attended illnesses.

Hospitalizations

Age-specific hospitalizations were estimated by applying the cumulative COVID-NET hospitalization rates for the study time frame to the population by age group. To obtain the age-specific cumulative hospitalization rates for our study time frame, we subtracted the age-specific cumulative hospitalization rates for the week prior to our study (the last epidemiologic week in March 2020) from

the cumulative hospitalization rates at the end of our study (the last epidemiologic week of March 2021). Because COVID-NET hospitalizations are COVID-19 confirmed cases, no adjustments for SARS-CoV-2 percent positive were included. Additionally, the coverage area of COVID-NET hospitals in the state of Maryland service the entire state, thus hospitalization rates could be applied to the total state populations by age group. 95% confidence intervals for COVID-19 hospitalization rates were calculated by adding and subtracting 1.96 times the standard deviation of the hospitalization rates in accordance with the WHO guidance on calculating 95% confidence intervals for Influenza burden estimations.[36] From here, hospitalization estimate confidence intervals were calculated by applying the 95% CI rates back to the total 2019 Vintage age-specific population.

Deaths

COVID-19 deaths were estimated with the multiplier model approach under the assumption that some deaths from COVID-19 in Maryland may have been attributed to pneumonia or other causes, resulting in underreporting of true COVID-19-associated deaths. While pneumonia deaths are available in real-time, other causes of death which have been identified to be associated with COVID-19, such as hypertension and diabetes, are not. Consequently, COVID-19 deaths were estimated by adding the number of COVID-19 ICD-coded and reported deaths to a proportion of pneumonia deaths we assumed to be misidentified COVID-19 associated deaths. These misidentified COVID-19 associated deaths were calculated by applying the age-specific proportion of SARS-CoV-2 positive tests to the number of pneumonia ICD-coded deaths. Applying the proportion of positive tests to pneumonia-coded deaths to identify incorrectly attributed deaths provides a conservative estimate of total COVID-19 deaths compared to applying the SARS-CoV-2 percent positive to the number of all-cause deaths, which would likely overestimate the true number of COVID-19 deaths. Standard 95% confidence intervals were calculated for COVID-19 associated death estimates.[36]

COVID-19 Time-series Excess Mortality Regression Model

We also estimated excess mortality due to COVID-19 using a time-series regression model to compare the death estimates we obtain from the multiplier model. Because the multiplier method provides conservative estimates of COVID-19 deaths, an excess mortality model which calculates baseline deaths from historical all-cause mortality was used to evaluate the estimates produced. Excess mortality models have been used to estimate influenza-associated mortality for several decades and are considered a reliable method for estimating deaths. We estimated excess mortality due to COVID-19 from April 2020-March 2021 using age-specific negative binomial time series logistic regression models. Separate models were run for those aged <65 years and those aged ≥ 65 years. Data was stratified into these age groups to achieve sample sizes which were sufficient for the regression models to produce reliable estimates. Specifically, deaths among the 0-17, 18-49, and 50-64 age groups in Maryland were relatively low in comparison to those aged ≥ 65 years and may not be sufficient for the model convergence. Additionally, the age groups in the death data provided by NCHS do not match the age groups from CNY used in the multiplier model approach and thus a binary age variable of <65 and those ≥65 years was used.

Age-specific excess mortality due to COVID-19 was estimated using the following negative binomial model:

$$Y = \alpha * \exp\left(\beta_0 + \beta_1(t) + \beta_2(t^2) + \beta_3\left[\sin\left(\frac{2t\pi}{52}\right)\right] + \beta_4\left[\cos\left(\frac{2t\pi}{52}\right)\right] + \beta_5(Flu) + \beta_6(COVID)\right)$$

where Y represented the number of deaths in a particular week, α was the offset term equal to the log of the age-specific population size, β_0 represented the intercept, β_1 represented a coefficient for the linear time trend, β_2 represented a coefficient associated with the quadratic time trend, β_3 and β_4 represented coefficients associated with seasonal fluctuations in deaths, and β_5 and β_6 represented the coefficient associated with the percentage of specimens testing positive for influenza (any type) and SARS-CoV-2, respectively, in a particular week.

Historic all-cause mortality data and viral influenza surveillance data beginning in the 27th week of 2015 (the beginning of the 2015-2016 influenza season) were used to establish baseline mortality. Any weeks which had missing death or viral data were considered to have zero reported deaths or zero positive test results for influenza or SARS-CoV-2 during that week. Excess deaths associated with COVID-19 or influenza were estimated by subtracting the number of baseline deaths from those predicted assuming SARS-CoV-2 and influenza circulation between March 28, 2020, and April 3, 2021.

Results

COVID-19 Burden Estimates

Between April 2020 and March 2021, we estimated a total of 615,945 COVID-19 symptomatic illnesses (UI: 414,440-623,671) across all age groups in the state of Maryland translating to a rate of 10,188 per 100,000 (UI: 6,839-10,316 per 100,000) (Table 2). Figure 1 depicts the estimates from the multiplier model in a burden pyramid for all ages and Figure 2 depicts the estimates for each age group. The highest absolute number of estimated symptomatic illnesses occurred among those aged 18-49 years with 249,115 (UI: 147,838-253,483) estimated symptomatic illnesses. The highest rate of symptomatic illness occurred among those ages 0-17 years with 17,652 symptomatic cases per 100,000 (UI: 14,876-17,787 per 100,000). The lowest estimated number and rate of symptomatic illness were among those aged ≥65 years with 37,441 symptomatic illnesses (UI: 16,738-38,043) and a rate of 3,903 per 100,000 (UI: 1,745-3,965 per 100,000). We estimated a total of 234,853 medically attended illnesses (UI: 258,385-221,450) across all age groups in the state of Maryland (Table 3). This suggests that nearly 40% of symptomatic cases in Maryland sought medical care for their COVID-19 illness. Our estimates of medically attended illnesses ranged across age groups from 15,865 to 103,257 among those aged ≥65 and those aged 0-17 years, respectively.

Across all age groups, we estimated 33,567 hospitalizations (95% CI: 32,823-34,311), which is a rate of 555 per 100,000 population (95% CI: 543-568 per 100,000) (Table 4). Those aged ≥65 years were estimated to have the highest number (14,929 with 95% CI: 14,551-15,307) and rate (1,556 per 100,000 with 95% CI: 1,517-1,596 per 100,000) hospitalizations. We estimated the fewest hospitalizations in those aged 0-17 years with 486 hospitalizations (95% CI: 475-496) equal to a rate of 36 per 100,000 (95% CI: 36-37 per 100,000).

A total of 9,662 deaths (95% CI: 8,489-10,834) attributable to COVID-19 across were estimated across all age groups in the state of Maryland between April 2020 and March 2021 (Table 5). The greatest number of deaths were estimated among those ≥65 years, with 7,944 (95% CI: 6,966-8,922) deaths and a rate of 828 per 100,000 (95% CI: 726-930 per 100,000). We estimated 299 deaths (95% CI: 248-351) in those aged 18-49 years and 0 deaths among those aged 0-17 years.

COVID-19 Time-series Excess Mortality Regression Model

Using the time-series excess mortality regression model, we estimated that 8,173 (95% UI: 6,757-9,628) total COVID-19 attributable deaths occurred in the state of Maryland from April 2020 to March 2021(Table 6). Among those aged <65 years, we estimated 2,271 (95% UI: 1,841-2,714) COVID-19 attributable deaths during the time period while those aged ≥65 years were estimated to have 5,902 (95% UI: 4,916-6,914) COVID-19 attributable deaths.

During the study period, the multiplier model approach estimated 9,606 total COVID-19 attributable deaths across all age groups, which is higher than the regression model's estimate of 8,173 deaths. Provisional COVID-19 death counts from NVSS report 9,320 deaths due to COVID-19 across all age-groups from April 1, 2020 to March 31, 2021,[29] which is in between the estimates provided by our two methods. Among those aged ≥65 years, the multiplier approach estimated 7,811 deaths compared to the 5,902 estimated with the regression model. According to provisional COVID-19 coded deaths from NVSS, there were 7,592 deaths among those aged ≥65 years and 1,728 deaths among those aged <65

years. The provisional death counts are quite similar to the multiplier method which estimated 1,683 COVID-19 attributable deaths among those aged <65 years after adding the estimates from those aged 0-17, 18-49, and 50-64 years. The multiplier method estimated 0 deaths among those aged 0-17 years which was consistent with what is seen in the provisional COVID-19 death counts which also report 0 deaths with several cells censored because death counts were low enough that they may be considered identifiable. Estimates in the other age groups were quite similar to those reported in the provisional death counts. These death estimates in those aged <65 years sum to an estimate which is lower than that predicted by the regression model (2,271 deaths).

Discussion

Using the multiplier model, we estimated a total of 615,495 symptomatic illnesses, 234,853 medically attended illnesses, 33,567 hospitalizations, and 9,662 deaths across all age groups in the state of Maryland from April 2020 to March 2021. Those aged <50 years contributed to a majority of the estimated symptomatic and medically attended illnesses, but a majority of hospitalizations and deaths were estimated to be among those aged ≥50 years. The estimated rates of hospitalization and death were the highest among those aged ≥65 years and over 80% of deaths in the state of Maryland from April 2020 to March 2021 were among those aged ≥65 years. The number of deaths estimated from the multiplier method were greater than those estimated by the time-series regression model.

The goal of this study was to explore the utility and efficacy of the multiplier model approach in local and international settings. Though we had conceptually built out the methodology for the multiplier model, it had not yet been utilized to estimate COVID-19 burden at the state level for an extended period of time. We estimated the COVID-19 burden in the state of Maryland for a 1-year period to help evaluate the proposed methodology being applied for a longer duration of time.

Because this is the first time that this multiplier approach methodology has been employed to provide COVID-19 disease burden estimates, we need to compare our results to other estimates and

data to determine if our results are reasonable. There are several data sources that can be used to evaluate how well our multiplier method estimated COVID-19 burden in the state of Maryland, including comparisons to reported statistics and other burden estimates. USA Facts is a non-partisan not-for-profit group which presents aggregated COVID-19 case and death data from the CDC, state, and local health departments. Because USA Facts reports daily cumulative death and case counts by state, we can subtract the cumulative counts reported on our study start date from those reported on our study end date to obtain the reported cumulative incidence of COVID-19 infections and deaths during our study timeframe. Between March 28, 2020 and April 3, 2021, USA Facts reported 414,665 confirmed COVID-19 cases in the state of Maryland.[37] Our total estimate of symptomatic illnesses using the multiplier model was 615,945, nearly 1.5 times greater than what was reported. Other sources provide estimates of COVID-19 infections by state, including the CDC's commercial laboratory seroprevalence survey. This ongoing seroprevalence survey estimates cumulative SARS-CoV-2 infections by state and age group (when possible) in two-week intervals dating back to July 2020. Seroprevalence estimates are obtained from clinical blood samples which have been submitted to commercial laboratories in all 50 states, unrelated to a COVID-19 illness.[38] According to this serosurvey, the CDC estimates 1.2 million infections (95%CI: 1.02 million–1.38 million) in the state of Maryland by the end of March 2021.[39] While we expected our burden estimates to be higher than confirmed reported case counts, our estimate is much lower than what is estimated by the seroprevalence survey.

A variety of factors could be contributing to the discrepancies between our estimation of COVID-19 symptomatic cases in Maryland and the reported cases or seroprevalence estimates. First, it is important to note that these comparisons are not entirely equivalent. We estimated symptomatic cases only, but the reported statistics and serology estimates include both asymptomatic and symptomatic cases. Without understanding the symptomatic fraction for COVID-19, we cannot adjust our estimates to account for asymptomatic illnesses which would potentially make our estimates more comparable to

those provided by the seroprevalence survey and reported counts. Despite these challenges in comparison, we would expect our estimate of symptomatic illnesses to be closer to that estimated by the serosurvey based on the CDC's seroprevalence estimate at around 20% of the state's population and the strong likelihood that the reported case numbers underestimate the true burden of disease in the state.

Our estimates may be influenced by bias that may result in lower than expected estimates. Due to the electronic nature of the participatory syndromic surveillance platform CNY, not all age groups are well represented in the self-reported symptom and medical care-seeking data. Most participants reporting into the system do so by text message, leaving older adults who may not use text messaging or cell phones underrepresented in the data. We also observed relatively low response rates among those ages 0-17 years (Supplemental Figure 1) which could also be due to limited cell phone use in this age group and because CNY currently only allows self-enrollment as compared to household enrollment in earlier platforms, such as Flu Near You. Our data also showed a decrease in responders into the system over the pandemic across all age groups (Supplemental Figure 1). CNY had high initial enrollment that coincided with the start of the pandemic. It is possible that people had greater interest in self-enrolling and routinely reporting about their health early in the pandemic but stopped reporting over time due to "pandemic fatigue". In addition to this phenomenon, it is possible that people may be more likely to respond when they are ill or when they know COVID-19 infection rates are high in their area. In our data, we saw higher rates of CLI among respondents earlier in the study period when the proportion of positive SARS-CoV-2 tests was also higher. As the proportion of positive tests fluctuated over time, the proportion of respondents reporting CLI symptoms followed a similar trend (Supplemental Figure 2). To account for relatively low sample sizes in some age strata in some weeks for the state of Maryland, we utilized symptom and health care-seeking proportions from the HHS region in our estimates. Rates of CLI were similar among all states in the region, suggesting that proportions for the region could be used

in place of those for the state of Maryland (Supplemental Figure 3). Similar to what was observed for the state of Maryland, total responses within HHS Region 3 decreased over time and the pattern was nearly the same at both levels (Supplemental Figure 1). However, using regional data provided more respondents in each age group and across time should lead to more reliable estimates. Bias may also be introduced into our calculations for symptomatic cases, medical attended illnesses, and deaths when we use the viral data as a proxy for circulating SARS-CoV-2. The proportion of positive SARS-CoV-2 tests in Maryland may be an underestimate of the true percent positive among individuals meeting a CLI case definition because testing occurs among those who were symptomatic and asymptomatic. This could lead to underestimates at these levels if the biased proportions are applied to the rates and population in calculations.

The serosurvey may underestimate the true proportion of Maryland's population that is seropositive because it utilizes blood samples taken from routine or sick visits that are unrelated to COVID-19. This study sample may not be generalizable to the greater population of Maryland. It is possible that those having blood drawn for routine care are more health conscious than the general population, leading to fewer COVID-19 infections and thus a conservative estimation by the seroprevalence survey. Considering this potential healthy user bias in the estimate of seroprevalence regardless of symptom status, we suspect that the true number of symptomatic cases during the study timeframe be close to 1.2 million and expected our estimate to be closer to this number.

One strength of our multiplier model approach is that it uses self-reported medical care-seeking behavior in calculating estimates of medically attended illnesses. There was a dramatic shift to how people in the US sought medical care throughout the pandemic. Some people may have avoided seeking medical care out of fear of exposure to the virus during transit or in medical facilities. Depending on symptoms, some people may have chosen not to seek medical care. Others may not have been able to seek medical care because some clinics were closed for some time due to COVID-19.[16,40] These changes

in medical care-seeking behavior can be hard to capture, but the use of self-reported care seeking behavior may better capture the changing behaviors of local regions better than other types of surveillance.

Our estimates for hospitalizations are nearly the same as what has been captured in COVID-NET. This was expected because COVID-NET hospitals in Maryland service the entire population of the state. In other states where COVID-NET coverage areas serve fewer residents, hospitalization rates would need to be adjusted to the state's population. Though COVID-NET is robust in capturing COVID-19 hospitalizations within its service areas, estimated hospitalizations may still be underestimated because it is unlikely that everyone who got ill from COVID-19 sought medical care during the pandemic or if they did seek care and were hospitalized, they may not have been tested for COVID-19. Data on COVID-19 testing practices at the COVID-NET sites are not currently available to evaluate the proportion of individuals that were tested for SARS-CoV-2 among those admitted for acute respiratory infections. We also do not have information on the sensitivity and specificity of the tests performed at the sites. This information would be needed to adjust for COVID-19 hospitalizations that were possibly missed by the COVID-NET system.

USA Facts reported 8,269 confirmed deaths in the state of Maryland between March 28, 2020 and April 3, 2021.[37] This is similar to the number estimated by our regression model, 8,173 deaths. We expected our regression model to estimate COVID-19 associated deaths similar to what has been reported because the model relies heavily on the proportion of SARS-CoV-2 positive tests in calculating predicted deaths. Since our multiplier model approach estimates deaths using COVID-19-coded and a portion of pneumonia-coded deaths, we expected that it may provide a conservative estimate of COVID-19 associated deaths. While the multiplier model estimated 9,667 deaths, the regression model produced overall estimates that were lower. One potential reason that our death estimates from the regression were lower than the reported cases could be that the calculated baseline may have been

higher than the true baseline deaths observed during the pandemic. It is quite possible that there were fewer deaths due to other causes of death which contribute to baseline deaths during the pandemic. As people participated in social distancing and decreased their activities, it is possible that there were fewer deaths from auto accidents or other injuries, for example. If this were the case, our regression model would overestimate the number of baseline deaths and thus underestimate the number of COVID-19 associated deaths. The multiplier method estimated slightly higher COVID-19 mortalities in the state of Maryland than the regression and reported numbers with 9,662 deaths estimated between April 2020 and March 2021. Though we account for potential COVID-19 deaths that were misclassified as pneumonia deaths, our result may underestimate the true number of deaths that were attributable to COVID-19. All mortality burden estimate methods that rely on NVSS reported deaths are subject to bias because death coding is not complete or final and may frequently change, affecting estimates. Deaths that were originally misidentified but associated with COVID-19 may later be correctly identified, raising the reported death counts from the disease. It is also possible that some deaths many never be attributed to COVID-19 though they were related to a COVID-19 illness. In either case, our methods would further underestimate the true number of deaths. Understanding the limitations and strengths of one's data sources and those which are used for comparison are key to evaluating the estimates produced by the multiplier modeling approach.

International Feasibility

In addition to its potential benefit for use in US settings, our multiplier approach for estimating COVID-19 disease burden may be valuable for the international community. This approach is a relatively simple method that can be applied with little statistical analyses and that allows for customization based on the data sources available to the user. In international settings where data quality and accessibility may vary, the flexibility of our method may prove useful to understanding the burden of COVID-19 in their populations. While we use the multiplier model approach to estimate COVID-19 burden at the

state-level in this study, we did not estimate burden using international data. Instead, we will describe some types of data that can be used in this method and discuss its feasibility internationally by highlighting examples of how it could be implemented in Albania and South Africa.

Our multiplier model can be customized in a number of ways to fit the needs of the user, but the most common customization will be replacing the data sources we have described with those available within their jurisdictions. Some countries have systems in place to capture mortality and code for cause of death similar to the NVSS in the United States. Several also use the tenth revision of the International Classification of Diseases (ICD-10) coding system, the most current version of the classification system designed to facilitate the collection, processing, and analysis of mortality statistics that is used across the globe.[41] Countries which have these systems in place would require few adjustments to the proposed methods for estimating COVID-19 attributable deaths using the multiplier model if COVID-19- and pneumonia-coded death data are available. Like in the US, COVID-19 death data may still be influenced by bias from underreporting or misclassification of COVID-19 deaths, leading to underreporting. Many countries, however, have systems which capture all-cause deaths, but not coded deaths. Provisional all-cause death data that is available in real-time could be used to estimate excess deaths attributable to COVID-19. If all-cause death data is only available for a proportion of the desired population, such as specific regions within a country, adjustments could be performed to estimate the deaths in the regions for which all deaths are not captured.

Some countries may have data systems that capture COVID-19 hospitalizations for a portion of the country which could be used in the COVID-19 burden estimation of hospitalizations with adjustment to their overall population and age-distribution. Other countries may have syndromic surveillance systems in hospitals or emergency departments which help monitor non-specific syndrome or symptoms among those presenting for care. This could help inform the rates of hospitalizations due to CLI and could be age adjusted to the population to obtain hospitalization estimates. These syndromic

surveillance systems also exist in primary care settings in some countries which can help estimate the number of medically attended illnesses with adjustment for the age specific populations. Data from active surveillance programs in hospitals could also be used to estimate hospitalization rates after adjusting for age distribution and coverage area of the hospital. Estimating the medically attended and symptomatic illness may be the more challenging levels of the burden pyramid to estimate. National passive syndromic surveillance platforms like CNY are not common, and more adjustments to the methods may be needed for these levels depending on the data source. Data sources would need to be evaluated to determine the best way to use the data and if any adjustments would be needed. We will further discuss data sources that could be used to estimate COVID-19 disease burden in Albania and South Africa.

Albania

Albania, a small Balkan country with a population of around 2.9 million people, has progressed from one of the poorest countries in Europe to an upper-middle-income country in recent decades.[42] After the disbandment of the communist model in the 1990s, the Albanian healthcare system underwent reform and has since transitioned into to a system that is mainly public with a majority of services provided by the state.[43,44]

Albania does not currently have a national participatory syndromic surveillance system like CNY, but other sources of data exist which can be utilized to estimate the lower levels of the burden pyramid. Instead, Albania has The Albanian Epidemiological Reporting Tool (ALERT) system: a national syndromic surveillance system which was established in 1999 to provide early detection of infectious disease outbreaks.[45] ALERT is a robust system which captures medically attended syndromes across 400 primary care sites and the emergency rooms of all hospitals in every district in Albania. Some of the syndromes captured in ALERT include upper and lower respiratory infections, rash with fever, unexplained fever, diarrhea with or without blood, suspected meningitis, and jaundice. This system has been used in the

past to estimate the burden of influenza based on the acute respiratory infection syndromes, upper and lower respiratory infections.[45] Because COVID-19-associated symptoms are not limited to respiratory symptoms, additional syndromes can be grouped together to try to better estimate the burden of patients seeking medical care for SARS-CoV-2 infections. Case definitions for the surveillance of COVID-19 can be utilized to determine which medically attended persons are presenting with CLI. If data are available weekly by age-group and region, the number of medically attended CLI in each region could be adjusted to match the age-distribution and population of that region and summed together for country totals by age group in a given week. Because syndromic data are collected by ALERT, it is possible that symptomatic illnesses could also be calculated from this dataset if additional information, like medical care-seeking percentage, is known to back calculate from the estimated number of medically attended illnesses.

It is important to note that utilizing the ALERT system to estimate COVID-19 medically attended illnesses in Albania also has its limitations. Within days of confirming their first COVID-19 cases, Albania entered a strict lockdown period which changed how citizens sought healthcare.[46] The prime minister of health directed any person who suspected they COVID-19 to call the National Medical Emergency Center's (NMEC) emergency tele*phone line for information on testing, isolation guidelines, and other health* recommendations.[47] Health care during the lockdown was mainly sought through these calls to the NMEC or emergency room visitations. Because of these changes impacting health care-seeking behavior, Albania's Syndromic Surveillance system was no longer capturing data on syndromes from March to June of 2020 when the restrictions began to lift. During this timeframe, NMEC collected data on the incoming calls and recorded all reported syndromes which have since been linked to public health testing records. To accommodate for the lapse in syndromic data captured during this time frame, it may be possible to further link the data from the NMEC and the ALERT system. If the NMEC

data can be linked and reliably fill in the gaps in the ALERT system, this would serve as a useful data source to estimate the number of medically attended illnesses in Albania.

South Africa

South Africa is a larger nation with nearly 59 million residents whose healthcare system is still improving since the end of the apartheid period.[48] The country has seen several waves of COVID-19, was considered a COVID-19 hotspot for some time, and the location where a SARS-CoV-2 variant strain emerged. In response to the pandemic, several new studies and expanded surveillance systems have been implemented to help understand COVID-19 disease burden in South Africa. South Africa has implemented a nationwide active hospital surveillance system for COVID-19 hospitalizations called DATCOV which could be used to estimate COVID-19 hospitalization burden in the country. DATCOV was established in March 2020 to comprehensively cover all hospitals in South Africa that have admitted a patient which is SARS-CoV-2 positive. This system is robust, and data has already been used to understand factors associated with hospitalizations in South Africa.[49] Weekly age-specific hospitalization rates from DATCOV can likely be used in the multiplier model and applied to the weekly age-specific dynamic susceptible population and proportion of positive SARS-CoV-2 tests to obtain an estimate of COVID-19 hospitalizations. Death data may be able to be extracted from DATCOV and utilized to estimate COVID-19-associated mortality in the country if the relationship between mortality and hospitalization is understood. All-cause death data is also available in near real-time from the National Statistics System from the Statistics of South Africa which could potentially calculate excess mortality from COVID-19 to get at the number of deaths attributable to the disease.[50]

South Africa does not currently have participatory syndromic surveillance platforms like the United States' CNY. One potential method to determine the number of symptomatic cases is to calculate estimates by applying the symptomatic fraction to the estimate of total cases which could be obtained from the National Institute for Communicable Diseases (NICD). Several cross-sectional serosurveys are

underway which will be used to estimate the true infection rate in the country. Given an established prevalence (seroprevalence) applied to the symptomatic fraction in community, they could calculate the number of symptomatic illnesses.

Study Summary and Impact

Understanding the true impact of a disease on the healthcare system and community can help guide public health preparations and interventions. Disease burden requires estimation because these parameters are difficult to directly measure due to the widespread and complicated mechanisms which diseases affect communities. Often, disease burden estimation techniques can require high-level knowledge in epidemiology and biostatistics. There remains a need for a straightforward approach which can be utilized in a variety of settings. Our multiplier model approach was developed with the idea of providing guidance to estimating disease burden within a state, at the state level, or even internationally. If others understand the components of the data required for this approach to burden estimation, it can be modified to use within their jurisdictions.

We evaluated the multiplier model approach by estimating burden at the state level. While there are limitations and sources of bias that can be introduced at various levels throughout the process, the approach estimated symptomatic illnesses, medically attended illnesses, hospitalizations, and deaths in the state of Maryland reasonably well. We also discussed how the approach could be implemented in international settings by describing data sources available in Albania and South Africa and how they could be used to estimate the different levels of the pyramid. Both countries have data sources that would likely enable estimation of COVID-19 burden using the multiplier model approach. Data sources would need to be evaluated to determine the best way to use the data and if any adjustments would be needed. Future studies are needed to test the efficacy of the methodology outside of the United States by estimating COVID-19 burden in an international setting, as we have done here with the state of Maryland.

There is great potential benefit for an approach which can guide local and international settings in estimating the COVID-19 burden in their jurisdiction. Public health planning must be well-informed in order to most effectively respond to the pandemic. Resources and action must be strategically used from the local to international level to help end the pandemic. Understanding the true burden of COVID-19 at the local, state, international, and global setting can help inform the strategy needed to help curb the pandemic.

Notes

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Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Tables

Table 1: Data sources used to calculate burden and severity of COVID-19.

	Data Source	Criteria/Case Definitions
Population	Vintage US Census Bureau	Maryland state population estimates from 2015-2019.
Syndromic surveillance	COVID Near You	Specific COVID-like illness case definition- Any 2 of the following: fever, chills, sore throat, body ache, headache, nausea, diarrhea, running nose, fatigue OR any 1 of the following: cough, shortness of breath, loss of taste/smell Broad COVID-like illness case definition- Any 1 of the following: fever, chills, sore throat, body ache, headache, nausea, diarrhea, running nose, fatigue, cough, shortness of breath, loss of taste/smell Medically attended illness case definition- Visitation to any of the following healthcare facilities: doctor office/HMO, urgent care center, in-store clinic, emergency room, hospital overnight, virtual care, and COVID-19 testing center
COVID-19 Percent Positives	National commercial and public health lab data	rt-PCR SARS-CoV-2 tests with known results.
Influenza Percent Positives	National commercial and public health lab data from FluView Interactive	Influenza positive tests by state and virus type
Hospitalizations	COVID-NET	All PCR positive SARS-CoV-2 hospitalized patients reported in Maryland
Deaths	National Center for Health Statistics	All-cause mortality, Pneumonia and COVID-19 ICD-10 coded deaths

Table 2: COVID-19 symptomatic illness estimates in Maryland by age group and for all ages for April 2020 – March 2021.

Age Group	Initial Susceptible Population	Symptomatic illness	Uncertainty Interval	Rate (per 100,000)	Uncertainty Interval
All Ages	6,045,680	615,945	413,440-623,671	10,188	6,839-10,316
0-17	1,334,687	235,603	198,544-237,402	17,652	14,876-17,787
18-49	2,523,385	249,115	147,838-253,483	9,872	5,859-10,045
50-64	1,228,212	93,786	50,320-94,743	7,636	4,097-7,714
65+	959,396	37,441	16,738-38,043	3,903	1,745-3,965

Table 3: COVID-19 medically attended illness estimates in Maryland by age group and for all ages for April 2020 – March 2021.

Age Group	Initial Susceptible Population	Medically Attended illness	Uncertainty Interval	Rate (per 100,000)	Uncertainty Interval
All Ages	6,045,680	234,853	221,450-258,385	3,885	3,663-4,274
0-17	1,334,687	103,257	10,3257-98,359	7,830	7,440-7,830
18-49	2,523,385	85,851	77,256-106,252	3,489	3,138-4,318
50-64	1,228,212	29,880	26,246-35,081	2,471	2,170-2,899
65+	959,396	15,865	14,691-18,693	1,669	1,545-1,967

Table 4: COVID-19 hospitalization estimates in Maryland by age group and for all ages for April 2020 – March 2021.

Age Group	Initial Susceptible Population	Hospitalizations	Uncertainty Interval	Rate (per 100,000)	Uncertainty Interval
All Ages	6,045,680	33,567	32,823-34,311	555	543-568
0-17	1,334,687	486	475-496	36	36-37
18-49	2,523,385	8,582	8,412-8,752	340	333-347
50-64	1,228,212	9,570	9,352-9,788	779	761-797
65+	959,396	14,929	14,551-15,307	1,556	1,517-1,596

Table 5: COVID-19 death estimates in Maryland by age group and for all ages for April 2020 – March 2021.

Age Group	Initial Susceptible Population	Deaths	Uncertainty Interval	Rate (per 100,000)	Uncertainty Interval
All Ages	6,045,680	9,662	8,489-10,834	162	140-179
0-17	1,334,687	0	0-0	0	0-0
18-49	2,523,385	299	248-351	12	10-14
50-64	1,228,212	1,418	1,260-1,577	115	103-128
65+	959,396	7,944	6,966-8,922	828	726-930

Table 6: Time-series regression estimated COVID-19 and Influenza associated deaths from April 2020 – March 2021 in Maryland

Age group (years)	COVID-19 associated deaths	95% UI
Total	8,173	6,757-9,628
0-65	2,271	1,841-2,714
≥65	5,902	4,916-6,914

Figures

Figure 1: COVID-19 disease burden pyramid for all ages in the state of Maryland from April 2020 to March 2021

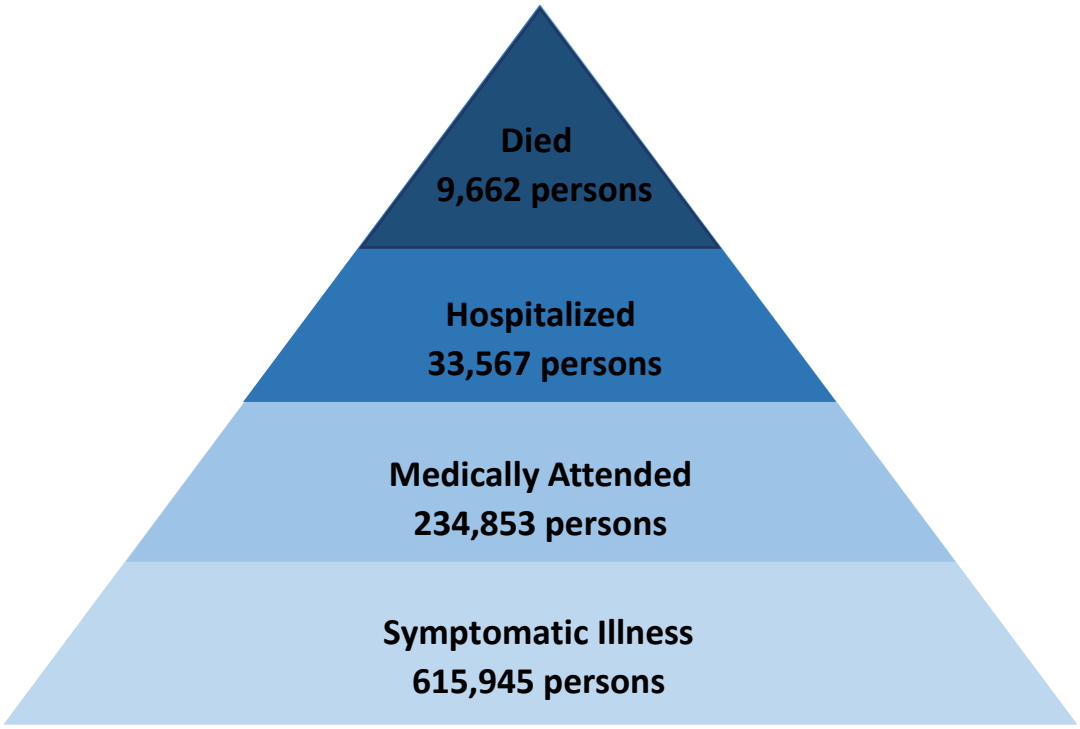
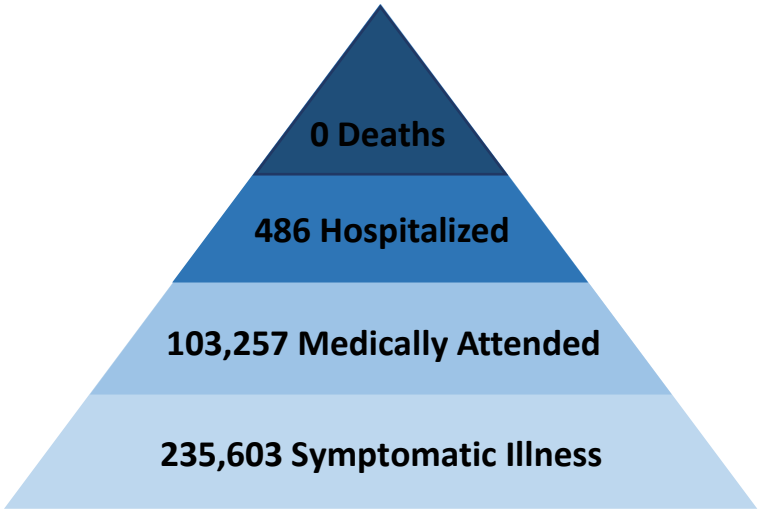
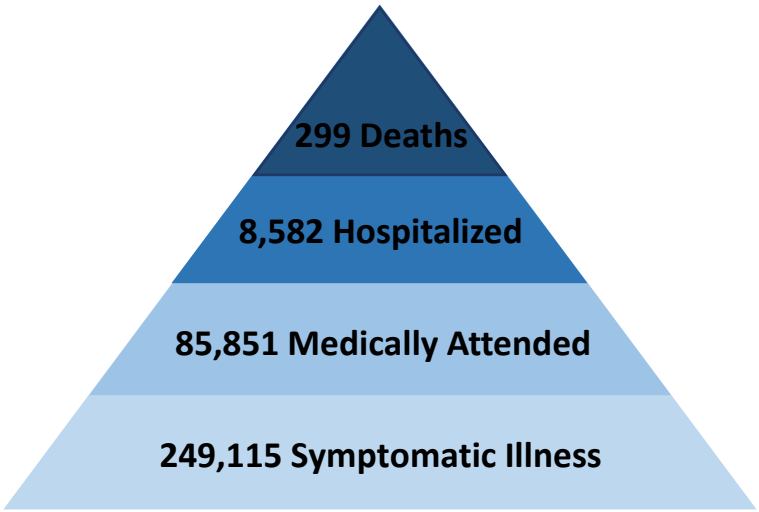


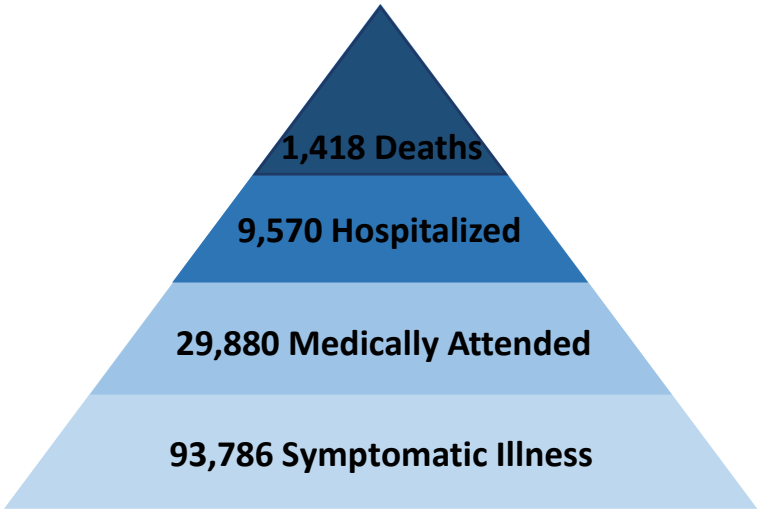
Figure 2: COVID-19 disease burden pyramid by age group in the state of Maryland from April 2020 to March 2021



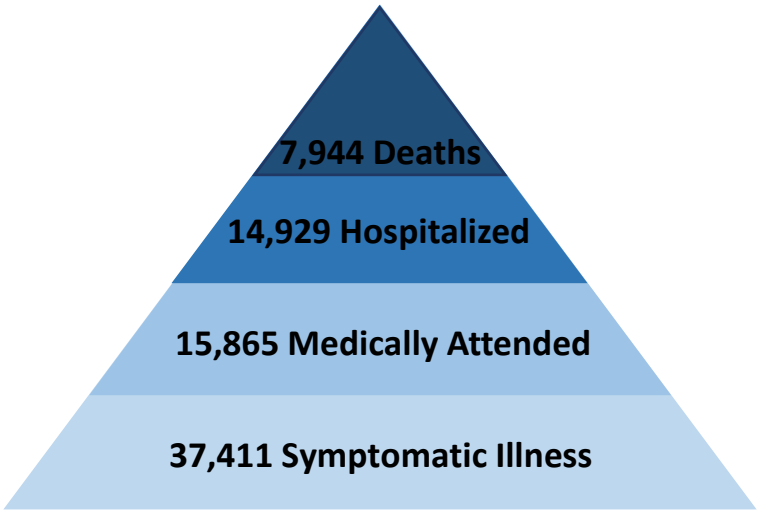
0-17 years



18-49 years

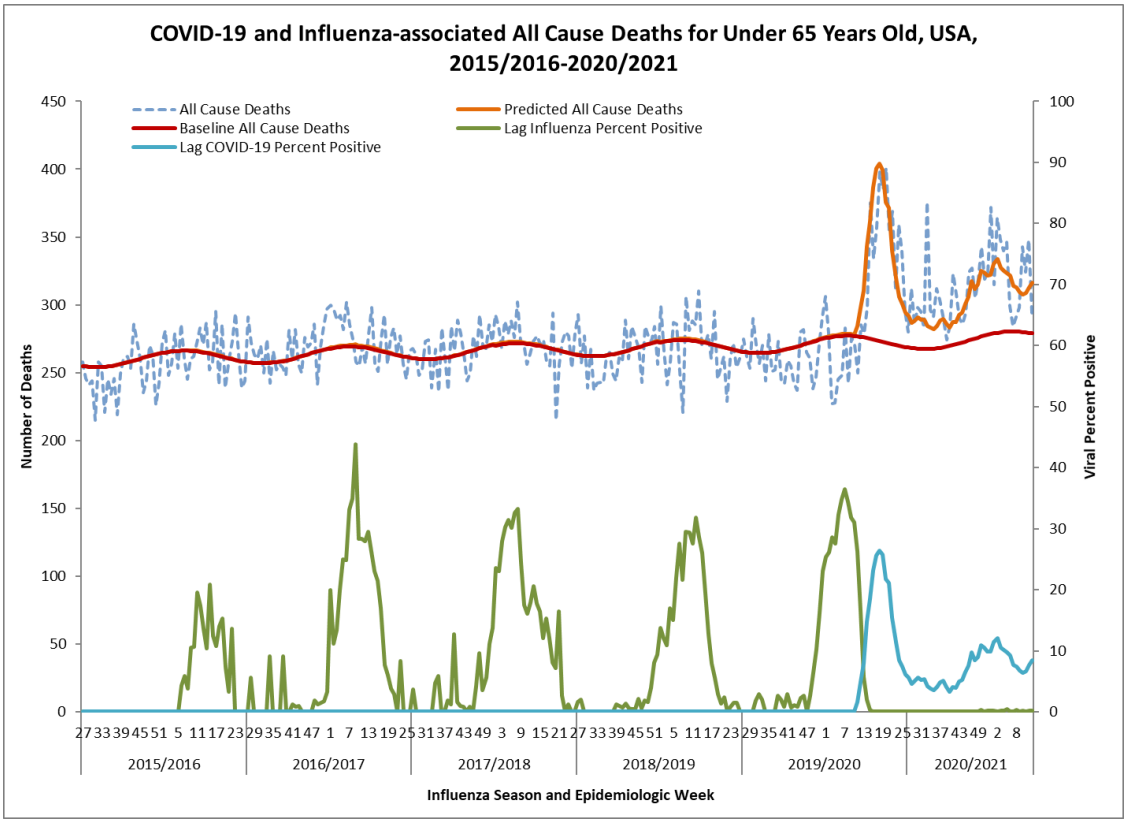


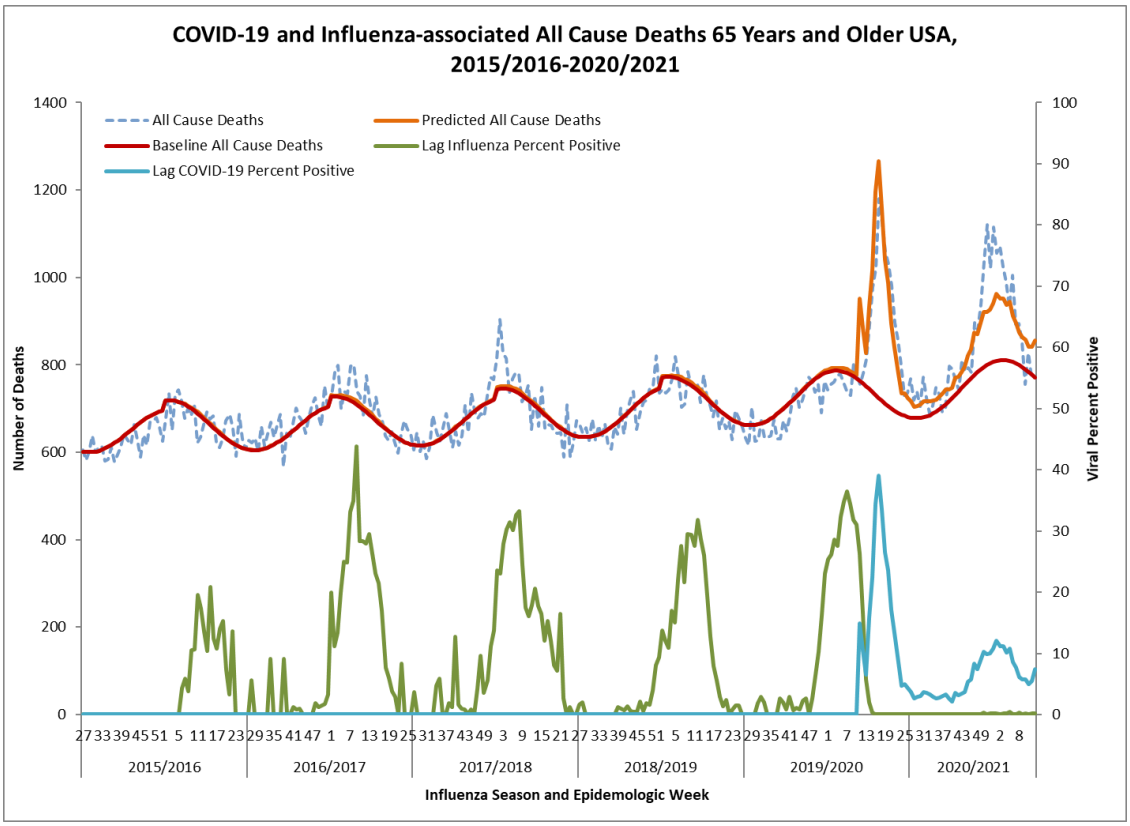
50-64 years



65+ years

Figure 3: COVID-19 Time-Series Excess Mortality Regression Models

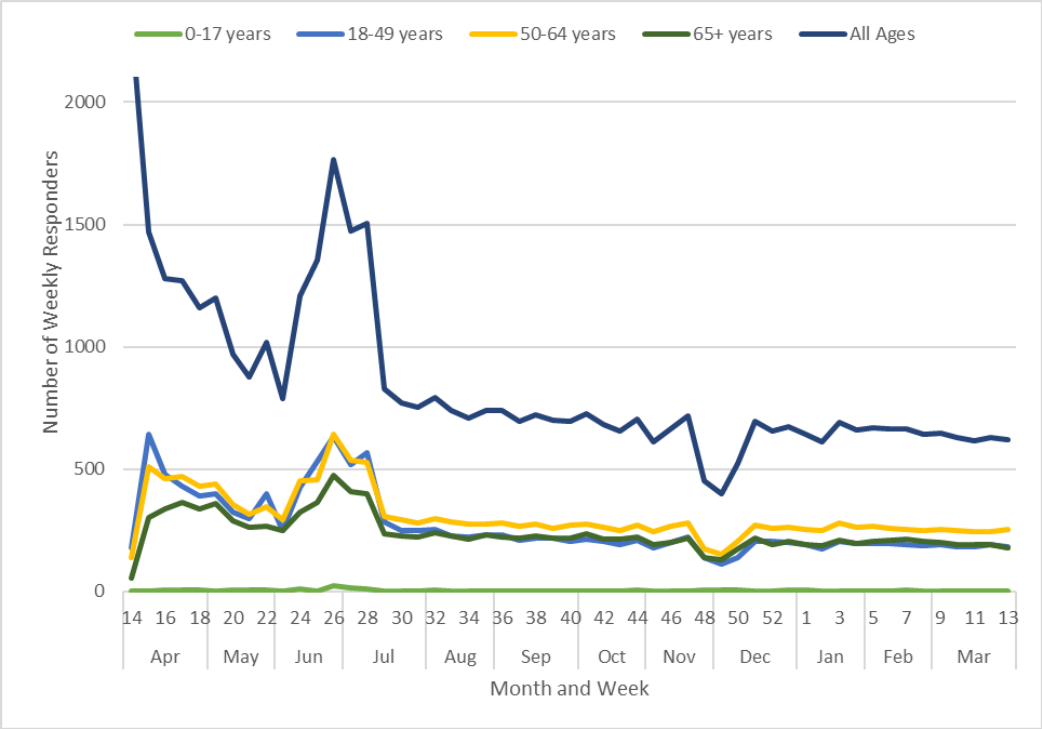




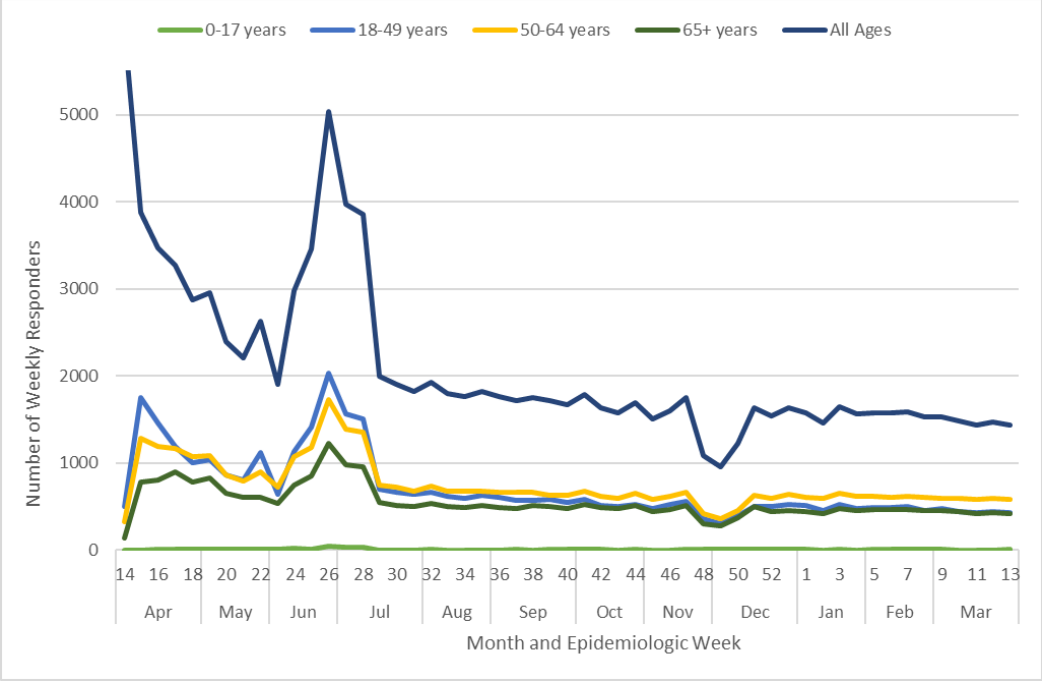
Supplemental Figures

Supplemental Figure 1: CNY Response numbers by age group in Maryland and HHS Region 3 from April 2020-March 2021

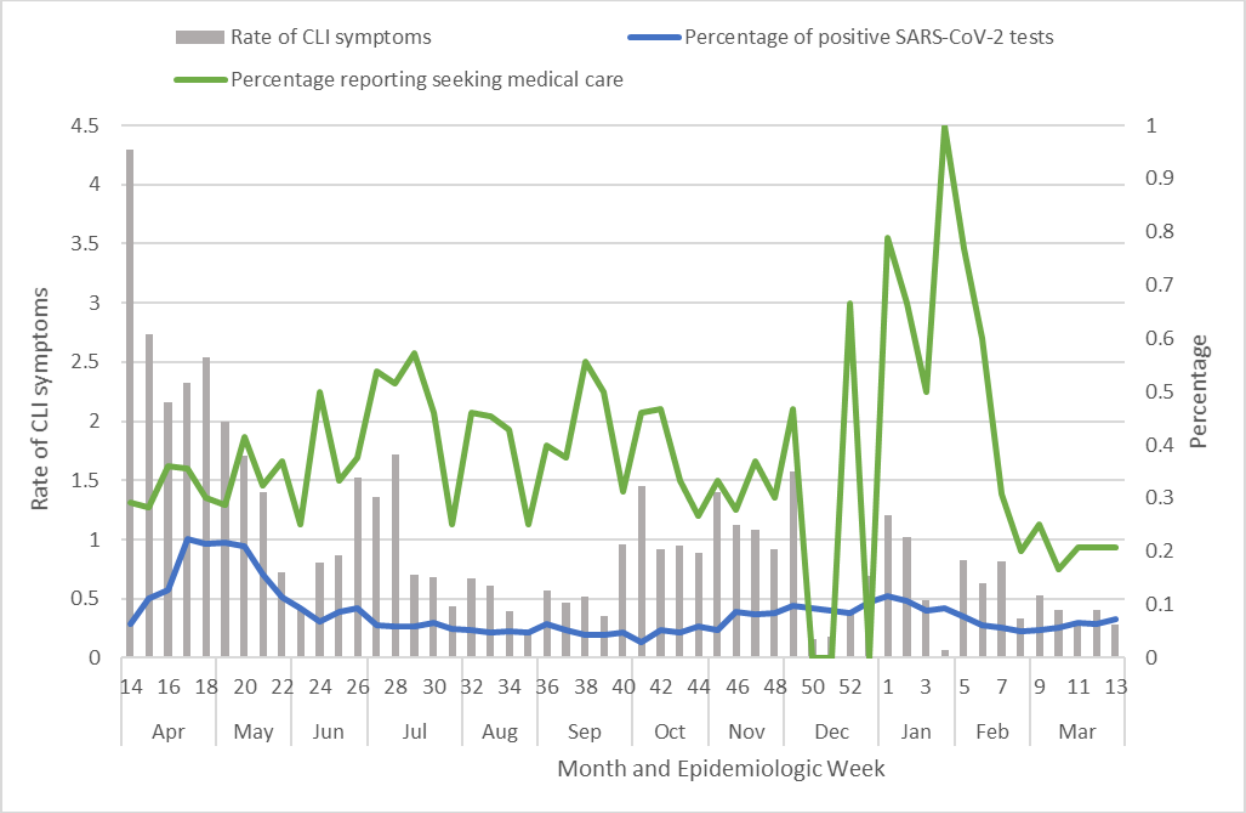
A. Maryland



B. HHS Region 3

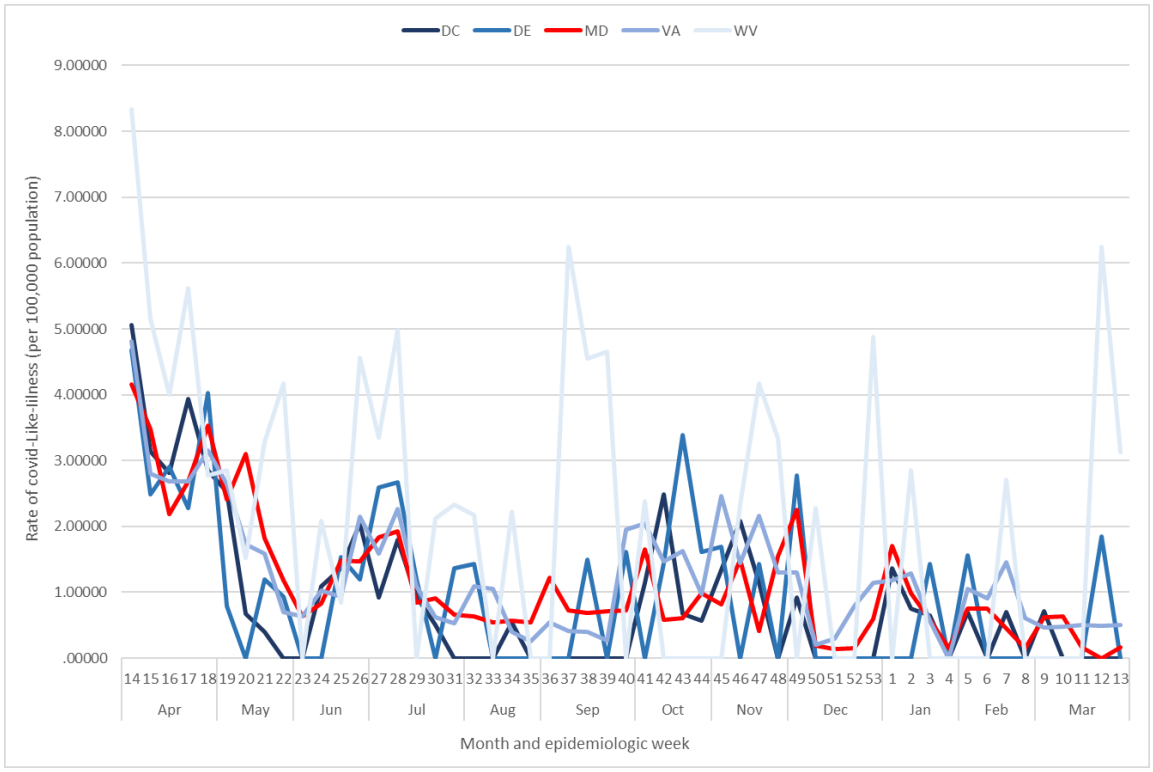


Supplemental Figure 2: Rates of CLI symptom reporting and testing proportions in HHS region 3 from April 2020-March 2021

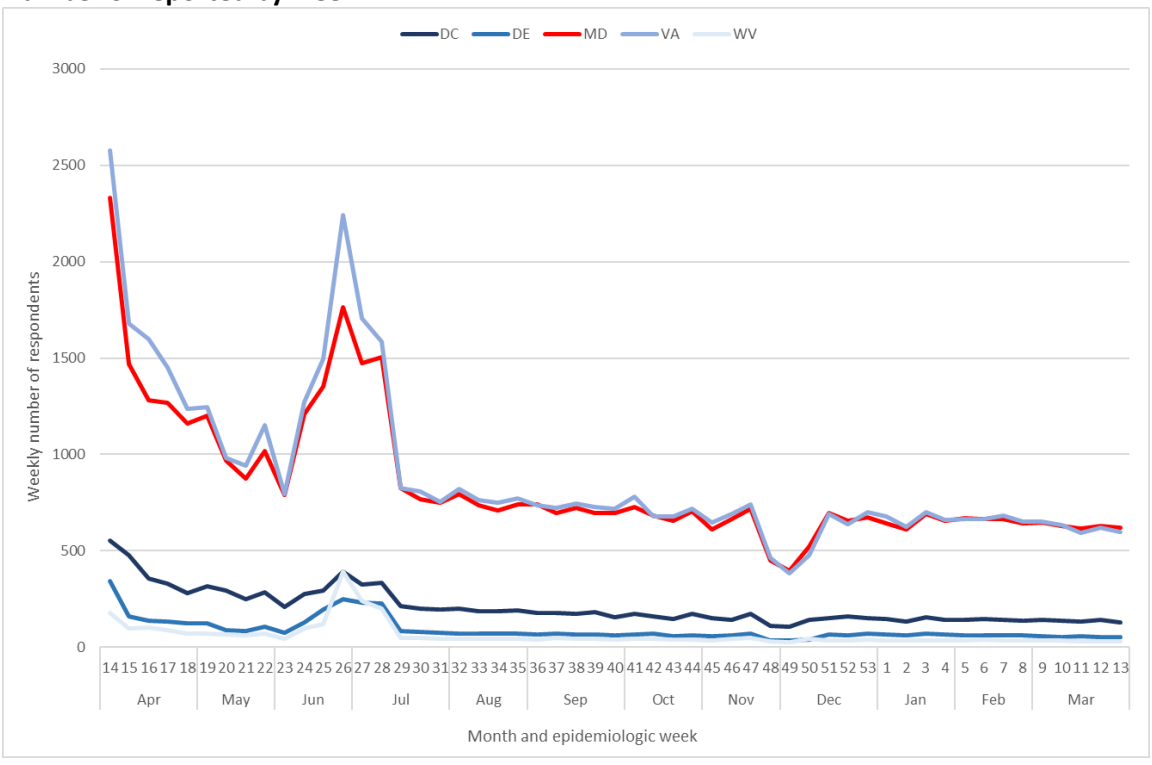


Supplemental Figure 3: Rate of CLI and total number of reporters into COVID Near You by state in HHS region 3 from April 2020 – March 2021

A. Rate of covid-like-illness



B. Number of reported by week



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