Using the COVID-19 to influenza ratio to estimate early pandemic spread in Wuhan, China and Seattle, US

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Abstract

Background: Pandemic SARS-CoV-2 was first reported in Wuhan, China on December 31, 2019. Twenty-one days later, the US identified its first case--a man who had traveled from Wuhan to the state of Washington. Recent studies in the Wuhan and Seattle metropolitan areas retrospectively tested samples taken from patients with COVID-like symptoms. In the Wuhan study, there were 4 SARS-CoV-2 positives and 7 influenza positives out of 26 adults outpatients who sought care for influenza-like-illness at two central hospitals prior to January 12, 2020. The Seattle study reported 25 SARS-CoV-2 positives and 442 influenza positives out of 2353 children and adults who reported acute respiratory illness prior to March 9, 2020. Here, we use these findings to extrapolate the early prevalence of symptomatic COVID-19 in Wuhan and Seattle.

Methods: For each city, we estimate the ratio of COVID-19 to influenza infections from the retrospective testing data and estimate the age-specific prevalence of influenza from surveillance reports during the same time period. Combining these, we approximate the total number of symptomatic COVID-19 infections.

Findings: In Wuhan, there were an estimated 1386 [95% CrI: 420-3793] symptomatic cases over 30 of COVID-19 between December 30, 2019 and January 12, 2020. In Seattle, we estimate that 2268 [95% CrI: 498, 6069] children under 18 and 4367 [95% CrI: 2776, 6526] adults were symptomatically infected between February 24 and March 9, 2020. We also find that the initial pandemic wave in Wuhan likely originated with

a single infected case who developed symptoms sometime between October 26 and December 13, 2020; in Seattle, the seeding likely occurred between December 25, 2019 and January 15, 2020.

Interpretation: The spread of COVID-19 in Wuhan and Seattle was far more extensive than initially reported. The virus likely spread for months in Wuhan before the lockdown. Given that COVID-19 appears to be overwhelmingly mild in children, our high estimate for symptomatic pediatric cases in Seattle suggests that there may have been thousands more mild cases at the time.

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Keywords: COVID-19, pediatric infections, adult infections, influenza, Wuhan, Seattle

Introduction

On December 31, 2019, a novel coronavirus (SARS-CoV-2) was identified in Wuhan, China. Three weeks later, on January 21st, the US Centers for Disease Control and Prevention (CDC) confirmed the first case of COVID-19 in the US. On January 15th, the man returned from a visit to Wuhan, China to Snohomish County in the Seattle Metropolitan Area of Washington state [1]. To mitigate local transmission and prevent global spread, China imposed a lockdown on Wuhan starting January 23rd. In the first months of the pandemic, confirmed case counts vastly unrepresented the rapid expansion of the pandemic as countries raced to ramp up testing and surveillance capabilities [2-5]. By the time of the Wuhan lockdown, only 571 cases of COVID-19 were reported in mainland China [6], 422 of which were in Wuhan [7]. The Seattle area reported only 245 confirmed COVID-19 cases and 36 COVID-19 deaths by March 9th [8].

Two studies--one in Wuhan [9] and the other in Seattle [10]--re-examined swabs taken from individuals with symptoms of acute respiratory illness during periods where SARS-CoV-2 may have been spreading undetected. Although some of these specimens

were previously tested for influenza viruses, none were tested for SARS-CoV-2. The Wuhan study tested 26 throat swabs taken from adults over age 30 who sought outpatient care at one of two central Wuhan hospitals for influenza-like-illness (ILI) between December 30, 2019 and January 12, 2020 [9]. Although no patients were confirmed COVID-19 cases, four retrospectively tested positive for the virus. In addition to the four COVID-19 positive samples, seven others tested positive for influenza.

The Seattle study performed RT-PCR tests for SARS-CoV2 and influenza on 2353 mid-nasal swabs collected from 299 children under 18 and 2,054 adults who reported symptoms of acute respiratory illness (ARI) between January 1, 2020 and March 9, 2020 [10]. Of these, 442 tested positive for influenza, 25 tested positive for COVID-19, and none tested positive for both viruses.

We note that the two studies have overlapping but not identical case definitions. In Seattle [10], ARI cases had at least two of these symptoms: "feeling feverish, headache, sore throat or itchy/scratchy throat, nausea or vomiting, rhinorrhea, fatigue, myalgia, dyspnea, diarrhea, ear pain or ear discharge, rash, or a new or worsening acute cough alone". In Wuhan [9], ILI cases included patients reporting fever (with a temperature of at least 100° F/37.8° C) and a cough or a sore throat without a known cause other than influenza [11].

Our study is premised on the assumption that influenza and SARS-CoV-2 were constrained by similar behavioral and environmental factors in early 2020. The two viruses have overlapping natural histories [12,13] and modes of transmission [13]. Both are respiratory pathogens with a wide spectrum of illness, from asymptomatic to fatal, with severity that depends on age and underlying conditions. They are similarly transmitted from person-to-person through direct contact, droplets and fomites [13-15]. Thus, we expect that once SARS-CoV-2 got a foothold in a city, spreading across multiple communities, its geographic and demographic patterns might mirror those of influenza. In Hong Kong, for example, COVID-19 interventions concurrently reduced the transmission rates (i.e., the daily reproduction number, Rt) of COVID-19 and influenza in early February 2020[15].

Here, we estimate the early prevalence of symptomatic COVID-19 cases in Wuhan and Seattle based on the ratio of SARS-CoV-2 to influenza test positivity (henceforth, the *covid-to-influenza ratio*) and the local prevalence of influenza in the two cities at the time of the corresponding retrospective study. We derive our estimates of covid-to-influenza positivity directly from the two studies and our estimates of local influenza prevalence from Chinese and US surveillance data.

Methods

Data

COVID-19 and influenza data in Wuhan

To estimate the covid-to-influenza ratio, we used the numbers of COVID-19 positive and influenza positive patients among tested ILI throat swab samples at two hospitals from December 30, 2019 to January 12, 2020 reported by a recent retrospective study [9]. Wuhan has almost 400 hospitals, which collectively have 81,700 beds and 81 million outpatient visits per year [16]. The data we analyzed from ref. [9] were collected from two hospitals that have large and representative catchments: Children's Hospital of Wuhan (the largest pediatric healthcare center in Wuhan that serves both women and children) [17,18] with 2000 beds and 1.9 million annual outpatient visits and Wuhan No. 1 Hospital [19], with over 3000 beds and 2 million annual outpatient visits. Both serve as sentinel sites in China's national influenza surveillance system [9]. Together they provide almost 5% of outpatient care in the Wuhan area. The data we analyzed from ref.[9] were collected from two hospitals that have large and representative catchments: Children's Hospital of Wuhan (the largest pediatric healthcare center in Wuhan, serving both children and adults) [17, 18] with 2000 beds and 1.9 million annual outpatient visits and Wuhan No. 1 Hospital [19], with over 3000 beds and 2 million annual outpatient visits. Both serve as sentinel sites in China's national influenza surveillance system[9]. **The SARS-CoV-2 and influenza virus among tested ILI throat swab samples are well kept at -70 °C before the SARS-CoV-2 experiments and detected by real-time PCR with reverse transcription**[9].

To estimate the age-stratified numbers of outpatient visits for ILI in Wuhan, we analyzed data from China CDC weekly reports for Wuhan, December 30, 2019-January 12, 2020 [9]. To estimate the age-stratified population sizes of Wuhan's 13 districts, we obtained data from the Sixth National Census of the People's Republic of China in 2010 [20], and scaled by the growth in overall Wuhan population between 2010 and 2019 reported by Wuhan Statistics Bureau [21].

COVID-19 and influenza data in Seattle

Our analysis of Seattle is restricted to the portion of the metropolitan area sampled by the Seattle Flu Study in ref. [10]. Specifically, we analyze King county, which contains the city of Seattle, and Snohomish county, where the first US COVID-19 case was identified. Roughly 77% of the 3.5 million metropolitan population reside in the two counties.

To estimate the covid-to-influenza ratio, we used the numbers of COVID-19 positive and influenza positive patients among tested mid-nasal swab samples from participants with symptoms of acute respiratory illness (ARI) in the Seattle Flu pandemic surveillance platform from January 1, 2020 to March 9, 2020 [10]. Our analysis combines viral positivity data from cases with ILI and ARI. We assume that the two populations are the same-individuals with ILI and ARI in Seattle during the study period-and refer to this population as ILI throughout the text and supplement. The ARI case definition in ref. [10] is at least "two of the following: feeling feverish, headache, sore throat or itchy/scratchy throat, nausea or vomiting, rhinorrhea, fatigue, myalgia, dyspnea, diarrhea, ear pain or ear discharge, rash, or a new or worsening acute cough alone". The CDC's case definition for ILI is "fever (temperature of 100° F [37.8° C] or greater) and a cough and/or a sore throat without a known cause other than influenza" [11]. Thus, the case definitions overlap considerably, but are not identical. The tested mid-nasal swab samples were kept at 4° C before the influenza and SARS-CoV-2 tests by TaqMan PT-PCR, with an average time from nasal swab collection to receipt at the study laboratory of 2.8 days [10].

We analyzed the age-stratified numbers of outpatient visits for ILI in HHS region 10 between January 1, 2020 and March 9, 2020 available on the CDC's FluView interactive website [22] and the age-stratified population sizes of the 22 Public Use M

icrodata Areas (PUMA' s) in King and Snohomish counties [10,20]. Details are provi ded in Table 1.

Method

Our methods for estimating the prevalence of symptomatic COVID-19 in Wuhan and Sea ttle are similar, but not identical. We describe our method for Wuhan in this sect ion and our method for Seattle in the Appendix. The key methodological difference is that the retrospective study in Wuhan [9] but not Seattle [10] reported the dat e of symptom onset for each positive influenza test. For Seattle, we took the extr a step of estimating these dates based on the total number of positives and the da ily influenza positivity reported by the CDC for HHS Region 10 (Supplementary Figu re S1, Tables S1 and S2).

For Wuhan, we assume that the age-specific risks of COVID-19 and influenza infecti on are identical in all 13 central districts of the city. Therefore, the ratio of COVID-19 to influenza adult outpatients (r) estimated from the subset of outpatien ts sampled in ref. [9] can be used to estimate the number of COVID-19 infections a cross all of central Wuhan (Figure 3).

Estimating COVID-19 adult infections in Wuhan

To estimate the number of COVID-19 infections we use a binomial distribution, den oted $B(N, p)$, where N is the total population in each district and p is an estimat e of the age specific prevalence of symptomatic COVID-19 in the population adjuste d by the proportion of individuals in that age group. We chose a binomial distribu tion as it is the most commonly used distribution to statistically model case coun ts when the population size and probability are known. We denote by $H_{d,a,\tau}$ the num ber of COVID-19 infections in district d and age range a (over 30 years) during th e focal fourteen-day period τ, and model it as:

$$H_{d,a,\tau} \mid N_d, \Theta_\tau^a, \Omega_\tau, \Phi_\tau, r \sim \mathrm{B}\left(N_d, \frac{\Theta_\tau^a}{\Omega_\tau} \cdot \Phi_\tau \cdot r\right)$$

where N_d is the number of people of all ages in district d; Θ_τ^a is the number of I LI outpatients in age group a over a period of time τ; Ω_τ is the number of all ca

use outpatients of all ages in Wuhan over a period of time τ; Φ_τ is the percent of influenza tests that are positive in the South Provinces of China during time period τ; the r is the ratio of COVID-19 outpatients to influenza outpatients over age 30. Given the small sample size, we could not reliably estimate COVID-19 prevalence by sex or narrow age brackets.

We take a Bayesian approach using Markov Chain Monte Carlo, where at each iteration we take a draw from the distributions of r and Ω_τ, and then use these to draw $H_{d,a,\tau}$ according to the specified binomial distribution. Since the other parameters are assumed to be known constants, we do not take draws of these parameters; the values of these parameters can be found in Table 1. $H_{d,a,\tau}$ is then specified by the set of draws, defining a predictive distribution that we use to calculate the mean and credible intervals for the number of COVID-19 infections. We chose a Bayesian approach to allow an intuitive structuring of the model and avoid making assumptions that are not appropriate for our small sample sizes.

To estimate the distribution of r and Ω_τ, we first derive r as the following posterior distribution. Let N denote the total number of adults in the sample, and x_c and x_f denote the observed number of adults who tested positive for COVID-19 and influenza, respectively. As before we assume a binomial distribution where

$$x_c \mid p_c, N \sim \mathrm{B}(N, p_c) \text{ and } x_f \mid p_f, N \sim \mathrm{B}(N, p_f).$$

If we assume uninformative priors on p_c and p_f[23],

$$p_c \sim \mathrm{Beta}(1,1) \text{ and } p_f \sim \mathrm{Beta}(1,1)$$

then the posterior distributions are known in closed form[23]:

$$p_c \mid x_c, N \sim \mathrm{Beta}(1 + x_c, 1 + N - x_c) \sim \mathrm{Beta}(5, 23)$$

$$p_f \mid x_p, N \sim \mathrm{Beta}(1 + x_f, 1 + N - x_f) \sim \mathrm{Beta}(8, 20)$$

We use Markov Chain Monte Carlo to draw from p_c and p_f at each iteration and calculate $r = p_c/p_f$. We combine these draws to obtain the distribution for r. Using this method we estimate that the ratio of COVID-19 to influenza adult hospitalizations across central Wuhan during December 30, 2019 to January 12, 2020 was 0.61 [95%

CrI: 0.20-1.64]. We use 10,000 draws and report the medians and 95% credible intervals of the resulting posterior predictive distribution for the number of COVID-19 infections for each district.

Estimating COVID-19 adult infections prior to the Wuhan lockdown

To project the number of adult infections in Wuhan prior to the closing on January 23, 2020 (H_{cum}), we assume

$$H_{\text{cum}} = \sum_{i=t_0}^{L} h_0 \cdot 2^{i/T_d}$$

where T_d is the epidemic doubling time, t_0 is the day of the first adult infection in Wuhan, and L corresponds to January 22, 2020 (the day before the Wuhan lockdown). We use our age- and district-stratified estimates for adult COVID-19 infections for December 30, 2019 to January 12, 2020 to estimate this quantity, under the assumption that the values reflect cumulative incident infections during that fourteen-day period (Figure 4).

We use Monte Carlo sampling to incorporate the uncertainty in both the epidemic doubling rate in Wuhan during this period [2] and adult infections from December 30, 2019 to January 12, 2020 ($H_{a,d,\tau}$). We take draws from the distribution of $H_{a,d,\tau}$ and T_d (summarized in Table 1) to estimate the time since the first adult infection by

$$\delta = T_D \left(\log_2 \left(\frac{H_\tau}{\sum_{i=0}^{13} 2^{i/T_d}} \right) \right).$$

That is, the estimated date of the first COVID-19 infection in Wuhan (t_0) is δ days prior to December 30, 2019. We then estimate H_{cum} according to the equation above to project the cumulative COVID-19 adult infections preceding the Wuhan lockdown.

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Results

Estimated symptomatic COVID-19 adult infections in the 13 central districts of Wuhan

Based on the numbers of confirmed SARS-CoV-2 and influenza cases in ref. [9], we estimate that the ratio of symptomatic COVID-19 to influenza infections in Wuhan from December 30, 2019 to January 12, 2020 was 0.61 [95% CrI: 0.20-1.64] for adults over 30. Coupling this ratio with influenza prevalence statistics derived from surveillance data, we estimate there were 1386 [95% CrI: 420-3793] for people over 30 years with symptomatic COVID-19 infections in Wuhan between December 30th and January 12th, ranging from 19 cases [95% CrI: 6-51] in suburban Hannan to 177 cases [95% CrI: 54-485] in central Wuchang (Figure 1, Table S3). Estimates for the epidemic doubling time for COVID-19 in Hubei Province have ranged from 5.2 [24] to 7.31 days [2]. These two values suggest a total of 12,939 [95% CrI: 2728-109,651] or 22,939 [95% CrI: 5034-119,864] symptomatically infected adults over age 30 prior to the January 23rd lockdown, respectively. Both estimates far exceed the 422 documented cases across all age groups [25]. Several studies have estimated that roughly half of infections are asymptomatic [26]. Thus, the number of undetected adult COVID-19 cases at that time may have reached 10,000. We further estimate that the Wuhan epidemic emerged from cases infected around November 17, 2019 [95% CrI: October 26-December 3, 2019] or December 2, 2019 [95% CrI: November 20-December 13, 2019], under the lower or higher reported doubling times, respectively (Figure 4).

We note that the Wuhan study [9] also tested swabs taken from 54 ILI patients under age 30. Of these, 30 tested positive for influenza and none tested positive for COVID-19. Given that there were likely symptomatic pediatric COVID-19 cases in Wuhan during the study period [27], we do not believe that the true prevalence in this age group was zero. Because estimates close to zero require greater amounts of data to estimate with any certainty, we lack the statistical power to reasonably es

timate the COVID-19 to influenza ratio based on the reported zero out of 54 withou t making additional assumptions. Thus, to avoid potentially problematic assumption s or invalid generalizations, we restricted our analysis to the over 30 age group.

Estimated symptomatic COVID-19 infections in King and Snohomish Counties

For the Seattle area, we similarly estimate that the ratio of symptomatic COVID-19 to influenza infections in children under 18 was 0.11 [95% CrI: 0.03-0.33] and in adults was 0.14 [95% CrI: 0.09-0.21] from February 24 and March 9, 2020. Based on this ratio and the concurrent prevalence of influenza in Seattle, we estimate that there were 6748 [95% CrI: 4133, 11020] symptomatic COVID-19 infections between Feb ruary 24th and March 9th. The age breakdown is 2268 [95% CrI: 498, 6069] symptomat ic cases in children under 18 and 4367 [95% CrI: 2776, 6526] cases in adults. The Seattle Flu Study [10] located the retrospectively detected COVID-19 cases down to the level of Public Use Microdata Areas (PUMA's), which are US Census statistical reporting units. Based simply on the population sizes of the 22 PUMA's in King an d Snohomish counties, we estimated that the PUMA-level prevalence of symptomatic C OVID-19 cases during this period ranged from 231 cases [95% CrI:199,265] in PUMA 1 1614 (Southwest King County) to 410 cases [95% CrI:364,459] in PUMA 11601 (Northwe st Seattle) (Figure 2).

A prior study estimated COVID-19 had a mean epidemic doubling time in Washington S tate in January and February, 2020 of 6.1 days [90% CrI: 5.1 to 8.2 days] [3]. Und er this range of doubling times, we estimate there were a total of 9068 [95% CrI: 8264-10,011] symptomatic COVID-19 infections in Seattle before March 9th. If we as sume 50% of infections are asymptomatic [26], then we project there may have been over 15,000 undetected COVID-19 cases at the time. We further estimate that the Se attle epidemic originated with cases that arrived infected around January 6, 2020 [95% CrI: December 25, 2019 - January 15, 2020] (Figure 4).

Discussion

In cities across the Northern Hemisphere, the emergence of the COVID-19 pandemic c oincided with the 2019-2020 influenza season [9,10]. Mild COVID-19 and influenza i nfections have overlapping constellations of symptoms that often fall within the c riteria for influenza-like-illness (ILI) and acute respiratory infections (ARI) [2 8]. Prior to widely available SARS-CoV-2 tests, symptomatic COVID-19 cases who sou ght care were likely to have been tested for influenza. A few studies have retriev ed and retrospectively tested swabs taken from such patients for SARS-CoV-2 and th ereby identified early undetected cases of COVID-19 [3,5,9,10]. Given the spatiote mporal overlap and epidemiological similarities between influenza and SARS-CoV-2, we hypothesized that the observed prevalence of influenza might shed light on the unseen early spread of COVID-19. To extrapolate COVID-19 prevalence from influenza surveillance data, we assume that the ratio of COVID-19 positive to influenza posi tive cases detected retrospectively in small samples generally holds for the surro unding metropolitan area.

We analyzed data provided by two studies--one in Wuhan [9] and the other in Seattl e [10]--that re-tested swabs taken from ILI and ARI cases in early 2020. The ident ification of overlooked COVID-19 cases in both cities was not surprising, given th e large numbers of cases, hospitalizations and deaths that were detected shortly a fter these retrospective periods. Nonetheless, the ratios of SARS-CoV-2 to influen za positive swabs were surprisingly high. In Wuhan, there were roughly two symptom atic cases of COVID-19 for every three cases of influenza; in Seattle, there was o ne pediatric case of symptomatic COVID-19 per every 9 influenza cases, and one per every seven in adults. Given that influenza was circulating widely at the time of these infections, these ratios led us to conclude that there may have been over 5, 000 undetected cases of symptomatic COVID-19 both in Wuhan prior to January 12th a nd in Seattle prior to March 9th.

Our results do not imply that health authorities were aware of these undocumented infections, rather that they went unseen during the early and uncertain stages of COVID-19 emergence in the two cities. In Wuhan, other data have suggested similar levels of *unseen* COVID-19 prior to the January 23, 2020 lockdown of the city. For

example, we previously estimated that there were 12,400 (95% CrI 3,112-58,465) total cases based on extrapolation from the timing and location of the first 19 COVID-19 cases imported from Wuhan to other countries [2]. These numbers are further corroborated by a similarly-derived estimate from Imperial College of 4,000 (1,000-9,700) cases as of January 18, 2020 [29]. Our estimate that the epidemic in Wuhan started in mid to late November of 2019 is consistent with the first known case reporting symptoms starting December 1, 2019 [30].

In Seattle, we estimate that sustained community transmission of SARS-CoV-2 began in early January (Figure 4), around the time of the first confirmed case [1]. Two recent phylogenetic studies using SARS-CoV-2 genomic data provide conflicting backcasts. The first suggests that a locally-infected case detected on February 24th could be traced back to the initial imported case detected on January 15th [3]; the second calls this claim into question and suggests that the current epidemic originated roughly four weeks later, in early February [5].

Limitations

Our estimates are based on sparse data and multiple assumptions that have resulted in wide credible intervals and potential biases. For one, we do not explicitly consider the accuracy of the viral tests. For example, the Wuhan study tested oropharyngeal (OP) swabs rather than (NP) nasopharyngeal swabs, which have lower sensitivity [31]. The SARS-CoV-2 RT-PCR tests used have a reported false negative rate of 29% [32] and false positive rate of 0.8% [33]. For influenza, both error rates are under 10% [34]. Under the maximum reported error rates for both viruses, we would expect that ref. [9] may have missed approximately 1.4 SARS-CoV-2 cases and over-diagnosed influenza by 1.5 cases. This would imply an even larger ratio of COVID-19 positive to influenza positive cases and a 41% higher overall prevalence of COVID-19 among adults over 30 in Wuhan during this period than we estimated. Larger samples using NP rather than OP swabs for the SARS-Cov-2 test would allow more precise estimation of the early prevalence of SARS-CoV-2 in cities worldwide.

Both studies leveraged data from existing surveillance systems that are designed to provide reliable and representative data on respiratory virus prevalence. Thus, we made two key assumptions. First, influenza and COVID-19 were widespread and exh

ibited similar epidemiological patterns throughout the 13 central Wuhan districts and throughout the 19 PUMA's of Seattle, during the study periods. Second, the studies provide representative data for these cities. In Wuhan, if SARS-CoV-2 was only spreading in the 6 districts where it was detected, then our estimate for the prevalence of SARS-CoV-2 would decrease by 51%. Nonetheless, we believe that our methodology and qualitative insights are robust, given that the two Wuhan hospitals serve as sentinels for the Chinese Influenza Surveillance System [9] and the high inter-district mobility within Wuhan [35]. Likewise, the Seattle Flu Study was designed to broadly sample the metropolitan area [36].

Finally, the validity of our estimates hinges on our assumption that influenza and COVID-19 spread similarly during the periods of the two retrospective studies. Both studies tested specimens taken during the heart of the influenza season, when transmission was rampant. The simultaneous global expansion of the COVID-19 pandemic suggests that conditions were equally favorable for the spread of SARS-CoV-2. Moreover, the two studies analyzed specimens collected through surveillance systems in China and the US that were specifically designed to provide reliable estimates of the prevalence of influenza and other similarly-spreading respiratory viruses. That said, influenza is highly seasonal and SARS-CoV-2 may exhibit very different seasonal or non-seasonal transmission dynamics. While we conjecture that our approach was robust for the short period when both viruses were circulating in the focal communities, it may not provide reliable estimates for samples taken over longer periods of time or during the influenza off-season.

With these caveats in mind, we conclude that our method provides a way to *roughly triangulate* the unseen emergence of the COVID-19 pandemic in cities around the world during the early months of 2020. Retrospective testing of swabs from ILI and ARI patients stored in laboratories can indicate the local ratio of symptomatic SARS-CoV-2 infections to symptomatic influenza infections. If we know the prevalence of influenza when and where the swabs were taken, then we can extrapolate the concurrent prevalence of COVID-19. This approach can elucidate the past as well as provide sentinel surveillance for novel respiratory viruses that co-circulate with influenza, prior to widely available testing.

The COVID-19 epidemics in Wuhan and Seattle were far more extensive than initially reported and had likely been spreading for several weeks before they became apparent. The large discrepancy between confirmed cases and true prevalence highlights the difficulty of determining infection fatality rates from readily available COVID-19 data.

Data sharing statement:

The clinical trial COVID-19-related data are published in refs. 9 and 10 and the influenza surveillance data are publicly available in refs. 9 and 22 for Wuhan and Seattle, respectively.

Conflict of interest

We declare no competing interests.

Author Contributions

Zhanwei Du, Ciara Nugent and Lauren Ancel Meyers: conceived the study, designed statistical methods, conducted analyses, interpreted results, wrote and revised the manuscript. Benjamin J. Cowling: conceived the study, interpreted results, and revised the manuscript. Emily Javan: collected the demographic and epidemiological data of Census Block Groups and Public Use Microdata Areas in the Seattle area and revised the manuscript.

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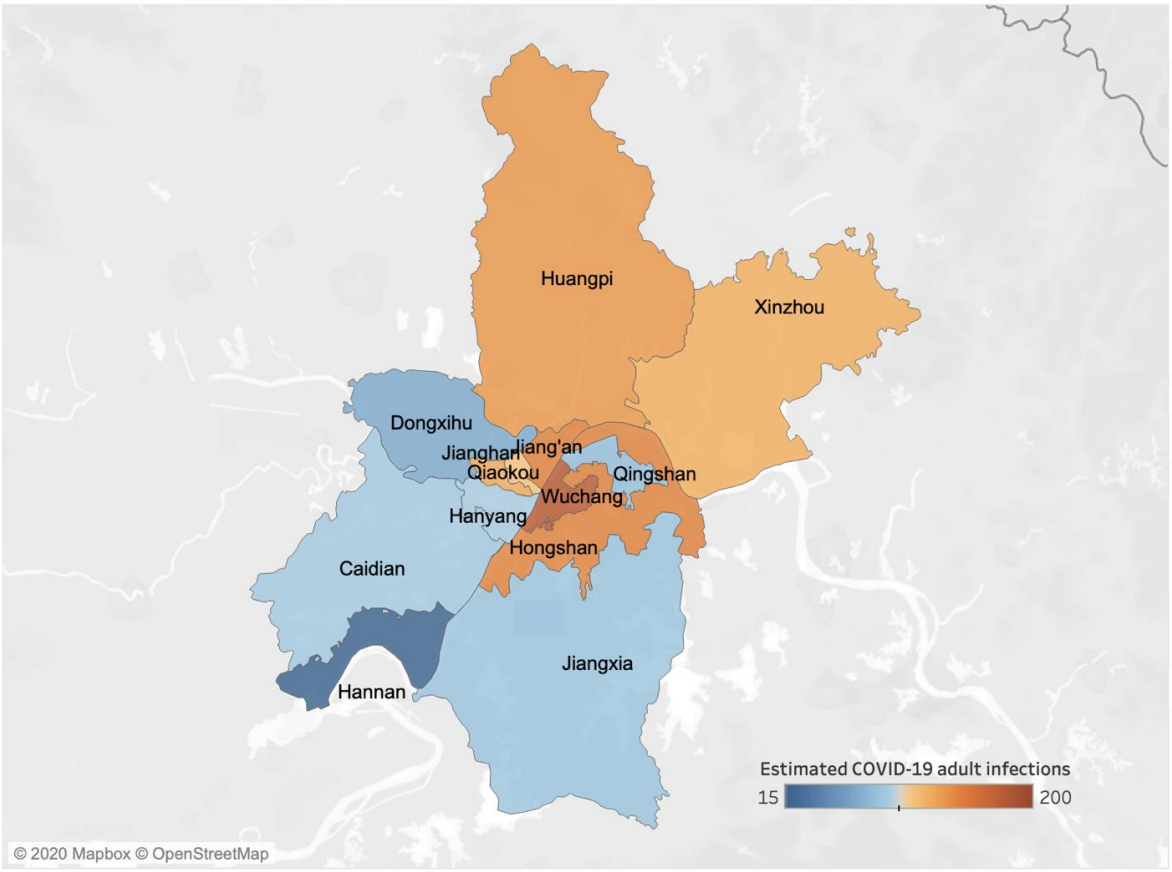

Figure 1. Estimated symptomatic COVID-19 infections of people over 30 years in the 13 districts of Wuhan from December 30, 2019 to January 12, 2020. A retrospective study identified four ILI cases of COVID-19 from two hospitals in central Wuhan [9]. We estimate that there were a total of 1386 [95% CrI: 420-3793] adult cases of COVID-19 during that 14-day period across the 13 central districts of Wuhan, ranging from 19 cases [95% CrI: 6-51] in suburban Hannan to 177 cases [95% CrI: 54-485] in central Wuchang, as indicated by shading (Table S3).

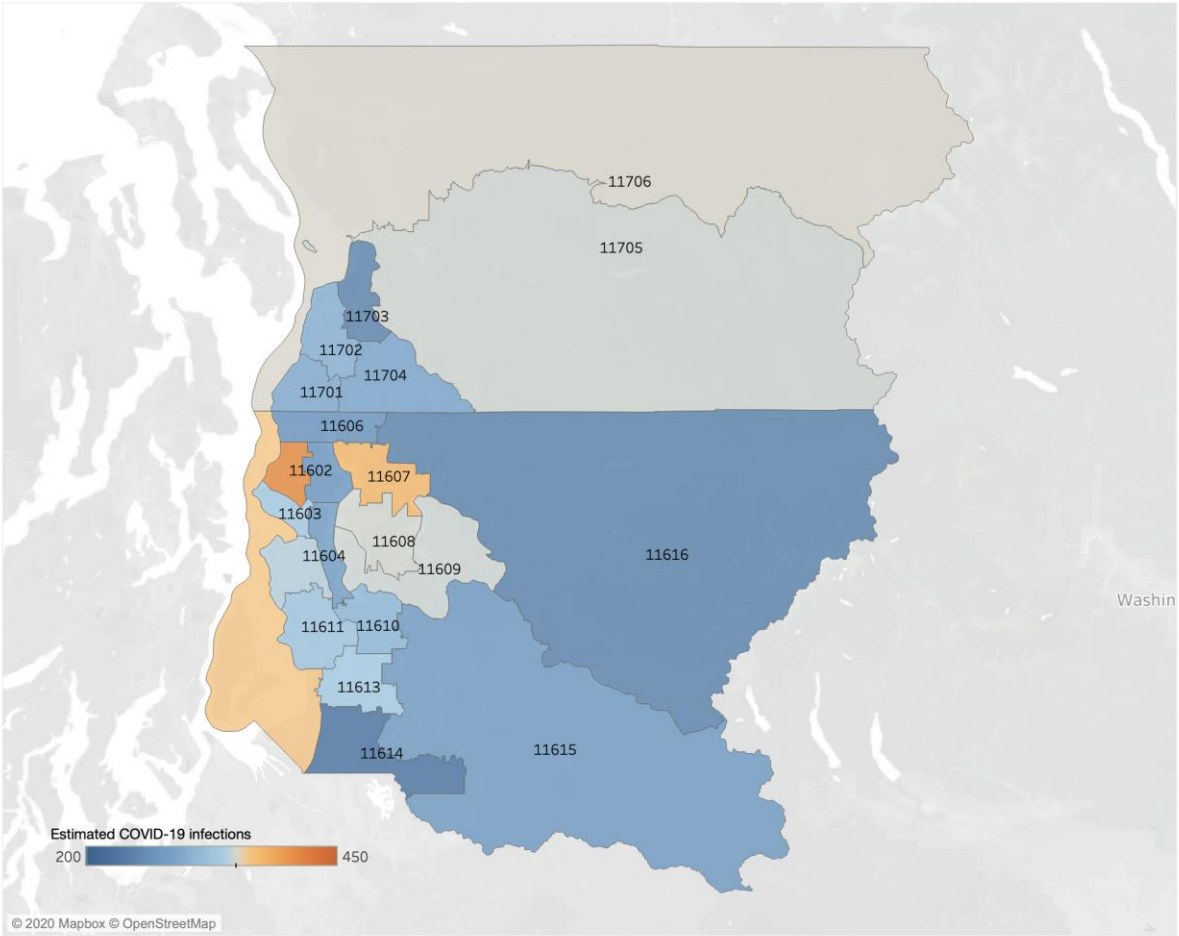

Figure 2. Estimated symptomatic COVID-19 infections of people over all ages in the 22 studied Public Use Microdata Areas of Seattle from February 24, 2020 to March 9, 2020. A retrospective study identified 2 children and 23 adult ILI cases associated with COVID-19 from the Seattle Flu pandemic surveillance platform [10]. We estimate that there were a total of 6748 [95% CrI: 4133, 11020] (2268 [95% CrI: 498, 6069] and 4367 [95% CrI: 2776, 6526] for people under and over 18 years, respectively) cases of COVID-19 cases during that 15-day period across the 22 PUMAs of Seattle, ranging from 231 cases [95% CrI:199,265] in PUMA 11614 to 410 cases [95% CrI:364,459] in PUMA 11601 (Table S2).

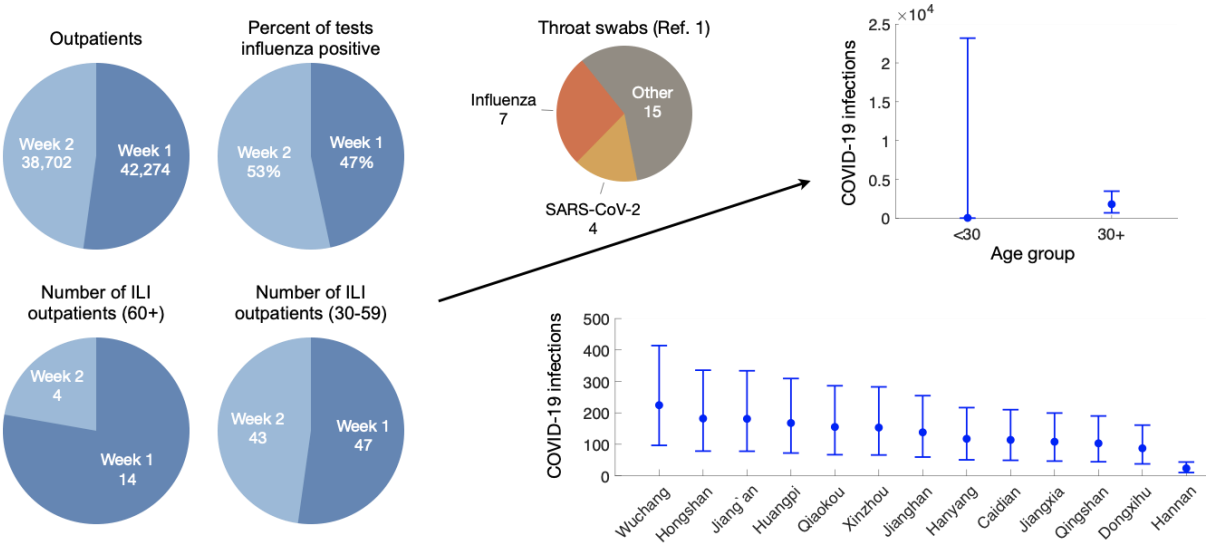

Figure 3. Estimating adult COVID-19 infections based on the ratio between patients retrospectively testing positive for COVID-19 and influenza in two hospitals in Central Wuhan from December 30, 2019 to January 12, 2020. First we use influenza surveillance data (number of outpatients, percent positive influenza tests, and number of ILI outpatients reported for the Wuhan region by the Chinese CDC) to estimate the proportion of adult outpatients (all cause) testing positive for influenza from December 30, 2019 to January 12, 2020 (left graphs). Second, we estimate the ratio of COVID-19 positive to influenza positive patients among adult outpatients with ILI, based on a recent retrospective study in two Wuhan hospitals (0.61 [95% CrI: 0.20-1.64]) [9]. We then estimate the number of symptomatic COVID-19 infections among adults across Wuhan during this time period based on the proportion of influenza positive outpatients and the ratio of COVID-19 to influenza positive outpatients, using Monte Carlo sampling to incorporate uncertainty in our estimates of both quantities (upper right). Finally, we estimate the age-specific COVID-19 adult infections for the 13 central districts in Wuhan based on the district level population sizes for each age group. Given that the four detected COVID-19 cases lived in central Wuhan in ref. [9], we assumed that risk was uniform across all 13 districts during the 14-day time period.

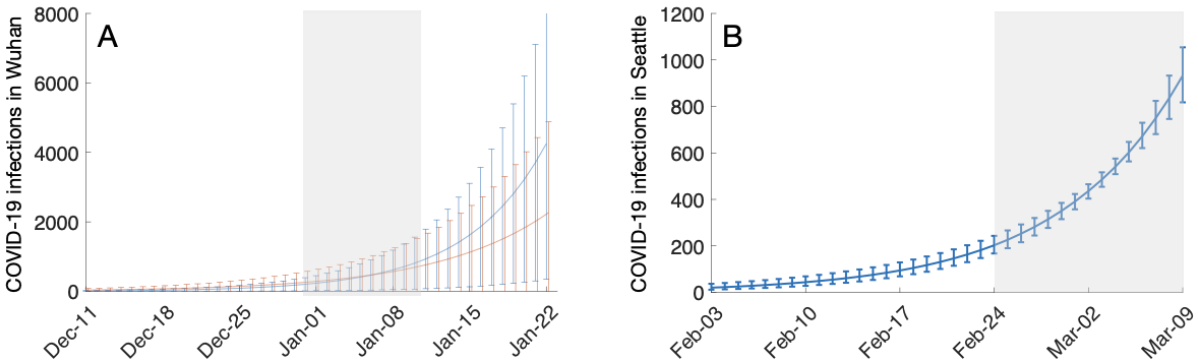

Figure 4. Estimating the number of symptomatic COVID-19 cases among all age groups in Wuhan prior to January 23, 2020 and all age groups in Seattle prior to March 9, 2020. (A) For Wuhan, we assume an epidemic doubling time of either 7.3 [95% CrI: 6.3-9.7] days (red) or 5.2 [95% CrI: 4.6-6.1] days (blue). We further assume the numbers of COVID-19 infections estimated for the 13 central districts (Table S3) are equal to the sum of the daily number of incident infections from December 30, 2019 to January 12, 2020. Using an exponential model of epidemic growth we estimate that the first COVID-19 infection occurred on (red) November 17, 2019 [95% CrI: October 26-December 3, 2019] or (blue) December 2, 2019 [95% CrI: November 20-December 13, 2019], and then project the daily COVID-19 infections until January 23, 2020. (B) For Seattle, we assume an epidemic doubling time of 6.1 [90% uncertainty interval of 5.1 to 8.2] days [3] and that the numbers of COVID-19 infections estimated across the 22 PUMA's are equal to the sum of the daily number of incident infections from February 24th to March 9th, 2020. Using an exponential model of epidemic growth we estimate the initial pandemic wave in Seattle originated with a single infected case who developed symptoms on January 6, 2020 [95% CrI: December 25, 2019 - January 15, 2020] and then project the daily COVID-19 infections until March 9, 2020. In both graphs, lines and bars indicate the median and 95% CrI estimates, respectively. Gray shading indicates the time period of our initial estimates.

Table 1. Model Parameters and Data Sources. Parameters with an age indicator (a) have separate values for the 30+ age ranges.

Symbol	Description	Values	Sources
$H_{d,a,\tau}$	Number of COVID-19 outpatients in age group a in district d over time period τ	Estimated	
r	Ratio of ILI outpatients that are COVID-19 positive versus influenza positive (adults over 30)	Age 30+: 0.61 [95% CrI: 0.20-1.64]	Ref. [9]: Of the 26 tested ILI throat swab samples taken from adults over age 30 who sought ILI treatment at two central Wuhan hospitals between December 30, 2019 and January 12, 2020, 7 tested positive for influenza and 4 tested positive for COVID-19. None of the cases tested positive for both viruses.
N_d	Age-stratified population sizes in district d	2010 population scaled by the ratio of the 2019 to the 2010 total Wuhan population	Sixth National Census of the People's Republic of China in 2010 [20] and total population of Wuhan in 2019 (11.08 million) [21]
Ω_τ	Number of outpatient visits (all causes) in Wuhan across all ages over time period τ	42,274 and 38,702 over two weeks, respectively	China CDC weekly reports of outpatient visits in Wuhan, December 30, 2019-January 12, 2020 [9]
Θ_τ^a	Number of ILI outpatients in age group a in Wuhan over time period τ	Age 30+: 61 and 47, for each of the two weeks, respectively	China CDC weekly reports of ILI outpatients in Wuhan, December 30, 2019-January 12, 2020 [9]
Φ_τ	Percent of influenza positive tests	25% and 28.6% for each of the two weeks, respectively	Ref. [9]: 25%, 28.6% adult (30+) influenza positive among 160 ILI throat swab samples, from December 30, 2019 to January 12, 2020.
T_d	Epidemic doubling time	7.3 [95% CrI: 6.3-9.7] days 5.2 [95% CrI: 4.6-6.1] days	Refs. [2] and [24]

Supplementary Appendix

Using the COVID-19 to influenza ratio to estimate early pandemic spread in Wuhan, China and Seattle, US

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Table S1. Model Parameters and Data Sources. Parameters with an age indicator (a) have separate values for the 0–17 and 18+ age ranges.

Symbol	Description	Values	Sources
$H^{a}_{d,\tau}$	Number of symptomatic COVID-19 cases in age group a in location d at time τ	Estimated at the Public Use Microdata Areas (PUMA) level per day for 0-17y and over 18y age groups.	Estimated
r^{a}	Ratio of ARI patients that are COVID-19 positive versus influenza positive in age group a	Between February 24 and March 9, 2020: Age 0-17y: 0.11 [95% CrI: 0.03–0.33] Over 18y: 0.14 [95% CrI: 0.09–0.21]	Ref. [1] tested 2353 mid-nasal swab samples from patients with acute respiratory illness (ARI), January 1-March 9, 2020. Of those, 442 and 25 tested positive for influenza and COVID-19, respectively (none were double positive).
N_d	Population size of location d	Public Use Microdata Area (PUMA) population sizes in Seattle metropolitan area estimated for 2014-2018	2018 American Community Survey 5-Year Data, released in 2019 [2]
Ω_τ	Number of outpatient visits (all causes and ages) at time τ	MMWR week 1 to week 11, 2020 for Region 10: [71870, 73781, 70333, 72732, 73329, 72597, 73331, 73118,	CDC weekly reports for HHS Region 10 (Alaska, Idaho, Oregon, and Washington), January 1-March 9, 2020[3]

Appendix: Symptomatic COVID-19 cases in Seattle

		72963, 72812, 68179]	
Θ_{τ}^{a}	Number of ILI outpatient visits in age group a at time τ	MMWR week 1 to week 11, 2020 for Region 10: Age 0-17y: [1645, 1125, 1037, 1198, 1169, 1088, 1111, 1172, 1164, 1389, 1419] Over 18y: [2305, 1855, 1436, 1546, 1581, 1375, 1420, 1429, 1650, 2436, 2592]	CDC weekly reports of ILI in HHS Region 10 (Alaska, Idaho, Oregon, and Washington), January 1-March 9, 2020[3]
Φ_{τ}	Percent of influenza positive tests at time τ	MMWR week 1 to week 11, 2020 for Region 10: [23.275, 20.9372, 18.8126, 21.2625, 19.097, 16.3656, 16.3466, 17.2397, 18.3453, 17.5661, 10.8454]	CDC weekly reports of influenza positive percents in HHS Region 10 (Alaska, Idaho, Oregon, and Washington), January 1-March 9, 2020[3]
ι_{τ}	Number of influenza positive in ref. [1] at time τ	442	Ref. [1] reports that a total of 442 swabs tested positive for influenza from January 1-March 9, 2020, but does not report influenza positivity by day or week.
x_{c}^{a}	Number of symptomatic COVID-19 cases in age group a at time τ	Between February 24 and March 9, 2020: Age 0-17y: 2 Over 18y: 23	Ref. [1] tested 2 and 23 tested COVID-19 positive for two age groups, respectively.
x_{f}^{a}	Number of influenza positive in age group a between February 24 and March 9, 2020	Age 0-17y: 23 Over 18y: 170	Estimated
$N_{a,\tau}$	Number of total tests of age group a in ref. [1] at time τ	Extracted from ref.[1] for 0-17y and over 18y age groups.	Data extracted from ref.[1] using a web plot digitizer[4], , January 1-March 9, 2020.
T_{d}	Epidemic doubling time	6.1 [90% uncertainty interval of 5.1 to 8.2] days	Ref. [5]

Appendix: Symptomatic COVID-19 cases in Seattle

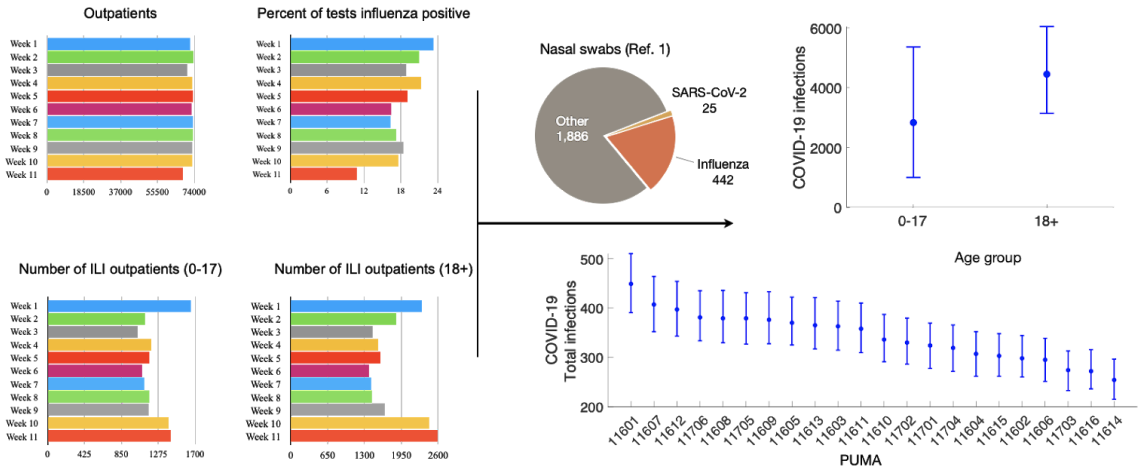

Figure S1. Estimating the number of symptomatic pediatric and adult COVID-19 infections based on the ratio between samples retrospectively testing positive for COVID-19 and influenza in Seattle from January 1st to March 9th, 2020 [6]**.** First, we analyze influenza surveillance data from the CDC FluView platform at the level of HHS region 10 [3], including the number of outpatients, percent positive influenza tests, and number of ILI outpatients. We combined these to estimate the number of outpatients (all cause) testing positive for influenza from January 1, 2020 to March 9, 2020 (left graphs). Second, we estimate the ratio of COVID-19 positive to influenza positive patients among pediatric and adult patients with ARI, based on a recent retrospective study in Seattle [6]. The ARI case definition in ref. [1] is at least "two of the following: feeling feverish, headache, sore throat or itchy/scratchy throat, nausea or vomiting, rhinorrhea, fatigue, myalgia, dyspnea, diarrhea, ear pain or ear discharge, rash, or a new or worsening acute cough alone", in contrast with the CDC's case definition for ILI is "fever (temperature of 100°F [37.8°C] or greater) and a cough and/or a sore throat without a known cause other than influenza"[7]. Thus, the case definitions overlap considerably, but are not identical. We estimate ratios of 0.11 [95% CrI: 0.03–0.33] and 0.14 [95% CrI: 0.09–0.21] for children under 18 and adults, respectively, between February 24 and March 9, 2020. We then estimate the number of symptomatic COVID-19 infections among pediatric and adult patients in Seattle during this time period based on the number of influenza positive patients and the ratio of COVID-19 to influenza positive patients, using Monte Carlo sampling to incorporate uncertainty in our estimates of both quantities (upper right). Finally, we estimate the age-specific COVID-19 infections for the 22 PUMA's of King and Snohomish counties in the Seattle Metropolitan Area based on their age-stratified population sizes, ordered from highest to lowest expected COVID-19 prevalence.

Appendix: Symptomatic COVID-19 cases in Seattle

Method

We estimate the ratio of COVID-19 to influenza patients (r) from ref. [6], the age-specific prevalence of influenza during the corresponding time period based on CDC surveillance data [3], and then combine the two to estimate the PUMA level prevalence of COVID-19 (Figure S1).

Estimating the number of influenza positive samples during the period of undetected COVID-19 transmission

Ref. [1] provides the total number of influenza positive swabs from January 1, 2020-March 9, 2020, but does not break down the results by date or age group. We use regional influenza surveillance data to estimate that breakdown, under the assumption that weekly and age-specific positivity in the ref. [1] sample mirrored that observed for HHS Region 10 as a whole. HHS Region 10 encompasses Alaska, Idaho, Oregon, and Washington.

In particular, the study reported 442 influenza positive patients for January 1, 2020-March 9, 2020 [1]. We apply the following method to estimate the subset of those patients who were influenza positive between February 24, 2020 and March 9, 2020, corresponding to the dates of the SARS-CoV-2 positive cases identified in ref. [1]. In short, we assume that the daily influenza positivity in the sample mirrored the overall influenza positivity reported by CDC FluView for HHS region 10 [3].

For a given day τ, we assume that the number of influenza positive cases in the sample for age group a is simply the number of tests conducted in that age group on that day $N_{a,\tau}$ times the regional influenza positivity ι_τ on that day, scaled to ensure that the total number of cases across the entire time period totalled 442.

$$x_{a,\tau} = N_{a,\tau}\iota_\tau \left(\frac{442}{\sum_{j=\text{Jan 1}}^{\text{Mar 9}} (N_{\text{ped},j} + N_{\text{adult},j})\iota_j} \right).$$

The CDC's FluView provides the number of tests performed and number of tests positive for influenza on a weekly basis. We assume that the daily positivity is equal to that of the corresponding week. The denominator is the *expected* number of influenza positive tests in the study based on the total number of tests performed daily and the weekly proportions of positive tests reported by the regional surveillance system. Remarkably it is equal to 433, which is almost identical to the actual 442 cases reported by the study [1].

For the purposes of estimating the ratio of SARS-CoV-2 to influenza positive cases, we aggregate these estimates into the total influenza positive pediatric ($x_f^{\text{ped}} = 23$) and adult ($x_f^{\text{adult}} = 170$) cases between February 24th and March 9th.

Estimating COVID-19 infections in Seattle

Let $H_{d,\tau}^{a}$ denote the number of COVID-19 infections in PUMA *d* (for each of the 22 PUMA's in King and Snohomish counties) and age group *a* (i.e., children under 18y or adults), during the focal fifteen-day period τ. We first estimate the ratio (r) of COVID-19 cases to influenza cases among pediatric and adult cases from the

retrospective sample [6] using a Bayesian approach (described below), and then use this to predict the patients in each PUMA and age range by assuming:

$$H^a_{d,\tau}|N_d, \lambda, \Theta^a_\tau, \Omega_\tau, \Phi_\tau, r \sim B(N_d, \frac{\lambda\Theta^a_\tau}{\Omega_\tau}\Phi_\tau r)$$

where N_d is the number of people in PUMA d; Θ^a_τ is the number of ILI outpatients in age group a over a period of time τ; Ω_τ is the number of all cause outpatients of all ages over a period of time τ; Φ_τ is the percent of influenza tests that are positive in the HHS Region 10 during time period τ; r is the ratio of COVID-19 to influenza cases. *B(N, p)* denotes the standard Binomial distribution. We assume that *H* is distributed binomially where *N* is the total population and *p* is the estimate of the prevalence of symptomatic COVID-19 in the population. In other words, we multiply the number of influenza positive cases by the ratio of ARI patients that have COVID-19 versus influenza, both estimated for Seattle from February 24 to March 9, 2020.

We take a Bayesian approach to derive r as the following posterior distribution. Let N^a denote the total number of cases in the sample in the sample for age group a (pediatric under 18y or adult). Let x^a_c denote the observed number SARS-CoV-12 positive cases in age group a between February 24th and March 9th and recall that x^a_f is the estimated number of influenza positive cases during this time period. Then

$$x^a_c|p^a_c, N^a \sim B(N^a, p^a_c) \text{ and } x^a_f|p^a_f, N^a \sim B(N^a, p^a_f).$$

If we assume uninformative priors on p^a_c and p^a_f,

$$p^a_c \sim Beta(1,1) \text{ and } p^a_f \sim Beta(1,1)$$

then the posterior distributions are known in closed form[8]:

$$p^{0\text{–}17}_c|x^{0\text{–}17}_c, N^{0\text{–}17} \sim Beta(1 + x^{0\text{–}17}_c, 1 + N^{0\text{–}17} - x^{0\text{–}17}_c) \sim Beta(3, 125)$$

$$p^{0\text{–}17}_f|x^{0\text{–}17}_f, N^{0\text{–}17} \sim Beta(1 + x^{0\text{–}17}_f, 1 + N^{0\text{–}17} - x^{0\text{–}17}_f) \sim Beta(24, 104)$$

and

$$p^{18+}_c|x^{18+}_c, N^{18+} \sim Beta(1 + x^{18+}_c, 1 + N^{18+} - x^{18+}_c) \sim Beta(24, 923)$$

$$p^{18+}_f|x^{18+}_f, N^{18+} \sim Beta(1 + x^{18+}_f, 1 + N^{18+} - x^{18+}_f \sim Beta(171, 776)$$

We use MCMC to take draws from p^a_c and p^a_f, and then calculate $r^a = \frac{p^a_c}{p^a_f}$ to obtain the distribution for r^a. We thereby estimate that the ratios of COVID-19 to influenza during February 24, 2020 to March 9, 2020 were 0.11 [95% CrI: 0.03–0.33] and 0.14 [95% CrI: 0.09–0.21] for children 0–17y and adults over 18y, respectively.

Appendix: Symptomatic COVID-19 cases in Seattle

Using 1,000 draws from the distribution of r^a, we estimate $H^a_{d,\tau}$ for each PUMA and age group, and point estimates for all other parameters given in Table S1. We report the means and 95% credible intervals of the resulting posterior predictive distribution for each PUMA.

Estimating COVID-19 infections prior to March 9, 2020

To backcast the number of infections in Seattle prior to March 9, 2020 (H_{cum}), we assume

$$H_{\text{cum}} = \sum_{i=t_0}^{L} h_0 \cdot 2^{i/T_d}$$

where T_d is the epidemic doubling time, t_0 is the day of the first infection in Seattle, and L corresponds to March 9, 2020. We use our age- and PUMA-stratified estimates for adult COVID-19 infections for February 24, 2020 to March 9, 2020 to estimate this quantity, under the assumption that the values reflect cumulative incident infections during that fourteen-day period (Figure 4).

We use Monte Carlo sampling to incorporate the uncertainty in both the epidemic doubling rate in Seattle during this period [9] and total infections from February 24, 2020 to March 9, 2020 ($H^a_{d,\tau}$). We take draws from the distribution of $H_\tau = \sum_d \sum_a H^a_{d,\tau}$ and T_d (summarized in Table S1) to estimate the time since the first infection by

$$\delta = T_d(log_2(\frac{H_\tau}{\sum_{i=0}^{14} 2^{i/T_d}})) .$$

That is, the estimated date of the first COVID-19 infection in Seattle (t_0) is δ days prior to February 24, 2020. We then estimate H_{cum} according to the equation above to project the cumulative COVID-19 infections preceding the Seattle lockdown.

Appendix: Symptomatic COVID-19 cases in Seattle

Table S2. Estimated COVID-19 infections in the 22 PUMAs of Seattle, from February 24, 2020 to March 9, 2020. Values are medians and 95% bounds across 1,000 Monte Carlo samples.

PUMA	Population	Infections		
		all	0-17	18+
11601	175,213	410 [95% CrI:364,459]	150 [95% CrI:121,179]	261 [95% CrI:227,295]
11602	116,083	272 [95% CrI:236,311]	99 [95% CrI:76,125]	173 [95% CrI:146,201]
11603	141,776	332 [95% CrI:292,375]	121 [95% CrI:96,153]	210 [95% CrI:184,243]
11604	119,177	280 [95% CrI:244,318]	101 [95% CrI:78,128]	178 [95% CrI:152,205]
11605	144,312	340 [95% CrI:298,381]	124 [95% CrI:99,151]	216 [95% CrI:184,246]
11606	114,608	269 [95% CrI:234,306]	98 [95% CrI:75,121]	171 [95% CrI:146,200]
11607	158,258	372 [95% CrI:329,417]	135 [95% CrI:108,164]	237 [95% CrI:208,269]
11608	147,938	348 [95% CrI:308,389]	126 [95% CrI:100,157]	221 [95% CrI:192,255]
11609	146,632	346 [95% CrI:304,390]	125 [95% CrI:99,156]	220 [95% CrI:189,252]
11610	131,325	308 [95% CrI:273,349]	111 [95% CrI:88,141]	196 [95% CrI:167,224]
11611	139,603	327 [95% CrI:289,368]	118 [95% CrI:94,145]	209 [95% CrI:178,241]
11612	154,565	362 [95% CrI:318,407]	131 [95% CrI:104,162]	231 [95% CrI:199,265]
11613	142,658	335 [95% CrI:297,379]	121 [95% CrI:98,149]	212 [95% CrI:183,245]
11614	98,399	231 [95% CrI:199,265]	84 [95% CrI:63,108]	147 [95% CrI:123,173]
11615	118,069	278 [95% CrI:243,316]	100 [95% CrI:77,126]	177 [95% CrI:149,206]
11616	105,922	249 [95% CrI:217,287]	89 [95% CrI:69,114]	158 [95% CrI:134,188]
11701	126,114	296 [95% CrI:261,335]	108 [95% CrI:85,135]	188 [95% CrI:159,216]
11702	128,584	302 [95% CrI:265,343]	109 [95% CrI:86,137]	192 [95% CrI:164,221]
11703	106,551	249 [95% CrI:214,288]	91 [95% CrI:69,118]	159 [95% CrI:133,185]
11704	124,149	291 [95% CrI:256,332]	106 [95% CrI:80,134]	186 [95% CrI:161,212]
11705	147,548	347 [95% CrI:304,389]	126 [95% CrI:99,155]	221 [95% CrI:189,251]
11706	148,447	350 [95% CrI:308,390]	127 [95% CrI:101,156]	223 [95% CrI:191,251]
Seattle	2,935,931	6748 [95% CrI: 4133, 11020]	2268 [95% CrI: 498, 6069]	4367 [95% CrI: 2776, 6526]

Appendix: Symptomatic COVID-19 cases in Seattle

Table S3. Estimated COVID-19 adult infections in the 13 central districts of Wuhan, from December 30, 2019 to January 12, 2020. Values are medians and 95% bounds across 1,000 Monte Carlo samples.

District	Population	Infections
		≥30
Hongshan*	1,574,315	143 (43-391)
Wuchang*	1,375,062	177 (54-485)
Jiangan*	1,014,584	144 (44-393)
Huangpi	990,782	132 (40-362)
Xinzhou	961,138	121 (37-331)
Qiaokou*	939,515	123 (37-335)
Jiangxia	894,731	85 (26-234)
Jianghan*	776,487	109 (33-298)
Caidian	700,950	90 (27-246)
Hanyang*	661,434	93 (28-254)
Qingshan	549,903	81 (25-223)
Dongxihu	511,906	69 (21-189)
Hannan	130,192	19 (6-51)
Wuhan	11,081,000	1386 (420-3793)

* These 7 districts are located in central Wuhan; the other six are suburban.

Appendix: Symptomatic COVID-19 cases in Seattle

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